THE NEUROLOGY OF CONSCIOUSNESS

SECOND EDITION

THE NEUROLOGY OF CONSCIOUSNESS

Cognitive Neuroscience and Neuropathology

SECOND EDITION

Edited by

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Foreword

Looking back is often disappointing and not really a good way of deciding what to do next. But in cognition research we can't help but muse on those who claimed as little as 25 years ago that consciousness was not a subject respectable neuroscientists should concern themselves with. The problem was too complex, the concept too ill-defined, the level of organization unreachable and so on. Predicting the future is a difficult game, which is presumably why, as a community, scientists prefer experimentation based on models, peer review, and evaluation. Happily so, this book clearly demonstrates that not only is consciousness a viable subject for scientific study but also that the diverse meanings of the word "consciousness" firm up as new measuring instruments and experimental methods become available.

As a word, "consciousness" is rich, means too many things and requires deconstruction to become tractable. There are, for example, the contents of consciousness, mechanisms that access them, issues of awareness, implicit and explicit ways of recovering conscious events and so on. In common language, all these are subsumed in one way or another under the single term, consciousness. A simple analogy might be with the term "memory"—understood by all, but dissection of that concept by science into various types and mechanisms has enriched its comprehension considerably. An initial division into normal "conscious access" and its disorders in humans is potentially helpful. It is a universal experience to oscillate daily between sleep and wakefulness, thereby regularly to experience loss of conscious access. Similarly, general anesthesia systematically manifests by a chemically elicited and reversible "loss of consciousness," a widely accepted use of the word consciousness in a medical context.

From the neurological standpoint, it is commonly held that to lose consciousness (in the sense of a global loss of conscious access) it is necessary to suffer bilateral hemispheric damage or a midbrain lesion. Certainly this is true, but there are states in which apparent changes in consciousness are found that are limited to bilateral thalamic damage; so, bi-hemispheric, but limited in extent to critical regions. Consciousness can be impaired by large intracerebral lesions, such as hemorrhages, tumors, or aneurysms, that distort the brain by occupying space and impinging directly on both hemispheres, or pushing down onto the midbrain or by disease of local origin that spreads to involve these regions, as in focal epilepsies. It can also result from metabolic starvation as in hypoxia or with poisoning, for example, with gases such as carbon dioxide, carbon monoxide, or nitrous oxide. These phenomena have been known for a long time and, though dramatic, they give little insight into the neurobiology of consciousness, other than by providing the gross anatomical substrate described above.

Generally disturbed consciousness can occur in milder form, sometimes manifesting as confusion, and can also be caused by poisoning or metabolic insults from various pharmacological or toxic agents. Sometimes these are taken voluntarily; often they can modify the contents of consciousness in a repeatable and predictable manner. Alcohol is a clear example and various psychoactive drugs can either alter consciousness by instilling a negative state (such as opiates) while others distort consciousness, invoking hallucinations or heightened awareness that is often imaginary but easily communicated to others (e.g., LSD, magic mushrooms, and the like). In this latter situation, the disturbances of consciousness are not just due to altered access but also to an interaction with the contents of consciousness.

As mentioned, an unconscious state that resembles slow-wave sleep can be induced in a controlled fashion by infusion of general anesthetics, with remarkable precision. Propofol, for instance, can induce a loss of consciousness and subsequent recovery in seconds by manipulating intravenous doses, indicating a precise threshold effect. The mechanisms by which drugs such as propofol, barbiturates, and benzodiazepines act are known in detail at the molecular level, and their sites have been explored by photo-labeling and X-ray crystallography at the atomic level. They act as positive allosteric modulators of receptors and ion channels, such as the $GABA_A$ receptor (the ionotropic receptor of the inhibitory neurotransmitter gamma-aminobutyric acid). By enhancing inhibition in the brain at this level, they depress a general excitation of the cerebral cortex that seems necessary for conscious access. But the precise

sub-cellular and neuronal targets at which they cause a loss of consciousness are still not fully identified.

The unconscious state that has been the most intriguing and that, it must be said, has caused the most difficulty is that of sleep. For example, sleep, in which we are considered unconscious, can be associated with total muscle atony but also with muscular activity, be it of the eyes or manifesting as more general movements. It is a state into which one can "drop," or awaken from with a startle. One cause of ambiguity is the observation that we dream in sleep and at times are able to recount some of the substance of those dreams when awake again. If an account of a dream can be given, is a subject conscious whilst unconscious? The awareness of spontaneous inner states implies access to content and hence consciousness, while unresponsiveness to the external world implies the opposite. Is a recounted dream episode a form of deferred consciousness, or is it the product of an interaction between level of awareness and access to the contents of consciousness? Different phenomenological features co-occur in different ways to produce a rich tapestry of sleep states, which is why we struggle with understanding a unitary concept of consciousness.

There are many, mostly anecdotal, accounts of people reporting altered states of consciousness, in the sense of loss of access, which nevertheless leave them with remembered fragments. One example is the reports of relative retention of memory from islands of time in otherwise severe retrograde amnesiacs. This may also be an explanation for the phenomenon of patchy abnormal memories that are retained in dementing amnesiacs. Also, being unresponsive in the motor sense does not mean being unconscious. This is manifested clinically in sleep paralysis, and in certain post-traumatic states, notably the locked-in syndrome. More intriguing theoretically is the observation that whilst apparently unresponsive, people can access information, albeit often in fragmentary fashion, and implicitly or explicitly memorize and then recount such "experiences" when returned to awareness or contact with the environment.

We also have to consider states of partial loss of consciousness. Some are states of altered consciousness in which some awareness is retained, though very frequently distorted, and about which some often partial report is possible. An example is the so-called out-of-body experience, which experimentation suggests is mainly due to alteration of multisensory integrative processes that are thought to underpin an awareness of "self" and so result in syndromes sometimes referred to as altered self-consciousness. The body is seen as extraneous, returning to the self before normal consciousness is established. In strokes, feelings can be attributed falsely to others or to other parts of the body. Lesions in local, relatively specific, cortical areas may induce states of partial consciousness, or even supernumerary consciousness. For example, the conviction that a person owns a third limb that appears or disappears when the real limb on the same side is moved. The phenomenon of painful phantom limbs is a particularly dramatic example of altered local consciousness. The phenomenon appears to depend on whether a limb is amputated when painful or painless. Amputation when pain is not controlled results in a phantom limb much more frequently than if there is good pre-operative analgesia. Such a phenomenon suggests the presence of a nociceptive memory that cannot be eradicated and remains as a conscious reportable local percept. The physiological basis of such partial phenomena has been explored in some detail experimentally in monkeys by intracortical recordings and in humans by neuroimaging, leading to suggestions that there is re-mapping and distortion of sensory fields corresponding to the body parts affected.

Even more dramatic are the disturbances of consciousness that affect a half-body. These can manifest as complete denial of the presence of paralysis, usually in the left side of the body, or misattribution of limbs to others with considerable conviction and against all evidence. Neuropsychologists have documented such phenomena at length. A very dramatic example occurs in normal people who fail to notice major changes in a visual scene, despite normal awareness, because they do not expect to see what happens. The classical example is the perambulation of a gorilla across a student campus; the gorilla is simply not seen despite, or perhaps because of, its extreme incongruity. The inability to detect an object in a visual hemi-field when another is shown simultaneously in the other one, despite normal recognition when shown alone, is but one example in patients with lesions of the parietal cortex on one side. In patients with hemi-neglect, one sees descriptions of landmarks to the right exclusively, resulting in conscious access to memories of a different set of buildings in a town square depending on a patient's perspective. The phenomenon of blindsight is another dramatic example of loss of conscious visual perception following a specifically localized cortical injury. The loss of conscious perception does not prevent detection of objects visually, as judged by guessing the presence or absence of stimulation in a blind field, which occurs at a rate significantly greater than by chance. This phenomenon is fascinating because it lies on the boundary of conscious and non-conscious sensory states.

There is a large body of psychological work that demonstrates normal humans are capable of much

goal-oriented and complex perception and action without the ability to describe what has happened and hence non-consciously. The preoccupied worker who drives home safely despite being totally absorbed by a work problem is a classic example. Deciphering the neural mechanisms involved in consciousness experimentally is a question of investigating them step-by-step, first with simple, though necessarily limited experimental paradigms and then with formal models with straightforward experimental predictions. The phenomenon of "perceptual hysteresis" describes how an object when perceived under slowly decreasing illumination can no longer be seen when it dims below a critical level; however, when progressively illuminated from a low level it is not recognized at the same illumination threshold, but one that is significantly higher. Another example is a paradigm known as "masking" which results in altered conscious perception by temporally associated, consecutive, visual or auditory sensory stimuli. For instance, a briefly flashed written word is consciously visible when presented in isolation but becomes subjectively invisible when closely followed by a second stimulus, such as a geometrical shape, which serves to mask it. The first stimulus, though not perceived, can nevertheless be shown to have an effect on subsequent behavior. Functional magnetic resonance imaging (MRI), magnetoencephalography (MEG), and electroencephalography (EEG) recordings of the brains of subjects doing a masking task reveal that conscious access is associated with an amplification of activity, which propagates to a distributed network of areas, including bilateral parietal, mesial frontal, and prefrontal cortices, coinciding with those described as associated with the "global neuronal workspace." Such psychophysical setups provide reproducible and interpretable measurements and an opportunity to explore the gray area between conscious and non-conscious states.

Time-resolved physiological methods such as event-related potential recordings, magnetoencephalography, and other electrophysiological recordings in humans and primates show that a consistent, though not exclusive, indicator of conscious access is a late ($\sim$300$-$500 ms), broadly distributed positive waveform called the P300. However, such recordings cannot be considered as sufficient markers of consciousness, or even as a measure of the level of conscious impairment. For example, the P300 component has been recorded in patients in the vegetative state that are considered unconscious. During the late time window characterized by the P300, the power of high-frequency fluctuations, primarily in the gamma-band ($>$30 Hz), as well as their phase synchronization across distant cortical sites increases. In most instances however, a late all-or-none pattern consisting of "ignition" of a large cortical network including prefrontal cortex is found after 200 ms. Similar data have been obtained in the visual, auditory, and motor modalities. They are all consistent with the predictions of the global neuronal workspace model, which is based upon the neuroanatomical proposal that a subset of cortical pyramidal cells with long-range excitatory axons form a horizontal network interconnecting diverse areas on top of multiple, specialized, automatic, and non-conscious processors. These pyramidal neurons are particularly dense in prefrontal, cingulate, and parietal$-$cingulate regions, together with their associated thalamocortical loops. They may contribute to long-distance top-down connections that feed back to all underlying areas, thus updating the concept of "re-afference" or re-entrant processing in a global cerebral context.

However, patients undergoing general anesthesia with loss of consciousness have also shown increased gamma power in their EEG, an observation that needs to be accounted for by any theory of consciousness. Along these lines, biophysical recordings correlating with access to consciousness are altered in schizophrenics and autistic patients and after lesions of the white matter. So, theoretical and philosophical debate continues about the necessary requirement of global neuronal workspace mobilization for conscious access. Under conditions of binocular rivalry or inattentional blindness, distinctions between perception with or without introspection and with or without explicit report have been recorded. Accordingly, consciousness with explicit report may mobilize the global neuronal workspace preferentially. These reflections illustrate ongoing research about the neuronal mechanisms of conscious access and raise the intriguing issue of a multi-stage chronological process which, in the case of the clinical observations mentioned above, can be disturbed anywhere from primary perception to verbal report.

Indeed, electrophysiological experiments showing electrical potentials associated with medial frontal cortices that occur 500$-$1000 ms before an action is made have gained much attention, especially in relation to the mechanisms of unconscious action preparation and even execution. The perceptual blink is another phenomenon that for some authors suggests that our consciousness of time is an accessory event to activity and conscious decision-making. Also, it has been argued that in the "masking"—mentioned above—an interactive effect may also be possible at the semantic level; at the level of report rather than of perception. These aspects of consciousness lend themselves to more experimental and theoretical investigations, for instance by developing new methods of multiple local and global monitoring of brain function in humans. The fleeting aspects of consciousness are as important as more stable states in understanding its mechanisms.

Observations such as those described above have also led to a conflation of the phenomenon of attention with that of consciousness. Some suggest that awareness and perception must interact to provide a reportable sensory phenomenon or motor action. For instance, there are those who believe that the defining characteristic or evidence that can be obtained for a conscious event is that it is reportable to the self or others.

The notion of conscious level has proved useful in clinical medicine, largely because of its prognostic value. Much recent work with comatose patients has led to elaboration of schemata of different levels in the continuum between complete loss of consciousness and wakefulness. These constructs deal with the state of awareness in addition to states of access to the contents of consciousness and responses to them. The interaction between them remains one of the mysteries of the complex set of brain functions we continue to call consciousness. These recent advances in classifying states of impaired consciousness also take into account the notion of local and global impairments of consciousness. They have used a novel type of report that itself rests on recordings of brain physiology. The reproduction of patterns of regionally distributed brain activity when people imagine complex behavior is compared to that found in people who cannot communicate by normal means, when they are invited to imagine the same behavior. Correspondence has been found in sufficient cases to suggest that there are conscious processes at work in some partially damaged brains that are capable of integrating various types of information and relating them to memories. These observations and their clinical consequences turn consciousness, at least in part, into a social phenomenon with strong links to communication.

It is becoming clear to the reader that taking the human neuroscience perspective, normal or pathological, the word consciousness remains ambiguous and so a book that dissects phenomena related to consciousness into individual components is welcome. What will it require to put the facts about each element together? It is true there are already models that help to classify and categorize the different phenomena associated with consciousness and conscious access and at least make an attempt to link them together. The difficulty is that the more the problem of consciousness is investigated, the more one realizes that it is a difficult problem indeed, involving many functions and many levels of brain organization, each interacting with others in unexplored and unexpected ways. There is a view—which is not shared by all—that no global synthesis will be possible without an understanding of the molecular, cellular, neural, and physiological principles that govern the various spatial and temporal levels of brain organization. In the study of consciousness we may be living at a time analogous to that which, with the rise of molecular biology, started the process of understanding how living organisms are constituted some 50 years ago. "Life" was difficult to define then and "vitalist" theories were still common. This is no longer the case today. The introduction of a diversity of novel methods and theoretical paradigms produced new knowledge about bacterial cells and subsequently about eukaryotic cells too, despite the continuing absence of a satisfactory *a priori* general definition of what "life" is. A similar process may be in the process of illuminating what consciousness and conscious access are.

The editors and contributors of this excellent text combine most of the knowledge and data that are currently available—from normality through disease. For that they are to be congratulated. Federating this information is a prerequisite to integrating it into more general processes, which is one of many steps we need to provide a better understanding of biological mechanisms engaged in conscious processing.

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Preface

> Thinking must never submit itself, neither to a dogma, nor to a party, nor to a passion, nor to an interest, nor to a preconceived idea, nor to anything whatsoever, except to the facts themselves, because for it to submit to anything else would be the end of its existence. ***Henri Poincaré (1854–1912)***

'Truth is sought for its own sake. And those who are engaged upon the quest for anything for its own sake are not interested in other things. Finding the truth is difficult, and the road to it is rough.' wrote Ibn al-Haytham (965–1039), a pioneer of the scientific method. This book addresses one of the biggest challenges of science; understanding the biological basis of human consciousness. It does so through observation and experimentation in neurological patients, formulating hypotheses about the neural correlates of consciousness and employing an objective and reproducible methodology. This scientific method, as first proposed by Isaac Newton (1643–1727), has proven utterly successful in replacing Dark Age 'magical thinking' with an intelligent, rational understanding of nature. Scientific methodology, however, also requires imagination and creativity. For instance, methodologically well-described experiments allowed Louis Pasteur (1822–1895) to reject the millennia-old Aristotelian (384–322 BC) view that living organisms could spontaneously arise from non-living matter. Pasteur's observations and genius gave rise to the germ theory of disease, which would lead to the use of antiseptics and antibiotics, saving innumerable lives.

The progress of science also largely depends upon the invention and improvement of technology and instruments. For example, the big breakthroughs of Galileo Galilei (1564–1642) were made possible thanks to eyeglass makers' improvements in lens-grinding techniques, which permitted the construction of his telescopes. Similarly, advances in engineering led to space observatories such as the Hubble Telescope shedding light on where we come from. Rigorous scientific measurements permitted to trace back the beginning of the universe to nearly 14 billion years; the age of the earth to more than 4.5 billion years; the origin of life on earth to (very) approximately 3.5 billion years; and the apparition of the earth's first simple animals to about 600 million years. Natural selection, as revealed by Charles Darwin (1809–1882) then gave rise to nervous systems as complex as the human brain, arguably the most complex object in the universe. And, somehow, through the interactions among its 100 billion neurons, connected by trillions of synapses, emerges our conscious experience of the world and of ourselves.

The study of consciousness has remained within the scope of philosophy for millennia. Recent empirical evidence from functional neuroimaging offers a new way to investigate the mind–body conundrum. It also gives new opportunities to the neurological community to improve our understanding and management of patients with disorders of consciousness. This second edition of *The Neurology of Consciousness* aims at revising our understanding of the anatomical and functional underpinnings of human consciousness by emphasizing a lesion approach through the study of neurological patients. This second edition seems critical to us as numerous recent findings and seminal articles have been published since the first edition of the book in 2009. The different chapters review the mapping of conscious perception and cognition in health (e.g., wakefulness, sleep, dreaming, sleepwalking and anaesthesia) and in disease (e.g., post-comatose states, seizures, split-brains, neglect, amnesia, dementia, and so on).

'A genuine glimpse into what consciousness is would be the scientific achievement, before which all past achievements would pale' wrote William James in 1899. Testable hypotheses on consciousness, even if still far away from solving all problems related to the neural substrate of consciousness, give us such a glimpse. In our view, scientific and technological advances complemented by an adequate theoretical framework will ultimately lead to an understanding of the neural substrate of consciousness.

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CHAPTER

1

Neuroanatomical Basis of Consciousness

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OUTLINE

INTRODUCTION

Consciousness is of great importance to normal human quality of life. The nature of consciousness and the best way to understand and define it have long generated lively debate among scientists, philosophers, clinicians, and the general public. From a neurological perspective, consciousness is classically described as emerging from brain systems that make up the *content* of consciousness, regulated by distinct systems that control the *level* of consciousness (Plum and Posner, 1982).

The content of consciousness is the substrate upon which levels of consciousness act. This content includes all the various types of information processed by hierarchically organized sensory, motor, emotional, and memory systems in the brain (Figure 1.1). Much of neuroscience is dedicated to understanding the normal functioning of these systems. Selective deficits in contents of consciousness, such as loss of a portion of one's visual field, or sudden impairment in spoken language, are also the main subject matter of clinical neurology.

However, level of consciousness can affect all of these specific functions. The level of consciousness is controlled by specialized cortical and subcortical systems that determine the amount of alertness, attention, and awareness (mnemonic, AAA) (Blumenfeld, 2002).

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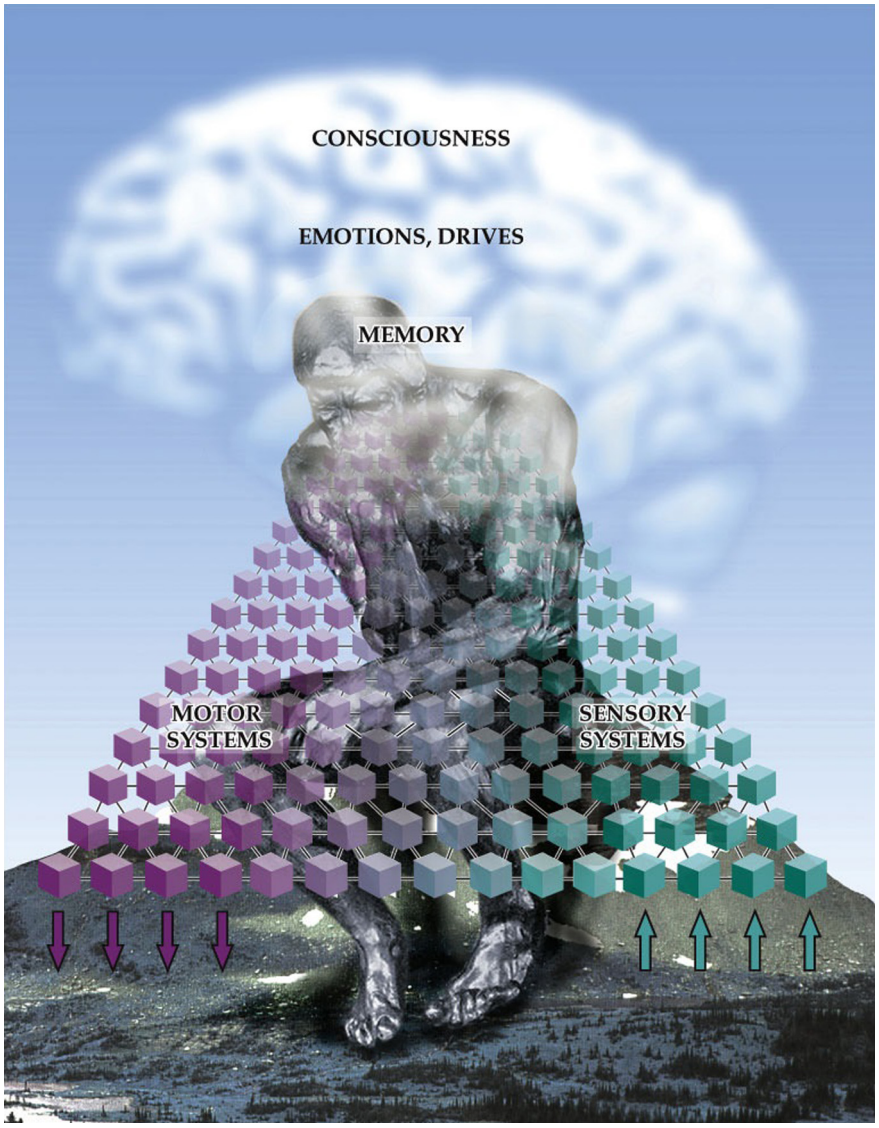

FIGURE 1.1 The content of consciousness. Parallel interconnected and hierarchically organized sensory and motor systems receive inputs, generate outputs, and perform internal processing on multiple levels, from relatively simple to highly abstract. Three additional special systems—mediating memory, emotions and drives, and consciousness itself—act on the other systems in a widely distributed manner, especially at the highest levels of processing. *Source: Modified with permission from Blumenfeld (2010).*

Basic alertness (arousal, wakefulness) is necessary for any meaningful responses to occur. Attention enables selective or sustained information to be processed. Finally, awareness is the ability to form experiences that can potentially be reported later. This chapter will review the neuroanatomical basis of brain systems that control the level of consciousness. In analogy with other cortical-subcortical systems such as the sensory, motor or limbic systems, the brain networks dedicated to regulating the level of consciousness can be referred to as the "consciousness system" (Blumenfeld, 2010, 2012). This chapter begins with an overview of the main cortical and subcortical structures that constitute the consciousness system. Next, the major subcortical networks that regulate level of consciousness are each discussed in turn, including the thalamus and subcortical arousal nuclei acting through multiple neurotransmitters (glutamate, acetylcholine, gamma amino butyric acid (GABA), norepinephrine, serotonin, dopamine, histamine, orexin) that arise from the upper brainstem, basal forebrain, and hypothalamus. The second half of the chapter reviews important cortical networks for controlling the level of alertness, attention, and awareness, including systems that select and encode conscious experiences into memories for subsequent report. This neuroanatomical review of the cortical and subcortical systems that control level of consciousness will serve as a general introduction to the normal functions as well as disorders of consciousness discussed in the remaining chapters in this book.

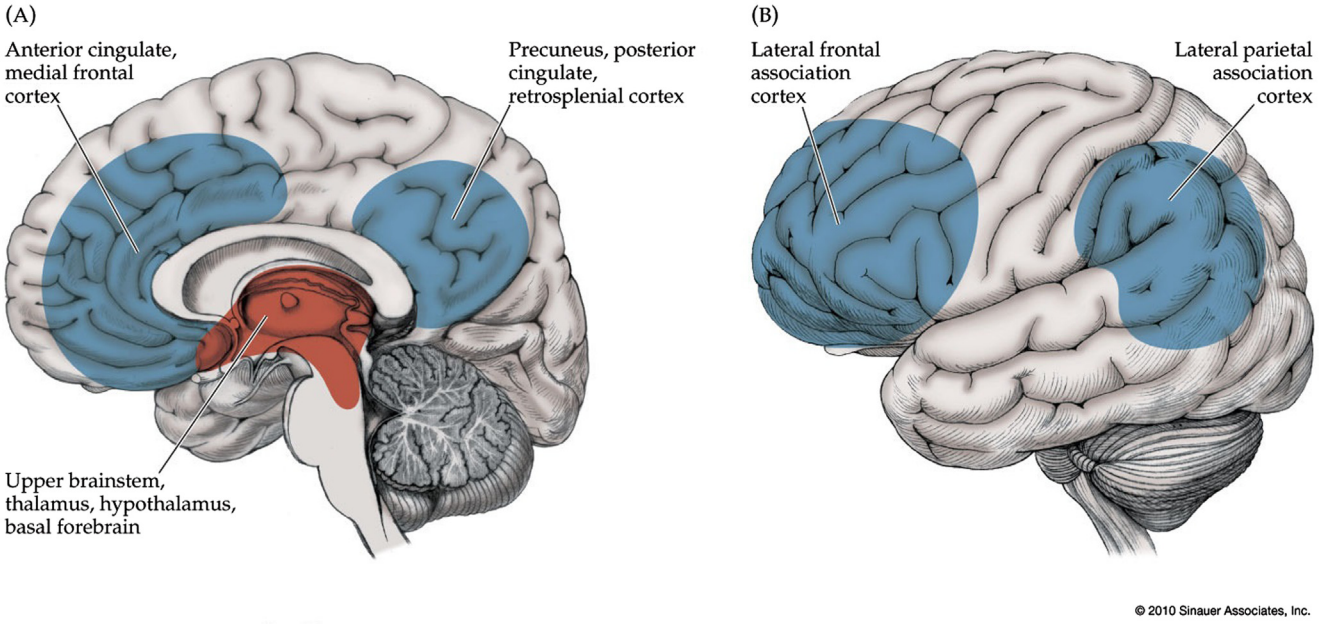

FIGURE 1.2 The consciousness system. Anatomical structures involved in regulating the level of consciousness, specifically controlling the level of alertness, attention and awareness. (A) Medial view showing cortical (blue) and subcortical (red) components of the consciousness system. (B) Lateral cortical components of the consciousness system. Note that other circuits not pictured here, such as the anterior insula, claustrum, basal ganglia, amygdala, and cerebellum, may also play a role in attention and other aspects of consciousness. *Source: Reproduced with permission from Blumenfeld (2010).*

THE CONSCIOUSNESS SYSTEM

The specialized brain networks controlling the level of consciousness can be referred to as the "consciousness system" (Blumenfeld, 2009, 2010) (Figure 1.2). It has long been recognized through studies based on human brain disorders (Penfield, 1950; Plum and Posner, 1972; Von Economo, 1930) as well as experimental animal models (Bremer, 1955; Moruzzi and Magoun, 1949; Steriade and McCarley, 2010) that the level of consciousness depends critically on both cortical and subcortical structures. Here we provide a brief overview of the cortical and subcortical networks comprising the consciousness system, which will be discussed in greater detail in the remaining sections of the chapter.

Cortical components of the consciousness system include the major regions of the higher-order "heteromodal" (Mesulam, 2000) association cortex (Figure 1.2; see also Figure 1.11). On the medial brain surface, important components are the medial frontal, anterior cingulate, posterior cingulate, and medial parietal (precuneus, retrosplenial) cortex (Figure 1.2A). On the lateral surface, major consciousness system networks include the lateral frontal, anterior insula, orbital frontal, and lateral temporal-parietal association cortex (Figure 1.2B).

It is important to recognize that individual components of the higher-order association cortex play important and well-studied roles in specific cognitive functions in the dominant and non-dominant hemispheres as described in the behavioral neurology literature (Heilman and Valenstein, 2003; Mesulam, 2000). Recently these same association cortex regions have also been described as participating in either so-called task-positive networks based on their activation during externally oriented attention (Asplund et al., 2010; Buschman and Miller, 2007; Dosenbach et al., 2007; Vanhaudenhuyse et al., 2011) or task-negative networks, also known as the "default mode" based on activity at rest (Fox et al., 2005; Raichle et al., 2001). Regardless of the heterogeneous functions of individual regions or networks, it is the *collective* activity of widespread areas of bilateral association cortex that determines the level of consciousness. Taken as a whole, the higher-order association cortex interacts with subcortical arousal systems (Steriade and McCarley, 2010) to exert powerful control over the overall level of arousal, attention, and awareness.

Subcortical components of the consciousness system include the upper brainstem activating systems, thalamus, hypothalamus, and basal forebrain (Figure 1.2A). It is likely that other subcortical structures (not shown) also participate, including portions of the basal ganglia, cerebellum, amygdala, and claustrum. Multiple parallel neurotransmitter systems participate in subcortical arousal including acetylcholine, glutamate, gamma amino butyric acid (GABA), norepinephrine, serotonin, dopamine, histamine, and orexin (Cooper et al., 2003; Saper et al., 2005; Steriade et al., 1997; Steriade and McCarley, 2010). Like the diverse cortical regions already discussed, these subcortical pathways

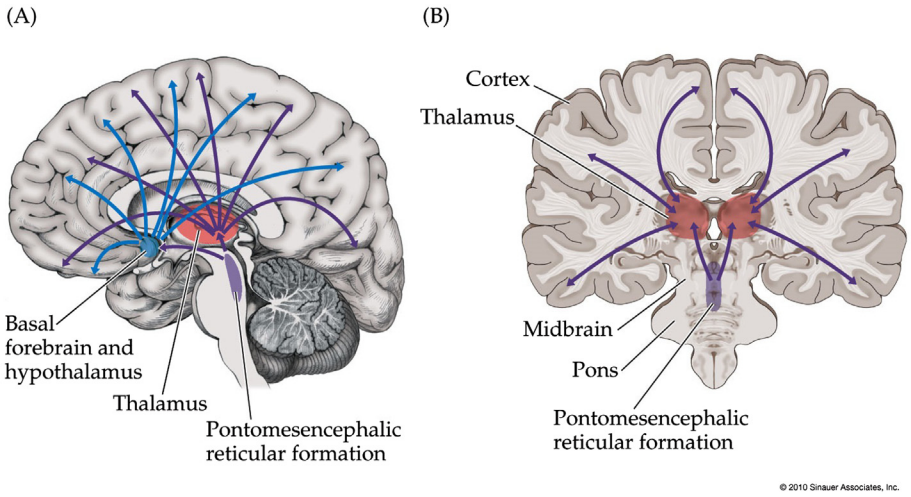

FIGURE 1.3 Arousal circuits of the pontomesencephalic reticular formation, thalamus, hypothalamus and basal forebrain. (A) Midsagittal view; (B) coronal view. Widespread projections to the cortex arise from outputs of the pontomesencephalic reticular formation relayed via the thalamic intralaminar nuclei, basal forebrain, and hypothalamus. *Source: Reproduced with permission from Blumenfeld (2010).*

each carry out individual roles, but it is the collective and parallel actions of all of these systems that together control the level of consciousness.

Understanding consciousness depends not only on neuroanatomy but also on neurophysiology. Although this chapter will focus on the "where" of consciousness, equally important is "how" these networks interact to form consciousness. Recent proposed physiological mechanisms for consciousness include synchronized oscillations (Buzsaki and Wang, 2012; Llinás and Paré, 1997; Singer, 1998), slow cortical potentials (Li et al., 2014), connectivity (Boly et al., 2011; Rosanova et al., 2012; Rubinov and Sporns, 2010), information integration (Tononi, 2005; Tononi and Koch, 2008), population neuroenergetics (Shulman et al., 2003), and recurrent or global neuronal processing (Dehaene et al., 1998; Lamme and Roelfsema, 2000; Sergent and Dehaene, 2004) among others. Much additional work is needed before the physiological mechanisms of consciousness are more definitely known. By contrast, when it comes to neuroanatomy, the past century of research has at least led to a basic understanding of the most important brain structures contributing to consciousness. We now turn in greater detail to these major cortical and subcortical networks that constitute the consciousness system.

SUBCORTICAL NETWORKS AND CONSCIOUSNESS

The main subcortical components of the consciousness system include the midbrain and upper pons, thalamus, hypothalamus, and basal forebrain (Figure 1.2). These structures contribute importantly to maintaining alertness and arousal. Attention and awareness are also facilitated by the same midline arousal systems, as well as by other subcortical networks including the superior colliculi, cerebellum, amygdala, basal ganglia, claustrum, and thalamic reticular nucleus (Crick and Koch, 2005; Dreher and Grafman, 2002; Krauzlis et al., 2013; O'Halloran et al., 2012; Zikopoulos and Barbas, 2012).

In terms of alertness and arousal, much has been learned about the basic anatomy of consciousness by understanding which brain lesions can cause coma. Coma is as a state of unarousable unresponsiveness in which the eyes are closed and no purposeful responses can be elicited (Fisher, 1969; Plum and Posner, 1972). Coma occurs either through bilateral damage to widespread cortical areas, or via lesions in a core set of structures lying in upper brainstem and medial diencephalon. These critical subcortical arousal structures were initially identified based on strokes and other localized disorders in human patients (Penfield, 1950; Plum and Posner, 1972; Von Economo, 1930) as well as lesion, disconnection, and stimulation experiments performed in animal models (Bremer, 1955; Moruzzi and Magoun, 1949; Steriade and McCarley, 2010). In the brainstem, the subcortical arousal systems begin in the upper pons and extend to the midbrain. Lesions in this small but critical region of the upper pons and midbrain produce profound coma, whereas lesions in the lower pons or medulla do not typically disrupt consciousness (Figure 1.3). The core brainstem arousal systems lie in the tegmentum and include a variety of nuclei embedded within the brainstem reticular formation. The tegmentum is sandwiched between the more ventral brainstem basis—containing ascending and descending white matter pathways; and the more

TABLE 1.1 Widespread Projection Systems in the Nervous System

Projection system	Location(s) of cell bodies	Main target(s)	Neurotransmitter receptor(s)[a,b]	Function(s)[c]
Reticular formation	Midbrain and rostral pons	Thalamic intralaminar nuclei, hypothalamus, basal forebrain	Unknown (glutamate?)[d]	Alertness
Intralaminar nuclei	Thalamic intralaminar nuclei	Cortex, striatum	(Glutamate?)	Alertness
Midline thalamic nuclei	Midline thalamic nuclei	Cortex	(Glutamate?)	Alertness
Norepinephrine	Pons: locus ceruleus and lateral tegmental area	Entire CNS	α_{1A-D}, α_{2A-D}, β_{1-3}	Alertness, attention, mood elevation
Dopamine	Midbrain: substantia nigra pars compacta and ventral tegmental area	Striatum, limbic cortex, amygdala, nucleus accumbens, prefrontal cortex	D_{1-5}	Movements, initiative, working memory
Serotonin	Midbrain, pons, and medulla: raphe nuclei	Entire CNS	5-HT_{1A-F}, 5-HT_{2A-C}, 5-HT_{3-7}	Alertness, mood elevation, breathing control
Histamine	Hypothalamus: tubero-mammillary nucleus; midbrain: reticular formation	Entire brain	H_{1-4}	Alertness
Orexin (hypocretin)	Posterior lateral hypothalamus	Entire brain	OX_1, OX_2	Alertness, food intake
Acetylcholine	Basal forebrain: nucleus basalis, medial septal nucleus, and nucleus of diagonal band	Cerebral cortex including hippocampus	Muscarinic (M_{1-5}), nicotinic subtypes	Alertness, memory
	Pontomesencephalic region: pedunculopontine nucleus and laterodorsal tegmental nucleus	Thalamus, cerebellum, pons, medulla	Muscarinic (M_{1-5}), nicotinic subtypes	Alertness, memory

[a]*Many of the neurons releasing the neuromodulatory transmitters listed here also release a variety of peptides, which are likely to play a neuromodulatory role as well.*
[b]*Additional receptor subtypes are constantly being added.*
[c]*Functions listed are highly simplified here; see references at the end of this chapter for additional details.*
[d]*Entries in parenthesis with question mark are uncertain.*
Source: Modified with permission from Blumenfeld (2010).

dorsal tectum—lying dorsal to the cerebral aqueduct or fourth ventricle. Lesions outside the brainstem tegmentum in the basis or tectum do not produce coma. Bilateral lesions of the thalamus, particularly in the intralaminar and midline thalamic nuclei, can also produce profound suppression of arousal.

Subsequent work has revealed that the subcortical arousal systems consist of multiple parallel neurotransmitter systems and pathways (Figure 1.3; Table 1.1). Unlike most pathways in the nervous system which project to relatively narrow target regions, the subcortical arousal systems belong to a set of widespread projecting systems (Table 1.1) that reach many structures or even the entire nervous system. Interestingly the projection systems arising from the upper brainstem including the midbrain and upper pons (pontomesencephalic reticular formation; Figure 1.3) tend to project upward to the cortex, diencephalon, and basal forebrain while those in the lower pons and medulla project downward to the brainstem, cerebellum, and spinal cord. The upward projecting systems were originally called the "ascending reticular activating system" (ARAS) (Moruzzi and Magoun, 1949) recognizing their important role in arousal. Although the term "ARAS" is still occasionally used, in reality these arousal systems arise from a variety of specific nuclei (Table 1.1) rather than from what was formerly considered a single diffusely organized system.

The subcortical arousal systems in the midbrain and upper pons have three main targets (Figure 1.3): (i) Putative glutamatergic neurons from the reticular formation and cholinergic neurons from the pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus (LDT) project mainly to the thalamus, particularly to the thalamic intralaminar nuclei which, in turn, increase cortical arousal. (ii) Other neurons project to the nucleus basalis and hypothalamus, which again relay arousal influences to the cortex. (iii) Finally, the monaminergic neurotransmitter systems (norepinephrine, dopamine, serotonin; not shown in Figure 1.3) project directly to the entire forebrain including the cortex and subcortical structures.

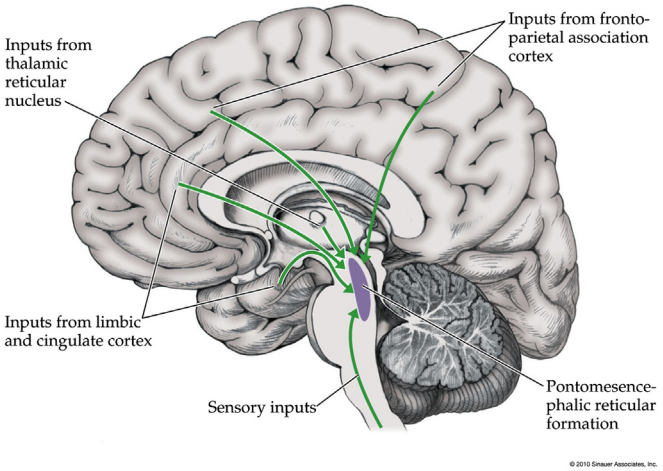

FIGURE 1.4 Major inputs to the pontomesencephalic reticular formation and related structures. *Source: Reproduced with permission from Blumenfeld (2010).*

In addition to these ascending connections, the subcortical arousal systems are also highly interconnected and strongly influence each other's function through multiple connections within and between the brainstem, thalamus, hypothalamus, and basal forebrain.

The upper brainstem arousal systems are influenced by a variety of inputs including numerous regions of the association cortex and limbic cortex, as well as sensory pathways such as the anterolateral pain transmission pathways (Figure 1.4). Inhibitory influences arise from the thalamic reticular nucleus (not to be confused with the reticular formation) as well as other GABAergic inputs (Parent and Steriade, 1981, 1984; Ropert and Steriade, 1981). The arousal systems are also strongly regulated by brainstem and hypothalamic circuits controlling circadian sleep rhythms (Saper et al., 2005, 2010).

The subcortical arousal systems will now each be discussed in greater detail to more fully appreciate the functional anatomy of these complex parallel arousal systems and their contributions to consciousness. It should be noted that, unlike gross lesions of the brainstem-diencephalic arousal systems, lesions or pharmacological blockade of the individual projecting neurotransmitter systems do not cause coma. Blockade of some neurotransmitters, especially acetylcholine or histamine, produces severe confusion and drowsiness, but not coma. Thus, the normal awake, conscious state does not depend on a single projection system, but rather on the parallel action of multiple anatomical and neurotransmitter systems acting together (Table 1.1). After discussing each of the major subcortical arousal systems, emphasizing their role in maintaining the alert state, we will then briefly discuss their role together with other subcortical structures (tectal region, basal ganglia, claustrum, cerebellum) in attention and awareness.

The Thalamus and Consciousness

Nearly all information destined for the cortex first reaches the thalamus. The thalamus transmits this information and then receives an even greater number of reciprocal connections back from the cortex. Therefore the thalamus plays a key role in all aspects of forebrain function including consciousness. The thalamus relays the content of consciousness, and also controls the level of consciousness through specialized circuits that regulate the level of arousal and are crucial for selective attention.

Organization of the thalamus can be described based on regions or based on projections. The regional organization of the thalamus divides the thalamic subnuclei proceeding from lateral to medial (Figure 1.5) into the thalamic reticular nucleus located most laterally, followed by the lateral nuclear group which contains the largest number of thalamic relay nuclei (Table 1.2). Continuing medially, next comes the Y-shaped white matter internal medullary lamina which separates the lateral, anterior, and medial nuclear groups from each other (Figure 1.5). Embedded within the internal medullary lamina lie the intralaminar nuclei. Finally a thin layer of midline thalamic nuclei are located most medially, adjacent to the third ventricle (Figure 1.5).

Projection patterns can also be used to classify the thalamic subnuclei (Table 1.2). Some, such as the ventral posterior lateral nucleus, a somatosensory relay in the lateral thalamus, project to a relatively localized region of cortex, and are referred to as specific relay nuclei. Others, such as the thalamic intralaminar nuclei, have more widespread projections to many cortical areas, and are called diffusely or widely projecting ("nonspecific") nuclei.

The specific thalamic relay nuclei communicate with the cortex regarding each sensory and motor function, and are therefore responsible for all the individual contents of consciousness. On the other hand, the widely projecting thalamic nuclei influence the overall level of cortical arousal, and therefore control the level of consciousness. The rostral intralaminar nuclei (central lateral, paracentral, central medial nuclei; Table 1.2) and midline thalamic nuclei are thought to be particularly important for activating the cortex (Figure 1.3). As was already discussed, the intralaminar thalamus plays a key role in transmitting arousal influences from the midbrain and upper pontine cholinergic and glutamatergic systems to the cortex.

The thalamic reticular nucleus forms a thin shell of predominantly GABAergic inhibitory neurons on the lateral thalamus (Figure 1.5). As axons traverse this nucleus traveling from thalamus to cortex or from cortex back to thalamus they give off collateral

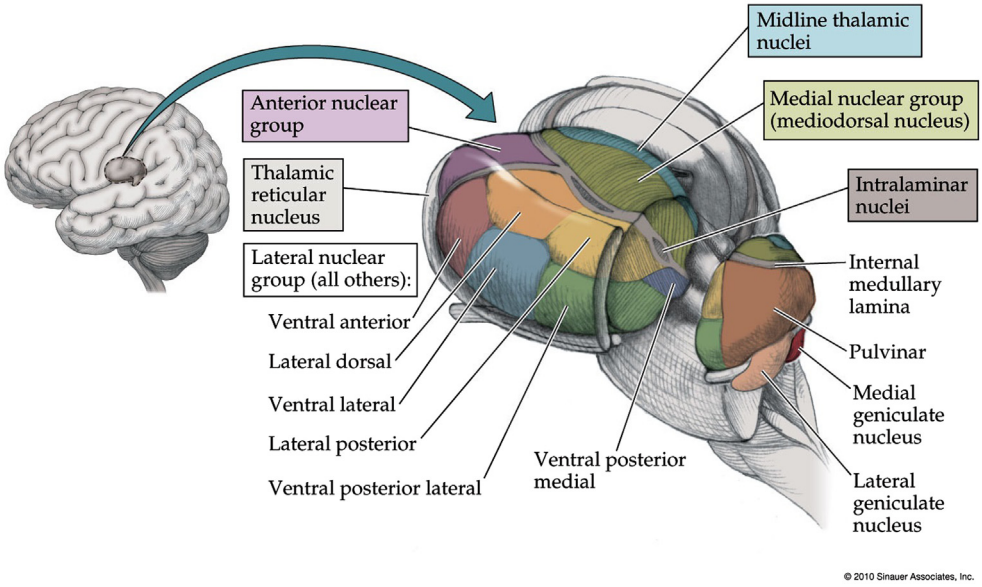

FIGURE 1.5 The thalamus. Main nuclear divisions and nuclei are shown (see also Table 1.2). The posterior portion of the reticular nucleus has been removed. *Source: Reproduced with permission from Blumenfeld (2010).*

branches to the thalamic reticular neurons. The thalamic reticular neurons, in turn, project to the thalamus and inhibit the specific thalamocortical neurons corresponding to individual corticothalamic loops. The reciprocal connections between thalamic relay nuclei and the thalamic reticular nucleus are thought to play an important role in generating corticothalamic rhythms during normal sleep and waking activity, as well as in pathological rhythms such as epilepsy (McCormick, 2002; McCormick and Bal, 1997; McCormick and Contreras, 2001; Steriade et al., 1993b). These physiological rhythms are crucial for regulating the level of consciousness. In addition, the thalamic reticular nucleus influences arousal through long-range inhibitory projections to the pontomesencephalic reticular formation (Parent and Steriade, 1984). Selective attention may also be mediated through the particular arrangement of reticular thalamic neurons and their directed inhibitory projections to the thalamus, which are capable of generating an inhibitory surround around a "searchlight" of focused attention in a narrow band of thalamocortical channels (Crick, 1984; Mayo, 2009; Pinault, 2004).

Glutamatergic and Related Arousal Systems

Glutamate is the most prevalent excitatory neurotransmitter of the central nervous system. For many of the arousal systems the most likely neurotransmitter is glutamate, although it has not been identified with certainty (Steriade and McCarley, 2010). Arousal system pathways probably mediated by glutamate include those arising from the midbrain and upper pontine reticular formation that project to the thalamus and basal forebrain (Steriade, 2004; Steriade et al., 1993a), as well as the widespread projections from the thalamic intralaminar nuclei to the cortex (Figure 1.3). It is not known whether other excitatory amino acid neurotransmitters such as aspartate might also play a significant role in arousal.

Cholinergic Arousal Systems

Acetylcholine is the major neurotransmitter of the peripheral nervous system, but in the central nervous system it has a more neuromodulatory function, where its role in arousal has been studied extensively. The two main sources of cholinergic projections neurons in the central nervous system lie in the brainstem pontomesencephalic reticular formation and in the basal forebrain (Figure 1.6; Table 1.1). At the junction of the midbrain and pons, the pedunculopontine nucleus is located in the lateral reticular formation, while the laterodorsal tegmental nucleus lies in the periaqueductal gray (Mesulam et al., 1983). The pedunculopontine nucleus stretches from the caudal midbrain substantia nigra *pars* reticulata into the rostral pons towards the superior cerebellar peduncle (Mena-Segovia et al., 2009; Rye et al., 1987). The nucleus has a gradient of increasing cholinergic and decreasing GABAergic neurons as it extends caudally, and also contains glutamatergic neurons (Wang and Morales, 2009). Cholinergic neurons from these brainstem nuclei project to the thalamus, including the intralaminar nuclei, playing an important role in arousal. Brainstem cholinergic

TABLE 1.2 Major Thalamic Nuclei

Nuclei[a]	Main inputs[b]	Main outputs	Diffuseness of projections to cortex[c]	Proposed functions
RELAY NUCLEI				
Lateral nuclear group				
Ventral posterior lateral nucleus	Medial lemniscus, spinothalamic tract	Somatosensory cortex	+	Relays somatosensory spinal inputs to cortex
Ventral posteromedial nucleus	Trigeminal lemniscus, trigeminothalamic tract, taste inputs	Somatosensory and taste cortex	+	Relays somatosensory cranial nerve inputs and taste to cortex
Lateral geniculate nucleus	Retina	Primary visual cortex	+	Relays visual inputs to cortex
Medial geniculate nucleus	Inferior colliculus	Primary auditory cortex	+	Relays auditory inputs to cortex
Ventral lateral nucleus	Internal globus pallidus, deep cerebellar nuclei, substantia nigra pars reticulata	Motor, premotor, and supplementary motor cortex	+	Relays basal ganglia and cerebellar inputs to cortex
Ventral anterior nucleus	Substantia nigra pars reticulata, internal globus pallidus, deep cerebellar nuclei	Widespread to frontal lobe, including prefrontal, premotor, and supplementary motor cortex	+++	Relays basal ganglia and cerebellar inputs to cortex
Pulvinar	Tectum (extrageniculate visual pathway), other sensory inputs	Parietotemporo-occipital association cortex	++	Behavioral orientation toward relevant visual and other stimuli
Lateral dorsal nucleus	See anterior nucleus	–	++	Functions with anterior nuclei
Lateral posterior nucleus	See pulvinar	–	++	Functions with pulvinar
Ventral medial nucleus	Midbrain reticular formation	Widespread to cortex	+++	May help maintain alert, conscious state
Medial nuclear group				
Mediodorsal nucleus (MD)	Amygdala, olfactory cortex, limbic basal ganglia	Frontal cortex	++	Limbic pathways, major relay to frontal cortex
Anterior nuclear group				
Anterior nucleus	Mammillary body, hippocampal formation	Cingulate gyrus	+	Limbic pathways
Midline thalamic nuclei				
Paraventricular, parataenial, interanteromedial, intermediodorsal, rhomboid, reuniens (medial ventral)	Hypothalamus, basal forebrain, amygdala, hippocampus	Amygdala, hippocampus, limbic cortex	++	Limbic pathways
INTRALAMINAR NUCLEI				
Rostral intralaminar nuclei				
Central medial nucleus	Deep cerebellar nuclei, globus pallidus, brainstem ascending reticular activating systems (ARAS), sensory pathways	Cerebral cortex, striatum	+++	Maintain alert consciousness; motor relay for basal ganglia and cerebellum
Paracentral nucleus				
Central lateral nucleus				
Caudal intralaminar nuclei				
Centromedian nucleus	Globus pallidus, ARAS, sensory pathways	Striatum, cerebral cortex	+++	Motor relay for basal ganglia
Parafascicular nucleus				
RETICULAR NUCLEUS				
Reticular nucleus	Cerebral cortex, thalamic relay and intralaminar nuclei, ARAS	Thalamic relay and intralaminar nuclei, ARAS	None	Regulates state of other thalamic nuclei

[a] *Some additional, smaller nuclei have not been included here.*

[b] *In addition to the inputs listed, all thalamic nuclei receive reciprocal inputs from the cortex and from the thalamic reticular nucleus. Modulatory cholinergic, noradrenergic, serotonergic, and histaminergic inputs also reach most thalamic nuclei.*

[c] *+ represents least diffuse (specific thalamic relay nuclei); ++ represents moderately diffuse; +++ represents most diffuse.*

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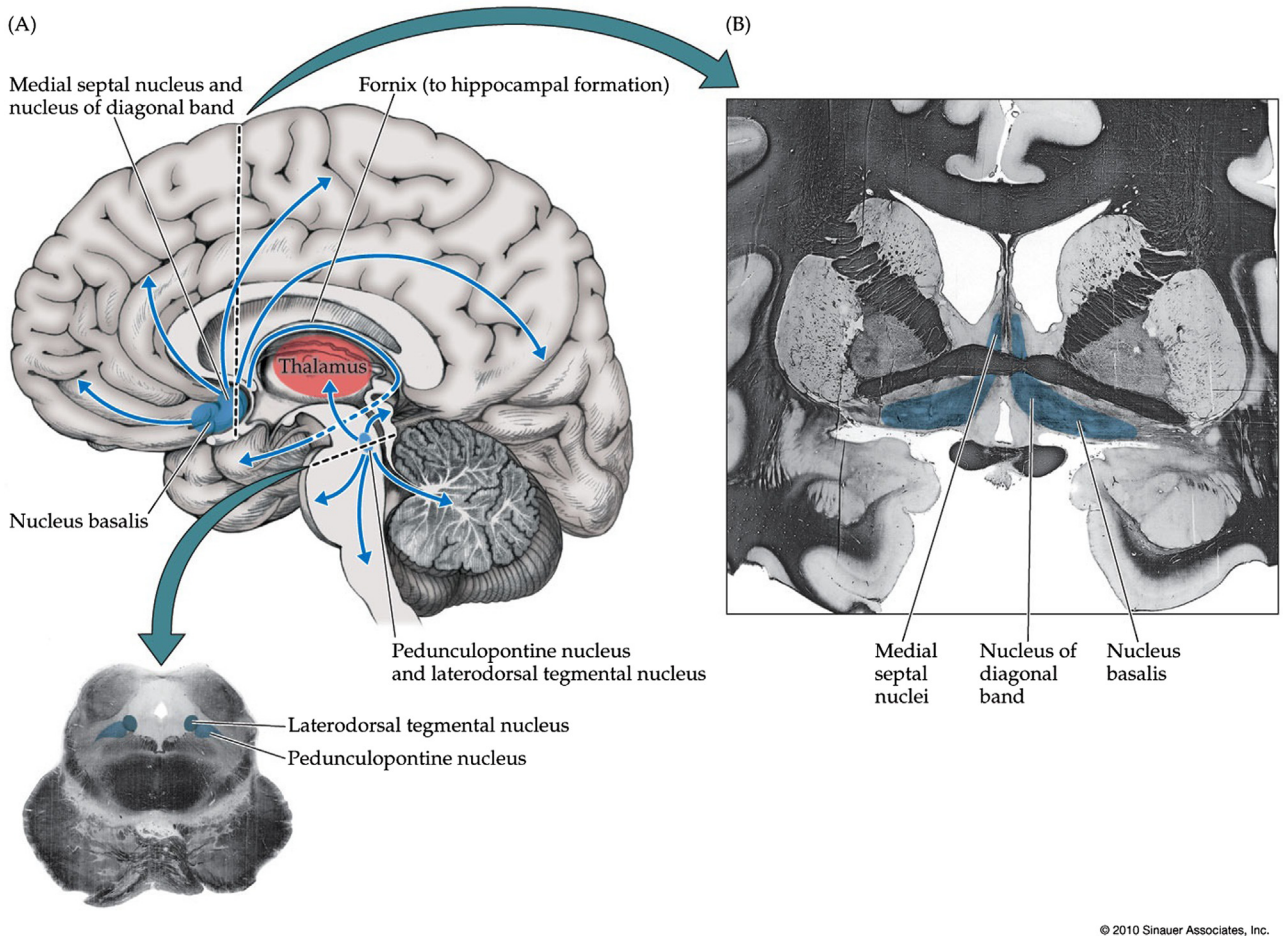

FIGURE 1.6 Cholinergic projection systems. (A) Overview and inset showing axial section through caudal midbrain. (B) Coronal section through basal forebrain. See also Table 1.1. *Source: Reproduced with permission from Blumenfeld (2010).*

arousal is thought to act synergistically with non-cholinergic putative glutamatergic pontomesencephalic neurons that project to intralaminar thalamus and basal forebrain (Figure 1.3) (Rasmusson et al., 1994, 1996; Steriade, 2004; Steriade et al., 1993a). In sleep, pontogeniculate waves arise from cholinergic brainstem neurons projecting to thalamocortical neurons in the lateral geniculate nucleus (Steriade et al., 1989, 1990). The pedunculopontine nucleus also has numerous ascending and descending motor projections and is involved in controlling locomotion (Inglis and Winn, 1995).

Interestingly, the brainstem has very few direct cholinergic projections to the cortex and nearly all facilitatory effects of the brainstem cholinergic systems on cortex are mediated via the thalamus (Beninato and Spencer, 1987; Cornwall et al., 1990; Hallanger et al., 1987; Hallanger and Wainer, 1988; Heckers et al., 1992; Jones and Webster, 1988; Satoh and Fibiger, 1986). The major source of cholinergic input to the cortex is the basal forebrain (Figure 1.6; Table 1.1). Cholinergic neurons in the nucleus basalis of Meynert and surrounding regions (substantia innominata, globus pallidus, and preoptic magnocellular nucleus) not only project to almost the entire neocortex (Mesulam et al., 1983; Rye et al., 1984) but also innervate some nuclei in the thalamus (reticular thalamic, mediodorsal, anteroventral/anteromedial, and ventromedial nuclei) (Heckers et al., 1992; Parent et al., 1988; Steriade et al., 1987). The hippocampal archicortex, however, receives cholinergic inputs mainly from the medial septal nuclei and nucleus of the diagonal band of Broca (Rye et al., 1984). Additional cholinergic neurons lie in the medial habenula, and short-range cholinergic neurons are present in the striatum and to a more limited extent within the cortex itself. Like the brainstem cholinergic nuclei, the basal forebrain contains both cholinergic and non-cholinergic neurons, including GABA and glutamate as transmitters among others (Brashear et al., 1986; Alvaro Duque et al., 2007).

The brainstem and basal forebrain cholinergic systems work together to abolish cortical slow wave

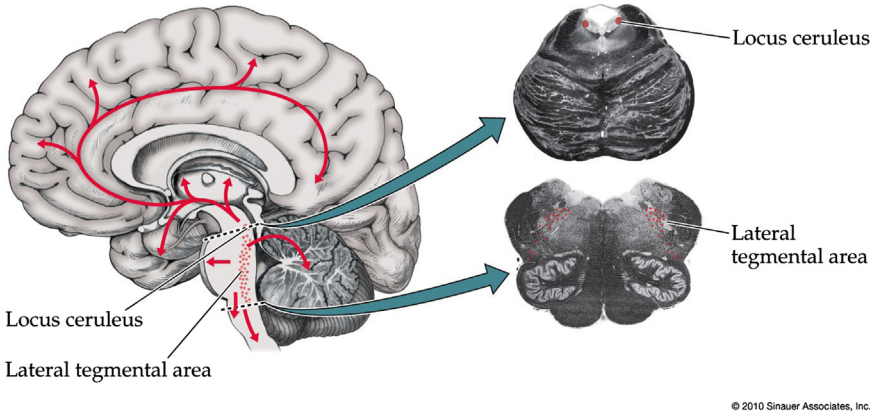

FIGURE 1.7 Noradrenergic projection systems. See also Table 1.1. *Source: Reproduced with permission from Blumenfeld (2010).*

activity and promote an alert state (Dringenberg and Olmstead, 2003; Steriade, 2004). Cholinergic arousal in the central nervous system is mediated predominantly by muscarinic acetylcholine receptors, although nicotinic receptors may also play an important role in arousal and attention (Bloem et al., 2014). As would be expected from the connections of cholinergic neurons described here, pharmacological blockade of central cholinergic neurotransmission produces an acute state of delirium and memory loss. However, despite the importance of acetylcholine in consciousness, selective damage to cholinergic neurotransmission does not produce coma (Blanco-Centurion et al., 2006, 2007; Buzsaki et al., 1988; Fuller et al., 2011), presumably because of the multiple parallel neurotransmitter systems participating in consciousness as already discussed.

GABAergic Arousal Systems

Found in local inhibitory interneurons throughout the cortex and subcortical structures, GABA is the most prevalent inhibitory neurotransmitter in the central nervous system and plays a major role in regulating arousal. Several long-range GABAergic projection systems also contribute to controlling arousal. Some GABAergic neurons in the basal forebrain are thought to promote arousal because these inhibitory neurons in turn project to cortical inhibitory interneurons (Freund and Meskenaite, 1992). However, the overall effects of basal forebrain GABAergic neurons on arousal may be heterogeneous because of variable firing patterns with respect to cortical activation and sleep-wake cycles (Hassani et al., 2009; Jones, 2004; Manns et al., 2000); and because parvalbumin-containing GABAergic neurons are related to cortical desynchrony whereas neuropeptide Y-containing neurons may have the opposite effect (Alvaro Duque et al., 2000, 2007).

Other important long-range GABAergic projections mainly inhibit arousal. These include neurons in the ventral lateral preoptic nucleus, which have widespread inhibitory projections to virtually all subcortical arousal systems (Saper et al., 2010); lateral septal GABAergic neurons thought to inhibit the basal forebrain and hypothalamus (Mesulam and Mufson, 1984; Varoqueaux and Poulain, 1999); and the thalamic reticular nucleus which contains GABAergic neurons projecting both to the remainder of the thalamus and to the brainstem reticular formation (Parent and Steriade, 1984; Steriade et al., 1984). In addition, GABAergic neurons in the globus pallidus internal segment inhibit regions of the thalamus including the intralaminar nuclei. It has been proposed that paradoxical arousal effects of GABA agonists such as zolpidem in minimally conscious state, or benzodiazepines in catatonia may occur when these agents inhibit the globus pallidus, thereby removing tonic inhibition of the intralaminar thalamus (Brown et al., 2010; Giacino et al., 2014). Activation of these multiple GABAergic inhibitory projections converging on the subcortical arousal systems has also been proposed as the mechanism for loss of consciousness in partial seizures (Blumenfeld, 2012; Englot and Blumenfeld, 2009).

Noradrenergic Arousal Systems

Norepinephrine (noradrenaline)-containing neurons are located in the locus ceruleus in the rostral pons adjacent to the fourth ventricle, as well as in the nearby lateral tegmental area extending into the more caudal pons and medulla (Figure 1.7; Table 1.1). Ascending noradrenergic projections reach the cortex, thalamus and hypothalamus (Foote et al., 1983; Morrison et al., 1981; Pickel et al., 1974) to regulate sleep-wake cycles, attention, and mood, while descending projections to the brainstem, cerebellum, and spinal cord modulate autonomic function and gating of pain. Many attention-enhancing drugs such as amphetamines augment noradrenergic function. Norepinephrine is thought to

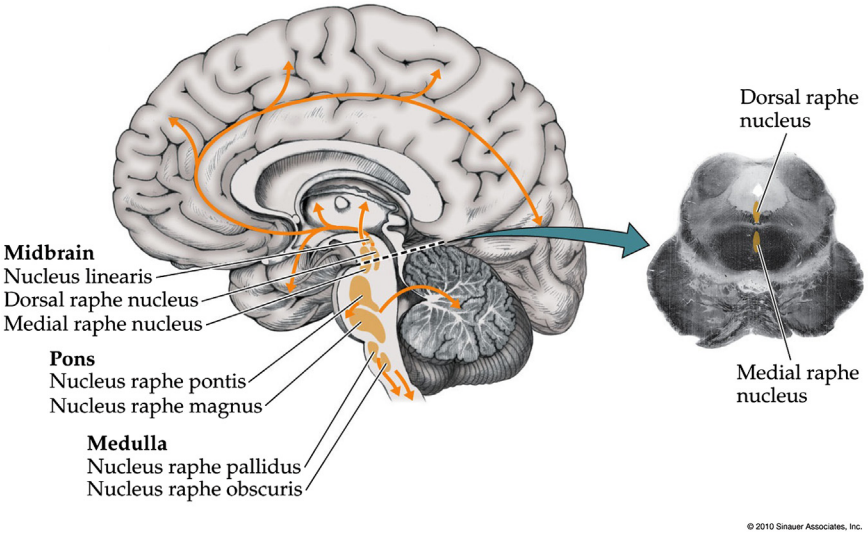

FIGURE 1.8 Serotonergic projections systems. See also Table 1.1. *Source: Reproduced with permission from Blumenfeld (2010).*

play an important role in promoting arousal (Berridge, 2008; Berridge et al., 2012; Constantinople and Bruno, 2011). For example, selective α-2 agonists such as clonidine or the anesthetic agent dexmedetomidine markedly depress arousal possibly by inhibiting locus ceruleus neurons (Correa-Sales et al., 1992; De Sarro et al., 1987; Scheinin and Schwinn, 1992). However, selective removal or blockade of noradrenergic neurons affects arousal but does not produce coma (Berridge et al., 1993; Blanco-Centurion et al., 2004, 2007; Cirelli and Tononi, 2004; Hunsley and Palmiter, 2003) again reinforcing the notion of multiple parallel systems promoting consciousness.

Serotoninergic Arousal Systems

Serotonergic neurons are found predominantly in the midline raphe nuclei of the midbrain, pons, and medulla (Figure 1.8; Table 1.1). The more rostral serotonergic neurons in the midbrain and upper pontine raphe nuclei project to the entire forebrain, participating in sleep-wake regulation; dysfunction of serotonergic systems is thought to play a role in a number of psychiatric disorders including depression, anxiety, obsessive-compulsive disorder, aggressive behavior, and eating disorders. More caudal serotonergic neurons in the pons and medulla are important for modulation of breathing, pain, temperature control, cardiovascular, and motor function.

The most important rostral raphe nuclei participating in arousal are the dorsal raphe and median raphe (Jacobs and Azmitia, 1992; Wiklund et al., 1981). The role of serotonergic neurons in arousal is complex, possibly because the large diversity of serotonin receptors (Hannon and Hoyer, 2008) leads to effects that either promote or inhibit arousal in different brain regions (Dugovic et al., 1989; Dzoljic et al., 1992; Kumar et al., 2007; Lemoine et al., 2007; Leonard and Llinás, 1994; Luebke et al., 1992; Monckton and McCormick, 2002; Muraki et al., 2004; Rogawski and Aghajanian, 1980). Rostral brainstem serotonergic neurons have been proposed to promote arousal in response to hypoventilation and increased carbon dioxide levels, perhaps playing an important role in preventing sudden infant death syndrome and sudden unexplained death in epilepsy (Buchanan and Richerson, 2010; Kinney et al., 2009; Richerson and Buchanan, 2011; Sowers et al., 2013).

Dopaminergic Arousal Systems

Most dopaminergic neurons are located in the ventral midbrain, either in the substantia nigra pars compacta or in the adjacent ventral tegmental area (Figure 1.9; Table 1.1). These mesencephalic nuclei give rise to the following three ascending dopaminergic projection systems: (i) the mesostriatal (nigrostriatal) pathway projects from the substantia nigra to the caudate and putamen (Matsuda et al., 2009); (ii) the mesolimbic pathway arises mainly from the ventral tegmental area and projects to limbic structures including the medial temporal lobe, amygdala, cingulate gyrus, septal nuclei, and nucleus accumbens (Fallon, 1981; Oades and Halliday, 1987); (iii) the mesocortical pathway arises mainly from the ventral tegmental area as well as scattered neurons in the vicinity of the substantia nigra and ventral periaqueductal gray, projecting to the prefrontal cortex (Figure 1.9) as well as to the thalamus (Garcia-Cabezas et al., 2009; Groenewegen, 1988; Lu et al., 2006; Sanchez-Gonzalez et al., 2005). Dopaminergic neurons

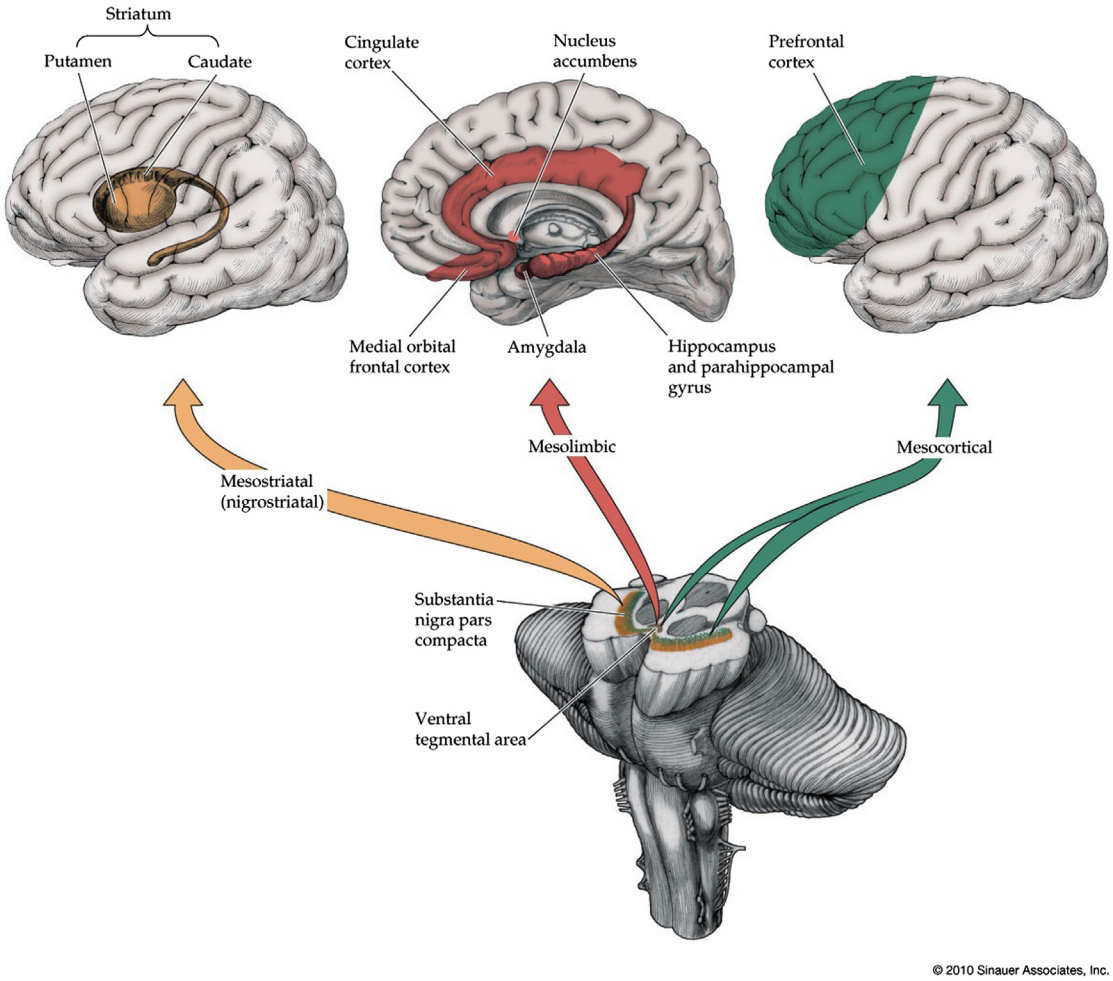

FIGURE 1.9 Dopaminergic projections systems. See also Table 1.1. *Source: Reproduced with permission from Blumenfeld (2010).*

in the ventral tegmental area also project caudally to various brainstem nuclei and to the spinal cord (Oades and Halliday, 1987).

Dopamine may contribute to maintaining the waking state at least in part through effects on other subcortical arousal circuits (Deutch et al., 1986; Lu et al., 2006; Neylan et al., 1992; Qu et al., 2008; Volkow et al., 2009). Effects of dopamine on the thalamus and cortex can be either excitatory or inhibitory (Bandyopadhyay and Hablitz, 2007; Govindaiah et al., 2010; Lavin and Grace, 1998; Penit-Soria et al., 1987). Impaired dopaminergic transmission to the prefrontal cortex has been proposed to be important for the apathetic negative symptoms of schizophrenia, and may also contribute to states of markedly reduced motivation, initiative and action/intention seen in frontal lobe disorders, abulia, and akinetic mutism (Combarros et al., 2000; Kim et al., 2007; Yang et al., 2007). Amantadine improves arousal in chronic disorders of consciousness, although it is unclear whether the mechanism is through enhanced dopaminergic neurotransmission or effects of this medication on other neurotransmitter systems (Giacino et al., 2012).

Histaminergic Arousal Systems

Histamine-containing neurons are found mainly in the tuberomamillary nucleus (Panula et al., 1984) of the posterior hypothalamus (Figure 1.10; Table 1.1), although a few scattered histaminergic neurons are also found in the midbrain reticular formation. Widespread ascending projections of histaminergic neurons from the tuberomamillary nucleus reach nearly the entire forebrain including cortex and thalamus, while descending projections target the brainstem and spinal cord (Brown et al., 2001; Hong and Lee, 2011; Lin et al., 1996; Panula et al., 1989).

Anti-histamine medications are intended to act on peripheral histamine release from mast cells, but are well-known to induce drowsiness presumably through central actions (White and Rumbold, 1988). Histamine can produce arousal effects on cortex (Dringenberg

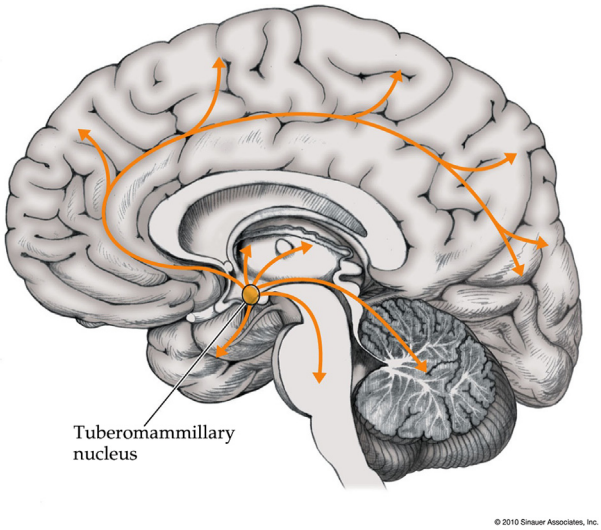

FIGURE 1.10 Histaminergic projections systems. See also Table 1.1. *Source: Reproduced with permission from Blumenfeld (2010).*

and Kuo, 2003; McCormick and Williamson, 1989) and thalamus (McCormick and Williamson, 1991). In addition to the cortex and thalamus, arousal actions of histamine may be mediated by activation of other subcortical arousal systems including other hypothalamic nuclei (Brown et al., 2001; Lin et al., 1994), the basal forebrain (Dringenberg and Kuo, 2003; Khateb et al., 1995; Zant et al., 2012), brainstem cholinergic (Khateb et al., 1990; Lin et al., 1996), and noradrenergic nuclei (Korotkova et al., 2005). Effects of histamine are receptor-dependent as activation of H_1 receptors promotes wakefulness, whereas H_3-receptors appear to have the opposite role (Huang et al., 2006; Khateb et al., 1990; Lin et al., 1990, 1996; Valjakka et al., 1996).

Orexinergic Arousal Systems

Orexin (hypocretin) is a peptide produced in neurons of the perifornical, lateral, and posterior hypothalamus (Peyron et al., 1998; Sakurai et al., 1998), which project to both cortex and virtually all subcortical arousal systems (Chemelli et al., 1999; Peyron et al., 1998) to promote the awake state. The arousal effects of orexin likely arise from both cortical and subcortical mechanisms (Bourgin et al., 2000; Eriksson et al., 2001; España et al., 2001; Hagan et al., 1999; Horvath et al., 1999; Kiyashchenko et al., 2002; Tsunematsu et al., 2011; van den Pol et al., 2002).

Abnormalities of the orexin system are thought to play a role in narcolepsy, a disorder characterized by excessive daytime sleepiness and pathological transitions into rapid eye movement sleep (Anaclet et al., 2009; Chemelli et al., 1999; Gerashchenko et al., 2003; Hara et al., 2001; Lin et al., 1999; Nishino et al., 2000; Peyron et al., 2000; Thannickal et al., 2000). The beneficial effects of modafenil in preventing the symptoms of narcolepsy may in part be through activation of orexin neurons (Chemelli et al., 1999).

Adenosine and Arousal

Although the neuroanatomical sources of adenosine are not well characterized, this neuromodulator may be important in mechanisms of conscious arousal (Huang et al., 2014; Liu and Gao, 2007). The effects of adenosine on arousal are generally inhibitory, and circadian fluctuations in adenosine levels peak just prior to the initiation of sleep. Adenosine receptors are found in both cortex and thalamus, where they have an overall inhibitory function on arousal. Caffeine blocks adenosine receptors and this may be one important mechanism whereby coffee promotes alertness (Huang et al., 2011; Lazarus et al., 2011).

Amygdala and Arousal

Because the amygdala has widespread and reciprocal cortical-subcortical connections that contribute to arousal particularly in response to emotions, it is appropriate to include this complex of nuclei located in the anteromedial temporal lobe as an important subcortical component of the consciousness system (Steriade and McCarley, 2010). The main components of the amygdaloid nuclear complex are the corticomedial, basolateral, and central nuclei, as well as the bed nucleus of the stria terminalis. The basolateral nucleus is largest in humans and has widespread direct and indirect connections to the cortex, basal forebrain, and medial thalamus (Aggleton, 2000; LeDoux, 2007). The smaller corticomedial nucleus participates in appetitive states via the hypothalamus, as well as in olfaction. The central nucleus, although smallest, has important connections with the hypothalamus and brainstem participating in arousal and autonomic control (LeDoux, 2007).

Attention and Awareness: Roles of Subcortical Arousal Systems, Tectal Region, Basal Ganglia, Claustrum, and Cerebellum

To complete our discussion of subcortical networks regulating the level of consciousness, it is important to again emphasize the functions of the consciousness system in controlling alertness, attention, and awareness, and to briefly mention several additional subcortical structures participating in these functions. As we have already discussed, the thalamus and other multiple parallel subcortical arousal systems in the upper brainstem, hypothalamus, and basal forebrain (Table 1.1) are essential for maintaining the alert state.

These same systems also play a key role in controlling attention and awareness not only in a permissive sense (e.g., being in a coma is not compatible with attention and awareness), but also by facilitating the additional processing in cortical and subcortical networks necessary for attention and for awareness.

Several additional subcortical structures also play a role. Components of the tectal region, specifically the superior colliculi and pretectal area form an important circuit along with the pulvinar of the thalamus to direct saccadic eye movements towards salient stimuli, and the same circuits also participate in directed attention (Krauzlis et al., 2013). The basal ganglia have major reciprocal connections with the thalamic intralaminar nuclei and this circuit as well as other basal ganglia connections may contribute to arousal and attention functions (Dreher and Grafman, 2002; Hager et al., 1998; Ring and Serra-Mestres, 2002). The claustrum is a thin layer of neurons located in the white matter between the putamen and insula, with widespread cortical connections that have been proposed to play an important role in the attention and awareness aspects of consciousness (Crick and Koch, 2005). Finally, the cerebellum has major reciprocal connections with the prefrontal cortex and has also been proposed to participate in attention, although this remains somewhat controversial (Baumann and Mattingley, 2014; Bischoff-Grethe et al., 2002; Dreher and Grafman, 2002; O'Halloran et al., 2012).

CORTICAL NETWORKS AND CONSCIOUSNESS

The cortical components of the consciousness system include widespread regions of association cortex in the bilateral cerebral hemispheres, particularly in the lateral frontal, anterior insula, lateral parietal (and adjacent temporal-occipital cortex), medial frontal, medial parietal (precuneus) and cingulate cortex (Figure 1.2). As has already been discussed, individual cortical components of the consciousness system have specific well-studied functions in behavioral neurology which contribute to the various contents of consciousness along with specific primary and secondary sensorimotor and limbic cortical areas (Figure 1.11). However, it is the collective action of widespread bilateral association cortex regions that gives rise to regulation of the level of alertness, attention, and conscious awareness.

In this section we will review the contributions of the cerebral cortex to arousal and the generation of an alert, awake state. We will next discuss attention in somewhat greater detail, describing several formulations of cortical systems that control different aspects of attention. The relationship between memory systems and consciousness will then be considered, as well as the role of cortical networks in self-awareness, planning voluntary action and free will. Finally, we will review cortical networks revealed by contrastive analysis (perceived vs non-perceived stimuli) to play an important role in conscious awareness.

The Cortex and Arousal

The most important input to subcortical arousal systems, including the thalamus, hypothalamus, basal forebrain, and the multiple brainstem arousal systems is the cerebral cortex itself. It has long been known that stimulation of the higher-order heteromodal frontoparietal association cortex increases arousal (Figure 1.11) (Segundo et al., 1955). Conversely, ablation of these same regions of the higher-order association cortex markedly decreases arousal (Ropert and Steriade, 1981; Steriade and McCarley, 2010; Watson, et al., 1977), although the subcortical arousal systems also receive inputs from primary sensorimotor cortices (Catsman-Berrevoets and Kuypers, 1981; Ropert and Steriade, 1981; Rossi and Brodal, 1956). In further support of the importance of the cerebral cortex in maintaining consciousness it was recognized by clinicians that unilateral cortical lesions usually do not markedly depress level of consciousness, but bilateral lesions of the association cortex can produce coma (Plum and Posner, 1972; Posner et al., 2007). The parietal cortex of the non-dominant (usually right) hemisphere appears to play a particularly important role in arousal where large lesions—although not producing coma—do often produce a markedly drowsy clinical state with forced eye closure. Thus, in addition to its important role in producing the specific individual contents of consciousness, the cerebral cortex is also a major driver in regulating the overall level of conscious arousal.

Attention and Consciousness

There has been recent debate on the relationship between attention and consciousness. Some view attention and consciousness as orthogonal functions that can be fully dissociated and operate independently (Koch and Tsuchiya, 2007). Others consider attention and consciousness to be essentially identical, constituting different names for the same set of functions (Prinz, 2000, 2012). Still others posit that attention is necessary for but not identical to consciousness because additional functions are needed for conscious awareness (Dehaene et al., 2006; Kouider and Dehaene, 2007). These very different understandings of the relationship between attention and consciousness may arise at least in part from different models for defining and understanding attention. There are a large number

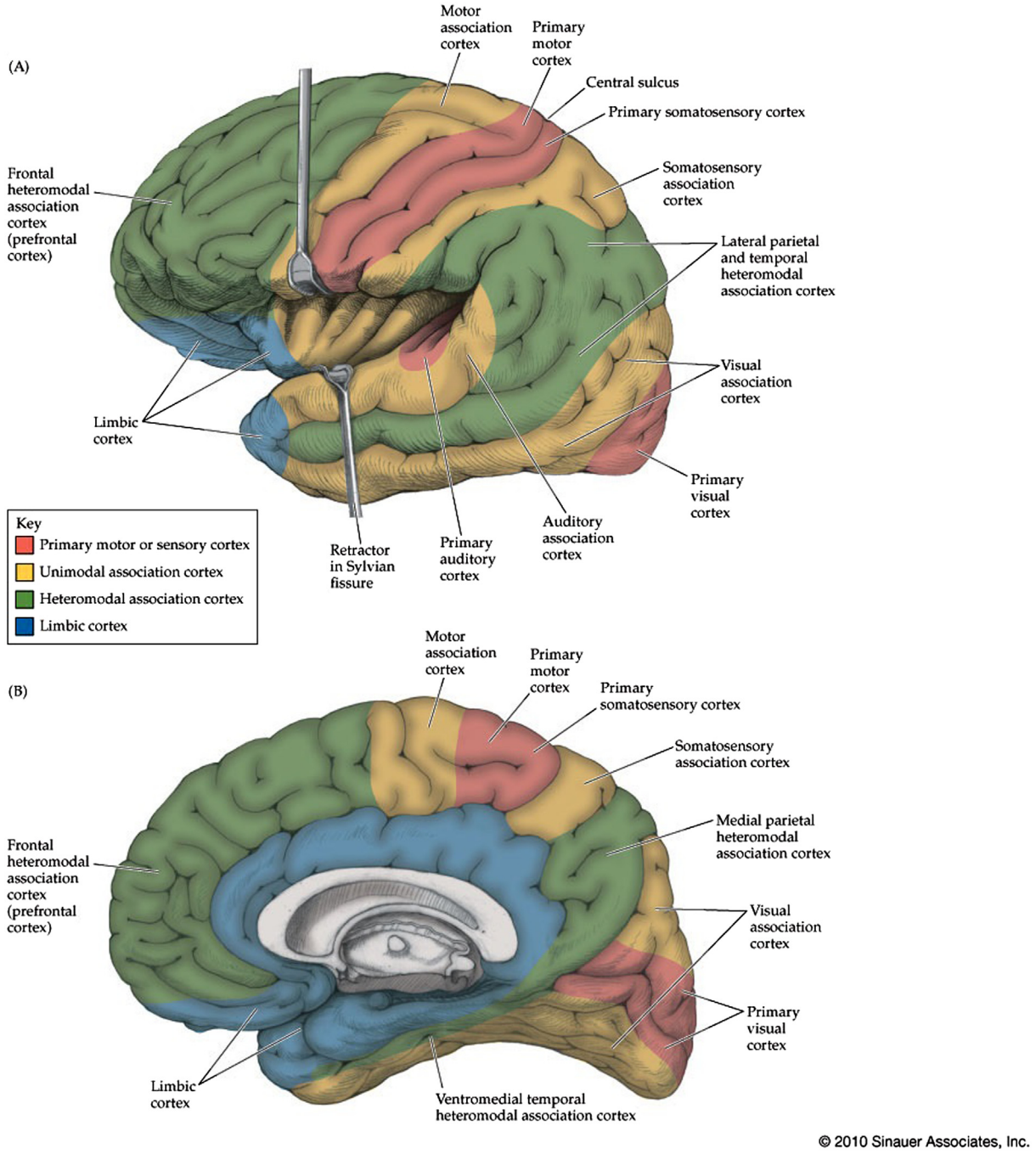

FIGURE 1.11 Cerebral cortex. (A) Lateral view. (B) Medial view. Main primary cortical and association cortical areas are indicated. Unimodal association cortex is modality-specific, whereas higher-order heteromodal association cortex combines information across modalities. Regions labeled here as limbic cortex include allocortical regions such as the hippocampus (archicortex) and pyriform cortex (paleocortex) as well as transitional paralimbic and neocortical areas such as the parahippocampal gyrus, cingulate gyrus, anterior insula, orbitofrontal cortex, and temporal pole. *Source: Reproduced with permission from Blumenfeld (2010).*

of models of attention and a complete discussion of the anatomy of attention is far beyond the scope of this chapter. However, here we will at least discuss a few of the major current formulations of attention especially in how their cortical anatomical underpinnings relate to understanding consciousness.

Hemispheric Dominance of Attention

Even more than the laterality of language, spatial attention is strongly lateralized and the large majority of individuals have dominant spatial attention in the right hemisphere (Heilman and Valenstein, 2003; Heilman et al., 2000; Mesulam, 2000). Contralateral

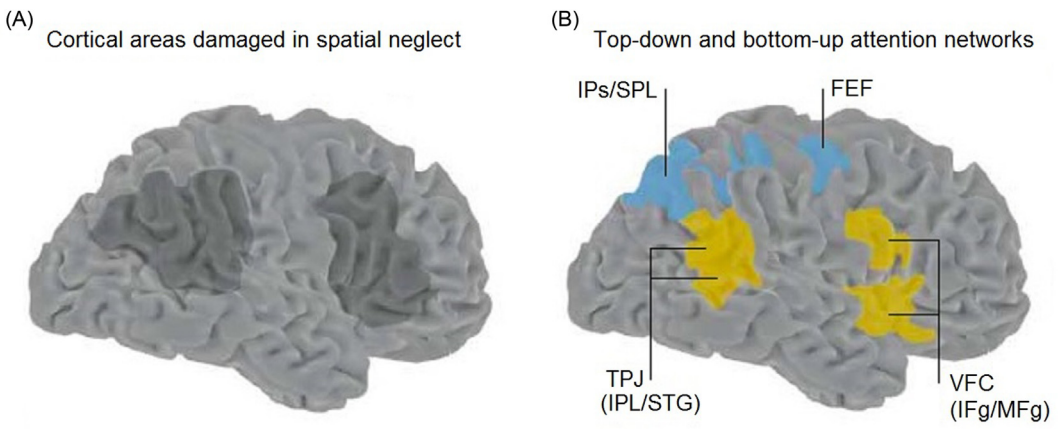

FIGURE 1.12 Top-down, bottom-up attention networks and hemineglect. (A) Areas commonly damaged in the right hemisphere that cause the contralateral hemineglect syndrome. (B) Dorsal and ventral frontoparietal attention. Areas in blue indicate the dorsal frontoparietal "top-down" attention network. FEF, frontal eye field; IPs/SPL, intraparietal sulcus/superior parietal lobule. Areas in orange indicate the stimulus-driven ventral frontoparietal "bottom-up" attention network. TPJ, temporoparietal junction (IPL/STG, inferior parietal lobule/superior temporal gyrus); VFC, ventral frontal cortex (IFg/MFg, inferior frontal gyrus/middle frontal gyrus). The areas damaged in neglect (A) better match the ventral network. *Source: Modified with permission from Corbetta and Shulman (2002).*

attentional neglect is more common and usually far more severe with lesions of the right hemisphere, especially with damage to the right lateral parietal cortex, although hemineglect can also be seen with right frontal lesions (Figure 1.12A). Unilateral neglect profoundly impairs the affected individual's ability to attend to visual, auditory, and tactile stimuli, to motor intention and indeed even to the very existence of the entire contralateral half of their body and the external world opposite to the side of their lesion. Although the impaired attention is usually most profound contralateral to right hemisphere lesions, there is also some attentional impairment which extends to the ipsilateral side so that overall attention is globally decreased (Heilman et al., 2000). Milder degrees of unilateral contralateral neglect are usually seen with left lateral parietal or left frontal lesions. Overall, these features of the neglect syndrome support a model in which attention functions are distributed between the association cortices in both hemispheres, but with a dominant role played by the right lateral parietal and frontal association cortex.

Some, even as early as Descartes, have argued that language is necessary for conscious thought (Descartes, 1637/1988, 1649/1970) and because the left hemisphere is usually dominant for language it could be viewed as more important for consciousness than the right. However, clearly non-verbal thoughts can still generate conscious experiences (Devinsky, 2000). Therefore, language might best be viewed as an important component of the content of consciousness (along with other specific functions such as visual perception, mathematical ability, judgment of distance, and so on), rather than as a necessary regulator of the overall level of consciousness. In some studies impaired consciousness is more common when the left hemisphere is impaired for example, due to stroke, or during selective administration of barbiturate anesthetics to one hemisphere at a time in the angiogram Wada test (Albert et al., 1976; Franczek et al., 1997; Schwartz, 1967), or with focal seizures originating in the left hemisphere (Englot et al., 2010; Gabr et al., 1989; Inoue and Mihara, 1998; Lux et al., 2002). However, it is difficult to determine whether a bias of testing methods which are heavily weighted towards verbal rather than non-verbal questions and responses might strongly influence these finding.

Affect, Motivation, and Attention

One important aspect of cortical attention networks that should not be overlooked is the major role of affect and motivational drives (Damasio and Carvalho, 2013; Heilman and Valenstein, 2003; Heilman et al., 2000; Satz and Heilman, 1983). Subjects who are emotionally motivated, for example, by seeking a reward, are clearly more successful in attention tasks (Heilman and Valenstein, 2003). The orbital frontal cortex and other limbic circuits have been implicated and are likely to be crucial for the motivational aspects of attention (Faw, 2003).

The Binding Problem

A classical quandary in understanding attention and consciousness is the question of where and how the diverse aspects of any particular percept come together to form a unified conscious experience. How do the look, smell, and sound of your friend come together in your brain as "Adam." Even within a

single modality, it is challenging to understand how for example, the different parts of a visual scene are unified as whole image. This question has been referred to as the binding problem (Singer, 2001). Many potential solutions have been proposed for how different components of sensory input are bound together into a single percept, including coherent high-frequency oscillations, lateral connections between neurons in particular cortical layers, among others (Singer, 2001; Zmigrod and Hommel, 2013). In terms of cortical anatomy some insights into how visual binding occurs may be gleaned from a particular disorder referred to as Balint syndrome (Barton, 2011; Heilman and Valenstein, 2003; Michel and Henaff, 2004). Patients with Balint syndrome experience simultagnosia, meaning that they perceive individual fragments or components of a visual scene one at a time without assembling them into a coherent whole. Balint syndrome is caused by bilateral lesions at the juncture between the dorsolateral parietal and occipital cortices (often due to strokes in the watershed territory between the posterior and middle cerebral arteries). It has been proposed that simultagnosia occurs because these lesions disconnect visual input from parietal and other association cortices needed to stitch together the individual components into a unified image. This suggests that one mechanism for attentional binding may be the interaction of primary cortices or unimodal association cortex with higher-order (heteromodal) parietal or other association cortices (Figure 1.11). In this case, one would predict that simultagnosia should occur not just in visual but in other (e.g., auditory or tactile) modalities when unimodal cortices are disconnected from the higher-order association cortex bilaterally, a topic for potential additional investigation in future work.

Top-Down and Bottom-Up Attention Networks

Emerging from other recent formulations of attention, including those proposed by Mesulam, Heilman, and Posner (Heilman and Valenstein, 2003; Mesulam, 2000; Posner and Dehaene, 1994; Posner and Petersen, 1990), the model of Corbetta and Shulman (2002) emphasizes two separate but interacting systems mediating the top-down and bottom-up aspects of attention (Figure 1.12B). In this scheme, goal-oriented selection of stimuli and responses is controlled by dorsal regions of the frontal and parietal association cortex, including the frontal eye fields and intraparietal sulcus. This top-down attention system is bilaterally distributed in both hemispheres. In contrast, a second attention system serves a stimulus-driven "circuit-breaking" role for grabbing and reorienting attention in response to salient or changing sensory stimuli. This bottom-up attention system is localized more ventrally in the temporal-parietal junction and the ventral frontal cortex (including the frontal operculum), and is strongly lateralized to the right hemisphere. One important area of ongoing research is how the two systems interact, for example, during stimulus-driven reorienting in visual search where sensory inputs affect goal-oriented attention and vice-versa.

Task-Positive and Task-Negative Networks

Another important way of describing cortical attention networks has arisen from functional neuroimaging studies during tasks compared to rest, as well as the analysis of resting functional connectivity. In a series of observations by Raichle et al. (2001), Shulman et al. (1997) and subsequently confirmed by other groups it was noted that, regardless of the specific task, a particular set of regions tends to show reduced activity during task blocks when functional neuroimaging data are analyzed by conventional block-design analyses contrasting task versus rest. These brain regions were dubbed the "default-mode network" (hypothesized to be relatively active at rest by default) or "task-negative networks." On the other hand, regions showing relatively increased activity during task blocks show greater variability depending on the specific task, but do show some general similarities between studies—particularly those involving attention—and have been referred to as "task-positive networks." Of interest, like many other important brain networks (Biswal et al., 1995, 1997), the default-mode and task-positive networks can be demonstrated in functional neuroimaging studies based on their high within-network connectivity using resting data in the absence of task (Fox et al., 2005; Fransson, 2005; Greicius et al., 2003). At rest, the default-mode and task-positive networks demonstrate high within-network functional connectivity (correlations over time) and these two networks are overall negatively correlated with each other (Figure 1.13). Based on both task-related analyses, and resting connectivity analyses, the default-mode network generally includes the following cortical regions bilaterally: precuneus/posterior cingulate, posterior-inferior parietal lobule (angular gyrus), ventral-anterior medial frontal, middle temporal gyrus, and medial temporal cortex (Figure 1.13) (Fox et al., 2005). The task-positive networks include the following cortical regions bilaterally: anterior insula/frontal operculum, supplementary motor/dorsal medial frontal lobe, lateral premotor cortex (includes frontal eye fields), anterior middle frontal gyrus, superior parietal lobule/anterior inferior parietal lobule, lateral inferior posterior temporal gyrus (lateral area 37) (Figure 1.13).

Because the concept of two large anti-correlated networks mediating attention switching in the brain may be over-simplified, a number of groups have

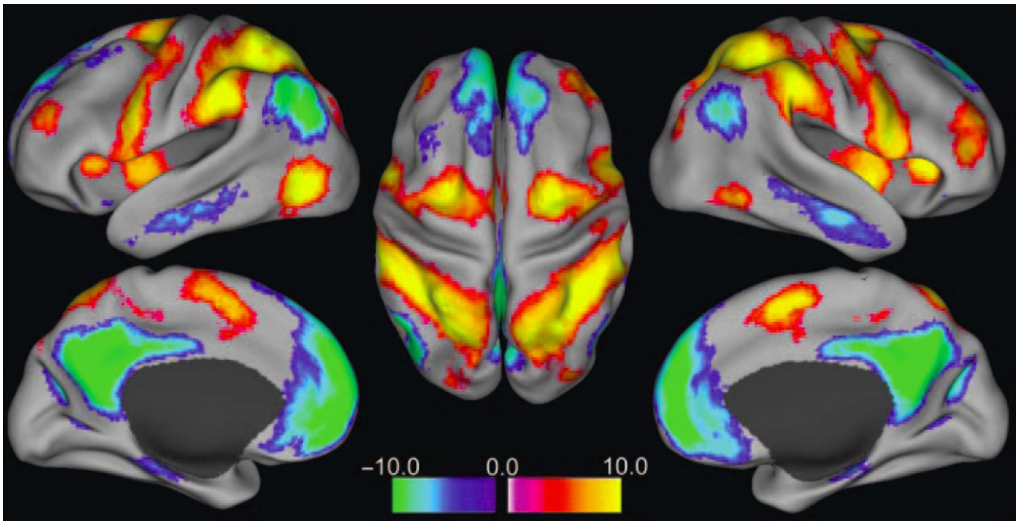

FIGURE 1.13 Task-positive and default-mode (task-negative) networks by resting functional connectivity analysis. A conjunction analysis was performed by including voxels significantly positively or negatively correlated with three seed regions in the task-positive network (intraparietal sulcus; frontal eye fields; lateral posterior-inferior temporal region) and three in the default-mode network (ventral medial prefrontal cortex; posterior cingulate/precuneus; lateral parietal cortex). Warm colors show regions correlated with the task-positive seeds or negatively correlated with default-mode seeds. Cool colors show regions correlated with the default-mode seeds or negatively correlated with task-positive seeds. *Source: Reproduced with permission from Fox et al. (2005).*

attempted to further refine these ideas and the field is still very much in evolution. It has been proposed that certain components of the task-positive network, referred to as the frontal parietal control network, might play a role in switching between externally directed attention mediated by the dorsal attention network (similar to top-down attention areas of Corbetta and Shulman discussed above) and internally directed attention mediated by the default-mode network (Gao and Lin, 2012; Vincent et al., 2008). There is evidence that the more lateral components of the task-positive network, particularly the dorsolateral frontal and parietal cortices are more important for externally directed attention, while the medial components of the default-mode network participate in internally directed attention (Demertzi et al., 2013; Vanhaudenhuyse et al., 2011). In another series of studies, Dosenbach et al. (2006, 2007, 2008) identified certain bilateral core components of the task-positive network, namely the dorsal anterior cingulate/medial superior frontal cortex (and adjacent supplementary motor area), and anterior insula/frontal operculum which constitute a common network involved in: (i) task initiation, (ii) sustained activity, and (iii) error detection (Figure 1.14). In contrast, they found that other areas in the task-positive and default-mode networks are activated or inactivated less consistently in these three different conditions. Again it is unclear if the functional imaging signals in anterior insula, which play a prominent role in this network, could also have a contribution from the nearby claustrum, a subcortical structure discussed above that might participate in attention and consciousness. In additional analyses based on resting functional connectivity and graph theory, the same group again emphasized the importance of what they refer to as the cingulo-opercular network, as distinct from the other task-positive and default-mode network nodes (Dosenbach et al., 2007). Another very interesting approach has been model-free analysis of functional neuroimaging data by simply using massive averaging of large data sets during a simple attention task (Gonzalez-Castillo et al., 2012). This type of analysis revealed that virtually the entire brain shows signals that vary over time in relation to the task, with a combination of transient or sustained increases and/or decreases depending on the specific brain region.

In summary, a large number of cortical networks have been shown to participate in different aspects of attention and to modulate their activity in relation to onset and end of attention tasks. The detailed roles that different components play in attention and consciousness, including anterior insula/frontal operculum, dorsal attention, default-mode, task-positive, bottom-up, top-down and other networks, will be important subjects for further investigation.

Memory Systems and Consciousness

As we have discussed, the level of consciousness depends on regulation of alertness, attention, and awareness. Alertness (arousal, wakefulness) can be

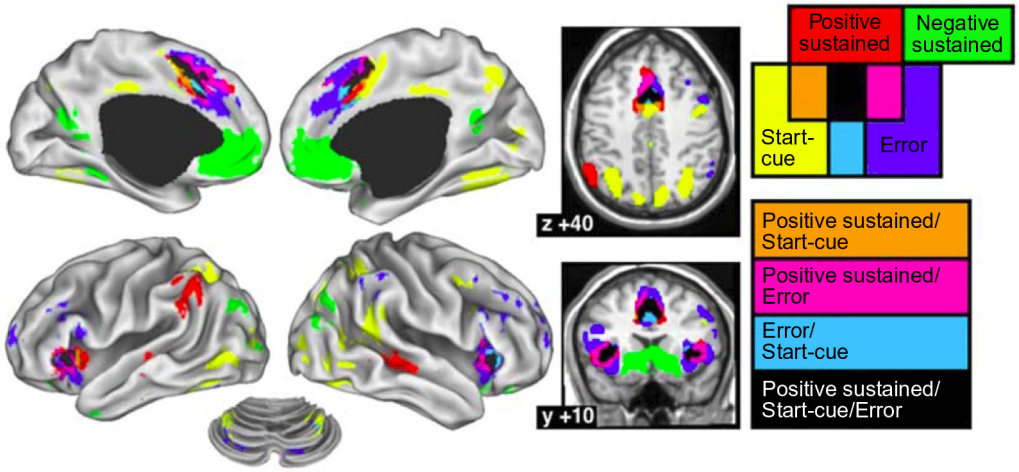

FIGURE 1.14 Core components of human task-related networks. Conjunction analysis of the fixed-effects maps for positive sustained, start-cue and error-related activity. The dorsal anterior cingulate/medial superior frontal cortex (and adjacent supplementary motor area), and anterior insula/frontal operculum carried positive sustained, start-cue and error-related activity across most of the tasks included in the analysis (conjunction regions shown in black). *Source: Reproduced with permission from Dosenbach et al. (2006).*

tested based on responses to simple questions or commands, and attention based on tasks requiring selective responses. Awareness, on the other hand, is demonstrated when a subject reports being aware of a particular stimulus or event. Because this report inevitably occurs after the event, testing of conscious awareness requires memory. Memory therefore plays a crucial role in the ability to report conscious experiences. In fact it may be useful to define awareness as the attentive and other processes necessary for events to be selected, handed off and encoded into memory for subsequent report.

Depending on whether report of conscious awareness occurs following a short or long delay, different memory systems may participate. Immediate recall or iconic memory most likely involves activity in primary and unimodal cortices and where events are initially processed (Coltheart, 1980; Loftus et al., 1992). Slightly more enduring memories lasting several seconds can enter working memory systems involving the dorsolateral frontal and parietal association cortices (Funahashi et al., 1993; Ikkai and Curtis, 2011). Some have defined consciousness based on the transfer of attended events into working memory (Prinz, 2012). Long-term memory storage of facts and autobiographical events requires the action of medial temporal and medial diencephalic memory circuits (Squire and Wixted, 2011; Tulving, 2002). Episodic or declarative memory, which depends on these anatomical systems, can be considered conscious memory in contrast to unconscious procedural memory that involves learning skills or unconscious priming. Because medial temporal and medial diencephalic memory systems are so specifically linked to the encoding of conscious experiences for subsequent report, investigating the "gateway" leading into these systems may be a productive approach for understanding the mechanisms of conscious awareness.

Volition and Conscious Free Will

Although much research has been done in the field of conscious perception particularly emphasizing the visual system, an equally important area of investigation is the mechanisms of conscious action including those governing planning and initiation of voluntary movement (Roskies, 2010). Understanding conscious action has important implications for determining moral and legal responsibility, as well as philosophical relevance including the definition of free will. Conscious action can be divided into planning, "premeditation" or initiation of future activities, and awareness of ongoing or completed deeds. The latter is more similar to conscious sensory perception, in the sense that it involves subsequent report of events that have already taken place. Conscious planning and initiation of voluntary movement as well as decision making on the other hand, likely involve other neuroanatomical circuits, as we will briefly discuss further below.

Motor planning depends on a distributed network including the premotor, supplementary motor and other frontal cortical circuits, interacting with parietal association cortex and subcortical networks especially in the basal ganglia (Roskies, 2010). Decision making is likewise a growing field in neuroscience, and recent work has again implicated distributed frontoparietal and subcortical circuits (Glimcher, 2003; Lau and Glimcher, 2008; Levy et al., 2010; Platt and Glimcher,

1999; Roskies, 2010). Based on stimulation mapping, some interesting dissociations have been found. Stimulation of the parietal cortex is accompanied by an awareness of voluntary movement initiation or urge to move even if no actual motion takes place (Desmurget et al., 1999, 2009; Desmurget and Sirigu, 2009). On the other hand, stimulation of the premotor cortex of the frontal lobe can produce actual movement even when the subject is unaware of the movement (Desmurget et al., 2009; Roskies, 2010). Finally, stimulation of the supplementary motor area produces an urge to move that may feel compulsory or involuntary (Fried et al., 1991).

Spontaneous voluntary movements are preceded 1−2 s earlier by a "readiness potential" or "Bereitschafts potential" that can be recorded from the scalp near the midline and has subsequently been localized to the supplementary motor area based on intracranial measurements (Fried et al., 2011). In a thought-provoking study, Benjamin Libet famously examined the timing of the readiness potential and provided evidence that it may precede the moment when individuals become consciously aware of their decision or will to move by several hundred milliseconds (Libet et al., 1982, 1983a,b). The interpretation of this study and its relation to free will has been hotly debated in later work (Herrmann et al., 2008; Jo et al., 2013; Schurger et al., 2012).

Self-Awareness and Embodiment

Although some consider self-awareness to be the defining *sine qua non* of consciousness, others view awareness of self to be just one example of the many things that an individual can be aware of, and therefore not necessary or sufficient for consciousness (Zeman, 2005). A closely related topic is the ability to have a first-person perspective or sense of embodiment arising from one's own individual point of view, which clearly makes an important contribution to the subjective feeling of awareness.

Awareness of self can be drastically and selectively impaired in certain neurological disorders, which may provide some insight into the neuroanatomical basis of self-awareness. For example, patients with lesions in the non-dominant (usually right) hemisphere particularly in the lateral parietal cortex are often agnostic to the very existence of the entire left side of their own bodies, and when specifically asked sometimes consider their left limbs to belong to someone else (Heilman et al., 2000). Frontal lobe dysfunction commonly leads to impaired self-monitoring or self-awareness, and is thought to underlie patient's inability to recognize their own deficits, for example when some patients confabulate instead of admitting to amnesia (Kopelman, 2014). One specialized form of self-awareness is awareness of one's own conscious awareness. This form of meta-cognition is also an important topic of investigation that may shed insights into what many consider the highest forms of consciousness (Zeman and Coebergh, 2013).

Important advances have recently been made in understanding the mechanisms that provide a first-person perspective by the innovative studies of Olaf Blanke and colleagues (Blanke, 2004; Blanke et al., 2002; Easton et al., 2009; Heydrich et al., 2010; Lenggenhager et al., 2009; Lopez et al., 2010). A series of investigations using patients with out-of-body experience, or functional neuroimaging and behavioral interventions to create an out-of-body experience in normal subjects, have revealed that the right temporal-parietal junction plays a crucial role in this unusual condition. Additional insights may come from ongoing investigation of other situations where the first-person perspective is altered, for example, during early development or in psychiatric disorders where depersonalization can occur (Bunning and Blanke, 2005; Lewis, 2011; Sierra and David, 2011).

Awareness: Conscious Report and Contrastive Analysis

Philosophers and scientists have long enjoyed a debate about whether or not consciousness can be understood through scientific investigation. The crux of the argument rests on the definitions of "consciousness" and "understanding." Some define the qualitative phenomenal aspects of consciousness or qualia, as internal subjective feelings of awareness accessible only through first-person experience, and define understanding consciousness as having that first-person experience (Chalmers, 1996). These definitions automatically exclude the possibility of understanding consciousness through scientific means because science requires external second-person observations. On the other hand, if one defines conscious awareness as an experience that can be described or reported to others, and if one defines understanding consciousness as identifying the necessary and sufficient physiological mechanisms for such an experience, then consciousness falls clearly in the realm of scientific investigation. The key to this second approach is that external report of consciousness is allowed as a method for investigating consciousness. Report of consciousness has its limitations of course, but so do all scientific methods and as long as the limitations are recognized and results interpreted cautiously, much progress can be made.

Taking this approach, a large number of studies have investigated the contrast between brain activity when a conscious event is reported or is not reported under very similar circumstances. This contrastive analysis has been performed in a variety of situations where events that are or are not reported can be obtained (Dehaene and Changeux, 2011; Lamme, 2006; Tononi

and Koch, 2008). For example, presentation of visual, tactile, or other stimuli at the threshold of detection yields approximately 50% that are reported. These studies have shown that consciously reported stimuli are accompanied by significantly greater activity in the bilateral frontal and parietal association cortex than with the unreported stimuli (Li et al., 2014; Palva et al., 2005; Wyart and Tallon-Baudry, 2008). Similarly, post-hoc analysis of items presented during memory encoding has demonstrated increased activity in fronto-parietal cortex during presentations of items that are later successfully reported (Burke et al., 2014). Another paradigm has been binocular rivalry, in which one image is presented to the left eye and a different image to the right eye, causing the perceived image to randomly alternate every few seconds between the two images (Blake and Logothetis, 2002; Polonsky et al., 2000). It was found that these alternating experiences can be related to alternating activity between different neurons in the temporal and parietal association cortex, particularly in a visual association cortex region in the inferior temporal lobe. Other paradigms including masking of visual stimuli by flanking stimuli presented immediately before or after the target, or use of the "attentional blink" have also been employed to control whether or not stimuli are perceived and consciously reported, again showing that consciously perceived stimuli have greater activations including larger neuroimaging signals, event-related potentials, or synchronized oscillations in the frontal and parietal association cortex (Dehaene and Changeux, 2011; Del Cul et al., 2009; Kouider and Dehaene, 2007; Marois et al., 2004).

In summary, multiple studies using contrastive analysis have demonstrated that events reported as consciously perceived give rise to greater activity in the bilateral frontal and parietal association cortex. These findings support the idea that the anatomical regions constituting the consciousness system (Figure 1.2) play an important role in regulating conscious awareness. Further work is needed to more firmly establish that these areas are necessary and sufficient for conscious events, for example through lesion/inactivation and activation studies. In addition, although much has been learned about the neuroanatomical structures participating in consciousness, further investigation will be crucial to firmly establish the physiological mechanisms through which consciousness is generated in these networks.

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CHAPTER

2

Functional Neuroimaging Techniques

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OUTLINE

The idea that regional cerebral blood flow (rCBF) is intimately related to brain function goes back more than a century. As is often the case in science, this idea was initially the result of unexpected observations (see Box 2.1 and Figure 2.1). In this chapter[1], we will introduce the area of functional brain imaging using techniques such as positron emission tomography (PET), single photon emission tomography (SPECT), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), event-related potentials (ERPs), electrocorticography (ECoG), magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), and transcranial magnetic stimulation (TMS). Each technique provides different information and has its own advantages and disadvantages in terms of cost, safety, and temporal and spatial resolution (Figure 2.2). After briefly discussing the functional neuroimaging techniques, we will present a short overview of study design and methods to

[1]This chapter is an updated version of Laureys et al. (2009).

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BOX 2.1

MEASURING BLOOD FLOW AS AN INDEX OF NEURAL ACTIVITY

The Italian physiologist Angelo Mosso studied pulsations of the living human brain that keep pace with the heartbeat (Mosso, 1881). These pulsations can be observed on the surface of the fontanels in newborn children. Mosso believed that they reflected blood flow in the brain. He observed similar pulsations in an adult with a post-traumatic skull defect over the frontal lobes. While studying this subject, a peasant named Bertino, Mosso observed a sudden increase in the magnitude of the "brain's heart-beats" when the ringing church bells signaled the time for a required prayer (indicated by an arrow in Figure 2.1). The changes in brain pulsations occurred independently of any change in pulsations in the forearm. Mosso understood that the bells had reminded Bertino of his obligation to say a silent Ave Maria. Intrigued by this observation, Mosso then asked Bertino to perform a mental calculation and again he observed an increase in pulsations and, presumably, in blood flow as the subject began the calculation and a second rise just as he answered. This was the first study ever to suggest that measurement of cerebral blood flow might be a way of assessing human cognition.

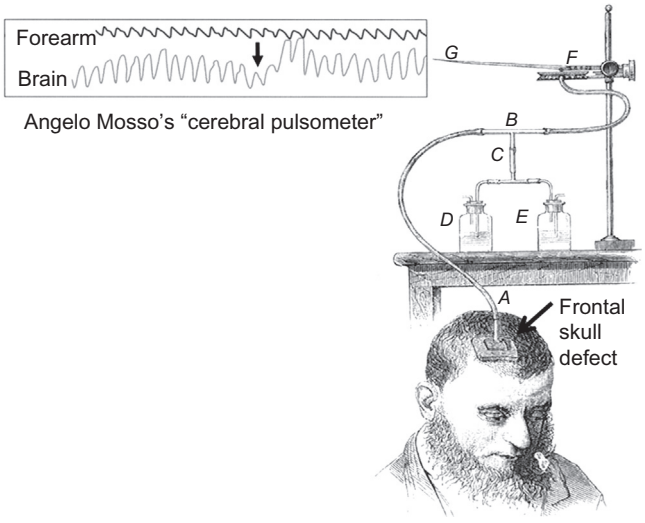

FIGURE 2.1 The "brain's heart-beats" recorded during inner speech (saying a silent Ave Maria indicated by the arrow) (1881). *Source: Adapted from Posner and Raichle (1994).*

Charles Roy and Charles Sherrington further characterized this relationship. They suggested that "the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity." One of the most extraordinary examples of this relationship was observed in Walter K., a German American sailor who consulted Dr. John Fulton for a humming noise in his head. Fulton, when listening with a stethoscope at the back of his patient's head, confirmed this bruit and organized an exploratory intervention. During neurosurgery, a large arteriovenous malformation overlying the visual cortex was observed. An attempt to remove the malformation failed and left Walter with a bony defect. His physicians could now hear the bruit even more clearly. The patient mentioned that the noise in his head became louder when he was using his eyes. As Dr. Fulton later published in *Brain*, "It was not difficult to convince ourselves that when the patient suddenly began to use his eyes after a prolonged period of rest in a dark room, there was a prompt and noticeable increase in the intensity of his bruit" (Fulton, 1928). Fulton's studies made him postulate that it was the effort of trying to discern objects that were just at the limit of his patient's acuity, which brought on the increases of the bruit. Merely shining light into his eyes when he was making no mental effort had no effect. This was a remarkable observation, the significance of which would not be appreciated for many years. It was probably the first ever recorded result of top-down influences on sensory processing (Posner and Raichle, 1994).

process and analyze the data obtained by these techniques. This chapter will not discuss structural neuroimaging (i.e., X-ray computed tomography (CT) and magnetic resonance imaging (MRI)—see Box 2.2).

POSITRON EMISSION TOMOGRAPHY

PET has its roots in tissue autoradiography, a method used for many years in animal studies to investigate organ metabolism and blood flow. Researchers in the field of tissue autoradiography became fascinated when CT was introduced in the 1970s. They realized that if the anatomy of an organ could be reconstructed by passing an X-ray beam through it, the distribution of a previously administered radioisotope could also be reconstructed *in vivo*. They simply had to measure the emission of radioactivity from the body section. With this insight was born the idea of autoradiography of living human subjects. A crucial element was the choice of the radioisotope. A class of radioisotopes was selected that emitted positrons (i.e., particles identical to electrons

except that they carry a positive charge). A positron will immediately combine with a nearby electron. They will annihilate each other, emitting two gamma rays in the process. Because each gamma ray travels in opposite directions, detectors around the sample can detect the gamma rays and locate their origin. The crucial role of positrons in human autoradiography gave rise to the name positron emission tomography, or PET (Ter-Pogossian et al., 1980).

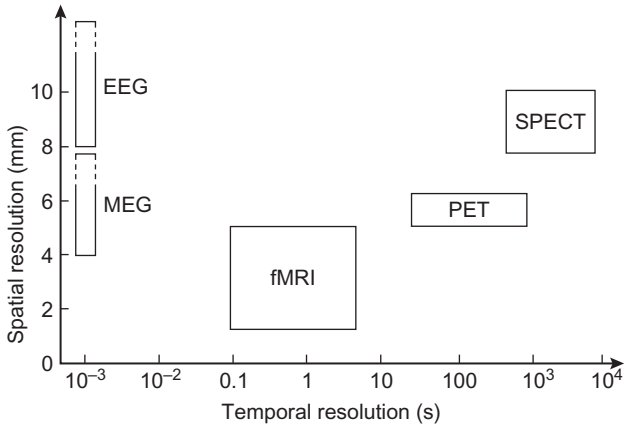

FIGURE 2.2 Approximation of the resolution in time and space of the most commonly employed functional neuroimaging techniques. *Source: Adapted from Laureys et al. (2002).*

Throughout the late 1970s and early 1980s, PET was rapidly developed to measure various activities in the brain, such as glucose metabolism, blood flow, oxygen consumption, and the uptake of drugs. Although PET is primarily a research tool for brain imaging, its increasing availability in medical centers for oncology makes its widespread application to neurological diseases more likely. The most frequently performed PET studies measure resting regional cerebral metabolic rates for glucose (rCMRGlu) or changes in rCBF as indirect index of neural synaptic activity (Magistretti and Pellerin, 1999). Recent developments are PET/CT combined imaging (offering improved attenuation correction and co-registration or fusion of the functional PET image with a high anatomic resolution CT image).

PET scanning involves the administration of positron-emitting radionuclides with short half-lives in which particle disintegration is captured by multiple sensors positioned around the head. The radiotracer is administered into a vein in the arm and is taken up by the brain through the bloodstream. After a course of a few millimeters the positron will interact with an electron in the brain tissue and produce two high-energy photons, at approximately 180° apart from each other. In the PET scanner, a ring of detectors around the subject's head can detect these coincident photons. As the radioactive compound accumulates in different regions

BOX 2.2

STRUCTURAL NEUROIMAGING

The modern era of medical imaging began in the early 1970s with the introduction of a remarkable technique called X-ray computed axial tomography, now known as CAT, X-ray CT, or just CT. It changed forever the practice of neurology because, for the first time, clinicians could non-invasively view the living brain (standard X-rays only reveal bone and some surrounding tissues). Second, it stimulated engineers and scientists to consider alternative ways of creating images of the body's interior using similar mathematical and computerized strategies for image reconstruction (e.g., SPECT and PET) (Posner and Raichle, 1994). Despite its wide availability, CT has been replaced by the more sensitive MRI as the procedure of choice for cerebral imaging. MRI stands for a vast and varied array of techniques that use no ionizing radiation and provides an enormous range of information. From an established ability to provide high-quality structural information, MR techniques are rapidly advancing and provide other clinically relevant physiologic information as spectroscopic studies illuminating the details of biochemical status (MR spectroscopy or MRS), blood oxygenation level allowing functional activation studies (functional MRI or fMRI), cerebral blood compartment (MR angiography or MRA); perfusion (perfusion-weighted MRI or PWI), water molecular diffusion (diffusion-weighted imaging or DWI), cerebral microstructure and fiber tracking (using diffusion anisotropy effects measured by diffusion tensor imaging or DTI, see Figure 2.3), magnetization transfer (MT) imaging, etc.

At present, MRI is the procedure of choice for the structural imaging of the brain. However, it is susceptible to movement artifacts and patients who are on life support systems, have gunshot wounds, or who have implanted MRI incompatible material (pace-makers, prostheses, etc.), still represent problems. The main limit on the wealth of diagnostic information that can be obtained for each patient is in the duration of the procedure. Ongoing refinements of fMRI, MRA, MRS, PWI, DWI, DTI and other MR techniques are allowing them to fit into routine clinical practice.

of the brain and positron annihilations occur, the scanner detects the coincident rays produced at all positions outside the head and reconstructs an image that depicts the location and concentration of the radioisotope within a plane of the brain. This emission scan is then corrected by comparison with the attenuation image made from a transmission scan of the subject's head. PET studies involve the use of a cyclotron to produce the radioactive tracers. The type of information of the PET image is determined by the administered radiolabeled compound. Oxygen-15, Fluorine-18, Carbon-11, and Nitrogen-13, are common radioisotopes, which can combine with other elements to create organic molecules that can substitute for natural substances, such as water, glucose, the L-DOPA, benzodiazepine-receptor ligands, etc. Using different compounds, PET can be used to assess regional blood flow, oxygen and glucose metabolism, neurotransmitter and drug uptake in the tissues of the working brain. PET can sample all parts of the brain with equal resolution and sensitivity. Typically, it can locate changes in activity with an accuracy of about 6 mm.

In the past decade, PET was the most widely used technique to assess the neural substrates of cognitive processes at the macroscopic level, but it is now superseded by fMRI. PET remains a powerful tool in receptor imaging (e.g., assessment of neurotransmitter or drug uptake) and molecular imaging (e.g., assessment of gene expression or protein synthesis) in both normal and pathological states (Phelps, 2000).

Cerebral Metabolic Rate for Glucose

To study regional cerebral glucose utilization, a positron-labeled deoxyglucose tracer is used (i.e., [^{18}F] fluorodeoxyglucose—FDG) (Huang et al., 1980). This tracer is taken up by active brain regions as if it was glucose. However, once inside the cell, FDG is phosphorylated by hexokinase to FDG-6-phosphate which is not a substrate for glucose transport and cannot be metabolized by phosphohexoseisomerase, the next enzyme in the glucose metabolic pathway. Thus, labeled FDG-6-phosphate becomes metabolically trapped within the intracellular compartment. The amount of radioactive label that eventually remains in each discrete region of the brain is related to the glucose uptake and metabolism of that particular region. An FDG-PET scan summates approximately 30 min of cerebral glucose metabolism and allows assessment of regional variations. The standardized uptake value is often used for a simple semi-quantitative analysis of FDG-PET (Figure 2.3). It not only allows the evaluation of images within a subject to study evolution of recovery or therapy monitoring but also for comparison between subjects. FDG-PET is a powerful method to evaluate patients with intractable seizures to identify seizure foci (Nasrallah and Dubroff, 2013). It also contributes to diagnosis of neurodegenerative diseases that cause dementia, and diagnosis of disorders of consciousness after severe brain injury (Heiss, 2012; Stender et al., 2014). Given the half-life of 18F (2 h), FDG-PET is, however, less suited for brain activation studies.

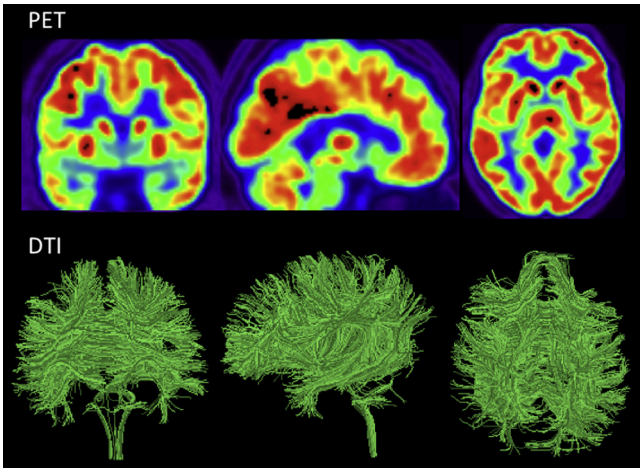

FIGURE 2.3 FDG-PET brain metabolism uptake and diffusion tensor imaging (DTI) in healthy subjects. Transaxial, sagittal, and coronal views. Note the most intense uptake is in the precuneus and striatum followed by the thalami and the occipital cortex. DTI shows the white matter tracks in the brain and brainstem of a healthy subject.

Cerebral Blood Flow

Most PET activation studies rely on the administration of radioactively labeled water—specifically, hydrogen combined with oxygen 15, a radioactive isotope of oxygen ($H_2{}^{15}O$). The labeled water emits copious numbers of positrons as it decays (hydrogen isotopes cannot be used, because they do not emit positrons). In just over a minute after intravenous injection, the radioactive water accumulates in the brain, forming an image of blood flow. The radioactivity of the water produces no deleterious effects. Oxygen 15 has a half-life of only 2 min; an entire sample decays almost completely in about 10 min (5 half-lives) into a nonradioactive form. The rapid decay substantially reduces the exposure of subjects to the potentially harmful effects of radiation. Moreover, only low doses of the radioactive label are necessary. The fast decay and small amounts permit many measures of blood flow to be made in a single experiment. In this way, $H_2{}^{15}O$-PET can take multiple pictures of the brain at work in different experimental conditions. Each picture represents the average neural activity of about 45 s. The total number of scans that can be made per subject (typically about 12 images) is

limited by the exposure to radiation. Cerebral blood flow studies are used not only in experimental cognitive research but also in clinical routine to detect residual cortical function after, for example, brain injury.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

In general, SPECT tracers are more limited than PET tracers in the kinds of brain activity they can monitor, but they are longer lasting. Thus, SPECT does not require an onsite cyclotron. However, most SPECT technology is relatively non-quantitative, does not permit measured attenuation correction and has a spatial resolution inferior to that of PET. On the other hand, SPECT is less expensive and more widely available.

Similar to PET, SPECT also uses radioactive tracers, but it involves the detection of individual photons (low-energy gamma rays) rather than positrons emitted at random from the radionuclide to be imaged. Typical radionuclides include Technetium-99m (^{99m}Tc) and Iodine-123 (^{123}I) with half-lives of 6 and 13 h, respectively. On average, SPECT acquisition times are 20–30 min.

Frequently used radiolabeled agents for brain perfusion SPECT are Tc-99m-hexamethyl propylamine oxime (Tc-99m-HMPAO; a lipid soluble macrocyclic amine) and Tc-99m-bicisate ethyl cysteinate dimer (Tc-99m-ECD). Long half-life, rapid brain uptake and slow clearance of most radiolabeled agents for brain perfusion SPECT offer the opportunity to inject the tracer at a time when scanning is impossible (e.g., during an epileptic crisis) and to scan (post-event) the associated distribution of activated brain regions. In addition to their use in determining perfusion, radiotracers can also be used to determine biochemical interactions such as receptor binding. For example, Iodine-123 labeled ligands such as IBZM, iodo-hydroxy-methoxy-*N*-[(ethyl-pyrrolidinyl) methyl]-benzamide, have been developed for imaging the dopamine receptor system (IBZM is a D2 receptor agonist that shows high uptake in the striatum).

FUNCTIONAL MAGNETIC RESONANCE IMAGING

fMRI can detect an increase in blood oxygen concentration that occurs in an area of heightened neuronal activity. The basis for this capacity comes from the way neurons make use of oxygen. Functionally induced increases in blood flow are accompanied by alterations in the amount of glucose the brain consumes but not in the amount of oxygen it uses. Indeed, despite the presence of abundant oxygen, the normal brain resorts to anaerobic metabolism during spurts of neuronal activity. Apparently, this physiologic behavior relies on tactics similar to that present in sprinter's muscles. It is not yet fully understood why the brain acts this way. Additional blood to the brain without a concomitant increase in oxygen consumption leads to a heightened concentration of oxygen in the small veins draining the active neural centers. The reason is that supply has increased, but the demand has not. Therefore, the extra oxygen delivered to the active part of brain simply returns to the general circulation by way of the draining veins.

The commonest form of fMRI is blood oxygenation level dependent (BOLD) imaging (Ogawa et al., 1990). The BOLD signal depends on the ratio of oxygenated to deoxygenated hemoglobin. In regions of neuronal activity this ratio changes as increased flow of oxygenated blood temporarily surpasses consumption, decreasing the level of paramagnetic deoxyhemoglobin. These localized changes cause increases in magnetic resonance signal, which are used as markers of functional activation. Ultrafast scanning can measure these changes in signal, which are mapped directly onto a high-resolution scan of the subject's anatomy. fMRI studies require magnets with field strengths superior to 1 T (recent fMRI magnets are 7 T and even 11 T). Some concerns have been raised about the intensity of the magnetic field to which the tissues are exposed in MRI, but so far there are no known harmful biological effects. The largest limiting factor is the claustrophobia some subjects may suffer as in most instrument designs the entire body must be inserted into a relatively narrow tunnel. Other limiting drawbacks are its susceptibility to subjects' movement artifacts and artifacts related to the use of metal-containing devices in the magnet (i.e., EEG wires, etc.).

Traditionally fMRI studies have measured changes in BOLD signal in response to a task performed by the subjects during specific times of the scanning session, as compared to a resting baseline. In the last decade, a number of fMRI studies have rather focused on the measurement of "resting state" spontaneous BOLD signal correlations between brain regions (Fox and Raichle, 2007). More advanced data analysis techniques also include the use of graph theoretical tools to quantify network hubs and organization features (Bullmore and Sporns, 2009) as well as the combination of these graph theory tools with large-scale computational models (Deco and Zihl, 2001). These resting state fMRI studies have led to significant insights into the way the brain is organized into functionally relevant networks in healthy humans (Bullmore and Sporns, 2009; Smith et al., 2013) as well as its alteration with brain disease (Stam, 2014; Fornito et al., 2015).

Recent advances in acquisition techniques, computational power and algorithms have also increased the speed of fMRI significantly, making real-time fMRI

feasible. Real-time fMRI allows for brain–computer interfaces (see Chapter 14) with a high spatiotemporal resolution. Recent studies have shown that such approaches can be used to provide online feedback of the BOLD signal and to learn the self-regulation of local brain activity (Weiskopf et al., 2007; Koush et al., 2012). This local self-regulation is being used as a new paradigm in cognitive neuroscience to study brain plasticity and the functional relevance of brain areas (see deCharms, 2008, for a review). More recently, it has even been possible to develop a spelling device based on real-time fMRI with subjects performing differently timed mental imagery tasks, allowing any freely chosen word production (i.e., letter-by-letter) (Sorger et al., 2012).

Other promising avenues emerging for future fMRI studies consist of high-field MRI allowing cortical column and laminar differentiation of BOLD signal analyses (Ugurbil, 2012), as well as large-scale meta-analyses allowing the objective quantification of reproducibility of results across fMRI studies (Fox et al., 2014).

MAGNETIC RESONANCE SPECTROSCOPY

MRI is generally associated with the signals from hydrogen nuclei (i.e., protons) because of the large numbers of hydrogen atoms in human tissue, including the brain, and the strong signals they provide. MRS not only makes measurements of protons, but also of nuclei such as phosphorus (^{31}P), carbon (^{13}C), and fluorine (^{19}F) (Dacey et al., 1991). It offers the potential of assessing brain function at metabolic and molecular levels. The technique uses natural emissions from atomic nuclei activated by magnetic fields to measure the concentration of endogenous molecules. Potential nuclei include ^{31}P, ^{13}C, ^{23}Na, ^{7}Li, in addition to ^{1}H. The ^{31}P MR spectrum can detect tissue concentrations of the phosphomonoesters phosphocholine and inorganic orthophosphate, the phosphodiesters glycerol-3-phosphoethanolamine and glycerol-3-phosphocholine, the triphosphate ATP, and other phosphorus-containing molecules including phosphocreatinine. ^{1}H spectroscopy offers the ability to measure lactate concentrations and neuronal markers such as *N*-acetyl aspartate. MRS permits quantitative analysis of these compounds *in vivo* with the potential of three-dimensional resolution within the brain.

ELECTROENCEPHALOGRAPHY

EEG is a non-invasive technique that allows the detection of spontaneous brain electrical activity from the scalp. It provides temporal resolution in the millisecond range. However, traditional EEG technology provides insufficient spatial detail to identify relationships between brain electrical events and structures and functions visualized by fMRI. Recent advances help to overcome this problem by recording EEG from more electrodes (experimental laboratories may use 256 electrodes, see Figure 2.4), by coregistering EEG data with anatomical

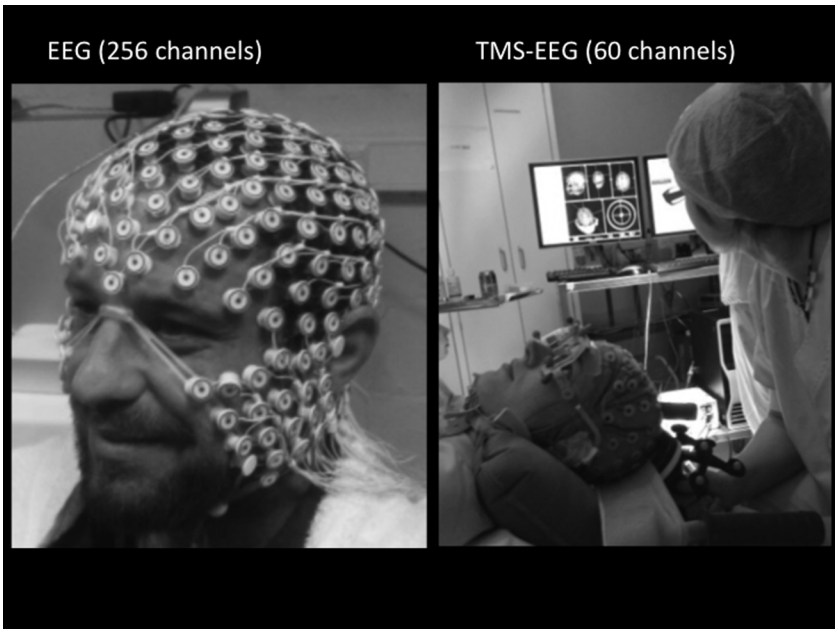

FIGURE 2.4 Setup of a high-density EEG with 256 channels (left-hand side) and TMS-EEG (right-hand side). TMS-EEG includes a 60-channel EEG net, a neuronavigation system, and a stimulation coil with tracking elements. The neuronavigation system is composed of 3D brain reconstruction, tracking goggles and an infrared tracking camera (not shown).

images, such as structural MRI, and by reducing the distortion caused by volume conduction of EEG signals through the skull and scalp. In addition, statistical measurements of sub-second interdependences between EEG time-series recorded from different locations can help to generate hypotheses about the instantaneous functional networks that form between different cortical regions during mental processing. Physiological and instrumental artifacts (e.g., subject's eye or head movements, heartbeats, or poor electrode contacts) can contaminate the EEG (and MEG). Care must be taken to correct or eliminate such artifacts before further analyses are performed. A way to reject these artifacts during the preprocessing step is through independent component analyses (ICA), which separates EEG data (but also fMRI data) into linearly independent components. The classification of these components as artifact (e.g., eye blinks, muscle activity) or "real" EEG signal (e.g., brain activity) often requires visual inspection by experts, but automated artifact elimination classifiers have recently been developed to standardize this procedure (Radüntz et al., 2015).

Scalp-recorded EEG in the waking state in healthy adults normally ranges from several to about 75 μV. The EEG signal is largely attributable to graded postsynaptic potentials of the cell body and large dendrites of vertically oriented pyramidal cells in cortical layers 3–5. These are synchronized by rhythmic discharges from thalamic nuclei, with the degree of synchronization of the underlying cortical activity reflected in the amplitude of the EEG. Most of the EEG signal originates in cortical regions near the recording electrode. The columnar structure of the cerebral cortex facilitates a large degree of their electrical summation rather than mutual cancellation. Thus, the EEG recorded at the scalp represents the passive conduction of currents produced by summating activity over large neuronal aggregates. Regional desynchronization of the EEG reflects increased mutual interaction of a subset of the population engaging in "cooperative activity" and is associated with decreases in amplitude.

To measure the EEG, electrodes are either directly attached to the scalp (e.g., with a strong glue called Collodion that allows long lasting recordings) or attached to a net with a standard montage (see Figure 2.4). The space between the electrode and the skin is then filled with conductive paste to ensure lowering of contact impedance at electrode–skin interface. Each electrode is connected with an electrically "neutral" lead attached to the ear, nose, chin, or chest (i.e., reference montage) or with an "active" lead located over a different scalp area (i.e., bipolar montage). Differential amplifiers are used to record voltage changes over time at each electrode. These signals are then digitized with 12 or more bits of precision and are sampled at a rate that is high enough to prevent aliasing of the signals of interest. EEGs are conventionally described as patterns of activity in five frequency ranges: delta (less than 4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–35 Hz; sometimes subdivided in low beta at 13–20 Hz and high beta at 21–35 Hz) and gamma activity (above 35 Hz). One can then describe the EEG according to these spontaneous neuronal oscillations. These oscillations reflect fluctuations of neuronal activity that emerge from the synchronous activation of large neuronal ensembles. Analyses of EEG data include long-range synchrony (i.e., synchronization between separated brain regions), phase (i.e., quantification of the difference between two oscillations according to some patterns of one of the oscillations with respect to the others), spectral power (i.e., amplitude of neural oscillation computed through a time frequency transformation), and cross-frequency coupling (e.g., phase-amplitude, amplitude-amplitude, frequency-amplitude, and phase-phase) (Aru et al., 2014; Roux and Uhlhaas, 2014).

EVOKED POTENTIALS

An evoked potential (EP) or ERP is the time-locked average of the EEG in response to a specific sensory, motor or cognitive event. Because of their low amplitude, especially in relation to the background EEG activity, a number of stimuli have to be recorded and averaged with a computer in order to permit their recognition and definition. The background EEG activity, which has no fixed temporal relationship to the stimulus, will be averaged out by this procedure (Lehembre et al., 2012).

Sensory evoked or "exogenous" potentials are recordings of cerebral or spinal potentials elicited by stimulation of specific sensory pathways (e.g., visual EPs elicited by monocular stimulation with a reversing checkerboard pattern; brainstem auditory EPs elicited by monaural stimulation with repetitive clicks; and somatosensory EPs elicited by electrical stimulation of a peripheral nerve). They are a routinely used means of monitoring the functional integrity of these pathways in neurology.

Certain EP components depend upon the mental attention of the subject and the setting in which the stimulus occurs, rather than simply on the physical characteristics of the stimulus. Such "event-related" or "endogenous" potentials (ERPs) are related in some manner to the cognitive aspects of distinguishing an occurring target stimulus (Kotchoubey, 2005). For clinical purposes, attention has been directed particularly at the so-called P300 or P3 component of the ERP (named after its positive polarity and latency of approximately

300−400 ms after onset of an auditory target stimulus—for example, an infrequent tone or the subject's own name (Perrin et al., 2006)). The P300 has been associated with cognitive information processing (e.g., memory, attention, consciousness, executive function) and its latency and amplitude possibly index different aspects of brain maturation (van Dinteren et al., 2014).

As a research tool, ERPs can provide valuable information about the timing and cortical distribution of the neuroelectrical activity generated during mental activity. An averaged EP waveform consists of a series of positive and negative waves; a significant difference in latency, amplitude, duration, or topography of one or more of these waves between experimental conditions which differ in one specific cognitive factor is assumed to reflect the mass neural activity associated with that cognitive factor (Kotchoubey, 2005). Measurements of changes in the amplitude and timings of peaks in the series of EP waves allows inferences to be made about the sequence and timing of task-associated processes, such as pre-stimulus preparation, encoding of stimulus features, conscious perception, operations such as matching or comparison of stimulus codes and memory codes, evaluation of the meaning of the stimulus, response selection and execution. Classical averaged EP method assume that the component subprocesses comprising a cognitive behavior do not vary in time from trial to trial (Gevins, 1998).

ELECTROCORTICOGRAPHY, INTRACEREBRAL LOCAL FIELD POTENTIALS, AND SINGLE-UNIT RECORDINGS

Because the EEG and ERP are recorded from the scalp, the electrophysiological signals are averaged across a large area of the cortical mantle. Any asynchronized pattern of activity within a population of neurons is therefore mainly lost to spatial averaging in the scalp EEG measurement. In contrast, ECoG measures electrical brain signals using subdural grid electrodes that are implanted on the surface of the brain. ECoG offers a closer look into the dynamics of electrophysiological signals within a local cortical tissue. Given the size of ECoG electrodes (~2 mm in diameter), the recording area underneath each electrode resembles the size of a standard voxel in the current neuroimaging methods (i.e., 10 mm^3). Thus, ECoG measures neuronal populations on a much more local scale than recordings from the scalp (Ritaccio et al., 2011). ECoG is an invasive procedure because a craniotomy is required to implant the electrode grid. There are therefore primarily used in epileptic patients to localize the epileptogenic zone prior to surgery, but patients can then agree to participate to any other brain research studies (Hill et al., 2012).

Single-unit recording has also recently emerged as a promising recording technique for use in human cognition research and cortical mapping. Single-unit electrode allows measuring the local field potential (also known as micro-, depth or intracranial EEG) when recorded by a small-size electrode in the brain. This invasive technique can then be applied to brain−computer interface technologies for brain control of external devices (Mukamel and Fried, 2012). In the clinical setting, intracerebral local field potential recordings can also be coupled with single-pulse electrical stimulation of the cerebral cortex allowing to study directly cortico-cortical communication and its changes across the sleep-wake cycle (Pigorini et al., 2015).

MAGNETOENCEPHALOGRAPHY

MEG is a non-invasive tool that measures the magnetic fields generated by electrical activity within the brain. Magnetic field tomography (a technique based on distributed source analysis of MEG data) makes possible the three-dimensional reconstruction of dynamic brain activity in humans with a temporal resolution better than 1 ms and a spatial accuracy of 2−5 mm at the cortical level (which deteriorates to 1−3 cm at depths of 6 cm or more). Electrical currents generate magnetic fields. Biomagnetic fields directly reflect electrophysiological events of the brain and pass through the skull without distortion. Hence, currents initiated at the synapses, and guided postsynaptically by cell structure produce the magnetic field detectable outside the head. MEG is most sensitive to activity in the fissural cortex, where the current is oriented parallel to the skull, whereas it does not detect sources that are oriented exactly radially to the skull.

The average electromagnetoencephalogram is about 10 pT (10^{-12} T) in amplitude; this is nine orders of magnitude smaller than the earth's steady magnetic field. The magnetic field produced by a single postsynaptic potential is too weak to be detected outside the head. Instead, what is detected is the macroscopic coherent activity of thousands of neurons. Measurements are performed inside magnetically shielded rooms. Sensitivity to such weak signals requires the use of cryogenic technologies. MEG instruments consist of superconducting quantum interference devices, operating at liquid helium temperatures of −269°C (Brenner et al., 1975). Recording neuromagnetic signals has been compared to listening for the footsteps of an ant in the middle of a rock concert.

The major advantage of techniques based on the measurements of cerebral electrical activity (i.e., EEG and MEG) is their uncompromised time resolution. Their major drawback, however, is their limited spatial

BOX 2.3

THE INVERSE PROBLEM

Like for EEG, MEG data have to be subjected to an inverse problem algorithm to obtain an estimate for the distribution of the activity in the brain (Darvas et al., 2004). Similar to PET, fMRI, and EEG these can then be displayed on cross-sectional anatomical images (obtained by MRI) of the same subject. The inverse problem relates to the difficulty to determine internal sources on the basis of measurements performed outside the head. The most common way to tackle this problem is to determine the single source current element (dipole) that most completely explains the EEG or MEG pattern. This can be done with a computer algorithm that starts from a random dipole position and orientation and keeps changing these parameters as long as the field pattern computed from the dipole keeps approaching the observed EEG or MEG pattern. When no further improvement is obtained, a minimum in the cost function has been reached; a source corresponding to this solution is called the equivalent current dipole (ECD). In most cases, however, the EEG or MEG data pattern cannot be accurately explained by a single source. In these cases, two or more dipoles could be used to explain the data, but this easily leads to computational difficulties in trying to determine the best multi-source solution. Alternatively, continuous solutions such as the minimum norm estimate might also be constructed (Nenonen et al., 1994). When interpreting EEG or MEG results it should be born in mind that the inverse problem is fundamentally non-unique. This means that even if the complete electric and magnetic field around the head could be measured precisely, an infinite number of current distributions in the brain could still be constructed that would explain the measured fields. It is always possible that some sources are missed, whatever the measurement setup. For example, MEG alone is insensitive to radially oriented sources, but even when combined with EEG, silent sources are possible. Full use of available techniques requires the use of estimation theory to derive optimal solutions based on all available information, including MRI, PET, and fMRI.

resolution. Indeed, accurate localization of the source of brain activity remains difficult (see Box 2.3). Furthermore, the resolution becomes poorer the deeper into the brain we attempt to image. The main advantages of MEG compared with EEG are its superior spatial accuracy and ease of use, particularly when a large number of channels are involved (currently over 300). On the other hand, EEG complements MEG in detecting source components not detected by MEG (i.e., radially oriented sources) (Naatanen et al., 1994). MEG is mostly used for experimental research but clinical applications are recently being developed. For instance, MEG is now employed in routine clinical practice for detecting and localizing pathological activity in epileptic patients, and in localizing brain regions for surgical planning in patients with brain tumors or intractable epilepsy (Stufflebeam et al., 2009).

TRANSCRANIAL MAGNETIC STIMULATION

TMS is a tool for the non-invasive stimulation of the superficial cortex. TMS is now commonly used in clinical neurology (e.g., to study central motor conduction time) and in research (e.g., to study brain connectivity). Stimulations can be induced via single, paired, or repetitive pulses. In principle, depending on stimulation parameters, TMS can excite (i.e., with high frequency stimulation, above 1 Hz) or inhibit (i.e., with low frequency stimulation, below 1 Hz) the arbitrary sites of the superficial cortex, allowing functional mapping and creation of transient functional lesions (Hallett, 2000).

For TMS, a brief, high-current pulse is produced in a coil of wire, which is placed above the scalp. A magnetic field is produced with lines of flux passing perpendicularly to the plane of the coil. An electric field is induced perpendicularly to the magnetic field. The extent of neuronal activation varies with the intensity of stimulation. TMS ordinarily does not activate corticospinal neurons directly; rather it activates them indirectly through synaptic inputs. Intracortical inhibition and facilitation are obtained using paired-pulse stimulations and reflect the activity of interneurons in the cortex (Lapitskaya et al., 2009, 2013). Repetitive TMS allows various brain areas to be stimulated and cognitive changes to be subsequently recorded (Miniussi and Rossini, 2011). Repetitive TMS can produce effects that last after the stimulation period, especially with protocols called "theta burst stimulation" (Huang et al., 2005; Hamidi et al., 2009; Oberman et al., 2011). In contrast, single-pulses TMS do not produce long-term change and are used to measure the effect of a perturbation without modifying the brain activity (Massimini et al., 2009; Johnson et al., 2012). Guidelines have been published for safe and effective use of TMS in

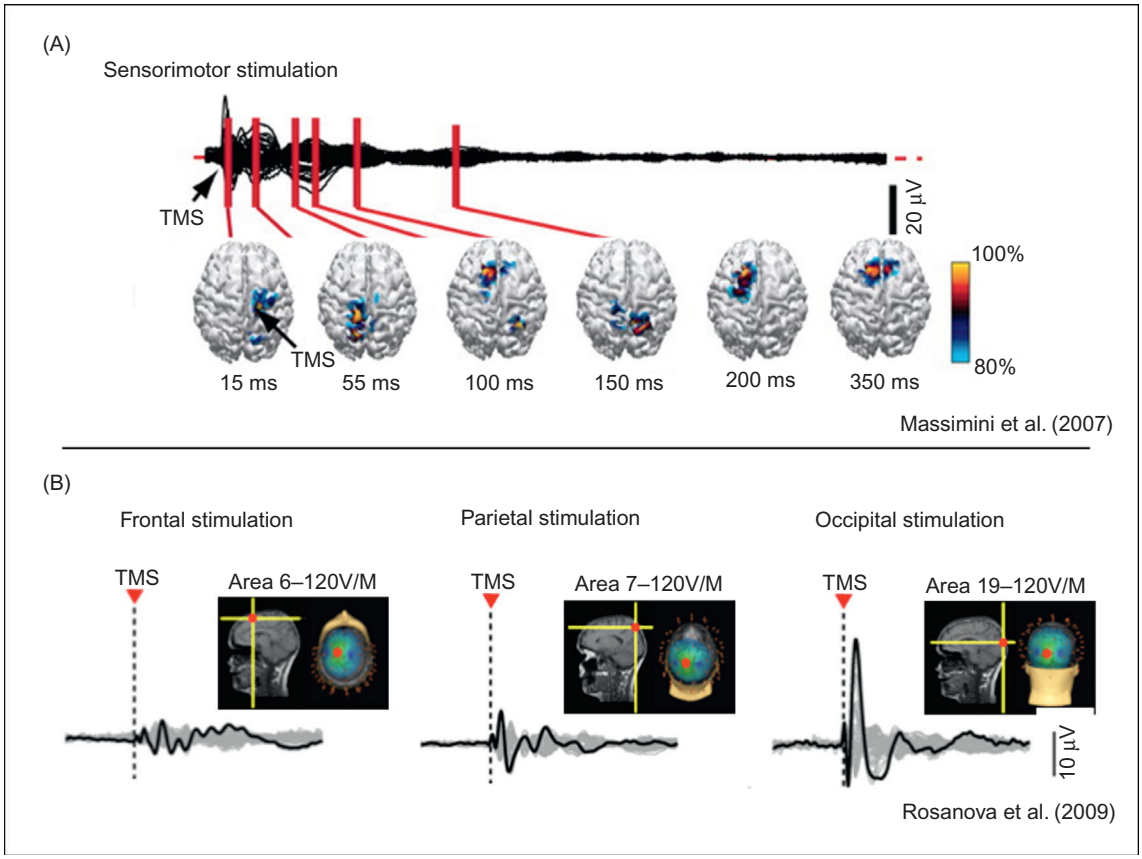

FIGURE 2.5 TMS-EEG in healthy awake subjects. (A) Cortical activation evoked by TMS delivered over the sensorimotor cortex. Averaged TMS-EPs recorded at all electrodes and superimposed in a butterfly diagram with current density distributions highlighting the location of maximum current sources. (B) Response under the TMS stimulation (black trace) and in other areas of the brain (gray traces) when stimulating frontal, parietal, and occipital cortices. Red spot illustrates the site of the stimulation. *Source: Adapted from Rosanova et al. (2009), Massimini et al. (2007).*

healthy and pathological population in order to prevent induction of seizures and to guide therapeutic use of TMS (Wassermann, 1998; Rossi et al., 2009; Lefaucheur et al., 2014; Nielson et al., 2014).

The classical neuropsychological paradigm is that of studying the effects of brain lesions on behavior. With TMS, this paradigm can be applied in a spatially and temporally restricted fashion to healthy volunteers. It is now widely used as a research tool to study aspects of human brain physiology including motor function, vision, language, and the pathophysiology of brain disorders. TMS allows the investigation of the relationship between focal cortical activity and behavior, to trace the timing at which activity in a particular cortical region contributes to a given task, and to map the functional connectivity between brain regions (Pascual-Leone et al., 2000). Combined with other brain-imaging techniques such as PET, EEG, and fMRI, TMS can be used to evaluate cortical excitability and connectivity (Paus, 1999; Massimini et al., 2005).

TMS coupled with high-density EEG (TMS-EEG) (Figure 2.4) allows the assessment of cortical reactivity directly, instead of corticospinal excitability or behavioral reactions to TMS. Single-pulse TMS induces the discharge of cortical neurons under the stimulator and EEG detects cortical electrical responses both locally and at distant sites (Figure 2.5A). This enables us to study cortical excitability and to infer the causal architecture of brain circuits (Massimini et al., 2009). Indeed, provided that a TMS-compatible amplifier and a neuronavigation system are employed together with state-of-the-art experimental and signal processing procedures, TMS-EEG allows us to precisely perturb a selected brain area and to record cortical responses in a reliable and reproducible way (Lioumis et al., 2009; Casarotto et al., 2010; Rosanova et al., 2012a; Mutanen et al., 2013; Gosseries et al., 2015). Accordingly, TMS-EEG has been used to measure fundamental properties of brain circuits (Gosseries et al., 2014). For instance, TMS applied over different corticothalamic modules result consistently in TMS-EPs dominated by EEG oscillations in the alpha, slow beta, fast beta, and gamma frequency bands (when stimulating occipital, parietal, frontal, and prefrontal sites, respectively) (Figure 2.5B) (Rosanova et al., 2009).

Notably, these natural frequencies are reduced in schizophrenia patients (Ferrarelli et al., 2012). Moreover, TMS-EPs recordings directly revealed changes in cortical excitability and effective connectivity during cognitive tasks (Mattavelli et al., 2013; Morishima et al., 2009), administration of GABAergic drugs (Premoli et al., 2014), and transcranial direct current stimulation (Romero Lauro et al., 2014; Pellicciari et al., 2013).

Most importantly, TMS-EEG measurements of cortical excitability, effective connectivity, and brain complexity have been recently used to successfully differentiate between consciousness and loss of consciousness occurring in healthy, pathological, and pharmacological conditions, such as non-rapid eye movement sleep, general anesthesia, and unresponsive wakefulness syndrome (i.e., vegetative state) (Rosanova et al., 2012b; Casali et al., 2013; Ferrarelli et al., 2010).

MULTIMODAL IMAGING ASSESSMENT

Combining various techniques offers a more complete characterization of the different aspects of brain activity during cognitive processing. fMRI and $H_2{}^{15}O$-PET measures local changes in brain hemodynamics induced by cognitive or perceptual tasks. These measures have a uniformly high spatial resolution of millimeters or less, but poor temporal resolution (about 1 s at best). Conversely, EEG and MEG instantaneously measure the current flows induced by synaptic activity, but the accurate localization of these current flows still remains challenging. Techniques have been developed that, in the context of brain anatomy visualized with structural MRI, use both hemodynamic and electromagnetic measures to get estimates of brain activation with higher spatial and temporal resolution. These methods range from simple juxtaposition to simultaneously integrated techniques. Multi-modality integration requires an improved understanding of the coupling between the physiological phenomena underlying the different signal modalities (Dale and Halgren, 2001). Acquisition of simultaneous EEG during fMRI provides an additional monitoring tool for the analysis of brain state fluctuations. The exploration of brain responses following inputs or in the context of state changes is crucial for a better understanding of the basic principles governing large-scale neuronal dynamics (Ritter and Villringer, 2006).

The combination of TMS with EEG and also with PET or fMRI permits the assessment of connectivity and excitability of the human cerebral cortex. PET and fMRI can define the anatomy of the circuits underlying a behavior of interest and electrical recording techniques can reveal the course of temporal events in these spatially defined circuits. Parallel information from different imaging modalities is currently used to constrain the EEG or MEG inverse solutions (see Box 2.3) to limited regions of the cerebrum. This approach provides optimal combined spatial and temporal resolution by exploiting the best aspects of each technology.

FUNCTIONAL NEUROIMAGING STUDY DESIGN

Mapping the human brain is distinct from the assumptions held by phrenologists of the nineteenth century. According to the German physician Franz Josef Gall, thought processes are localized in single brain areas identified by bumps on the skull. Gall posited that complex behavioral traits (e.g., ideality, cautiousness, imitation, self-esteem, calculation, etc.) could be related to the size of these bumps. Although the "bumps theory" was fanciful, the idea of a functional segregation of the brain was not. In 1861, by carefully studying the brain of a man who had lost the faculty of speech after a left inferior frontal lesion, Paul Broca became convinced that different functions could be localized in different parts of the cerebrum. At present, more than a century of neuropsychological investigations in brain damaged patients has confirmed that a cortical area can be specialized for some aspects of perceptual or sensorimotor processing and that this specialization is anatomically segregated in the cortex. In our current vision of brain function, however, functional segregation holds for simple processes, rather than for complex behaviors or traits such as those described by phrenologists. By now, the view is that the cortical infrastructure supporting a single function (and a fortiori a complex behavior) may involve many specialized areas that combine resources by functional integration between them. Hence, functional integration is mediated by the interactions between functionally segregated areas, and functional segregation is meaningful only in the context of functional integration and vice versa.

In this framework, the foundation for most of functional neuroimaging studies is that complex behaviors can be broken down into a set of constituent mental operations. In order to read this text, for example, you must recognize that a string of letters is a word; then recognize the meaning of words, phrases, and sentences; and finally create mental images. The methodological challenge is first to separate each of these tasks from a cognitive perspective and second to determine those parts of the brain that are active and those that are dormant during their performance. In the past, cognitive neuroscientists have relied on studies of laboratory animals and patients with localized brain lesions to gain insight into the brain's functions. Imaging techniques, however, permit us to visualize

safely the anatomy and the function of the human brain, both in normal and in pathological conditions.

It is amazing that the most widely used strategy for functional neuroimaging of the past 20 years is based on an idea first introduced to psychology in 1868. Indeed, Franciscus C. Donders, a Dutch ophthalmologist and physiologist, then proposed a general method to estimate cognitive processes based on a simple logic. He subtracted the time needed to respond to a light (with, say, a press of a key) from the time needed to respond to a particular color of light. He found that discriminating color required about 50 ms more than simply responding to the light. In this way, Donders was the first to isolate a basic mental process and to obtain a measure of the time needed by the brain to perform this specific process (Donders, 1969).

The classical strategy in functional neuroimaging is designed to accomplish a similar subtraction but in terms of the brain areas implementing the mental process. In particular, images of neural activity (being it blood flow measured by fMRI or electrical activity measured by EEG, MEG, or ECoG) taken before a task is begun can be compared with those obtained when the brain is engaged in that task—see also Chapter 6, on "resting state" studies. The two periods are referred to as control state and task state. It is important to carefully choose each state so as to isolate as best as possible a limited number of operations. Subtracting neural activity measurements made in the control state from each task indicates those parts of the brain active during a particular task. To achieve reliable data, averages are made of many experimental trials in the same person or of responses across many individual subjects. Averaging enables the detection of changes in neural activity associated with mental activity that would otherwise be easily confused with spurious shifts resulting from noise.

It is important to stress that this methodological approach, known as the cognitive subtraction paradigm, has an important drawback. Indeed, in order to isolate the neural substrate of a given cognitive component of interest, it must be assumed that the only difference between the control state and task state is the component of interest to the exception of any other stimulus or task-related processes. Unfortunately, this cannot always be easily and fully guaranteed. Analytic strategies, however, have been devised to circumvent this problem (see below), and cognitive subtraction designs remain the foundation of a large amount of functional neuroimaging experiments.

ANALYZING BRAIN-IMAGING DATA

Regional differences among brain scans have long been characterized thanks to hand-drawn regions of interest (ROIs). This approach reduced the information from hundreds of thousands of voxels (volume elements that in three dimensions corresponds to a pixel with a given slice thickness) to a handful of ROI measurements, with a somewhat imprecise anatomical validity. More powerful voxel-based statistical methods have however been developed recently. Although several solutions are in use in neuroscience laboratories, one of the most popular methods for the analysis of neuroimaging data is statistical parametric mapping (SPM). SPM is a standardized method that refers to the construction and assessment of spatially extended statistical processes used to test hypotheses about neuroimaging data (PET, SPECT, fMRI but also EEG). Statistical parametric maps can be thought of as "X-rays" of the significance of an effect, which can be projected on a three-dimensional representation of the brain. These ideas have been instantiated in a software (last version called SPM12) by Karl Friston and coworkers at the Wellcome Department of Cognitive Neurology in London (http//www.fil.ion.ucl.ac.uk/spm). SPM has become one of the most widely used and validated method to analyze functional neuroimaging data. Another analytical tool that is more and more used for mapping human brain activity is Analysis of Functional NeuroImages (AFNI), which is a set of C programs for processing, analyzing, and displaying functional MRI data (http://afni.nimh.nih.gov/afni/). AFNI was originally developed by Robert W. Cox at the Medical College of Wisconsin in 1994. There are two basic approaches when analyzing and interpreting functional neuroimaging data. They are based upon the distinction between functional segregation and integration.

Functional Segregation

Using a functional specialization concept of the brain, the following sets of approaches are based on detecting focal differences. They generally fall into one of three broad categories: (i) The subtractive or categorical designs are predicated on the assumption that the difference between two tasks can be formulated as a separable cognitive or sensorimotor component, and that the regionally specific differences in brain activity identify the corresponding functional area (i.e., the cognitive subtraction paradigm). Its utilization ranges from the functional anatomy of word processing to the functional specialization in visual cortex, an application that has been validated by electrophysiological studies in monkeys (Zeki, 1993). (ii) The parametric or dimensional design assumes that regional physiology will vary systematically with the degree of cognitive or sensorimotor processing. Parametric designs may avoid many of the shortcomings of "cognitive subtraction." A fundamental difference between subtractive

and parametric designs lies in treating a cognitive process not as a categorical invariant but as a dimension that can be expressed to a greater or lesser extent in relation to the brain's regional activity. (iii) Factorial or interaction designs are also well suited to avoid the drawbacks of simple subtraction paradigms. Two or more factors can be combined in the same experiment, and the interaction term will assess the effect of one factor while excluding the effect of the other.

Functional Integration

The functional role played by any component (e.g., a neuron or a specific brain area) of a connected system (e.g., the brain) is largely defined by its connections. Connectionist approaches to understanding the integration of brain functions are well established (Hebb, 1964). The nature and organizational principles of intra- (Goldman-Rakic, 1988) and subcortical (Mesulam, 1990) connections have provided a basis for mechanistic descriptions of brain function, referring to parallel, massively distributed, and interconnected (sub)cortical areas. Anatomical connectivity, mainly determined by neuroanatomic tracer experiments in animals, is a necessary underpinning for these models. The concepts of functional and effective connectivity were developed in the analysis of separable spike trains obtained from multi-unit electrode recordings. However, the neurophysiological measurements obtained from functional neuroimaging have a very different timescale (seconds vs. milliseconds) and nature (metabolic or hemodynamic vs. spike trains) than those obtained from electrophysiological studies.

At present, analytical tools are available to assess the functional or effective connectivity between distant cerebral areas (Friston et al., 1997). *Functional connectivity* is defined as the temporal correlation of a neurophysiological index (i.e., blood flow) measured in different remote brain areas, whereas *effective connectivity* is defined as the influence one neural system exerts over another (Buchel and Friston, 1997). In this context, a *psychophysiological interaction* can be assessed in the framework of the general linear model to explain the activity in one cortical area in terms of an interaction between the influences of another area in a given experimental context (Friston et al., 1997). Put simply, the statistical analysis will identify brain regions that show condition-dependent differences in the way their activity relates to the activity in another (chosen) area. Alternatively, exploratory data driven approaches based on ICA can be employed (McKeown et al., 1998). Other effective connectivity analyses using dynamic causal modeling (DCM; Friston et al., 2003) will be described below.

Preprocessing of Volumetric Functional Neuroimaging Data

Voxel-based analyses of PET, fMRI or source space EEG/MEG images require the data to be in the same anatomical space. For PET and functional MRI data, this is obtained by spatial realignment. Indeed, in such experiments movement related variance components represent one of the most serious confounds. Therefore, scans from each subject are realigned using an optimization procedure minimizing the residual sum of squares (Friston et al., 1995). In a second step, the realigned images are spatially normalized. They are subject to non-linear warping so that they match a template that already conforms to a standard anatomical space (Talairach and Tournoux, 1988). Indeed, pooling neuroimaging data from grossly different individual brains requires a procedure to spatially normalize the individual brains to an idealized or standard brain for the purpose of achieving overlap between corresponding anatomical and functional areas in different subjects. The Talairach and Tournoux (1988) atlas was initially developed—and has proven very useful—for anatomical normalization required for neurosurgical procedures, particularly those at brain sites close to the origin of the reference system (i.e., the anterior and posterior commissures). Each point within Talairach space into which brains are transformed is defined using three coordinates (expressed in millimeters). The first coordinate defines the position in x, that is, from left (negative) to right (positive) with 0 mm corresponding to the interhemispheric line. The second defines the position in y, that is, from posterior (negative) to anterior (positive) with 0 mm corresponding to the anterior commissure. The third defines the position in z, that is, from bottom (negative) to top (positive) with 0 mm corresponding to the plane through anterior and posterior commissures. This standard coordinate system facilitates the reporting of results in a conventional way and facilitates comparisons between peak voxels obtained in experiments from different laboratories. Similar spatial normalization is to date more commonly performed using the Montreal National Institute coordinate space (Evans et al., 1993; Collins et al., 1994).

After spatial normalization, images are commonly spatially smoothed (i.e., convolved with a isotropic Gaussian kernel). Smoothing individual images prior to a statistical analysis offers: (i) an improved signal to noise ratio, (ii) a conditioning of the data so that they conform more closely to the Gaussian field model which lies at the basis of the correction procedure for multiple statistical comparisons, (iii) a better overlap between the localization of anatomical and functional brain areas from different subjects which permits intersubject

averaging. Spatial smoothing is sometimes, however, not performed if the analysis is used in single subject space (e.g., for multivariate pattern analysis studies, see below) where optimal spatial resolution is to be aimed.

Statistical Analysis

The data obtained after PET, fMRI, or EEG/MEG volumetric images preprocessing consist of a matrix of many hundredth thousandths of voxels/time points for each subject and for each condition. Each of these voxels is characterized by the x, y, and z spatial coordinates in the standard space and a value representing the functional activity in that voxel (e.g., BOLD signal, blood flow, glucose metabolism, power in a given EEG frequency band). The statistical analysis corresponds to modeling the data in order to partition observed neurophysiological states or responses into components of interest, confounds of no interest and an error term. This partitioning is effected using the framework of the general linear model to estimate the components in terms of parameters associated with the design matrix. The analysis of regionally specific effects uses the general linear model to assess differences among parameter estimates (specified by a contrast) in a univariate sense, by referring to the error variance. The significance of each contrast is assessed with a statistic with a Student's t distribution under the null hypothesis for each and every voxel (Albus et al., 2007; Alkire, 2008). Multi-voxel pattern analysis (MVPA) is another way to analyze neuroimaging data which has recently gained increasing interest because it allows the detection of differences between conditions with higher sensitivity than the conventional univariate analysis reviewed above (Yang et al., 2012). MVPA focuses on the analysis and comparison of distributed patterns of activity where data from individual voxels at the whole brain level or within a particular region are jointly analyzed. A common use of MVPA is to decode brain activity, that is, to decode the information that is represented in the subject's brain at a particular point in time. MVPA tools are also often referred to as machine learning classifier and can be employed for diagnosis and prognosis in clinical neuroimaging (Haller et al., 2014).

Statistical Inference

The final stage is to make statistical inferences and characterize the responses observed using the fitted responses or parameter estimates. On one hand, with an *a priori* anatomically constrained hypothesis about effects in a particular brain location, the Z value in that region (e.g., in the SPM Alkire, 2008) can be used to test the hypothesis (i.e., *uncorrected* P value; or (better) a small volume corrected p value calculated). On the other hand, if an anatomical site cannot be predicted *a priori*, a correction for multiple non-independent comparisons is required. Therefore, the theory of Gaussian fields (Friston, 1997) provides a way for correcting the P value for the multiple non-independent comparisons implicit in the analysis. This correction depends on the search volume, the residual degrees of freedom due to error and the final image smoothness estimate. The obtained corrected and uncorrected p values pertain to different levels of inference in terms of (i) the significance of the effect in a particular voxel, (ii) the significance of the coactivation of a cluster of voxels in a specific region, and (iii) the significance of the coactivation of several clusters in the whole brain. Only in cases of well-documented prior neuroanatomical knowledge about the expected result, small volume corrected or uncorrected P values can be accepted. By specifying different contrasts, one can test for the variety of effects described above, and the significance values above a chosen threshold are comprehensively represented in a map where each voxel is represented at its proper location on the brain template and where the T value in this voxel for a given contrast is represented by use of a color intensity code.

Computational Neuroimaging and DCM

Another recent advance in functional neuroimaging data analysis allows using realistic biophysical models to provide a mechanistic explanation at the neuronal level of changes in macro-scale functional imaging data features observed between different experimental conditions. A highly promising framework using this approach is the one using DCM (Friston et al., 2003). For example, current DCM tools for EEG and MEG data already use refined realistic biophysical models, incorporating details of cortical laminar organization as well as layer-specific connectivity to explain changes in observed EEG or MEG data features in neuronal terms. Such DCM analyses identify which connectivity features best explain the measured EEG or MEG data modeled as the response of a network of sources, where each source corresponds to a neural mass model of several subpopulations in the cortex (David et al., 2008). The basic idea is to manipulate the (real) system (e.g., by changing experimental conditions) and model the experimental effects in terms of changes in coupling between these neuronal sources. Estimated parameter changes across experimental conditions then serve as summary statistics in classical tests (analysis of variance and post-hoc t-tests) of condition-specific effects over subjects. Such computational neuroimaging techniques represent a highly promising tool to incorporate our increasingly precise knowledge of the neural mechanisms underlying the generation of BOLD and electrophysiological responses in observed macro-scale functional neuroimaging data

analysis. This could allow a more precise interpretation of these data features in neuronal terms (Friston, 2009). For example, DCM models have started to have been successfully applied to detect differential changes in layer-specific feed-forward versus feedback connectivity underlying changes in EEG and ERP patterns observed in lesional or pharmacological models of unconsciousness (Boly et al., 2011, 2012).

CONCLUSION

Functional neuroimaging experiments provide a vast amount of information. Recent efforts to create neuroscience databases could organize and quickly disseminate such a repository of data. As demonstrated in many chapters of this book, wise use of these powerful tools and the information they produce can aid our understanding and management of consciousness and its related disorders. Clearly, neuroimaging is heading us toward a much richer grasp of the relation between the human mind and the brain.

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CHAPTER

3

Neuronal Oscillations, Coherence, and Consciousness

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OUTLINE

A large body of neuropsychological and physiological evidence suggests that consciousness has to be understood as a function of numerous interacting systems, such as sensory areas, memory structures, centers for executive control as well as circuits mediating emotion and motivation (Crick and Koch, 1990; Newman and Baars, 1993; Tononi and Edelman, 1998; Engel et al., 1999; Engel and Singer, 2001; Lamme, 2006; Dehaene et al., 2006; Tononi and Koch, 2008; Dehaene and Changeux, 2011). Thus, any theory about the neural mechanisms of consciousness must explain how multiple component processes can be integrated and how large-scale interactions can emerge within and across distributed neural systems. Furthermore, such a theory must specify mechanisms for the dynamic selection of subsets of neuronal responses, because only a fraction of all available information gains access to consciousness. In this chapter, we consider the potential relevance of oscillatory neural signals for the emergence of consciousness. We will suggest that changes in the strength or the coupling of oscillatory signals may relate to the selection of signals for access to consciousness, to structuring of conscious contents, to large-scale integration across different brain regions, and to buildup of a "global workspace." In recent years, empirical evidence is emerging which indeed suggests that coherent oscillatory activity may relate to these different prerequisites and, thus, may be critical to understanding the neural basis of consciousness.

RELEVANCE OF OSCILLATORY SIGNALS

Oscillatory brain signals are usually categorized into five frequency bands: delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (>30 Hz). A large body of evidence suggests that oscillatory activity in these frequency bands is linked to a broad variety of perceptual, sensorimotor, and cognitive operations (Singer and Gray, 1995; Engel et al., 2001; Palva and Palva, 2007; Fries, 2009; Engel and Fries, 2010; Siegel et al., 2012; Lisman and Jensen,

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2013). Oscillatory activity in the delta-band has been related to motivational processes, the brain reward system, and is the predominant frequency during deep sleep phases (Başar et al., 2000; Knyazev, 2007). Activity in the theta-band has been linked to working memory functions, emotional arousal, fear learning, and attentional sampling (Knyazev, 2007; Jensen and Lisman, 2005; Fries, 2009; Landau and Fries, 2012; Lisman and Jensen, 2013). The prominent alpha-band rhythm, which has been discovered in the human electroencephalogram (EEG) by Hans Berger in the late 1920s, has been suggested to reflect cortical operations during the awake resting-state in the absence of sensory inputs. It has been proposed that alpha-band oscillations may relate to disengagement of task-irrelevant brain areas (Klimesch et al., 2006; Jensen and Mazaheri, 2010), as well as working memory function and short-term-memory retention (Palva and Palva, 2007). Neuronal responses in the beta-band have been frequently linked to sensorimotor processing (Roelfsema et al., 1997; Brovelli et al., 2004) as well as many other functions including, for instance, working memory and top-down processing (Engel and Fries, 2010; Bastos et al., 2015a,b).

Neural signals in the gamma-frequency range have received considerable attention in the past two decades. Although the phenomenon of fast neuronal oscillations had already been described 50 years earlier, it started to attract major interest only in the late 1980s, when it was shown to correlate with perceptual binding (Gray et al., 1989). Fast oscillations in the gamma-frequency range have been found in a large number of different neural systems and across a wide range of species (for review, see Singer and Gray, 1995; Engel et al., 2001; Fries, 2009; Siegel et al., 2012). In animal studies, early observations on gamma oscillations were made in the visual and olfactory systems (Fröhlich, 1913; Adrian, 1950; Freeman, 1968). In humans, gamma-band activity was demonstrated first in the auditory cortex (Galambos et al., 1981). In the past three decades, studies in animals and humans have reported gamma-frequency oscillations in all sensory systems, in memory systems, motor system, as well as in association regions (for review, see Singer and Gray, 1995; Engel et al., 2001; Fries, 2009; Siegel et al., 2012). The putative functions of synchronization in the gamma-band seem to be particularly diverse, ranging from perceptual integration, stimulus selection, sensorimotor integration, movement preparation to memory formation, attention, and consciousness (Singer and Gray, 1995; Engel et al., 2001; Engel and Singer, 2001; Fries, 2005, 2009; Engel and Fries, 2010; Siegel et al., 2012). Typically, the observed amount of gamma is positively correlated with increased processing load and, thus, with the level of attention, as well as with the difficulty or integrative nature of the processing (Fries, 2009).

Crick and Koch (1990) were the first to suggest a relation between the occurrence of synchronized oscillations and consciousness. Inspired by the finding that visual stimuli can elicit synchronized oscillatory activity in the visual cortex (Gray et al., 1989), they proposed that an attentional mechanism induces synchronous oscillations in selected neuronal populations, and that this temporal structure would facilitate transfer of the encoded information to working memory. According to their view, only appropriately bound, or integrated, neuronal activity could enter short-term memory and, hence, become available for access to awareness, that is, the conscious experience of sensory signals.

In the past two decades, numerous authors have advocated a relationship between consciousness and integration of signals across neural populations. Damasio (1990) suggested that conscious recall of sensory contents requires the binding of distributed information stored in spatially separate cortical areas. Llinas and Ribary (1994) have argued that arousal (i.e., an increased level of consciousness) and awareness result from the activation of nonspecific thalamocortical circuits which serve to bind sensory contents encoded by specific thalamocortical loops. Newman and Baars (1993) have suggested that unspecific and specific thalamocortical systems interact to form a global workspace, where bound contents become globally available and, hence, lead to the emergence of conscious states. A related view has been expressed by von der Malsburg (1997) who postulated that the degree of consciousness attributable to a whole cognitive system may covary with the degree of coherence, or functional coupling, between different neural subsystems. Tononi and Edelman (1998) have suggested that consciousness requires binding or, in their terms, re-entrant interactions between systems performing perceptual categorization and brain structures related to working memory and action planning. Early on, we have suggested that coupled neuronal oscillations may underlie the large-scale interactions supporting consciousness (Engel et al., 1999; Engel and Singer, 2001), a notion that will be further elaborated in the remainder of this chapter.

Several authors have emphasized that interaction of bottom-up and top-down processing may be a prerequisite for the emergence of conscious states. Grossberg (1999) has proposed that conscious states result from a resonance, or match, between top-down priming and bottom-up processing of incoming information, which allows learning and binding of information into coherent internal representations. Similarly, on the basis of the global workspace hypothesis, Dehaene et al. (2006) have argued that consciousness requires large-scale reverberating interactions involving frontoparietal networks that implement top-down processing. Lamme (2003, 2006) has also emphasized the large-scale nature

of neural processing required for consciousness and has proposed that recurrent processing between high- and low-level areas has to occur. This notion is also a key ingredient of the integrated information theory of consciousness (Tononi and Koch, 2008).

Taken together, all these authors seem to imply (i) that consciousness results from a cooperative process in a highly distributed network, and is not attributable to a single brain structure or process; and (ii) that only coherent activity, resulting from the operation of integrative mechanisms, could become functionally salient, causally efficacious and globally available, and, thus could lead to the emergence of conscious mental states and their respective behavioral manifestations. The critical point is that dynamic integration may not only help to achieve the "unity" of consciousness but may also gate the access to awareness and, hence, turn subconscious information into conscious mental contents. In what follows, we will discuss evidence that demonstrates the relevance of dynamic coupling by coherent neuronal oscillations to key processes that seem to be required for the emergence of conscious mental states.

DYNAMIC COUPLING BY NEURAL COHERENCE

Originally, the notion that temporal correlations might be important for dynamic integration of neural signals was proposed in the context of perceptual processing and integration of object features (von der Malsburg, 1994; Singer and Gray, 1995). This hypothesis has been strongly motivated by the insight that perception, like most other cognitive functions, is based on highly parallel information processing involving large neural assemblies spread across numerous brain areas. According to this hypothesis, synchronization of spatially separate neurons is a key principle of brain function since it allows the formation of functionally coherent activity patterns supporting particular cognitive functions.

A critical assumption in this framework is that synchrony in a distributed network of neurons is subject to both bottom-up and top-down influences (Engel et al., 2001; Engel and Fries, 2010). Thus, temporal correlations might subserve a dual function in such networks. On the one hand, synchrony could permit the rapid and reliable selection of perceptually or behaviorally relevant information. Because precisely synchronized discharges have a high impact on the respective postsynaptic cells, the information tagged by such a temporal label could be rapidly and preferentially relayed to other processing centers (Fries, 2005, 2009). On the other hand, formation of assemblies is not only constrained by stimulus-related information, but much more strongly by the intrinsic dynamics of the system (Engel et al., 2001, 2013). Factors like attention, predictions, or previous knowledge are often crucial for the processing and integration of sensory information. Therefore, we assume that temporally coordinated signals from other regions of the network can have a strong impact on sensory regions by modulating the local neural dynamics in a top-down manner (Engel et al., 2001; Bastos et al., 2015a,b). Such modulatory top-down signals implementing dynamic contextual predictions could arise, for instance, from regions involved in memory and action planning. Thus, both bottom-up routing of signals and top-down modulation of processing call for highly selective neuronal communication that is thought to be mediated by correlated oscillatory fluctuation of the activity of the cell populations involved (Engel et al., 2001; Fries, 2005, 2009; Bastos et al., 2015a,b).

As mentioned already, the basic phenomenon of correlated oscillatory activity is well documented for a wide range of neural systems and species. Numerous studies have shown that neurons in both cortical and subcortical centers of the visual system typically respond with fast oscillatory activity that can be synchronized with precision in the millisecond range (for review, see Singer and Gray, 1995; Engel et al., 2001). Direct support for the relevance of oscillatory coupling for perceptual integration comes from studies showing that neuronal synchronization in the cortex depends on the stimulus configuration. In the visual systems of cats and monkeys, it could be demonstrated that spatially separate cells show strong synchronization only if they respond to the same visual object. However, if responding to two independent stimuli, the cells fire in a less correlated manner or even without any fixed temporal relationship (Gray et al., 1989; Kreiter and Singer, 1996; Castelo-Branco et al., 2000). The experiments demonstrate that Gestalt criteria such as continuity or coherent motion, which have psychophysically been shown to support perceptual grouping, are important for the establishment of synchrony among neurons in the visual cortex. In humans, coherent visual stimuli have been shown to lead to augmentation of gamma-band power, reflecting enhanced neural interactions in this frequency range (Siegel et al., 2007).

Beyond the visual modality, coherent oscillatory activity has also been observed in the auditory (Brosch et al., 2002; Debener et al., 2003), somatosensory (Bauer et al., 2006), and olfactory (Wehr and Laurent, 1996) systems. Moreover, synchrony has been implicated in processes such as attentional selection (Fries et al., 2001; Gross et al., 2004; Buschman and Miller, 2007; Gregoriou et al., 2009, 2012; Bosman et al., 2012; Grothe et al., 2012), sensorimotor integration (Roelfsema et al., 1997; Brovelli et al., 2004; Womelsdorf et al., 2006), decision making (Donner et al., 2009), movement preparation (Sanes and Donoghue, 1993; Baker et al., 1999; Jenkinson et al., 2012), and memory formation (Fell et al., 2001; Csicsvari

et al., 2003; Gruber and Müller, 2005; Herrmann et al., 2004; Jensen and Lisman, 2005). Collectively, these data provide strong support for the hypothesis that synchronization of neural signals is a key mechanism for integrating and selecting information in distributed networks (Singer and Gray, 1995; Engel et al., 2001). What they suggest is that coherence of neural signals allows to set up highly specific patterns of effective neuronal coupling, thus enabling the flexible and context-dependent binding, the selection of relevant information and the efficient routing of signals through processing pathways (Salinas and Sejnowski, 2001; Fries, 2005; Womelsdorf et al., 2007).

RELATION OF OSCILLATIONS AND COHERENCE TO LEVELS OF CONSCIOUSNESS

Evidence from both animal and human experiments suggests that neural synchrony may be of critical relevance for the emergence of consciousness in at least two respects. First, oscillations of different frequency ranges may relate to the buildup of conscious states and, thus, to changes in the *level* of consciousness; second, oscillations may facilitate the selection of sensory information for access to awareness and, thus, have an impact on the *contents* of consciousness. In this section, we discuss the relation between oscillatory activity in specific frequency ranges and the level of consciousness. Substantial evidence demonstrates that state changes leading to alterations in the level of consciousness are associated with variations in oscillatory signals and large-scale neural coherence. Well-studied examples include changes in arousal resulting from sleep-waking cycles and transitions between wakefulness and anesthesia.

It has long been known that the frequency ranges of cortical oscillatory activity are modulated with arousal (Moruzzi and Magoun, 1949). More recent studies have clearly established that high-frequency oscillations are particularly prominent during epochs of higher vigilance and that synchronization across neuronal populations increases during states characterized by arousal (for review, see Urbano et al., 2012). Thus, experiments in rats (Franken et al., 1994; Brankačk et al., 2012) and cats (Steriade et al., 1996; Steriade, 1997) have shown that gamma-band synchronization is enhanced during rapid-eye movement (REM) sleep and waking compared to deep sleep. In addition, REM sleep is associated with enhanced theta-gamma cross-frequency coupling (Brankačk et al., 2012). Moreover, electrical activation of the midbrain reticular formation (one of the structures responsible for change of vigilance states) has been shown to induce a shift from low to high oscillation frequencies and an increase of stimulus-induced synchronization in the visual cortex (Munk et al., 1996). It seems likely that the increasing availability of faster coupling patterns reflects an enhanced readiness for specific neural communication in states of higher arousal.

As in other mammals, cortical activity in humans shows an enhancement of high-frequency EEG components during states of increased arousal, sleep-waking transitions and REM sleep. Several studies using EEG or magnetoencephalography (MEG) in healthy humans indicate that in the awake state and during REM sleep, gamma-band frequencies are present which are diminished during deep sleep (Llinás and Ribary, 1993, 1994; Uchida et al., 2001; Le Van Quyen et al., 2010). The similarity of high-frequency activity during REM phases and the awake state suggests that, in both cases, synchrony in this frequency band correlates with similar processes leading to consciousness, which are just differently modulated by external stimulation (Llinás and Ribary, 1994). Similar evidence for high-frequency cortical activity related to arousal is available from intraoperative human recordings (Moll et al., 2009). It should be noted, however, that bursts of gamma-band activity have also been observed to precede states of unconsciousness during epileptic seizures (Worrell et al., 2004). This suggests that high-frequency oscillations *per se* are not sufficient to implement states of increased arousal. As further discussed below and in the next section, specific coupling of such oscillations across neural populations seems required.

Anesthesia provides a highly interesting setting for studying physiological mechanisms underlying consciousness, albeit with the caveat that the mechanisms of drug-induced modulation of levels of consciousness may only partly correspond to those involved in state changes without medication. A substantial number of studies have addressed changes of oscillatory activity during anesthesia (for review, see e.g., Brown et al., 2010; McCarthy et al., 2012).

Using propofol-induced anesthesia as a model, a recent study has addressed the interplay between incoming sensory information and state-dependent intrinsic large-scale cortical dynamics (Supp et al., 2011). Intrinsic cortical dynamics modulates the processing of sensory information and therefore may be critical for conscious perception. In a recent study, this hypothesis was tested by EEG recording during stepwise drug-induced loss of consciousness in healthy human participants (Figure 3.1). It was observed that progressive loss of consciousness was tightly linked to the emergence of a hypersynchronous cortical rhythm in the alpha-frequency range (8–14 Hz). This drug-induced ongoing alpha activity was widely distributed across frontal cortex (Figure 3.1A and B). Stimulus-related responses to median nerve stimulation comprised an early component in primary somatosensory cortex and a late component also

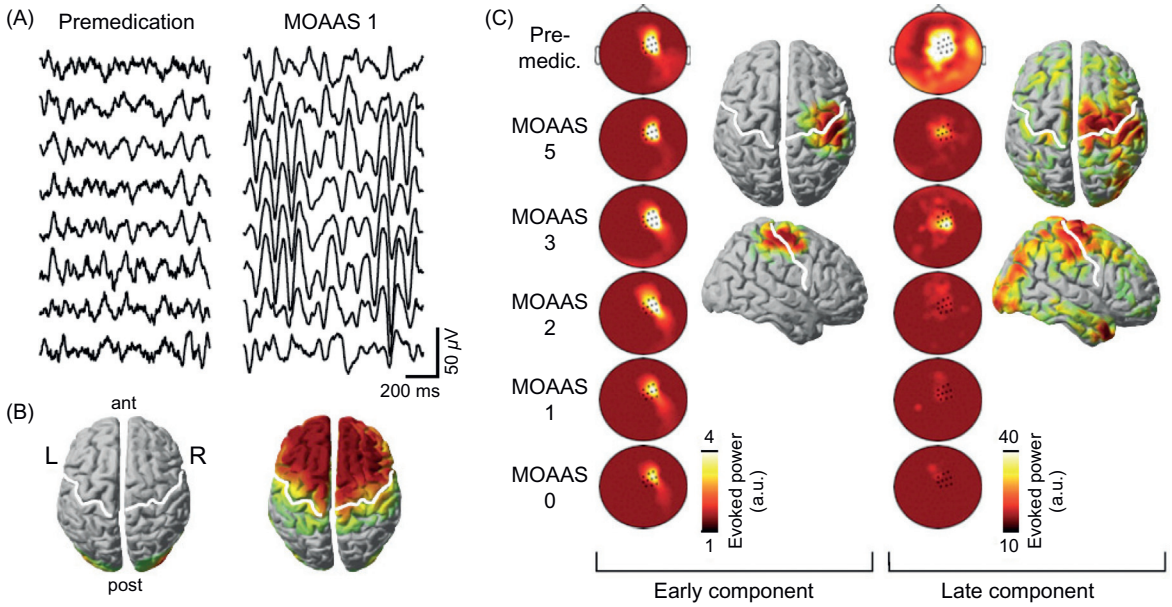

FIGURE 3.1 Impairment of conscious access by hypercoherent oscillations under propofol anesthesia. (A) EEG was recorded before drug application (premedication) and during intravenous administration of increasing levels of propofol. Shifts in the participant's state of sedation induced by a given drug level were quantified by a standardized rating scale (MOAAS) ranging from 5 (fully conscious) to 0 (unresponsive). Single participant's EEG traces exemplify the emergence of an alpha-frequency rhythm during loss of consciousness. (B) As compared to premedication (left), alpha power strongly increased in frontal brain areas during loss of consciousness (right, MOAAS 1). (C) During each block, participants received electrical median nerve stimuli at their left wrist. Source reconstruction revealed an early response component largely confined to contralateral primary somatosensory cortex. In addition, a late response component was observed that also involved right temporal and parietal brain areas. The topographies display the modulation of the early (left) and late (right) components with increasing sedation, showing a persistent early response across all sedation levels but a breakdown for the late component. *Source: Modified from Supp et al. (2011).*

involving temporal and parietal regions. During progressive sedation, the early response was maintained, whereas the late response was reduced and eventually vanished (Figure 3.1C). The antagonistic relation between the late sensory response and ongoing alpha activity held for constant drug levels on the single-trial level. Specifically, the late response component was negatively correlated with the power and long-range coherence of ongoing frontal alpha activity. These results suggest that blocking of cortical communication by hypersynchronous ongoing activity may be a key mechanism for the loss of consciousness under anesthesia.

Other studies have also related altered oscillatory cross-frequency coupling to the loss of consciousness under anesthesia. Under propofol-induced anesthesia, the emerging alpha-range rhythm can show different modes of coupling to slow (<1 Hz) oscillations that seem to involve spatially different neuronal networks (Mukamel et al., 2014). In conclusion, consciousness may depend on a delicate balance between locally specific information processing and the coupling structure of intrinsic global cortical dynamics (Engel et al., 2013). Under anesthesia, abnormal low-frequency coupling seems to be one possible mechanism that prevents specific large-scale interactions needed for processing and selection of information. In the same vein, excessive unspecific synchrony seems to relate to the loss of consciousness during epileptic seizures (Bartolomei and Naccache, 2011).

RELATION OF OSCILLATIONS AND COHERENCE TO CONTENTS OF CONSCIOUSNESS

A relation of oscillatory activity to changes in the contents of conscious states is suggested by studies that have applied bistable or ambiguous perceptual conditions while recording oscillatory coupling across neural assemblies. Early evidence was obtained in experiments in which activity was recorded from the visual cortex of awake cats under conditions of binocular rivalry (Fries et al., 1997, 2002). Binocular rivalry is a particularly interesting case of dynamic response selection that occurs when the images in the two eyes are incongruent and cannot be fused into a coherent percept. In this case, only signals from one of the two eyes are selected and perceived at any given time, whereas those from the other eye are suppressed. In normal subjects, perception alternates between the stimuli presented to left and right eye, respectively. Obviously, this experimental situation is particularly

suited for studying the basis of consciousness, because neuronal responses to a given stimulus can be studied either with or without an accompanying awareness (Crick and Koch, 1990; Engel et al., 1999).

Fries and colleagues (1997, 2002) tested the hypothesis that response selection in early visual areas might be achieved by modulation of oscillatory neuronal coupling. These measurements were performed in awake strabismic cats with electrodes chronically implanted in primary and secondary visual cortex. The animals were subjected to dichoptic visual stimulation, that is, patterns moving in different directions were simultaneously presented to the left and the right eye, respectively. Due to the strabismus, one eye was dominant, that is, that eye's stimulus was perceived when equal contrast stimuli were given to both eyes. The results obtained with this experimental approach showed that visual cortical neurons driven by the dominant and the suppressed eye, respectively, did not differ in the strength of their firing rate response to visual stimulation. They showed, however, profound differences with respect to their synchronization. Neurons supporting the dominant percept increased their synchrony, whereas cells processing the suppressed visual pattern decreased their coupling. This effect was observed specifically in the gamma-frequency band (Fries et al., 1997, 2002). These studies clearly suggest that changes in the contents of consciousness, as evident during binocular rivalry, are associated with fluctuations in neural coupling. Studies on bistable perception in monkey visual cortex also support these conclusions (Wilke et al., 2006).

In humans, studies using ambiguous stimulus settings also suggest a clear relation between intrinsic fluctuations of dynamic coupling and changes in the perceptual state. Doesburg and coworkers (2005) recorded EEG during binocular rivalry and reported that increases in gamma-band coupling preceded the subjects' perceptual switches. Using a dynamic apparent motion stimulus, Rose and Büchel (2005) showed that perceptual changes were associated with fluctuations of gamma-band coupling across the cerebral hemispheres. In a similar vein, fluctuations in beta-band coupling have been shown to predict the perceptual state in an ambiguous audio-visual paradigm (Hipp et al., 2011) (Figure 3.2). Neuronal activity was reconstructed from the EEG of human subjects presented with two moving bars that could be perceived either as bouncing or passing (Figure 3.2A). Long-range beta-band coherence between frontoparietal and visual cortex was observed during the processing of the ambiguous motion stimulus, which was enhanced for about 1 s around the time of bar overlap (Figure 3.2B). Coherence was enhanced in a widespread cortical network including bilateral frontal eye fields, posterior parietal cortex and motion-sensitive visual areas (Figure 3.2C). Importantly, the beta-band coherence within this network was found to predict whether the subjects perceived the bars as bouncing or passing (Figure 3.2D). Taken together, these studies strongly suggest that intrinsically generated fluctuations in neural coupling during the processing of ambiguous stimuli are relevant for controlling changes in the subjects' conscious perceptual contents.

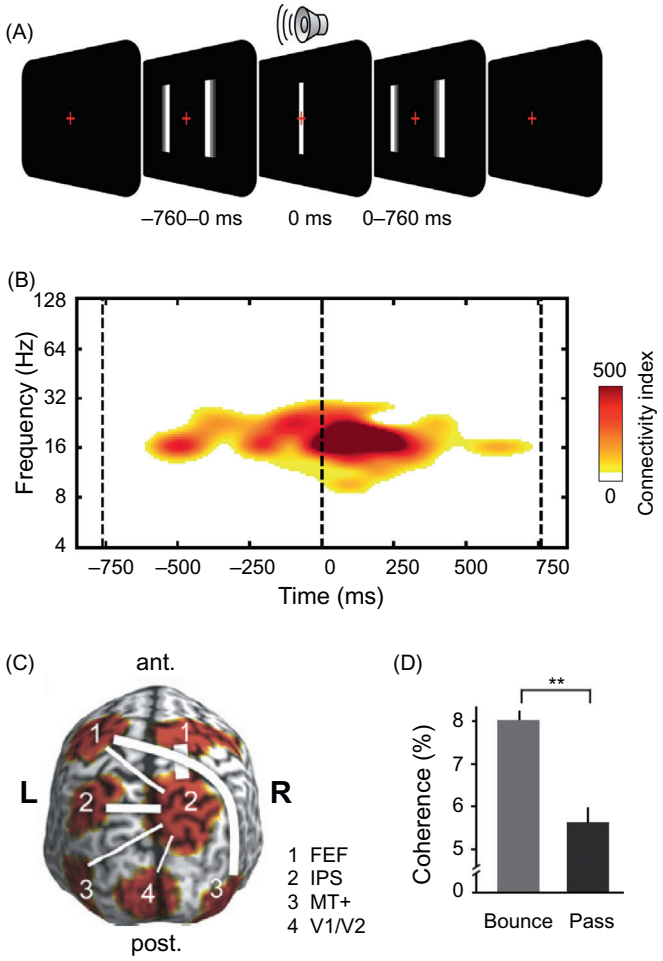

FIGURE 3.2 Selection of conscious contents by coherent oscillations in bistable perception. (A) While EEG was recorded, participants watched a screen on which two bars approached, briefly overlapped, and moved apart again. At the time of overlap of the bars, a brief click sound was played. Participants perceived this stimulus either as two bouncing or passing bars, with the percept spontaneously changing across trials. (B) Around the time when the stimulus became perceptually ambiguous, beta-band coherence (15–30 Hz) was enhanced. (C) Beta-band coupling (white lines indicate coherence strength) occurred in a large-scale cortical network including bilateral frontal eye fields (FEF), posterior parietal cortex (IPS), visual areas involved in motion processing (MT+) as well as early visual cortex (V1/V2). (D) The strength of beta-band coupling predicted the subjects' percept: stronger beta-band coherence predicted perceiving the bars as bouncing, whereas weaker coherence predicted the percept of passing bars. *Source: Modified from Hipp et al. (2011).*

Evidence for a relation between oscillations and conscious processing has also been obtained in studies using masking paradigms. In a study comparing the processing of visible and invisible word stimuli in a delayed match-to-sample task, stimulus visibility was found to be associated with enhanced long-range synchronization in the gamma-band (Melloni et al., 2007). Combining a similar paradigm with intracranial recordings in epilepsy patients, another study has observed enhanced beta-band coherence for visible compared to invisible stimuli (Gaillard et al., 2009). A recent MEG study has reported that conscious word-form perception correlates with alpha-band suppression in occipito-temporal cortex (Levy et al., 2013).

As stated above, we assume that conscious awareness requires a mechanism that selects relevant information and enhances its impact on subsequent processing stages. Evidently, attention is of particular importance for the selection of signals and top-down modulation of sensory processing. Therefore, investigation of attentional mechanisms seems highly relevant for understanding consciousness (Engel and Singer, 2001; Dehaene et al., 2006). Strong evidence for attentional modulation of neural synchrony is provided by experiments in behaving monkeys. One of the earliest studies (Steinmetz et al., 2000) investigated cross-modal attentional shifts in monkeys that had to direct attention to either visual or tactile stimuli that were presented simultaneously. Synchrony among neurons in somatosensory cortex depended strongly on the monkey's attention. If the monkey shifted attention to the visual task, temporal correlations typically decreased among somatosensory cells, as compared to task epochs during which attention was not distracted from the somatosensory stimuli.

In the visual system of monkeys, attentional effects on oscillatory synchrony were first investigated by recordings from area V4 (Fries et al., 2001). In this study, two stimuli were presented simultaneously on a screen, one inside the receptive fields of the recorded neurons and the other nearby. The animals had to detect subtle changes in one or the other stimulus. If attention was shifted towards the stimulus processed by the recorded cells, there was a marked increase in local synchronization. This finding was confirmed by Taylor and coworkers (2005) using a demanding visual task that required monkeys to track changes in an object's shape over time. In both studies, the attentional effects were observed specifically in the gamma-frequency band. A recent study has provided evidence that this attentional enhancement of synchrony in local populations in area V4 strongly involves the locking of putative inhibitory interneurons (Vinck et al., 2013). Recent studies in monkeys have also demonstrated an attention-specific enhancement of long-range gamma-band coupling between V4 and V1 (Figure 3.3) (Bosman et al., 2012; Grothe et al., 2012) and between V4 and the frontal eye field (Gregoriou et al., 2009, 2012). These data clearly demonstrate that gamma-band coupling is not only relevant for local processing, but also for long-range functional communication (Fries, 2005, 2009).

Buschman and Miller (2007) provided evidence that beta-band activity can also be associated with attentional selection. The authors trained monkeys to detect a target amongst a set of distractors in either a pop-out or a serial search regime. Analysis of coherence between frontal and parietal signals revealed that interactions occurred predominantly in the beta-band during search, that is, in the condition involving a strong endogenous top-down processing component. In contrast, coupling was more prominent in the gamma-band in the pop-out condition, where performance primarily depended on the saliency of the target stimulus. These data support the hypothesis that endogenously driven top-down attention may be associated with large-scale communication in lower frequency bands, whereas coupling may occur at higher frequencies when bottom-up signals need to be conveyed (Engel and Fries, 2010).

A relation between attention and modulation of synchronized oscillations is also well established for the human brain. Evidence from EEG and MEG studies shows that high-frequency oscillations are enhanced by attention in the human visual system (e.g., Tallon-Baudry et al., 2005; Kranczioch et al., 2006, 2007; Vidal et al., 2006; Engell and McCarthy, 2010; Müsch et al., 2014). Similar evidence is available for the auditory system (e.g., Tiitinen et al., 1993; Debener et al., 2003) and the tactile system (e.g., Bauer et al., 2006). In all these studies, attention was observed to specifically enhance gamma-band activity. An MEG study also demonstrated that attention selectively modulates large-scale coupling of oscillatory signals in the human brain (Siegel et al., 2008). Subjects were simultaneously presented with two weak motion stimuli in the left and right visual hemifield. At the beginning of each trial, a cue instructed subjects to attend to one of the two stimuli and to assess its motion direction. The authors combined MEG with source reconstruction to characterize the phase coherence between motion-sensitive visual areas, the posterior parietal cortex and the frontal eye fields. Attention selectively enhanced gamma-band phase coherence between these regions in the hemisphere that processed the attended stimulus. This enhancement in the gamma-band was accompanied by a reduction of coherence in the alpha- and beta-range. Other findings also suggest an important role for lower frequencies. One MEG study (Gross et al., 2004) investigated the neuronal basis of the attentional blink, that is, a transient reduction of

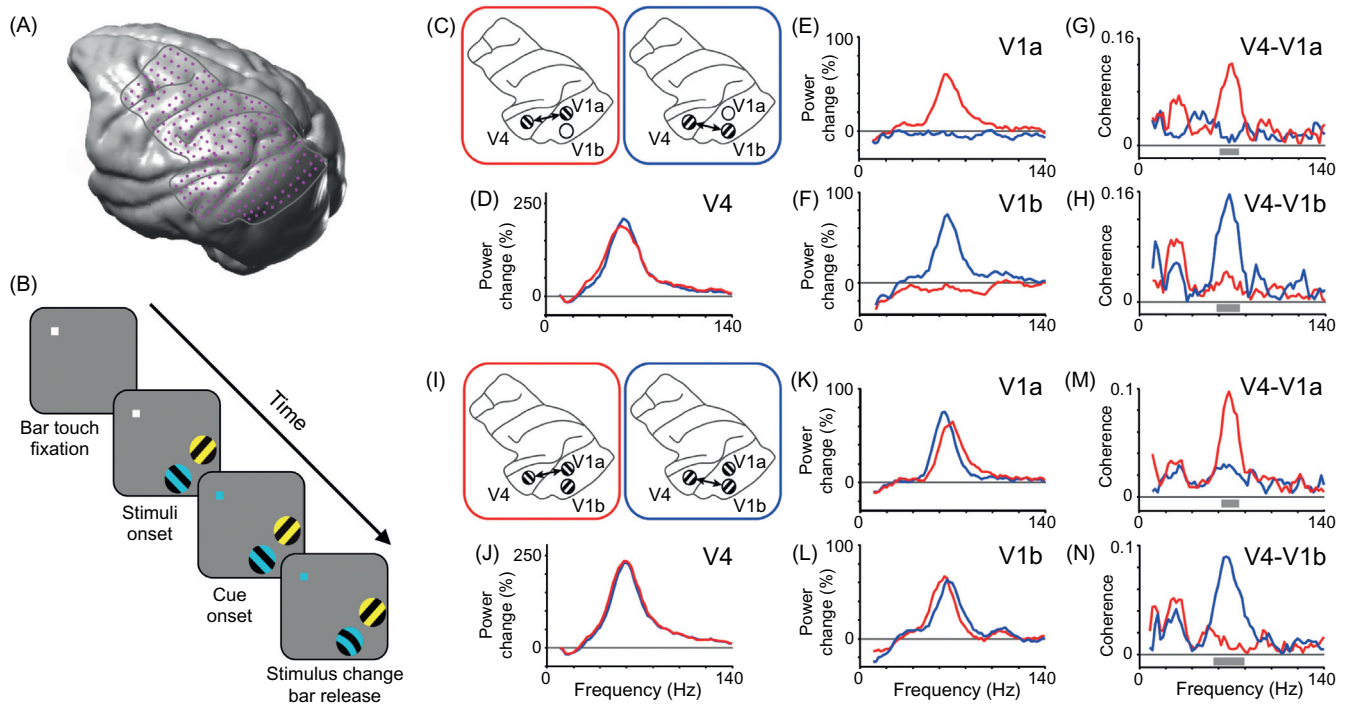

FIGURE 3.3 Attentional selection through specific inter-areal gamma-band synchronization. (A) Rendering of a monkey brain with the locations of 252 electrodes in an electrocorticographic grid. (B) Selective attention task. A yellow and a blue tinted grating were presented, with random color assignment. The fixation point assumed the color of one of the stimuli, thereby cueing this stimulus to be behaviorally relevant (target) and the other to be irrelevant (distractor). Up to several seconds later, either the target or the distractor transiently changed shape, and the monkey was rewarded for releasing the bar upon target changes. (C–N) Example triplet recording of one V4 and two V1 sites, using data between cue presentation and stimulus change. (C) Illustration of the two single-stimulus conditions, corresponding to the red/blue lines in (D–H). Both conditions induced gamma-band activity in V4, but only the condition labeled red (blue) activated site V1a (V1b). The double arrow illustrates the presumed pattern of interaction between neuronal groups. (D–F) Spectral power changes (relative to pre-stimulus baseline) for the indicated sites. (G–H) Coherence spectra for the indicated site pairs. Gray bars indicate frequencies with a significant effect. Note that there was a specific interaction, as reflected in enhanced gamma-band coherence, between the V4 site and the respective site driven in V1. (I) Illustration of the two attention conditions with simultaneous presentation of both stimuli and attentional selection of one or the other stimulus, corresponding to the red/blue lines in (J–N). The arrows indicate the selective interaction of the V4 site with the behaviorally relevant V1 site. (J–L) Spectral power changes (relative to pre-stimulus baseline) for the indicated sites. (M–N) Coherence spectra for the indicated site pairs. Importantly, there was a specific attention-related enhancement of gamma-band coherence between the V4 site and the attended site in V1. *Source: Modified from Bosman et al. (2012).*

attention which often occurs if more than one target has to be processed in a series of rapidly presented stimuli. When subjects successfully detected target letters in a rapid visual stream of letters, coherent beta-band oscillations were enhanced between MEG sensors overlying the temporal cortex, prefrontal cortex and posterior parietal cortex. Thus, fluctuations in the strength of large-scale beta-band coherence may reflect fluctuations in visual attention that, in turn, cause fluctuations in behavioral performance.

Taken together, the studies reviewed above clearly suggest that neural oscillations and local as well as long-range coupling of oscillatory signals are highly relevant for attentional selection. Hence, it can be argued that these mechanisms may be highly relevant for regulating the access of signals to the conscious workspace. However, it should be mentioned that the relation between attention and consciousness is controversial (Tallon-Baudry, 2011). While some authors argue that attention (at least in many cases) may be a prerequisite for access of signals to consciousness (Newman and Baars, 1993; Engel and Singer, 2001; Dehaene et al., 2006), others have proposed that processes underlying attention and consciousness may operate in a more parallel fashion (Lamme, 2003; Koch and Tsuchiya, 2007; Tallon-Baudry, 2011; see also Chapter 5). This is supported by experiments that have attempted to dissociate attentional selection and conscious access. In recent studies by Wyart and Tallon-Baudry (2008, 2009), subjects were cued to attend to the left or to the right hemifield, and were then presented with a faint oriented grating, either on the attended or unattended side. On each trial, subjects were asked whether they had consciously experienced the stimulus or not. Each stimulus can therefore be classified,

on the one hand, as attended or unattended and, on the other hand, as consciously perceived or not. Interestingly, these two cognitive functions were expressed separately in distinct sub-frequency ranges within the gamma range.

Apparently, further work will be needed to clarify the relation between attention and consciousness. The data on bistable perception and on stimulus masking discussed above suggest that selection of contents for access to awareness is also possible without strong involvement of attentional control. Thus, communication by specific coupling of oscillatory signals may provide a rather generic mechanism which may come into play in both attentional and non-attentional forms of signal selection.

Most accounts on the neural mechanisms of consciousness assume that awareness is necessarily associated with some form of short-term memory and that conscious contents need to be maintained in working memory (Crick and Koch, 1990; Tononi and Edelman, 1998; Engel and Singer, 2001; Lamme, 2003; Baars et al., 2013). It had been postulated early on that coupled oscillations might not only serve for selecting relevant signals, but that the same mechanism might support working memory by transiently stabilizing, through synchrony, the relevant neuronal population (Crick and Koch, 1990). The relationship between oscillations and working memory has been the subject of a large number of studies, which have been reviewed comprehensively by other authors (see Fell and Axmacher, 2011; Lisman and Jensen, 2013; Roux and Uhlhaas, 2013). These studies demonstrate the relevance of oscillatory signals in multiple frequency ranges for working memory processes. In particular, theta-band oscillations and gamma-band oscillations have been shown to be relevant for temporally structuring and maintaining working memory contents (Jensen and Lisman, 2005; Lisman and Jensen, 2013).

Taken together, these data demonstrate that processes relevant to selecting and maintaining the contents of conscious mental states can be associated with specific changes in neural synchrony, thus supporting the proposal that coherence in neuronal assemblies may be a necessary condition for the occurrence of awareness (Crick and Koch, 1990; Engel et al., 1999; Engel and Singer, 2001). The data suggest that the selection of signals for access to awareness is not only dependent on bottom-up factors, but also strongly constrained by intrinsically generated large-scale dynamic patterns, which result from reentrant interactions of prefrontal, premotor, memory, and limbic regions with sensory brain areas. As suggested by Tononi and Edelman (1998), large-scale assemblies activated by such interactions may constitute a "dynamic core" that could control the access of signals to awareness and provide the substrate for a global workspace (Newman and Baars, 1993; Dehaene et al., 2006; Dehaene and Changeux, 2011).

CONCLUSIONS: COHERENCE AND CONSCIOUSNESS

The studies reviewed above strongly suggest that the temporal dynamics in neuronal activity may be critical for the emergence of conscious mental states. As discussed above, specific changes in oscillatory signals and in coherence of population activity may relate to regulation of the *level* of consciousness. Moreover, coherence may serve for the integration, structuring, selection, and communication of relevant signals. Therefore, changes in the pattern of neuronal coherence, both locally and across regions, may lead to changes in the *contents* of consciousness.

According to our view, both aspects of consciousness critically depend on dynamic coupling modes that are intrinsically generated in large-scale networks supporting consciousness and not driven by external events (Engel et al., 2013). An important point to be mentioned is that large-scale coherence is not equivalent to uniform synchrony. Indeed, global synchronization is associated with a low complexity of neural interactions which, as observed in deep sleep or epilepsy, is counterproductive to consciousness. As discussed above, drug-induced anesthesia seems associated with excessive unspecific coupling in low-frequency ranges that prevents specific large-scale interactions and, thus, presumably leads to a breakdown of the global workspace. Our proposal is summarized in the remainder of this section.

As mentioned above, arousal is characterized by an enhanced precision of neuronal synchrony and a shift to higher oscillation frequencies, indicating that thalamocortical systems change from large-scale synchrony into states with more specific, regionalized temporal patterning. We propose that central activating systems may act to modify, in a task- and context-dependent manner, the efficacy of dynamic integration mechanisms. Arousal may lead to enhanced readiness of thalamocortical circuits for specific coupling. By changing both the spatial range and the specificity of neuronal interactions arousal mechanisms, thus, contribute to more specific information processing.

As an additional prerequisite, consciousness requires the completion of basic sensory processing steps, including detection and binding of object features. These processes seem critical for structuring the contents of conscious states. We suggest that this may be implemented in the temporal domain. Synchrony as an integrative mechanism allows establishing specific relationships between neural discharges which are, in principle, independent of spatial proximity or direct neuronal connections. Synchrony is not only determined by the stimulus, but is modulated in a context- and task-dependent way by cooperative interactions within the cortical network.

Current awareness theories assume that not all results of sensory processing contribute to consciousness. Rather, as an additional step, part of the information is subjected to a selection process that gates access to awareness. We propose that selection can be mediated by neural synchronization, as temporally coincident signals are more easily detected by other neural assemblies than temporally dispersed signals. Only activity patterns carrying a strong temporal signature may be functionally efficacious and globally available and, therefore, such a signature may be a fundamental prerequisite for making information available to other brain centers. The selection is controlled both by bottom-up (e.g., stimulus novelty) and top-down (e.g., attention, expectancy, memory contents) influences, which can lead to competition among different assemblies and result in changes of synchrony. It should be emphasized that the notion of selection, as we have employed it here, is broader than the notion of attention.

Furthermore, coherence in neural populations may be ideally suited to promote maintenance of selected contents in working memory. Synchronized assemblies may transiently stabilize in some reverberatory state, endowing them with competitive advantage over temporally disorganized activity. This may provide the basis for working memory necessary to achieve the holding of situational context in the respective processing areas. The information carried by such assemblies during working memory states may become conscious.

Moreover, the mechanism advocated here may account for the global availability (Newman and Baars, 1993; von der Malsburg, 1997; Tononi and Edelman, 1998; Dehaene et al., 2006) of conscious information, because temporal signatures that reliably propagate across systems may be suited to establish patterns of large-scale coherence, thus enabling specific communication across different modules or systems. By the same token, our proposal could have implications for higher-order consciousness which seems to require the activation of motivation and action planning systems, episodic memory and, eventually, symbol processing capacities. With all likelihood, these faculties will require cross-system interactions that could also be mediated by coherent neural oscillations.

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CHAPTER

4

Neural Correlates of Visual Consciousness

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OUTLINE

BRAIN ACTIVITY ASSOCIATED WITH VISUAL STIMULI THAT DO NOT REACH AWARENESS

Visual stimuli that remain invisible to the observer can nevertheless influence both behavior and brain activity (though see Holender and Duscherer, 2004 for a skeptical critique). For example, words presented briefly and immediately preceding a mask cannot be seen but nevertheless subsequent responses of the observer can be primed by these masked and invisible words in a fashion related to their meaning (Marcel, 1983). This shows that the words have been processed unconsciously to the point of semantic identification. Evidence for substantial processing of visual stimuli that do not enter awareness is not restricted to words. For example, orientation-selective aftereffects can result from exposure to grating stimuli that are too fine to be consciously perceived (He and MacLeod, 2001), suggesting orientation selective but unconscious activation of visual cortex. During binocular rivalry incompatible monocular images compete for perceptual dominance. Despite complete perceptual dominance of one monocular image, sensitivity to input from the suppressed eye is only moderately (but not fully) reduced (Wales and Fox, 1970; Watanabe et al., 2004). Indeed, selective adaptation by suppressed images can be of equal magnitude as for dominant images (Blake and Fox, 1974), suggesting that information about visual stimulation may reach at least early visual areas largely unattenuated.

Such behavioral findings are consistent with measurements of brain activity associated with the presentation of visual stimuli that do not reach awareness (Figure 4.1). Activation related to features of masked and invisible stimuli (including words) can be identified in early retinotopic visual cortex (Haynes et al., 2005b; Haynes and Rees, 2005a), motion-selective areas (Moutoussis and Zeki, 2006), word-selective areas (Dehaene et al., 2001), and object-selective areas of both ventral (Moutoussis and Zeki, 2002) and dorsal (Fang and He, 2005) visual

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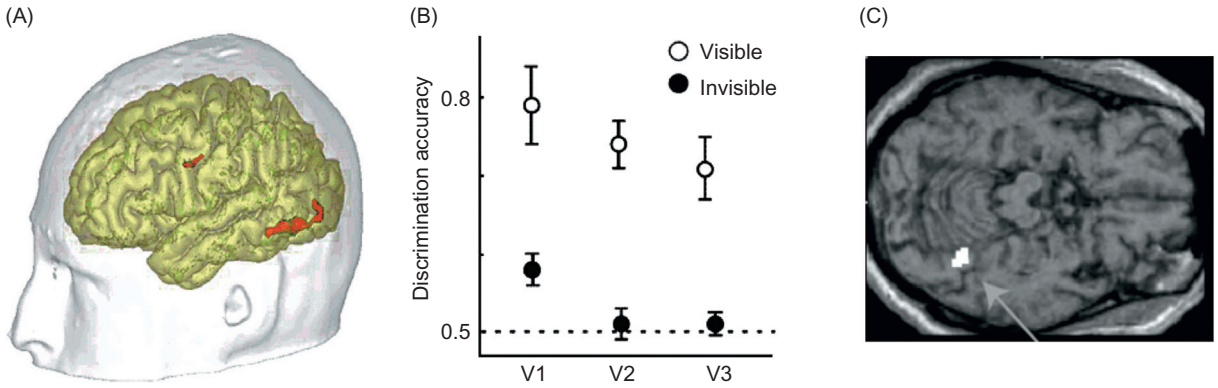

FIGURE 4.1 Activation of sensory cortices by stimuli that remain unconscious. (A) Masked and invisible words nevertheless evoke activation (shown in orange, superimposed on an anatomical image of the brain) of the fusiform gyrus. See Dehaene et al. (2001) for further details. (B) Activity measured using BOLD contrast functional MRI in human V1–V3 can be used to discriminate the orientation (right or left-tilted) of a grating stimulus. Open symbols representing mean decoding accuracy for a group of subjects (error bars one SE) for visible stimuli; closed symbols for similarly oriented stimuli rendered invisible by masking. Note that the orientation of invisible stimuli can still be discriminated at a rate significantly better than chance in human V1. See Haynes and Rees (2005a) for further details. (C) Activity in the fusiform face area evoked by a face (vs a house) stimulus presented in the neglected left hemifield of a patient with parietal neglect and left visual extinction. See Rees et al. (2002) for further details. *Source: (A) Reprinted by permission from Macmillan Publishers Ltd, Dehaene et al. (2001).*

pathways. Such observations of brain activity associated with invisible stimuli are not restricted to masking paradigms, as unconscious activation of the ventral visual pathway during the attentional blink can reflect both object identity (Marois et al., 2000) and semantic processing of visual stimuli (Luck et al., 1996; Vogel et al., 1998). Changes in an object that are not perceived due to introduction of visual flicker between changes nevertheless lead to category-specific activity in the ventral visual pathway (Beck et al., 2001) and this activity can precede conscious change detection (Niedeggen et al., 2001). Moreover, brain activation associated with unconscious perception is not confined to the cortex. Subcortical structures associated with emotional processing such as the amygdala can be activated by fearful face stimuli that are rendered invisible through masking (Morris et al., 1999), in response to the emotional content of invisible words (Naccache et al., 2005) or during suppression in binocular rivalry (Pasley et al., 2004).

Visual cortex can also be activated by stimuli that do not reach awareness in patients with damage to parietal cortex causing visual extinction. Patients with visual extinction show deficient awareness for contralesional visual stimuli, particularly when a competing stimulus is also present ipsilesionally. When visual stimuli are presented to patients with visual extinction, areas of both primary and extrastriate visual cortex that are activated by a seen left visual field stimulus are also activated by an unseen and extinguished left visual field stimulus (Rees et al., 2000, 2002; Vuilleumier et al., 2001). The unconscious processing of an extinguished face stimulus extends to face-selective cortex in the fusiform gyrus (Rees et al., 2002); and the amygdala and orbitofrontal cortex can also be activated by unseen emotional stimuli (Vuilleumier et al., 2002).

Taken together, behavioral and brain imaging techniques therefore show that visual stimuli presented outside awareness can still be subject to considerable processing in many (if not all) areas of visual cortex plus associated subcortical structures. This renders a simple division of different areas of visual cortex into those supporting conscious or unconscious processing impossible. The empirical challenge is therefore to specify what aspects of processing are special about stimuli that enter visual awareness compared to those that remain invisible. This requires the use of experimental paradigms where changes in the contents of visual awareness occur without corresponding changes in visual stimulation or behavior (Frith et al., 1999). Any consequent changes in brain activity are thus correlated directly with changes in the contents of visual awareness and not confounded by changes in unconscious processing associated with visual stimulation or behavior. Such paradigms can be classified according to the nature of the changes in awareness that result (Frith et al., 1999).

UNPROMPTED (INVOLUNTARY) CHANGES IN THE CONTENTS OF VISUAL AWARENESS

Paradigms used to study the neural correlates of changes in the contents of visual awareness can be broadly divided into those that make use of situations where the contents of visual awareness change spontaneously in the absence of any changes in the sensory

input; and deliberate changes in the contents of consciousness, associated with either a change in the context in which a stimulus is presented or associated with a deliberate act of will on the part of the observer. Examples of spontaneous changes in the contents of visual awareness include hallucinations, differences in visual perception when stimuli are presented near sensory thresholds, or ambiguous figures where the same visual input can be interpreted in several different ways.

Near-Threshold Visual Stimulation

Varying the elementary features of a visual stimulus such as its contrast, luminance or duration of presentation can be used to define a perceptual threshold at which the stimulus becomes impossible to detect or discriminate. Presenting stimuli to observers just above such a threshold can be used to compare brain responses to physically identical stimuli that either enter awareness or remain unconscious. In primary visual cortex, when a simple low contrast grating is detected then the grating evokes significantly more activity than when it does not reach consciousness (Ress and Heeger, 2003). For more complex visual stimuli, activity in the ventral visual pathway evoked by objects correlates strongly with recognition performance, and successful detection of a face stimulus presented during the attentional blink evokes activity in the "fusiform face area" (FFA), plus prefrontal cortex (Marois et al., 2004).

Conscious recognition of visually presented words is associated with both enhancement of activity in ventral visual cortex (Dehaene et al., 2001) and parietal cortical activation (Kjaer et al., 2001). Successful identification evokes an event-related negativity (Ojanen et al., 2003; Wilenius-Emet et al., 2004) and is associated with occipital magnetoencephalography (MEG) responses (Vanni et al., 1996), spontaneous electrical oscillations at a frequency near 40 Hz (Summerfield et al., 2002), and modulation of the parieto-occipital alpha rhythm (Vanni et al., 1997). This electrophysiological evidence is consistent with interactions between visual and parietal cortex mediating successful identification. However, brain activity associated with successful detection occurs very soon after the stimulus is presented, prior to the emergence of differences in activity over areas of parietal and prefrontal cortex.

The ability of observers to detect changes in a picture can also be rendered particularly difficult to detect by introducing a flicker between changes. Such physical changes to a picture that do not result in changes in visual awareness nevertheless evoke some activity in the ventral visual pathway (Beck et al., 2001; Huettel et al., 2001), and that activity can precede conscious change detection (Niedeggen et al., 2001). When the change is consciously perceived, there is further enhancement of activity in ventral visual cortical areas that represent the type of change, plus activation of parietal and prefrontal cortices (Beck et al., 2001; Koivisto and Revonsuo, 2003) that may reflect the deployment of attention (Pessoa and Ungerleider, 2004).

Ambiguous Visual Stimuli

Binocular rivalry is a popular and enduring paradigm to study the neural correlates of consciousness (Tong et al., 2006). When dissimilar images are presented to the two eyes, they compete for perceptual dominance so that each image is visible in turn for a few seconds while the other is suppressed. Such binocular rivalry is associated with suppression of monocular representations that can also be modulated by high-level influences such as perceptual grouping. Because perceptual transitions between each monocular view occur spontaneously without any change in the physical stimulus, neural correlates of the contents of awareness for each monocular percept may be distinguished from neural correlates attributable to stimulus characteristics (Figure 4.2).

Signals recorded using functional magnetic resonance imaging (fMRI) from the human lateral geniculate nucleus (LGN) exhibit such fluctuations during rivalry (Haynes et al., 2005a; Wunderlich et al., 2005). Regions of the LGN that show strong eye preference also demonstrate strongly reduced activity during binocular rivalry when the stimulus presented in their preferred eye is perceptually suppressed. Primary visual cortex shows a similar pattern of changes in activity correlated with changes in the contents of consciousness (Polonsky et al., 2000; Tong and Engel, 2001; Lee and Blake, 2002; Lee et al., 2005). In general (though see Tong and Engel, 2001) such fluctuations in activity are about half as large as those evoked by non-rivalrous stimulus alternation. This indicates that the suppressed image during rivalry undergoes a considerable degree of unconscious processing. Further along the ventral stream, responses in the FFA during rivalry are equal in magnitude to responses evoked by non-rivalrous stimuli (Tong et al., 1998). This suggests that neural competition during rivalry may have been resolved by these later stages of visual processing.

Other forms of bistable perception do not necessarily involve binocular competition. Nevertheless, a consistent finding is that these paradigms also result in activation of visual cortical structures that correspond to the attributes of whichever competing visual percept the observer currently reports (Kleinschmidt et al., 1998; Sterzer et al., 2002, 2003).

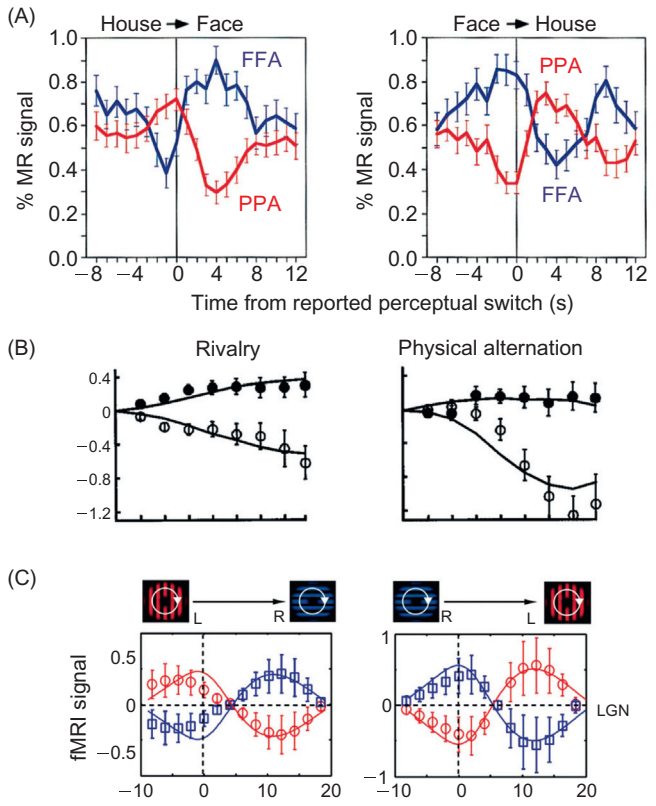

FIGURE 4.2 Fluctuations in activity in visual pathways associated with conscious perception during binocular rivalry. (A) Fusiform face area (FFA). Activity measured using functional magnetic resonance imaging (fMRI) from human FFA and parahippocampal place area (PPA) is plotted as a function of time relative to a perceptual switch from house to face (left panel) or face to house (right panel). It is apparent that activity in the FFA is higher when a face is perceived during binocular rivalry than when it is suppressed; and activity in the PPA is similarly higher when a house is perceived than when it is suppressed. For further details see Tong et al. (1998). (B) Binocular rivalry in primary visual cortex (V1). Activity measured using fMRI from human primary visual cortex is plotted as a function of time after a perceptual switch where the subsequent perception is of a high contrast stimulus (solid symbols) or low contrast stimulus (open symbols). The left hand panel plots activity following a perceptual switch due to binocular rivalry, while the right hand panel plots activity following a deliberate physical switch of monocular (non-rivalrous) stimuli. V1 activity therefore corresponds to perception during binocular rivalry and the amplitude changes are similar to those seen during physical alternation of corresponding monocular stimuli. For further details see Polonsky et al. (2000). (C) Rivalry in the lateral geniculate nucleus (LGN). Activity measured using fMRI is plotted as a function of time for voxels in the LGN selective for left eye stimuli (red symbols) or right eye stimuli (blue symbols) around the time (vertical dotted line) of a perceptual switch between left and right eye views (left panel) or right and left eye views (right panel). Reciprocal changes in signal in the different eye-selective voxels as a function of perceptual state can be readily seen. For further details see Haynes et al. (2005a). *Source: (A) Reprinted from Tong et al. (1998), with permission from Elsevier. (B) Reprinted by permission from Macmillan Publishers Ltd, Polonsky et al. (2000).*

In addition to showing that activity in ventral visual cortex is correlated with the contents of consciousness, studies of ambiguous figures have also provided evidence to suggest the involvement of areas of frontal and parietal cortex in visual awareness. These studies focused on activity that was time locked to the transitions between different perceptual states. Cortical regions whose activity reflects perceptual transitions include ventral extrastriate cortex, and also parietal and frontal regions previously implicated in the control of attention (Lumer et al., 1998). However, whereas extrastriate areas are also engaged by non-rivalrous perceptual changes, activity in frontal and parietal cortex is specifically associated with the perceptual alternations during rivalry. Similar parietal and frontal regions are active during perceptual transitions occurring while viewing a range of bistable figures (such as the Necker cube and Rubins face/vase) (Kleinschmidt et al., 1998) and during stereo pop-out, as compared to those regions active during stable viewing (Portas et al., 2000a). Although frontal and parietal areas play a prominent role in the organization of behavior, their involvement in rivalry is independent of motor report (Lumer and Rees, 1999). Activity is coordinated between ventral visual areas, parietal areas, and prefrontal areas in a way that is not linked to external motor or sensory events but instead varies in strength with the frequency of perceptual events. This suggests that functional interactions between visual and frontoparietal cortex may make an important contribution to visual awareness.

The information encoded in early visual cortex during binocular rivalry is sufficient to reconstruct the dynamic stream of consciousness. Information that is contained in the multivariate pattern of responses to stimulus features in V1–V3 and recorded using fMRI can be used to accurately predict, and therefore track, changes in conscious contents during rivalry (Haynes and Rees, 2005b). Accurate decoding is possible for extended periods of time during rivalry while awareness undergoes many spontaneous changes. Furthermore, accurate prediction during binocular rivalry can be established using signals recorded during stable monocular viewing, showing that prediction generalizes across different viewing conditions and does not require or rely on motor responses. It is therefore possible to predict the dynamically changing time course of subjective experience using brain activity alone. This raises the possibility that more complex dynamic changes in consciousness could be decoded from brain activity (see also Chapter 17 on brain–computer interfaces), though this in turn raises important questions about whether such an approach will be able to generalize to novel mental states (Haynes and Rees, 2006).

Hallucinations

A hallucination is a sensory perception experienced in the absence of an external stimulus (as distinct from an illusion, which is a misperception of an

external stimulus induced by context; see below). Hallucinations therefore dissociate neural processing associated with visual awareness from sensory stimulation, and are typically (though not exclusively) associated with damage to the visual system or psychiatric disorders. Patients with damage to the early visual system who experience hallucinations of color, faces, textures, and objects exhibit activity in functionally specialized areas of visual cortex corresponding to the contents of their hallucinations (Ffytche et al., 1998). Similarly, patients with schizophrenia who experience visual and auditory hallucinations show activity in modality-specific cortex during hallucinatory episodes (Silbersweig et al., 1995; Oertel et al., 2007). Thus, changes in the content of visual awareness are correlated with content-specific modulation of visual cortex activity.

Summary

Common to these experimental paradigms are spontaneous changes in visual experience that are not accompanied by corresponding changes in visual input. Accordingly, neural activity correlated with the contents of consciousness can be dissociated from that associated with unconscious sensory processing. Both primary visual cortex and higher areas of the visual system show changes in activity strongly correlated with changes in the contents of visual awareness. In addition, changes in the contents of visual awareness associated with bistable perception are associated with time-locked activation of dorsolateral prefrontal and parietal cortex, implicating a network of cortical structures in visual awareness.

DELIBERATE CHANGES TO THE CONTENTS OF VISUAL AWARENESS

The second major group of experimental paradigms used to investigate visual awareness employ situations where deliberate changes are made either to the type of visual stimulation (e.g., the temporal or spatial context in which a stimulus is presented, giving rise to visual illusions) or where visual stimulation is constant but top-down signals associated with attention or imagery are varied.

Illusions

In contrast to hallucinations, illusions are misperceptions of external stimuli that are represented in awareness in an incorrect fashion. The content of the illusory perception typically depends on the context in which it occurs. For example, when a moving grating is divided by a large gap, observers report seeing a moving "phantom" in the gap and there is enhanced activity in the locations in early retinotopic visual cortex that correspond to the visual field location where the illusion is perceived (Meng et al., 2005). Moreover, when phantom-inducing gratings are paired with competing stimuli that induce binocular rivalry, spontaneous fluctuations in conscious perception of the phantom occur together with changes in early visual activity. Similarly, V1 activation can be found on the path of apparent motion (Muckli et al., 2005) and is associated with strengthened feedback connections to that retinotopic location from cortical area V5/MT (Sterzer et al., 2006).

When a featureless achromatic target is placed on a textured pattern and steadily viewed in peripheral vision, after a few seconds it seems to fill-in with the surrounding texture, similar to the perceptual experience of patients with scotomas from damage to the visual pathways. Signals associated with such a target are reduced (but not entirely abolished) in contralateral visual cortex when it becomes invisible (Mendola et al., 2006; Weil et al., 2007), consistent with involvement of primary visual cortex in generating such an "artificial scotoma" and with earlier findings that long-range color filling-in is also associated with activity in primary visual cortex (Sasaki and Watanabe, 2004).

Primary visual cortex is also implicated in a number of other illusions (Figure 4.3). For example, when two objects subtending identical angles in the visual field are made to appear to be different sizes by changing the particular three-dimensional context, the spatial extent of activation in V1 reflects the perceived rather than actual angular size of the objects (Murray et al., 2006). These data thus show a rather close

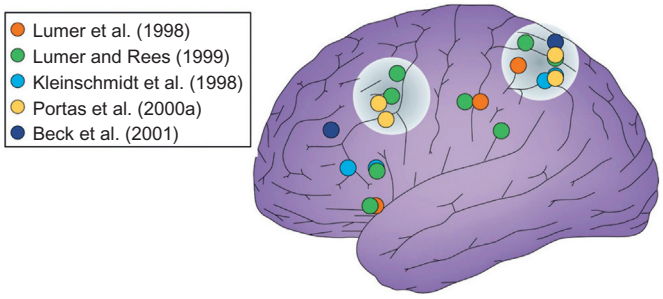

FIGURE 4.3 Parietal and prefrontal correlates of perceptual awareness. Foci of parietal and prefrontal activity measured using fMRI and associated with switches in the contents of consciousness independent of changes in physical stimulation are plotted on an anatomical brain image in a standard stereotactic space. Studies shown identify the neural correlates of perceptual switches during rivalry (Lumer et al., 1998; Lumer and Rees, 1999), during bistable perception generally (Kleinschmidt et al., 1998), associated with stereo pop-out (Portas et al., 2000a) or change detection (Beck et al., 2001). Clustering of activated foci (white circles) is apparent in superior parietal and dorsolateral prefrontal cortex.

correspondence between either the level or spatial extent of V1 activation and the perceived phenomenal properties of the visual world. Such a correspondence between V1 activity and the contents of visual awareness extends to cross-modal influences on visual perception. Irrelevant auditory stimulation can lead to illusory perception of a single flash as two flashes. In such circumstances, primary visual cortex shows enhanced activity compared to physically identical stimulation that is perceived correctly (Watkins et al., 2006). Moreover, this illusion is associated with very early modulation of MEG responses over posterior occipital sensors (Shams et al., 2005). Responses in human V1 can therefore be altered by sound and can reflect subjective perception rather than the physically present visual stimulus.

Illusions can also affect activity in higher visual areas. Perception of illusory or implied motion in a static visual stimulus results in activation of V5/MT (Zeki et al., 1993; Kourtzi and Kanwisher, 2000), while perception of illusory contours activates areas of early retinotopic extrastriate cortex (Hirsch et al., 1995; Mendola et al., 1999; Ritzl et al., 2003). Finally, sensory aftereffects are illusory sensory perceptions in the absence of sensory stimulation that typically occur following an extended period of adaptation to a sensory stimulus. Aftereffects that are contingent on prior adaptation to color or motion activate either V4 (Sakai et al., 1995; Hadjikhani et al., 1998; Barnes et al., 1999) or V5/MT (Tootell et al., 1995; He et al., 1998; Culham et al., 1999), respectively, and the time course of such activation reflects phenomenal experience (Tootell et al., 1995; He et al., 1998).

Attention

When subjects are engaged in a demanding task, irrelevant but highly salient stimuli outside the immediate focus of attention can go entirely unnoticed. This phenomenon is known as inattentional blindness, and suggests that visual awareness may depend on attention. Brain activity evoked by irrelevant sensory stimulation in ventral occipital and temporal cortex is reduced when attention is withdrawn (Frith and Allen, 1983; Rees et al., 1997, 2001; Yi et al., 2004). Moreover, when inattentional blindness results for unattended words, then brain activity no longer differentiates between such meaningful words and random letters (Rees et al., 1999). This suggests that attention is necessary both for brain activity associated with the higher processing of sensory stimuli, and for their subsequent representation in the contents of visual awareness. However, the availability of attention can strongly influence the processing of stimuli in early visual cortex that are rendered entirely invisible by binocular suppression (Bahrami et al., 2007). Thus although attention might be necessary, it cannot be a sufficient condition for awareness (see Chapter 6 for further discussion of the relationship between attention and awareness).

Imagination

A conscious percept can be created by the act of imagination. In these circumstances there is a striking correspondence between the pattern of activation of visual cortices in response to sensory stimulation and to imagery resulting from top-down signals alone. In retinotopic visual cortex, patterns of activation evoked by visual imagery of flickering checkerboard correspond topographically to the patterns evoked by presentation of similar visual stimuli (Slotnick et al., 2005). In extrastriate cortex, color imagery activates color-selective area V4 (Rich et al., 2006). Neuronal populations further along the ventral visual pathway with stimulus specificity for faces or places are activated during imagery of these categories of object (O'Craven and Kanwisher, 2000). Finally, in patients with implanted electrodes for pre-surgical epilepsy mapping, single neurons in the human medial temporal lobe that fire selectively when particular visual stimuli are presented (Kreiman et al., 2000b) are also activated when the individual imagines the same stimuli (Kreiman et al., 2000a).

Sleep and Anesthesia

Global alterations in the level of consciousness obviously lead to corresponding modifications in the ability to be aware of the environment. In contrast to the large number of studies in awake observers, there have been relatively few enquiries that address how activity in visual cortex is modified by global changes in level of consciousness (though see Chapter 10 for a more general discussion of anesthesia plus Chapter 8 for a discussion of sleep). There is a dose dependent reduction in activation of V1 with thiopental (Martin et al., 2000), but that study did not measure depth of anesthesia so could not correlate such findings with level of consciousness. Subanesthetic isoflurane affects task-induced activation in frontal and parietal, but not visual cortices during performance of a visual search task (Heinke and Schwarzbauer, 2001). Visual evoked potentials can still be obtained during anesthesia, although somewhat unreliably in the operative environment (Wiedemayer et al., 2003), indicating some preservation of cortical processing.

Considering sensory processing more generally, primary auditory cortex activity can still be elicited

when auditory stimuli are presented to subjects rendered unconscious through sleep (Portas et al., 2000b) or coma (Laureys et al., 2002), but activation of higher order multimodal association cortex in coma appears to be absent and any thalamocortical coupling is decreased relative to the conscious state (Laureys et al., 2000). Thus, it seems that primary auditory cortex continues to process stimuli when conscious state is perturbed, but activity in secondary sensory and higher cortical areas is strikingly reduced (see also Chapter 13 on brain activity in the vegetative state), consistent with a role for these areas in representing the contents of consciousness. However, whether such a generalization holds true for the visual modality remains to be established.

Summary

Common to these experimental paradigms are changes in visual experience induced by the presence (vs. absence) of a particular spatial and temporal context, or by the presence (vs. absence) of top-down signals, without corresponding physical stimulus changes. Activity in functionally specialized areas of the visual system changes in correspondence with the changes in visual awareness; and as for spontaneous changes in the contents of visual awareness, areas of dorsolateral prefrontal and parietal cortex are also activated.

NECESSARY AND SUFFICIENT CORRELATES OF CONSCIOUSNESS

fMRI and EEG/MEG studies in normal subjects, such as those discussed above, reveal the correlation between particular contents of consciousness and specific types of neural activity. However, they can neither ascertain whether this neural activity plays a causal role in determining the contents of consciousness, nor determine with certainty the necessary and sufficient correlates of consciousness. In order to do this, neural activity must be manipulated either experimentally (e.g., using transcranial magnetic stimulation (TMS)) or as a consequence of neurological disease causing brain damage (see also Chapters 11–27 for further discussion of pathological conditions and consciousness).

In individuals who are blind following retinal damage, phosphenes can be elicited by TMS of visual cortex. However, such stimulation does not elicit phosphenes when blindness results from damage to primary visual cortex (Cowey and Walsh, 2000). This suggests that while retinal stimulation is not necessary for conscious visual experience of phosphenes, activity in primary visual cortex may be required. Indeed, visual experiences of varying complexity can be elicited by direct stimulation of the ventral visual pathway, confirming that retinal and subcortical processing may not be necessary for conscious visual experience, although it is not possible to entirely rule out their involvement through feedback loops (Lee et al., 2000). This suggests that visual input from the retina and subcortical structures is not necessary for conscious visual experience. Whether V1 activity is necessary is more controversial. Activation of extrastriate cortex in the absence of awareness occurs when the blind visual field is stimulated in patients with damage to V1 (Ptito et al., 1999; Goebel et al., 2001). However, in at least some patients with V1 damage, residual conscious vision may return in the absence of functional ipsilesional V1 (Kleiser et al., 2001). Reconciling these two observations is only possible if some specific functional aspect of V1 activity, such as its overall level or precise timing, plays a role in determining the contents of consciousness. Consistent with this, awareness of motion is impaired if feedback signals from V5/MT to V1 are disrupted by TMS (Pascual-Leone and Walsh, 2001; Silvanto et al., 2005). Similarly, using TMS to disrupt processing of a mask presented following a target can lead to unmasking and corresponding visibility of the original target (Ro et al., 2003). These data suggest that signals in V1 representing feedback from other ventral visual (or higher cortical) areas may be required for awareness. Indeed, coupling is disrupted between the V1 representation of a visual stimulus and higher visual areas when that stimulus is rendered invisible by masking (Haynes et al., 2005b).

As previously discussed, damage to frontal and parietal cortex can lead to visual extinction and visual neglect in which awareness is lost for objects presented in one-half of the visual field, even though processing of visual stimuli in visual cortex may continue. This implies that signals in parietal and (possibly) frontal cortex are necessary for normal visual awareness. Consistent with such a notion, disruption of right parietal cortex using TMS leads to a greater rate of change blindness (Beck et al., 2006). Parietal damage can also affect the rate of perceptual alternations in binocular rivalry (Bonneh et al., 2004), supporting a causal role for these structures in bistable perception. Moreover, when patients with parietal damage become aware of previously extinguished stimuli, such awareness is associated with enhanced covariation of activity in undamaged parietal, prefrontal, and visual areas (Vuilleumier et al., 2001). This suggests that interaction between frontal, parietal, and stimulus-specific representations in visual cortices may be required for visual awareness.

OVERALL SUMMARY AND FUTURE DIRECTIONS

In the last decade, substantial progress has been made in establishing the patterns of brain activity in visual cortices associated with purely unconscious processing, and the changes in such activity that are correlated with different contents of visual awareness. Perhaps the most consistent finding is that activity in specific functionally specialized regions of visual cortex is necessary in order to experience particular contents of consciousness. For example, if the visual motion area V5/MT is damaged, or its activity disrupted, then motion will not be perceived. Thus, activity in functionally specialized areas of the visual system is necessary for awareness of the attribute that is represented in the neuronal specificities within that area. However, activity is also consistently observed in such areas in the absence of any awareness of the specific attribute represented. Thus activity in functionally specialized regions of visual cortex is necessary but not sufficient for awareness. Activity associated with unconscious processing is typically either weaker or has a different character (e.g., no 40 Hz oscillations; see Chapter 4 for further details) to that associated with conscious processing. But associations of parietal and frontal activity with awareness, plus long-range coupling of these structures with appropriate sensory representations during awareness, suggest that activated sensory representations may have to interact with higher areas to be represented in the contents of visual awareness. The challenge for the next decade is thus to more precisely delineate whether differences in the level or character of neuronal activity in functionally specialized areas are sufficient for awareness, or whether interactions with additional areas are also required.

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CHAPTER

5

The Relationship Between Consciousness and Top-Down Attention

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OUTLINE

INTRODUCTION

Commonly used in both everyday speech and scholarly literature, the terms "attention" and "consciousness" have resisted clear and compelling definitions. As argued elsewhere (Crick and Koch, 2003; Koch, 2004) this unfortunate state of affairs will probably remain until the mechanistic basis of these phenomena has been thoroughly enunciated.

Few would dispute that the relationship between selective attention and perceptual consciousness is an intimate one. When we pay attention to an object, we usually become conscious of its various attributes; when we shift attention away, the object fades from consciousness. This has prompted many to posit that these two processes are inextricably interwoven, if not identical (O'Regan and Noe, 2001; Posner, 1994, 2012; Merikle and Joordens, 1997; Jackendoff, 1996; Prinz, 2004; Chun and Wolfe, 2000; Mole, 2008; Marchetti, 2012; De Brigard and Prinz, 2010; Cohen and Dennett, 2011). Others, going back to the nineteenth century (Wundt, 1874), however, have argued that attention and consciousness are distinct phenomena, with distinct functions and neuronal mechanisms (Iwasaki, 1993; Hardcastle, 1997; Naccache et al., 2002; Lamme, 2003; Woodman and Luck, 2003; Kentridge et al., 2004; Koch, 2004; Baars, 2005; Block,

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2005; Dehaene et al., 2006; Bachmann, 2006; Koch and Tsuchiya, 2007; van Boxtel et al., 2010a; Lamme, 2010).

Even if the latter proposition is true, what is the nature of their causal interaction? Can we pay attention to an object or aspect of an object that is not consciously perceived? Is paying attention necessary for consciousness (Dehaene et al., 2006; Cohen et al., 2012), or can conscious perception occur outside the spotlight of attention?

We here summarize recent psychophysical, neuroimaging, and neurophysiological evidence in favor of a dissociation between selective attention and consciousness, and provide functional justifications for this reasoning. We argue that events or objects can be attended to without being consciously perceived. Furthermore, an event or object can be consciously perceived in the near absence of top-down attentional amplification of neural signals. We review some remarkable evidence that top-down attention and consciousness can have opposing effects. We also refer to neuroimaging studies that measured attentional modulation of fMRI responses to invisible stimuli and that dissociated the effects of attention and consciousness by independently manipulating the visibility of and top-down attention to the stimuli. Finally, we speculate on the neuronal substrate of consciousness without top-down attention and discuss optogenetic studies in mice that promise to test the very idea of conscious perception without any top-down attention.

Note that our usage of "attention" always implies selective attention, rather than the processes that control the overall level of arousal and alertness. Furthermore, we restrict this review to visual attention and visual consciousness, as visual perception and the neurophysiology of vision is much better understood than that of other sensory modalities. For other modalities, see several articles featured in Tsuchiya and van Boxtel (2013).

Our usage of "consciousness" is not restricted to "visual consciousness" but, *mutatis mutandis*, applies to all forms of consciousness, whether perceptual or not. Indeed, we consider self-consciousness, highly developed in adult humans, to be a subclass of conscious experiences. Likewise, the feeling of freely willing an action, such as raising one's arm, sometimes also referred to as *agency* (Fried et al., 1991; Wegner, 2002), is another subclass of conscious experience. While these experiences differ from the experiences associated with feeling pain or seeing red, common to all is subjectivity, is phenomenology. The question that this chapter addresses is the extent to which this feeling depends on selective attention.

FUNCTIONAL CONSIDERATIONS

Let us start by considering the functional roles of visual attention (Carrasco, 2011). Complex organisms, such as brains, suffer from informational overload. In primates, about one million fibers leave each eye and carry on the order of one megabyte per second of raw information. One way to deal with this deluge of data is to select a small fraction and process this reduced input in real-time, while the non-attended portion of the input is processed at a reduced bandwidth. In this view, attention selects information of current relevance to the organism while the non-attended data suffer from benign neglect.

At the neuronal level, attentional selection is implemented in at least three ways (Kastner and Ungerleider, 2000); (i) it increases the baseline neuronal activity (but also see Otazu et al., 2009); (ii) it amplifies the neuronal response to the selected location, feature, and object; this may occur by reducing noise correlations among neighboring neurons (Cohen and Maunsell, 2009; Mitchell et al., 2009) or by inactivating sub-types of different inhibitory interneurons (Zhang et al., 2014); and (iii) it suppresses the neuronal response to features, objects, or events that are not selected. In the discussion on the relationship between consciousness and attention, the second aspect of attention, attentional amplification, is most relevant. The third aspect is also critical when attention resolves competition among visual objects.

Since the late nineteenth century, selection is known to be based on either bottom-up, exogenous or top-down, endogenous factors (James, 1890; Braun and Julesz, 1998; Duncan, 1998). Exogenous cues are image-immanent features that transiently attract attention or eye gaze, independent of any particular task. Thus, if an object attribute (e.g., flicker, motion, color, orientation, depth, or texture) differs significantly from its value in some neighborhood, the object will be salient. This definition of bottom-up saliency has been implemented into a popular suite of neuromorphic vision algorithms that have at their core a topographic saliency map that encodes the saliency or conspicuity of locations in the visual field independent of the task (Itti and Koch, 2001) (see http://ilab.usc.edu/toolkit/ for a C++ implementation and http://www.saliencytoolbox.net/ for a Matlab toolbox). Such algorithms account for a significant fraction of fixational eye movements (Parkhurst et al., 2002; Peters et al., 2005; Mannan et al., 2009). Higher-order features, such as faces and text, also contribute to the computation of global saliency, as these objects strongly attract eye movements in a task-independent manner (Cerf et al., 2009). Candidates for one or more saliency maps in the primate brain include the initial responses of neurons in the frontal eye field (FEF), the lateral or posterior intraparietal sulcus (LIP) (Constantinidis and Steinmetz, 2005; Thompson and Bichot, 2005; Bogler et al., 2011) and in the superficial layers of the superior colliculus (White et al., 2014).

Under many conditions, however, subjects can disregard salient, bottom-up cues when searching for

particular objects in a scene by dint of top-down, task-dependent control of attention (Henderson et al., 2006). Bringing top-down, sustained attention to bear on an object or event in a scene takes time. Top-down attention selects sensory inputs defined by a circumscribed region in space (*spatial attention*) or time (*temporal attention*), by a particular feature (*feature-based attention*), or by an object (*object-based attention*). It is the relationship between these volitionally-controlled forms of top-down, selective, endogenous attention and consciousness that is the topic of this chapter. (For an evidence that top-down, voluntary spatial attention and bottom-up, involuntary attention interact with consciousness in different manners, see Hsu et al., 2011.)

When considering functions of consciousness, it is useful to distinguish two concepts: "phenomenal consciousness" and "access consciousness" (Block, 1996, 2007). Phenomenal consciousness is defined as "what it is like to have any one specific experience" and it is closely related to the philosophical concepts of qualia (a quale is the singular form for the Latin word qualia). A representation is access-conscious if it is posed for direct control of reasoning, reporting, and action—that is, those aspects of any experience that can be reported or remembered. Cognitively accessed contents of consciousness are stored for working memory and flexibly guide present and future behaviors. It remains controversial whether phenomenal experience overflows access consciousness.

Many candidate functions for the cognitively accessed contents of consciousness have been proposed, ranging from summarizing all relevant information pertaining to the current state of the organism and its environment and making this compact summary accessible to the planning stages of the brain, to detecting anomalies and errors, decision making, language, inferring the internal state of other animals, setting long-term goals, making recursive models, and logical inference. While all these functions are clearly related to access consciousness, it is not clear how the raw feeling of any one conscious experience, its qualia or phenomenal consciousness, relates to any of the above functions.

Integrated Information Theory (IIT) (Tononi, 2004; Oizumi et al., 2014) offers a distinctive take on this issue. IIT views information from the point of view of causation. The information content of an experience is specified by the "form" of the associated conceptual structure and quantified by the non-negative number Φ^{max}. Information is *intrinsic* and *causal*: it is assessed from the intrinsic perspective of a system based on how its mechanisms and present state affect the probability of its own past and future states (intrinsic cause-effect power; Oizumi et al., 2014). IIT identifies integrated information as the maximal causal-effect power that the system exerts on itself. Maximal cause-effect power is what consciousness is (an identity relation). IIT argues that organisms with higher Φ^{max} will experience richer phenomenology and cope with the environment in a more adaptive manner compared to competitors with less integrated information (Φ^{max}). Indeed, digital organisms ("animats") whose brains evolve over 60,000 generations by simulated natural selection in a maze show a monotonic relationship between integrated information and adaptation. Similarly, as animats evolved to catch falling blocks in a *Tetris*-like scenario, they increase fitness along with both Φ^{max} and the number of irreducible causal functions (called "concepts" Oizumi et al., 2014; Albantakis et al., 2014). Moreover, while in simpler environments, animats with modular, feedforward brains that have zero Φ^{max}—and therefore no consciousness—can do well, only animats with high Φ^{max} and therefore a larger capacity for consciousness evolve to adapt to more complex environments (Edlund et al., 2011; Joshi et al., 2013; Albantakis et al., 2014).

In sum, while the scientific community has relatively clear ideas concerning the putative functions of selective attention, the functions—if any—of phenomenal consciousness remain elusive. However, it is clear that long as attention and consciousness have different biological functions, they cannot be the same processes.

Then, how exactly do they differ, and under what circumstances? Our 2×2 matrix (Table 5.1) lists four possible ways in which attention and consciousness interact. Each cell contains a particular percept or behavior depending on whether or not it requires top-down attention and whether it necessarily gives rise to consciousness.

THE FOURFOLD WAY OF PROCESSING VISUAL EVENTS

While many scholars agree that attention and consciousness are distinct, some insist that the former is necessary for the latter, and that non-attended events remain subliminal (Dehaene et al., 2006; Cohen et al., 2012). For example, Dehaene and colleagues (2006) argue that without top-down attentional amplification, an event cannot be consciously perceived (preconscious). The evidence reviewed below argues otherwise, at least for some types of percepts.

More than a century of research efforts have quantified the ample benefits that accrue to attended and consciously perceived events. For example Mack and Rock (1998) compellingly demonstrate that subjects must attend to become conscious of novel or unexpected stimuli. Integrating information over large distances in space and time or across modalities requires attention and consciousness, while neither may be required over smaller distances (Mudrik et al., 2014).

TABLE 5.1 A Fourfold Classification of Percepts and Behaviors Depending on Whether or Not Top-Down Attentional Amplification Is Necessary for Them to Occur and Whether or Not These Percepts and Behaviors Necessarily Give Rise to Consciousness

	Does not necessarily give rise to consciousness	**Is always associated with consciousness**
Can occur under limited top-down attentional allocation	Formation of afterimages	Iconic memory
	Rapid vision (<120 ms)	Gist
	Zombie behaviors	Animal and gender detection in dual tasks
	Storing primitive information for short durations	Partial reportability
	Basic summary statistics (e.g., size and number)	
	Local, weak integration of information	
Requires top-down attention	Pop-out	Storing information in working memory for flexible use
	Priming	Detection and discrimination of unexpected and unfamiliar stimuli
	Adaptation	Full reportability
	Processing of objects	Global, strong integration of information
	Visual search	
	Thoughts	
	Eye-of-origin information	

The items placed in the lower right quadrant of our attention × consciousness design matrix (Table 5.1) require selective top-down attention and will give rise to a conscious experience.

On the other end of the spectrum are visual behaviors that can occur without the need of top-down attention and that may not give rise to consciousness. These may be supported by predominantly feedforward processing, composed of a net-wave of spiking activity moving from the retina into primary visual cortex and beyond. They can be also triggered by previously trained sensory-motor activity that is mediated by feedforward processing. Further, reverberating neuronal activity that remains confined to the primary visual cortex and never arrives high-level association cortex can also produce these percepts and behaviors. Such processing, that is not amplified by top-down attention and does not give rise to consciousness, however, can still be causally effective and leave traces that can be picked up with sensitive behavioral techniques. For instance, such stimuli can subsequently cause negative afterimages (Hofstoetter et al., 2004; Tsuchiya and Koch, 2005; Gilroy and Blake, 2005; Brascamp et al., 2010; van Boxtel et al., 2010b). These occupy the upper left quadrant of Table 5.1.

Working memory stores information for a short period of time, up to several seconds, so that the information can be manipulated for future use in a flexible fashion. Many cognitive neuroscientists assert that actively stored items are perceived consciously and selected by attention, placing working memory in the bottom right quadrant of Table 5.1 (Baars and Franklin, 2003). However, some form of short-term, flexible storage of stimulus information is also possible without consciously seeing the stimulus or attending to it. Monkeys whose primary visual cortex has been removed exhibit blindsight behaviors as do patients (Takaura et al., 2011): when forced, the monkeys can make saccades to a target presented in the blind field accurately. Surprisingly, the lesioned monkeys can also saccade to the target location, even after the target vanishes from the display up to 2.4 s (Takaura et al., 2011). Healthy human volunteers can also retain information about the orientation of a masked invisible stimulus and use it as a template for subsequent orientation discrimination (Soto et al., 2011; see also Soto and Silvanto, 2014 and Hassin et al., 2009). These recent studies call into question the relationship between attention and consciousness as necessary subcomponents of working memory.

When subjects are briefly shown a group of objects in a display, some basic summary statistics, such as the average size or the number of elements, are behaviorally accessible without attention. Computing the average or counting objects proceeds before selective attention can be deployed (Oriet and Brand, 2013). Furthermore, perceptually invisible, masked objects also contribute to the estimation of the mean size and numerosity (Choo and Franconeri, 2010). As far as we know, however, an orthogonal 2×2 manipulation of attention and consciousness has not yet been performed to investigate the nature of statistical perception.

What about the two remaining quadrants, covering events that require top-down attention but that do not necessarily give rise to conscious perception, and events that can give rise to consciousness without top-down attentional amplification? These can be studied with techniques that independently manipulate top-down attention and visual consciousness (Boxes 5.1 and 5.2).

ATTENTION WITHOUT CONSCIOUSNESS

Much neuronal processing causes observable motor behavior without giving rise to consciousness (Hassin et al., 2005). The implicit effects of such non-conscious processing can be revealed by careful psychophysical probing. After prolonged viewing of some sensory stimuli, subjects exhibit reduced sensitivity to the same stimulus presented afterwards, a phenomenon called an *aftereffect*. Interestingly, even if the stimulus is not consciously perceived, strong aftereffects can be induced (Blake and Fox, 1974; Blake et al., 2006). In *priming*, briefly presented stimuli influence subsequent behaviors. Some types of priming can occur even when priming stimuli remain invisible (Kouider and Dehaene, 2007). This non-conscious processing, however, can be strongly modulated by the availability of top-down attention or can be completely eliminated when top-down attention is directed away from stimuli that induce the non-conscious percepts and behaviors (lower left quadrant in Table 5.1).

In *visual crowding*, the orientation of a peripherally-presented grating can be rendered inaccessible to consciousness by neighboring gratings. Here, the surrounded target grating can be detected consciously, yet its tilt angle cannot be discriminated at all. The central target grating, therefore, is above the detection and below the discrimination threshold, a classic example of "partial awareness" (Kouider et al., 2010). This crowded grating, however, remains sufficiently potent to induce an orientation-dependent aftereffect (He et al., 1996). A similar aftereffect can be induced by an indiscriminable grating defined by illusory contour (Montaser-Kouhsari and Rajimehr, 2005). This aftereffect depends strongly on the availability of top-down spatial attention: it can only be induced when subjects actively try to attend to the orientation of the indiscriminable grating (Montaser-Kouhsari and Rajimehr, 2005). Naccache and colleagues (2002) elicited priming for invisible flashed words (suppressed by a combination of forward and backward masking) but only if the subject was attending to the invisible prime-target pair at the appropriate time; without temporal attentional amplifications, the invisible word failed to elicit priming.

Attention without consciousness has been investigated using stimuli that themselves do not give rise to consciousness (Rajimehr, 2004; Norman et al., 2013). To achieve reliable and prolonged invisibility a technique, called continuous flash suppression or CFS for short, is often used (Tsuchiya and Koch, 2005; Tsuchiya et al., 2006; Yang and Blake, 2012). In CFS, an image is presented to one eye, which is rendered invisible for seconds to minutes (Tsuchiya and Koch, 2005) by flashing randomly generated, edge-rich, stimuli to the other eye at around 10 Hz in the corresponding retinal location. The potency of such invisible stimuli to attract bottom-up attention has been a particular focus of research. Using CFS, invisible male/female nudes have been shown to attract covert attention (Jiang et al., 2006). Interestingly, in heterosexuals, these effects are only apparent for nudes of the opposite sex. Note that by themselves (i.e., without the binocular mask), these stimuli are clearly visible. Another study using CFS revealed that pop-out target can attract bottom-up attention even if the entire stimulus array itself is rendered invisible (Hsieh et al., 2011). However, this non-conscious pop-out effect depends on top-down spatial attention: when distracted by another task at the fixation, this pop-out effect disappears (Hsieh et al., 2011). Not only spatial attention but also feature-based attention can spread to and act on invisible stimuli (Melcher et al., 2005; Kanai et al., 2006). Indeed, when searching for an object in a cluttered scene (e.g., keys in a messy room), attention is paid to an invisible object and its associated features. The blindsight patient GY has the usual reaction-time advantages for the detection of targets in his blind visual field when attentionally cued, even when the cues are located in his blind field and are therefore invisible to him (Kentridge et al., 1999a,b, 2004).

Although visual information enters the brain separately through the two eyes, subjects have very poor conscious to access "eye-of-origin" information when information is presented to one eye only—that is, "did

BOX 5.1

PSYCHOPHYSICAL TOOLS TO MANIPULATE TOP-DOWN ATTENTION

Top-down attention and consciousness are usually tightly coupled. To dissociate these two, experimental tools that manipulate either one independently in a specific manner with few side effects are called for.

There exist at least two forms of selective attention: stimulus-driven, bottom-up, saliency-mediated attention as well as task- and goal-dependent top-down attention, with some intermediate forms. Previously neutral stimuli (such as text, or images of guns) can be associated with reward or punishment to acquire additional saliency. Biologically relevant stimuli may be preferred or disliked based on individual difference (e.g., snakes, spiders, sexual arousing pictures).

A variety of techniques to manipulate these components of attention have been invented. It is not always easy to compare them, as each method interferes with attention at a different level of processing (Sperling and Dosher, 1986; VanRullen et al., 2004).

In *Posner's cueing paradigm*, popular to study orienting (Posner et al., 1980), a target is preceded by a cue that appears at the target location or at fixation. Attentional effects are inferred in terms of reaction time and accuracy of target detection. Variants of the methods demonstrated that invisible cue can direct attention to the cued location (Jiang et al., 2006; McCormick, 1997; Rajimehr, 2004; Sumner et al., 2006; Kentridge et al., 2004), supporting attention without consciousness. A study by Kok and colleagues (2012), however, casts doubt on a large body of Posner-type manipulations that manipulated the probability that a cue predicts the target location; these studies might have confounded attention with expectation, both of which are likely to have distinct biological functions and underlying mechanisms (Summerfield and Egner, 2009).

In *visual search*, subjects need to find a target among distractors; reaction time is related to the number of distractors. When the search slope is steep, the search process is said to be *serial*, and when flat, *parallel*. The former is usually taken as the evidence of serial processing by top-down attention. However, the steep serial search may arise due to completely bottom-up factors (Wolfe, 1998). This exemplifies a case where dual tasks and visual search methods may yield inconsistent results.

The *dual-tasks paradigm* (Sperling and Dosher, 1986; Braun and Julesz, 1998; Braun and Sagi, 1990) manipulates top-down, focal attention without affecting bottom-up saliency; a central, attentional-demanding discrimination task is presented at the center of gaze, while a secondary stimulus is projected somewhere into the periphery. Subjects either carry out the central, the peripheral or both tasks simultaneously while the scene and its layout remains the same. Surprisingly, seemingly complex peripheral tasks can be done equally well under either single-task or dual-tasks condition, while other, computationally simpler, tasks deteriorate when performed simultaneously with the central task (Figure 5.2). The dual-tasks paradigm quantifies what type of stimulus attributes can be performed under no or little spatial attention (VanRullen et al., 2004).

Most importantly, the dual-tasks paradigm can be easily combined with a multitude of visual illusions that render stimuli invisible, allowing the independent manipulation of top-down attention and consciousness (Watanabe et al., 2011; van Boxtel et al., 2010b).

The inference of attentional requirements from dual-tasks performance demand a caution. High proficiency in such tasks is only achieved after extensive training of many hours. Such an extended training phase may render the task quite different from what naïve subjects do (Braun, 1998; Joseph et al., 1997) and may well reflect the involvement of different brain regions.

Finally, there is a class of neurological conditions as well as visual illusions in normal subjects where stimuli become invisible because of impairments in the mechanisms of top-down or bottom-up attention. Neglect and extinction (Driver and Mattingley, 1998), attentional blink (Raymond et al., 1992; Chun and Potter, 1995), inattentional blindness (Mack and Rock, 1998), and change blindness (Simons and Rensink, 2005) are sometimes used as positive evidence for "without attention, no consciousness" (O'Regan and Noe, 2001). Although some attributes of the visual input need attentional amplification to rise to the level of consciousness, other aspects, such as the gist of the scene and its emotional content, are quite resistant to such attentional manipulations (Mack and Rock, 1998; Anderson and Phelps, 2001).

Cohen and colleagues (2012) argue that four different psychophysical techniques—attentional blink, inattentional blindness, change blindness and the dual-task—should be used in conjunction to test whether or not consciousness without attention is possible. They argue that in some of these conditions, even faces and natural scene cannot be perceptually experienced if top-down attention fail to amplify the signal. It is unclear, however, how much of "blindness" in these phenomena is due to the lack of top-down attentional amplification. Attentional blink, inattentional blink, and change blindness are composed of distinct cognitive processes, such as backward masking, memory consolidation (Wolfe, 1999), and expectation (Braun, 2001; Summerfield and Egner, 2009; Kok et al., 2012). Some of these non-attentional components may play a more significant role than the top-down selective attentional amplification in mediating perceptual blindness in these situations (Tsuchiya and Koch, 2014).

BOX 5.2

HOW TO MEASURE VISUAL CONSCIOUSNESS

Visual consciousness can be manipulated using a multitude of illusions, such as backward masking, the standing wave of invisibility (Macknik and Livingstone, 1998), crowding, bistable figures, binocular rivalry, flash suppression, continuous flash suppression, motion-induced blindness, chromatic flicker fusion (Jiang et al., 2007), and attentional blink (for a review see Kim and Blake, 2005). These techniques control the visibility of an object or part of thereof in both space and time. Yet how is visibility assayed? More generally, how can the degree of consciousness be probed?

The most lenient criterion is to accept what subjects subsequently report verbally (e.g., "I never saw the face"). Though widely used, such as when obtaining reports right after a block of trials, this method is unsatisfactory because unattended items or task-irrelevant (implicit) features of stimuli may be inaccessible in subsequent recognition or recall tasks, called inattentional amnesia (Wolfe, 1999; Lovibond and Shanks, 2002). A more stringent criterion for non-conscious processing is to ask subjects about their experience directly at the time the stimulus is processed. When subjects deny seeing stimuli, the stimulus is processed at a *subjectively non-conscious* level. Although many studies adopt this convention, it suffers from a possibility of individual differences in decision criteria; for the same subjective experience of visibility, some subjects may deny seeing a stimulus while others may report seeing it, because their criterion of what to count as "seen" differs.

Taking into account criterion differences, one can compute signal discriminability (or d') within the framework of signal detection theory. When subjects show no discriminability ($d' = 0$) for a stimulus, it can safely be assumed that they are not conscious of that particular stimulus dimension being tested for (e.g., male vs female face gender discrimination). A recently developed Bayesian framework estimates how convincing the demonstrated invisibility is (Dienes, 2011). For example, subjects can be given two alternative temporal intervals (or locations), each of which contains the stimulus equally often. In this procedure, care needs to be taken to intermix trials of low and high visibility to keep subjects motivated (Lin and Murray, 2014). If observers perform at chance in detecting/discriminating one from the other, they are (objectively) unaware of the stimulus (our use of "subjective" and "objective" here refers to the method used, not to the nature of the conscious experience, which is of course always subjective in terms of its phenomenology). When these protocols are used carefully, there is excellent agreement between objective and subjective measures of consciousness (Del Cul et al., 2007). Note that above-chance behavioral discrimination performance does not necessarily demonstrate conscious awareness, since patients with blindsight exhibit precisely such performance.

Objective-performance-based definitions of consciousness, however, are flawed because they do not directly reflect phenomenal experience, which is the central issue. By applying the objective measure of signal discriminability to one's own judgment of whether the stimulus is seen or not, one can *objectively* measure *subjectivity*. That is, one can consider the discriminability (d') of one's own experience, a form of metacognition. For this method, subjects first make a detection/discrimination judgment, then rate the confidence in their decision. Defining "hit" as proportion of high-confidence ratings given the decision was correct—p(high confidence | correct)—and "false alarm" as the proportion of high-confidence ratings given the decision was incorrect—p(high confidence | incorrect)—one can calculate the signal discriminability. In signal detection theory, this is called Type 2 analysis, which has been applied to evaluate above-chance behavior in non-conscious perception (Kolb and Braun, 1995; Kunimoto et al., 2001; Szczepanowski and Pessoa, 2007; Galvin et al., 2003; Maniscalco and Lau, 2012; Kanai et al., 2010; Barrett et al., 2013).

Reflecting upon one's own judgment may require substantial internal focus, and such an act itself can modify conscious experience significantly (Maia and McClelland, 2004). *Post-decision wagering* minimizes this contamination due to introspection (Kunimoto et al., 2001; Persaud et al., 2007). Following each response, subjects wager on their performance, betting either high or low. When the subject is confident that she saw the stimulus, reward maximization would presume that she would wager a higher amount than when she is unaware of the stimulus. Here, subjects' awareness is gauged by their discriminability of their own judgment. This method proves to be easy and intuitive for subjects to use and very effective in reflecting one's subjective aspects of consciousness while minimizing interference to the quality of the experience. Persaud and colleagues (2007) observed non-conscious, above-chance behaviors in blindsight patients, implicit learning, and Iowa gambling task while demonstrating no-conscious access to the information by post-decision wagering. Note, however, the post-decision wagering is subject to loss- or risk aversion, a concept in behavioral economics,

BOX 5.2 (*cont'd*)

which needs to be carefully teased apart from the effects of conscious phenomenology (Wang et al., 2012; Sandberg et al., 2010; Clifford et al., 2008; Dienes and Seth, 2010; Koch and Preuschoff, 2007; Fleming and Dolan, 2010; Schurger and Sher, 2008).

While confidence rating and post-decision wagering asks subjects to rate their confidence in their perceptual "decisions," the perceptual awareness scale (PAS) (Ramsøy and Overgaard, 2004; Sandberg et al., 2010, 2011) directly asks subjects to describe their qualitative experience on a scale from "no experience," to "brief glimpse," "almost clear image" to "absolutely clear image." All methods referred here (confidence rating, post-decision wagering, and PAS) can be used to compute the accuracy of metacognition. Furthermore, by focusing on the trials in which subjects reported invisibility of the stimulus, metacognitive accuracy about invisibility judgment can be assessed. (Kanai et al., 2010).

As the study of consciousness matures, the methodological development in how to assess consciousness continues to be refined and more sophisticated (Seth et al., 2008).

I see that stimulus with my left or my right eye?" (Wolfe and Franzel, 1988; Schwarzkopf et al., 2010). However, an odd-ball stimulus defined by the eye-of-origin attracts involuntary, bottom-up attention (Ooi and He, 1999; Zhaoping, 2008). Furthermore, subjects can prolong or shorten the duration of invisibility of a target stimulus suppressed by CFS by voluntarily attending to a cue that is projected to either the same or opposite eye as the suppressing Mondrian patterns (Zhang et al., 2012). That is, consciously inaccessible eye-of-origin information can guide voluntary, top-down attention to select and modulate incoming visual information (Zhang et al., 2012).

In conclusion, attentional selection does not necessarily engender phenomenal conscious sensations, although it may often do so. Attention without consciousness has been demonstrated with both top-down and bottom-up as well as spatial, temporal, feature-based, object-based (Norman et al., 2013) as well as eye-based attention across many different stimuli and tasks (for reviews, see Dehaene et al., 2006; van Boxtel et al., 2010a; Cohen et al., 2012). By last count, at least 40 experiments report such an effect (Tsuchiya and Koch, 2014). Collectively, they demonstrate that the neuronal mechanisms that support these attentional effects are, by themselves, insufficient to give rise to consciousness.

CONSCIOUSNESS IN THE ABSENCE OF ATTENTION

Yet the converse can also occur and may be quite common (upper right quadrant in Table 5.1). Take perception of a single object (say a bar) in an otherwise empty display, a non-ecological but common arrangement in many experiments. Here, what function would top-down, selective attention need to perform without any competing item in or around fixation? Indeed, the most popular neuronal model of attention, *biased competition* (Desimone and Duncan, 1995) predicts that in the absence of competition, no or little attentional enhancement occurs.

Gist Perception

When focusing intensely on one event, the world is not reduced to a tunnel, with everything outside the focus of attention gone. Rather, visual processing at the para-fovea, extending to the periphery, efficiently encodes the statistical properties of the visual fields (Freeman and Simoncelli, 2011; Rosenholtz et al., 2012). As a result, a concise summary, or gist, of the world surrounding us seems always consciously accessible. Indeed, gist of the scene is immune from inattentional blindness (Mack and Rock, 1998); when a photograph covering the entire background is briefly flashed completely unexpectedly onto a screen, subjects can accurately report a summary of what it contains. In the 30 ms necessary to apprehend the gist of a scene (Biederman, 1972; Fei-Fei et al., 2007), top-down attention cannot play much of a role (because gist is a property associated with the entire image, any process that locally enhances features is going to be only of limited use). Perception of gist is a highly vivid, yet coarse, conscious sensation (Campana and Tallon-Baudry, 2013) (Figure 5.1).

Dual-Tasks Paradigm

In a dual-tasks paradigm, the subject's attention is drawn to a demanding central task, while at the same time a secondary stimulus is flashed somewhere in the periphery (see Box 5.1). Using the identical retinal layout, the subject either performs the central task, or the peripheral task, or both simultaneously (Sperling and Dosher, 1986; Braun and Julesz, 1998; Braun and Sagi, 1990). With focal attention busy at the center, the subject can still distinguish a natural scene containing

an animal (or a vehicle) from one that does not include an animal (or a vehicle) while being unable to distinguish a red-green bisected disk from a green-red one (Li et al., 2002). Likewise, subjects can tell male from female faces or distinguish a famous from a non-famous face (Reddy et al., 2004, 2006), but are frustrated by tasks that are computationally much simpler (e.g., discriminating a rotated letter "L" from a rotated "T") (see Figure 5.2 for other perceptual attributes tested in the dual-tasks paradigm).

While we cannot be sure that observers do not deploy some limited amount of top-down attention in these dual-tasks experiments that require training and concentration (that is, high arousal), it remains true that subjects can perform certain discriminations but not others with no or little top-down attentional amplification.

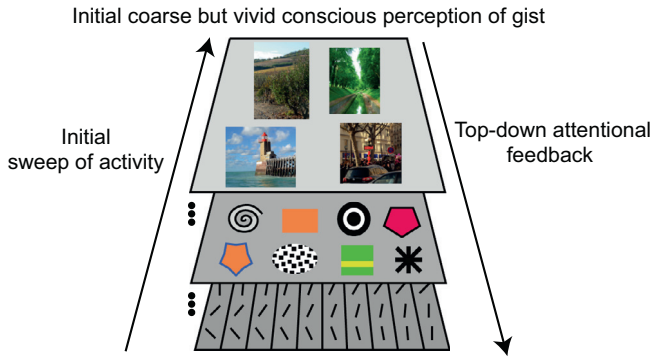

FIGURE 5.1 The coarse vividness hypothesis by Campana and Tallon-Baudry (2013). The initial sweep of activity processed through the ventral visual pathway may be sufficient to give rise to integrated and meaningful conscious perception of gist. However, this coarse representation lacks a detailed description of the scene (e.g., exact spatial locations of an object) which requires top-down attentional feedback. In this view, the perception of gist is a prime example of vivid and coarse consciousness without top-down attention.

OPPOSING EFFECTS OF CONSCIOUSNESS AND ATTENTION

The More You Attend, the Less You See

In most conditions, paying attention improves the processing of stimuli, typically their identification or discrimination. Under certain conditions, however, conscious detection of a target can be impaired when subjects pay attention to the target.

When observers try to find two embedded targets within a rapidly flashed stream of stimuli, they often fail to see the second target, a phenomenon known as the *attentional blink* (Raymond et al., 1992; Chun and Potter, 1995). Counter-intuitively, Olivers and Nieuwenhuis (2005) found that observers can see both the first and the second targets better when they are distracted by a simultaneous auditory task or encouraged to think about task-irrelevant events. Surprisingly, relaxing has been also shown to improve visual search, especially when the search is very difficult but not when the search is easy (Smilek et al., 2006). Even in a simple low-level detection task, low spatial frequency stimuli can be better discriminated without than with spatial attention (Wong and Weisstein, 1982, 1983; Yeshurun and Carrasco, 1998).

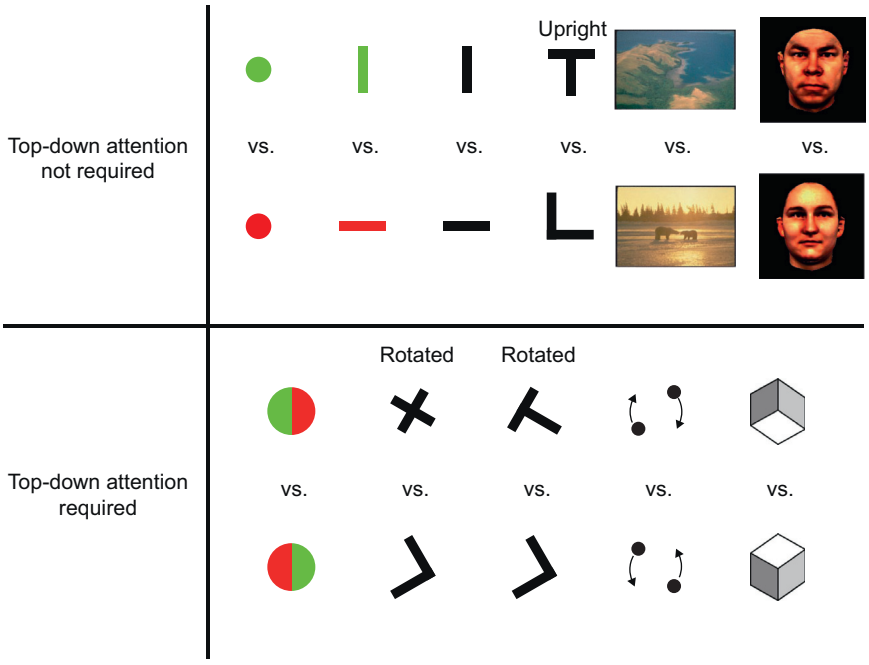

FIGURE 5.2 Various types of visual discriminations and their dependency on top-down attention. The top panel lists perceptual discriminations that require no or little top-down attention (color, orientation, conjunction of color and orientation, upright letters, scene gist, gender, and identity of faces), while the bottom row lists those that require substantial amount of top-down attention (red/green vs. green/red bisected discs, rotated letters, rotation directions of balls, lighting from upwards or downwards), as assessed by the dual-tasks paradigm. This protocol compares discrimination performance of an identical retinal stimulus when fully and when poorly attended (Braun and Julesz, 1998; Lee et al., 1999; Li et al., 2002; Reddy et al., 2004, 2006; VanRullen et al., 2004; Fei-Fei et al., 2005).

These cases imply that focally attending to the task in space or time alters neuronal processing, yet it can impair conscious detection of target.

Impaired task performance due to attention occurs in everyday life as well. Athletes performing their high-performance skills can do better under skill-irrelevant dual-tasks conditions (i.e., paying attention to tones) than when paying attention to their exhaustively trained behaviors (Beilock et al., 2002). Similar effects are reported even in non-athletes during keyboard typing (Logan and Crump, 2009).

While top-down attention usually facilitates perceptual learning of task-relevant stimuli, it can interfere with task-irrelevant and implicit learning (Choi et al., 2009). Attending to a location impedes task-irrelevant perceptual learning (Choi et al., 2009). During implicit learning, attentively trying to discover the underlying complex rule delays learning and impairs subsequent recognition (Reber, 1976). Recognition memory can decrease when the subject's attention is directed to the task-relevant complex kaleidoscopic visual stimulus under certain circumstances (Voss et al., 2008; Voss and Paller, 2009).

Finally, a more direct demonstration of "the more you attend, the less you see" comes from several visual illusions. In *motion-induced blindness* (Bonneh et al., 2001), a salient target can be rendered invisible when it is surrounded by moving dots. Here, the more salient, bottom-up attention-grabbing the stationary yellow targets are, the longer the suppression (Bonneh et al., 2001). Furthermore, when more top-down spatial attention is paid to the salient targets, they disappear faster (Geng et al., 2007; Schölvinck and Rees, 2009). In *Troxler fading* (Troxler, 1804), a stimulus placed in the visual periphery fades from view when fixation is held correctly. This fading happens faster when attention is directed to the peripheral stimulus (Babington-Smith, 1961; Lou, 1999). Similarly, *afterimages* (Bachmann and Murd, 2010) as well as *motion aftereffects* (Murd and Bachmann, 2011) disappear faster when spatial attention is directed to see them better. In all of the above cases, the more subjects try to experience a percept vividly by paying attention to it, the less visible it becomes!

Independent Manipulation of Attention and Consciousness

Recently, researchers have started manipulating consciousness and attention independently using the same stimuli within a single paradigm in perceptual and behavioral tasks (Kanai et al., 2006; van Boxtel et al., 2010b; Van den Bussche et al., 2010) (see Boxes 5.1 and 5.2). These studies typically manipulate the conscious visibility of a target stimulus via backward, lateral or inter-ocular masking (Kim and Blake, 2005; Tsuchiya and Koch, 2005); if the stimulus is not seen and not reported on, it is not consciously perceived. At the same time, top-down attention is manipulated using a dual-task design.

When manipulated independently in this manner, consciousness and attention affect the duration of afterimages in opposing ways (van Boxtel et al., 2010b). A number of experiments showed, paradoxically, that attending to a stimulus reduces the duration of its induced afterimage (Suzuki and Grabowecky, 2003; Lou, 2001; Wede and Francis, 2007; Lak, 2008; Baijal and Srinivasan, 2009) and, independently, that perceptual invisibility of a stimulus reduces the duration of afterimage (Tsuchiya and Koch, 2005; Gilroy and Blake, 2005). Because the effects of consciousness depend on the details of the afterimage-inducing stimulus (e.g., spatial frequency Brascamp et al., 2010), it is critical to use the same stimuli to study the effects of consciousness and attention.

These opposing perceptual effects of attention and consciousness become easier to understand if the neuronal mechanisms that support them are largely independent and can be dissociable (Tallon-Baudry, 2011). Indeed, neuroimaging and neurophysiological studies have started uncovering the neuronal basis of attention and consciousness to be highly dissociable when each is manipulated independently.

NEURONAL MEASURES OF DISSOCIATIONS BETWEEN ATTENTION AND CONSCIOUSNESS

The neuronal footprints of non-conscious processing of visual information have been tracked using both event-related potentials and functional magnetic resonance imaging (fMRI; for a review see Dehaene and Changeux, 2011). Only recently have such tools been applied to separate the neuronal mechanisms of top-down attention from conscious and non-conscious processing (Woodman and Luck, 2003; Koivisto et al., 2006; Koivisto et al., 2005; Bahrami et al., 2007; Tsushima et al., 2006; Lee et al., 2007; Watanabe et al., 2011; Wyart and Tallon-Baudry, 2008).

Neurophysiological evidence for attention without consciousness came from a fMRI study (Bahrami et al., 2007), demonstrating that the processing of objects hidden from sight (with $d' = 0$, or no possibility to detect stimulus above chance (see Box 5.1)) via continuous flash suppression depended on the availability of spatial attention. Bahrami and colleagues varied the load of the central task in a dual-task design. The hemodynamic blood-oxygen-level-dependent (BOLD) response to the invisible, peripheral objects in primary visual cortex, V1, was stronger when the central task was easy, that is, when spatial attention was available for processing the invisible, peripheral stimulus than

when the central task was hard and more attentional resources were drawn to it. In other words, attention modulates the fMRI response of an invisible stimulus.

Watanabe and colleagues (2011) employed a 2×2 factorial design to independently manipulate consciousness and attention while recording fMRI signals from the primary visual cortex (V1) in humans. They found that the V1 hemodynamic response is strongly modulated by spatial attention, consistent with (Bahrami et al., 2007), but not by the conscious visibility of a grating, consistent with (Crick and Koch, 1995). Similar effects have been reported for neuronal activity recorded via microelectrodes from monkey V1 (Maier et al., 2011). These two experiments challenge many previous fMRI studies (Polonsky et al., 2000; Haynes et al., 2005; Wunderlich et al., 2005) that used binocular rivalry and located the neuronal correlates of consciousness to V1 and even the lateral geniculate nucleus of the thalamus (also see Maier et al., 2008 on the difference between single neuron activity and hemodynamic response in monkey V1). A recent study (Yuval-Greenberg and Heeger, 2013) reported significant effects of stimulus visibility in V1 fMRI BOLD activity using CFS, unlike the earlier study by Watanabe and colleagues. The overall design is similar except that Yuval-Greenberg and Heeger used three times more trials per subjects than the earlier experiment. Yet even if there is a statistically significant effect of visibility on V1 BOLD activity, our central conclusion remains the same: selective attention modulates V1 activity more so than stimulus visibility (standing in for conscious awareness of the stimulus) during binocular rivalry and CFS.

The controversy over fMRI studies with binocular rivalry and CFS exemplifies the necessity of separating consciousness from attention; unless explicitly manipulated independently, the neuronal correlates of consciousness can, and usually will, co-vary with the neuronal correlates of attention (Tse et al., 2005; Koch and Tsuchiya, 2012).

An even more paradoxical effect—that invisible stimuli can be more distracting than visible ones—was discovered by Tsushima and colleagues (2006). In this study, subjects had to detect foveally-placed targets in a stream of characters—a *rapid serial visual presentation* task—surrounded by an annulus of moving dots. The fraction of dots moving coherently in one direction (motion *coherence*)—was varied from 0% (truly random dot motion) to 50% (half of the dots move in the same direction). When the central task was combined with the task-irrelevant surround motion, the central performance *dropped* when the coherent motion was perceptually below threshold (say at 5%, where the cloud of dots was not perceived to move coherently) compared to when the motion coherence was 0% or above threshold (e.g., 20%). This counterintuitive finding was explained by the parallel fMRI study in which the authors looked at BOLD activity in area MT+, which reflects the degree of distraction by motion stimuli, and in the lateral prefrontal cortex (LPFC), which provides an attentional suppression signal to MT+. Compatible with the behavioral findings, invisible motion did not elicit activity in the LPFC, resulting in higher distractor-related activity in MT+. On the other hand, visible motion evoked a stronger LPFC signal but a weaker MT+ one. The authors hypothesize that invisible motion activates MT+, impairing performance, but not the LPFC, which fails to inhibit MT+; thereby stimuli that are not consciously perceived can escape inhibitory control, a phenomenon more familiar from psychoanalysis than from sensory psychology.

Using faint stimuli, Wyart and Tallon-Baudry (2008) also performed 2×2 manipulation of spatial attention (cued or not cued) and consciousness (visible or not visible). Their magnetoencepalographic signals revealed independent neural correlates of visual awareness (54–64 Hz, 240–250 ms post stimulus) over the contralateral visual cortex, regardless of the location of attention, and spatial attention (76–90 Hz, 350–500 ms post stimulus) over parietal cortex, regardless of stimulus visibility.

Finally, the neural signatures of consciousness are also being sought in the absence of attentional selection and read-out in an inattentional blindness paradigm (Pitts et al., 2012; Pitts et al., 2014). Vandenbroucke and colleagues (2014) were able to classify non-reported visual percepts—here a group of Pack-man icons that induced illusory Kanizsa figure from other groups of stimuli that did not induce illusory percept—via multi-voxel pattern analysis in visual topographic regions. Remarkably, the unique neural signature for the non-reported Kanizsa figure was observed in the subjects who were subsequently able to report the figure as well as in those who could not, that is, who were inattentionally blind. This result is consistent with an idea that stimuli that are not cognitively accessed are still perceptually interpreted, up to the representation of illusory surfaces.

RELATIONSHIP TO OTHER CONCEPTUAL FRAMEWORKS FOR TOP-DOWN ATTENTION AND CONSCIOUSNESS

How do these experimental dissociations of top-down attention and consciousness relate to dominant models, theories, and conceptual frameworks in cognitive neuroscience?

When we attend to a face or to an object within a cluttered scene, we usually become conscious of its attributes, with all of the attendant privileges of consciousness (e.g., access to working memory and, in linguistic competent individuals, verbal reportability).

While the minimal neuronal mechanisms jointly sufficient for any one conscious visual percept remain elusive, a number of models posit that they must involve neuronal populations in extra-striate visual cortices having a reciprocal relationship—mediated by long-range cortico-cortical feedforward and feedback projections—with neurons in parietal, temporal, and prefrontal cortices (Tononi and Edelman, 1998; Lamme and Roelfsema, 2000; Crick and Koch, 2003; Dehaene et al., 2003; Baars, 2005). Furthermore, a number of elegant fMRI experiments (Haynes and Rees, 2005; Lee et al., 2007) are consistent with the hypothesis that primary visual cortex (V1) is necessary, but not sufficient for visual consciousness (Crick and Koch, 1995).

Decades of electrophysiological recordings in monkeys have proven that the spiking responses of neurons in the ventral visual stream (e.g., in areas V4 and IT) representing attended stimuli are boosted at the expense of the response to non-attended items (Desimone and Duncan, 1995). According to Crick and Koch (1995), this enables these neurons to establish a reciprocal relationship with neurons in the dorsolateral prefrontal cortex and related regions that are involved in working memory and planning (and language in humans), leading to reverberatory neuronal activity that outlasts the initial stimulus duration. Critical to the formation of such a single and integrated coalition of neurons are the long-range axons of pyramidal neurons that project from the back to the front of cortex and their targets in the front that project back to the upper stages of the ventral pathway (possibly involving stages of the thalamus, such as the pulvinar (Crick and Koch, 1998)) as well as the claustrum (Crick and Koch, 2005; Koubeissi et al., 2014). When such a wide-ranging coalition has established itself, the subject becomes conscious of its representational contents and gains access to short-term memory, planning, and language generation stages.

But what happens to those stimuli that do not benefit from attentional boosting? Depending on the exact circumstances (visual clutter in the scene, contrast, stimulus duration) these stimuli may likewise establish coalitions of neurons, aided by local (i.e., within the cortical area) and semi-local feedback (i.e., feedback projections that remain consigned to visual cortex) loops. However, as these coalitions of neurons lack coordinated support from feedback from prefrontal cortex, thalamus, and claustrum, their firing activity is less vigorous and may decay much more quickly. Yet aided by the neuronal representation of the entire scene, these weaker and more local coalitions may still be sufficient for some phenomenal consciousness (Block, 1996, 2007; Lamme, 2006, 2010), even though the associated coalition does not reach into the front of the brain to enable access consciousness for verbal or motor report or working memory (Frässle, 2014). In other words, for visual phenomenal consciousness, coalitions in the back of the cortex might be sufficient, while access consciousness might require the associated coalition to reach into the frontal lobe.

Block (2007, 2011, 2012) has argued that phenomenally conscious states may sometimes not be cognitively accessible, in the sense that they are consciously experienced but that subjects may only have limited access to their attributes as assayed by recall or alternative-forced choice judgments. This view captures not only the general experience that "we see much more than we can report upon" but also verbal reports from subjects participating in the classical iconic memory experiment (Sperling, 1960; Landman et al., 2003). That is, a discrepancy between the vivid, conscious impression of a field of letters or bars arranged on a circle on the one hand and limited access to the detailed properties of the individual elements on the other hand (unless top-down attention is directed to a subset of stimuli using appropriate cues). In this sense, the phenomenal impression of a field of whole letters without being able to access each individual element making up this experience (for instance, the identity and location of every letter in the entire display) may be an instance of what we have been calling consciousness without top-down attention (Koch and Tsuchiya, 2008). Note, however, that the converse is not true. Consciousness without top-down attention, such as faces presented in the periphery in a dual-task, can be phenomenally experienced and cognitively accessed. A related concept is the "coarse and vivid" hypothesis by Campana and Tallon-Baudry (2013).

While phenomenology without any cognitive access is hard to establish, the neuronal effects of cognitive access can be deduced by employing a no-report paradigm, which has been gaining popularity in recent neuroimaging and neurophysiological studies (Frässle et al., 2014; Wilke et al., 2009; Vandenbroucke et al., 2014; Pitts et al., 2012; Pitts et al., 2014). In these studies, an initial experiment establishes the neural activity that is correlated with concurrent subjective and objective reports, for instance, during binocular rivalry. Subsequently, this neural activity is contrasted with the activity recorded under the same experimental setup, but now, without overt subjective reports, reducing the effects of cognitive access. With this no-report paradigm, Frässle and colleagues (2014) found that right frontal cortical activation during binocular rivalry, which had been previously claimed as the central neural correlate of consciousness (Rees, 2001; Bor and Seth, 2012; Dehaene and Changeux, 2011), is abolished by eliminating the act of reporting. Note, however, that even without reports, subjects continue to experience binocular rivalry and that their perceptual switches can be decoded by objective eye movements (Figure 5.3). No-report paradigms will be critical to distinguish the core neuronal correlates of phenomenal consciousness from neuronal pre-requisites or

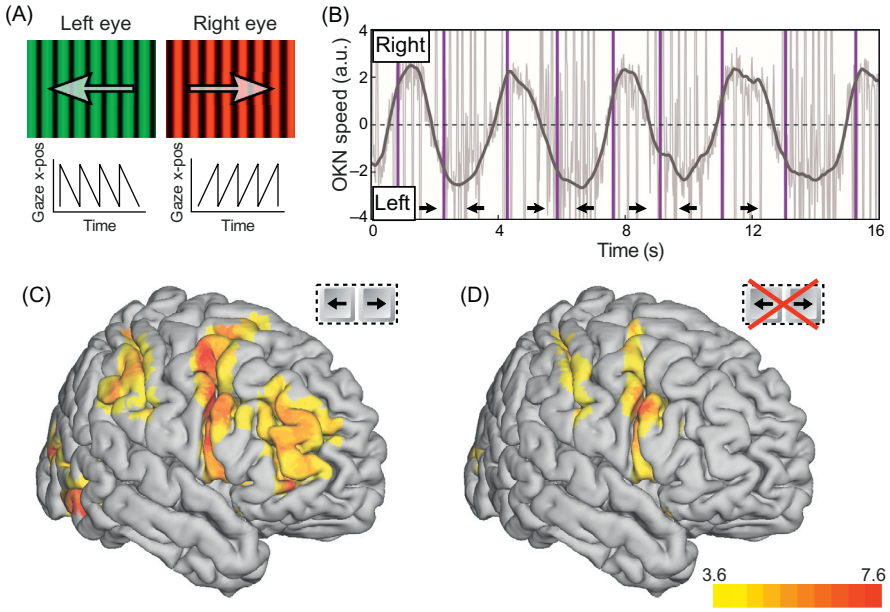

FIGURE 5.3 A no-report paradigm applied to binocular rivalry. (A) Green, leftward moving and red, rightward moving gratings were presented to the left and right eyes, respectively. This not only induces vigorous binocular rivalry between the two stimuli but also an optokinetic nystagmus (OKN), with characteristic slow and fast phase eye movements (Enoksson, 1963; Fox et al., 1975). (B) The speed of the OKN's slow phase (thick gray lines) can be used to infer the perceptual state of subjects (arrows at the bottom), which nicely coincides with their perceptual reports signaled via button presses (purple vertical lines). That is, when the subject reports seeing a red and rightward moving grating, both eyes execute the slow phase of the OKN to the right (see also Leopold et al., 1995). (C) and (D) fMRI BOLD contrasts at the time of perceptual transitions during rivalry compared with those during replay when subjects either (C) reported or (D) did not report their percept. Most of the right dorsolateral prefrontal cortex activation disappeared when subjects passively experienced rivalry without reports, implying that the right frontal activation is not a core neural correlate of consciousness (Aru et al., 2012; de Graaf et al., 2012) but may be a consequence of the need to report it. *Source: Taken from Frässle et al. (2014).*

consequences of consciousness, such as reports, working memory, and attention (Miller, 2007; Aru et al., 2012; de Graaf et al., 2012).

Another influential theory and model of consciousness is the global workspace theory of consciousness (Baars, 2005) and its elaboration into the global neuronal workspace (GNW) (Dehaene and Changeux, 2011). Dehaene and colleagues (2006) propose a tripartite ontology whereby any physical stimulus triggers either *subliminal*, *preconscious*, or *conscious processing*. What decides the fate of any stimulus is its strength and whether or not top-down attention is deployed. Their distinction maps onto ours if subliminal processing is equated with the upper and lower left quadrants and preconscious with the upper right quadrant. One important difference is our assumption that consciousness can occur without top-down attention (upper right quadrant in Table 5.1. Also see Cohen et al., 2012). Furthermore, the result of the above-mentioned no-report experiment of Frässle and colleagues (2014) challenges a central assumptions of GNW—that the central broadcasting that gives rise to conscious perception must always occur in prefrontal cortex.

Recently, Graziano and Kastner (2011) proposed that conscious awareness can be considered as a perceptual reconstruction or model of attention, both of one's own as well as that of other people. It is a second-order representation of attention ("what am I looking at and what are other people looking at"). Their view on the relationship between attention and consciousness is left ambiguous[1] (see the commentaries in Koch, 2011).

OPTOGENETIC STUDIES TO ACHIEVE CONSCIOUSNESS WITH NO ATTENTION IN ANIMALS

How can we test if it is possible to perceive anything in the complete absence of top-down attention? No psychophysical manipulation may be effective in completely eliminating top-down selective attention (Cohen et al., 2012). A more radical alternative is to directly and mechanistically intervene into the brain to turn off top-down attention. Brain science has developed highly specific molecular tools to directly, transiently, reversibly but invasively manipulate the brain at the circuit level.

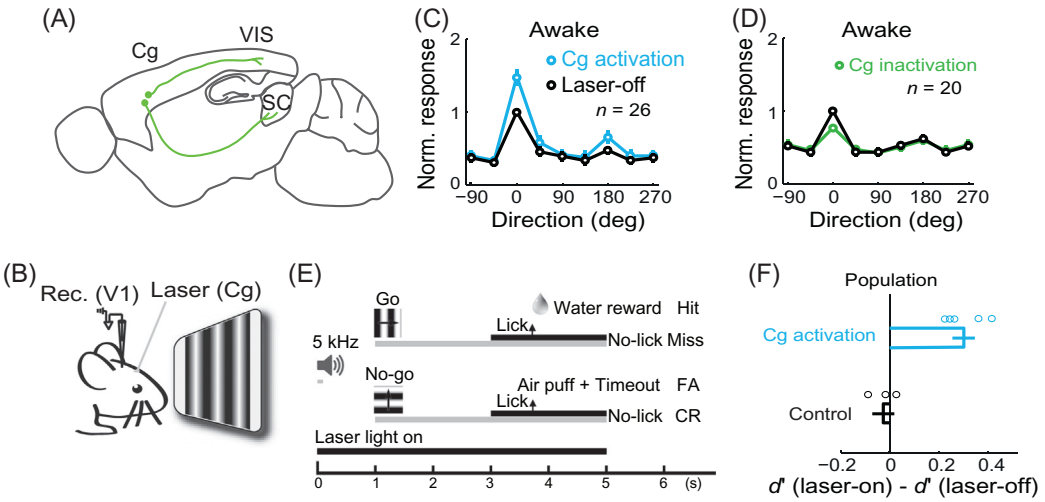

FIGURE 5.4 Optogenetic manipulation of top-down attention. (A) The cingulate cortex (Cg) in mice is anatomically and functionally homologous to the frontal eye field in primates, an important source of top-down spatial attention. (B) A genetically targeted subset of neurons in Cg, which directly project to the primary visual cortex (V1), can be selectively activated or inactivated by optogenetical tools, while neuronal activity can be simultaneously recorded from single neurons in V1. (C) and (D) Cg activation enhanced (C) and inactivation reduced (D) the orientation tuning of the V1 neurons. (E) In the behavioral task, mice performed a go/no-go orientation discrimination task by licking/no-licking a water tube (Lee et al., 2012). (F) The behavioral performance of orientation discrimination in these animals was enhanced by selective activation of the cingulate neurons. Such optogenetic techniques are becoming ever more precise in terms of their ability to intervene into the many tangled circuits of the central nervous system. Thus, it may soon be possible to experimentally block all top-down attentional modulation in such animals on a trial-to-trial basis and evaluate their behavior.

At present, the most powerful way to accomplish this is to rely on rapidly advancing optogenetic techniques in animals, especially in mice (Deisseroth, 2011; Yizhar et al., 2011) and to a lesser extent in monkeys (Han et al., 2009; Gerits et al., 2012; Diester et al., 2011). While experiments in animals pose their own challenges for consciousness research (Boly et al., 2013), techniques available for animal research is much more powerful than those available for human research. With the combined knowledge of cell-type specific brain-wide connectivity (Oh et al., 2014) and molecular promoters expressed by these neurons and their interconnections, it has become possible to transiently knock out the axons that project to early visual cortices from frontal and parietal areas as well as higher-order visual cortices. In the limit, one would obtain a purely feedforward set of cortical regions (with local inter-areal feedback) but no modulatory input from sub-granular layers in higher regions reaching down into superficial layers into earlier cortical or thalamic regions (Cruikshank et al., 2010).

Consider the experiment by Zhang and colleagues (2014). In primates, the neuronal source of top-down attentional amplification includes parts of frontoparietal cortex (Tsushima et al., 2006), such as FEF (Noudoost et al., 2010; Bressler et al., 2008). In mice, an anatomical and functional homologue area is the cingulate cortex (Cg) (Figure 5.4A). Selective activation and inactivation of Cg neurons (Figure 5.4B) that project to the early visual areas (V1) enhanced or reduced orientation tuning of the V1 neurons (Figure 5.4C and D). Remarkably, Cg activation also enhanced behavioral performance of the mice (e.g., 0° vs 90° orientation discrimination in a go/no-go task, Figure 5.4E and F).

As is exemplified in the study by Zhang and colleagues, the extraordinary rapid development of ever more refined transgenic mice as well as viral techniques, both of which target specific, molecular and projectional defined neuronal populations that can be labeled, and turned on or off from anywhere from milliseconds to hours has given systems neuroscience an amazing ability to delicately, reversibly and transiently intervene and to observe the phenotype at the behavioral and at the circuit level (Huang and Zeng, 2013). The temporal precision of experimental control is better than 10 ms while the spatial one is limited by the size of the optical stimulation.

A major drawback of these molecular tools is their invasive nature, making them currently unsuitable for routine human use (although clinical trials for therapeutic intervention to alleviate retinal blindness in patients are being considered). Multi-focused ultrasound inactivation is a promising interventional technique that

is now being tested in patients in clinical trials to study the extent to which gray-matter volumes on the order of several mm can be safely and routinely activated or inactivated (Legon et al., 2014; Bystritsky et al., 2011; Min et al., 2011; Tyler et al., 2008; Yoo et al., 2011).

If top-down attention were to be completely, but transiently, inactivated by such a manipulation, the affected animal should be unable to perform a visual discrimination task if the target is presented together with distractors, whereas they would be able to perform the task at the normal, pre-intervention level if the target is presented without distraction. This would demonstrate that top-down attention would not be necessary for processing a single, isolated stimulus in an otherwise empty visual field. (Note in the above-mentioned study in mice, behavioral performance under Cg inactivation was not reported. It is also unclear if the visual orientation discrimination requires substantial amount of attention for mice such that it cannot be performed under the dual-task paradigm.)

To make sure that these tasks are performed consciously, the mice or monkeys could be trained to report their confidence via post-decision wagering (Kepecs et al., 2008; Kiani and Shadlen, 2009; Persaud et al., 2007). As the confidence or metacognitive judgment is likely to be mediated by medial orbito-frontal areas (Fleming et al., 2010) (but also see Komura et al., 2013), knocking out top-down attention in the cingulate cortex might not affect confidence judgment.

CONCLUDING REMARKS: DO THESE CONCLUSIONS HOLD FOR REAL LIFE?

It could be contested that top-down attention without consciousness and consciousness with little or no top-down attention are arcane laboratory curiosities, with little relevance to the real world. We believe otherwise.

A lasting insight into human behavior—eloquently articulated by Friedrich Nietzsche and, later on, by Sigmund Freud—is that much action bypasses conscious perception and introspection. In particular, Goodale and Milner (2004) isolated highly trained, automatic, stereotyped and fluid visuo-motor behaviors that function in the absence of phenomenal experience. As anybody who runs mountain trails, climbs, plays soccer, or drives home on automatic pilot knows, such sensory-motor skills—dubbed *zombie behaviors* (Koch and Crick, 2001)—require rapid and sophisticated sensory processing. Confirming a long held belief among trainers, athletes performing their high-performance skills can do better under skill-irrelevant dual-tasks conditions (i.e., paying attention to tones) than when paying attention to their exhaustively trained behaviors (Beilock et al., 2002). This also appears to be true for keyboard typing, something most of us are highly trained at (Logan and Crump, 2009).

The history of any scientific concept (e.g., energy, atom, gene) is one of increasing differentiation and sophistication until its essence can be explained in a quantitative and mechanistic manner in terms of elements operating at a lower, more elemental level. We are very far from this ideal in the inchoate science of consciousness. Yet functional considerations and the empirical and conceptual spadework of many early twenty-first century scholars make it clear that these psychologically defined concepts, top-down attention and consciousness, so often conflated, are not the same. One consequence of this distinction is that many of the neuronal correlates of consciousness that have been reported are probably confounded by the neuronal correlates of attention (Macknik and Martinez-Conde, 2007; Watanabe et al., 2011; Koch and Tsuchiya, 2012; Miller, 2007; Aru et al., 2012; de Graaf et al., 2012). These empirical and functional considerations clear the deck for a concerted attack, employing powerful interventionalist tools in nonhuman animals or in people, on the core problem—that of identifying the necessary and sufficient neural causes of any one conscious percept.

QUESTIONS FOR FURTHER RESEARCH

1. How much of the quality of *gist*, a high-level semantic description of a scene (e.g., two people drinking, a man walking a dog), depend on focal, top-down attention? Specifically, how good are people at describing the gist of novel, natural scenes verbally under dual-tasks conditions (Fei-Fei et al., 2007)? Can people give good metacognitive confidence judgment about the unattended aspects of the scene (Kunimoto et al., 2001; Kanai et al., 2010; Persaud et al., 2007)? In most dual tasks, subjects are exposed to a lengthy training to stabilize the performance. Is conscious perception of gist without attention possible in untrained subjects (Joseph et al., 1997; Braun, 1998)?
2. Certain simple tasks (e.g., rotated L vs T, red/green vs green/red, Figure 5.2) seem impossible to perform even after extended period of training (Fei-Fei et al., 2005). Why? Are none of the aspects of these unattended stimuli perceived when attention is withdrawn? Or, are the elementary features or the global impression of these objects perceived? Is the positional relationship of elementary features difficult to perceive under poor attention? Can psychophysical and computational modeling of peripheral vision

predict what aspects of the neuronal processing are affected by attention (Freeman and Simoncelli, 2011; Rosenholtz et al., 2012)?

3. What are the neuronal mechanisms that lead to improved zombie behaviors in the near absence of top-down attention (Beilock et al., 2002; Logan and Crump, 2009)? Do those aspects of reasoning, language processing and thinking that proceed in the absence of consciousness (Jackendoff, 1996) function better without top-down attention? What are the neuronal mechanisms where attention or consciousness interferes with the desired task performance?
4. This review focuses on the selective amplification (and to a lesser extent inhibition) by top-down attention and its relationship to consciousness. Another potential role for top-down attention is to integrate information. While integration of information has been suspected to be the core of consciousness (for a review see Mudrik et al., 2014), the precise relation between integration, consciousness and attention is unclear. Many experiments have already established that a consciously perceived object can influence the processing of invisible objects, a form of integration of conscious and non-conscious perceived objects. Beyond such integration, recent studies demonstrate that integration of information between features within a natural photograph (Mudrik et al., 2011) and multiplication of two digits (Garcia-Orza et al., 2009) is possible even when the stimulus array itself remains perceptually invisible. What is the limit of non-conscious integration, in terms of spatial and temporal windows as well as cross modalities (Mudrik et al., 2014; Faivre et al., 2014)? Does non-conscious information integration depend on top-down attention? Theoretically, what is the role of the top-down attention in the IIT of consciousness (Tononi, 2004; Oizumi et al., 2014)? What does the theory say about consciousness without attention, attention without consciousness, and the opposing effects of consciousness and attention?
5. What are the effects of attention and consciousness during perceptual switches of multi-stable percepts? Some studies report that withdrawing top-down attention from ambiguous stimuli reduces the rate of perceptual switches (Paffen et al., 2006; Pastukhov and Braun, 2007), while others claim that it completely abolishes binocular rivalry (Zhang et al., 2011; Brascamp and Blake, 2012). With respect to consciousness, do perceptual switches occur even when the ambiguous stimulus itself is rendered invisible? When a left-going cloud of dots is presented to one eye and a right-going cloud to the other eye, these dots alternate in conscious perception, a form of binocular rivalry. Platonov and Goossens (2014) found that when the luminance of the dots is lowered, subjects start to lose conscious sensation of visual motion in the display. Strikingly, however, subjects can still guess the direction of the motion, which exhibit typical properties of binocular rivalry; the strength of the stimulus on the left eye determines the dominance duration of the (guessed and invisible) stimulus on the right eye, and the detection threshold for a probe presented to the suppressed eye is higher than that to the dominant eye. Such binocular rivalry between invisible stimuli are consistent with two recent independent reports (Dieter et al., 2013; Zou et al., 2014). Can such perceptual switching occur during loss of consciousness due to anesthesia (Bahmani et al., 2014) or sleep?

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NOTE

1. For instance, "Awareness, therefore, is not the same thing as attention, . . ." (p. 3) and "In the present hypothesis, therefore, the relationship between attention and awareness is rather complex" (ibid. p. 12).

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CHAPTER

6

Intrinsic Brain Activity and Consciousness

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OUTLINE

THE BRAIN AT REST

Even when the mind is free to rest and do nothing, spontaneous cognition tends to gravitate toward thoughts and feelings. This means that the apparently idle brain is, instead, constantly active. The first biological evidence for a constantly active brain came from electroencephalographic (EEG) recordings back in 1929. At that time, Berger (1929) showed that electrical oscillations detected by EEG did not cease even when the subject was not performing any particular task. More recently, brain imaging research corroborated these first EEG observations. Positron emission tomography (PET) studies were provoked to focus on intrinsic activity when metabolic decreases were serendipitously noticed during task performance as compared to a passive state, such as visual fixation or eyes closed. These decreases were systematically observed for specific brain areas, namely the posterior cingulate cortex and adjacent precuneus as well as the anterior cingulate cortex and mesiofrontal regions, widely known as the default mode network (DMN; Figure 6.1) (Binder et al., 1999; Mazoyer et al., 2001; Shulman et al., 1997).

An evident question was whether these task-related deactivations were merely "activations" during resting state or something more fundamental to brain function. To address this question, two critical observations were made. First, during task performance, typically there is an excess in oxygen availability compared to the oxygen consumed in certain brain regions; hence, "activation" can be defined as the transient fall in the ratio of the oxygen consumed to the oxygen delivered (i.e., the oxygen extraction fraction (OEF)). Second, during rest, blood flow and oxygen consumption are closely matched, namely that the OEF is uniform around the brain. Consequently, the "activations" as defined above were expected to be absent in a resting state (Raichle et al., 2001).

Indeed, it was found that the brain at rest did not show any "activations" even in the regions which showed systematic metabolic decreases during task performance. In contrast, these areas were characterized by an ongoing functionality which was interrupted during goal-directed behaviors, and hence were considered as default functions (Raichle et al., 2001). Consequently, the DMN regions did not differ from any other brain areas during rest from a physiological

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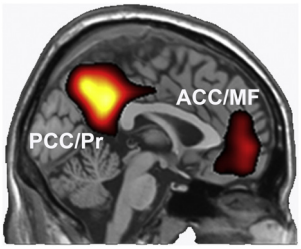

FIGURE 6.1 The default mode network was initially identified by means of positron emission tomography as a set of regions showing systematic deactivations during task performance. The network classically encompassed posterior cingulate cortex and adjacent precuneus (PCC/Pr) as well as anterior cingulate cortex and mesiofrontal areas (ACC/MF). Using functional magnetic resonance imaging, the same areas showed functional connectivity also during resting state, suggesting that this intrinsic mode of activity is fundamental to brain function.

perspective. Such brain activity has been coined as the brain's "dark energy" because the brain uses most of its forces for ongoing, spontaneous functions (Raichle, 2010). This is interesting if one considers that the human brain is approximately 2% of the weight of the body and yet accounts for 20% of its energy consumption (Raichle and Snyder, 2009). It has been estimated that up to 80% of this energy consumption is used to support neuronal signaling, suggesting that most of the consumed energy is used for functional activities. Stimulus and performance-evoked alterations, instead, are small by comparison (typically 5%) and rarely do they change overall brain energy consumption (Raichle and Mintun, 2006). In other words, conscious reportable awareness rests upon a complex, dynamically organized, not necessarily conscious state of brain activity that is energetically expensive. The legitimate question, then, is to what degree the resting state paradigm can be used for studying consciousness-related processes.

THE RESTING STATE PARADIGM

The resting state paradigm is particularly appealing because it does not require sophisticated experimental setup to administer external stimuli and surpasses the need for subject's collaboration (Soddu et al., 2011). As such, it is suitable for the study of subjects who are unable to communicate in a functional manner, such as babies, neurologic and neuropsychiatric patients. In particular, resting state analyses can be used in the clinical setting to identify group differences, obtain patient-specific diagnostic and prognostic information, perform longitudinal studies and monitor treatment effects, cluster heterogeneous diseases, such as schizophrenia, or even guide treatments, such as surgical interventions (Fox and Greicius, 2010). Therefore, to decipher the conscious counterpart of resting state is of major clinical importance.

Using functional magnetic resonance imaging (fMRI), the brain's activity at rest is characterized by spontaneous low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal, in the range of 0.01−0.1 Hz. These spontaneous BOLD fluctuations cannot be attributed to peripheral noise, like cardiac and respiratory fluctuations, motion of the subject etc. Rather, they show synchronized activity with other functionally related brain regions (Fox and Raichle, 2007) in a way that the brain can be organized in large-scale cerebral networks (Figure 6.2) (Damoiseaux et al., 2006). The first demonstration that fluctuations in the fMRI signal in absence of a task were correlated among functionally related areas, and therefore that resting signals were not just noise, was done by Biswal and collaborators (1995). In this seminal work, the sensorimotor cortex was activated after bilateral finger movement; at the same time during rest, low frequency fMRI signal fluctuations within these regions were functionally connected, namely that they showed increased temporal correlations among each other (Friston, 1994). In that sense, for the first time low-frequency fluctuations were linked to the analyses of resting state functional connectivity.

Collection of fMRI Resting State Data

A first debate over fMRI resting state connectivity analyses concerns methods of collecting "rest" data. The issue refers to whether fMRI data collected as pure rest scans (i.e., continuous collection of fMRI volumes), or as interleaved resting blocks (i.e., volumes corresponding to resting periods or to eye fixation in block or mixed blocked designs), or as residual time courses (i.e., from event-related designs) can lead to different connectivity maps. When rest volumes from mixed blocked/event-related design and the residuals from event-related data were compared to with pure rest data, it was found that the interleaved resting periods were both qualitatively and quantitatively similar to those of pure scans. On the other hand, residuals had distinct quantitative differences, meaning that after direct statistical comparison to pure rest, regions such as posterior cingulate/precuneus and lateral parietal areas showed decreased correlation coefficients (Fair et al., 2007).

Others, however, question this conclusion, on the grounds that subjects can be in different cognitive or affective state when performing a challenging mental or emotional task. It was indeed found that such differential subjective states might affect either the rest

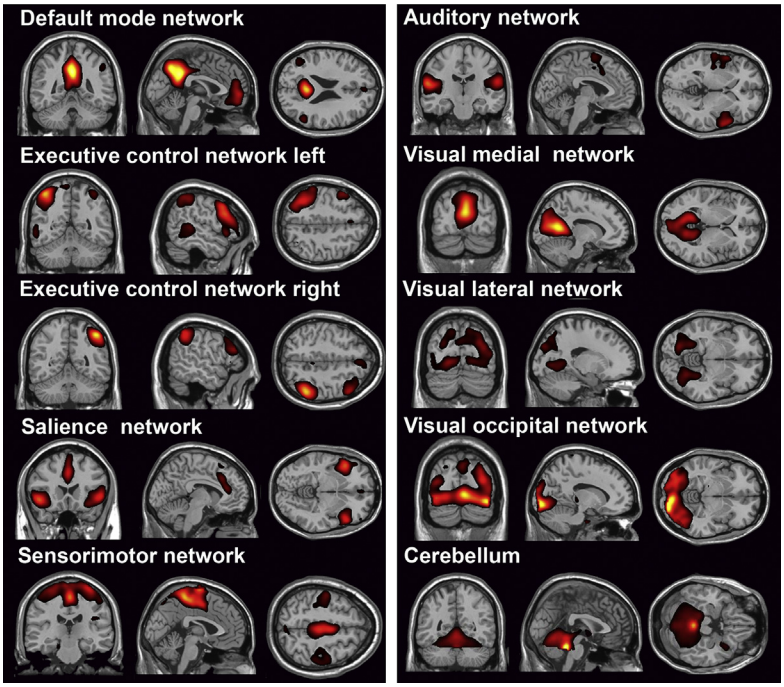

FIGURE 6.2 By means of neuroimaging during resting state, several networks of cognitive relevance can be identified in healthy conditions. The figure illustrates functional connectivity in 10 intrinsic connectivity networks as identified by data-driven independent component analysis performed on fMRI data obtained from 10 healthy volunteers. Group-level spatial maps are rendered on a structural T1 magnetic resonance template in coronal, sagittal and axial sections. *Source: Figure is adapted from Heine et al. (2012).*

blocks taken from a blocked design or the pure rest scans acquired directly after the task (Pyka et al., 2009). There are methods to statistically mitigate the effects of task blocks from a block design, such as to regress out task effects or by means of a Hanning function that de-weights the time points at the beginning and end of the rest blocks. Conceptually, these studies show that many factors influence resting-state functional connectivity. Practically, perhaps the best solution is to acquire continuous pure rest scans at the beginning of the scanning session to minimize the influence of cognitive and emotional tasks that vary across studies (Whitfield-Gabrieli and Ford, 2012).

Analysis of fMRI Resting State Data

For the analysis of resting state fMRI acquisitions, two main approaches are currently employed: hypothesis-driven seed-voxel correlation analysis and data-driven independent component analysis (ICA). The seed-voxel approach uses extracted fMRI signal from a region of interest and determines the temporal correlation between this signal (the seed) and the time course from all other brain voxels. This creates a whole-brain voxel-wise functional connectivity map of covariance with the seed region. This approach is the most direct way to measure functional connectivity. It is attractive and elegant for many researchers as the data can be interpreted relatively easily when a well-defined seed area is used. A drawback with this methodology concerns the selection of a proper seed region because, in principle, it can lead to as many possible overlapping networks as the number of possible seeds (Cole et al., 2010).

Data-driven ICA overcomes the need of *a priori* seed regions by analyzing whole-brain connectivity patterns. ICA divides an entire dataset into different maximally statistical independent components and, thus, is able to isolate cortical connectivity maps from non-neural signals (Beckmann et al., 2005). Spontaneous activity is therefore automatically separated from noise, such as head motion or physiological confounds (Beckmann and Smith, 2004). This method has the advantage that it can evaluate and compare the coherence of activity in multiple distributed voxels and hence divide different brain networks into different components (Figure 6.2). However, the determination of the proper dimensionality, namely the "right" number of estimated components, is debatable. For example, the extraction of many components can result in the spatial segregation of the network of interest into multiple sub-networks (Smith et al., 2009). Also, ICA does not provide any classification or ordering of the independent components. It is therefore perceived as more difficult to understand due to the complex representation of the data. One way to identify the network of interest is to calculate the fit between the components' spatial pattern and the pattern of a predefined template which represents the network (Greicius et al., 2004). Nevertheless, in cases of deformed brains such as in patients with traumatic brain injuries, the result should be interpreted with caution. This is because in the extreme conditions where a patient

shows only one component of neuronal origin, the use of a single template-matching method would lead to identify this component as the network (template) we are investigating each time (Heine et al., 2012; Soddu et al., 2012). This issue can be overcome by means of a multiple-template matching procedure, where the goodness of fit is maximized among several pairs of component-template comparisons, and hence the chances to identify the "proper" network are higher (Demertzi et al., 2014).

INTRINSIC BRAIN ACTIVITY REFLECTS REPORTABLE AWARENESS

The topographies of spontaneous resting state networks often resemble the functional networks recruited by fMRI tasks (Fox et al., 2006). Thus, these networks are also known as intrinsic connectivity networks (Seeley et al., 2007). Intrinsic connectivity networks account for a significant fraction of the variability in measured event-related BOLD responses (Fox et al., 2006). For example, BOLD response magnitude can predict perception of visual contrast (Ress and Heeger, 2003), identification of fearful expressions (Pessoa and Padmala, 2005), and working memory performance (Pessoa et al., 2002). Interestingly, such inter-trial variability cannot be attributed to the physical properties of the stimuli but rather to the intrinsic organization of the brain. Similarly, paradigms which study prestimulus activity, assumingly reflecting resting state activity, showed that the subsequent perception of somatosensory stimuli close to perceptual threshold was linked to an elevated baseline activity of a lateral frontoparietal network (which is related to vigilance and monitoring of the external world). Conversely, a negative correlation was found between reports of conscious perception of the stimulus and baseline activity in a set of regions encompassing posterior cingulate/precuneus and temporoparietal cortices (DMN), relating to introspection and self-oriented processes (Boly et al., 2007). Likewise, prestimulus connectivity in brain areas related to the subjective perception of the body (anterior insular cortex) and to the modulation of pain (brainstem) determined whether a noxious event was to be perceived as painful (Ploner et al., 2010). Taken together, these studies suggest that baseline fMRI BOLD fluctuations may profoundly modify conscious reportable awareness.

In an oversimplified way, one could reduce the phenomenological complexity of conscious awareness into two components: external awareness, that is, everything we perceive through our senses (what we see, hear, feel, smell, and taste), and internal awareness or self-related mentation (Demertzi et al., 2013). In a combined fMRI-behavioral experiment, it was first shown that behavioral ratings of external and internal awareness had an anticorrelating pattern, switching their dominance on average every 20 s. It was further shown that subjective ratings for external awareness correlated with the activity of a lateral fronto-parieto-temporal set of regions. Conversely, behavioral reports of internal awareness were linked to the activity of midline anterior cingulate/mesiofrontal areas as well as posterior cingulate/precuneal cortices (Vanhaudenhuyse et al., 2011). These findings highlight that the anticorrelated pattern between the internal and external awareness system is of functional relevance to conscious awareness (Demertzi et al., 2013). Interestingly, such anticorrelated activity is also observed in the BOLD fMRI signal of resting state acquisitions so that the brain's baseline is organized in two widespread brain networks: an "extrinsic" and an "intrinsic" network (Figure 6.3) (Fox et al., 2005; Fransson, 2005; Golland et al., 2007; Tian et al., 2007). These two systems are also known as "task positive" (encompassing inferior parietal sulcus and inferior parietal lobule, precentral regions, dorsal lateral prefrontal cortex, MT+, insula, frontal operculum, and supplementary motor area) and "task negative" (encompassing regions of the DMN such as in the posterior cingulate and retrosplenial cortex, medial prefrontal, lateral parietal, superior frontal, parahippocampal gyri, inferior temporal, and cerebellar tonsils) (Fox et al., 2005) to describe the dampening of activation of the DMN during task performance (Mazoyer et al., 2001; Shulman et al., 1997). In contrast to the task-negative network/DMN which appear to include same brain regions, the task-positive network can be further subdivided into the salience network (implicated in the orientation towards important external stimuli, such as pain; Seeley et al., 2007), the dorsal attention network (proposed to mediate the top-down guided voluntary allocation of attention; Corbetta and Shulman, 2002), and (left and right) executive control/frontoparietal networks (involved in cognitive and language paradigms, perceptual, somesthetic and nociception processing; Laird et al., 2011).

Importantly, the anticorrelated task-positive and task-negative networks have been shown to be robust and reliable (Damoiseaux et al., 2006; Shehzad et al., 2009; Van Dijk et al., 2010; Zuo et al., 2010). Although currently it remains unclear how these competing brain systems are exactly regulated, it has been shown that the degree to which they are anticorrelated significantly associates with cognitive function (Keller et al., 2015; Whitfield-Gabrieli et al., 2009). For example, greater anticorrelation has been linked with superior task performance (Hampson et al., 2010; Kelly et al., 2008), suggesting that stronger anticorrelations reflect a more effective capacity to switch between internal and external modes of attention. Considering its

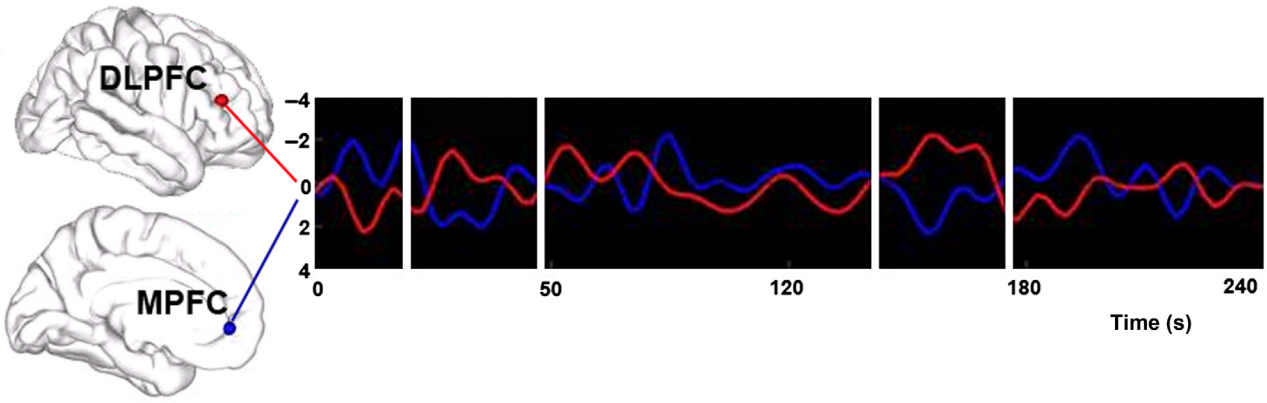

FIGURE 6.3 FMRI resting state is characterized by systems-level anticorrelations between the task-positive network (in red; encompassing mainly lateral frontoparietal areas) and of the default mode network (in blue; encompassing mainly medial anterior and posterior regions). The panel illustrates BOLD anticorrelated activity between key regions of each network, namely the dorsolateral prefrontal cortex of the task-positive network (DLPFC, in red) and the medial prefrontal cortex of the default mode network (MPFC, in blue). The cognitive significance of this activity in different mind states can be reflected as changes in functional connectivity.

subdivisions, the task-positive network conveys complex interactions with the DMN, such as that the salience can mediate the relationship between the DMN and the executive networks (Di and Biswal, 2014; Menon and Uddin, 2010; Sridharan et al., 2008).

From a theoretical perspective, the anticorrelation between the extrinsic and the intrinsic systems can be viewed as an alternating balance between the external and the internal milieu. According to a suggested framework, two complementary states of system imbalance are possible, where one system can be in a hyperfunctional state, while the other is hypoactive. Extrinsic system hyperfunction is expected to lead to a state of total sensorimotor absorption or "lost self." In contrast, intrinsic or default system hyperfunction is expected to lead to a state of complete detachment from the external world. A state where both extrinsic and intrinsic systems are hypofunctional is predicted to lead to markedly impaired consciousness as seen in disorders of consciousness (Soddu et al., 2009). Interestingly, a recent investigation in patients with disorders of consciousness showed that, next to DMN hypoconnectivity, a limbic system hyperconnectivity was observed, potentially reflecting a persistent engagement of residual neural activity in self-reinforcing neural loops, which, in turn, could disrupt normal connectivity (Di Perri et al., 2013).

A more recent proposal, adopting a similar systems-level approach, points to the functional separation of the dorsal and ventral subcomponents of the posterior cingulate cortex: the ventral posterior cingulate cortex appears to be highly integrated within the DMN, and is involved in internally directed cognition (e.g., memory retrieval and planning) whereas the dorsal posterior cingulate cortex shows a highly complex pattern of connectivity, with prominent connections to the frontal lobes (Leech et al., 2012). According to the suggested model, differential regional activity can be explained by considering three components, namely the arousal state, the milieu of attention (internal vs. external) and the breadth of attention (narrow vs. broad). The model proposes that through its interactions with the prefrontal cortex, the dorsal posterior cingulate is involved in controlling attentional focus. Hence, interactions of these posterior cingulate sub-regions with other intrinsic connectivity networks are then involved in shifting the balance of attention along an internal/external and broad/narrow dimension (Leech and Sharp, 2014).

Methodological Issues of the Anticorrelations

Importantly, the measurement of anticorrelations cannot be discussed without mentioning the methodological issues that have been raised since their first description. In particular, it has been suggested that the BOLD anticorrelations appear as a result of regressing out the brain's global signal. The global signal is the average signal across all voxels in the brain that needs to be removed when performing seed-based analysis to improve the specificity of functional connectivity (Fox et al., 2005; Van Dijk et al., 2010; Weissenbacher et al., 2009). This is because the global signal correlates with respiration-induced fMRI fluctuations, and hence it is thought to be of non-neuronal origin. Indeed, it has been observed that variation in breathing rate and depth during rest has a significant impact on functional connectivity because the induced fMRI signal changes can occur at similar spatial locations and temporal frequencies (Birn et al., 2006). One practical consequence of removing the global signal is that positive functional connectivity within the DMN is dramatically reduced. On the one hand, this suggests a reduction in false

positive rates. On the other, the global signal regression shifts the distribution of the correlation values in the negative direction, such that they must sum to less than or equal to zero (Murphy et al., 2009). Thus, it has been suggested that anticorrelations in resting-state connectivity may be artificially introduced by global signal regression (Murphy et al., 2009). An alternative method proposes an anatomical component-based noise correction method (aCompCor; Behzadi et al., 2007), which models the influence of noise as a voxel-specific linear combination of multiple empirically estimated noise sources, such as the white matter and the cerebrospinal fluid. This is done by deriving principal components from these noise regions and by including them as nuisance parameters within the general linear model.

Although the interpretation of anticorrelation is still under debate, several lines of evidence support that they are of functional significance. First, the global signal does not distribute specifically to regions of the anticorrelated networks (Fox et al., 2009). Second, anticorrelated relationships between the DMN and executive attention components of the resting-state networks have been found using ICA as well, which does not involve global signal regression (Cole et al., 2010; Demertzi et al., 2011; Zuo et al., 2010). Third, computational simulations of monkey and human brains suggest existence of spontaneous anticorrelated networks (Deco et al., 2009). Fourth, the neuronal origins of the anticorrelated BOLD fluctuations have been explored by electrophysiological work in cats, in which anticorrelated fluctuations of local field potential have been shown between homologues of the DMN and the task-positive network (Popa et al., 2009). Finally, anticorrelations are associated with behavior (Hampson et al., 2010; Kelly et al., 2008), and abnormalities in anticorrelated networks characterize neuropsychiatric disorders, such as schizophrenia (Whitfield-Gabrieli et al., 2009), attention deficit hyperactivity disorder (Castellanos et al., 2008), bipolar disorder (Chai et al., 2011), and Alzheimer's disease (Wang et al., 2007). Such imbalance between the two systems can be also observed in healthy but altered states of awareness, like hypnosis (Demertzi et al., 2011). More specifically, compared to autiobiographical mental imagery during which the subject's own pleasant memories had to be recollected, in hypnosis (i.e., revivication of these pleasant memories after hypnotic induction) there were reductions in functional connectivity in the external awareness system. Interestingly, these reductions in connectivity were parallel to subjective ratings of increased sense of dissociation from the environment and reduced intensity of external thoughts, next to a relatively lower connectivity of the DMN (Demertzi et al., 2011). Taken together, resting state fMRI connectivity studies of modified awareness in healthy and psychopathological conditions suggest a tight link between intrinsic anticorrelations and reportable awareness.

The Functional Significance of Intrinsic Brain Activity

As mentioned above, a current challenge is to decipher the functional role of the systems-level intrinsic connectivity. To date, considerable evidence supports the view that the DMN mediates consideration of one's own thoughts and feelings, or self-referential processing (D'Argembeau et al., 2005; Gusnard and Raichle, 2001; Johnson et al., 2002; Kelley et al., 2002; Moran et al., 2006; Northoff and Bermpohl, 2004; Whitfield-Gabrieli et al., 2011). In these studies, people typically make judgments about their own feelings or about their own characters. Although self-referential tasks involve stimulus presentation and task performance rather than rest, they engage two medial core components of the DMN, namely the medial prefrontal and the posterior cingulate cortex. Indeed, these midline regions have been thought to be involved not only with self-referential processing, but also with remembering one's past, planning one's future, and forming one's beliefs (Buckner et al., 2008; Raichle and Snyder, 2007). The frequent activation of these DMN components in memory retrieval can be interpreted as a sort of time travel to one's own past to retrieve memory for a prior experience. Interestingly, greater activation is associated both with worse memory encoding (which requires attention to one's external environment) and better memory retrieval (which requires attention to one's internal environment) (Daselaar et al., 2009). What appears to be shared across the kinds of tasks that activate these DMN midline regions is a focus on oneself—one's feelings, one's character, one's memories, and one's aspirations. Therefore, as people are at rest, it may be hypothesized that they are spontaneously engaged in self-reflection because the same brain regions are activated in active and controlled tasks that demand self-reflection.

Although there is a striking similarity between the DMN and brain regions activated by self-reference tasks, the two networks are not identical. Explicit self-reference preferentially engages dorsal mesiofrontal areas, rest preferentially engages the precuneus, and both self-reference and rest commonly engage ventral mesiofrontal and posterior cingulate cortex. These findings indicate that there are both associations and dissociations between the neural systems underlying explicit self-reference and the DMN (Whitfield-Gabrieli et al., 2011). Components of the DMN have also been activated

in social cognition—thinking about other people or what other people are thinking about (theory of mind) (Saxe et al., 2004; Schilbach et al., 2008). The overlap in brain regions between areas engaged in reflection about oneself and reflection about other people raises the possibility that thinking about other minds involves a sort of simulation of the same processes that are engaged in thinking about oneself.

Taken together, changes in the DMN functional connectivity could reflect restricted abilities for self-referential processing. One should keep in mind, though, that our limited understanding of the dynamic neural complexity underlying consciousness, its resistance to quantification in the absence of communication, and the persistence of functional connectivity in unresponsive conditions like in anesthetized monkeys (Vincent et al., 2007) make it difficult to establish strong claims about self-consciousness in non-communicating subjects. With regard to the latter issue, indeed there is a strong link between functional connectivity and the underlying anatomical connections (Honey et al., 2009). The challenge lies as to how one can best identify the contribution of each source of connectivity to consciousness. In a recent study with primates scanned under wakefulness, moderate and deep anesthesia, it was shown that during propofol-induced unconsciousness, functional connectivity was reduced for long-range connections and it was fluctuating less among distinct consciousness states, compared to wakefulness. Interestingly, the brain's "preference" for this state during anesthesia was mostly explained by the underlying structural connectivity (Barttfeld et al., 2015). These findings highlight the relative contribution of resting state functional and structural connectivity to consciousness, with potential applications in conditions of reduced levels of consciousness with healthy and pathological human subjects.

INTRINSIC BRAIN ACTIVITY REFLECTS LEVELS OF CONSCIOUSNESS

From a clinical perspective, the level of consciousness is evidenced by eye opening (Laureys, 2005). In that sense, in conditions like sleep, anesthesia, and coma subjects remain unresponsive to external stimulation, at least in a way which reveals conscious perception. Therefore, by studying systems-level (Figure 6.2) resting state fMRI connectivity changes in physiological, pharmacological and pathological alterations of consciousness, one can better understand the functional role of intrinsic brain activity to healthy consciousness.

With regard to sleep, DMN connectivity shows no changes during light sleep (Horovitz et al., 2008; Larson-Prior et al., 2009). As sleep advances, there is a decrease between frontal and posterior parts for the DMN, yet connectivity does not fully disappear (Horovitz et al., 2009). In deep sleep, the intrinsic architecture changes by showing increased modularity, which hinders the brain to integrate information (Boly et al., 2012). Connectivity of the executive control networks is not altered during light sleep (Larson-Prior et al., 2009) but shows reductions in deep sleep (Sämann et al., 2011). The visual lateral network (mostly implicated in processing complex stimuli), the visual medial network (involved in simple visual stimuli) and the visual occipital network (activated with higher-order visual stimuli) (Laird et al., 2011) show no difference in connectivity in light sleep (Larson-Prior et al., 2009), Finally, the cerebellum which is associated with action and somesthesis (Laird et al., 2011), has not been thoroughly studied in altered states of consciousness yet.

With regard to sedation and anesthesia, little (Greicius et al., 2008) or no changes (Stamatakis et al., 2010) in DMN connectivity have been observed during moderate sedation. In unconsciousness induced by propofol (Boveroux et al., 2010; Schrouff et al., 2011) and sevoflurane (Martuzzi et al., 2010) decreases in connectivity were observed in the posterior cingulate of the DMN. Posterior cingulate changes during sedation were found to further include regions not traditionally considered to be part of the DMN, such as the motor/somatosensory cortex, anterior thalamic nuclei, and the reticular activating system (Stamatakis et al., 2010). The executive control networks showed reduced functional connectivity after propofol intake (Boveroux et al., 2010; Schrouff et al., 2011). The salience network under light sevoflurane showed increased connectivity between the anterior cingulate cortex and the insula, although connectivity between the insula and the secondary somatosensory cortex was reduced (Martuzzi et al., 2010). The sensorimotor network during light sedation showed increases in functional connectivity (Greicius et al., 2008) whereas no changes were identified for the visual network (Boveroux, et al., 2010; Martuzzi, et al., 2010).

With regard to coma and disorders of consciousness, connectivity in the DMN posterior cingulate was shown to be indistinguishable between controls and patients with locked-in syndrome (i.e., conscious but severely paralyzed), relatively preserved in patients in minimally conscious state (i.e., who show fluctuating signs of awareness but who remain unable to communicate), significantly reduced in patients in a vegetative state (i.e., awake but unconscious) (Demertzi et al., 2014; Vanhaudenhuyse et al., 2010) and could not be identified in brain death (i.e., irreversible coma with absent brainstem reflexes) (Boly et al., 2009). The

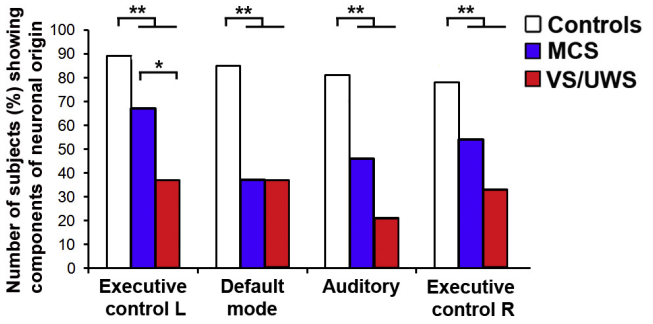

FIGURE 6.4 Systems-level resting state fMRI is disrupted in patients with disorders of consciousness, such as in minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome (VS/UWS). The figure illustrates that proportionally fewer patients, compared to healthy controls, show intrinsic connectivity networks of "neuronal" origin. Neuronality here refers to the spatial and temporal properties of the independent components, which were identified as the systems of interest, i.e., the executive control networks left and right, the default mode and the auditory network. *Source: Figure adapted from Demertzi et al. (2014).*

bilateral executive control networks were significantly less identifiable in terms of spatial and neural properties in patients compared to healthy controls (Figure 6.4) (Demertzi et al., 2014). The auditory system was among the sensory networks to be severely disrupted in terms of "neuronal" properties in patients (Figure 6.4). Interestingly, machine learning classification was able to accurately separate healthy controls from patients with 85% accuracy based on information about "neuronality" of this system and the DMN (Demertzi et al., 2014).

WHAT TO EXPECT FOR THE FUTURE

An intriguing direction for clinical translation is the use of real-time fMRI neurofeedback as a treatment for psychiatric diseases. Typically, during real-time fMRI patients are provided with a display (e.g., a thermometer-like representation) conveying the magnitude of activation in a specific brain region. Patients are then asked to use this feedback in order to increase or decrease their brain activation from that region. This setup allows patients to learn to regulate their brain activity, which can influence the mental processes mediated by that region (Caria et al., 2010; deCharms et al., 2005). The many neuroimaging studies of neuropsychiatric diseases are identifying brain regions and circuits that are atypical or dysfunctional in those diseases, such as the DMN, and these regions and circuits can be rationale disease-specific targets for learned regulation. Indeed, there is initial evidence that real-time fMRI targeted at clinically relevant brain sites can yield some positive outcomes in patients, including targeting the anterior cingulate cortex in chronic pain syndrome (deCharms et al., 2005) and auditory cortex in chronic tinnitus (Haller et al., 2010). Perhaps learned regulation of the DMN or other networks would minimize symptoms or enhance cognition in schizophrenia, depression, and other neuropsychiatric disorders (Whitfield-Gabrieli and Ford, 2012).

Finally, the resting state paradigm is expected to assist single-patient clinical diagnosis and prognosis. Especially for patients in non-communicating states of impaired consciousness, so far resting state fMRI-based differentiation of patients in separate clinical categories has been performed either at the group-level (Crone et al., 2014; Vanhaudenhuyse et al., 2010) or concerned the classification between healthy and pathological groups (Demertzi et al., 2014). A future challenge is to identify sensitive features which will be able to automatically separate between patients in distinct clinical states, such it has been previously performed with PET (Phillips et al., 2011) and EEG (Casali et al., 2013).

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CHAPTER

7

Sleep and Dreaming

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OUTLINE

Studying mental activity during sleep offers a unique opportunity to find out how changes in consciousness are associated with changes in brain activity. Indeed, sleep brings about at once the most common and the most dramatic change in consciousness that healthy subjects are likely to witness—from the near-fading of all experience to the bizarre hallucinations of dreams. At the same time, the brain goes through an orderly progression of sleep stages, which can be identified by recording the electroencephalogram (EEG), eye movements (EOG, electroculogram), and muscle tone (EMG, electromyogram), and which indicate that major changes in brain activity are taking place. Within each sleep stage, there are frequent, short-lasting EEG phenomena,

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such as slow oscillations and spindles, which indicate precise times at which brain activity undergoes important fluctuations. There are also orderly spatial changes in the activation of many brain regions, as indicated by imaging studies. All of this happens spontaneously and reliably every night. Moreover, similar changes occur in animals, which have spearheaded detailed studies of the underlying neural mechanisms.

This chapter will first examine how sleep is traditionally subdivided into different stages that alternate in the course of the night, and will consider the brain centers that determine whether we are asleep or awake. This chapter will then discuss how brain activity changes between sleep and wakefulness, and consider how this leads to the characteristic modifications of consciousness.

SLEEP STAGES AND CYCLES

In the course of the night, the electroencephalogram (EEG), electroculogram (EOG), and electromyogram (EMG) patterns undergo coordinated changes that are used to distinguish among different sleep stages (Figure 7.1).

Wakefulness

During wakefulness, the EEG is characterized by waves of low amplitude and high frequency. This kind of EEG pattern is known as *low-voltage fast-activity* or *activated*. When the eyes close in preparation for sleep, EEG alpha activity (8–13 Hz) becomes prominent, particularly in occipital regions. Such alpha activity is thought to correspond to an "idling" rhythm in visual areas. The waking EOG reveals frequent voluntary eye movements and eye blinks. The EMG reveals tonic muscle activity with additional phasic activity related to voluntary movements.

Sleep is traditionally categorized into non-rapid eye movement (NREM) sleep and REM sleep. Human NREM sleep, in turn, is divided into stages N1, N2, and N3.

NREM Sleep: Stage N1

Falling asleep is a gradual phenomenon of progressive disconnection from the environment. Sleep is usually entered through a transitional state, stage N1, characterized by loss of alpha activity and the appearance of a low-voltage mixed-frequency EEG pattern with prominent theta activity (3–7 Hz). Eye movements become slow and rolling, and muscle tone relaxes. Although there is decreased awareness of sensory stimuli, a subject in stage N1 may deny that he is asleep. Motor activity may persist for a number of seconds during stage N1. Occasionally individuals experience sudden muscle contractions (hypnic jerks), sometimes accompanied by a sense of falling and dream-like imagery. Individuals deprived of sleep often have "microsleep" episodes that consist of brief (5–10 s) bouts of stage N1 sleep; these episodes can have serious consequences in situations that demand constant attention, such as driving a car.

NREM Sleep: Stage N2

After a few minutes in stage N1, people usually progress to stage N2 sleep. Stage N2 is heralded in the

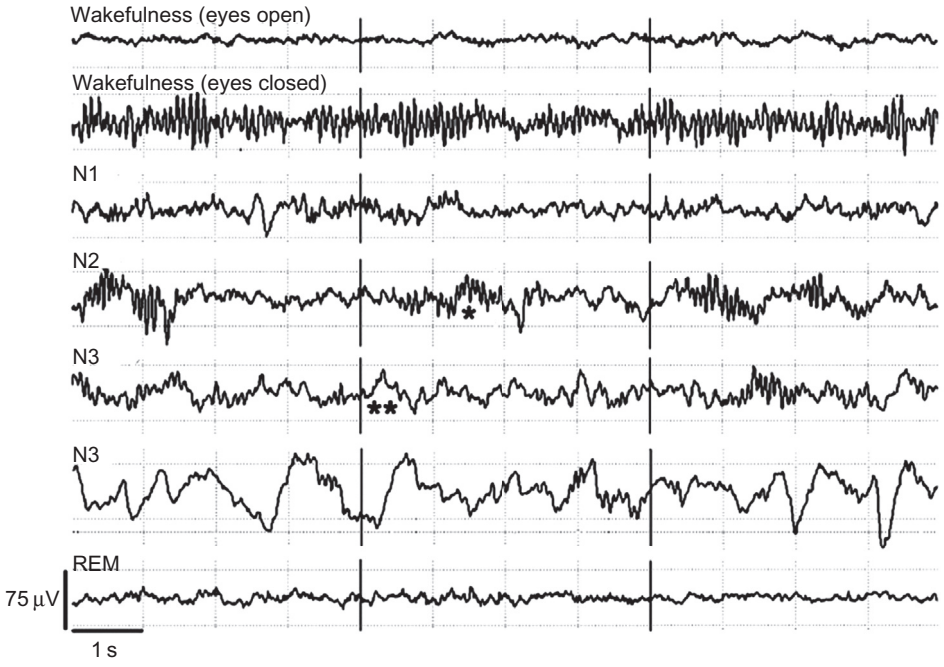

FIGURE 7.1 The human EEG during wakefulness and the different stages of sleep (*, sleep spindles; **, slow wave).

EEG by the appearance of K-complexes and sleep spindles, which are especially evident over central regions. K-complexes are made up of a high-amplitude negative sharp wave followed by a positive slow wave, and are often triggered by external stimuli. Sleep spindles are waxing and waning oscillations at around 12–15 Hz that last about 1 s and occur 5–10 times a minute. Eye movements and muscle tone are much reduced. At a behavioral level, stage N2 qualifies fully as sleep because people are partially disconnected from the environment, meaning that they do not respond to the events around them—their *arousal threshold* is increased. If stimuli are strong enough to wake them up, people in stage N2 will generally confirm that they were asleep.

NREM Sleep: Stage N3

Stage N2 is followed, especially at the beginning of the night, by a period called stage N3, during which the EEG shows prominent slow waves in the delta range (0.5–2 Hz, >75 μV in humans). Eye movements cease during stage N3 and EMG activity decreases further. Stage N3 is also referred to as *slow-wave sleep*, *delta sleep*, or *deep sleep*, since the threshold for arousal is higher than in stage N2. The process of awakening from slow-wave sleep is drawn out, and subjects often remain confused for some time.

REM Sleep

After deepening through stages N2–N3, NREM sleep lightens and returns to stage N2, after which the sleeper enters REM sleep (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957) also referred to as *paradoxical sleep* (Jouvet, 1962, 1965, 1998) because the EEG during REM sleep is similar to the activated EEG of waking or of stage N1. Indeed, the EEG of REM sleep is characterized by low-voltage fast-activity, often with increased power in the theta band (3–7 Hz). REM sleep is not subdivided into stages, but is rather described in terms of distinct tonic and phasic components. Tonic aspects are present throughout REM sleep. They include the activated EEG and, a generalized loss of muscle tone (except for the extraocular and middle ear muscles and the diaphragm), penile erections, and pupillary constriction (as a reflection of a parasympathetic dominance). Phasic features, which occur episodically during REM sleep, include irregular bursts of REM and brief contractions of middle ear and other muscles (twitches). Behaviorally, REM sleep is deep sleep, with an arousal threshold that is as high as in slow-wave sleep.

The Sleep Cycle

The succession of NREM sleep stages followed by an episode of REM sleep is called a sleep cycle, and lasts approximately 90–110 min in humans. As shown in Figure 7.2, there are a total of 4–5 cycles every night. Slow-wave sleep is prominent early in the night, especially during the first sleep cycle, and diminishes as the night progresses. As slow-wave sleep wanes, periods of REM sleep lengthen and show greater phasic activity. The proportion of time spent in each stage and the pattern of stages across the night is fairly consistent in normal adults. A healthy young adult will typically spend about 5% of the sleep period in stage N1, about 50% in stage N2, 20–25% in stage N3 (slow-wave sleep), and 20–25% in REM sleep.

Sleep During the Lifespan

Sleep patterns change markedly across the lifespan (Carskadon et al., 2002, 2004; Peirano et al., 2003; Jenni and Carskadon, 2004; Ohayon et al., 2004). Newborn infants spend 16–18 h per day sleeping, with an early version of REM sleep, called active sleep, occupying about half of their sleep time. At approximately 3–4 months of age, when sleep starts to become consolidated during the night, the sleep EEG shows more mature waveforms characteristic of NREM and REM sleep. During early childhood, total sleep time decreases and the REM-sleep proportion drops to

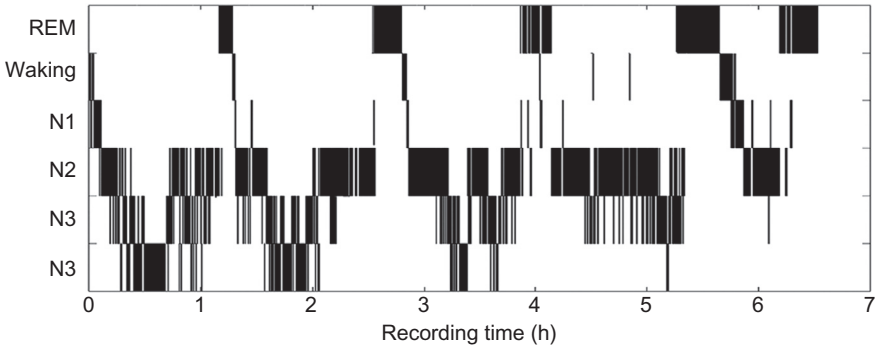

FIGURE 7.2 Hypnogram for an all-night recording in a young man. Note the occurrence of five sleep cycles, the predominance of slow-wave sleep (stage N3—the two of N3 rows correspond to stages 3 and 4 of the previous staging convention) early in the night and the increasing length of REM sleep episodes later in the night.

adult levels. The proportion of NREM sleep spent in slow-wave sleep increases during the first year of life, reaches a peak, declines during adolescence and adulthood, and may disappear entirely by age 60.

BRAIN CENTERS REGULATING WAKEFULNESS AND SLEEP

Wakefulness System

Maintenance of wakefulness is dependent on several heterogeneous cell groups extending from the upper pons and midbrain (the so-called *reticular activating system*, RAS (Lindsley et al., 1949; Moruzzi and Magoun, 1949)), to the posterior hypothalamus and basal forebrain. These cell groups are strategically placed so that they can release, over wide regions of the brain, neuromodulators and neurotransmitters that produce EEG activation, such as acetylcholine, histamine, norepinephrine, glutamate, and hypocretin (Figure 7.3, red). Cholinergic cells are located in the basal forebrain and in two small nuclei in the pons: the *pedunculopontine tegmental* and *lateral dorsal tegmental* nuclei (*PPT/LDT*). Both basal forebrain and pontine cholinergic cells fire at high rates in wakefulness and REM sleep, and decrease or stop firing during NREM sleep (el Mansari et al., 1989; Hobson et al., 1975; Lee et al., 2005a). Pontine cholinergic cells project to the thalamus, where they help depolarize specific and intralaminar thalamic nuclei. The latter, which are dispersed throughout the thalamus and project diffusely to the cortex, fire at very high frequencies during both wakefulness and REM sleep and help to synchronize cortical firing in the gamma (>28 Hz) range (McCormick, 1989; Steriade, 2004; Jones, 2005a). Cholinergic cells in the dorsal brainstem and nearby non-cholinergic cells also project to other cholinergic and non-cholinergic cells (many of them glutamatergic) in the basal forebrain, which in turn provide an excitatory input to the entire cortex (Jones, 2003, 2005a,b).

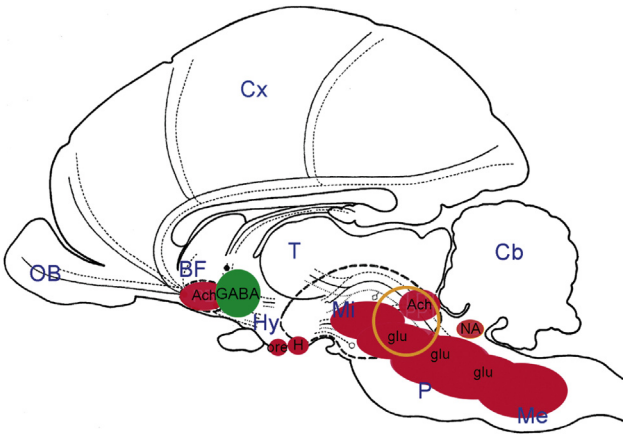

FIGURE 7.3 The major brain areas involved in initiating and maintaining wakefulness (red), NREM sleep (green), and REM sleep (orange). OB, olfactory bulb; Cx, cerebral cortex; Cb, cerebellum; T, thalamus; BF, basal forebrain; Hy, hypothalamus; Mi, midbrain; P, pons; Me, medulla oblongata; Ach, acetylcholine; glu, glutamate; NA, norepinephrine; H, histamine; ore, orexin/hypocretin.

Cholinergic neurons in the pons also project to the posterior hypothalamus, where histaminergic neurons are located in the *tuberomammillary nucleus* (Brown et al., 2001). Histaminergic neurons, which project throughout the cortex, fire at the highest rates during wakefulness and are inhibited during both NREM and REM sleep (Takahashi et al., 2006). Probably the largest contingent of the wakefulness-promoting system is made up by cells dispersed throughout the brainstem reticular formation and the basal forebrain that do not release conventional neuromodulators, but rather the ubiquitous neurotransmitter glutamate. By binding to metabotropic receptors, glutamate can act as a neuromodulator and influence the excitability of target cells. The firing patterns of these glutamatergic cells are not well characterized (Jones, 2003, 2005a,b). Noradrenergic cells are concentrated in the *locus coeruleus* in the upper pons, from where they project throughout the brain (Foote et al., 1980; Aston-Jones and Bloom, 1981a,b; Aston-Jones and Cohen, 2005; Berridge and Abercrombie, 1999). They fire tonically during wakefulness, and emit short, phasic bursts of activity during behavioral choices or salient events (Hobson et al., 1975; Foote et al., 1980; Aston-Jones and Bloom, 1981a,b; Aston-Jones and Cohen, 2005; Berridge and Abercrombie, 1999). By contrast, locus coeruleus neurons decrease their firing during NREM sleep, and cease firing altogether during REM sleep. Serotoninergic cells from the *dorsal raphe* nucleus also project widely throughout the brain and, like noradrenergic neurons, fire at higher levels in waking, lower levels in NREM sleep, and fall silent during REM sleep. However, in contrast to noradrenergic neurons, serotoninergic neurons are inactivated when animals make behavioral choices or orient to salient stimuli, and are activated instead during repetitive motor activity such as locomoting, grooming, or feeding (McGinty and Harper, 1976; Jacobs et al., 2002). Dopamine-containing neurons located in the substantia nigra and ventral tegmental area, which innervate the frontal cortex, basal forebrain, and limbic structures, do not appear to change their firing rate depending on behavioral state, though blocking dopamine reuptake is known to promote arousal (Monti and Monti, 2007). Finally, the peptide hypocretin (also known as orexin) is produced by cells in the posterior hypothalamus that provide excitatory input to all components of the waking system (Sakurai, 2007; Peyron et al., 1998).

These cells, too, are most active during waking, especially in relation to motor activity and exploratory behavior, and almost stop firing during both NREM and REM sleep (Lee et al., 2005b; Mileykovskiy et al., 2005).

Altogether, the main mechanism by which these neuromodulators and neurotransmitters produce cortical activation is by closing leakage potassium channels on the cell membrane of cortical and thalamic neurons, thus keeping cells depolarized and ready to fire.

Sleep System

At sleep onset, wakefulness-promoting neuronal groups are actively inhibited by antagonistic neuronal populations located in the hypothalamus and basal forebrain (Figure 7.3, green). Decreasing levels of acetylcholine and other waking-promoting neuromodulators and neurotransmitters lead to the opening of leak potassium channels in cortical and thalamic neurons, which become hyperpolarized and begin oscillating at low frequencies. Cell groups scattered within the anterior hypothalamus, including the ventrolateral preoptic area (Szymusiak et al., 1998; Sherin et al., 1996) and the median preoptic nucleus (Suntsova et al., 2002), as well as in the basal forebrain, are involved in the initiation and maintenance of sleep. These neurons tend to fire during sleep and stop firing during wakefulness. When they are active, many of them release GABA and the peptide galanin, and inhibit most waking-promoting areas, including cholinergic, noradrenergic, histaminergic, hypocretinergic, and serotonergic cells. In turn, the latter inhibit several sleep-promoting neuronal groups (Szymusiak et al., 2001; McGinty and Szymusiak, 2003; McGinty et al., 2004; Saper et al., 2005). This reciprocal inhibition provides state stability, in that each state reinforces itself as well as inhibits the opponent state.

REM-Sleep Generator

This consists of pontine cholinergic cell groups (LDT and PPT) that are part of the wakefulness system, and nearby cell groups in the medial pontine reticular formation and medulla (Jouvet, 1962; Hobson et al., 1975; McCarley, 2004, 2011; Siegel, 2005; Luppi et al., 2012). Lesions in these areas eliminate REM sleep without significantly disrupting NREM sleep. Pontine cholinergic neurons produce EEG activation by releasing acetylcholine to the thalamus and to cholinergic and glutamatergic basal forebrain neurons that in turn activate the limbic system and cortex. However, while during wakefulness other waking-promoting neuronal groups, such as noradrenergic, histaminergic, hypocretinergic, and serotonergic neurons, are also active, they are inhibited during REM sleep. Other REM-active neurons in the dorsal pons are responsible for the tonic inhibition of muscle tone during REM sleep. Finally, neurons in the medial pontine reticular formation fire in bursts and produce phasic events of REM sleep, such as REM and muscle twitches.

NEURAL CORRELATES OF WAKEFULNESS AND SLEEP

Wakefulness, NREM, and REM sleep are accompanied by changes in spontaneous neural activity, metabolism, and responsiveness to stimuli.

Spontaneous Neural Activity

Wakefulness

The waking EEG, characterized by the presence of low-voltage fast-activity, is known as *activated* because most cortical neurons are steadily depolarized close to their firing threshold (Figure 7.4, left), and are thus ready to respond to the slightest change in their inputs. The readiness to respond of cortical and thalamic neurons enables fast and effective interactions among distributed regions of the thalamocortical system, resulting in a continuously changing sequence of specific firing patterns. Superimposed on the low-voltage fast-activity background of wakefulness one frequently observes rhythmic oscillatory episodes within the alpha

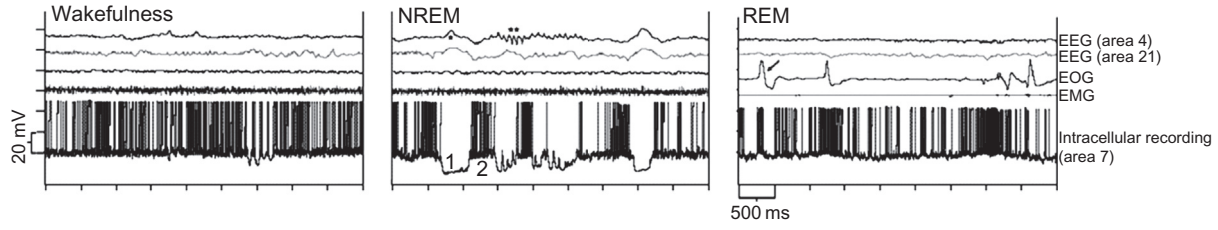

FIGURE 7.4 Simultaneous EEG, EOG, EMG, and intracellular cortical recording in a cat. During NREM sleep, the EEG trace shows slow waves (*) and sleep spindles (**), while the intracellular trace reveals the occurrence of slow oscillations in membrane potential (1 and 2 indicate down-state and up-state).

(8–13 Hz), beta (14–28 Hz), and gamma (>28 Hz) range, which are usually localized to specific cortical areas. These waking rhythms are due to the activation of oscillatory mechanisms intrinsic to each cell as well as to the entrainment of oscillatory circuits among excitatory and inhibitory neurons.

NREM Sleep

The EEG of NREM sleep differs markedly from that of wakefulness because of the occurrence of slow waves (0.5–2 Hz in humans), K-complexes, and sleep spindles. The opening of leakage potassium channels due to the reduced levels of acetylcholine and other neuromodulators draws cortical and thalamic cells toward hyperpolarization and triggers a series of membrane currents that produce the *slow oscillation* (Figure 7.4, center) (Steriade et al., 2001). As shown by intracellular recordings, the slow oscillation is made up of a hyperpolarization phase or *down-state*, which lasts a few hundreds of milliseconds, and a slightly longer depolarization phase or *up-state*. The down-state is associated with the virtual absence of synaptic activity within cortical networks. During the up-state, by contrast, cortical cells fire at rates that are as high or even higher than those seen in waking, and may even show periods of fast oscillatory activity in the gamma range. The slow oscillation is found in virtually every cortical neuron, and is synchronized across much of the cortical mantle by cortico-cortical and thalamo-cortical connections, which is why the EEG records high-voltage, low-frequency waves. Human EEG recordings using 256 channels have revealed that EEG slow waves behave as traveling waves that sweep across a large portion of the cerebral cortex (Massimini et al., 2004). Most of the time, the sweep starts in the very front of the brain and propagates front to back. These sweeps occur very infrequently during stage N1, around five times a minute during stage N2, and more than ten times a minute in stage N3. Thus, a wave of depolarization and intense synaptic activity, followed by a wave of hyperpolarization and synaptic silence, sweeps across the brain more and more frequently just as NREM sleep becomes deeper. Studies using intracerebral EEG recordings in epileptic patients have demonstrated that particularly toward the end of the night, the slow oscillation tends to occur locally, asynchronously across different brain regions (Nir et al., 2011). These studies also demonstrated that small amplitude slow waves in the scalp EEG mostly represent local waves, occurring out of phase across different brain regions, as opposed to large amplitude "global" EEG slow waves that are in phase across different brain regions. *K-complexes*, which can be triggered by external stimuli and appear particularly prominent because they are not immediately preceded or followed by other slow waves, are most likely the EEG correlate of such global slow oscillations due to the near-synchronous activation of the cortical mantle by the RAS (as opposed to a single cortical source) (Siclari et al., 2014a).

Sleep Spindles

Sleep spindles occur during the depolarized phase of the slow oscillation and are generated in thalamic circuits as a consequence of cortical firing. When the cortex enters an up-state, strong cortical firing excites GABAergic neurons in the reticular nucleus of the thalamus. These in turn strongly inhibit thalamocortical neurons, triggering intrinsic currents that produce a rebound burst of action potentials. These bursts percolate within local thalamoreticular circuits and produce oscillatory firing at around 12–15 Hz. Thalamic spindle sequences reach back to the cortex and are globally synchronized by corticothalamic circuits, where they appear in the EEG as sleep spindles.

REM Sleep

During REM sleep, the EEG returns to an activated, low-voltage fast-activity pattern that is similar to that of quiet wakefulness or stage N1 (Figure 7.4, right). As in wakefulness, the tonic depolarization of cortical and thalamic neurons is caused by the closure of leakage potassium channels. In fact, during REM sleep, acetylcholine and other neuromodulators are released again at high levels, just as in wakefulness, and neuronal firing rates in several brain areas tend to be higher.

Metabolism and Blood Flow

Recently, the data obtained by recording the activity of individual neurons have been complemented by imaging studies that provide a simultaneous picture of synaptic activity over the entire brain, although at much lower resolution.

NREM Sleep

Positron emission tomography (PET) studies show that metabolic activity and blood flow are globally reduced in NREM sleep compared to resting wakefulness (Maquet et al., 1997; Braun et al., 1997). During slow-wave sleep, metabolic activity can be reduced by as much as 40%. Metabolic activity is mostly due to the energetic requirements of synaptic transmission, and its reduction during NREM sleep is thus most likely due to the hyperpolarized phase of the slow oscillation, during which synaptic activity is essentially abolished. At a regional level, activation is especially reduced in the thalamus, due to its profound hyperpolarization during NREM sleep. In the cerebral cortex,

activation is reduced in dorsolateral prefrontal cortex, orbitofrontal and anterior cingulate cortex. This deactivation is to be expected given that slow waves are especially prominent in these areas. Parietal cortex, precuneus, and posterior cingulate cortex, as well as medial temporal cortex also show relative deactivations. As discussed in other chapters, the deactivation of thalamus and associated frontoparietal networks is seen in other conditions characterized by reduced consciousness, such as coma, vegetative state, and anesthesia. By contrast, primary sensory cortices are not deactivated compared to resting wakefulness. Basal ganglia and cerebellum are also deactivated, probably because of the reduced inflow from cortical areas.

REM Sleep

During REM sleep, absolute levels of blood flow and metabolic activity are high, reaching levels similar to those seen during wakefulness, as would be expected based on the tonic depolarization and high firing rates of neurons. There are, however, interesting regional differences (Braun et al., 1997; Maquet et al., 1996). Some brain areas are more active in REM sleep than in wakefulness. For example, there is a strong activation of limbic areas, including the amygdala and the parahippocampal cortex. Cerebral cortical areas that receive strong inputs from the amygdala, such as the anterior cingulate and the parietal lobule, are also activated, as are extrastriate areas. By contrast, the rest of parietal cortex, precuneus, posterior cingulate cortex, and dorsolateral prefrontal cortex are relatively deactivated. As will be mentioned in the next section, these regional activations and inactivations are consistent with the differences in mental state between sleep and wakefulness.

Upon awakening, blood flow is rapidly re-established in brainstem and thalamus, as well as in the anterior cingulate cortex (Balkin et al., 2002). However, it can take up to 20 min for blood flow to be fully re-established in other brain areas, notably dorsolateral prefrontal cortex. It is likely that this sluggish reactivation is responsible for the phenomenon of *sleep inertia*—a post-awakening deficit in alertness and performance that can last for tens of minutes.

Responsiveness to Stimuli

The most striking behavioral consequence of falling asleep is a progressive disconnection from the environment: the threshold for responding to peripheral stimuli gradually increases with the succession of NREM sleep stages N1–N3, and remains high during REM sleep. Since cortical neurons continue to fire actively during sleep, how does this disconnection come about?

NREM Sleep

Due to the progressive, intermittent hyperpolarization of thalamocortical neurons, sensory stimuli that normally would be relayed to the cortex often fail to do so because they do not manage to fire thalamocortical cells. In addition, the rhythmic hyperpolarization during sleep spindles is especially effective in blocking incoming stimuli, since it imposes an intrinsic oscillatory rhythm that effectively decouples inputs from outputs. Thus, the "thalamic gate" to the cerebral cortex is partially closed (Steriade, 2003). However, sensory stimuli in various modalities can still elicit evoked potentials from the cerebral cortex, and neuroimaging studies have shown that primary cortical areas are still being activated (Portas et al., 2000). As suggested by studies using transcranial magnetic stimulation (TMS) in conjunction with high-density EEG (Massimini et al., 2005), it is likely that during NREM sleep the activation of primary sensory areas is not followed by the activation of higher-order areas because of a breakdown in cortical effective connectivity.

REM Sleep

With the transition from NREM to REM sleep, neurons return to be steadily depolarized much as they are during quiet wakefulness, yet sensory stimuli are still ignored, as if the brain was focusing on its internal activities rather than on the environment (Llinas and Pare, 1991), not unlike states of intense absorption. While the underlying mechanisms are not clear, the prefrontal and parietal cortical areas that are deactivated in REM sleep are important for directing and sustaining attention to sensory cortices. Sensory inputs reaching primary cortices would then find themselves to be systematically unattended. It is likely that the reduced activity in these cortical regions is a direct consequence of changes in the neuromodulatory milieu during REM sleep. Specifically, the reduction of serotonin release during REM sleep may favor a dissociative–hallucinogenic state, as seen with certain psychoactive compounds. In addition, low levels of noradrenaline may contribute to perceptual disconnection during REM sleep. Indeed, noradrenaline is known to bias behavioral orientation toward the external versus the internal environment (Aston-Jones and Bloom, 1981b) and insufficient noradrenergic suppression may account for anesthesia awareness, a condition in which individuals become connected and experience their actual surroundings during anesthesia (Sanders et al., 2012). Other possible mechanisms underlying perceptual disconnection could involve higher order thalamic nuclei, such as the pulvinar,

which could impair cortico-cortical connectivity between unimodal sensorimotor areas and higher order heteromodal areas during REM sleep (Chow et al., 2013). Finally, the posterior cingulate cortex, a region that is relatively deactivated during REM sleep, may well constitute a key region for connectedness. In a recent single-case study, the subcortical connectivity of the left posterior cingulate cortex was disrupted using intraoperative electrostimulation, which repeatedly led to disconnection. The patient became behaviorally unresponsive and later reported "dream-like" conscious experiences unrelated to his actual environment in the operating room, including experiencing the sun, finding himself on the beach, and being surrounded by a white landscape (Herbet et al., 2014).

Nevertheless, in contrast to a person in a coma or a vegetative state, a sleeping person can always be awakened if stimuli are strong enough, or especially meaningful. For example, it is well known that the sound of one's name, or the wailing of a baby, are among the most effective signals for awakening.

CONSCIOUSNESS IN SLEEP

There are two main lessons to be learned from the study of consciousness in sleep. The first is that, during certain phases of sleep, the level of consciousness can decrease and at times nearly vanish, despite the fact that neural activity in the thalamocortical system is relatively stable. The second is that, during other phases of sleep, vivid conscious experience is possible despite the sensory and motor disconnection from the environment and the loss of self-reflective thoughts.

Changes in the Level of Consciousness

Studying mental activity during sleep offers a unique opportunity to find out how changes in brain activity are associated with changes in consciousness (Hobson, 1998). When REM sleep was discovered, it was immediately noticed that, if subjects were awakened from that stage of sleep and asked whether they had a dream, they would say so at least 80% of the time. Subjects invariably reported dreams that were vivid, with characteristically intricate plots and changes of scene. Awakenings from NREM sleep, instead, yielded dreams 20% of the time or less. These findings led to the approximate equation of a physiological state, REM sleep, with a cognitive state, dreams. This equation was encouraged by the remarkable similarity between the EEG of REM sleep with that of wakefulness, as opposed to that of NREM sleep. It seemed natural to infer that the activated (low voltage, fast activity) EEG of waking and REM sleep would support vivid conscious experience, while the deactivated (high voltage, slow activity) EEG of NREM sleep would not.

However, later studies have shown that the relationship between consciousness and sleep stages is more complicated. By just changing the question from "tell me if you had a dream" to "tell me anything that was going through your mind just before you woke up," the percentages of recalls from NREM sleep reaches as high as 60%. It is now clear that reports indicative of conscious experience, including dream-like experiences, can be elicited during any stage of sleep (Hobson et al., 2000; Hobson, 2002).

Sleep Onset

Reports at sleep onset are very frequent (80–90% of the time) but also very short. Usually people report hallucinatory experiences, the so-called *hypnagogic hallucinations* (Greek for "leading into sleep"). In contrast to typical dreams, hypnagogic hallucinations are often static, similar to single snapshots or a short sequence of still frames. They typically contain fewer emotions and characters, less self-representations, and tend to be less bizarre and closer to reality (Cicogna et al., 1998; Rowley et al., 1998). Not infrequently, sleep onset experiences contain elements of activities that have been performed prior to sleep (Stickgold et al., 2000; Wamsley et al., 2010). For instance a subject may report: "... I could feel myself moving just the way the sea moves our boat when I was out fishing today" (Hobson, 2002). A recent high-density study of the transition to sleep showed that at the beginning of the falling-asleep period, slow waves tend to affect some regions (the frontal cortex, particularly the medial region) more than others (the occipital, temporal, and lateral posterior parietal areas), while later, they are more evenly distributed over the cortical surface (Siclari et al., 2014a). This pronounced anterior-posterior slow-wave gradient at sleep onset is likely to explain certain features of mental activity in this period. The visual character and vestibular sensations that are typical of sleep onset experiences may for instance be related to the fact that the primary visual cortex and the lateral parieto-temporal areas are still relatively unaffected by slow waves (and thus still "awake"), while the lack of voluntary control and insight into the hallucinatory character of the experience could reflect "local sleep" in prefrontal regions.

NREM Sleep Stages N2 and N3

A substantial number of awakenings from NREM sleep yield no report whatsoever, especially early in the night when stage N3 is prevalent. Thus, early slow-wave sleep is the only phase of adult life during

which healthy human subjects may deny that they were experiencing anything at all. On the other hand, between 60% and 80% of the time, awakenings from NREM sleep yield reports with experiential content. The length of NREM reports is widely distributed. Their median length is similar to that of reports from sleep onset. However, there are many very short reports early in the night and much longer reports later in the night (Stickgold et al., 2001), considerably longer than those typically obtained at sleep onset or even during quiet wakefulness. Reports from NREM sleep, especially early in the night, are often thought-like, for example: "I kept thinking about my upcoming exam and about the subject matter that it will contain..." Later in the night, they can be much more hallucinatory and, generally speaking, more dream-like.

REM Sleep

Awakenings from REM sleep yield reports 80–90% of the time, a percentage similar to that obtained at sleep onset. Especially in the morning hours, the percentage is close to 100%. Most REM reports have the characteristics of typical dreams: complex, temporally unfolding hallucinatory episodes that can be as vivid as waking experience. For example, as reported by Hobson (2002): *As the climbing party rounds the trail to the right, I am suddenly on a bicycle, which I steer through the group of climbers. It becomes clear that I make a complete circuit of the peak (at this level) by staying on the grass. There is, in fact, a manicured lawn surface continuing between the rocks and the crags ... Then the scene changes to Martha's Vineyard Island (though I was still on the same bicycle) ... and then to a shopping center, a restaurant, a dance, and a meeting of faculty colleagues ... one of my colleague's wives is seen as a blonde when, in reality, she is a brunette. The sense of movement, which is continuous, becomes particularly delightful when I become practically weightless and glide along a golf fairway. At the dance there is a Baltic group wearing embroidered peasant garb and stamping the floor to a loud band (I can hear the drums especially).* Remarkably, the median word count of REM sleep reports is even higher than that of wakefulness reports, whether quiet or active. This finding seems to fit with the notion that dreams are single-minded, and thus less frequently interrupted by extraneous thoughts than waking consciousness. Also, the average length of REM reports increases with the duration of the REM sleep episode. By contrast, there is no such relationship for NREM sleep reports (Stickgold et al., 2001).

What are the processes underlying the systematic changes in the level of consciousness during different phases of sleep? At first, it was assumed that the fading of consciousness during certain phases of sleep was due to the brain shutting down. However, while metabolism is reduced, the thalamocortical system remains active also during stage N3, with mean firing rates during the up-state of the slow oscillation that are comparable to those of quiet wakefulness (Steriade, 2003). Indeed, most other aspects of neural activity during the up-state of the sleep slow oscillation, including gamma activity, resemble those observed during wakefulness (Sejnowski and Destexhe, 2000). Why, then, does consciousness fade during certain phases of sleep and return during others?

An intriguing possibility is that the level of consciousness during sleep may be related to the degree of bistability of thalamocortical networks. Even though the level of activation of cortical neurons during the up-state of NREM slow oscillations is as high as in wakefulness and REM sleep, the up-state of NREM sleep is intrinsically unstable, in that it is inexorably terminated by the occurrence of a down-state—a generalized, stereotypical cessation of activity that can last for a tenth of a second or more. The transition from up- to down-states appears to be due to depolarization-dependent potassium currents and to short-term synaptic depression, both of which increase with the amount of prior activation (Steriade, 2003). Indeed, during NREM sleep the stimulation of cortical neurons typically precipitates a down-state, and even spontaneous activity cannot last for long before a down-state is triggered.

From this perspective, the incidence of spontaneous slow waves can provide a telling indicator of the degree of bistability in thalamocortical networks. Thus, during stage N1, at the transition between wakefulness and sleep, the cortex enjoys periods of activation that can last up to a minute before a large slow wave sweeps through, which is consistent with reports of short, hallucinatory sequences upon awakening. In stage N2 early in the night, the EEG is similar to that of stage N1, but the intervals between large slow waves are much shorter, on average 12 s. Accordingly, reports are not only short, but also thought-like in character. In stage N2 later in the morning, the intervals between large slow waves are longer, and reports are correspondingly longer and more dream-like. The hallmark of slow-wave sleep, which is prevalent early in the night, are the large slow waves that sweep through the cortex more than ten times a minute in stage N3 (Figure 7.5), suggesting an extreme degree of bistability. Correspondingly, reports are usually of short duration and often thought-like; at times, no experiential content is reported. Recent EEG studies, in which sleep consciousness was systematically assessed using serial awakening paradigms (Siclari et al., 2013) confirmed that reports of unconsciousness were preceded by higher power in the delta range and a higher slow-wave density compared to reports of

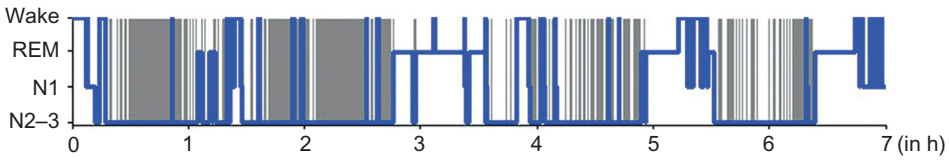

FIGURE 7.5 Incidence of large slow waves depending on sleep stage and time of night.

consciousness (Chellappa et al., 2011; Siclari et al., 2012). In stark contrast, during REM sleep, which predominates later in the night, the EEG is tonically activated and there are no slow waves sweeping the cortex. Accordingly, REM reports are on average much longer (2–7 times longer) than NREM reports, and usually yield vivid, prototypical dreams.

Why would the level of consciousness reflect the degree of bistability of thalamocortical networks? A possible answer is offered by the integrated information theory of consciousness (Tononi, 2004; Oizumi et al., 2014), which states that the level or quantity of consciousness is given by a system's capacity to generate integrated information. According to the theory, the brain substrate of consciousness is a complex of neural elements within the thalamocortical system that has a large repertoire of available states (*information*), yet cannot be decomposed into a collection of causally independent subsystems (*integration*). In this view, integrated information would be high during wakefulness because thalamocortical networks have a large repertoire of global firing patterns that are continuously available on a background of tonic depolarization. During early NREM sleep, by contrast, the ensuing bistability would reduce this global repertoire through two mechanisms. First, a local activation would cause a local down-state preventing effective interactions with other brain areas. As a consequence, the main thalamocortical complex would break down into causally independent modules (loss of integration). Second, to the extent that global activation patterns can still occur, they too would be rapidly followed by a global, stereotypical down-state, thereby greatly reducing the repertoire of available states (loss of information).

To test these predictions, it is not sufficient to observe activity levels or patterns of temporal correlations among distant brain regions (*functional connectivity*), but it is crucial to employ a perturbational or causal approach (*effective connectivity*). For this purpose, TMS-evoked brain responses were recorded using a high-density EEG system to investigate to what extent cortical regions can interact causally (*integration*) and produce differentiated responses (*information*) (Massimini et al., 2005). As shown in Figure 7.6A, TMS applied to various cortical regions during wakefulness induced a sustained response made of changing patterns of activity. Specifically, a sequence of time-locked, high-frequency (20–35 Hz) oscillations occurred in the first 100 ms and was followed by a few slower (8–12 Hz) components that persisted until 300 ms. Source modeling revealed that the initial response to TMS was followed by spatially and temporally differentiated patterns of activation presumably mediated by long-range ipsilateral and transcallosal connections.

As soon as the subjects transitioned into stage N1, the TMS-evoked response grew stronger at early latencies but became shorter in duration due to dampening of later fast waves. With the onset of NREM sleep, the brain response to TMS changed markedly. The initial wave doubled in amplitude and became slower. Following this large wave, no further TMS-locked activity could be detected, except for a negative rebound between 80 and 140 ms. Specifically, fast waves, still visible during stage N1, were completely obliterated, and all TMS-evoked activity had ceased by 150 ms. Moreover, as shown in Figure 7.6B left, the activity evoked by TMS remained localized to the site of stimulation and did not propagate to connected brain regions, presumably because of the induction of a local down-state. This finding indicates that during early NREM sleep, when the level of consciousness is reduced, effective connectivity among cortical regions breaks down, implying a corresponding breakdown of cortical integration.

In subsequent experiments, it was found that, when applied to a median centroparietal region, each TMS pulse would trigger a full-fledged, high-amplitude slow wave that closely resembled spontaneous ones and that traveled through much of the cortex (Massimini et al., 2007). Spatially, the TMS-evoked slow wave was associated with a broad and stereotypical response: cortical currents spread, like an oil-spot, from the stimulated site to the rest of the brain. The large negative peak evoked by the TMS pulse, corresponding to a global cortical down-state, demonstrates that during early NREM sleep activation is inevitably followed by deactivation, suggesting that the repertoire of possible firing patterns (information) is drastically reduced (Figure 7.6B, right). Importantly, such stereotypical responses could be induced even when, for the preceding seconds, there were no slow waves in the spontaneous EEG, indicating that perturbations can reveal the potential bistability of a system irrespective of its observed state.

By contrast, during REM sleep late in the night, when dreams become long and vivid and the level

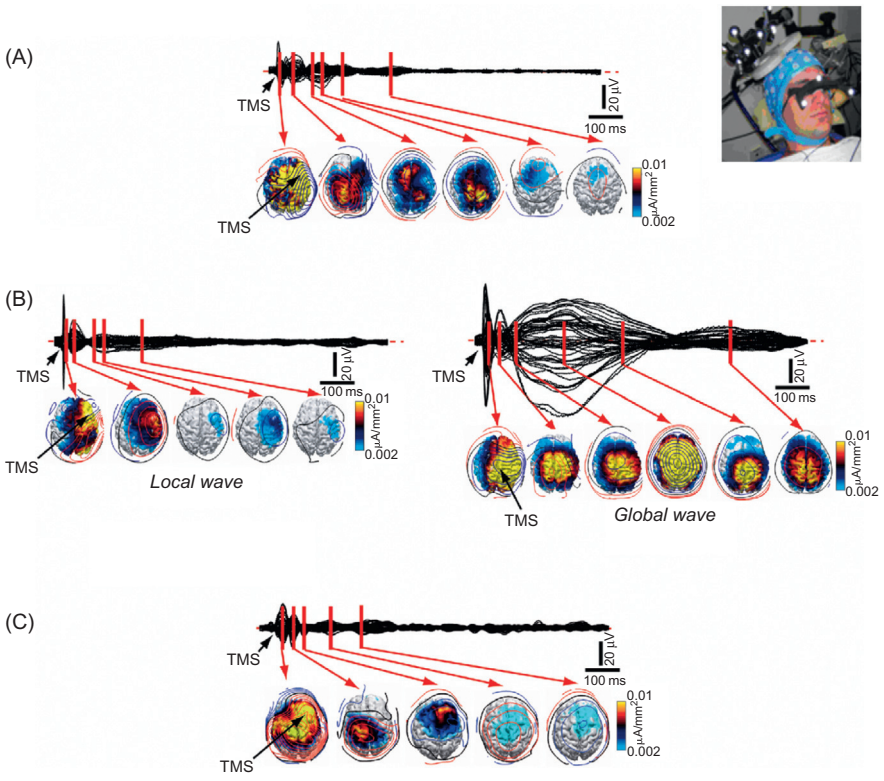

FIGURE 7.6 Spatiotemporal cortical current maps of TMS-induced activity during (A) wakefulness, (B) NREM, and (C) REM sleep. On the top right is the setup for TMS/EEG. From the EEG data, current sources corresponding to periods of significant activations were plotted on the subject's MRI. Note for TMS during wakefulness the rapidly changing patterns of activation, lasting up to 300 ms and involving several different areas (right premotor cortex stimulation is shown, but similar results are observed for other stimulation sites, including midline entroparietal regions); for TMS during NREM sleep either a brief activation that remains localized to the area of stimulation (right premotor cortex stimulation) or a global wave of activation that affects indiscriminately and stereotypically the entire cortex (midline centroparietal stimulation); and for TMS during REM sleep, an intermediate pattern of activation. *Source: From Massimini et al. (2005, 2007, 2010).*

of consciousness returns to levels close to those of wakefulness, the responses to TMS also recovers and comes to resemble more closely those observed during wakefulness (Massimini et al., 2010): as shown in Figure 7.6C, evoked patterns of activity become more complex and spatially differentiated, although some late components are still missing. Altogether, these TMS–EEG measurements suggest that the sleeping brain, despite being active and reactive, changes dramatically in its capacity to generate integrated information: it either breaks down in causally independent modules, or it bursts into a global, stereotypical response, in line with the predictions of the integrated information theory (Tononi, 2004). Importantly, the use of a perturbational approach (TMS–EEG) reveals that during NREM sleep cortical circuits may be intrinsically bistable even during periods of stable ongoing EEG with no overt slow waves.

Dreams: Consciousness in the Absence of Sensory Inputs and Self-Reflection

Just as striking as the near-loss of consciousness during certain phases of sleep is its remarkable preservation during other phases. This is especially true of REM sleep awakenings, which yield reports of vivid dreams in the majority of cases. Perhaps the most remarkable property of dreams is how similar they can be to waking consciousness, to the point that the dreamer may be uncertain whether he is awake or asleep. This means that the sleeping brain, disconnected from the real world, is capable of generating an imagined world, a virtual reality, which is fairly similar to the real one and is indeed experienced as real (Box 7.1). Perceptual modalities and submodalities that are experienced in wakefulness are represented in dreams: dreams are highly visual, in full color, rich of different shapes and movements, but they also have sound, tactile feelings, smells, and tastes, as well as pleasure and pain (Hobson et al., 2000). The categories that are the stuff of dreams are the same as those that constitute the fabric of wakefulness—objects, animals, people, faces, places, and so on. Dream experiences are not necessarily all vivid and perceptual—there are also faint ideas, just as in wakefulness, and various kinds of thoughts. Dreams are also rich in emotion: in fact, emotions are often very intense, especially fear and anxiety. Hearing speech or conversation is also extremely frequent, and speech patterns are as grammatically correct as in waking life. Finally, there is a good correlation between our waking and dreaming selves with respect to mood, imaginativeness, and predominant concerns. For example, people dream most often about the individuals and interests that preoccupy them in waking life, and they show aggression in dreams toward the same people with whom they are in conflict in waking life.

BOX 7.1

NEUROCOGNITIVE MODELS OF DREAMING

Building on the cognitive model of Foulkes (1985) and on the work of Hall on content analysis of dreams (Hall and Van de Castle, 1966), William Domhoff has attempted a synthesis that he calls the neurocognitive model of dreaming (Domhoff and Hall, 1996; Domhoff, 2003). Domhoff proposes that dreaming is what the mature brain does when (i) primary sensory cortices are relatively inactivated, thus enforcing a partial disconnection from the external world; (ii) dorsolateral prefrontal cortices are relatively inactivated, thus reducing our ability to exercise reflection and decision making; and (iii) a subsystem of brain regions, comprising limbic and paralimbic structures as well as several association areas at the temporo-parieto-occipital junction, is at a sufficient level of activation. According to Domhoff's model, dream-like experiences can occur not only in NREM sleep, but also during wakefulness, provided sensory and prefrontal cortices are sufficiently quiet.

Like Foulkes, Domhoff emphasizes that the dreaming subsystem, when activated, is drawing on memory schemas and general knowledge to produce a kind of dramatized version of the world, and that these dramatizations are an active act of imagination, rather than a mere reaction to random activation. More specifically, Domhoff argues that the system of scripts and schemas activated in dreams is nothing else but the organizational basis for all human knowledge and beliefs. Basic-level categories, which can be represented by a single image, reflect distinctions among types of animals, such as cats and dogs, types of social interactions, such as friendly and aggressive, or types of actions, such as walking and running. Spatial relations categories are, for example, "up," "down," "in front of," and "in back of." Finally, sensorimotor categories are based on experiences related to temperature, motion, and touch. The systematic occurrence of basic experiential categories in dreams is confirmed by the analysis of thousands of dreams from all over the world according to the Hall/Van de Castle system (Hall and Van de Castle, 1966).

Dreams may also build upon figurative thinking: conceptual metaphors, metonymies, ironies, and conceptual blends. As pointed out by Lakoff and Johnson (2003), hundreds of primary conceptual metaphors actually map common experiential categories. For example, basic experiences like warmth and motion are used to understand more difficult concepts like friendship (they have a warm relationship) and time (time flies by). Just as in waking thought, figurative thinking may be used in dreams when it expresses a conception better and more succinctly than an experiential concept does. To this extent, some dreams may indeed be symbolic.

Finally, based on content analysis, Domhoff concludes that most dreams deal with personal concerns—typical ones are being inappropriately dressed, being lost, or being late for an examination. Personal concerns are very stable over the years, as well as across cultures, which may explain why dreams themes are stable across life across individuals, and around the world. Such personal concerns are also the subject of recurrent dreams, and of the repetitive nightmares experienced by people suffering from post-traumatic stress disorder (generally in stage N2). Curiously, personal concerns in dreams are often stuck in the past, in a way that fits with the persistence of negative memories stored in the amygdala and other limbic circuits that are part of the brain's fear system.

Taken together, these remarkable similarities between waking and dreaming consciousness suggest that conscious experiences in both wakefulness and sleep share similar anatomo-functional substrates. This was recently illustrated by an fMRI study, in which a machine-learning algorithm was trained while subjects were watching natural images in form of movies. In the second part of the experiment, this algorithm was successfully used to decode the content of conscious experiences that occurred in the falling asleep period (Horikawa et al., 2013) (Figure 7.7A). As an example, the algorithm correctly predicted that the subject was most likely seeing "characters" in the 30s before the awakening (Figure 7.7B). Indeed, when awakened, the subject reported: "What I was just looking at was *some kind of characters*. There was something like a *writing paper* for composing an essay, and I was looking at the characters from the essay or whatever it was (. . .)." Another recent study, in which brain activity was recorded at high density, and subjects were awakened at pseudorandom intervals and retrospectively reported if they had been conscious during sleep and of what identified content-specific activations for faces, places, movement and speech that closely matched those observed in wakefulness during perception of the same contents (Siclari et al., 2014b).

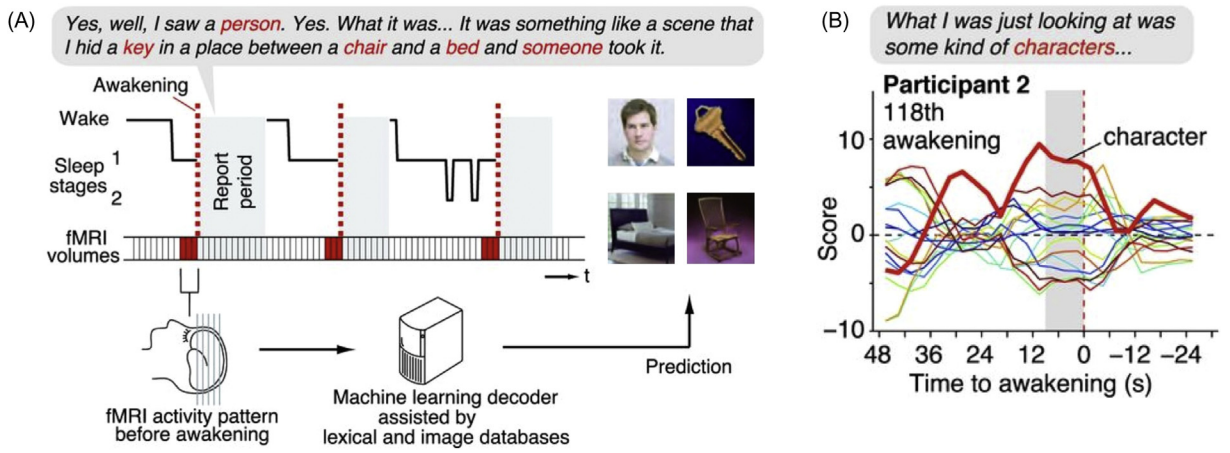

FIGURE 7.7 Schematic representation of experimental paradigm (A) and of results (B) of a study in which the content of visual imagery at sleep content was successfully decoded (Horikawa et al., 2013). (A) fMRI data were acquired from sleeping participants simultaneously with polysomnography. Participants were awakened during sleep stage 1 or 2 (red dashed line) and verbally reported their visual experience during sleep. fMRI data immediately before awakening (an average of 3 volumes (=9 s)) were used as the input for main decoding analyses. Words describing visual objects or scenes (red letters) were extracted. The visual contents were predicted using machine-learning decoders trained on fMRI responses to natural images. (B) Example of a time course of synset scores (indicating how likely the synset is to be present in each report) for an individual sleep sample. Each colored line represents a different synset, the red line represents the synset "character" that the subject subsequently reports in this case. *Source: From Horikawa et al. (2013). Reprinted with permission from AAAS.*

Despite the similarities between waking and consciousness, dreaming consciousness often presents some distinctive features. These include: (i) disconnection from the environment, (ii) internal generation of a world-analog, (iii) reduction of voluntary control and reflective thought, (iv) amnesia, and (v) high emotional involvement.

Disconnection

The most obvious difference between dreaming and waking consciousness is the profound disconnection of the dreamer from his current environment. Only occasionally do external stimuli manage to be incorporated in dreams, the most effective being a spray of water or pressure on the limbs. The disconnection is so effective that even the regular erections occurring during REM sleep dreams almost never make it into the dream's content. It is also difficult to influence dream content with pre-sleep stimuli, even strong ones such as viewing a horror movie just before going to bed. Instead, all sensory experiences in dreams are generated internally: they are, strictly speaking, hallucinations. The disconnection is also evident on the motor side. For example, a feeling of weightlessness is commonplace in dreams, as is the experience of floating or flying. It is possible that the peculiar, effortless nature of motor activities in dreams has something to do with the activation of motor programs in the absence of proprioceptive feedback signaling. As would be expected, the sensory and motor disconnection of dreams are neatly reflected in the reduced activation of primary sensory and motor areas in PET studies of REM sleep (Braun et al., 1998).

Internal Generation of a World-Analog

Given the sleeper's disconnection from the external world, all dream consciousness is generated internally. Dreams, rather than being at the mercy of bottom-up signals and events from the environment, take a top-down approach by following a narrative script and using a set of well-rehearsed formulas: if waking consciousness is like watching a news broadcast, dreaming is more like watching a movie produced by an imaginative director (rather than by a camera bouncing around at random). In selecting scenes, the dream director is not particularly choosey: any actor, dress, means of transportation, or food item that is readily available will do. Indeed, as in some B-movies, characters and objects seem to be chosen for their role in each scene, with little regard for factual truth or plausibility, and without caring about the mixing of incongruent characteristics, or inconsistencies between one scene and the other (Nir and Tononi, 2010). Thus, chimerical creatures, sudden transformations, and physically impossible objects are not infrequent. While the ability to dream requires the ability to imagine, dream images are generally more vivid than visual imagery during wakefulness, presumably because they do not have to compete with external signals. Also, in dreams there is a strong tendency for a single train of related thoughts and images to persist for extended periods without disruption or competition from other thoughts or

images ("single-mindedness" (Rechtschaffen, 1978)). From a neuroimaging perspective, the internal generation of a world-analog is consistent with the strong activation of temporo-occipital and parahippocampal association areas that is observed in REM sleep (Braun et al., 1997; Maquet et al., 1996).

Reduced Voluntary Control and Reflective Thought

During dreaming there is a prominent reduction of voluntary control, whether of action, thought, or attention. With the exception of lucid dreaming (see below), the dreamer has no control over what he is going to dream, and is largely a passive spectator. Reflective thought processes are also impaired in characteristic ways. Again with exception of lucid dreams, dreaming is almost always delusional, in the sense that events and characters in the dream are taken for real. While the dreamer experiences thoughts, there is a severe impairment of the ability to pursue goals effectively, to analyze situations intelligently, to question assumptions, to reason properly, and to make appropriate decisions. For example, holding contradictory beliefs is quite common in dreams, and a dreamer easily accepts impossible events or situations, such as flying. There is often uncertainty about orientation in space (where one is in the dream), about time (when the dream is taking place in personal history), and person (confusion about the gender, age, and identity of dream characters). When dreaming, one cannot stop and reflect rationally on what one should be doing, nor imagine other scenarios (after all, one is already imagining the dream). Once again, these characteristics of dreaming consciousness are consistent with neuroimaging findings: dorsolateral prefrontal cortex, which is involved in volitional control and self-monitoring, is especially deactivated during REM sleep (Braun et al., 1997; Maquet et al., 1996).

Amnesia

Memory is drastically impaired both within the dream and for the dream. Working memory is not working well, as it is extremely difficult to hold anything in mind during a dream. Episodic memory is also not functioning properly. Remarkably little makes it into dreams of recent episodes of the dreamer's life. While individual items from waking experience sometimes are incorporated into a dream, they do so in new and unrelated contexts, and true declarative memories for wakening episodes are found in a very small percentage of dreams. For example, in a study where subjects had intensively played the computer game Tetris, there was no episodic memory in subsequent dreams that the subject had indeed played Tetris. In fact, dreams of healthy subjects were indistinguishable from those of profoundly amnesic subjects, who could not remember having played Tetris whether they were dreaming or awake. In contrast, both normal and amnesic subjects often reported perceptual fragments, such as falling blocks on a computer screen, especially at sleep onset, but there were no episodic memories associated with these fragments (Stickgold et al., 2000). Even previous events within a dream are soon forgotten and do not appear to influence the subsequent evolution of dream experiences. Instead, dreams are characterized by what has been called "hyperassociativity," as if the network of association were much wider and less constricted than in wakefulness. Finally, dreams themselves are extremely fleeting: if the dreamer does not wake up, they are generally lost, and even upon awakening they vanish extremely rapidly unless they are written down or recorded. This is true even of the most intense dreams, even if they are accompanied by great emotion. It is not clear why the dreaming brain is so profoundly amnestic since, for example, parahippocampal and limbic circuits are highly active during REM sleep ((Braun et al., 1997; Maquet et al., 1996) although prefrontal cortex, which also plays a role in episodic memory, is deactivated. As is the case with daydreaming (see below), the source and structure of experienced events (external, highly constrained, vs. internal, less constrained) is a crucial determinant of recall. Perhaps changes in neuromodulators also play a role, specifically the silence of noradrenergic neurons whose activity is involved in the conversion of neural activity into neural plasticity (Cirelli et al., 1996).

Hyperemotionality

Many dreams are characterized by a high degree of emotional involvement, especially fear and anxiety, to a degree rare in waking life. This has led to the suggestion that the initial impetus for constructing dream narratives may originate in perceived threats or conflicts. Whether or not this interpretation has merits, REM sleep is in fact associated with a marked activation of limbic and paralimbic structures such as the amygdala, the anterior cingulate cortex, the insula, and medial orbitofrontal cortex.

In summary, there are many aspects of dreaming consciousness that can be found in textbooks of psychopathology, including hallucinations, delusions, reduced orientation and attention, impaired memory, loss of voluntary control, and reflective thought. Since hallucinations and delusions are the hallmark of psychosis, it is not surprising that a connection between dreams and madness has often been suggested. However, the closest psychiatric conditions are not the major psychoses, but the so-called acute confusional state or delirium, which is often due to withdrawal from alcohol and drugs and is characterized by many of the same symptoms as dreams—hallucinations and

delusions, impaired orientation and attention, intense emotions, loss of directed thought and self-reflection, frequent confabulations, as well as by a reduced responsiveness to the external world (Hobson, 1997). The remarkable regional differences in activation during REM sleep as compared to wakefulness are probably responsible for many of the differences between waking and dreaming consciousness (Hobson et al., 2000). It is still unclear what is responsible in turn for these regional differences, although once again it is likely that neuromodulatory systems may be involved. For example, since monoaminergic systems are silent during REM sleep, acetylcholine is alone in maintaining brain activation. Consistent with imaging results, cholinergic innervation is especially strong in limbic and paralimbic areas and much weaker in dorsolateral prefrontal cortex.

Neuropsychology of Dreaming

The analysis of patients with brain lesions indicates that the ability to dream depends on specific forebrain regions rather than on the brainstem REM sleep generator (Bischof and Bassetti, 2004; Solms, 1997). In most cases of global cessation of dreaming, there is damage to the parieto-temporo-occipital junction (uni- or bilaterally), while the brainstem and the polygraphic features of REM sleep are preserved. The parieto-temporo-occipital junction is important for mental imagery, for spatial cognition (on the right side) and for symbolic cognition (on the left side), all central features of dreaming. More restricted lesions produce the cessation of visual dreaming. In all these patients, these functions were at least partially impaired during wakefulness. Thus, the ability to dream seems to go hand in hand with the ability to imagine and with visuospatial skills. Indeed, these areas are among those that are most activated during REM sleep, although it is unknown to what extent they may be activated during NREM dreaming.

The close relationship between dream generation and waking imagery is borne out by longitudinal studies of dreaming in children, which show that dreaming progresses in parallel with the child's waking ability to imagine and his visuospatial skills (Box 7.2). Thus, children of age 2–3, although they obviously can see and even speak of everyday people, objects, and events, cannot imagine them, nor can they dream of them. Similarly, if people are blind from birth, they cannot construct visual images during wakefulness, nor can they dream visually (dreams of blind people are otherwise just as vivid as those of sighted subjects). However, if people become blind after the age of seven, they generally can still construct visual images, and they do have visual dreams (Hollins, 1985; Buchel et al., 1998).

Global cessation of dreaming can also be produced by bilateral lesions of white matter tracts underlying ventromedial prefrontal cortex (Solms, 1997). White matter tracts in this region are the ones that used to be severed in prefrontal leucotomy, once performed on many schizophrenic patients. Most leucotomized patients complained of global cessation of dreaming as well as of lack in initiative, curiosity, and fantasy in waking life. Many of the nerve fibers traveling in the ventromedial white matter originate or end in limbic areas. In addition, the ventromedial white matter contains dopaminergic projections to the frontal lobe. Once again, these lesion data are consistent with imaging results since limbic areas are highly active during REM sleep. By contrast, lesions of forebrain areas that are deactivated during REM sleep, such as the dorsolateral prefrontal cortex, sensorimotor cortex, and primary visual cortex, do not affect the ability to dream. Also, many patients with brainstem lesions are able to dream, though it is unclear whether REM sleep is preserved. However, it is well known that certain antidepressant treatments that suppress REM sleep do not eliminate dreaming.

DISSOCIATED STATES

This last section will consider a series of conditions that lie as it were in between waking and sleep: they partake of some features typical of waking consciousness as well as of some characteristics of consciousness in sleep—that is, they represent dissociated states (Mahowald and Schenck, 2005). Some of these conditions, such as daydreaming and lucid dreaming, are perfectly normal, and can even be learned; others occur in the context of certain sleep disorders. Other conditions, known as *parasomnias*, include some of the most remarkable examples of pathological dissociation between consciousness, awareness of the environment, reflective consciousness, and behavior.

Daydreaming

A common definition of daydreaming is "a dream-like musing or fantasy while awake, especially of the fulfillment of wishes or hopes." For experimental purposes, daydreaming can be defined as "stimulus-independent mentation," that is, as waking images and thoughts that are independent of the task at hand (Singer, 1993). Daydreaming is extremely common. Indeed, no matter how hard one concentrates on the task at hand, a surprising amount of time is spent

BOX 7.2

THE DEVELOPMENT OF DREAMS

When do children start dreaming, and what kind of dreams do they have? These questions have been addressed in a series of studies by Foulkes (1999) in children between the ages of 3 and 15 years. Foulkes's laboratory studies showed that children under the age of 7 awakened from REM sleep recall dreaming only 20% of the time, compared with 80–90% in adults. NREM sleep awakenings before age 7 produced some recall only 6% of the time. For both REM and NREM sleep awakenings, recall came first from awakenings late in the night.

Preschoolers' dreams are often static and plain, such as seeing an animal, thinking about eating or sleeping—"they are more like a slide than a movie." There are no characters that move, no social interactions, very little feeling of any sort, and they do not include the dreamer as an active character. There are also no autobiographic, episodic memories, and Foulkes suggests that the paucity of childrens' dreams is closely related to infantile amnesia: both would be due to the inability of preschoolers to exercise conscious episodic recollection. Children's dreams are more positive than adult dreams: preschoolers never reported fear in dreams, and there are few aggressions, misfortunes, and negative emotions. Note that children who have *night terrors*, in which they awaken early in the night from slow-wave sleep and display intense fear and agitation, are terrorized not by any dream, but by disorientation due to incomplete awakening.

Between ages 5 and 7 dream reports become longer, although still infrequent. Dreams may contain short sequences of events in which characters move about and interact, but the dream narratives are not very well developed. At around age 7, dream reports become longer and more frequent, the child's self becomes an actual participant in the dream, with thoughts and even feelings, and dreams begin to acquire a narrative structure and to reflect autobiographic, episodic memories.

Foulkes also found that recall frequency was best correlated with the ability to produce waking mental imagery, and not with language ability. If childrens' dreams seem rare and not well developed, then, it is not because of an inability to report dreams. Instead, the frequency of dream reporting in young children is correlated with their visuospatial skills. Visuospatial skills are known to depend on the parietal lobes, which are not fully myelinated until age 7. Recall that blind adults have visual imagination and dreaming only if they lost their sight after age 7. These data suggest that dreaming is a gradual cognitive development that is tightly linked to the development of visual imagination. According to Foulkes, studying the development of dreams is tantamount to studying the development of consciousness.

drifting off into fantasies and interior monologues of one kind or another. If subjects are periodically interrupted for thought sampling during a signal-detection task, they report stimulus-independent mentation at least 35% of the time, even under heavy processing loads. Their reports also indicate discontinuities and scene changes that are more frequent than in REM sleep. There have been attempts at further categorizing waking mental activities and validating such categories using questionnaires and factor analysis. Relevant dimensions are (i) directed or operant vs. non-directed or respondent thought (the former voluntarily directed toward accomplishing a task); (ii) stimulus bound vs. stimulus independent; (iii) realistic vs. fanciful; (iv) well-integrated (orderly, connected, coherent) vs. degenerated; and (v) vivid vs. non-vivid. A prototypical daydream would be non-directed, stimulus-independent, fanciful, and non-integrated. Recall of waking images and thoughts experienced while daydreaming can be as poor as dream recall, possibly because, just as dream images, daydreaming images cannot be referenced by external events. Most often, individuals are only aware that they are daydreaming for short moments (Schooler et al., 2011) and lack the capacity to maintain this meta-awareness for prolonged periods of time, another feature that is common to daydreams and dreams that occur during sleep. The neural circuits involved in daydreaming are beginning to be studied. For instance, using both thought sampling and brain imaging (Mason et al., 2007), a recent study showed that mind wandering is associated with activity in the same default network of cortical regions that are active when the brain is not actively engaged in a task (Raichle et al., 2001). Regions of the default network that exhibited greater activity during mind wandering included bilateral medial prefrontal cortex, anterior cingulate, posterior cingulate, precuneus, insula, left angular gyrus, as well as superior temporal cortex. In addition, individuals' reports of the tendency of their minds to wander were correlated with activity in this network (Mason et al., 2007). Another study showed that in addition to the default-mode network,

parts of the executive network, including the dorsal anterior cingulate cortex and the dorsolateral prefrontal cortex, were also recruited during mind wandering (Christoff et al., 2009). Based on these results, however, it would seem that the circuits activated during daydreaming may actually be different from those involved in dreaming, given that, for instance, posterior cingulate, precuneus, and lateral parietal cortex and dorsolateral prefrontal cortex are relatively deactivated during REM sleep (Braun et al., 1997; Maquet et al., 1996; Schwartz et al., 2005).

Lucid Dreaming

Dreams usually involve loss of self-reflection and of reality testing. Hallucinations and delusions in dreams are typically thought to be real rather than dreamed up. Sometimes, however, a dreamer can become aware that he is dreaming (LaBerge et al., 1990; LaBerge, 1980, 1992, 2000). Under such circumstances, the dreamer is able to remember the circumstances of waking life, to think clearly, and to act deliberately upon reflection, all while experiencing a dream world that seems vividly real. Lucid dreaming can be cultivated, typically by a pre-sleep auto-suggestion procedure: the key is to remember that, if one is experiencing something bizarre, such as floating in space, it must be a dream rather than a waking experience. In fact, lucid dreamers often attempt to fly: if they succeed, they know they are probably dreaming. Lucid dreaming has been extensively studied in the laboratory by asking trained subjects to carry out distinctive patterns of voluntary eye movements when they realize they are dreaming, for example, a left-right-left-right eye movement sequence (Erlacher et al., 2013). The prearranged eye movement signals appear on the polygraph records during REM sleep, proving that the subjects had indeed been lucid during uninterrupted REM sleep. This strategy has been used to demonstrate that time intervals estimated in lucid dreams are very close to actual clock time, that dreamed breathing corresponds to actual respiration, and that dreamed movements result in corresponding patterns of muscle twitching. Stable lucid dreams apparently only occur during REM sleep, especially in the early morning, when REM sleep is accompanied by intense phasic phenomena. Recent case studies suggest that brain areas that are relatively deactivated during REM sleep, such as the primary visual areas, the precuneus, and dorsolateral prefrontal cortex, become activated during lucid dreaming (Dresler et al., 2012), supporting the concept that lucid dreaming represents a dissociation between wakefulness and REM sleep, not only with respect to phenomenological features (preserved reflective consciousness), but also in terms of brain activity (reactivation of normally deactivated areas). In addition, EEG studies have documented increased frontal gamma activity during lucid dreaming (Voss et al., 2009) and high-frequency transcranial current stimulation over the frontal and temporal cortex has been used to increase lucidity, insight, and voluntary control in REM sleep dreams (Voss et al., 2014; Stumbrys et al., 2013). Results of another recent study suggest that lucid dreaming represents a particular form of metacognition. The authors of this work showed that frequent lucid dreamers displayed increased gray matter volume in the fronto-polar cortex compared to control subjects, and also found that this area was active during a thought-monitoring task in wakefulness (Filevich et al., 2015).

Sleepwalking and Other Disorders of Arousal

Sleepwalking refers to various complex motor behaviors, including walking, that are initiated during deep NREM sleep, typically during stage N3 (see also Chapter 8). Patients usually stand up and walk around quietly and aimlessly with open eyes and sometimes speak, though slowly and often inarticulately. They move as if they were wide awake, but awareness of their actions is very restricted. Occasionally, sleepwalkers become agitated, with thrashing about, screaming, running, and exhibiting aggressive behavior. A highly publicized case is that of Ken Parks, a sleepwalker who, after falling asleep at home, arose to drive to his in-laws, strangled his father-in-law into unconsciousness, and stabbed his mother-in-law to her death. Some episodes, referred to as confusional arousals, do not involve deambulation and are typically limited to sitting up, fumbling, picking at bedclothes, or mumbling.

Sleepwalking is frequent in children, but it can persist in up to 1% of adults. In predisposed individuals, attacks can be precipitated by forced arousals, for example, by placing the subject afoot. Sleepwalking is regarded as a disorder of arousal with frequent but incomplete awakening from slow-wave sleep. Although it was traditionally assumed that individuals did not have any memory of sleepwalking, recent work suggests that amnesia for the episodes, at least in adults, is often incomplete. In fact, upon awakening, up to 80% of sleepwalkers report some form of mental activity (Zadra et al., 2013). Experiences are generally brief, consisting of a single scene, and tend to be unpleasant, with aggression, misfortune, and apprehension being common themes (Oudiette et al., 2009). In over 60% of cases, sleepwalkers recall behaviors that they displayed during somnambulistic episodes and can report perceptual elements from their actual

surroundings (Zadra et al., 2013). Sometimes, the behavior of the sleepwalker matches the content of the hallucinatory experience (Oudiette et al., 2009), suggesting that at least in some cases, motor activity directly reflects dream content.

Somnambulistic episodes begin while the EEG shows high-amplitude slow waves (Perrault et al., 2014; Jaar et al., 2010). During the episodes, the EEG decreases in amplitude and increases in frequency, usually leading to the appearance of mixed-frequency patterns typical of stage N1. There may also be rhythms resembling the alpha rhythm of waking, but slower by 1–2 Hz and not abolished by eye opening or visual stimulation. During short episodes of sitting up with eyes open and moving around, the EEG may show slow waves throughout—providing a clear-cut dissociation between observable behavior, brain activity, and consciousness.

An influential study has succeeded in performing neuroimaging during a sleepwalking episode using single photon emission computed tomography, a variant of PET (Bassetti et al., 2000) (Chapter 8). The patient, a 16-year-old man, stood up with his eyes open and a scared facial expression. After a few seconds, he sat down, pulled on the EEG leads and spoke a few unintelligible words. The EEG showed diffuse, high-voltage rhythmic slow-wave activity. Compared to waking, regional cerebral blood flow was decreased during sleepwalking in frontoparietal associative cortices, just as it is in slow-wave sleep. This deactivation of prefrontal cortices during normal sleep and sleepwalking is consistent with the lack of self-reflective consciousness and recall that characterize both conditions. However, blood flow was higher during sleepwalking than in slow-wave sleep in the posterior cingulate cortex and anterior cerebellum, and the thalamus was not deactivated as it is during normal slow-wave sleep. Thus, at least in this patient, sleepwalking seems to arise from the selective activation of thalamo-cingulate circuits and the persisting deactivation of other thalamocortical systems. Similar results were obtained in two recent case studies of patients undergoing intracerebral EEG recordings as part of a preoperative work-up for epilepsy surgery (Terzaghi et al., 2009, 2012) who incidentally displayed confusional arousals during nocturnal recordings. During the episodes, the EEG revealed fast, wake-like activity in some areas, like the frontal and central cingulate cortex, and sleep features in others, including slow waves in the frontal (Terzaghi et al., 2009, 2012) and parietal (Terzaghi et al., 2009) associative areas (including parts of the dorsolateral inferior, middle and superior frontal gyri and the superior and inferior parietal gyri), and sleep spindles in the hippocampus (Terzaghi et al., 2012). Normally, the entire forebrain is either awake or asleep. Sleepwalking and confusional arousals thus appear to constitute a dissociated state where some brain areas are "awake" while others are "asleep." It is likely that, in different patients or at different times in the same patient, different areas may be awake or asleep.

Sleep talking is a more frequent occurrence than sleepwalking, and it can occur both in NREM and REM sleep. The majority of sleep speeches contain at least a few words, but they range from a single, mumbled utterance to several minutes of perfectly intelligible talk, the latter more frequently associated with REM sleep. Sometimes sleep talk is clearly a soliloquy, at other times it may resemble telephone conversation. While there is some correspondence between sleep talking and dream content, more often one has the impression of multiple, concurrent streams of mental activity that occur independently and in parallel. Such instances suggest that the speech-production system may be active in relative isolation from dream consciousness, thereby constituting another example of dissociation.

REM Sleep Behavior Disorder

This disorder, which affects mostly elderly males, is characterized by vigorous, often violent episodes of dream enactment, with punching, kicking, and leaping from bed (Mahowald and Schenck, 2005). Patients often injure themselves or their spouses. For example, a male subject would dream of defending his wife, but in enacting his dream he would actually forcefully strike her in bed. Polysomnographic recordings demonstrate that such episodes occur during REM sleep. People with REM sleep behavior disorder can usually recall their dreams in detail. Conscious experience during an episode is extremely vivid, as in the most animated dreams, and is fully consistent with the motor activity displayed.

Much before the clinical syndrome was recognized in humans, sleep researchers had observed that, if certain regions of the pons that are normally responsible for inhibiting muscle tone and motor programs during REM sleep are lesioned, cats seem to "enact their dreams" of raging, attacking, fleeing, or eating while not responding to external stimuli (Morrison, 1988; Jouvet, 1979; Sastre and Jouvet, 1979). In humans, the disorder most often occurs without an obvious cause, but it is sometimes associated with neurological conditions. It may indeed result from minute lesions in the pons, it frequently anticipates the development of Parkinson's or other neurodegenerative disorders, and it may be triggered acutely by certain drugs (certain antidepressants) or by withdrawal (ethanol).

Narcolepsy and Cataplexy

Narcolepsy is characterized by daytime sleepiness (sleep attacks), cataplexy (muscle weakness attacks), hypnagogic hallucinations, and sleep paralysis (Mahowald and Schenck, 2005). In addition, night-time sleep is generally fragmented and often experienced as unrefreshing. Narcolepsy usually begins with excessive sleepiness and unintentional naps in the teens and twenties. Sleepiness is especially strong during periods of inactivity and may be relieved by short naps. When narcoleptics fall asleep, they usually go straight into REM sleep. Recent studies show that narcoleptic individuals experience more frequent lucid dreaming compared to controls (Dodet et al., 2014; Rak et al., 2014), both during night-time sleep and daytime naps (Dodet et al., 2014). During the day, patients often complain that they have a short attention span and poor memory, and sometimes behave in an automatic, uncontrolled way. In more than half of the cases, narcolepsy is accompanied by cataplexy. This is a sudden loss of muscle tone, typically brought on by strong emotions such as laughter or anger. The sudden weakness may be generalized and force the patient to collapse to the ground, or it may be localized to the voice, the chin, or a limb. Each episode generally lasts only a few minutes. Consciousness and awareness of the environment are preserved during cataplectic attacks, unless sleep intervenes. Hypnagogic hallucinations are dream-like hallucinations, mostly visual, that occur at sleep onset or when drowsy. Sleep paralysis is a frightening feeling of being fully conscious but unable to move, which may occur on awakening or falling asleep, like a temporary version of the locked-in syndrome (see Chapter 12). Healthy individuals can experience hypnagogic hallucinations, especially when sleep deprived, and may also experience sleep paralysis. However, while laughter and other emotional stimuli can produce muscle relaxation in healthy subjects, cataplexy is definitely an abnormal phenomenon. Sleep paralysis and cataplexy are probably due to the inappropriate activation of the brainstem mechanisms responsible for abolishing muscle tone during REM sleep. Narcolepsy–cataplexy are known to be associated with a defect in the hypocretin–orexin system (Dauvilliers et al., 2007). Narcoleptic dogs and mice have a mutation in the gene for hypocretin or its receptors and, in the brain of narcoleptic patients, there is a loss of hypocretin cell groups in the posterior hypothalamus.

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CHAPTER

8

Sleepwalking: Dissociation Between "Body Sleep" and "Mind Sleep"

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OUTLINE

DEFINITION

Sleepwalking (SW, syn. somnambulism) consists of complex motor behaviors that interrupt night sleep. It is initiated during sudden arousals from slow wave sleep (SWS) and culminates in a deambulatory activity with an altered state of consciousness and judgement (American Academy of Sleep Medicine, 2005).

HISTORICAL REMARKS

SW has been known since ancient times (Galen and Socrates may have been somnambulic) (Goetz, 1987). Homer described in "Odyssey" a youth named Elpenor who after awakening from deep sleep ran off a roof injuring himself. Dante described in "La Divina Commedia" the SW of the Purgatory's souls, and Shakespeare the SW of "Macbeth." In his book *Dracula* Bram Stoker described hereditary SW in the Westerna family.

Violence and injuries related to SW and their forensic implications have been discussed in the medical literature since the nineteenth century (Yellowlees, 1878; Charcot, 1892). Neurologists at the turn to the twentieth century (including Charcot, Dejerine, and Oppenheim) discussed the existence of epileptic, psychogenic (hysterical, hypnosis-induced), toxic (alcoholic), post-traumatic, and sleep-related deambulatory episodes (poriomania, dromomania) (Charcot, 1887–1888, 1892; Dejerine, 1914; Oppenheim, 1913).

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In his classical book *Sleep and Wakefulness* (first edition in 1939) Nathaniel Kleitman pointed out that the term SW, if used to denote walking while asleep, represents a misnomer since it corresponds rather to "walking in the course of an interruption of night's sleep" (Kleitman, 1939). The first systematic clinical studies on SW were performed in the 1940s and 1950s in the US army (Sandler, 1945). Systematic polysomnographic studies of SW were performed first in the 1960s (Gastaut and Brougton, 1965; Jacobson et al., 1965; Kales et al., 1966).

Pathophysiologically, De Morsier suggested in the 1930s an analogy between SW and daytime states with impaired consciousness such as confusional states and epileptic automatisms (De Morsier, 1931). Kleitman (1939) underlined the difference between wakefulness and consciousness in the context of SW. Broughton expanded these concepts proposing SW as a disorder of arousal (with increased but incomplete arousability from SWS) because of the co-existence in SW of mental confusion, automatic behavior, non-reactivity to external stimuli, retrograde amnesia and decreased amplitude/increased latencies of visual evoked potentials (Broughton, 1968).

EPIDEMIOLOGY

The frequency of SW is age-dependent (Laberge et al., 2000). The peak frequency of about 10–15% is observed in children around the age of 8–12 years (American Academy of Sleep Medicine, 2005; Laberge et al., 2000; Petit et al., 2007). In one out of four cases SW persists beyond the age of 10 years (Laberge et al., 2000).

In adults the frequency of SW has been estimated to be around 2–4%, although less than 1% present SW at least weekly (Hublin et al., 1997; Ohayon et al., 1999). SW affects both genders equally (American Academy of Sleep Medicine, 2005; Laberge et al., 2000; Ohayon et al., 1999). A positive family history of SW is frequent (see below).

CLINICAL FEATURES

During SW patients wake up suddenly, sit up, look around with a confused stare, leave the bed and deambulate. Movements are typically slow and clumsy at the beginning, more coordinated and physiologic later (patients often can avoid obstacles while walking). Movements can be repetitive and purposeless, on other occasions they appear complex and meaningful (eating, drinking, cooking, driving a car) (Schenck and Mahowald, 1995). Occasionally, movements are rapid (Figure 8.1). The patient suddenly jumps out of bed, appears agitated and belligerent and may even run (a situation for which the term "somnomania" was suggested (Yellowlees, 1878)).

FIGURE 8.1 30-year old man (B.S.) with SW. Three pictures (12 s separate the first from the last picture) taken from a nocturnal videography documents the abrupt beginning of a SW episode.

During SW the eyes are open and staring. Patients can speak and answer to questions, usually however in an incomprehensible manner. Shouting can accompany agitated SW episodes. Autonomic activation (sweating, tachycardia, tachypnea) is more common in confusional arousals and sleep terrors than in SW.

Patients are difficult to awaken, and when awakened appear confused. They may return spontaneously to bed and lie down. There is usually no recall of SW episodes. Dream-like experiences are, however,

occasionally reported particularly in adult SW (Bassetti and Vadilonga, 2000). Occasionally SW appears to respond to a perceived threat (fire, earthquake, bomb) (Yellowlees, 1878; Kavey et al., 1990).

Complications

Self-injuries are possible, more frequently in adult SW. This may occur during such acts as jumping out of the window or walking on a roof (Broughton et al., 1994).

Violence during SW occurs mainly in adult and male patients (in 30% of 74 adult sleepwalkers in an own series (Bassetti and Vadilonga, 2000)). Reports of homicidal, filicidal, and suicidal SW have been known since the nineteenth century (Yellowlees, 1878; Broughton et al., 1994; Brouardel et al., 1893; Hartmann, 1983; Gottlieb et al., 1986; Bornstein et al., 1995; Cartwright, 2004). In a systematic review of 32 cases drawn from medical and forensic literature, physical contact and proximity were found to be often involved in violent behavior associated with SW/sleep terrors (Pressmann, 2007a).

Nocturnal eating (somnophagia), often rapid and compulsory, can appear in association with SW, in females more than males (Vetrugno et al., 2006). In a series of 74 adults sleepwalkers nocturnal eating was reported by 34% of patients (Bassetti and Vadilonga, 2000).

Abnormal sexual behavior during sleep (sleep sex, sexsomnia) in form of indecent exposure, sexual intercourse, sexual assault, moaning, and masturbation have also been reported in association with SW, in males more than females (Andersen et al., 2007).

Onset/Course

More often, SW appears between the age of 5 and 15 years, with a peak around 8–12 years. Earlier and later onsets (including "de novo" in adulthood) are possible (Kavey et al., 1990). Childhood SW usually disappears around puberty.

Typically, SW occurs once per night and in the first third of the night (about 1 h after sleep onset). The frequency of SW is, however, very variable and can range from few episodes in a lifetime up to several (Charcot, 1887–1888; Dejerine, 1914) episodes per night (Kavey et al., 1990). In addition, SW can occur also in the latter two-thirds of the night and even during daytime naps (Kavey et al., 1990). The duration of SW ranges from 1–3 to 7–10 min, rarely longer. Patients are typically difficult to be awaken during an SW episode. Episodes of SW often end with the patient returning to his bed.

Associated Features

Patients with SW have a higher frequency of sleep terrors (*pavor nocturnus*), confusional arousals, enuresis and sleep talking (Yellowlees, 1878; Broughton, 1968; Ohayon et al., 1999). In some but not all studies an association with bruxism and sleep starts was observed (Ohayon et al., 1999). An association with complex nocturnal hallucinations has also been reported (Kavey and Whyte, 1993; Silber et al., 2005).

Migraine and psychiatric symptoms/disturbances have also been linked with SW (Ohayon et al., 1999; Barabas et al., 1983; Casez et al., 2005).

NEUROPHYSIOLOGICAL FEATURES

Neurophysiologically it has been known since the 1960s that SW occurs during sudden but in complete arousals (Figure 8.2) from SWS (Jacobson et al., 1965; Broughton, 1968). Less commonly SW, particularly in adults, may occur out of other sleep stages (Kavey et al., 1990; Joncas et al., 2002).

SW episodes are rarely recorded in the sleep laboratory (Jacobson et al., 1965; Broughton, 1968). An episode of SW is typically preceded by high amounts of slow wave activity occasionally in form of high-voltage, rhythmic slow delta waves which are typically accentuated over the frontal and central derivations (hypersynchronous delta waves, HSD (Jacobson et al., 1965; Pilon et al., 2006)). Occasionally runs of alpha waves can appear diffusely or focally (e.g., over the central regions) in the delta wave sleep preceding a SW episode (Guilleminault et al., 2001). The heart rate accelerates abruptly during but not before the sudden arousal.

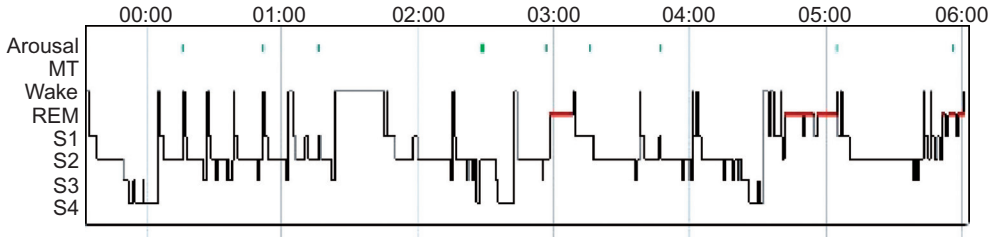

FIGURE 8.2 32-year old man (T.K.) with SW. About 1 h after sleep onset six recurrent episodes of sudden arousal from slow wave sleep.

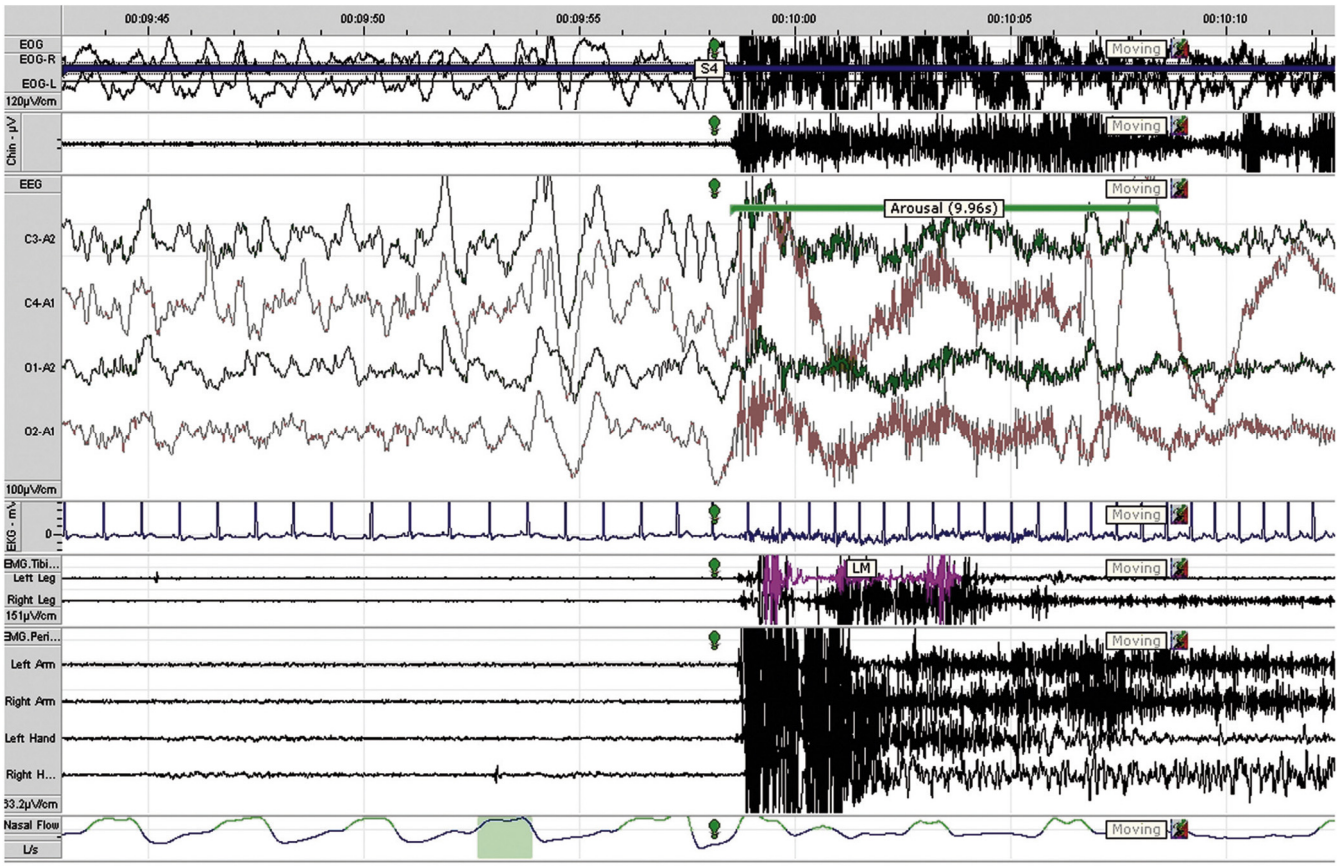

FIGURE 8.3 27-year old man (S.B.) with SW. About 1 h after sleep onset sudden arousal from slow wave sleep.

The post-arousal electroencephalography (EEG) demonstrates variable patterns including rhythmic, high-voltage frontally accentuated delta activity (which seems to be associated with rather simple behavioral episodes (Zadra et al., 2004)); diffuse delta–theta activity; mixed delta–theta–alpha–beta activity (Figure 8.3); alpha or beta activity (Zadra et al., 2004; Schenck et al., 1998).

The polysomnography of patients with SW is characterized by an increased fragmentation of SWS (particularly during the first non-rapid eye movement (NREM) episode) and by the recurrent appearance of HSD (Jacobson et al., 1965; Pilon et al., 2006). The number of arousals from SWS is increased (Blatt et al., 1991) whereas the amounts of SWS are decreased (Gaudreau et al., 2000; Espa et al., 2000). An abnormal cyclic alternating pattern with a decrease in phase 1 and increase in phase 2 was observed in chronic sleepwalkers (Guilleminault et al., 2006).

Sleep deprivation may increase the diagnostic yield of sleep studies in SW (Joncas et al., 2002). It is noteworthy that sleep deprivation leads also to an increase in HSD (Pilon et al., 2006).

Occasionally, particularly in adult SW, phasic muscle activity during rapid eye movement (REM) sleep is increased (in 20% of 74 patients with adult sleepwalkers in an own study (Bassetti and Vadilonga, 2000)). Some series noted an increased frequency of sleep disordered breathing and periodic limb movements in sleep in patients with SW (see "Triggering Factors").

The EEG is typically normal in sleepwalkers (Bassetti and Vadilonga, 2000; Soldatos et al., 1980). During sleep as well as wakefulness, focal epileptiform activities have been however sporadically observed.

ETIOLOGY

SW arises from genetic, developmental, somatic, and psychological factors. Predisposing, priming, and precipitating factors have been identified.

Predisposing Factors: Genetic Influences

The familial occurrence of SW was first documented in 1942 (Davis et al., 1942). The frequency of SW in first-degree relatives is at least ten times greater than in the general population (Kales et al., 1980). In a twin study,

monozygotic twins were found to be concordant for the symptom SW six times more than dizygotic twins (Bakwin, 1970). In the Finnish Twin Cohort the frequency of SW was similar in monozygotic and dizygotic twins, however, the concordance rate was also higher for monozygotic twins (0.55 vs 0.32) (Hublin et al., 1997). The phenotypic variance related to genetic factors has been estimated to be about 57–66% in childhood SW and 36–80% in adult SW (Hublin et al., 1997).

The HLA marker DQB1*05 may represent a susceptibility marker for SW (Lecendraux et al., 2003). In a study of 60 sleepwalkers this marker was found in 35% of patients (vs. 15% of matched controls).

Priming Factors: Psychiatric and Neurological Influences

Current or past mental disorders are more common in patients with SW than in patients without SW (Ohayon et al., 1999). Schizoid, obsessive, compulsive, anxious, phobic, depressive symptoms or profiles have been found in patients with SW (Hartmann, 1983; Bornstein et al., 1995; Scott, 1988). Overall the link between psychopathology and SW is considered, however, to be weak (American Academy of Sleep Medicine, 2005). Furthermore, a history of major psychological trauma appears to be rare in SW (Hartman et al., 2001).

Several disorders of the central nervous system including stroke, head trauma, encephalitis, Tourette's syndrome, and migraine have been linked with (often adult) SW (Mori et al., 1990; Hughes, 2007). In the absence of a specific correlation between SW and the topographical, pathological or neurochemical characteristics of these brain disorders the nature of the link between SW and neurological conditions (as this is the case also for psychiatric disorders) appears to be non-specific.

Triggering Factors: Precipitating Influences

Several triggering factors are known from clinical experience. However, only a few systematic studies have been performed. The pertinent literature was reviewed recently (Pressmann, 2007b).

Sleep fragmentation: This may be related to sleep disordered breathing (Espa et al., 2002; Guilleminault et al., 2003), restless legs/periodic limb movements in sleep, internal stimuli (e.g., bladder distension) or external stimuli (light, noise) (American Academy of Sleep Medicine, 2005). This may play a role in the observed association between SW and thyrotoxicosis (Hughes, 2007). In a series of 74 adult sleepwalkers sleep disordered breathing was found "only" in 25% of patients and periodic limb movements in 12% of patients (Bassetti and Vadilonga, 2000).

SWS rebound: This can be observed, for example, after sleep deprivation and at the beginning of CPAP treatment for sleep apnea (Millman et al., 1991). Experimentally a sleep deprivation of 36 h has led to an increase in frequency and complexity of episodes during the recovery night compared with baseline in patients with SW (Joncas et al., 2002).

Fever is often reported to trigger episodes of SW (American Academy of Sleep Medicine, 2005).

Alcohol, often in combination of other factors, is not infrequently involved (Broughton et al., 1994; Hartmann, 1983). Up to 10% of adult patients with SW consume alcohol at bedtime (Ohayon et al., 1999). Direct experimental evidence that alcohol may trigger or worsen SW is however lacking (Pressmann et al., 2007).

Several *medications* including zolpidem/benzodiazepines (Sansone and Sansone, 2008; Lauerma, 1991), thioridazine/neuroleptics (Scott, 1988; Huapaya, 1979), stimulants/aminergic (dopaminergic) drugs (Bornstein et al., 1995; Khazaal et al., 2003), antidepressants/serotonin reuptake inhibitors (e.g., paroxetin) (Huapaya, 1979), antihistaminics (Huapaya, 1979), and lithium (Charney et al., 1979) may trigger SW episodes also in the absence of a positive history of SW (Huapaya, 1979). Nevertheless, only 4% of adult patients with SW consume psychotropic drugs (Ohayon et al., 1999).

Mental stress is often reported by patients as triggers of SW or as involved in increasing its frequency (Ohayon et al., 1999).

Pregnancy usually leads to a decrease of SW (Hughes, 2007).

PATHOPHYSIOLOGY

Any pathophysiological model of SW must explain the simultaneous appearance of (i) complex motor behaviors (including deambulation) out of deep sleep in and (ii) an impaired state of consciousness. The co-existence of complex motor behaviors and impaired consciousness corresponds to a state dissociation (between "body and mind sleep"), the neurophysiological, anatomical, and chemical nature and origin of which remains speculative (Mahowald and Schenck, 1992).

Animal and human data suggests that the variety of complex motor behaviors associated with SW could arise from the activation of neuronal networks in subcortical and brainstem regions responsible for the generation of (innate, archaic) emotional and motor behaviors. The activation of such "central pattern generators" during SW, epileptic or psychogenic spells could explain the similar phenomenology of complex motor behaviors (including deambulation, eating, sexual activity, violent acts) seen with such different underlying conditions (Berntson and Micco, 1976;

Mahowald and Schenck, 2000; Tassinari et al., 2005). If this hypothesis is correct, SW could be viewed as a disorder characterized by the "hyper-arousability" of specific (striato-limbic?) neuronal networks.

The impaired state of consciousness typical of SW implies on the other hand an insufficient activation of prefrontal cortical areas necessary for purposeful behavior/planning, insight/judgement and inhibition of emotional responses. These areas have been shown by neuroimaging studies to be inactivated during physiological sleep.[1] The incomplete/difficult awakening of sleepwalkers from deep sleep could therefore correspond to a "hypo-arousability" of (prefrontal?) cortical areas. This hypothesis could explain why factors that increase SWS (which exhibits maximal power over the prefrontal areas (Werth et al., 1997)) trigger SW as well as the similarities between the mental state of sleepwalkers and that of normal subjects with protracted/difficult awakening from sleep (sleep inertia, sleep drunkenness).

One SPECT (single photon emission computed tomography) study supports the concept of state dissociation underlying SW. Compared to cerebral blood flow (CBF) data obtained in 24 subjects during wakefulness the CBF of a single patient during SW was found to be increased in the posterior cingulate cortex and cerebellar vermis and decreased in frontal and parietal association cortices (Figure 8.4) (Bassetti et al., 1999). This observation, in line with Broughton's original suggestion of SW as an arousal disorder, suggests the presence of a specific activation of thalamo-cingulocortical pathways (implicated in the control of complex motor and emotional behavior) while other thalamocortical pathways (including those projecting to the frontal lobes) remain inhibited. The appearance at the different ages and during different nights in the same patient of SW, sleep terrors, confusional arousals could be explained by the recruitment of distinct although partially overlapping thalamo-cingulo-cortical pathways.

The fundamental cause of state dissociation in SW remains unknown. The existence of different predisposing, priming and triggering factors of SW (see "Etiology") as well as of different forms of SW (see "Differential Diagnosis") prove that the dynamic physiological reorganization that the brain undergoes at the transition from one state to another (in the case of SW from deep sleep to lighter sleep/wakefulness) represents a complex and fragile process that undergoes developmental maturation and can be impaired by different (neurological, psychological, pharmacological…) factors.

Although SW may represent a behavioral disorder unique to the human species (Kantha, 2003), dissociated states of being are known also in the animal kingdom (e.g., unihemispheric sleep in dolphins, flight during sleep in birds) (Mahowald and Schenck, 2000). This offers the opportunity for an experimental approach to the study of the above mentioned "dynamical reorganizational brain processes" and its dysfunctions.

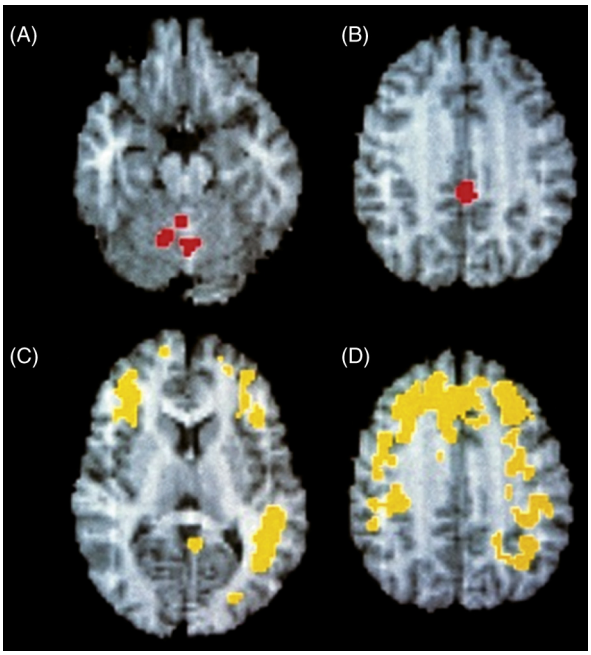

FIGURE 8.4 SPECT findings in a 22-year old man with familial SW (with permission from Bassetti and Vadilonga, 2000). The highest increases of regional cerebral blood flow (>25%) during SW compared with quiet stage 3 to 4 NREM sleep are found in the anterior cerebellum—i.e., vermis (A), and in the posterior cingulate cortex (Brodmann area 23 [Tailarach coordinate $x = -4$, $y = -40$, $z = 31$], (B)). However, in relation to data from normal volunteers during wakefulness ($n = 24$), large areas of frontal and parietal association cortices remain deactivated during SW, as shown in the corresponding parametric maps (z-threshold = −3). Note the inclusion of the dorsolateral prefrontal cortex (C), mesial frontal cortex (D) and left angular gyrus (C) within these areas.

The association of SW with migraine suggests the possible involvement of the serotonin system in both (Barabas et al., 1983; Casez et al., 2005). This hypothesis is further supported by the observation that several factors known to trigger SW (including fever, lithium, and antidepressants) activate the serotoninergic system (Juszczack and Swiergiel, 2005). The involvement of cholinergic and GABA(A) pathways has been proposed based on theoretical speculations and the result of transcranial magnetic stimulation studies in awake sleepwalkers (Oliviero et al., 2005). Considering the essential physiological role of the hypocretin (orexin) system in state stabilization (Saper et al., 2001) and the fact that narcolepsy represents the dissociated disorder "par excellence" (Baumann and Bassetti, 2005), an involvement of this hypothalamic system—possibly with the dopamine system (which is known to interact with the hypocretin system (Harris and Aston-Jones, 2006))—appears also to be possible.

DIAGNOSIS

The diagnosis is usually based on typical history. Videography done at home can be of diagnostic help. Sleep studies in the sleep laboratory rarely documents episodes of SW but can show the typical polysomnographical/EEG findings of patients with SW. Furthermore, they can help to rule our disorders that may erroneously be diagnosed as SW (e.g., sleep epilepsy). Finally, sleep tests can rule out the co-existence of sleep disorders that may trigger SW episodes (sleep disordered breathing, periodic limb movements in sleep).

DIFFERENTIAL DIAGNOSIS

Is it SW?

In otherwise healthy subjects SW must be differentiated mainly from REM sleep behavior disorder and other parasomnias, nocturnal (morpheic) seizures, dissociative spells, toxic encephalopathies (secondary to drug/alcohol intake and leading to incomplete/confusional arousals and sleep drunkenness, "syndrome d'Elpénor" (Bornstein et al., 1995)), metabolic encephalopathies (e.g., hypoglycemia secondary to insulinoma (Suzuki et al., 2007)), and nocturnal volitional (waking) behavior/malingering (see Table 8.1).

In elderly patients with cognitive impairment, sensory deprivation in the night may lead to episodes of nocturnal confusion (sundowning phenomena).

In patients with neurological and psychiatric disorders, deambulatory activity (pacing), if appearing at night, may also be mistaken for SW. Wandering behavior is in fact quite common in Alzheimer's disease. It is typically associated with severe dementia, disturbed sleep, delusions, injuries, and caregiver distress (Rolland et al., 2005). Its pathophysiology remains obscure.

Diagnostic Work-Up: Which Form/Cause of SW?

See Table 8.1.

1. SW in the context of arousal disorders (NREM parasomnias)
   This is certainly the most common and best known form of SW.
2. SW in the context of parasomnia overlap syndrome
   These patients exhibit both SW and REM sleep behavior disorder (Schenck et al., 1997).
   The existence of SW in the context of REM sleep behavior remains controversial/poorly known (Tachibana et al., 1991; De Cock Cochen et al., 2007).
3. SW in the context of nocturnal epilepsy (epileptic wandering)
   Nocturnal seizures of temporal and frontal lobe have been reported to manifest with somnambulism (usually called in this context "epileptic nocturnal wandering") (Pedley and Guilleminault, 1977; Plazzi et al., 1995; Nobili et al., 2002). This existence of epileptic wandering was known already by Charcot (Goetz, 1987, 2004). Patients may exhibit during such episodes dystonic postures and violent behaviors. The EEG displays an epileptiform activity.
4. SW in the context of psychogenic disorders
   Psychogenic dissociative states, as discussed already by Charcot, can present with SW (Charcot, 1892; Schenck et al., 1989).
5. SW in neurological disorders
   This is a yet poorly known context for SW.
   Besides the association of SW with migraine, stroke, head trauma, and encephalitis (Barabas et al., 1983; Casez et al., 2005), SW was linked more recently with neurodegenerative disorders such as Machado-Joseph and Parkinson's disease (Kushida et al., 1995; Poryazova et al., 2007).

TABLE 8.1 Diagnostic Approach and Differential Diagnosis of SW

IS IT SW OR ANOTHER NOCTURNAL MOTOR "SPELL"?
History/videography/video-polysomnography are decisive
SW "sensu strictu"
REM sleep behavior disorder (without SW)
Nocturnal epilepsy (without SW)
Confusional arousals/sleep drunkenness
Idiopathic
Secondary to sleep apnea or other sleep disorders
Secondary to toxic/metabolic encephalopathy
Nocturnal wandering/sundowning in demented (Alzheimer's) patients
Dissociative "spells"
Volitional (waking) behavior
IT IS SW, WHICH FORM/CAUSE?
History, clinical context/examination and ancillary tests (e.g., brain MRI, EEG. . .) are decisive
In the context of:
NREM parasomnia
Overlap parasomnia or REM sleep behavior disorder
Neurological disorders (including Parkinson)
Nocturnal epilepsy (epileptic wandering)
Psychiatric disorders

TREATMENT

Triggering factors and predisposition situations should be avoided.

The patients' sleep environment should be made safe (sleeping on the first floor, securing doors/windows, removing potentially dangerous objects, etc.).

Stress-reducing treatments (including hypnosis) can be of help in selected patients (Reid, 1975).

Clonazepam (0.5 mg at bedtime, to be increased up to 2–3 mg) is the drug of first choice for SW (Schenck and Mahowald, 1996).

Other benzodiazepines (including flurazepam, triazolam, and diazepam), antiepileptics (including carbamazepine, phenytoin, and gabapentin), antidepressants (including imipramine, trazodone, and paroxetin) and melatonin have been reported to be effective in both childhood and adult SW, although only in single cases or very small series (Kavey et al., 1990; Hughes, 2007; Wilson et al., 1997; Liliwhite et al., 1994; Guilleminault et al., 2005; Cooper, 1987).

Treatment of sleep disordered breathing can improve the control of SW (Guilleminault et al., 2005).

FORENSIC ASPECTS

Already Charcot—in the late nineteenth century—was involved in a medico-legal expertise of a patient accused of attempted murder and pleading innocence because he was a somnambulist. In a famous case published in 1878 the patient, asked to plead, said "I am guilty in my sleep, but not guilty in my senses" (Yellowlees, 1878). Seven criteria have been suggested by Mahowald for the evaluation of sleep-related violence cases: (i) presence of sleep disorder by history/sleep tests; (ii) duration of "spells"; (iii) character of behavior (senseless?); (iv) behavior after the "spell" (perplexity, horror?); (v) amnesia; (vi) timing of "spell" after sleep onset, and (vii) prior sleep deprivation (Mahowald et al., 1990).

CONCLUSION

The complex, semi-purposeful behavior observed during SW can be viewed as the result of a specific and isolated activation of specific (striato-limbic?) neuronal networks during SWS. This state dissociation results from a wide range of genetic, neurological, psychiatric and triggering influences.

Clinically, SW is relevant because of the associated risk of injuries and violence and the fact that, particularly in adults, a variety of disorders (including epilepsy) may lead to an automatic deambulatory activity during sleep.

Scientifically, the study of SW offers a unique perspective on the control mechanisms of complex emotional behaviors and more generally on dissociated states of being.

Overall, SW—while raising fundamental questions about the biological bases of consciousness, behavior and free will—represents a fascinating challenge for modern neuroscience.

NOTE

1. This explains the neuropsychological characteristics of mental activities in sleep including dreams (Schwartz and Maquet, 2002).

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CHAPTER

9

Consciousness and Anesthesia

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OUTLINE

INTRODUCTION

Consciousness not only is arguably the most compelling subject of scholarly inquiry, but also perhaps the most difficult to study. The field of anesthesiology is in a unique position to facilitate the investigation of this problem, because the drugs in common use during clinical care infallibly suppress consciousness in a reversible manner. As such, general anesthetics have been explored increasingly as scientific probes to understand consciousness (Mashour, 2006; Alkire et al., 2008). The mechanisms and measurement of consciousness also have direct clinical relevance for the anesthesiologist: the awareness and explicit episodic recall of surgical events occurs in approximately 1–2 cases/1000 in the unselected surgical population (Sandin et al., 2000; Sebel et al., 2004; Mashour et al., 2012) and up to 1% in the high-risk surgical population, which includes patients presenting for cardiac or emergent trauma surgery (Myles et al., 2004). Since this complication is associated with a high incidence of posttraumatic stress disorder (Leslie et al., 2010), there is a strong motivation to prevent unintended consciousness in the operating room. Unfortunately, commercially available electroencephalographic monitors are not superior to traditional methods of assessing anesthetic depth in the prevention of intraoperative awareness with explicit recall (Avidan et al., 2011; Mashour et al., 2012). In order to develop more sophisticated and reliable brain monitors for the perioperative period, advances in the neurobiology of consciousness and anesthesia are required (Mashour et al., 2011).

In the context of this chapter, consciousness refers exclusively to "subjective experience," which has

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TABLE 9.1 Summary of Major Molecular Actions of General Anesthetics

	$GABA_A$	Glycine	nACh (muscle)	nACh (neuronal)	$5HT_3$	AMPA	Kainate	NMDA	TASK1	HCN1
Etomidate					0	n/a	n/a	n/a		0
Propofol					0		0		0	
Barbiturates								0	n/a	n/a
Ketamine		0				0	0		n/a	
Isoflurane										
Sevoflurane					n/a	0	n/a			n/a
Nitrous oxide									n/a	n/a

GABA-A, γ-amino butyric acid type A; nACh, nicotinic acetylcholine; $5HT_3$, 5-hydroxytryptamine (serotonin) type 3; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; TASK-1, TWIK (two-pore domain weakly inwardly rectifying potassium)-related, acid sensitive potassium channel type 1; HCN1, hyperpolarisation-activated cation channel type 1.

This table represents a basic and non-comprehensive overview of the receptor and channel targets of intravenous and inhaled anesthetics. (Red, strongly activating; orange, weakly activating; dark blue, strongly inhibiting; pale blue, weakly inhibiting; 0, no effect; n/a, data unavailable.)
Source: Table reproduced from Pandit (2014), with permission.

been functionally described by Searle as what is lost when we fall into a dreamless sleep and what returns when we awake (Searle, 1998). Generally speaking, the subjective experience of interest in the human studies of anesthetic mechanism relates to consciousness of the environment. Anesthetic-induced unconsciousness in humans is typically defined by the loss of responsiveness to a verbal command, which is still consistent with the possibility of dream states (Noreika et al., 2011); for rodent studies, the most common surrogate of anesthetic-induced unconsciousness is the loss of the righting reflex.

SYSTEMS-BASED APPROACH TO ANESTHETIC-INDUCED UNCONSCIOUSNESS

Traditionally, the focus of anesthetic-induced unconsciousness has been at the biophysical level (Campagna et al., 2003). However, in the past decade there has been a shift from lipids and proteins as molecular targets of general anesthetics (see Table 9.1) to paradigms rooted in systems neuroscience and the neurobiology of consciousness (Mashour, 2006, 2013a; Alkire et al., 2008; Brown et al., 2010, 2011). This chapter reflects a systems neuroscience approach to consciousness and anesthesia, and spans the subcortical centers that mediate states of wakefulness and arousal to the thalamocortical and corticocortical networks that are thought to mediate experience itself.

ANESTHETIC EFFECTS ON SUBCORTICAL NUCLEI REGULATING WAKEFULNESS

It was hypothesized in the mid-1990s that anesthetics suppress consciousness by co-opting the subcortical nuclei controlling sleep-wake cycles (Lydic and Biebuyck, 1994). There is, indeed, evidence that anesthetics interact with a number of these nuclei (Franks, 2008), but the precise interactions and contributions to the state of general anesthesia remain unclear. The following is a description of select subcortical nuclei in the brainstem and hypothalamus that may be targets of general anesthetics.

Brainstem

Locus ceruleus (LC)—The LC, the source of norepinephrine in the brain, is located in the pons and projects widely throughout the cortex (Jones, 2011). LC activity is highest during waking consciousness, is decreased during non-rapid eye movement (NREM) sleep, and is at its nadir during rapid eye movement (REM) sleep (Figure 9.1—top row in red) (Aston-Jones and Bloom, 1981; Takahashi et al., 2010). Thus, LC is associated with cortical arousal during wakefulness and not during REM sleep (Figure 9.1—top row in red), suggesting that it may play a role in "connected" consciousness (i.e., consciousness connected to the environment) (Sanders et al., 2012). LC neurons are hyperpolarized by halothane (Sirois et al., 2000) and, when modulated directly, can affect arousal states

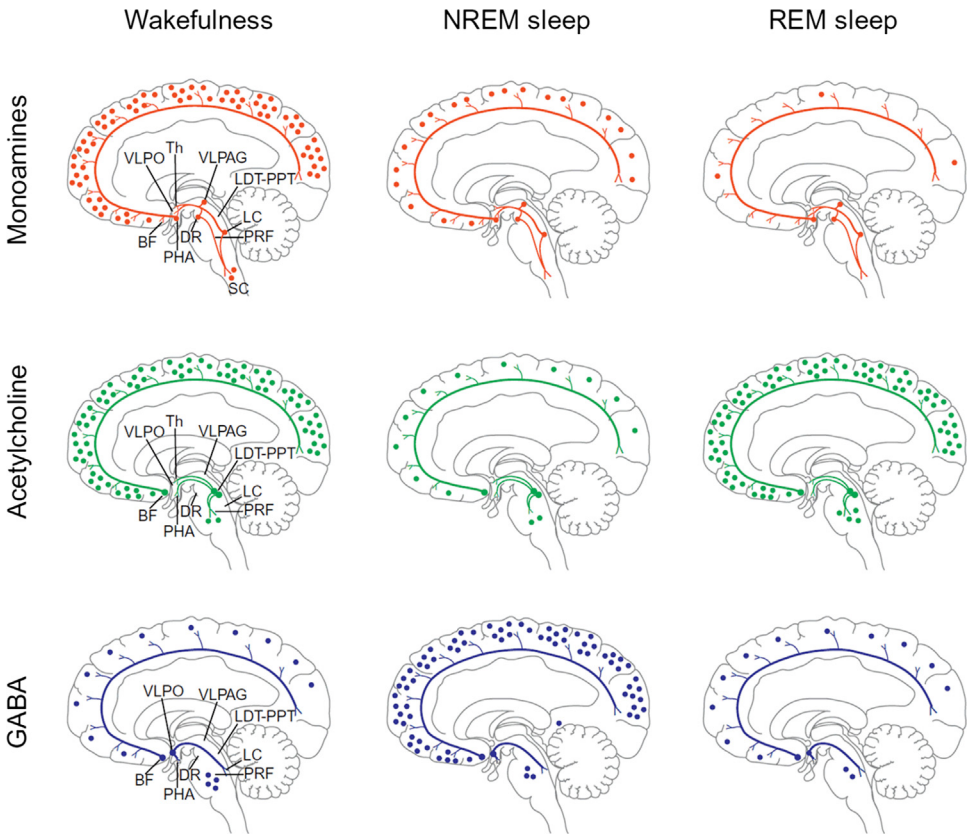

FIGURE 9.1 Basic neurochemistry of sleep-wake states. This figure schematizes the state-dependent changes in monoaminergic (red), cholinergic (green), and gamma-aminobutyric acid (GABA)ergic (blue) neurotransmitter systems across the sleep-wake cycle. Density of the dots at the schematized nerve terminal reflects the state-dependent increases or decreases of release of the particular neurotransmitter. BF, basal forebrain; DR, dorsal raphe; LC, locus ceruleus; LDT/PPT, laterodorsal and pedunculopontine tegmentum; PHA, posterior hypothalamic area; PRF, pontine reticular formation; SC, spinal cord; Th, thalamus; VLPAG, ventral periaqueductal gray; VLPO, ventrolateral preoptic nucleus. *Source: Figure reproduced from Baghdoyan and Lydic (2012), with permission.*

and emergence times during isoflurane anesthesia (Vazey and Aston-Jones, 2014). Norepinephrine transmission from the LC to the basal forebrain may be of particular relevance to anesthetic depth (Pillay et al., 2011).

Dexmedetomidine is an alpha-2 adrenergic agonist used for sedation that mimics NREM sleep in terms of neurophysiology and reversibility after exposure to a noxious stimulus. The LC has been a focus of research into the mechanisms of dexmedetomidine given the fact that agonizing the presynaptic alpha-2 adrenergic receptor can suppress firing of noradrenergic neurons and thus reduce cortical stimulation. Microinjection of dexmedetomidine in the LC results in reduced levels of consciousness (Correa-Sales et al., 1992); expression of c-fos, a marker of cellular metabolism that reflects antecedent neuronal activity, after exposure to dexmedetomidine resembles patterns seen during NREM sleep in that the LC and tuberomammillary nucleus (TMN) are deactivated, while the ventrolateral preoptic nucleus (VLPO) is activated (Nelson et al., 2003). However, knock-out mice lacking dopamine-beta-hydroxylase (an enzyme required for the synthesis of norepinephrine) demonstrate a *hypersensitivity* to dexmedetomidine, suggesting alternative mechanisms of action (Hu et al., 2012). Interestingly, the intravenous anesthetic ketamine appears to depend on LC function, as demonstrated through studies of c-fos expression (Lu et al., 2008) and lesioning (Kushikata et al., 2011).

Laterodorsal/pedunculopontine tegmentum (LDT/PPT)—The LDT and PPT are located in the pons and, along with the basal forebrain, are the brain's source of acetylcholine (Woolf and Butcher, 2011). LDT and PPT project to hypothalamus and thalamus, with a known role in the generation of slow oscillations and sleep spindles (Steriade, 2003). As with the LC, activity of the LDT/PPT is high during wakefulness and lower during NREM sleep (Jones, 2011). In contrast to the LC and other monoaminergic neurons, the cholinergic LDT/PPT is also active during REM sleep, a state of cortical arousal. Thus, cortical activation across the sleep-wake cycle is associated with high cholinergic

tone (Figure 9.1—middle row in green). Although less well studied than other subcortical nuclei for a role in anesthetic-induced unconsciousness, general anesthetics are known to modulate cholinergic projections from the LDT/PPT. Sleep spindles occur during halothane anesthesia and are associated with decreased cholinergic transmission to the medial pontine reticular formation (PRF) (Keifer et al., 1994, 1996). There is also evidence that synaptic and extrasynaptic gamma-aminobutyric acid (GABA) receptors play a role in modulating LDT neurons (Kohlmeier and Kristiansen, 2010), which could provide a direct link to the molecular mechanisms of GABAergic anesthetics.

PRF—The PRF is part of the reticular activating system, which has been known since the 1940s to serve an important role in cortical arousal (Moruzzi and Magoun, 1949). Although GABA is typically associated with neuronal depression across the sleep-wake cycle (Figure 9.1—bottom row in blue), levels of GABA in the PRF are positively associated with cortical *arousal* (Vanini et al., 2011). There is increased time spent in the waking state when the $GABA_A$ receptor agonist muscimol is microinjected in the PRF (Flint et al., 2010); when the $GABA_A$ antagonist bicuculline is microinjected, wakefulness is suppressed. Vanini and colleagues (2008) found that *decreased* levels of GABA in the PRF correlated with isoflurane-induced unconsciousness. Of note, GABA in the PRF appears to be involved in the neurobiology of anesthetic induction but not emergence (Vanini et al., 2014), an asymmetry that will be discussed further when considering hypothalamic nuclei. The PRF also contains what is referred to as the "mesopontine tegmental anesthesia area." When pentobarbital is microinjected in this area, a reversible state similar to general anesthesia is induced (Abulafia et al., 2009).

Ventral tegmental area (VTA)—Dopaminergic neurons of the VTA in the midbrain do not exhibit dramatic state-dependent changes and thus have not been considered central to sleep-wake control. This view has been challenged in sleep neurobiology (Dahan et al., 2007; Ueno et al., 2012), but there has also been a recent interest in the reversal of anesthetic-induced unconsciousness through dopaminergic VTA neurons. Dopamine agonists can reverse the effects of both isoflurane and propofol (Solt et al., 2011; Chemali et al., 2012), which may be mediated selectively through the VTA. This hypothesis is supported by recent data demonstrating that electrical stimulation of the VTA, but not the substantia nigra, can reverse anesthetic-induced unconsciousness (Solt et al., 2014).

Hypothalamus

VLPO—VLPO is a structure in the anterior hypothalamus that transmits GABA and galanin (Gaus et al., 2002), with neuronal populations that are maximally active during NREM and REM sleep (Sherin et al., 1996; Szymusiak et al., 1998). Activity of the VLPO during sleep is correlated with inhibition of arousal centers in the brainstem and hypothalamus (Sherin et al., 1996; Saper et al., 2005). As one of the few "sleep-ON" neuronal populations, VLPO has received considerable interest as a target of general anesthetics. Systemic administration of GABAergic anesthetics such as propofol is associated with increased expression of c-fos (Nelson et al., 2002). The role of VLPO activity during sleep and its activation during general anesthesia would predict that lesions of this area would lead to anesthetic resistance. However, Eikermann et al. (2011) conducted studies of rats with chronic lesions of VLPO, finding that ablation of VLPO resulted in sleep deprivation (as expected) but also *hypersensitivity* to the effects of isoflurane. This is consistent with the findings of Moore and colleagues (2012), who demonstrated that acute lesions of VLPO conferred resistance to the effects of isoflurane, an effect that appeared to be mediated specifically through the sleep-active neurons in VLPO, but who also found that chronic lesions cause hypersensitivity. Thus, VLPO is neither necessary nor sufficient for anesthetic-induced unconsciousness, although it may play a contributory role.

Orexinergic neurons—This neuronal subpopulation is located in the lateral hypothalamus and transmits orexin A and B (also referred to as hypocretins). These neurons provide an important arousal stimulus for the cortex and also innervate arousal centers in the brainstem and basal forebrain. Orexinergic neurons fire maximally in the waking state, are suppressed during NREM sleep, and show occasional bursts during phasic REM sleep (Mileykovskiy et al., 2005; Lee et al., 2005). Both human and animal narcolepsy has been associated with an impaired orexinergic system (Nishino et al., 2000; Lin et al., 1999). Reports of narcoleptic patients with prolonged emergence from general anesthesia (Mesa et al., 2000) have motivated the study of orexin in the anesthetic mechanism. Orexins attenuate the effects of isoflurane (Yasuda et al., 2003), propofol (Zecharia et al., 2009), ketamine (Tose et al., 2009), and barbiturates (Kushikata et al., 2003). Infusion of orexin in the basal forebrain is associated with cortical arousal and faster recovery from the effects of sevoflurane (Dong et al., 2009) and isoflurane (Dong et al., 2006). Microinjection of propofol in the perifornical region of the hypothalamus (the locus of orexinergic neurons) is associated with a reduction of cortical acetylcholine (Gamou et al., 2010); as noted before, states of lower cholinergic tone are associated with unconsciousness. Kelz et al. (2008) found that genetic or pharmacologic blockade of orexinergic signaling affects only the recovery phase of general

anesthesia (as opposed to the induction phase). These data demonstrate that the asymmetry of induction and emergence states likely relates to a distinct neurobiology rather than, as previously hypothesized, the pharmacokinetic onset or offset of anesthetic drugs. In support of these data, propofol reduces c-fos expression in orexinergic neurons and infusion of orexin in the basal forebrain affects recovery but not induction (Zhang et al., 2012). However, a recent study in human surgical patients suggests that plasma levels of orexin A are not associated with delayed emergence in the elderly (Wang et al., 2014).

TMN—The TMN is located in the caudal hypothalamus and transmits histamine; both TMN activity and histamine levels are highest during wakefulness and lowest during sleep (Chu et al., 2004). Of relevance to mechanisms of sleep- and anesthetic-induced unconsciousness, the TMN has a relationship of reciprocal inhibition with the sleep-promoting GABAergic neurons of the VLPO (Sherin et al., 1996; Saper et al., 2005; Liu et al., 2010). Histamine release is depressed during sleep (Strecker et al., 2002) and halothane anesthesia (Mammoto et al., 1997). Systemic administration of propofol, pentothal and the GABA agonist muscimol all result in decreased c-fos expression in the TMN, suggesting depressed activity (Nelson et al., 2002). The arousal-promoting effects of histamine are mediated, in part, through the basal forebrain; application of histamine to this area results in reduced electroencephalographic depression during isoflurane anesthesia (Luo and Leung, 2009). However, the role of the TMN in anesthetic mechanisms is still unclear, since the genetic removal of $GABA_A$ receptors from histaminergic neurons demonstrates no effect on propofol-induced unconsciousness (Zecharia et al., 2012).

ROLE OF THE THALAMUS AND THALAMOCORTICAL SYSTEM IN ANESTHETIC-INDUCED UNCONSCIOUSNESS

The thalamus is comprised of approximately 50 nuclei and subnuclei; some nuclei receive sensory input primarily from the periphery (the so-called specific or lower-order nuclei) and others receive input primarily from the cortex and serve a more multimodal, integrative function (the so-called nonspecific or higher-order nuclei). Given the importance of the thalamus in sensory perception and sleep-wake neurobiology, the structure has been a focus of considerable attention regarding its role in anesthetic-induced unconsciousness. Alkire et al. (2000) proposed that the thalamus serves as an ON/OFF "switch" for anesthetic state transitions, based on the consistent metabolic depression of the thalamus by a number of inhaled and intravenous anesthetics (Alkire et al., 1997, 1999; Fiset et al., 1999) (The notable exception is ketamine, which increases glucose metabolism (Langsjo et al., 2005).) This switch would work by anesthetics hyperpolarizing the thalamus, shifting tonic firing to burst firing and thus preventing afferent sensory stimuli from arousing the cortex. Evidence for this proposal has been derived primarily from animal experiments, in which stimulation of the centromedial thalamus—by either nicotine or antibodies blocking voltage-gated potassium channels—could lead to reanimation despite continued delivery of general anesthetics (Alkire et al., 2007, 2009). Voltage-gated potassium channels (Shaker family) in the centromedial thalamus have been shown *in vitro* and *in vivo* to be an important target of volatile anesthetics (Lioudyno et al., 2013). In humans, central thalamic activation has been shown to result in behavioral improvement in patients with traumatic brain injury (Schiff et al., 2007). A positron emission tomography study in humans demonstrated that activation of the thalamus is correlated with recovery from anesthesia (Langsjo et al., 2012). Thus, a wide variety of anesthetics suppress the thalamus, there is a molecular target for general anesthetics in the centromedial thalamus that can account for this depression, and activation of the thalamus appears to be important for recovery.

Despite these compelling results, it is not yet clear if depression and reactivation of the thalamus is leading or following a mechanistic cascade. The higher-order nuclei of the thalamus have been proposed as a kind of "computational blackboard" for the cortex, primarily to receive cortical input and may be responsible for stabilizing or facilitating cortical communication (Ward, 2011; Saalmann et al., 2012; Saalmann, 2014). Thus, if the mechanism of anesthetic-induced unconsciousness was achieved primarily through a cortical mechanism, we would expect to see a depressed thalamus as a consequence rather than a cause. Velly et al. (2007) investigated the primacy of cortical versus subcortical roles in the mechanism of anesthetic-induced unconsciousness through a neurophysiologic study using scalp electroencephalography (EEG; reflecting cortical activity) and subthalamic nuclei electrodes (which were argued to reflect thalamic activity). Loss of consciousness due to multiple anesthetics was associated with cortical rather than subcortical changes, suggesting that the depression of the thalamus was an effect of the depressed cortex rather than the cause. However, activity in the thalamus was not directly recorded. By contrast, a recent study of neurosurgical patients with cortical electrodes and thalamic electrodes in the ventroposterolateral nucleus (a sensory area) demonstrated a

concomitant depression of activity after induction with propofol (Verdonck et al., 2014). Finally, a recent study of anesthetic-induced unconsciousness in rodents identified neurophysiological changes in the centromedial thalamus prior to changes in the cortex (Baker et al., 2014), but the mechanistic implications remain unclear.

In addition to the potential roles of "switch" and "cortical read-out" (which are not mutually exclusive), the thalamus may also actively participate in achieving anesthetic-induced unconsciousness through hypersynchrony in the alpha bandwidth. A computational study using modeling and human electroencephalographic data suggested that the action of propofol on GABA receptors in the nucleus reticularis generates a hypersynchronous alpha rhythm (8–13 Hz) with the frontal cortex (Ching et al., 2010), which may block the flexible cortical processing required for normal consciousness (Supp et al., 2011). The interaction of the thalamus and cortex and its role in anesthetic-induced unconsciousness motivates further discussion of thalamocortical connectivity. The closely integrated function of the thalamus and cortex allows us to consider a single *thalamocortical system* as a target for the effects of general anesthetics. This system undergoes state-dependent changes across the sleep-wake cycle and is thought to play a critical role in consciousness. Positron emission tomography studies demonstrating the metabolic depression of the thalamus by halothane and isoflurane were reanalyzed to show a disruption of thalamocortical connectivity during general anesthesia (White and Alkire, 2003). More recent studies using functional magnetic resonance imaging (fMRI) have clarified the role of impaired thalamocortical connectivity in anesthetic-induced unconsciousness. One study identified a propofol-induced disruption of connectivity between the thalamus and frontal-parietal networks, which are thought to be important for consciousness (Boveroux et al., 2010); impaired functional connectivity of the thalamus and posterior parietal cortex has also been found in humans exposed to 1% sevoflurane (Martuzzi et al., 2010). Of note, thalamocortical disconnections between higher-order nuclei and the cortex were more pronounced and better correlated with cognitive changes than connections between sensory nuclei and the cortex (Liu et al., 2013). However, impaired thalamocortical connectivity has not been consistently associated with anesthetic-induced unconsciousness. A fMRI study of propofol-induced unconsciousness demonstrated more significant functional disconnections between the cortex and putamen, rather than the thalamocortical system (Mhuircheartaigh et al., 2010); further work by this group showed that higher doses of propofol lead to an "internal dialog" of the thalamocortical system, which becomes disconnected from the sensory system (Mhuircheartaigh et al., 2013). Supporting the putamen-cortical disconnection, functional disruptions between the cortex and the basal ganglia during general anesthesia have also been identified in rats exposed to isoflurane (Liang et al., 2012) and humans exposed to propofol (Schroter et al., 2012).

DISRUPTING CORTICOCORTICAL CONNECTIVITY AND COMMUNICATION AS A MECHANISM OF ANESTHETIC-INDUCED UNCONSCIOUSNESS

Although the first neuroimaging studies of anesthetic-induced unconsciousness were conducted in the 1990s (Alkire et al., 1997), it is only in the past decade that studies of functional, directional, and effective connectivity across the cortex have been a focus of anesthetic mechanisms research. Various patterns of disrupted functional connectivity across the cortex during anesthetic-induced unconsciousness have been demonstrated using fMRI in humans (Peltier et al., 2005; Martuzzi et al., 2010; Boveroux et al., 2010; Stamatakis et al., 2010; Schrouff et al., 2011; Monti et al., 2013; Liu et al., 2012, 2014; Amico et al., 2014). The general theme of these studies is that primary sensory networks are relatively preserved despite propofol- or sevoflurane-induced loss of consciousness while higher-order cortical networks become functionally disconnected (Figure 9.2). Furthermore, recent studies suggest corticocortical rather than thalamocortical disconnections as critical for unconsciousness (Monti et al., 2013), supporting a top-down mechanism for general anesthesia (Mashour, 2014). Further investigation will be required to clarify the role of corticocortical versus thalamocortical connectivity.

Recently, the mechanism of anesthetic-induced unconsciousness has been studied with the technique of simultaneous fMRI/EEG. Jordan et al. (2013) identified a functional disconnection of anterior and posterior brain structures that correlated with a reduction of an information-theoretic EEG measure (symbolic transfer entropy) in the anterior-to-posterior direction (Figure 9.3). This recent finding prompts a review of EEG data suggesting reduction of functional, directional, and effective connectivity across the cortex. In 2001, John et al. reported quantitative EEG analysis of 176 surgical patients anesthetized with a variety of anesthetics; functional disconnections across anterior-posterior and interhemispheric axes were correlated with general anesthesia. However, subsequent work in rodents and humans suggested that anesthetic-mediated disruption

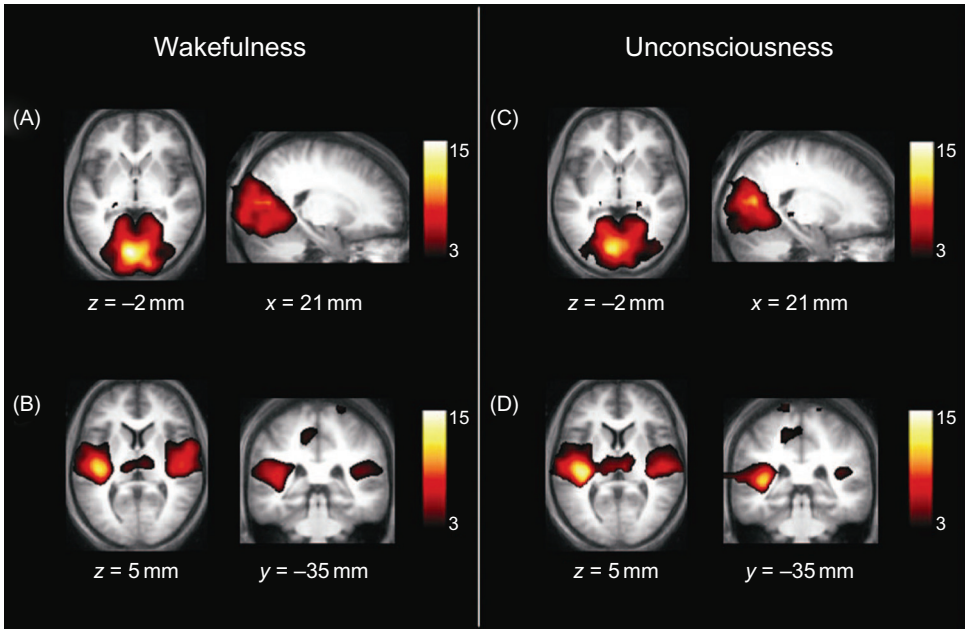

FIGURE 9.2 Primary sensory networks are preserved despite propofol-induced unconsciousness. Data from a functional magnetic resonance imaging study showing transverse and sagittal sections of primary visual (A) and (C) and auditory (B) and (D) cortices during wakefulness (A) and (B) and propofol-induced unconsciousness (C) and (D); note the relative preservation across states. *Source: Figure reproduced from Boveroux et al. (2010), with permission.*

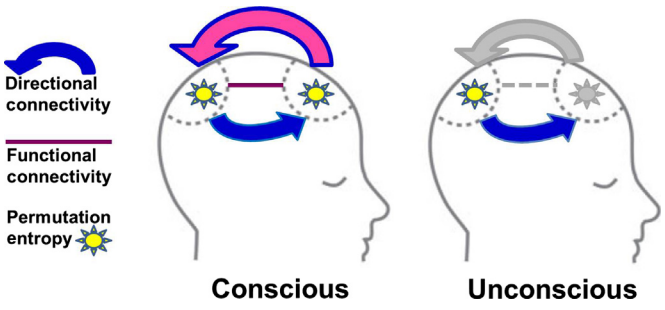

FIGURE 9.3 Summary of functional and directional connectivity changes after propofol-induced unconsciousness. The authors used concomitant electroencephalography and functional magnetic resonance imaging to study propofol-induced unconsciousness. They identified reductions of anterior-to-posterior directional connectivity (symbolized by arrows, with gray color indicating a reduction), anterior-posterior functional connectivity (symbolized by lines, with gray color/dash indicating a reduction), and frontal permutation entropy (symbolized by stars, with gray color indicating a reduction). *Source: Figure reproduced from Mashour (2013b), with permission.*

of connectivity between anterior and posterior brain regions may be more selective. Imas et al. (2005) measured transfer entropy in rats during visual flash stimuli and found that during isoflurane-induced unconsciousness, the anterior-to-posterior communication (known as re-entrant, recurrent or feedback connectivity) was disrupted, while posterior-to-anterior communication (feedforward connectivity) was maintained. EEG studies in healthy volunteers and surgical patients supported these preclinical findings by identifying a selective suppression of re-entrant/feedback connectivity in frontal-parietal networks (Lee et al., 2009; Ku et al., 2011). Importantly, this finding was observed with propofol, sevoflurane, and ketamine, three anesthetics with markedly different molecular mechanisms and neurophysiologic profiles (Lee et al., 2013b). A study of propofol using high-density EEG has confirmed the selective suppression of frontal-to-parietal connectivity and, using dynamic causal modeling, supported a corticocortical (rather than thalamocortical) origin of the phenomenon (Boly et al., 2012). The selective loss of re-entrant/feedback connectivity during general anesthesia is of particular interest given the proposed role of top-down processes in consciousness (Dehaene and Changeux, 2011).

The reduction of connectivity and surrogates for information transfer in frontal-parietal networks likely reflects a more global disruption of cortical communication. A study in humans using high-density EEG and transcranial magnetic stimulation revealed an inhibition of cortical effective connectivity after midazolam-induced unconsciousness (Ferrarelli et al., 2010), which is consistent with findings during NREM sleep (Massimini et al., 2005). Calculation of perturbational complexity after transcranial magnetic stimulation in humans has revealed a consistent reduction of cortical communication across physiologic, pharmacologic, and

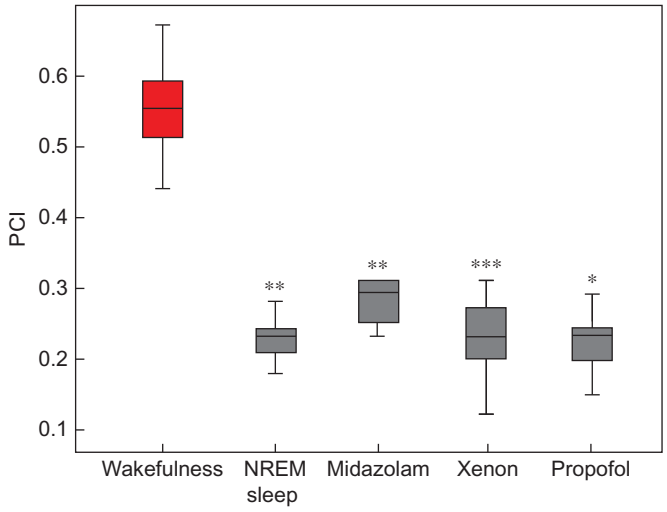

FIGURE 9.4 Reduction of perturbational complexity in the cortex during sleep- and anesthetic-induced unconsciousness. The authors measured the perturbational complexity index (PCI) based on electroencephalography and transcranial magnetic stimulation. Note the reduction in complexity of cortical response during non-rapid eye movement sleep (NREM) and a variety of anesthetics with diverse molecular targets. *Source: Figure reproduced from Casali et al. (2013), with permission.*

pathologic states of unconsciousness (Figure 9.4) (Casali et al., 2013). An electrocorticography study of three epilepsy patients with implanted cortical grids and a 96-channel microarray sheds light on this potential mechanism (Lewis et al., 2012). Within 5 s of propofol-induced unconsciousness there was a dramatic increase in the power of slow oscillations, which was coupled to consolidated periods of neuronal spike activity. Importantly, there was a reduction of phase coupling of the slow oscillations themselves with increasing distance across the cortex. Thus, neuronal spike activity was fragmented into an on/off pattern that was temporally uncoordinated across the cortex. This fragmentation of neural activity in time and space is likely associated with a dramatic reduction in the probability of meaningful corticocortical communication.

NETWORK-LEVEL ORGANIZATION DURING ANESTHETIC-INDUCED UNCONSCIOUSNESS

Intuition might suggest that the marked disruptions of connectivity caused by general anesthetics are associated with a generalized breakdown of functional networks in the brain. However, this is surprisingly not the case. Functional architecture associated with the performance of human sensory and motor tasks is still present in anesthetized non-human primates (Vincent et al., 2007). Using electrocorticography in humans receiving propofol, it has been shown that important functional organization is preserved during general anesthesia and serves as a backdrop of more dynamic neurophysiologic changes (Breshears et al., 2010). Global principles of topology such as scale-free organization—which implies the existence of highly-connected nodes that can facilitate network stability—are actually preserved during general anesthesia with both intravenous and inhaled anesthetics (Lee et al., 2010; Schroter et al., 2012). Key organizational network properties such as "small-worldness" (in which hubs allow shortcuts across the network) are maintained in humans and rodents despite anesthetic-induced unconsciousness (Schroter et al., 2012; Liang et al., 2012). The maintenance of small-world organization may be achieved by a reconfiguration of hub structure during general anesthesia, with measures of centrality shifting from critical hubs in the posterior parietal cortex to the frontal cortex (Lee et al., 2013a). Although there are many network similarities of pharmacologic and pathologic states of unconsciousness, it has recently been shown that general anesthesia is associated with a maintenance of scale-free functional connectivity, while unresponsive wakefulness syndrome (also known as the vegetative state) is not (Liu et al., 2014). The neural mechanisms underlying this observation have not been clarified but potentially relate to the functional disconnections in pharmacological states of unconsciousness (e.g., due to general anesthesia) versus the potential for structural disconnections in pathological states of unconsciousness (e.g., due to brain trauma). It is therefore possible that—despite ostensibly similar disruptions of corticocortical communication—the preservation of key network organizational principles (such as scale-free distributions or small-worldness) may account for the relative reversibility of general anesthesia compared with pathologic states of unconsciousness.

USING GENERAL ANESTHETICS TO TEST THEORIES OF CONSCIOUSNESS

A theory of consciousness should provide a mechanistic explanation that can answer two fundamental questions:

1. What makes a state conscious versus unconscious?
2. What gives a conscious state its particular phenomenal character versus some alternative phenomenal character?

Beyond these mechanistic considerations, it is desirable for a theory of consciousness to have an associated quantitative measure for levels of consciousness and a method by which to characterize subjective qualities in

an objective way. Following is a brief review of four current and major neuroscientific theories of conscious experience: global neuronal workspace (GNW) theory, re-entrant processing theory, predictive coding, and integrated information theory (IIT).

GNW Theory

The premise underlying the GNW theory is that information processed in various isolated and unconscious cognitive modules within the brain becomes "broadcast" into a mental workspace that then allows widespread access to many other cognitive systems. At any given moment, this broadcasting highlights a single neural representation, while other potentially competing representations are suppressed. GNW allows for both local efficiency in the processing of unconscious or automatic content as well as the transient broadcast of that information for further integration, verbal report, motor response, and other higher-order cognitive processes. The theory originated as a psychological "global workspace" (Baars, 1993) but has more recently been defined in neuroscientific terms (Dehaene and Changeux, 2011). The GNW is thought to be maintained by long-range excitatory neurons populating the prefrontal, cingulate, and parietal cortices as well as thalamocortical loops (Dehaene and Changeux, 2011). GNW is supported by the empirical findings that conscious perception is correlated better with widespread activation of more extended frontal-parietal networks as opposed to primary sensory cortices (Del Cul et al., 2007); conversely, states of unconsciousness (such as general anesthesia) are better correlated with deactivation of frontal-parietal networks whereas primary sensory networks can remain active (Boveroux et al., 2010). GNW theory is derived from an information processing perspective of the brain, in which information is received from the environment, automatically processed in isolated modules, then reaches a threshold for neurocognitive "ignition" that allows broadcasting to arise throughout the neuronal workspace. However, it might be argued that GNW theory is a theory of *access consciousness* given its emphasis on making phenomenal experiences available to higher cortical processes.

Re-entrant Processing Theory

Re-entrant processing is another neuroscientific theory of consciousness with considerable empirical support (Edelman and Gally, 2013). Re-entrant processing—also referred to as recurrent, reverberant, reafferent, or feedback processing—appears to serve a role of integration and can happen both within sensory systems as well as across the global brain hierarchy itself. In order to provide context for the theory, it will be helpful to consider the basic pathway of visual processing. After stimulation of the retina and a relay in the lateral geniculate nucleus of the thalamus, visual stimuli are processed in the primary visual cortex (V1, in the occipital lobe). Importantly, activity in V1 is not correlated with conscious experience and information gets processed in higher-order visual areas in two "streams." The dorsal stream proceeds in the caudorostral "feedforward" direction to the prefrontal cortex (and processes the "where" aspect of the visual stimulus) whereas the ventral stream proceeds in the feedforward direction to the temporal lobe (and processes the "what" aspect of the visual stimulus). However, even this advanced processing does not seem to correlate well with conscious experience (Lamme and Roelfsema, 2000). For conscious experience to occur, there appears to be a requirement for *re-entrant* signaling from higher-order areas back to more primary areas. The neurochemistry of feedforward and re-entrant processes in the visual system has been mapped in terms of glutamatergic signaling, with AMPA receptors mediating feedforward pathways and NMDA receptors mediating re-entrant pathways (Self et al., 2012). As noted, it is also known that feedforward pathways can persist during general anesthesia, whereas re-entrant pathways appear to be selectively suppressed (Imas et al., 2005; Lee et al., 2013b).

Predictive Coding Theory

In the first two theories of consciousness presented, information was received by the brain from the environment and then processed hierarchically to generate conscious experience. Predictive coding reverses the process: rather than information coming *into* the brain in order to generate consciousness, the brain reaches *out* with a prior model of perceptual reality (Clark, 2013). Sensory information received by the brain is not used to generate consciousness, per se, but rather to detect errors or gaps between the model generated by the brain and what is being sensed in the environment. Thus, in this scenario, the "feedforward" component of perception is not moving in a bottom-up direction (e.g., from primary visual to prefrontal cortex) but rather is top-down within a hierarchical cognitive architecture. When errors are detected through a feedback process based on signal input to lower centers such as the primary sensory cortex, the model can be revised and updated accordingly. In fact, it is precisely this prediction error that needs to be coded for in order to adjust the model, allowing for minimization of energy or the work of the brain. Predictive coding is

a Bayesian perspective of brain function, in which "priors" (i.e., pre-existing models) are updated and revised according to new information from the environment (Moutoussis et al., 2014). For this theory, events that remain stable and consistent within the model will not require much conscious attention, while errors in prediction (e.g., novelty, surprise, awareness of potential threat, pain, etc.) account for much of the conscious content.

Integrated Information Theory

IIT argues that two essential features of conscious experience are *differentiation* (e.g., a multimodal perception that includes color, sound, smell, etc.) and *integration* (i.e., the experience of all differentiated elements at once) (Oizumi et al., 2014). Accordingly, for a given system such as a brain to be conscious, it must have functional differentiation with the capacity to integrate the output of specialized modules in order to generate information above and beyond the simple sum of its parts. In neural terms, the thalamocortical system is thought to be a prime candidate for the substrate of consciousness by meeting the dual requirements of cortical specialization and large-scale synthesis of neural processing. By contrast, consider the cerebellum, which—despite its complexity—does not cross the critical threshold of functional segregation/integration and therefore is less relevant to consciousness. It is critical to note that, for other theories discussed, integration of information is merely considered important or necessary for consciousness; for IIT, integrated information *is* consciousness. IIT therefore moves beyond necessity and sufficiency to an identity relationship between integrated information and consciousness. Furthermore, IIT is neither a classical information processing nor a representational theory of consciousness. Information is generated *by the system, for the system*—in the case of the brain, it is important to note that information does not get transmitted or "imported" from the world. Thus, with IIT, consciousness is essentially a closed system, in which information is generated to form experiences that "match" the world (possibly through evolutionary selection). In other words, for IIT, consciousness is essentially an oneiric state that happens to help us navigate the environment.

General anesthetics disrupt consciousness by impairing neural processes sustaining wakefulness, awareness or both. Although their utility in the clinical world is indisputable, can general anesthetics help us better understand consciousness? Although it would be difficult to argue that the use of anesthetics could alone solve the "hard problem" of consciousness, these unique drugs have played an important role in both supporting and refuting existing theories of consciousness. In general terms, any proposed neural correlate or cause of consciousness should either be eliminated or modulated during the state of anesthetic-induced unconsciousness; proposed structural or functional substrates of consciousness that persist during general anesthesia are likely not strong contenders to explain conscious processing. For example, 40 Hz synchrony has been shown to be maintained or even increased during general anesthesia (Murphy et al., 2011). Thus, while precise temporal coordination in the low gamma bandwidth may potentially be important for consciousness, gamma synchrony, per se, cannot be a neural correlate of consciousness since it is found in the anesthetized state. Similarly, the fact that general anesthetics do not seem to grossly impair primary sensory networks (Boveroux et al., 2010) supports the proposition that primary sensory processing is not sufficient for consciousness. Conversely, disruption of frontal-parietal networks and top-down connectivity during anesthetic-induced unconsciousness is consistent with a number of theories that might be classified as "higher-order." However, impaired top-down connectivity from the frontal cortex does not, in itself, help us clearly distinguish between the theories of GNW, re-entrant processing, predictive coding and IIT—this higher-order network fragmentation during general anesthesia is potentially consistent with all theories. Future studies using general anesthetics must be carefully designed in order to help clarify and differentiate the evidence supporting different theories of consciousness.

CONCLUSION

General anesthetics revolutionized the field of medicine in the mid-nineteenth century and anesthesiology continues to play a critical role in safe and comfortable patient care. The mechanism of anesthetic-induced unconsciousness remains to be fully elucidated, but a multiscale explanatory framework from molecular events to impaired cortical dynamics is emerging. The field of anesthesiology has much to gain from recent and future advances in the science of consciousness. Likewise, the use of general anesthetics to probe the mechanisms of consciousness has been a successful endeavor and promises to make future contributions to our understanding.

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CHAPTER

10

The Assessment of Conscious Awareness in the Vegetative State

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OUTLINE

INTRODUCTION

In recent years, improvements in intensive care have increased the number of patients who survive severe acute brain injuries. Although the majority of these patients recover from coma within the first days of the insult, others evolve to a state of "wakeful unawareness" or vegetative state. Clinically, recognizing unambiguous signs of conscious perception of the environment and of the self in such patients can be extremely challenging. This difficulty is reflected in frequent misdiagnoses of the condition and confusion between the vegetative state and related conditions such as minimally conscious state and locked-in syndrome (Andrews et al., 1996; Childs et al., 1993). Like all severely brain-injured patients, bedside evaluation of residual brain function in vegetative state is difficult because motor responses may be very limited or inconsistent. In addition, the clinical assessment of cognitive function relies on inferences drawn from present or absent responses to external stimuli at the time of the examination (Wade and Johnston, 1999). Recent advances in functional neuroimaging suggest a novel solution to this problem; in several cases, the so-called "activation" studies have been used to identify residual cognitive function and even *conscious awareness* in patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical methods. Indeed, in some patients, communication with the outside world via simple "yes" and "no" questions has been achieved, even in cases where no possibility for behavioral interaction exists. In this chapter, we first describe the major clinical characteristics of vegetative state following severe brain injury. We then discuss the contribution of neuroimaging studies to the assessment of conscious awareness in the vegetative state, including the recent use of reproducible and task-dependent fMRI responses as a form of "communication" in patients who are assumed to be vegetative. Finally, we review the major methodological impediments to conducting studies in disorders of consciousness.

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CLINICAL DESCRIPTION

Patients in the vegetative state are awake, but are assumed to be entirely unaware of self and environment (Jennett, 2002; Jennett and Plum, 1972). Jennett and Plum cited the Oxford English Dictionary to clarify their choice of the term "vegetative": to be vegetative is to "live a merely physical life devoid of intellectual activity or social intercourse" and vegetative describes "an organic body capable of growth and development but devoid of sensation and thought." "*Persistent* vegetative state" is arbitrarily coined as a vegetative state present 1 month after acute traumatic or non-traumatic brain injury but does not imply irreversibility ("Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS," 1994). "*Permanent* vegetative state" denotes irreversibility. The Multi-Society Task Force on vegetative state concluded that 3 months following a non-traumatic brain injury and 12 months after traumatic injury, the condition of vegetative patients may be regarded as "permanent." These guidelines are best applied to patients who have suffered diffuse traumatic brain injuries and post anoxic events; other non-traumatic etiologies may be less well predicted (see e.g., Menon et al., 1998; Wilson et al., 2001) and require further considerations of etiology and mechanism in evaluating prognosis. Even after long and arbitrary delays, some exceptional patients may show limited recovery. This is more likely in patients with non-traumatic coma without cardiac arrest who survive in the vegetative state for more than 3 months. The diagnosis of vegetative state should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures ("Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS," 1994). It is essential to establish the formal absence of any sign of conscious perception or deliberate action before making the diagnosis.

RESTING BRAIN FUNCTION

In the vegetative state, the brainstem is relatively spared whereas the gray or white matter of both cerebral hemispheres is widely and severely injured. Overall cortical metabolism of vegetative patients is 40–50% of normal values (Beuthien-Baumann et al., 2003; Boly et al., 2004; DeVolder et al., 1990; Edgren et al., 2003; Laureys et al., 1999a,b; Levy et al., 1987; Momose et al., 1989; Rudolf et al., 1999, 2002; Schiff et al., 2002; Tommasino et al., 1995). Some studies, however, have found normal cerebral metabolism (Schiff et al., 2002) or blood flow (Agardh et al., 1983) in patients in a persistent vegetative state. In *permanent* vegetative state (i.e., 12 months after a trauma or 3 months following a non-traumatic brain injury), brain metabolism values drop to 30–40% of normal values (Figure 10.1) (Tommasino et al., 1995). This progressive loss of metabolic functioning over time is the result of progressive Wallerian and transsynaptic neuronal degeneration. Characteristic of vegetative patients is a relative sparing of metabolism in the brainstem (encompassing the pedunculopontine reticular formation, the hypothalamus, and the basal forebrain) (Laureys et al., 2000b). The functional preservation of these structures allows for the preserved arousal and autonomic functions in these patients.

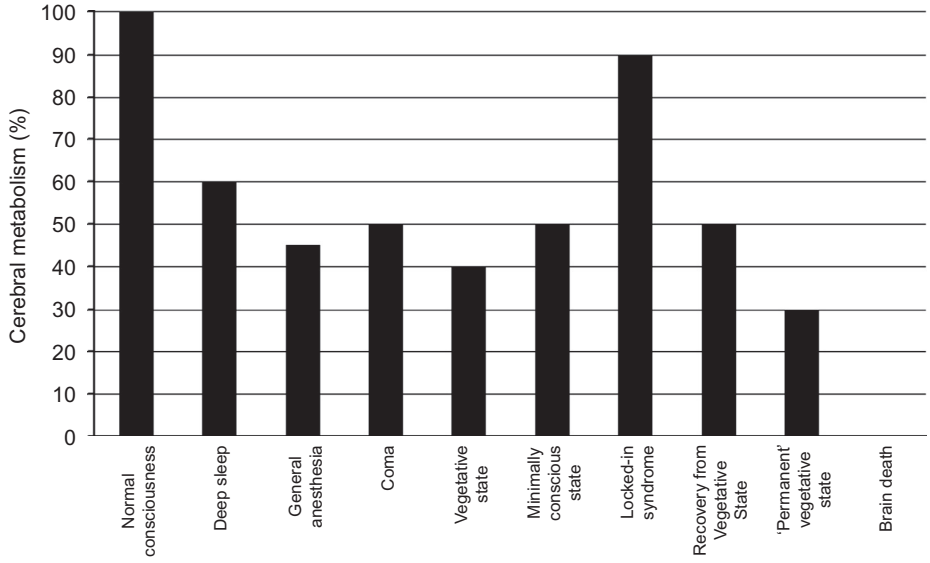

FIGURE 10.1 Cerebral metabolism in the different diagnostic groups.

BOX 10.1

VEGETATIVE PATIENTS WITH ATYPICAL BEHAVIORAL FRAGMENTS

Stereotyped responses to external stimuli, such as grimacing, crying, or occasional vocalization are frequently observed on examination of vegetative state patients. These behaviors are assumed to arise primarily from brainstem circuits and limbic cortical regions that are preserved in the vegetative state. Rarely, however, patients meeting the diagnostic criteria for the vegetative state exhibit behavioral features that *prima facie* appear to contravene the diagnosis. A series of studies of chronic vegetative patients examined with multimodal imaging techniques identified three such patients with unusual behavioral fragments. Using FDG-PET, structural MRI and magnetoencephalography (MEG) preserved islands of higher resting brain metabolism measured by PET imaging and incompletely preserved evoked MEG gamma-band responses were correlated with structural imaging and behavioral fragments (Schiff et al., 2002). Among those studied was a patient who had been in a vegetative state for 20 years who infrequently expressed single words (typically epithets) in isolation of environmental stimulation (Schiff et al., 1999). MRI images demonstrated severe subcortical injuries. Resting FDG-PET measurements of the patient's brain revealed a global cerebral metabolic rate of <50% of normal across most brain regions with small regions in the left hemisphere expressing higher levels of metabolism (Figure 10.2). MEG responses to bilateral auditory stimulation were confined to the left hemisphere and localized to primary auditory areas. Taken together, the imaging and neurophysiological data appeared to identify isolated sparing of left sided thalamo-cortical-basal ganglia loops that normally support language function in Heschl's gyrus, Broca's area, and Wernicke's area. Similar observations in two other vegetative state patients provide novel evidence that isolated cerebral networks may remain active in rare vegetative state patients. Importantly, the preservation of these isolated behaviors does not herald further recovery in patients in chronic vegetative states who have been repeatedly examined and carefully studied with imaging tools. Reliable observations of such unusual features should prompt further investigation in an individual patient.

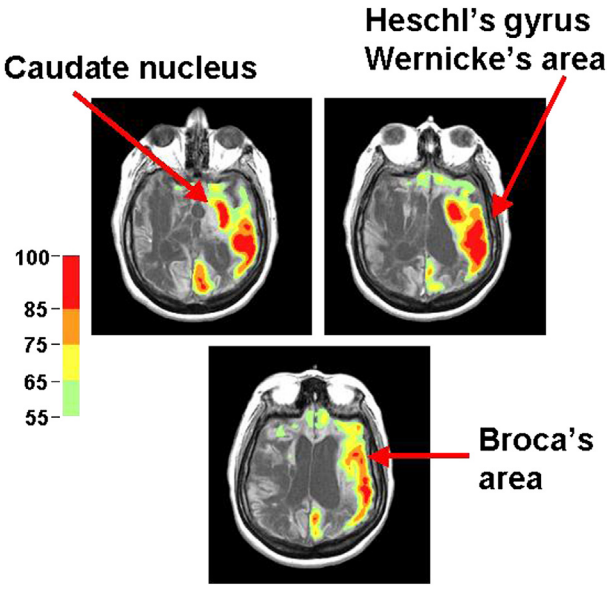

FIGURE 10.2 Preservation of regional cerebral metabolic activity in a vegetative state patient. FDG-PET data for vegetative state patient with occasional expression of isolated words is displayed co-registered with structural MRI (*Source*: Data from Schiff et al., 2002). PET voxels are normalized by region and expressed on a color scale ranging from 55% to 100% of normal.

Another hallmark of the vegetative state is a systematic impairment of metabolism in the polymodal associative cortices (bilateral prefrontal regions, Broca's area, parieto-temporal and posterior parietal areas and precuneus) (Laureys et al., 1999a). These regions are known to be important in various functions that are necessary for consciousness, such as attention, memory, and language (Baars et al., 2003). It is still unknown whether the observed metabolic impairment in this large cortical network reflects an irreversible structural neuronal loss (Rudolf et al., 2000) or functional and potentially reversible damage. However, in those rare and fortunate cases where vegetative patients recover awareness of self and environment, positron emission tomography (PET) shows a functional recovery of metabolism in these same cortical regions (Laureys et al., 1999b). Moreover, the resumption of long-range functional connectivity between these associative cortices and the intralaminar thalamic nuclei parallels the restoration of their functional integrity (Laureys et al., 2000c). The cellular mechanisms which underlie this functional normalization remain unclear: axonal sprouting, neurite outgrowth, cell division (known to occur predominantly in associative cortices in normal primates) (Gould et al., 1999) have been proposed as candidate processes (Laureys et al., 2000d) (Box 10.1).

PASSIVE NEUROIMAGING STUDIES

While metabolic studies are useful, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are *potentially* recruitable, rather than relating neural activity within such regions to specific cognitive processes (Momose et al., 1989). On the other hand, methods such as $H_2{}^{15}O$ PET and functional magnetic resonance imaging (fMRI) can be used to link residual neural activity to the presence of covert cognitive *function*. In short, passive functional neuroimaging studies have the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow (rCBF) or changes in regional cerebral hemodynamics) to controlled external stimulation in the absence of any overt response (e.g., a motor action) on the part of the patient. In the first of such studies, $H_2{}^{15}O$ PET was used to measure rCBF in a post-traumatic vegetative patient during an auditorily presented story told by his mother (de Jong et al., 1997). Compared to non-word sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. In another patient diagnosed as vegetative, Menon et al. (1998) also used PET, but to study covert *visual* processing in response to familiar faces. During "experimental" scans, the patient was presented with pictures of the faces of family and close friends, while during "control" scans scrambled versions of the same images were presented which contained no meaningful visual information whatsoever. Previous imaging studies in healthy volunteers have shown that such tasks produce robust activity in the right fusiform gyrus, the so-called human "face area" (e.g., Haxby et al., 1991, 1994). The same visual association region was activated in the vegetative patient when the familiar face stimuli were compared to the meaningless visual images (Menon et al., 1998).

In cohort studies of patients unequivocally meeting the clinical diagnosis of the vegetative state, simple noxious somatosensory (Laureys et al., 2002) and auditory (Boly et al., 2004; Laureys et al., 2000a) stimuli have shown systematic activation of primary sensory cortices and lack of activation in higher-order associative cortices from which they were functionally disconnected. High intensity noxious electrical stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in each and every one of the 15 vegetative patients studied, even in the absence of detectable cortical evoked potentials (Laureys et al., 2002). However, secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices, which were activated in all control subjects, failed to show significant activation in a single vegetative patient.

Moreover, in the vegetative state patients, the activated primary somatosensory cortex was shown to exist as an island, functionally disconnected from higher-order associative cortices of the pain-matrix. Similarly, although simple auditory click stimuli activated bilateral primary auditory cortices in vegetative patients, hierarchically higher-order multimodal association cortices were not activated. Moreover, a cascade of functional disconnections were observed along the auditory cortical pathways, from primary auditory areas to multimodal and limbic areas (Laureys et al., 2000a), suggesting that the observed residual cortical processing in the vegetative state does not lead to integrative processes which are thought to be necessary for awareness (Box 10.2).

A question that is often asked of such studies, however, is whether the presence of "normal" brain activation in patients who are diagnosed as vegetative indicates a level of conscious awareness. Many types of stimuli, including faces, speech and pain will elicit relatively "automatic" responses from the brain; that is to say, they will occur without the need for willful intervention on the part of the participant (e.g., you cannot choose to *not* recognize a face, or to *not* understand speech that is presented clearly in your native language). By the same argument, "normal" neural responses in patients who are diagnosed as vegetative do not necessarily indicate that these patients have any conscious experience associated with processing those same types of stimuli. Thus, such patients *may* retain discreet islands of subconscious cognitive function, which exist in the absence of awareness.

The logic described above exposes a central conundrum in the study of conscious awareness and in particular, how it relates to the vegetative state. Deeper philosophical considerations notwithstanding, the only reliable method that we have for determining if another being is consciously aware is to ask him/her. The answer may take the form of a spoken response or a non-verbal signal (which may be as simple as the blink of an eye, as documented cases of the locked-in syndrome have demonstrated), but it is this answer that allows us to infer conscious awareness. In short, our ability to know unequivocally that another being is consciously aware is ultimately determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response. But what if the ability to blink an eye or move a hand is lost, yet conscious awareness remains? By definition, patients who are diagnosed as vegetative are not able to elicit such behavioral responses. Following the logic of this argument then, even if such a patient *were* consciously aware, he/she would, by definition, have no means for conveying that information to the outside world.

BOX 10.2

METHODOLOGICAL ISSUES

The acquisition, analysis, and interpretation of neuroimaging data in severe brain injury is methodologically extremely complex. In quantitative PET studies, the absolute value of cerebral metabolic rates depends on many assumptions for which a consensus has not been established in cases of cerebral pathology. For example, the estimation of the cerebral metabolic rate of glucose using ^{18}F-FDG-PET requires a correction factor, known as the lumped constant. It is generally accepted that this lumped constant is stable in normal brains. However, in traumatic brain injury, a significant global *decrease* in lumped constant has recently been reported (Wu et al., 2004) and in severe ischemia, regional lumped constant values are known to *increase* significantly as a result of glucose transport limitation (Hamlin et al., 2001). Second, cerebral glucose use as measured by ^{18}F-FDG may not always be tightly coupled with oxygen use in patients because altered metabolic states, including anaerobic glycolysis, may occur acutely after brain injury (Bergsneider et al., 2001; Goodman et al., 1999; Hovda et al., 1992). Third, because PET provides measurements per unit volume of intracranial contents, they may be affected by the inclusion of metabolically inactive spaces such as cerebrospinal fluid or by brain atrophy which may artificially lower the calculated cerebral metabolism (Herscovitch et al., 1986; Videen et al., 1988).

As described in the main text, the so-called "activation studies" using $H_2{}^{15}O$ PET or fMRI together with established sensory paradigms provide a direct method for assessing cognitive processing and even conscious awareness in severely brain-injured patients. However, like metabolic studies, these investigations are methodologically complex and the results are rarely equivocal. For example, in brain-injured patients, the coupling between neuronal activity and local hemodynamics, essential for all $H_2{}^{15}O$ PET and fMRI activation measurements, is likely to be different from healthy controls (Gsell et al., 2000; Hamzei et al., 2003; Rossini et al., 2004; Sakatani et al., 2003), making interpretation of such data sets extremely difficult. Notwithstanding this basic methodological concern, the choice of experimental paradigm is also critical. For example, abnormal brainstem auditory evoked responses may make the use of auditory stimuli inappropriate and alternative stimuli (i.e., visual) should be considered. The paradigm should also be sufficiently complex to exercise the cognitive processes of interest, preferably beyond those that are simply involved in stimulus perception, yet not so complex that they might easily overload residual cognitive capacities in a tired or inattentive patient. In addition, it is essential that the experimental paradigm chosen produces well-documented, anatomically specific, robust, and reproducible activation patterns in healthy volunteers in order to facilitate interpretation of imaging data in patients. In vegetative state, episodes of low arousal and sleep are also frequently observed and close patient monitoring (preferably by means of simultaneous electroencephalographic recording) during activation scans is essential to avoid such periods. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly scans acquired using fMRI. Data processing of functional neuroimaging data may also present challenging problems in patients with acute brain injury. For example, the presence of gross hydrocephalus or focal pathology may complicate co-registration of functional data (e.g., acquired with PET or fMRI) to anatomical data (e.g., acquired using structural MRI), and the normalization of images to a healthy reference brain. Under these circumstances statistical assessment of activation patterns is complex and interpretation of activation foci in terms of standard stereotaxic coordinates may be impossible. Finally, where PET methodology is employed, issues of radiation burden must also be considered and may preclude longitudinal or follow-up studies in many patients.

ACTIVE NEUROIMAGING STUDIES

A novel approach to this conundrum has been the development of the so-called "active" fMRI paradigms that render awareness reportable in patients who are either entirely behaviorally non-responsive and therefore diagnosed as vegetative (Owen et al., 2006; Boly et al., 2007) or partially responsive and diagnosed as minimally conscious state (Bardin et al., 2011, 2012). In contrast to passive functional neuroimaging studies, active studies require participants to respond to task-specific demands by willfully modulating their own neural activity. In other words, the neural responses required are not produced automatically by the eliciting stimulus, but rather depend on time-dependent and sustained responses generated by the participants themselves. Such behavior (albeit neural "behavior") provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness (Zeman, 2009).

BOX 10.3

OTHER FMRI APPROACHES TO DETECTING CONSCIOUSNESS IN NON-RESPONSIVE PATIENTS

In addition to the use of mental imagery, another approach to detecting covert awareness after brain injury is to target processes that require the willful adoption of "mind-sets" in carefully matched (perceptually identical) experimental and control conditions. For example, Monti et al. (2009) presented healthy volunteers with a series of neutral words, and alternatively instructed them to just listen, or to count, the number of times a given word was repeated. As predicted, the counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a severely brain-injured patient produced a very similar pattern of activity, confirming that he could willfully adopt differential mind-sets as a function of the task conditions and could actively maintain these mind-sets across time; covert abilities that were entirely absent from his documented behavioral repertoire. As in the tennis/spatial navigation examples described in the main text, because the external stimuli (a series of words) were identical in the two conditions any difference in brain activity observed cannot reflect an "automatic" brain response (i.e., one that can occur in the absence of consciousness). Rather, the activity must reflect the fact that the patient has performed a particular action (albeit a "brain action") in response to the stimuli on one (but not the other) presentation; in this sense, the brain response is entirely analogous to a (motor) response to command and should carry the same weight as evidence of awareness.

Following similar logic, Monti et al. (2013) used an entirely different type of approach to demonstrate that a patient who was entirely unable to exhibit any signs of command following during standard behavioral testing, could nevertheless demonstrate reliable and robust responses in predefined brain regions by willfully modulating his brain activity. The stimuli used were superimposed pictures of faces and houses. When healthy volunteers are requested, following a cue tone, to shift their attentional focus from a face to a house (or vice versa), a distinct shift in fMRI activity from the fusiform gyrus (the FFA), to the parahippocampal gyrus (the "parahippocampal place area") is observed (or vice versa) (Monti et al., 2013). With continuous, repeated cues, this effect manifests as a time-locked alternation of activity between these two functionally distinct brain regions, despite the fact that the stimulus remains unchanged throughout. Thus, this change is driven, not by the external stimulus per se, but by the will, or the intention, of the participant to focus on one, or the other, aspect of the stimulus and is therefore a reliable indicator of conscious intent. When asked to perform the same task, the activity observed in the patient closely resembled the activity observed in the healthy volunteers and, as such, provided the only conclusive evidence that he could indeed follow commands (Monti et al., 2013).

The most successful techniques in active paradigms make use of the general principle observed in studies of healthy participants that imagining performing a particular task generates a robust and reliable pattern of brain activity in the fMRI scanner that is similar to actually performing the activity itself. For example, imagining moving or squeezing the hands will generate activity in the motor and premotor cortices (Jeannerod and Frak, 1999), while imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and the posterior parietal cortex that have been widely implicated in map-reading and other so-called spatial navigation tasks (Aguirre et al., 1996) (Box 10.3).

In one study (Boly et al., 2007), 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word "tennis" (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word "house" (thereby eliciting imaginary spatial navigation). Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one (100%) of the participants scanned. In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe and the lateral premotor cortices; all regions that have been shown to contribute to imaginary, or real, spatial navigation (Aguirre et al., 1996; Boly et al., 2007). A recent follow-up study has demonstrated that such responses can be reliably produced in single-participants (classified correctly in at least 80% of cases) using a hospital-grade 1.5T scanner, lending the technique to widespread clinical use (Fernandez-Espejo et al., 2014).

The robustness and reliability of these fMRI responses across individuals means that activity in these regions can be used as a neural proxy for

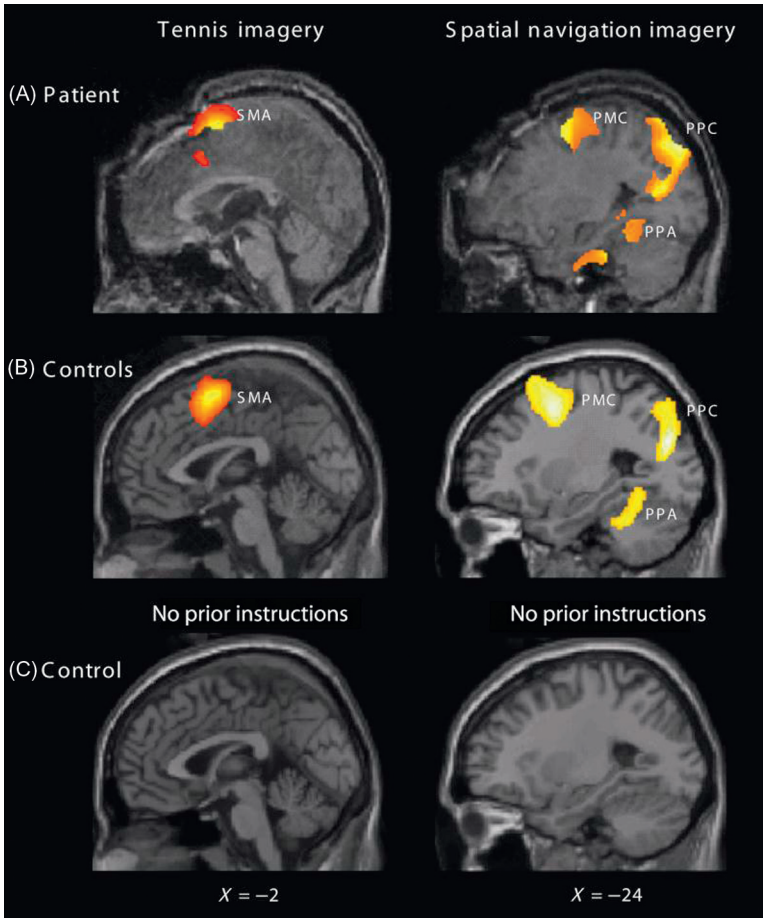

FIGURE 10.3 (A) Supplementary motor area (SMA) activity during tennis imagery and parahippocampal gyrus (PPA), posterior parietal lobe (PPC) and lateral premotor cortex (PMC) activity while imagining moving around a house in the patient described by Owen et al. (2006). (B) Statistically indistinguishable activity in all four brain regions in a group of 12 healthy volunteers asked to perform the same imagery tasks. (C) The result when a healthy volunteer underwent exactly the same fMRI procedure as the patient described by Owen et al. (2006), with the exception that non-instructive sentences (e.g., "The man played tennis," "The man walked around his house") were used. Using an identical statistical model to that used with the patient, *no* significant sustained activity was observed in the SMA, PPA, the PPC, the PMC, nor any other brain region. All results are similarly thresholded at FDR $p < 0.05$, corrected for multiple comparisons.

behavior, confirming that the participant retains the ability to understand instructions, to carry out different mental tasks in response to those instructions and, therefore, is able to exhibit willed, voluntary behavior in the absence of any overt action. Thus, like any other form of action that requires *response selection*, these brain responses require awareness of the various contingencies that govern the relationship between any given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining the task). Put simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur.

Owen et al. (2006, 2007) used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity (Figure 10.3). The patient, who was involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of 6 months prior to the fMRI scan. During the scanning session, the patient was instructed to perform the two mental imagery tasks described above. When she was asked to imagine playing tennis, statistically significant activity was observed repeatedly in the supplementary motor area (Owen et al., 2006) that was indistinguishable from that observed in the healthy volunteers (Boly et al., 2007). Moreover, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex and the lateral premotor cortex which was again, indistinguishable from those observed in healthy volunteers (Owen et al., 2006, 2007). On this basis, it was concluded that, despite fulfilling all of the clinical criteria for a

diagnosis of vegetative state, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming beyond any doubt that she was consciously aware of herself and her surroundings. In a follow-up study of 23 patients who were behaviorally diagnosed as vegetative, Monti et al. (2010) showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner.

After a severe brain injury, when the request to move a hand or a finger is followed by an appropriate motor response, the diagnosis can change from vegetative state (no evidence of awareness) to minimally conscious state (some evidence of awareness). By analogy then, if the request to activate the supplementary motor area of the brain by imagining moving the hand is followed by an appropriate brain response, shouldn't we give that response the very same weight? Skeptics may argue that brain responses are somehow less physical, reliable or immediate than motor responses but, as is the case with motor responses, all of these arguments can be dispelled with careful measurement, replication, and objective verification (Boly et al., 2007; Fernandez-Espejo and Owen, 2013; Hampshire et al., 2012; Monti et al., 2010; Naci et al., 2013; Naci and Owen, 2013; Owen et al., 2006, 2007). For example, if a patient who was assumed to be unaware raised his/her hand to command on just one occasion, there would remain some doubt about the presence of awareness given the possibility that this movement was a chance occurrence, coincident with the instruction. However, if that same patient were able to repeat this response to command on ten occasions, there would remain little doubt that the patient was aware. By the same token, if that patient was able to activate his/her supplementary motor area in response to command (e.g., by being told to imagine hand movements), and was able to do this on every one of ten trials, would we not have to accept that this patient was consciously aware? Like most neuroimaging investigations, replication of this sort was inherent in both of the studies described above (Monti et al., 2010; Owen et al., 2006), because correct classification of the characteristic neural signatures required statistically similar significant results across repeated trials.

It has been suggested that fMRI responses of this sort could reflect an "implicit preconscious neural response" to the key words that were used in those studies (Greenberg, 2007; Nachev and Husain, 2007). While no empirical evidence exists to support this possibility, it is nevertheless important to consider its theoretical plausibility. In the volunteers studied by (Boly et al., 2007), and in the patients reported by Owen et al. (2006) and Monti et al. (2010), the observed activity was not transient, but persisted for the full 30 s of each imagery task that is, far longer than would be expected, even given the hemodynamics of the fMRI response. In fact, these task-specific changes persisted until the volunteers and the patients were cued with another stimulus indicating that they should switch tasks. No evidence exists to show that single-word stimuli (such as "tennis," "house," or "rest") can unconsciously elicit sustained (i.e., 30 s) hemodynamic responses in the supplementary motor area, the parahippocampal gyrus, the posterior parietal cortex or the lateral premotor cortex premotor cortex, yet considerable data exists to suggest that they cannot. For example, although it is well documented that some words can, under certain circumstances, elicit wholly automatic neural responses, such responses are typically transient and last for just a few seconds. In addition, the activation patterns observed in the studies by Boly et al. (2007), Owen et al. (2006), and Monti et al. (2010), were entirely predicted and were not in brain regions that are known to be involved in word processing, but rather, in regions that are known to be involved in the two imagery tasks (also see Weiskopf et al., 2004). In short, temporally sustained fMRI responses in these regions of the brain are impossible to explain in terms of automatic responses to either single "key" words or to short sentences containing those words. In fact, non-instructive sentences containing the same key words (e.g., "The man enjoyed playing tennis") have been shown to produce no sustained activity in any of these brain regions in healthy volunteers, nor is activity seen when the words "tennis" and "house" are presented to naïve participants who have not been previously instructed to perform the imagery tasks (Owen et al., 2007) (Figure 10.3). The most parsimonious explanation is, therefore, that patients who display sustained and reproducible brain activation during visual mental imagery tasks are consciously aware and following instructions, even in the complete or partial absence of behavioral responsiveness.

COMMUNICATION

Owen and Coleman (2008) extended the general principles discussed above, by which active mental rehearsal is used to signify awareness, to show that communication of "yes" and "no" responses was possible using the same approach. Thus, a healthy volunteer was able to reliably convey a "yes" response by imagining playing tennis and a "no" response by imaging moving around a house, thereby providing the answers to simple questions posed by the experimenters using only their brain activity. This technique was further refined by Monti et al. (2010) who

successfully decoded three "yes" and "no" responses from each of 16 healthy participants with 100% classification accuracy using only their real time changes in the supplementary motor area (during tennis imagery) and the parahippocampal place area (during spatial navigation). Moreover, in one traumatic brain injury patient, who had been repeatedly diagnosed as vegetative over a 5-year period, similar questions were posed and successfully decoded using the same approach (Monti et al. 2010). Thus, this patient was able to convey biographical information that was not known to the experimenters at the time (but was verified as factually correct) such as his father's name and the last place that he had visited on vacation before his accident 5 years earlier. In contrast, and despite a re-classification to minimally conscious state following the fMRI scan, it remained impossible to establish any form of communication with this patient at the bedside.

An obvious application for approaches of this sort is to begin to involve some of these patients in the decision-making processes involved in their own therapeutic care and management. To date, this has only been achieved successfully in one patient, who had been repeatedly diagnosed as vegetative for 12 years following a severe closed head injury (Fernandez-Espejo and Owen, 2013). Indeed, over one 14-month period from 2011 to 2013, the patient underwent 20 standardized behavioral assessments by a multidisciplinary team, at different times of the day and in different postural positions, using the Coma Recovery Scale-Revised (Giacino et al., 2004). In February 2012, 12 years and 2 months after his accident, the patient was first scanned using the fMRI mental imagery approach described above (Monti et al., 2010; Owen et al., 2006). The patient was able to provide correct answers to multiple externally verifiable questions, including autobiographical and other basic factual information. Two non-verifiable questions were then posed, including one pertaining to his care preferences (e.g., whether he liked watching hockey games on TV), and another to details about his current clinical condition (e.g., whether he was in any physical pain). Within the time-constrains of the scanning visits, the majority of responses to these questions were verified in independent sessions that posed the reverse questions (e.g., "Is your name Mike?" vs "Is your name Scott?"). At the time of the patient's death in 2013, answers to 12 different questions had been obtained across several sessions, despite the fact that the patient remained entirely physically non-responsive at the bedside (Fernandez-Espejo and Owen, 2013).

In the technique described above, the patient's ability to turn his or her attention to a specific scenario is required and serves as a "neural proxy" for a physical "response to command." By linking scenarios to "yes" responses and "no" responses, respectively, communication is possible. Similarly, Naci and colleagues (Naci et al., 2013; Naci and Owen, 2013) developed a novel tool for communicating with non-responsive patients based on how they selectively directed their attention to sounds while in the fMRI scanner. It is well established that selective attention can significantly enhance the neural representation of attended sounds (Bidet-Caulet et al., 2007). In their first study (Naci et al., 2013), 15 healthy volunteers answered questions (e.g., "Do you have brothers or sisters?") in the fMRI scanner by selectively attending to the appropriate word ("yes" or "no"), which was played to them auditorily, interspersed with "distractor" stimuli (digits 1–9). Ninety percent of the answers were decoded correctly based on activity changes within the attention network of the brain (i.e., 90% classification accuracy). Moreover, majority of the volunteers conveyed their answers with less than 3 min of scanning, which represents a significant time saving over the mental imagery methods described above (Boly et al., 2007; Owen et al., 2006, 2007). Indeed, a formal comparison between the two approaches revealed improved individual success rates and an overall reduction in the scanning times required to correctly detect responses; 100% of volunteers showed significant task-appropriate activity to the selective attention task, compared to 87% to the motor imagery. This result is consistent with previous studies showing that a proportion of healthy volunteers do not produce reliably classifiable brain activation during mental imagery tasks (Boly et al., 2007).

In their follow-up study (Naci and Owen, 2013), the same approach was used to test for residual conscious awareness and communication abilities in three behaviorally non-responsive, brain-injured patients. As in the previous study of healthy participants, the patients had to either "count" or "relax" as they heard a sequence of sounds. The word *count* at the beginning of the sequence instructed the patient to count the occurrences of a target word (*yes* or *no*), while the word *relax* instructed them to relax and ignore the sequence of words. Reliable activity increases in the attention network of the brain after the word *count* relative to the word *relax* was taken as evidence of command following. All three patients (two of whom were diagnosed as being in a minimally conscious state and one as being in a vegetative state) were able to convey their ability to follow commands inside the fMRI scanner by following the instructions in this way. In stark contrast, extremely limited or a complete lack of behavioral responsivity was observed in repeated bedside assessments of all three patients. These results confirm that selective attention is an appropriate vehicle for detecting covert awareness in some behaviorally

non-responsive patients who are presumed to mostly or entirely lack any cognitive abilities whatsoever.

In a following series of scans, communication was also attempted in two of the patients. The communication scans were similar to those in the command-following scan, with one exception. Instead of an instruction (count or relax), a binary question (e.g., "Is your name Steven?") preceded each sound sequence. Thus, each patient then had to willfully choose which word to attend to (count) and which to ignore, depending on which answer he wished to convey to the specific question that had been asked. Using this method, the two patients (one diagnosed as minimally conscious state and one diagnosed as vegetative state) were able to use selective attention to repeatedly communicate correct answers to questions that were posed to them by the experimenters (Naci and Owen, 2013). In the absence of external cues as to which word the patient was attending to, the functional brain activation served as the only indicator of the patient's intentions—and in both cases, led to the correct answers being decoded. For example, when asked, "Are you in a supermarket?" one patient showed significantly more activation for "no" than "yes" sequences in a network of brain areas that had been previously activated when that patient was focusing attention on external cues. Conversely, when asked, "Are you in a hospital?" the patient showed significantly more activation for "yes" than "no" sequences in the same regions. Despite his diagnosis (vegetative state for 12 years), the fMRI approach allowed this patient to establish interactive communication with the research team in four different fMRI sessions. The patient's brain responses within specific regions were remarkably consistent and reliable across two different scanning visits, 5 months apart, during which the patient maintained the long-standing vegetative state diagnosis. For all four questions, the patient produced a robust neural response and was able to provide the correct answer with 100% classification accuracy. The patient's brain activity in the communication scans not only further corroborated that he was, indeed, consciously aware but also revealed that he had far richer cognitive reserves than could be assumed based on his clinical diagnosis. In particular, beyond the ability to pay attention, these included autobiographical knowledge and awareness of his location in time and space.

CONCLUSIONS

Vegetative state presents unique problems for diagnosis, prognosis, treatment, and everyday management. At the patient's bedside, the evaluation of possible cognitive function in these patients is difficult because voluntary movements may be very small, inconsistent, and easily exhausted. Functional neuroimaging offers a complimentary approach to the clinical assessment of patients with vegetative state and other altered states of consciousness and can objectively describe (using population norms) the regional distribution of cerebral activity at rest and under various conditions of stimulation. In addition, functional neuroimaging has demonstrated preserved cognitive function, and even covert awareness, in patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical methods. Most recently, the use of task-dependent fMRI responses as a form of "communication" in these patients represents an important milestone. In our opinion, the future use of functional neuroimaging will not only substantially increase our understanding of severely brain-injured patients, but will allow us to make high-level assessments of residual cognitive function and answer clinically relevant questions.

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CHAPTER

11

Minimally Conscious State

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OUTLINE

Clinicians specializing in the care of patients with severe brain injury are well acquainted with the clinical features of coma and the vegetative state (VS). Both of these disorders are characterized by the complete absence of behavioral signs of self and environmental awareness. VS can be readily distinguished from coma by observing for spontaneous or elicited eye-opening, which occurs in VS and not in coma (Jennett and Plum, 1972). The reemergence of eye-opening signals that the ascending arousal system has regained control over wakefulness, although individuals in VS remain completely unaware of self or environment. In VS, the brainstem also maintains control over vital homeostatic functions including respiration, heart rate and thermal regulation. Although these functions may still be compromised during VS, life-sustaining interventions such as mechanical ventilation are usually not required. Note that, given the negative connotation of the term "vegetative state," The European Task Force on Disorders of Consciousness et al. (2010) has recently proposed to use the more neutral and descriptive term "unresponsive wakefulness syndrome."

Recovery from VS is variable in rate and degree (Multi-Society Task Force on PVS, 1994). Some

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individuals rapidly recover behavioral signs of consciousness within the first few weeks of injury while others demonstrate slower, more gradual recovery of cognitive function over a period of months or, in rare cases, years (Estraneo et al., 2013). In a minority of cases, cognitive functions fail to reemerge and VS evolves into a permanent condition (American Congress of Rehabilitation Medicine, 1995). In those who do recover, the transition from unconsciousness to consciousness is characteristically subtle, often marked by ambiguous signs of consciousness. For example, visual pursuit is often the first sign of conscious awareness to emerge, but this behavior can be similar in appearance to roving eye movements that typically occur during VS. During this transitional period, command-following is often difficult to differentiate from random movement on bedside assessment (Giacino and Zasler, 1995). Further complicating matters, even when clear signs of conscious behavior have been observed, they may be difficult to replicate within or across examinations (Giacino et al., 2004).

In 1995, the American Congress of Rehabilitation Medicine introduced the term *minimally responsive state (MRS)* to describe patients manifesting inconsistent but clearly discernible signs of conscious behavior (American Congress of Rehabilitation Medicine, 1995). A key element of this new diagnostic category was the requirement that behaviors thought to be indicative of consciousness be viewed as unequivocally "meaningful" by the examiner. In view of concerns that patients in coma and VS also display some degree of behavioral (albeit reflexive) responsiveness, an expert panel known as the Aspen Workgroup recommended that the term, MRS, be replaced by *minimally conscious state (MCS)* to emphasize the partial preservation of consciousness that distinguishes this condition from coma and VS (Giacino and Kalmar, 1997). In 2002, a consensus-based case definition for MCS was published in association with recommendations for specific diagnostic criteria (Giacino et al., 2002). These recommendations were subsequently endorsed by the American Association of Neurological Surgeons, American Congress of Rehabilitation Medicine, American Academy of Physical Medicine and Rehabilitation, the Child Neurology Society and the Brain Injury Association of America, Inc.

Motivated in part by alarming published estimates of misdiagnosis of VS ranging from 15% to 43% (Schnakers et al., 2009; Andrews et al., 1996; Childs et al., 1993), a primary aim of the Aspen Workgroup was to establish operationally defined criteria for MCS to facilitate differentiation of this condition from VS. A closely aligned aim was to provide a common frame of reference for researchers involved in the scientific study of this condition. Since publication of the MCS case definition, the number of reports addressing assessment, prognosis, pathophysiology, outcome, and ethical issues has increased steadily (Hirschberg and Giacino, 2011). Despite the broad acceptance of MCS as a distinct clinical syndrome, there is evidence that diagnostic accuracy has not improved. Schnakers and colleagues (2009) found that 41% of patients in a network of Belgian hospitals were diagnosed incorrectly by expert team consensus, when compared to the diagnosis obtained using a standardized assessment instrument, the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2002), as the "gold standard."

The objectives of this chapter are to provide a broad overview of the clinical and pathophysiologic features of MCS, to consider the therapeutic implications of these characteristics, to identify key issues in clinical practice and to suggest future directions for research.

DEFINITION AND DIAGNOSTIC CRITERIA

MCS is a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated on clinical examination (Giacino et al., 2002). To establish the diagnosis, there must be evidence of at least one clear-cut behavioral sign of cognitive processing *and* the behavior must be reproduced at least once within the same examination. Because behavioral fluctuation is common during MCS, it is generally necessary to conduct serial examinations before an accurate diagnosis can be made. Complicating diagnosis further, patients may vacillate between VS and MCS before the level of consciousness stabilizes (Giacino and Trott, 2004).

MCS is diagnosed when there is clear evidence of *one or more* of the following behaviors:

- Simple command-following
- Gestural or verbal yes/no responses (regardless of accuracy)
- Intelligible verbalization
- Movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity.

Examples of contingent motor and affective responses include (i) episodes of crying, smiling, or laughter produced by the linguistic or visual content of emotional but not neutral stimuli, (ii) vocalizations or gestures that occur in direct response to verbal prompts, (iii) reaching for objects with a clear relationship between object location and direction of reach, (iv) touching or holding objects in a manner that accommodates the size and shape of the object, and

TABLE 11.1 Comparison of the Behavioral Features of Coma, VS, MCS −, MCS +, and Emergence from MCS

	Emerged from MCS	MCS +	MCS −	VS	Coma
Eye opening	Spontaneous	Spontaneous	**Spontaneous**	**Spontaneous**	**None**
Movement	**Functional object use**	Automatic/object manipulation	**Automatic/object manipulation**	Reflexive/patterned	None
Response to pain	N/A	Localization	**Localization**	Flexion withdrawal/posturing	Posturing/none
Visual response	Object recognition	**Object recognition**	**Object localization/pursuit/fixation**	Startle	None
Affective response	Contingent	Contingent	Contingent	Random	None
Response to command	Consistent/reproducible	**Reproducible**	None	None	None
Verbalization	Intelligible words	**Intelligible words**	Random vocalization/none	None	None
Communication	**Reliable**	Unreliable	**Unreliable**	None	None

The defining features of each condition are shown in **bolded** text.

(v) visual pursuit or sustained fixation in response to moving or salient stimuli.

Some investigators and practitioners have argued that MCS should be divided into two subtypes based on evidence that language function is retained (Bruno et al., 2012). The "MCS +" subcategory encompasses patients who show clear evidence of receptive or expressive language function. In contrast, the "MCS −" designation is applied to those who demonstrate only non-linguistic signs of conscious awareness. The specific behaviors required to fulfill the criteria for MCS + and MCS − have been the subject of scientific inquiry and scholarly discussion over the last 3 years and require further empirical investigation before incorporation into clinical practice.

Behavioral parameters have also been defined to mark emergence from MCS (Giacino et al., 2002). Resolution of MCS is signaled by the return of one of two complex behaviors:

- Reliable and consistent interactive communication. Communicative responses may occur through speech, writing, yes/no signals or augmentative communication devices.

  or

- Functional object use. Functional object use requires discrimination and appropriate use of two or more objects presented by the examiner. In MCS, there may be evidence of object manipulation but there is no apparent awareness of how the object is used.

Table 11.1 summarizes the behavioral features of coma, VS, MCS −, MCS + and emergence from MCS.

The criteria for emergence from MCS were intended to reflect recovered capacity for meaningful environmental interaction. The clinical appropriateness of these behavioral benchmarks has been questioned by some authors. Taylor and colleagues (2007) have suggested that the requirements for *reliable* communication and *functional* object use conflate features of post-traumatic amnesia (PTA) with MCS. They note that loss of executive control during PTA may cause disturbances in language and praxis, which may preclude satisfaction of the diagnostic criteria for emergence from MCS, consequently prolonging the duration of this condition. Moreover, they suggest that if a patient is able to follow simple instructions and attempts to answer yes/no questions, regardless of accuracy, these behaviors no longer represent "minimal" evidence of consciousness but rather, an ability to actively engage in environmental interactions. They propose that it is more appropriate to describe the impact of PTA and confusion on behavioral performance at this point, rather than maintain the diagnosis of MCS.

Investigators have recently initiated empirical efforts to establish the threshold for emergence from MCS using Item Response Theory (IRT) (Gerrard et al., 2014; La Porta et al., 2013). Rasch modeling, a form of IRT analysis, has been used to separate persons into statistically distinct groups, based on the interaction between ability level and the level of difficulty of the test item. Ultimately, Rasch analysis produces item maps that reveal how specific items (in this case, behaviors) cluster together and establishes their location along the continuum of difficulty. This procedure offers the opportunity to employ a data-driven (vs. expert opinion) approach to determining the operational criteria for emergence from MCS. Using this technique, Gerrard and colleagues (2014) have shown the unidimensionality of the CRS-R and the hierarchical

structure of the CRS-R subscales. La Porta and colleagues (2013) also showed the unidimensionality of the CRS-R as well as a consistence of the scores across gender, age, time post-injury, and setting.

BEDSIDE ASSESSMENT METHODS

The approach to assessment of patients with disorders of consciousness (DOC) must consider two factors that may influence examination findings and lead to misdiagnosis. In light of the behavioral fluctuations that commonly occur in this population, evaluations should be repeated over time and measures should be sensitive enough to detect subtle but clinically meaningful changes in neurobehavioral responsiveness. Conventional bedside assessment procedures and neurosurgical rating scales such as the Glasgow Coma Scale (GCS; Teasdale and Jennett, 1974) have limited utility when used to monitor progress in patients with prolonged disturbance in consciousness. These procedures detect relatively gross changes in behavior and are not designed to distinguish random or reflexive behaviors from those that are volitional. The Full Outline of UnResponsiveness score (FOUR score) has greater sensitivity than the GCS for detecting different levels of brainstem function in the acute stage of severe brain injury (Wijdicks et al., 2005), but because the FOUR score does not assess for visual fixation, it may not capture the transition from VS to MCS (Schnakers et al., 2006; Bruno et al., 2011). To address these shortcomings, both standardized and individualized assessment procedures have been devised. Standardized rating scales assess a broad range of neurobehavioral functions and rely on fixed administration and scoring procedures.

Other standardized neurobehavioral assessment measures include the CRS-R (Giacino et al., 2004), the Coma-Near Coma Scale (CNC) (Rappaport et al., 1992), the Western Neurosensory Stimulation Profile (WNNSP) (Ansell and Keenan, 1989), the Western Head Injury Matrix (WHIM) (Shiel et al., 2000), and the Sensory Modality and Rehabilitation Technique (SMART) (Wilson and Gill-Thwaites, 2000). Although item content varies across measures, all evaluate behavioral responses to a variety of auditory, visual, motor, and communication prompts. All of these instruments have been shown to have adequate reliability and validity, however, there is considerable variability in their psychometric integrity and clinical utility. Of these measures, the CRS-R is the only one that directly incorporates the existing diagnostic criteria for coma, VS and MCS into the administration and scoring scheme. Giacino and colleagues (2004) compared the CRS-R to the DRS in 80 patients with DOC and found that although the two scales produced the same diagnosis in 87% of cases, the CRS-R identified 10 patients in MCS who were classified as VS on the DRS. There were no cases in which the DRS detected features of MCS missed by the CRS-R. Schnakers and colleagues (2006) administered the GCS, CRS-R, and the FOUR score to 60 patients with acute (i.e., trauma center) and subacute (i.e., rehabilitation center) brain injury resulting in disturbance in consciousness. Among the 29 patients diagnosed with VS on the GCS, four were found to have at least one sign of consciousness on the FOUR. However, the CRS-R detected evidence of MCS in seven additional patients diagnosed with VS on the FOUR. All seven of these patients showed sustained visual fixation, a clinical sign heralding recovery from VS.

In 2010, the American Congress of Rehabilitation Medicine published the results of the first evidence-based review of neurobehavioral rating scales designed specifically for patients with DOC (Seel et al., 2010). Six of the 13 scales that qualified for the review were recommended for use in clinical practice. The CRS-R received the strongest recommendation ("minor reservations"), based on its performance across a panel of psychometric quality indicators. The CRS-R is also one of the Traumatic Brain Injury (TBI) Common Data Elements (CDE) suggested by the US National Institute of Neurological Disorders and Stroke (NINDS) and the method of choice for monitoring recovery of consciousness in TBI research (Hicks et al., 2013; Wilde et al., 2010).

Clinicians involved in the care of MCS patients often encounter situations in which the patients' behavioral responses are ambiguous or occur too infrequently to clearly discern their significance. These problems are often due to injury-related sensory, motor and arousal deficits. For this reason, a technique referred to as *Individualized Quantitative Behavioral Assessment (IQBA)* was developed by Whyte and colleagues (Whyte and DiPasquale, 1995; Whyte et al., 1999). IQBA is intended to address case-specific questions using individually tailored assessment procedures, operationally defined target responses and controls for examiner and response bias. Once the target behavior (e.g., command-following, visual tracking) has been operationalized, the frequency of the behavior is recorded following administration of an appropriate command, following an incompatible command and during a rest interval. Data are analyzed statistically to determine whether the target behavior occurs significantly more often in one condition relative to the others. When the frequency of the behavior is greater during the "rest" condition

relative to the "command" condition, for example, this observation suggests that the behavior represents random movement rather than a purposeful response to the command.

IQBA can be applied across a broad array of behaviors and can address virtually any type of clinical question. McMillan (1996) employed an IQBA protocol to determine whether a minimally responsive, TBI patient could reliably communicate a preference concerning withdrawal of life-sustaining treatment. Responses to questions were executed using a button press. Results indicated that the number of affirmative responses to "wish to live" questions was significantly greater than chance suggesting that the patient could participate in end-of-life decision-making. McMillan's findings were subsequently replicated in a second IQBA assessment conducted by different group of examiners (Shiel and Wilson, 1998).

BEDSIDE ASSESSMENT AND DIAGNOSTIC ACCURACY

Differentiating MCS from VS can be challenging as voluntary and reflexive behaviors may be difficult to distinguish and subtle signs of consciousness may be missed. The development of diagnostic criteria for MCS (Giacino et al., 2002) would reasonably be expected to reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established (Childs et al., 1993; Andrews et al., 1996; Stender et al., 2014). However, a study comparing standard bedside examination to examination with the CRS-R found that 41% of patients believed to be in VS based on non-standardized bedside examination were misdiagnosed (Schnakers et al., 2009). This study also found that the majority of cases with an uncertain diagnosis were in MCS (89%), not in VS. Another 10% diagnosed with MCS based on bedside examination had actually emerged from this condition according to the CRS-R assessment.

The high rate of misdiagnosis reported likely reflects several different sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, patient and environment. Examiner error may arise when the range of behaviors sampled is too narrow, response-time windows are over or under-inclusive, criteria for judging purposeful responses are poorly defined and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection from these errors (Estraneo et al., 2014b), although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy. The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness (e.g., metabolic and infectious encephalopathies), pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity or paralysis), or cognitive disturbance (e.g., aphasia, apraxia, agnosia) also decrease the probability of observing signs of consciousness (Schnakers et al., 2014). Finally, the environment in which the patient is evaluated may bias assessment findings. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise/heat/light can all decrease or distort voluntary behavioral responses.

Examiner bias can be minimized by using standardized tools, but diagnostic accuracy is not always within the examiner's control. This is particularly troubling as clinical management, from treatment of pain to rehabilitative therapies and end-of-life decision-making often depends on the behavioral observations of the examiner.

PAIN ASSESSMENT AND THE NOCICEPTION COMA SCALE-REVISED

Providing information as to whether a patient with DOC is in pain is important to both clinicians and families. However, self-report is not an option in patients with DOC because of the inability to communicate. The Nociception Coma Scale (NCS) is the first standardized tool developed to assess nociceptive pain in patients with severe brain injury. The first version of the NCS (Schnakers et al., 2010) consisted of four subscales assessing motor, verbal, visual responses as well as facial expression. The NCS has been validated in patients in intensive care, inpatient neurology/neurosurgery units, rehabilitation centers, and nursing homes. The scale has demonstrated good inter-rater reliability and concurrent validity. In comparison to other pain scales developed for non-communicative patients, the NCS has broader coverage and better diagnostic sensitivity, suggesting that it is an appropriate assessment tool for this population. The visual subscale was subsequently deleted after further analysis showed that significantly higher scores were obtained on the motor, verbal and facial expression subscales (and not on the visual subscale) following application of noxious versus non-noxious stimuli (Chatelle et al., 2012a). A cut-off score of 4 (sensitivity of 73% and specificity of 97%) has been defined as a potential clinical threshold for detecting pain in

patients with DOC (Chatelle et al., 2012a) and there is some evidence that NCS-R total scores correlate with activity in the anterior cingulate cortex, which is involved in processing unpleasant experiences (Chatelle et al., 2014a).

Even though the NCS-R seems to represent a rapid, standardized and sensitive scale, additional investigations will have to be performed in order to develop a complete battery of valid and sensitive measures for clinicians to efficiently detect pain, both acute and chronic (indeed, the prevalence of recurrent headaches after a TBI, but also of neuropathic pain after thalamic lesion and chronic pain in presence of recurrent bedsores, severe spasticity or uncomfortable deformities is actually high) (Borsook, 2012). Such tools will not only allow clinicians to prevent and treat pain in this challenging population but they will also lead to develop guidelines that are currently inexistent and hence crucially needed. Finally, such tools will allow better characterization of behavioral patterns linked to pain in MCS patients and to better understand ambiguous behaviors such as grimaces. Indeed, grimacing is considered as a reliable indicator of pain in the assessment of non-communicative patients (Schnakers et al., 2012). However, the Multi-Society Task Force (1994) does not consider this behavior as a necessary sign of conscious perception. Patients showing no sign of consciousness except grimaces to noxious stimuli can therefore be diagnosed as being in a VS. Additional research is needed to better understand the neural correlates underlying this potential indicator of painful experience.

INCIDENCE AND PREVALENCE

The incidence and prevalence of MCS are difficult to estimate because of the lack of adequate surveillance outside of primary care settings. In the United States, most patients with DOC are transferred to long-term care facilities following relatively brief stays at a trauma (7–30 days) or inpatient rehabilitation (30–60 days) center. Long-term care facilities are often ill-equipped to manage patients in MCS as clinical staff generally lacks specialized training in assessment, which may allow subtle but diagnostically meaningful changes to go undetected. Further complicating surveillance efforts, there is no International Classification of Diseases diagnostic code for MCS and the prevalence of MCS is influenced by survival, which is dependent upon access to care, quality of care and decisions to withdraw care.

A preliminary study concerning the prevalence of MCS was performed by Strauss and colleagues (2000). These researchers developed an operational definition for MCS based on a large state registry used by the California Department of Developmental Services to track medical care and services administered to residents between the ages of 3 and 15. Of the 5075 individuals in the registry who met criteria for VS or MCS, 11% were judged to be in VS and 89% in MCS. Extrapolating from US census data for the general adult population, the prevalence of MCS was estimated to be between 112,000 and 280,000. These results suggest that the prevalence of MCS may be sevenfold higher than that of VS. A recent systematic review identified five cross-sectional prevalence surveys on DOC, using MEDLINE, EBM Reviews, and EMBASE databases (Pisa et al., 2014). This review estimated a prevalence of 1.5 per 100,000 inhabitants for MCS as compared to 0.2–3.4 per 100,000 inhabitants for VS. The authors identified significant heterogeneity in the estimation of prevalence and in the formulation of a diagnosis (i.e., VS vs MCS), thus limiting any direct comparison among studies.

Two studies have also investigated the incidence of DOC. A Swedish-Icelandic study followed a cohort of 84 patients with severe TBI (i.e., GCS 3–8 during the first 24 h) up to a year post-injury (Godbolt et al., 2013). At 3 weeks, 36 patients (43%) were classified as DOC. Among them, 6 patients (17%) were comatose, 17 patients (47%) were VS and 13 patients (36%) were MCS. At 1 year, all MCS patients, 9 VS patients (53%) and no comatose patients had emerged from MCS, suggesting that 10% of the initial sample (8/84) still were in DOC. The second prospective study involved Norwegian patients with severe TBI (Løvstad et al., 2014). The study reported that only 2% of the sample had disturbance in consciousness at 3 months post-injury and 1% at 1 year post-injury. The authors estimated that the incidence was lower in MCS as compared to VS at 3 months (0.03 vs 0.06 per 100,000) but was higher at 1 year (0.04 vs 0.01 per 100,000). A general conclusion cannot be drawn from these two studies as they were performed in different countries, involved different health policies that could have influenced the results observed and were based on small samples. International multicenter studies are needed to more accurately estimate the global incidence of patients with persistent DOC.

PROGNOSIS AND OUTCOME

Formal prognostic guidelines do not exist for MCS. However, the original report describing this condition states that most of those who remain in MCS for 12 months will remain permanently severely disabled. Outcomes research conducted over the last 10 years has produced consistent evidence suggesting that recovery after severe brain injury continues longer

than previously believed and that approximately one in five patients eventually achieves independence at home or in the community. Patients in MCS improve faster and have better prospects for functional recovery than those in VS, and outcomes are generally more favorable for those with traumatic versus non-traumatic injuries (Katz et al., 2009; Whyte et al., 2013; Estraneo et al., 2014a).

A recent study tracked the course of recovery of consciousness in 108 patients who were enrolled in the National Institute on Disability and Rehabilitation Research (NIDRR)-sponsored TBI Model System and had consistent follow-up over a 5-year period (Nakase-Richardson et al., 2012). All subjects had prolonged DOC on admission to rehabilitation, defined as a GCS Motor subscale score <6 and failure to follow commands on two consecutive days during the acute care stay. Within the subgroup of patients who failed to recover command-following by discharge from the rehabilitation program, 54% did so by 1 year post-injury and an additional 22% did so between years 1 and 5. Of those with earlier return to consciousness, 56–85% achieved independence on one or more functional domains of the Functional Independence Measure, an observational rating scale that assesses self-care (e.g., toileting), mobility (e.g., walking, transfers), and cognition (e.g., memory, communication, problem solving). 19–36% of those who did not recover command-following by discharge achieved functional independence in the home or community, although these changes stabilized after 2 years. In contrast, the early recovery group continued to show a significant increase in the number of persons achieving independence between 2 and 5 years post-TBI.

Late improvements in functional outcome have also been reported in a series of single-center studies. Lammi and colleagues (2005) followed 18 patients in MCS after TBI for 2–5 years after discharge from an inpatient brain injury rehabilitation program in Australia. The authors found that 15% of their sample had partial to no disability on the DRS (i.e., 50% had regained independence in activities of daily living) at follow-up while 20% fell in the extremely severe to vegetative category. These figures were similar to those reported in an earlier study by Giacino and Kalmar in which 23% of their sample had no worse than partial disability at 12 months and 17% were classified as extremely severe to vegetative. In both studies, the most common outcome was moderate disability, which occurred in approximately 50% of patients (Giacino and Kalmar, 1997). Katz and colleagues (2009) followed a consecutive series of 36 patients admitted to rehabilitation in VS ($n = 11$) or MCS ($n = 25$) after TBI ($n = 22$) or non-TBI ($n = 14$) for up to 4 years post-injury and tracked recovery of specific milestones. The investigators found that 72% of the cohort emerged from MCS, 58% of this group fully recovered orientation and, of those followed over 1 year, nearly half achieved household independence and 22% returned to work or school. Patients admitted in VS took significantly longer than those admitted in MCS to emerge from MCS (VS mean = 16.4 weeks; MCS mean = 7.4 weeks) and to regain orientation (VS mean = 30.1 weeks; MCS mean = 11.5 weeks).

In summary, evidence accumulated over the last decade indicates that meaningful recovery persists well after 12 months post-injury in approximately 20% of persons with prolonged DOC and suggests that current guidance on the timeframes for permanence in VS and MCS should be revisited.

NEURODIAGNOSTIC TECHNOLOGIES AND POTENTIAL CLINICAL APPLICATIONS

The use of advanced imaging techniques in patients with MCS has been motivated by several goals, including detection of covert cognition not identified by bedside exam and identification of imaging biomarkers that may predict outcomes and therapeutic responses. Currently, the sensitivity and specificity of advanced functional imaging techniques for detecting evidence of conscious awareness remains unknown pending large, multicenter studies. Similarly, the clinical utility of advanced imaging tools for prognosis and treatment selection remains unproven. Nevertheless, the development of advanced structural and functional imaging tools to facilitate diagnosis, prognosis, and therapeutic decision-making is a growing area of research with significant potential to improve care for patients with MCS.

FUNCTIONAL BRAIN IMAGING FOR DIFFERENTIATING MCS FROM VS

In VS patients, metabolic dysfunction has been reported in a wide range of brain regions including the polymodal associative cortices: lateral and medial frontal regions bilaterally, parieto-temporal and posterior parietal areas bilaterally, posterior cingulate, and precuneal cortices (Laureys et al., 1999). Many of these impaired areas are involved in the default mode network (DMN), which is mostly active at rest and is implicated in internally directed cognitive processes such as daydreaming, mind-wandering, stimulus-independent thoughts, or self-related thoughts. Besides metabolic dysfunction in these areas, recent studies have shown that functional connectivity within the default network is lower in VS as compared to conscious patients (see Figure 11.1). More specifically, the precuneus (an area known to be crucial to conscious

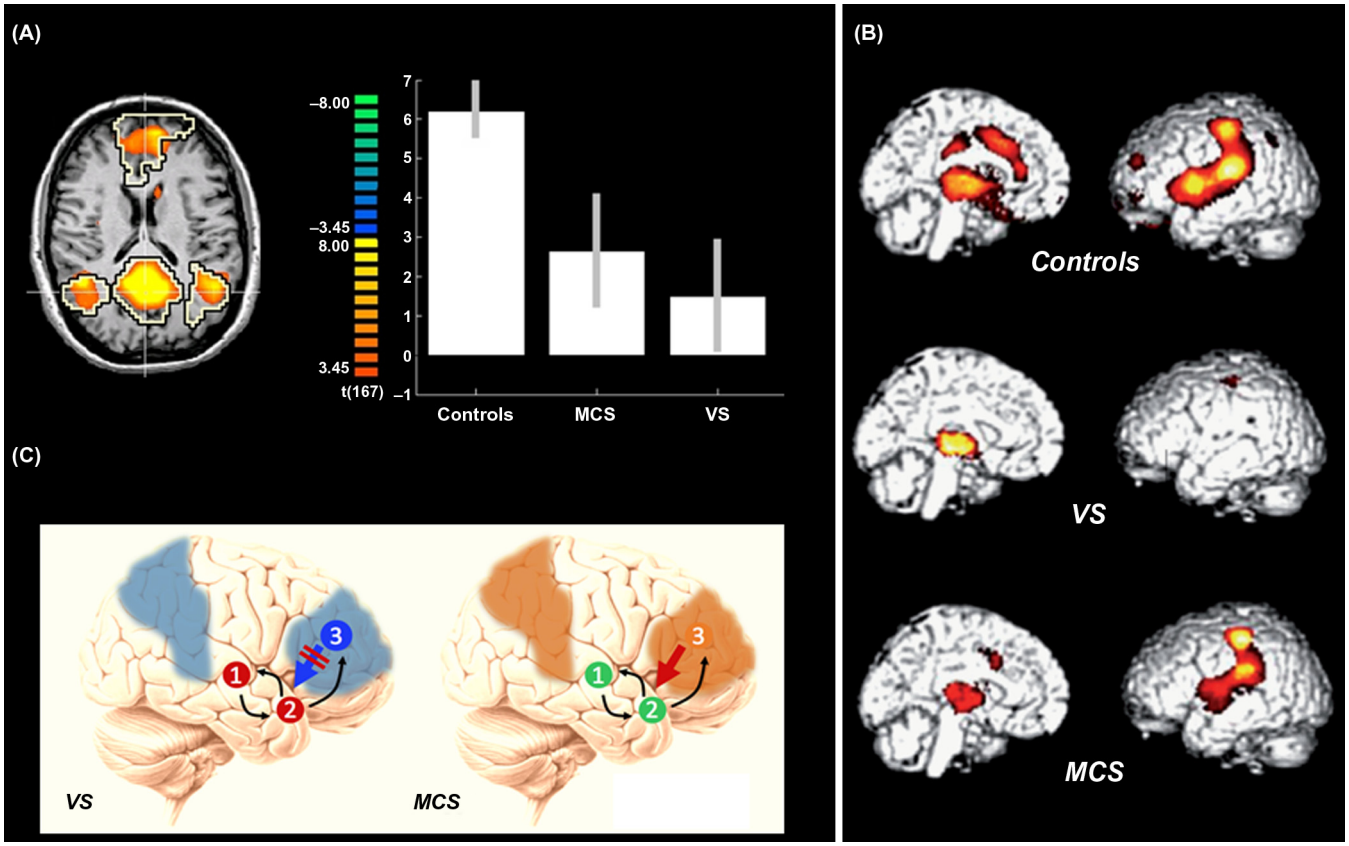

FIGURE 11.1 Residual brain activity in disorders of consciousness. Residual brain activity within the default network at rest (A) and in response to noxious stimulation (B) in patients in a vegetative state (VS) versus in a minimally conscious state (MCS). (*Source*: Adapted from Vanhaudenhuyse et al., 2010 and Boly et al., 2008a,b). Panel (C) illustrates the deficit in connectivity (particularly, long distance top-down connectivity) in VS versus MCS patients. (*Source*: Adapted from Boly et al., 2011).

processing) is significantly less connected to other areas of the network in VS patients as compared to MCS patients and patients with locked-in syndrome (LIS; Vanhaudenhuyse et al., 2010). Similar findings differentiating VS from MCS have been observed when using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) to examine brain activity in response to stimulation (Fingelkurts et al., 2012; Demertzi et al., 2014). Activation studies using auditory stimulation (i.e., tones) have shown preserved functioning in the primary auditory cortex without encompassing other brain areas (such as the temporoparietal junction) (Laureys et al., 2000a). Similarly, noxious stimulation (i.e., electrical stimulation of the median nerve) activated in VS patients only a part of the network involved in the low-level sensory-discriminative processing of pain (i.e., midbrain, contralateral thalamus, and primary somatosensory cortex) (see Figure 11.1) (Laureys et al., 2002). In both activation studies, low-level primary cortical activity seems to be isolated from higher-level associative cortical activity (Laureys et al., 2000a 2002). Furthermore, recent findings from an auditory evoked event-related potential study suggest that long distance connectivity (e.g., between frontal and temporal areas) is more impaired than short distance connectivity (e.g., areas within the temporal gyrus) in VS, which may be crucial for integrative brain processing leading to consciousness (see Figure 11.1) (Boly et al., 2011). There is not only a disruption in signal processing at a cortical level but also in signal transmission from the subcortical to the cortical level. The reemergence of functional connectivity between the thalamus and associative areas has been found in patients recovering from the VS (Laureys et al., 2000b). This observation is particularly important as the thalamus constitutes a relay in transmitting sensory/motor signals from subcortical to cortical areas and has a key role in conscious processing. In fact, Lutkenhoff and colleagues (2013) have recently shown that the extent of atrophy observed in the anterior thalamic nucleus predicts recovery of consciousness at 6 months post-injury.

These results suggest the presence of impaired and disconnected residual brain activity in VS patients, which appears to be inconsistent with conscious

perception. This disconnected, poorly integrated state of brain activity differs from that of MCS patients, as demonstrated by fMRI, PET, and EEG studies. Activity in the precuneus and posterior cingulate cortex (the most active regions in awakening and the least active under general anesthesia or during deep slow wave sleep) is greater than that observed in VS patients. In contrast with the limited brain activation found in VS, functional imaging studies using auditory stimulation reveal a larger temporal activation in MCS (encompassing the temporoparietal junction) (Schiff et al., 2005; Bekinschtein et al., 2004; Boly et al., 2004). The valence of an auditory stimulus can lead to a difference of brain activation in these patients. Patients in MCS seem to activate a broader region of the temporal lobe and the amygdala in response to an emotional auditory stimulus than in response to non-emotional auditory stimulation (Bekinschtein et al., 2004). In the setting of noxious stimulation, Boly and colleagues (2008a) showed that MCS patients experience brain activation similar to that of controls (involving the anterior cingulate area, which is related to pain unpleasantness) (see Figure 11.1). In parallel, a longitudinal case report by Bekinschtein and colleagues (2005) showed fronto-temporo-parietal activation as opposed to isolated left temporal activation in response to words when the patient evolved from VS to MCS.

In addition to higher levels of brain activation, greater cortico-cortical and thalamo-cortical connectivity has been demonstrated in MCS patients as compared to those in VS (Laureys et al., 2000b; Boly et al., 2004, 2008a,b; Rosanova et al., 2012). These data suggest that, unlike patients in VS, those in MCS may have sufficient cortical integration and access to afferent information to enable conscious perception. Casali and colleagues (2013) proposed the perturbational complexity index (PCI) as a measure of effective connectivity by calculating the spatial and temporal response of the brain to a perturbation induced by transcranial magnetic stimulation (TMS). The PCI distinguished alert healthy volunteers from volunteers who were anesthetized, sedated and asleep, and differentiated patients who were conscious (locked-in, emerged from MCS and in MCS) from those who were unconscious (VS). The PCI requires further validation before being implemented in clinical practice.

PATIENTS WITH COVERT COGNITION

For almost 10 years, clinicians have been faced with the challenge of caring for a new group of patients who fail to demonstrate behavioral signs of consciousness on bedside examination but are able to respond mentally to active neuroimaging or EEG paradigms. In 2006, Owen and colleagues reported the landmark case of a young woman who was clinically diagnosed as being in VS. Yet, when performing a mental imagery task during an fMRI scan, her brain activity was similar to the pattern of activity observed in healthy controls. Activation in the supplementary motor area was observed when imagining playing tennis (motor imagery), and in the premotor cortex, parahippocampal gyrus and the posterior parietal cortex when imagining moving around her home (spatial imagery). Some have argued that the words tennis and house may have automatically triggered the patterns of activation observed as words may elicit automatic neural responses in the absence of consciousness. However, such automatic activation typically lasts for a few seconds and occurs in regions of the brain that are associated with word processing. In this case, the activation lasted for the duration of the entire task (30 s) and persisted until the patient was asked to rest. In addition, the activation was not observed in brain regions that are known to be involved in word processing (Owen et al., 2006). In this sense, the decision to follow the instruction "imagine playing tennis" rather than simply "rest" appears to be a willful action that reflects consciousness. It should be noted that Cruse and colleagues (2012) observed more frequent activation during motor imagery in MCS patients with traumatic versus non-traumatic injuries—a finding not observed in patients in VS (Cruse et al., 2011).

Monti and colleagues (2010) used a modified version of the motor and spatial imagery paradigms to test yes-no communication responses in 54 patients diagnosed with VS and MCS. Patients were asked to answer autobiographical questions by using motor and spatial imagery as surrogates for "yes" or "no," respectively. One patient in MCS, although unable to communicate behaviorally, responded correctly to five of the six questions presented, suggesting significant preservation of cognitive function. Additional studies have since been published confirming the existence of patients with active cognitive processing who fail to exhibit overt behavioral responses (Monti, 2012).

In some cases, particularly during the acute phase, it may be difficult to differentiate LIS from VS, as both conditions are characterized by an absence of oriented motor and verbal responses. Misdiagnosis has indeed been shown to occur frequently in LIS (Laureys et al., 2005). Unlike patients in VS, those with LIS are usually able to use vertical eye movements and eye blinking to communicate and structural neuroimaging studies show a selective ventropontine lesion (which produces paralysis of all four limbs without interfering with consciousness or cognition). Functional neuroimaging studies typically show preserved supratentorial brain activity with hypometabolism constrained to the

cerebellum. Interestingly, significant hyperactivity has been observed bilaterally in the amygdala of acute LIS patients, perhaps reflecting anxiety generated by the inability to move or speak (stressing the importance of appropriate anxiety treatment soon after diagnosis) (Laureys et al., 2005). To explain the discrepancy observed between motor and cognitive functions in some severely brain-injured patients, Schiff proposed a "mesocircuit" model, inferring interruption in the cortico-striato-pallido-thalamo-cortical circuit (Schiff, 2010). Finally, further investigation is needed to better understand residual cognitive functioning in those patients as recent evidences suggest the presence of attentional impairments (Schnakers et al., 2014).

STRUCTURAL BRAIN IMAGING IN MCS

The use of structural neuroimaging techniques to elucidate the neuroanatomic basis of MCS is an emerging area of research that complements the functional neuroimaging studies described above. Just as fMRI, PET, and EEG studies have identified biomarkers that correlate with the transition from VS to MCS and emergence from MCS, structural MRI studies are beginning to reveal the neuroanatomic connections that are necessary for emergence of awareness. Preliminary data from correlative structural-functional imaging studies support the intuitive hypothesis that cognitive functions depend upon the integrity of structural networks that subserve those functions (Hagmann et al., 2008; Honey et al., 2010; Pernice et al., 2011). Yet, it has also been demonstrated that there is a complex interdependent relationship between brain structure and function, with structure only partially predicting function (Honey et al., 2009; Sui et al., 2013). This observation may be explained by inherent differences in structural and functional network properties, as well as methodological differences in structural and functional imaging techniques. Further complicating the relationship between structure and function in patients with severe brain injury is the heterogeneous nature of neuronal plasticity. Intact structures may be incorporated into new functional networks to compensate for injury to neighboring or contralateral homologous regions (Bagnato et al., 2013). This complex link between structure and function underscores the importance of a multimodal approach that integrates structural and functional imaging data to assess cognition in patients with DOC.

The most commonly used technique for structural imaging investigations of patients with DOC is diffusion tensor imaging (DTI), which measures the integrity of axonal pathways within the white matter of the brain. In addition, DTI provides mean diffusivity measurements that can identify tissue infarction, which is of particular importance in patients with DOC caused by hypoxic-ischemic events. Fernández-Espejo and colleagues (2011) performed DTI at 1–19 months post-ictus in 10 VS and 15 MCS patients and demonstrated that mean diffusivity within the subcortical white matter and thalamus, but not the brainstem, differentiated the VS and MCS cohorts with a classification accuracy of 95%. These DTI findings highlight the critical role of the thalamus in awareness and are consistent with morphometric imaging data correlating severity of thalamic atrophy to level of consciousness after brain injury (Lutkenhoff et al., 2013), as well as with histopathological data demonstrating an association between thalamic atrophy and VS (Kinney et al., 1994; Adams et al., 2000; Maxwell et al., 2004). Notably, the absence of a difference in DTI measurements within the brainstems of the VS and MCS cohorts in Fernández-Espejo's analysis is also consistent with current concepts about the structural basis for the distinction between VS and MCS. Specifically, these two states of altered consciousness are distinguished by level of awareness, which is primarily mediated by thalamocortical and cortico-cortical networks, not by level of arousal, which is primarily controlled by the subcortical ascending arousal system that connects the brainstem, hypothalamus, thalamus, and basal forebrain.

In a subsequent network-based study, DTI tractography was used to analyze the neuroanatomic basis of awareness in MCS, as compared to VS (Fernández-Espejo et al., 2012). In this type of analysis, DTI measurements of white matter integrity are used to assess white matter connections between gray matter regions (i.e., nodes) within neuroanatomic networks. The network investigated in this study was the DMN, based upon the association between DMN connectivity and level of consciousness demonstrated by resting-state fMRI (Vanhaudenhuyse et al., 2010). In this structural DMN analysis, the strength of connectivity between key network nodes, which include the posterior cingulate/precuneus, medial prefrontal cortex, thalamus, and temporoparietal junction, correlated with level of awareness as defined by behavioral assessment. Not only did DMN connectivity differentiate between patients in VS, MCS and emergence from MCS, but connectivity within the posterior thalamo-cortical circuit of the DMN (i.e., posterior cingulate/precuneus and thalamus) distinguished patients in MCS− and MCS+. This structural connectivity finding, if validated in future studies, suggests that DTI tractography provides critical information about the potential for command-following and functional communication within the MCS subgroup of patients with DOC.

Another fundamental aspect of the neuroanatomy of MCS that is an active area of investigation is the

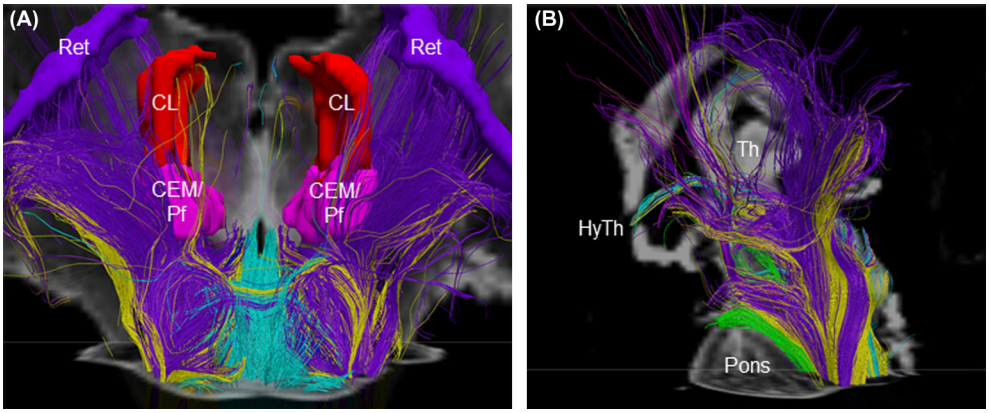

FIGURE 11.2 High angular resolution diffusion imaging (HARDI) tractography of ascending arousal system pathways in the healthy human brain. Fiber tracts are color-coded according to the brainstem nucleus from which they originate: purple, (cholinergic) pedunculopontine nucleus; yellow, (glutamatergic) parabrachial complex; turquoise, (serotonergic) dorsal raphé; dark blue, (noradrenergic) locus coeruleus; green, (serotonergic) median raphé; pink, (dopaminergic) ventral tegmental area. (A) Dorsal view of fiber tracts connecting with thalamic nuclei: reticular nucleus (Ret, purple), central lateral nucleus (CL, red), and centromedian/parafascicular nucleus (CEM/Pf, pink). Fiber tracts are superimposed on an axial non-diffusion-weighted ($b = 0$ s/mm^2) image ($b0$) at the level of the inferior colliculi and a coronal $b0$ image at the mid-thalamus. The $b0$ images are semitransparent so that the fiber tract trajectories can be seen as they cross the coronal plane. (B) Left lateral view of fiber tracts connecting with the hypothalamus (HyTh) ventrally and the thalamus (Th) rostrally. Fiber tracts are superimposed on an axial $b0$ image at the level of the mid-pons and a sagittal $b0$ image at the midline. Of note, the fiber tracts emanating from each nucleus extend both rostrally and caudally, likely representing ascending and descending pathways of the arousal system. *For additional details regarding HARDI tractography methods, see* Edlow et al. (2012).

number and types of connections that are required for the brainstem ascending arousal system to activate the DMN. Given its small brainstem nuclei and its reticular meshwork of fibers (Nauta and Kuypers, 1958), the ascending arousal system has historically evaded detection by most structural imaging techniques. Recently, with the advent of high angular resolution DTI techniques that can identify complex networks of crossing fibers, Edlow and colleagues (2012, 2013) mapped the brainstem arousal network in the healthy and injured human brain (see Figure 11.2). These initial structural connectivity analyses suggest that disruptions to neurotransmitter-specific circuits within the brainstem arousal network can be identified in patients with acute severe brain injury and in patients recovering from DOC. Furthermore, Newcombe and colleagues (2010) demonstrated that DTI tractography detects etiology-specific patterns of brainstem injury in patients with traumatic and anoxic VS, and Jang and colleagues (2014) demonstrated that DTI tractography detects decreased fiber tracts between the pontine reticular formation and the intralaminar nuclei of the thalamus in patients with impaired arousal after hypoxic-ischemic injury. Nevertheless, the specific circuits within the arousal network that are needed to activate the DMN and other cortical awareness networks remain unknown. There is evidence from animal models that brainstem arousal nuclei, such as the locus coeruleus, exert significant influence on the overall activity, or "gain" of the cortex (Aston-Jones and Cohen, 2005; Carter et al., 2010), but it remains to be determined which circuits of the brainstem ascending arousal network have the greatest impact on cortical activation in humans.

As structural connectivity techniques begin to provide the resolution necessary to map consciousness networks in patients with DOC, an important consideration in the interpretation of these data is the lack of information about the direction of electrical signaling and the number of synapses within a given network. This methodological limitation, which is inherent to DTI tractography, is particularly relevant when considering the event-related potential results of Boly and colleagues. Using a mismatch negativity paradigm, these investigators showed that "top-down" signaling from frontal cortex to temporal cortex may be essential for the emergence of conscious awareness (Boly et al., 2011). Although a structural connectivity technique may be able to detect white matter connections between these gray matter regions, functional techniques will invariably be needed to clarify whether the structural connections support recurrent, "top-down" signaling or only unidirectional, "bottom-up" neuronal processes. Nevertheless, from the perspectives of the global neuronal workspace theory of consciousness (Dehaene et al., 2006) and the information integration theory of consciousness (Tononi, 2004) structural imaging techniques provide a critical foundation for delineating the neuronal architecture upon which stimuli are processed and integrated.

At the present time, the application of structural imaging tools to patients with MCS has mostly focused

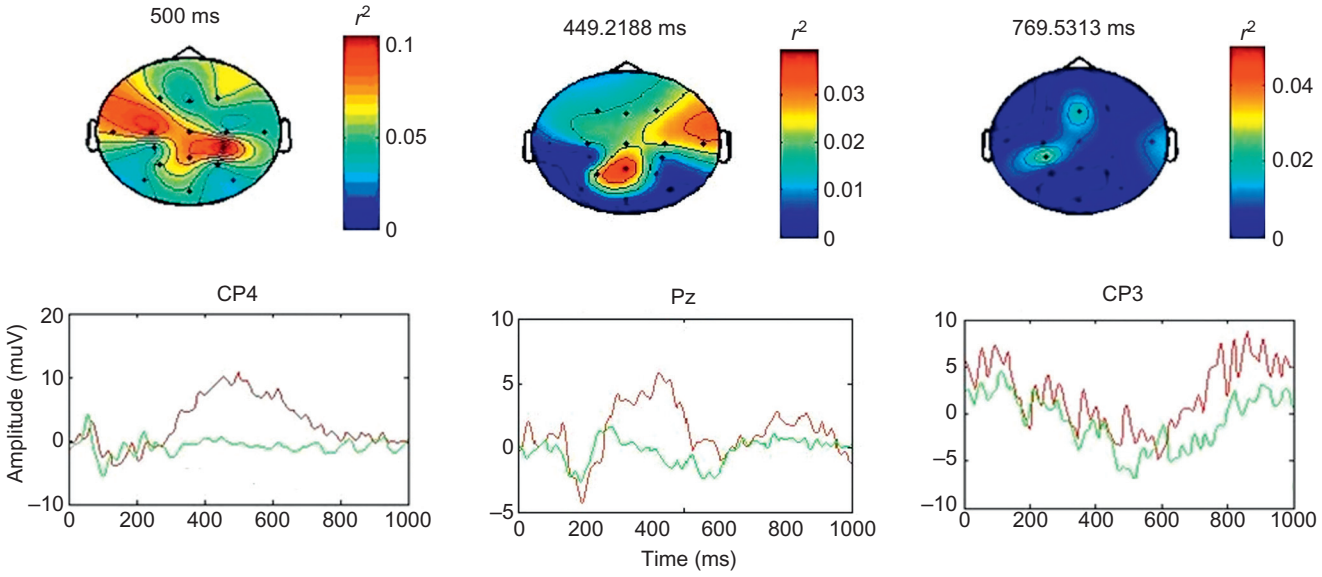

FIGURE 11.3 Example of EEG response to an auditory-based brain-computer interface in healthy controls and severely brain-injured patients. P3 response (positive deflection observed in the EEG around 300−500 ms in response to a salient stimulus) in a control subject (left), a patient with locked-in syndrome (middle) and a patient in a minimally conscious state (right) when they are asked to count a target word "yes" presented randomly in a series of other words (no, stop, go). On the top, distribution of the observed response to the target word (i.e., "yes") is shown. The colors in the images in the upper row represent the difference in the observed response between the target word and non-target stimuli (i.e., no, stop, go). The greater the difference, the more the region will be colored red-orange. Below, averaging over all responses for the other three words (non-targets: no, stop, go; in green) and for all responses to target words (yes; in brown) is shown. (*Source*: Adapted from Lulé et al., 2013). Note the spatial and temporal variability in the response between the three cases.

on characterizing the phenomenology of imaging biomarkers that differentiate MCS from VS and other DOC. An emerging area of structural imaging research is to identify early predictors of recovery in patients with severe brain injury. Recent structural studies suggest that DTI-based prognostic models outperform clinical prognostic models in patients with severe TBI and hypoxic-ischemic injury (Neuro Imaging for Coma Emergence and Recovery Consortium, 2012a,b). In addition, DTI tractography studies in the severe TBI population have demonstrated correlations between the structural integrity of specific white matter bundles and recovery of their associated neurocognitive functions (Wang et al., 2011; Newcombe et al., 2011). Nevertheless, these prognostic studies classified the acutely brain-injured patients by GCS score as opposed to CRS-R score, and therefore it remains unclear whether these DTI-based prognostic models sufficiently differentiate outcomes between patients in VS, MCS − , and MCS + .

THE USE OF BRAIN-COMPUTER INTERFACES IN CLINICAL SETTINGS: ETHICAL ISSUES AND FUTURE PERSPECTIVES

Establishing an accurate diagnosis in the broad population of patients with DOC is essential because of the population of patients who retain conscious awareness but have no or very limited means of communicating their thoughts and feelings (Schnakers et al., 2009). Previous studies suggest that MCS patients have partially preserved emotional, language, and pain processing networks (Laureys et al., 2004; Schiff et al., 2005; Boly et al., 2008a,b). Not only does accurate diagnosis have implications for clinical care and quality of life, it may also impact end-of-life decisions as withdrawal of artificial nutrition and hydration is accepted in several countries for patients in VS, but not for MCS (Ferreira, 2007; Manning, 2012).

There is an emerging area of research focusing on the use of brain-computer interfaces (BCIs). BCIs are motor-independent systems that use brain activity to drive external devices or computer interfaces (Wolpaw et al., 2002). BCI represents a complementary tool for improving the accuracy of diagnosis in DOC, while also providing some patients with a means of self-expression. Previous studies using fMRI and EEG-based BCIs have demonstrated diagnostic utility for detection of consciousness at the bedside (Chatelle et al., 2012b; Lulé et al., 2013; Lesenfants et al., 2014; Habbal et al., 2014; Pan et al., 2014).

BCIs are of particular interest when the subject retains command-following ability, as the software and hardware may be extendable to test for basic (binary) communication (see Figure 11.3). The downstream

objective is to refine this procedure so that it is easy to use and fast (e.g., automatic detection of artefacts, single-trial classification, no prior training required), enabling complex ideas to be communicated to the outside world.

At present, BCIs are limited by a high rate of false negative errors (i.e., failure of the system to detect command-following when it is evident at the bedside) (Chatelle et al., 2014b). This suggests that current BCIs may require a higher level of cognitive ability (e.g., sustained attention, flexibility, memory) than traditional bedside testing. In addition, the presence of apraxia, neglect, aphasia (Majerus et al., 2009), sensory impairment, akinetic mutism, vigilance fluctuation, and lack of motivation can impair a patient's ability to perform a selected task. Thus, the probability of detecting conscious awareness via BCI is likely to vary significantly across paradigms. Current paradigms are not ready to be applied to individual patients but may eventually become a practice option when combined with other testing modalities and techniques (Gosseries et al., 2014).

Overall, the development of new BCIs tailored for patients with DOC will inevitably increase the need to define guidelines for treatment and diagnostic assessment to improve the comfort, quality of life and communication of those patients. BCI may be useful when assessing command-following in patients with ambiguous behavioral responses (Prasad et al., 2010) and may assume a role in augmentative communication (Schnakers et al., 2008b; Müller-Putz et al., 2013). Studies examining the applicability of BCI for guiding rehabilitation programs are needed and the medical community will need to consider the ethical implications of adapting the definition of competency for patients who are able to engage in decision-making about rehabilitative treatment and end-of-life care (Bendtsen, 2013).

THERAPEUTIC INTERVENTIONS

Most existing therapeutic interventions used to treat MCS remain unproven as there are few definitive randomized controlled trials. The only treatment that has been convincingly shown to favorably alter the course of recovery following severe brain injury is amantadine hydrochloride, an *N*-methyl-D antagonist believed to indirectly influence dopaminergic activity. Giacino and colleagues (2012) conducted an 11-site international, multicenter, randomized, controlled trial in which amantadine or placebo was administered to 184 patients diagnosed with post-traumatic VS or MCS between 4 and 16 weeks post-injury. Participants were treated for 4 weeks, after which the study drug was discontinued. Rate of recovery as measured by the DRS was significantly faster in the amantadine group as compared to those who received placebo. In addition, the percentage of individuals who recovered functionally meaningful behaviors such as consistent command-following, intelligible speech, reliable yes-or-no communication and functional object use during the active treatment phase was higher in the amantadine group. Amantadine appeared to be effective regardless of the interval since injury or whether patients were in VS or MCS at enrollment, and no significant adverse effects were associated with amantadine use. Finally, a modulation of the fronto-parietal network has been shown following the administration of amantadine (Schnakers et al., 2008a).

There is some evidence from two placebo-controlled, double-blind, single-dose studies (including 60 and 84 patients, respectively) that zolpidem, a selective GABA receptor agonist usually recommended for insomnia because of its sedative, anxiolytic, and myorelaxant effects, paradoxically increases arousal level and behavioral responsiveness in some patients with DOC (Whyte and Myers, 2009; Schiff, 2010; Thonnard et al., 2013; Whyte et al., 2014; Chatelle et al., 2014c). Transient treatment-related improvements were observed in command-following, yes-no signaling and functional object use within 1−2 h of administration (Thonnard et al., 2013; Whyte et al., 2014). However, the response rate was low in both samples with only 2−5% of subjects who responded to the drug (on the basis of post-treatment changes in CRS-R performance).

Finally, it is interesting to note that Midazolam (a well-known benzodiazepine) has recently shown effects on consciousness. Carboncini and colleagues (2014) have reported the case of a MCS patient who recovered functional communication after midazolam infusion. An electrophysiological recording performed before and after the administration of the medication has revealed a change in the power spectrum profile with a diminution of lower frequencies (7 Hz), an increase in higher frequencies (15 Hz) and an increased connectivity between electrodes within those ranges.

There is growing interest in the use of invasive and non-invasive brain stimulation techniques to restore cognitive and behavioral functions in patients with prolonged DOC. The central premise used to guide these therapies is that electrical or magnetic stimulation elicits action potentials and depolarization of target neurons in cortical networks that underlie key functional systems (e.g., arousal, drive, language) responsible for behavioral initiation and control. Using a blinded alternating crossover design, Schiff et al. (2007) observed treatment-related behavioral improvements in a TBI patient in MCS who was treated with deep brain stimulation of the thalamic intralaminar nuclei more than 6 years post-onset.

Significant improvements were noted in the consistency of functional limb movements (e.g., praxis, social gestures), behavioral persistence, and oral feeding, possibly reflecting direct activation of frontal cortical and basal ganglia systems innervated by neuronal populations within the anterior intralaminar and adjacent paralaminar regions of the thalamus. The generalizability of these findings is unknown as this study used a single-subject design and the influence of the pathophysiology of this particular subject's brain injury on the effects reported is unknown. Nonetheless, replication of these findings will have important implications for clinical practice.

Non-invasive brain stimulation techniques such as TMS and transcranial direct current stimulation (tDCS) have also been applied to patients in MCS. Thibaut et al. (2014) investigated the application of tDCS in 55 patients with DOC using a double-blind, sham-controlled crossover design. In each patient, a single tDCS and sham session were applied over the left dorsolateral prefrontal cortex. Although visual pursuit and responses to command were observed in some patients in MCS only after tDCS, there was no significant difference in functional outcome at 1 year between responders and non-responders. The authors concluded that short-duration tDCS transiently improves level of consciousness. Piccione and colleagues (2011) used a blinded single-subject time-series design to evaluate the behavioral effects of repetitive TMS on a TBI patient who was in MCS for 5 years. The patient received either repetitive TMS or median nerve stimulation as placebo to the primary motor cortex. The authors reported that responses to command, object reaching and object manipulation were observed within 6 h of undergoing repetitive TMS and not after application of median nerve stimulation. While these results demonstrate proof-of-principle, further investigation is necessary to assess the long-term effects of brain stimulation on recovery of consciousness and function.

Treatment interventions emphasizing sensory stimulation date back to the 1970s and are among the most commonly used in patients with disturbance in consciousness. The assumption underlying sensory stimulation is that structured stimulation (i.e., visual, auditory, tactile, olfactory, and gustatory) avoids sensory deprivation and promotes neuroplasticity thereby optimizing recovery. Numerous studies have investigated the effectiveness of sensory stimulation in patients with DOC. Most published reports represent uncontrolled case series and descriptive case reports or have been compromised by significant methodological biases, including lack of blinding and failure to control for spontaneous recovery. As such, the existing evidence base is too weak to either support or refute the effectiveness of sensory stimulation (Di and Schnakers, 2012).

DIRECTIONS FOR FUTURE RESEARCH

Since publication of the case definition for MCS in 2002, the pace of research on this condition has accelerated dramatically. We have gained a better understanding of the pathophysiology underlying MCS, and how it differs from normal consciousness and other DOC. These advances have been aided by refinements in behavioral measures, EEG techniques and neuroimaging procedures designed to detect cognition, and by more sophisticated approaches to data analysis. At the same time, the sensitivity and specificity of these tools have not been adequately tested, which serves to maintain our present-day reliance on behavioral observations as the gold standard for conscious awareness. While the effectiveness of most therapeutic interventions remains poorly supported, there is compelling evidence for the first time that the normal course of recovery from severe brain injury can be altered pharmacologically via administration of amantadine hydrochloride. A deeper understanding of the pathophysiologic substrate of MCS will enable more precise targeting of neuromodulatory treatments aimed at restoring functional abilities.

MCS represents an important area of study, not just because of the significant personal, economic and social toll it levies on those affected, but also because it offers clues to understanding how the brain constitutes human consciousness. To continue to advance the field, the next wave of research will need to address some critical questions:

- *Should DOC be viewed as distinct clinical entities with well-defined borders, or as dynamic, clinically inconstant states governed by fluctuations in the underlying neurophysiologic substrate?* Disturbances in thalamocortical connectivity perturb neuronal firing patterns which disorganize activity across widely distributed networks and may account for the phasic breakdown in goal-directed behavior and cognition characteristic of MCS (Schiff and Posner, 2007; Schiff, 2010). Further elucidation of this phenomenon will help to inform diagnostic classification schemes.
- *What is the best approach to diagnostic and prognostic assessment?* Clinicians have an expanding toolbox of multimodal assessment measures at their disposal, ranging from standardized bedside scales to EEG tests and neuroimaging procedures. Time-consuming and expensive technology-based approaches (e.g., fMRI, cognitive evoked potentials) have not been adequately evaluated for sensitivity

and specificity and do not yet have clear indications for use in clinical practice. Increased attention to biostatistical modeling may improve understanding of the relationship between measures of consciousness, level of consciousness and functional outcome.

- *What is the natural history of MCS?* Evidence accumulated over the last 5 years makes clear that MCS is typically a transitional state and suggests that entry into this state within 60 days presages favorable outcome following TBI. Recovery commonly extends beyond 1 year and approximately one in five patients with prolonged disturbance in consciousness regain some degree of functional independence (Nakase-Richardson et al., 2012; Katz et al., 2009). There is a need to identify early behavioral markers of favorable recovery to facilitate outcome prediction, disposition planning and long-term care needs.
- *Are there effective treatments for MCS?* At present, amantadine chloride is the only treatment that has been clearly demonstrated to promote recovery from MCS in a multicenter randomized controlled trial (Giacino et al., 2012). There are other pharmacologic and neuromodulatory interventions that have shown efficacy in pilot studies and well-designed single-subject case reports (Schiff et al., 2007; Thibaut et al., 2014) but these treatments require further investigation in carefully controlled clinical trials to reduce the risk of bias. The effectiveness of comprehensive multidisciplinary rehabilitation programs remains remarkably under-studied, largely due to challenging logistical problems (e.g., acquiring sufficient sample size, controlling for spontaneous recovery, caregiver willingness to withhold non-target treatments).

CONCLUSIONS

MCS has garnered significant attention clinically and scientifically since publication of the original case definition in 2002 (Giacino et al., 2002). It is now clear that this condition is clinically distinct from VS and carries a generally favorable prognosis for functional recovery when it arises from TBI and is diagnosed early after injury. The potential for significant recovery following MCS is explained, in part, by the underlying neurophysiologic substrate, which shows generally preserved connectivity in functional networks responsible for mediating self and environmental awareness. Advanced neuroimaging and EEG techniques, coupled with more precise behavioral assessment procedures, have yielded new evidence suggesting that MCS can be parsed into clinical subtypes, which may be associated with distinct functional and prognostic features. More specific profiling of clinical, neuroanatomic and pathophysiologic features is a key step toward achieving greater precision in targeting treatment interventions. The recent discovery that amantadine hydrochloride can increase the pace of recovery in patients with post-traumatic DOC is important not just because it offers clinicians an effective treatment option, but also because it is proof-of-principle that it is possible to alter the course of recovery from severe brain injury. From a scientific perspective, the syndrome of MCS has provided a platform for the study of human consciousness and has provided important clues to understanding how the brain constitutes and expresses self and environmental awareness.

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CHAPTER

12

Consciousness in the Locked-In Syndrome

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OUTLINE

Thirty years ago a stroke left me in a coma. When I awoke I found myself completely paralyzed and unable to speak… I didn't know what paralysis was until I could move nothing but my eyes. I didn't know what loneliness was until I had to wait all night in the dark, in pain from head to foot, vainly hoping for someone to come with a teardrop of comfort. I didn't know what silence was until the only sound I could make was that of my own breath issuing from a hole drilled into my throat.

Tavalaro and Tayson (1997)

DEFINITION

The locked-in syndrome (LIS) or pseudocoma was first described by Plum and Posner in 1966 referring to the constellation of quadriplegia and anarthria brought about by the disruption of the brainstem's corticospinal and corticobulbar pathways, respectively (Plum and Posner, 1983). In the LIS, consciousness remains intact whereas in coma or in the unresponsive wakefulness syndrome (previously called the vegetative state, see Chapter 10) consciousness is lost. The patient is locked inside his body, able to perceive his environment but extremely limited in interacting with it voluntarily.

The American Congress of Rehabilitation Medicine defined LIS by (i) the presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor); (ii) aphonia or severe hypophonia; (iii) quadriplegia or quadriparesis; (iv) preserved cognitive abilities; and (v) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid (American Congress of Rehabilitation Medicine, 1995). Based on the severity of motor impairment, LIS can be subcategorized in (i) "*classical LIS*," when patients are quadriplegic, aphonic and use vertical eye movements or blinking to communicate; (ii) "*incomplete*

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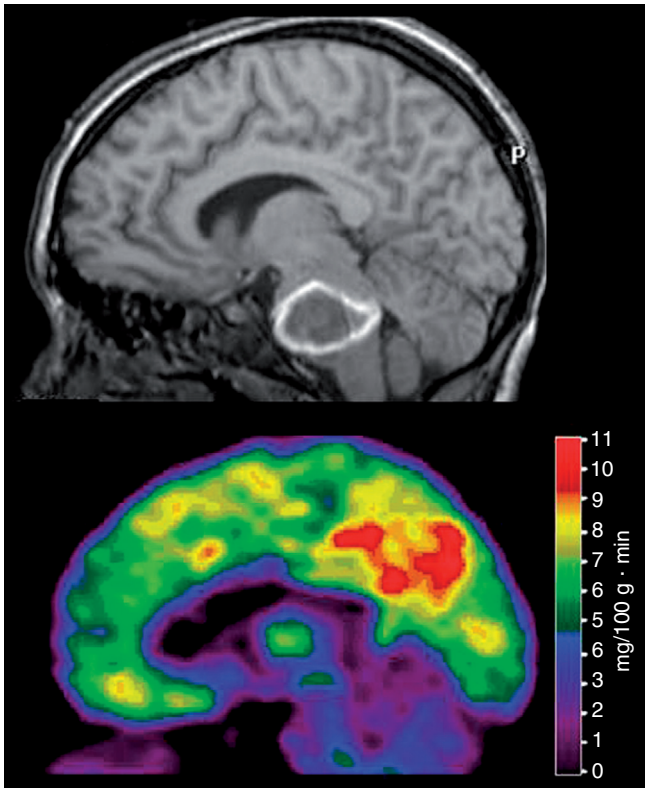

FIGURE 12.1 Brainstem lesion but preserved cortex in LIS patients. Upper panel: Magnetic resonance image (sagittal section) showing a massive hemorrhage in the brainstem (circular hyperintensity) causing a locked-in syndrome in a 13-year old girl.
Lower panel: ^{18}F-fluorodeoxyglucose—Positron Emission Tomography illustrating decreased metabolism in the brainstem (blue) but intact metabolism in the cortex in the acute phase of the LIS when eye-coded communication was difficult due to fluctuating vigilance. The color scale shows the amount of glucose metabolized per 100 g of brain tissue per minute. Statistical analysis revealed that metabolism in the supratentorial gray matter was not significantly lower than healthy controls. *Source: Taken from Laureys et al. (2004b).*

LIS," when patients have remnants of voluntary motion other than vertical eye movements; and (iii) "*total LIS*," when patients are entirely immobile (including eye movements) (Bauer et al., 1979).

ETIOLOGY

LIS is most frequently caused by a bilateral ventral pontine lesion (e.g., Plum and Posner, 1983; Patterson and Grabois, 1986) (Figure 12.1). In rarer instances, it can be the result of a mesencephalic lesion (e.g., Bauer et al., 1979; Chia, 1991; Meienberg et al., 1979). The most common etiology of LIS is vascular pathology, either a basilar artery occlusion or a pontine hemorrhage (Laureys et al., 2005). Another relatively frequent cause is traumatic brain injury (Britt et al., 1977; Golubovic et al., 2004; Fitzgerald et al., 1997; Rae-Grant et al., 1989; Keane, 1986; Landrieu et al., 1984). Following trauma, LIS may be caused either directly by brainstem lesions, secondary to vertebral artery damage and vertebrobasilar arterial occlusion or to compression of the cerebral peduncles from tentorial herniation (Keane, 1986). It has also been reported secondary to subarachnoid hemorrhage and vascular spasm of the basilar artery, a brainstem tumor, central pontine myelinolysis, encephalitis, pontine abscess, brainstem drug toxicity, vaccine reaction, and prolonged hypoglycemia (Laureys et al., 2005). In children, review of the literature confirms that the most common etiology is ventral pontine stroke (20 out of 33 published cases; i.e., 61%), most frequently caused by a vertebrobasilar artery thrombosis or occlusion (for a review see Bruno et al., 2009).

A comparable awake conscious state simulating unresponsiveness may also occur in severe cases of peripheral polyneuropathy as a result of total paralysis of limb, bulbar and ocular musculature. Another important cause of complete LIS can be observed in end-stage amyotrophic lateral sclerosis (i.e., motor neuron disease) (Hayashi and Kato, 1989; Kennedy and Bakay, 1998; Kotchoubey et al., 2003). Transient LIS cases have also been reported after Guillain-Barré polyradiculoneuropathy (Bakshi et al., 1997; Ragazzoni et al., 2000; Loeb et al., 1984; Wang and Zhu, 2012), severe post-infectious polyneuropathy (Carroll and Mastaglia, 1979; O'Donnell, 1979) (vertical eye movements are not selectively spared in these extensive peripheral disconnection syndromes), basilar artery vasospasm (Lacroix et al., 2012), and snakebite envenomation (Azad et al., 2013). Temporary pharmacologically induced LIS can also sporadically be observed in general anesthesia when patients receive muscle relaxants together with inadequate amounts of anesthetic drugs (e.g., Sandin et al., 2000). Testimonies from victims relate that the worst aspect of the experience was the anxious desire to move or speak while being unable to do so (Anonymous, 1973; Brighouse and Norman, 1992; Peduto et al., 1994). Awake-paralyzed patients undergoing surgery may develop posttraumatic stress disorder (for review see Sigalovsky, 2003). Finally, sleep paralysis is another case where subjects temporarily experiences an inability to move, speak or react due to the inhibition of voluntary muscle movement while ocular and respiratory movements remain intact (Sharpless and Barber, 2011).

MISDIAGNOSIS

Clinical experience shows how difficult it is to recognize unambiguous signs of conscious perception of the environment and of the self in severely brain-injured patients. The rarity of LIS causes the diagnosis

BOX 12.1

FAMOUS LOCKED-IN PATIENTS

The locked-in syndrome was first described in Alexandre Dumas's novel the Count of Monte Cristo (1844–1845) (Dumas, 1997). Herein, Monsieur Noirtier de Villefort, was depicted as "a corpse with living eyes." M. Noirtier had been in this state for more than 6 years, and he could only communicate by blinking his eyes. His helper pointed at words in a dictionary and the monsignor indicated with his eyes the words he wanted. Some years later, Emile Zola wrote in his novel Thérèse Raquin (Zola, 1979) (1868) about a paralyzed woman who "was buried alive in a dead body" and "had language only in her eyes." Dumas and Zola highlighted the locked-in condition before the medical community did.

For a long time, LIS has mainly been a retrospective diagnosis based on post-mortem findings (Patterson and Grabois, 1986; Haig et al., 1986). Medical technology now can achieve long survival in such cases—the longest history of this condition being 37 years (French Association of Locked-In Syndrome—ALIS). Computerized devices now allow the LIS patient and other patients with severe motor impairment to "speak." The preeminent physicist Stephen Hawking, author of the best sellers *A Brief History of Time* and *The Universe in a Nutshell*, is able to communicate solely through the use of a computerized voice synthesizer. With one finger, he selects words presented serially on a computer screen; the words are then stored and later presented as a synthesized and coherent message (http://www.hawking.org.uk). The continuing brilliant productivity of Hawking despite his failure to move or speak illustrates that LIS patients can be productive members of the society.

In December 1995, Jean-Dominique Bauby, aged 43 and editor in chief of the fashion magazine "Elle," had a brainstem stroke. He emerged from a coma several weeks later to find himself in a LIS only able to move his left eyelid and with very little hope of recovery. Bauby wanted to show the world that this pathology, which impedes movement and speech, does not prevent patients from living. He has proven it in an extraordinary book in which he composed each passage mentally and then dictated it, letter by letter, to an amanuensis who painstakingly recited a frequency-ordered alphabet until Bauby chose a letter by blinking his left eyelid once to signify "yes." His book (Bauby, 1997) *The Diving Bell and the Butterfly* became a best-seller only weeks after his death due to septic shock on March 9, 1997. The poignant movie from the book came out in 2007. Bauby created an ALIS aimed to help patients with this condition and their families (http://alis-asso.fr). Since its creation in 1997, ALIS has registered 713 locked-in patients (situation in March 2015).

to be often missed or delayed (Bruno et al., 2009; Gallo and Fontanarosa, 1989; Trojano et al., 2010). Signs of consciousness (such as vertical eye movements in response to verbal commands) should be tested in patients apparently being in a coma or in unresponsive state, especially if a brainstem lesion is detected. More specifically, oculomotor assessments should be systematically performed to help in the rapid identification of LIS patients (Barbic et al., 2012). Indeed, early detection of LIS is important with regard to nursing, including adapted pain treatment (Boly et al., 2008), and possible end-of-life decisions (Kompanje, 2010). A study performed in collaboration with the French Association for locked-in syndrome (ALIS; see Box 12.1) showed that, in 33% of the cases, it was a relative of the LIS patient, and not the physician, who first realized that the patient was conscious and could communicate via eye movements (Bruno et al., 2008b, 2009). The time elapsed between the acute insult and diagnosis of LIS was on average 2.5 months. Several patients were, however, only diagnosed 4 years after their brain injury (Laureys et al., 2005). This delay can be explained by the rarity of the syndrome, the difficulty to recognize unambiguous but limited signs of consciousness (i.e., voluntary eye movements or blinking) (Leon-Carrion et al., 2002a; Majerus et al., 2005), a reduced level of consciousness in the acute setting (Nikic et al., 2013) as well as because of additional cognitive (Schnakers et al., 2008) or sensory deficits such as deafness (Smart et al., 2008; Keane, 1985) or dysacousia (Bruno et al., 2009).

SURVIVAL AND MORTALITY

It has been stated that long-term survival in LIS is rare (Ohry, 1990). Mortality is indeed high in acute LIS (75% for vascular cases and 41% for non-vascular cases) with a median survival time of 42 days and 87% of the deaths occurring in the first 4 months (Patterson and Grabois, 1986; Nikic et al., 2013). In 1987, Haig et al. first reported on the life expectancy of persons with LIS, showing that individuals can actually survive for significant periods of time. Including 29 patients from a major US rehabilitation hospital who had been in a LIS for more than 1 year, they reported

formal survival curves at 5 year (Katz et al., 1992) and 10-year follow-up (Doble et al., 2003). These authors have shown that once a patient has medically stabilized in LIS for more than a year, 10-year survival is 83% and 20-year survival is 40% (Doble et al., 2003).

Data from the ALIS database ($n = 250$) show that survivors are younger at onset than those who die (survivor mean 45 ± 14 years, deceased subjects 56 ± 13 years, $p > 0.05$). The mean time spent locked-in is 6 ± 4 years (range 14 days to 29 years). Reported causes of death for the 42 deceased subjects are predominantly infections (40%, most frequently pneumonia), primary brainstem stroke (25%), recurrent brainstem stroke (10%), patient's refusal of artificial nutrition and hydration (10%) and other causes (i.e., cardiac arrest, gastrostomy-surgery, heart failure, and hepatitis) (Laureys et al., 2005). It should be noted that the ALIS database does not contain the many LIS patients who die in the acute setting without being reported to the association. Recruitment of the ALIS database is based on case reporting by family and healthcare workers prompted by the exceptional media publicity of ALIS in France and tracked by continuing yearly surveys. This recruitment bias should, however, be taken into account when interpreting the presented data.

PROGNOSIS AND OUTCOME

Classically, the motor recovery of LIS of vascular origin is very limited (Patterson and Grabois, 1986; Doble et al., 2003) even if rare cases of good recovery have been reported (McCusker et al., 1982; Ebinger et al., 1985). Chang and Morariu (1979) reported the first transient LIS caused by a traumatic damage of the brainstem. In their milestone paper, Patterson and Grabois reported earlier and more complete recovery in non-vascular LIS compared to vascular LIS when reviewing 139 patients (six cases from the author's rehabilitation center in Texas, USA and 133 taken from 71 published studies between 1959 and 1983) (Patterson and Grabois, 1986). Return of horizontal pursuit eye movements within 4 weeks post-onset are thought to be predictive of good recovery (Chia, 1991).

LIS is uncommon enough that many clinicians do not know how to approach rehabilitation and there are no existing guidelines as how to organize the revalidation process. Casanova et al. (2003) followed 14 LIS patients in three Italian rehabilitation centers for a period of 5 months to 6 years. They reported that intensive and early rehabilitative care improved functional outcome and reduced mortality rate when compared to the previous studies by Patterson and Grabois (1986) and Haig et al. (1987). Richard et al. (1995) followed 11 LIS patients for 7 months to 10 years and observed that despite the persisting serious motor deficit, all patients did recover some distal control of fingers and toe movements, often allowing a functional use of a digital switch. The motor improvement occurred with a distal to proximal progression and included a striking axial hypotonia. Laureys et al. (2005), in collaboration with ALIS, showed significant recovery of head movement in 92% of patients, 65% showed small movement in one of the upper limbs (finger, hand, or arm) and 74% show a small movement in lower limbs (foot or leg) (results obtained in 95 patients). A recent study also showed that, out of 88 LIS patients (>6 months after the insult, median duration 9 years, range 10 months to 29 years), 74% had recovered some speech production. 25% of these patients could produce unintelligible sounds and 49% could functionally communicate with words (14%) or complete sentences (35%) (Lugo et al., 2015). Despite the limited motor and verbal recovery of LIS patients, nearly 70% of the LIS patients can return to living at home (Laureys et al., 2005; Lugo et al., 2015).

COMMUNICATION

Communication is a major challenge for LIS patients. Especially in intensive care, it is essential that medical staff establishes communication as soon as possible. In order to functionally communicate, it is necessary for the patient to be motivated and to be able to receive (verbally or visually; i.e., written commands) and emit information. The first contact to be made with these patients is through a code using eyelid blinks or vertical eye movements. In cases of bilateral ptosis, the eyelids need to be manually opened in order to verify voluntary eye movements on command. To establish a yes/no eye code, the following instructions can either suffice: "yes" is indicated by one blink and "no" by two, or look up indicates "yes" and look down "no." In practice, the patient's best eye movement should be chosen, and the same eye code should be used by all interlocutors. Such a code will only permit to communicate via closed questions (i.e., yes/no answers on presented questions). The principal aim of reeducation is to reestablish a genuine exchange with the LIS patients by putting into place various codes to permit them to reach a higher level of communication, and thus to achieve an active participation. With sufficient practice, it is possible for LIS patients to communicate complex ideas by coded eye movements. Feldman has first described a LIS patient who used jaw and eyelid movements to communicate in Morse code (Feldman, 1971). A recent case study also reported a LIS patient who could produce

written output using a chin-controlled Morse system decoded by a computer (Gayraud et al., 2014).

Most frequently used are alphabetical communication systems. The simplest way is to list the alphabet and ask the LIS patient to make a prearranged eye movement to indicate a letter. Some patients prefer a listing of the letters sorted in function of appearance rate in usual language (i.e., in the English language: E—T—A—O—I—N—S—R—H—L—D—C—U—M—F—P—G—W—Y—B—V—K—X—J—Q—Z). The interlocutor pronounces the letters beginning with the most frequently used, E, and continues until the patient blinks after hearing the desired letter which the interlocutor then notes. It is necessary to begin over again for each letter to form words and phrases. The rapidity of this system depends upon practice and the ability of patient and interlocutor to work together. The interlocutor may be able to guess at a word or a phrase before all the letters have been pronounced. It is sufficient for him to pronounce the word or the rest of the sentence. The patient than confirms the word by making his eye code for "yes" or disproves by making his eye code for "no." Other spelling systems such as the vowels and consonants code or specific grids organized alphabetically in columns and rows have been developed to allow faster and easier use (Laureys et al., 2005; Kopsky et al., 2014).

Lugo et al. in collaboration with ALIS showed that, out of 88 patients, 50% used primarily eye movements to answer yes/no questions, either alone (25%), or in combination with head movements (16%), with sounds (6%) or with other gestures such as fingers movements (3%). For open questions and more elaborated communication, 67% of the patients used a specific and predefined code for communication. The most frequently used was the vowels and consonants code (31%) followed by the ESARIN code (i.e., code using letters sorted in function of appearance rate in French language) (15%). Among the 33% who did not report the use of any specific code for communication, 28% could verbalize (Lugo et al., 2015).

The above discussed communication systems all require assistance from others. Recent developments in informatics are drastically changing the lives of patients with LIS. Instead of passively responding to the requests of others, new communication facilitation devices coupled to computers now allow the patient to initiate conversations (Laureys et al., 2005) (Figure 12.2). Experts in rehabilitation engineering and speech-language pathology are continuingly improving various brain–computer interfaces (BCI, see also Chapter 14). BCIs are a mean of communication in which messages or commands that an individual sends to the external world do not pass through the brain's normal

FIGURE 12.2 Communication systems via small movements. (A) A chin-contactor (white arrow) allows the LIS patient to control his wheelchair and a head mounted contactor allows him to use an adapted personal computer; (B) finger-controlled text-to-speech synthesizer. *Source: Taken from Bruno et al. (2009).*

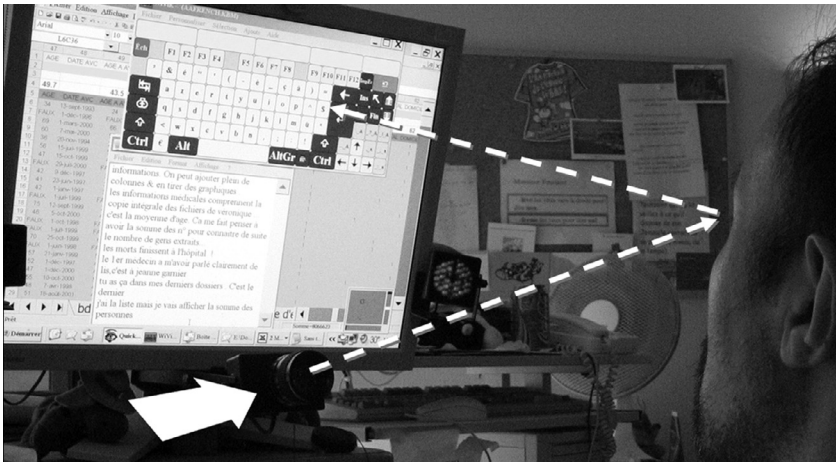

FIGURE 12.3 Communication via eye tracking system. A LIS person updates the database of ALIS, moving the cursor on screen by eye movements. An infrared camera (white arrow) mounted below the monitor observes one of the user's eyes, an image processing software continually analyzes the video image of the eye and determines where the user is looking on the screen. The user looks at a virtual keyboard that is displayed on the monitor and uses his eye as a computer-mouse. To "click" he looks at the key for a specified period of time (typically a fraction of a second) or blinks. An array of menu keys allows the user to control his environment, use a speech synthesizer, browse the world wide web or send e-mail independently (picture used with kind permission from DT). With a similar device, Philippe Vigand, who has been locked-in since 1990, has written a testimony of his LIS experience in an astonishing book "Putain de silence" translated as "Only the Eyes Say Yes" (Vigand and Vigand, 2000).

output pathways of peripheral nerves and muscles (Kubler and Neumann, 2005). These patient–computer interfaces such as infrared eye movement sensors which can be coupled to on-screen virtual keyboards allowing the LIS survivor to control his environment, use a word processor (which can be coupled to a text-to-speech synthesizer), operate a telephone of fax, or access the Internet and use e-mail (Figure 12.3; Box 12.2).

Wilhelm et al. (2006) have shown that mental manipulation of salivary pH may be an alternative way to document consciousness in LIS patients. The authors were able to establish communication by training the patient to vary salivary pH through the use of food imagery. Yes/no responses were obtained by having the patient imagine the taste of lemon or milk. Plotkin et al. (2010) showed that sniffing allowed complete LIS participants to write texts by using an (sniff-dependent) interface that measures nasal pressure and converts it into electrical signals (Plotkin et al., 2010). Recently, Stoll et al. (2013) showed that pupil size measured by a bedside camera could be used to communicate with LIS patients. This paradigm used mental arithmetic as a tool for patients to control and maximize their pupil dilation to signal their responses (Figure 12.4).

Birbaumer et al. (1999) also reported that LIS patients following amyotrophic lateral sclerosis were able to communicate without any verbal or motor report but this time only through their electrical brain activity. The authors showed that patients who lack muscular control can learn to control variations of their slow cortical potentials of their electroencephalogram sufficiently accurately to operate an electronic spelling device. P300-based event-related potential spelling systems were also developed recently permitting to use noninvasive BCIs to communicate volitional messages with LIS patients (Sellers et al., 2014; Combaz et al., 2013). Likewise, Lesenfants et al. (2014) showed the possible use of steady-state visually evoked potential-based BCI to communicate with LIS patients (Figure 12.5). The authors, however, emphasize that the potential clinical use needs to be further explored (Lesenfants et al., 2014). BCI based on somatosensory stimulation was also developed to establish communication in which patients could elicit a P300 wave through a vibrotactile oddball paradigm (Lugo et al., 2014). Recently, bedside near-infrared spectroscopy could also be used to communicate with a completely LIS patient (Gallegos-Ayala et al., 2014).

All these recent BCI studies highlight the need to identify the best technique and the best stimulus modality for a particular patient (Kaufmann et al., 2013). Importantly, in case of sensory or cognitive dysfunctions, communication must be adjusted and adapted (Smart et al., 2008; Keane, 1985). Smart et al. (2008) reported a case of a LIS patient who presented with a hearing deficit and who could benefit from an augmentative communication system designed to exploit his preserved cognitive functions by using visual cues, written questions, eye-gaze computer system and speech-generating devices. In the near future, independent BCI home use could positively influence the quality of life of LIS patients and support

BOX 12.2

TESTIMONIES WRITTEN BY LIS SURVIVORS

Some memoirs written by LIS patients well illustrate the clinical challenge of recognizing a LIS. A striking example is "Look up for yes" written by Julia Tavalaro (Tavalaro and Tayson, 1997). In 1966, 32-year old Tavalaro fell into a coma following a subarachnoid hemorrhage. She remained in a coma for 7 months and gradually woke up to find herself in a New York State chronic care facility. There, she was known as "the vegetable" and it was not until 1973 (i.e., after 6 years) that her family identified a voluntary "attempt to smile" when Julia was told a dirty joke. This made speech therapist Arlene Kraat break through Julia's isolation. With the speech therapist pointing to each letter on a letter board, Julia began to use her eyes to spell out her thoughts and relate the turmoil of her terrible years in captivity. She later used a communication device, started to write poetry and could cheek-control her wheelchair around the hospital. Julia Tavalaro died in 2003 at age 68 from aspiration pneumonia.

Another poignant testimony comes from Philippe Vigand, author of *Only the Eyes Say Yes* (original publication in 1997) and formerly publishing executive with the French conglomerate Hachette. The book is written in two parts, the first by Philippe, the second by his wife Stéphane detailing *her* experiences. In 1990, Philippe Vigand, then 32 years old, presented a vertebral artery dissection and remained in a coma for 2 months. Philippe and his wife write that at first, doctors believed he was a "vegetable and was treated as such." His wife eventually realized that he was blinking his eyes in response to her comments and questions to him but had difficulties convincing the treating physicians. It was speech therapist Philippe Van Eeckhout who formally made the diagnosis of LIS: when testing Vigand's gag reflex, Van Eeckhout was bit in his finger and yelled "chameau" (French for "camel"), whereupon the patient started to grin. On the subsequent question "how much is 2 plus 2" Vigand blinked four times confirming his cognitive capacities. He later communicated his first phrase by means of a letter board: "my feet hurt." After many months of hospital care, Vigand was brought home, where an infrared camera attached to a computer enabled him to "speak." The couple conceived a child after Philippe became paralyzed and he has written his second book (dealing with the menaced French ecosystem) on the beach of the Martinique isles (Vigand, 2002) illustrating that LIS patients can resume a significant role in family and society.

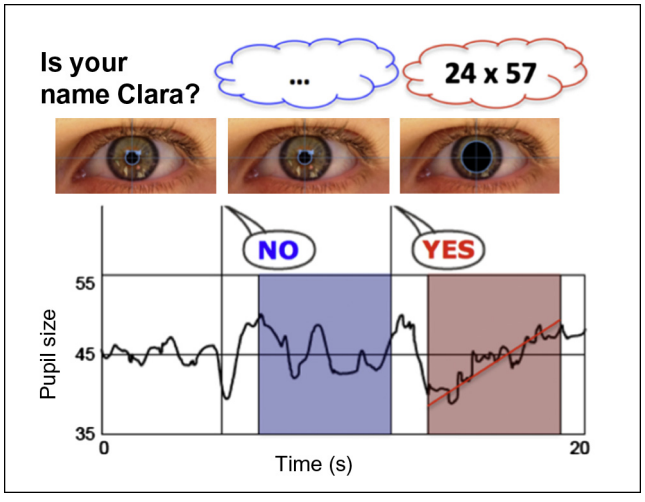

FIGURE 12.4 Communication via pupil size. This paradigm uses complex mental arithmetic as a tool for LIS patients to control and maximize their pupil dilation to signal their responses. The instruction is to perform the calculation if the response is "yes" and to ignore the calculation to say "no." Bottom: The slope of the difference signal (black trace) is determined by linear regression (red line), and referred to as pupil slope of the trial. All pupil slopes for the patient split by questions for which the correct answer corresponds to the first (blue) or the second (red) interval. *Source: Adapted from Stoll et al. (2013).*

social inclusion (Holz et al., 2015; Nijboer, 2015). For example, a BCI called Brain Painting application has recently been developed to allow LIS patients to paint via their electrical brain activity (Zickler et al., 2013), and so far, one patient has presented her brain paintings in two exhibitions (see Chapter 14).

RESIDUAL BRAIN FUNCTION

Neuropsychological Testing

In clinical practice, neuropsychological testing employed to evaluate cognitive functioning classically needs verbal or written responses. However, due to the severity of motor and verbal deficits, there is no systematic neuropsychological evaluation in LIS patients. Most case reports, however, failed to show any significant cognitive impairment when LIS patients were tested 1 year or more after the brainstem insult (for review see Laureys et al., 2005; Wilson et al., 2011). Allain et al. (1998) performed extensive neuropsychological testing in two LIS patients studied 2 and 3 years after their basilar artery thrombosis. Patients communicated via a communication print-writer

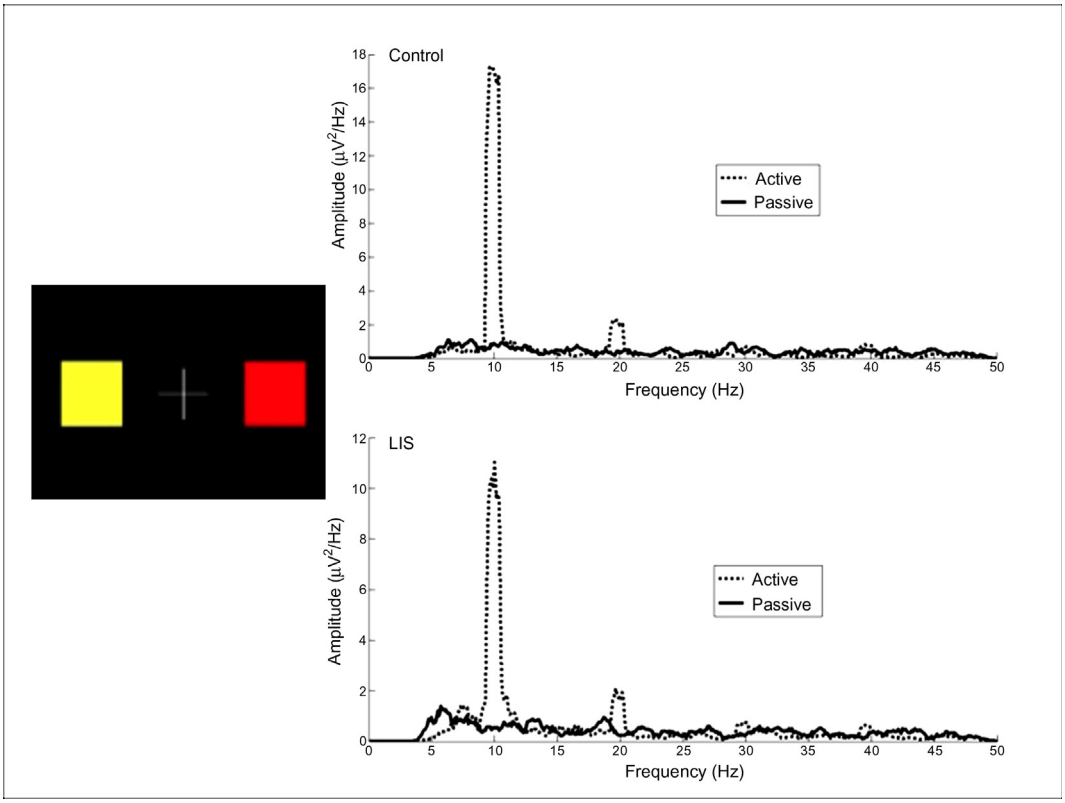

FIGURE 12.5 Communication via electrical brain activity. The electronic visual stimulation unit is composed of a yellow square that flickers at the frequency of 10 Hz and a red square that flashes at 14 Hz. The participants are instructed to focus on the yellow square to respond "yes" and on the red square to respond "no." Mean power spectra recorded in a control subject (upper) and in a patient in LIS (lower) from electroencephalography (here, from electrode O_2). Power spectrum obtained when subjects passively looked at the pattern is depicted with full lines ("passive"), and with dotted lines when subjects actively focused attention on the target stimulus ("active," i.e., focus on the yellow square to say "yes" and red square to say "no"). Note that they both responded "yes" (10 Hz). *Source: Adapted from Lesenfants et al. (2014).*

system and showed no impairment of language, memory and intellectual functioning. Cappa et al. (Cappa et al., 1985; Cappa and Vignolo, 1982) studied one patient who was LIS for over 12 years and observed intact performances on language, calculation, spatial orientation, right-left discrimination, and personality testing. New and Thomas (2005) assessed cognitive functioning in a LIS patient 6 months after basilar artery occlusion and noted significant reduction in speed of processing, moderate impairment of perceptual organization and executive skills, mild difficulties with attention, concentration, and new learning of verbal information. Interestingly, they subsequently observed progressive improvement in most areas of cognitive functioning until over 2 years after his brainstem stroke.

In a survey conducted by ALIS and Leon-Carrion et al. (2002a) in 44 chronic LIS patients, 86% reported a good attentional level, all but two patients could watch and follow a film on TV and all but one were well-oriented in time (mean duration of LIS was 5 years). Schnakers et al. and ALIS (Schnakers et al., 2008) adapted a standard battery of neuropsychological testing (i.e., sustained and selective attention, working and episodic memory, executive functioning, phonological and lexico-semantic processing and vocabulary knowledge) to an eye-response mode for specific use in LIS patients. Overall, performances in the LIS patients studied 3–6 years after their brainstem insult were not significantly different from matched healthy controls who, like the LIS patients, had to respond solely via eye movements. These data re-emphasize the fact that LIS due to purely pontine lesions, without any other brain damage, is characterized by the restoration of a globally intact cognitive potential. However, in a more recent study, Pistoia et al. (2010) reported that LIS patients were significantly less accurate than healthy controls in recognizing negative emotional facial expressions and they tended to confound negative emotions with each other.

Electrophysiologic Measurements and Functional Neuroimaging

Markland (1976) reviewed electroencephalographic (EEG) recordings in eight patients with LIS and reported that it was normal or minimally slow in seven of them but all showed reactivity to external stimuli. These results were confirmed by Bassetti et al. (1994) who observed a predominance of reactive alpha activity in six LIS patients. In their seminal paper, Patterson and Grabois (1986) reported normal EEG findings in 39 (45%) and abnormal (mostly slowing over the temporal or frontal channels or more diffuse slowing) in 48 (55%) patients out of 87 reviewed patients. Jacome and Morilla-Pastor (1990), however, reported three patients with acute brainstem strokes and LIS whose repeated EEG recordings exhibited an "alpha coma" pattern including an unreactive alpha rhythm to multimodal stimuli. Unreactive EEG in LIS was also reported by Gutling et al. (1996), confirming that lack of alpha reactivity is not a reliable indicator of unconsciousness and cannot be used to distinguish the "locked-in" patients from those comatose due to a brainstem lesion. Nevertheless, the presence of a relatively normal reactive EEG rhythm in a patient who appears to be unconscious should alert one to the possibility of a LIS.

Somatosensory evoked potentials are known to be unreliable predictors of prognosis in LIS patients (Bassetti et al., 1994; Towle et al., 1989) but motor evoked potentials have been proposed to evaluate their potential motor recovery (e.g., Bassetti et al., 1994). Cognitive event-related potentials in patients with LIS may have a role in differential diagnosis of brainstem lesions (Onofrj et al., 1997) and have also shown their utility to document consciousness in total LIS due to end-stage amyotrophic lateral sclerosis (Kotchoubey et al., 2003) and fulminant Guillain-Barré syndrome (Ragazzoni et al., 2000). Laureys et al. (2004a) showed event-related potentials in LIS patients showing a positive P300 component only evoked by the patient's own name and not by other names. It should, however, be noted that such responses can also be evoked in minimally conscious patients (Laureys et al., 2004a) and that they even persist in the unresponsive wakefulness syndrome (Perrin et al., 2006) and sleeping healthy subjects (Perrin et al., 1999). Using an active event-related paradigm, an unresponsive patient was presented sequences of names and was instructed to count the occurrence of her own name. The P300 response recorded for the voluntarily counted own name was larger than while passively listening suggesting that the patient was conscious (she was in fact in a complete LIS) (Schnakers et al., 2009). Finally, Rosanova et al. employed transcranial magnetic stimulation together with high-density EEG to probe the brain and evaluate brain connectivity at the bedside of LIS patients. The authors showed that LIS brain responses were not significantly different from healthy control subjects (Rosanova et al., 2012; Casali et al., 2013) (Figure 12.6).

Classically, structural brain imaging, including advanced diffusion tensor imaging, may show isolated lesions (bilateral infarction, hemorrhage, or tumor) of the ventral portion of the basis pontis or midbrain (e.g., Leon-Carrion et al., 2002b) (Figure 12.6). More recently, several functional magnetic resonance imaging (fMRI) studies have shown that default mode network connectivity patterns in LIS patients are not significantly different from healthy controls, suggesting preserved resting-state connectivity in LIS (Vanhaudenhuyse et al., 2010; Soddu et al., 2012; Ovadia-Caro et al., 2012). Likewise, chronic LIS patients do not seem to differ from healthy subjects when performing active fMRI paradigm, that is, for example, when they have to imagine playing tennis (Boly et al., 2007; Heine et al., 2015) (Figure 12.6).

Using PET scanning, higher metabolic levels have been observed in the brains of patients in a LIS compared to patients in the unresponsive wakefulness syndrome (Levy et al., 1987). PET studies (Laureys et al., 2003, 2004b; Thibaut et al., 2012) indicate that no supratentorial cortical area showed significantly lower metabolism in acute and chronic LIS patients when compared to age-matched healthy controls. The absence of metabolic signs of reduced function in any area of the gray matter re-emphasizes the fact that LIS patients suffer from a pure motor de-efferentation and recover intellectual capacity (Thibaut et al., 2012). Importantly, significantly hyperactivity was observed in bilateral amygdala of acute, but not chronic, LIS patients (Laureys et al., 2005). Previous PET studies in normal volunteers have demonstrated amygdala activation in relation to negative emotions such as fear and anxiety (e.g., Calder et al., 2001). It is difficult to make judgments about patient's thoughts and feelings when they awake from their coma in a motionless shell. However, in the absence of decreased neural activity in any cortical region, we assume that the increased activity in the amygdala in acute non-communicative LIS patients relates to the terrifying situation of an intact awareness in a sensitive being, experiencing frustration, stress, and anguish, locked in an immobile body. These findings emphasize the need to quickly make the diagnosis and also recognize the terrifying situation of a pseudocoma (i.e., LIS) at the intensive care or coma unit. Healthcare workers should adapt their bedside-behavior and consider pharmacological anxiolytic therapy for LIS patients, taking into account the intense emotional state they go through.

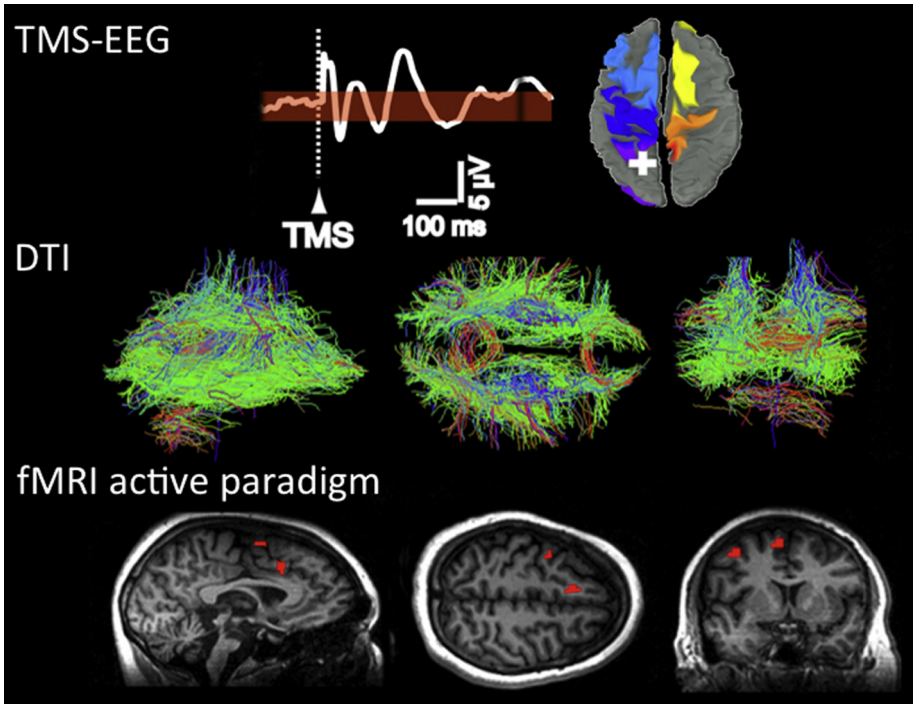

FIGURE 12.6 Neuroimaging results in a chronic LIS patient. Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) shows cortical EEG evoked response under the stimulation area (left) and the subsequent widespread of the activation (color-coded by brain area, right). The MRI diffusion tensor imaging (DTI) shows the structural connectivity (i.e., white matter tracts, color-coded by axis) and the fMRI active paradigm (here, tennis imagery) shows specific motor-independent response to command. Note that healthy control subjects present similar results, with the exception of a preserved brainstem (not shown). *Source: Adapted from Rosanova et al. (2012), Heine et al. (2015).*

DAILY ACTIVITIES

For those not dealing with these patients on a daily basis, it is surprising to see how chronic LIS patients, with the help of family and friends, still have essential social interaction and meaningful lives (Bruno et al., 2011; Nizzi et al., 2012). Doble et al. (2003) reported that most of their chronic LIS patients continued to remain active through eye and facial movements. Listed activities included: TV, radio, music, books on tape, visiting with family, visit vacation home, e-mail, telephone, teaching, movies, shows, the beach, bars, school, and vocational training. They also reported an attorney who uses Morse code eye blinks to provide legal opinions and keeps up with colleagues through fax and e-mail. Another patient taught math to third graders using a mouth stick to trigger an electronic voice device. The authors reported being impressed with the social interactions of chronic LIS patients and stated it was apparent that the patients were actively involved in family and personal decisions, and that their presence was valued at home. Only 4 out of the 13 patients used computers consistently, 2 accessed the Internet and 1 was able to complete the telephone interview by himself using a computer and voice synthesizer (Laureys et al., 2005).

QUALITY OF LIFE

Limitations of communication make quality of life assessments in LIS particularly difficult (Murrell, 1999). The average population and some physicians who take care of acute LIS may consider that the quality of life of LIS patients is very limited (Laureys et al., 2005). However, many early and recent studies reported that most of the patients in LIS, including complete LIS, have a good to excellent quality of life despite being socially isolated and experiencing severe difficulties in performing daily tasks (Bruno et al., 2011; Albrecht and Devlieger, 1999; Lule et al., 2009; Rousseau et al., 2013; Snoeys et al., 2013). The links between symptoms and quality of life seems neither simple nor direct (Ware et al., 1993). A study conducted by the ALIS assessed the quality of life of 17 chronic (>1 year) LIS patients who did not show major recovery. The patients unsurprisingly showed maximal limitations in physical activities but self-scored perception of mental health (evaluating mental well-being and psychological distress) and personal general health were not significantly lower than values from age-matched control subjects (Laureys et al., 2005; Ghorbel, 2002). Note that perception of mental

health and the presence of physical pain was correlated to the frequency of suicidal thought. Leon-Carrion et al. (2002a) showed that about half of the assessed patients regarded their mood as good ($n = 44$). Similarly, Doble et al. (2003) studied 13 LIS patients and reported that more than half were satisfied with life in general.

Collaborating with the ALIS, we recently reported on the overall quality of life of 65 chronic LIS patients. Patients were asked to fill in a structured questionnaire aided by their proxies (Bruno et al., 2011). The French postal version of the Reintegration to Normal Living Index was used to evaluate the degree to which a patient has been able to return to a normal life (Wood-Dauphinee and Williams, 1987; Daneski et al., 2003). The overall quality of life was rated by means of the Anamnestic Comparative Self-Assessment (ACSA; Bernheim, 1999), whose biographical +5 and −5 scale anchors were the patients' memories of the best period in their life before LIS (+5) and their worst period ever (−5). 51% of respondents self-reported severe restrictions in community reintegration in line with previous studies in paraplegia following spinal cord injury (May and Warren, 2002; Tonack et al., 2008). Only 21% were engaged most of the day in activities that they considered important. The majority (82%) was comfortable with personal relationships and only a minority was dissatisfied with their participation in recreational (12%) or social (40%) activities. 72% of the patients professed happiness (47/65 patients; median ACSA +3) and 28% unhappiness (18/65 patients; median ACSA −4) (Figure 12.7). In the unhappy group, depression, suicidal ideas, consideration or wish for euthanasia, and wish not to be resuscitated in case of cardiac arrest were reported more frequently (28%). The variables associated with unhappiness were dissatisfaction with mobility in the community, with recreational activities and with the capacity to deal with life events. Shorter time in LIS, anxiety and non-recovery of speech production were also associated with unhappiness. The self-reported happiness may suggest that these patients have succeeded in adapting to their condition of extreme physical disability. According to Cummins' theory of subjective well-being, their homeostatic resources may have overcome even in the formidable challenge of LIS (Cummins, 2003). Hence, these findings highlight the strength of homeostatic processes of adaptation to chronic (often definitive) extreme disability. The "happy" subgroup of LIS survivors may indeed be those respondents capable of high flexibility and plasticity who have fully succeeded in recalibrating, reprioritizing, and reorienting their needs and values. In that perspective, low raters cope poorly because they cannot shed the needs and values from their previous life. Because such an adaptation process is lengthy, this hypothesis is consistent with the observed positive association of quality of life with duration of time in LIS, corroborating previous studies on quality of life in spinal cord injury patients (Tonack et al., 2008; Calmels et al., 2003).

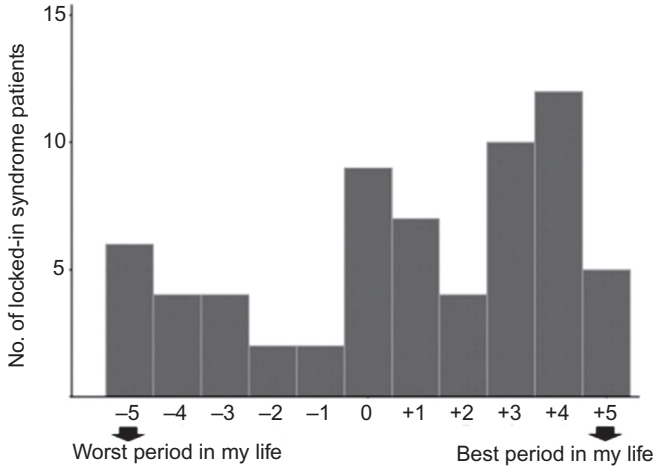

FIGURE 12.7 Distribution of Anamnestic Comparative Self-Assessment ratings in 65 chronic LIS patients. Most LIS patients reported a decent quality of life (72% of the included patients). A minority of patients (28%), however, reported a poor quality of life, which was often related to the short duration of LIS, the absence of social interaction, and the absence of motor or verbal recovery. *Source: Adapted from Bruno et al. (2011).*

In 2012, we assessed the self-reported quality of life of 44 LIS patients, with a specific attention to their sense of self. Again, a majority of patients (65%) reported a positive quality of life and a preserved sense of self, independently of LIS duration. Interestingly, there was a large discrepancy between patients' self reports and healthcare providers' predictions in terms of life satisfaction in LIS (Nizzi et al., 2012). Similarly, attitudes towards pain and end-of-life issues in LIS seem to vary when taking the first-person versus third-person point of view. For example, 75% of healthy subjects interviewed in a European study disagreed with treatment withdrawal in LIS patients, but if they imagined themselves in this condition only 46% of them wished to be kept alive (Demertzi et al., 2014). These studies emphasize the need to focus on the patients' perspective when making medical decisions for LIS patients.

THE RIGHT TO DIE OR THE RIGHT TO LIVE?

As stated by The American Academy of Neurology (AAN), patients with profound and permanent paralysis have the right to make healthcare decisions about themselves including to accept or refuse life-sustaining therapy (Ethics and Humanities Subcommittee of the

AAN, 1993). Bruno et al. (2008c) have questioned 97 clinicians and at the affirmation: "*Being LIS is worse than being in a vegetative state or in a minimally conscious state*?", 66% said "yes" and 34% said "no." Some healthcare professionals who have no experience with chronic LIS survivors might believe that LIS patients want to die but as we have seen above many studies showed that patients typically have a wish to live. In 1993, Anderson et al. reported that all questioned LIS patients wanted life-sustaining treatment. A previous study by ALIS showed that 75% of chronic LIS patients without motor recovery rarely or never had suicidal thoughts. At the question: "*would you like to receive antibiotics in case of pneumonia*," 80% answered "yes" and in reply to the question "*would you like reanimation to be tempted in case of cardiac arrest*," 62% said "yes" (Laureys et al., 2005). Similarly, in a survey conducted by Bruno et al. (2008c) nearly two thirds of studied LIS patients ($n = 54$) never had suicidal thoughts. In line with these findings, Doble et al. (2003) reported that none of the questioned chronic LIS patients had a "do not resuscitate" order, more than a half had never considered or discussed euthanasia. These authors also noted that none of the 15 deaths of their study cohort of chronic LIS patients ($n = 29$) could be attributed to euthanasia.

In accordance with the principle of patient autonomy, physicians should respect the right of LIS patients to accept or refuse any treatment. At least two conditions are necessary for full autonomy, patients need to have intact cognitive abilities and they must be able to communicate their thoughts and wishes. The development of new technologies, including recent BCIs (De Massari et al., 2013; Oken et al., 2014), is now allowing caregivers to gain increasing access to the wishes of LIS patients. Since previous studies have demonstrated that caregivers' beliefs about what it is like to be in a LIS do not match patients' reports, it is once again important to include the first-person perspective of the patients when making life decisions in LIS.

Likewise, in amyotrophic lateral sclerosis, ill-informed patients are regularly advised by physicians to refuse intubation and withhold life-saving interventions (Christakis and Asch, 1993; Trail et al., 2003). However, ventilator users with neuromuscular disease report meaningful life satisfaction (Kubler et al., 2005). Bach (2003) warns that "virtually no patients are appropriately counseled about all therapeutic options" and states that advance directives, although appropriate for patients with terminal cancer, are inappropriate for patients with severe motor disability.

Katz et al. (1992) cite the Hastings Center Report, "Who speaks for the patient with LIS?". With the initial handicap of communicating only through eyeblink who can decide whether the patient is competent to consent to or to refuse treatment? (Steffen and Franklin, 1985). With regard to end-of-life decisions taken in LIS patients, an illustrative case is reported by Fred (1986). His 80-year old mother became locked-in. In concert with the attending physician, without consent of the patient herself, the decision was made to "have her senses dulled" and provide supportive care only. She died shortly thereafter with a temperature of 109°F (43°C). In the accompanying editorial, Stumpf (1986) commented that "human life is to be preserved as long as there is consciousness and cognitive function in contrast to a vegetative state or neocortical death."

CONCLUSION

The discussed data stress the need for critical care physicians who are confronted to acute LIS to recognize this infrequent syndrome as early as possible. Healthcare workers who take care of acute LIS patients need a better understanding of the long-term outcome of LIS. Opposite to the beliefs of many caregivers, LIS patients self-report a meaningful quality of life and the demand for euthanasia exists but is uncommon. Studies emphasize LIS patients' right to autonomy and demonstrate their ability to exercise it, including taking end-of-life decisions. The strength of medical and communication-technological progress for patients with severe neurological conditions is that it makes them more and more like all the rest of us (Bruno et al., 2008a). Clinicians should realize that quality of life often equates with social interactions rather than physical capacities. It is important to emphasize that only the medically stabilized, informed LIS patient is able to accept or to refuse life-sustaining treatment. LIS patients should not only be denied the right to die—and to die—but also, and more importantly, they should not be denied the right to live—and to live with dignity and with the best possible care.

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CHAPTER

13

Consciousness and Dementia: How the Brain Loses Its Self

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OUTLINE

According to the information integration theory of consciousness (Tononi, 2001, 2005), consciousness corresponds to the brain's ability to rapidly integrate information. This ability to integrate information requires a well-functioning thalamocortical system (Tononi, 2005; Plum, 1991). Indeed, extensive lesions of the thalamocortical system are usually associated with a global loss of consciousness, such as that seen in comatose patients (Laureys et al., 2004). Also, in patients who have undergone surgical sectioning of the corpus callosum for therapeutic purposes, leading to a splitting of the thalamocortical system, consciousness is split as well (Tononi, 2005). Neural activity that correlates with conscious experience appears to be widely distributed over the cortex, indicating that consciousness is based on the optimal functioning of a distributed thalamocortical network rather than on the activity of a specific single cortical region (Tononi, 2005). This also is in line with the observation that lesions of selected cortical areas result in the impairment of specific submodalities of conscious experience, such as the perception of faces, but do not produce any alteration of global consciousness (Kolb and Whishaw, 1996).

Alzheimer's disease is the most common form of dementing disorder in the elderly, affecting more than 5% of individuals aged 65 years and older and almost one out of two individuals over 85 years of age (Bachman et al., 1992). Patients with Alzheimer's disease show a progressive, multivariate, and irreversible deterioration in their cognitive ability. Different aspects of consciousness also may be impaired, including conscious processing of information and awareness of disease condition (Salmon et al., 2005, 2006).

Cognitive impairment in Alzheimer's disease is the consequence of the functional and anatomical disruption of cortical integrity due to the progressive development of the neuropathological process. The

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availability of modern brain imaging methodologies, including positron emission tomography (PET) and magnetic resonance imaging, in combination with sophisticated experimental paradigms, has made it possible to examine in a non-invasive manner the neurometabolic bases of mental function in healthy human subjects and in patients with dementia (Salmon et al., 2005, 2006; Pietrini et al., 1996, 2000a). Because the neuropathological process may progress to affect preferentially different cortical areas in individual patients, dementia represents a valuable "natural model" to investigate the effects of distinct patterns of disruption of cortical integrity on consciousness.

In this chapter we will review what we have learned in this respect from combined behavioral and *in vivo* brain imaging studies in patients with Alzheimer's disease and frontotemporal dementia.

COGNITIVE IMPAIRMENT AND DISRUPTION OF BRAIN FUNCTIONAL INTEGRITY IN ALZHEIMER'S DISEASE

Disturbances of attention and memory are typically the first clinical manifestations in patients with Alzheimer's disease and may remain the only symptoms for a long time. Impairments in attentional and executive functions, abstract reasoning, semantic memory, visuoperceptual skills along with alterations in personality and behavior, and loss of insight into the disease condition then occur in different combinations in individual patients (Salmon et al., 2006, 2007; Pietrini et al., 1996; Grady et al., 1988; Haxby et al., 1990; Mendez et al., 1990).

Cognitive impairment is due to the insidious development of a neuropathological process characterized by the presence of senile plaques, neurofibrillary tangles, and loss of neurons and their synaptic projections (Terry and Katzman, 1983; Whitehouse et al., 1981). These neuropathological lesions affect mostly the neocortical association areas of the parietal, temporal, and frontal lobes and limbic regions and show a regional distribution that may vary among individual patients (Terry and Katzman, 1983; Braak and Braak, 1991; Lewis et al., 1987; Hof et al., 1995). Typically, the neuropathological process starts in the medial temporal lobe structures, including the entorhinal cortex and the hippocampal formation, and subsequently spreads to the neocortical association areas of the temporal, parietal and frontal lobes, leading to the disruption of various mental functions (Braak and Braak, 1991; Lewis et al., 1987; Van Hoesen et al., 1991).

Over the past three decades, many studies have been conducted with PET to measure regional cerebral glucose metabolism and blood flow in patients with Alzheimer's disease examined at rest (eyes patched, ears plugged, no sensory stimulation) as well as during a variety of cognitive tasks (see Pietrini et al., 2000a for a review). Measures of both cerebral glucose metabolism and blood flow are reliable indices of neuronal synaptic activity, as they reflect the brain's metabolic need for glucose and oxygen in order to produce adenosine triphosphate (ATP). ATP in the central nervous system is mostly required for maintenance and restoration of ionic gradients and cell membrane potentials due to electrical activity associated with action potentials and transmission of impulses from neuron to neuron (Whittam, 1962; Jueptner and Weiller, 1995). Therefore, changes in synaptical activity lead to parallel changes in the demand for ATP and, in turn, for glucose utilization and capillary blood flow in the same brain regions. Indeed, the frequency of action potentials and the rate of glucose utilization show a direct linear correlation (Jueptner and Weiller, 1995; Sokoloff, 1981; Schwartz et al., 1979; Kadekaro et al., 1985, 1987).

Overall, the PET studies conducted in several laboratories across the world have been consistent in providing the following pieces of evidence (Figure 13.1):

1. *Cerebral glucose metabolism is impaired in Alzheimer's disease*. Regional cerebral glucose metabolism measured at rest is significantly reduced in patients with Alzheimer's disease, compared to matched healthy individuals, mostly in the association neocortical areas, with a relative sparing of primary neocortical and subcortical regions and cerebellum, at least until the later stages of the disease (Pietrini et al., 1996, 2000a,b; Duara et al., 1986; Grady and Rapoport, 1992; Kumar et al., 1991).
2. *Metabolic abnormalities worsen with progression of dementia*. With progression of dementia severity, brain metabolic reductions in patients with Alzheimer's disease become more and more severe and extend to include the remainder of the neocortical mantle, with only a relative preservation of the sensorimotor and primary visual cortices, subcortical structures, and cerebellum (Pietrini et al., 2000a,b; Duara et al., 1986; Grady and Rapoport, 1992; Kumar et al., 1991). Furthermore, progression of dementia is associated with a progressive decline in the ability to increase synaptic activity in response to stimulation up to a point when, in the advanced stages of disease, there is minimal or null synaptic metabolic increment over rest, indicating that synapses in those brain regions are no longer functional (Pietrini et al., 2000c).
3. *Cerebral metabolic alterations are heterogeneous*. Metabolic abnormalities may show a different

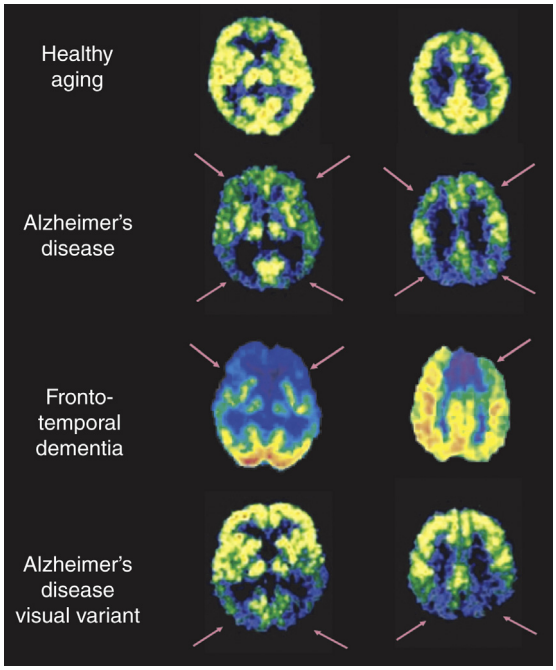

FIGURE 13.1 Regional cerebral glucose utilization as measured by PET in a healthy control subject, in a representative patient with the classical form of Alzheimer's disease, in a frontotemporal dementia patient, and in a patient suffering from the visual variant of Alzheimer's disease. Brain metabolism was determined with subjects in the resting state (eyes patched and ears plugged, no sensory stimulation). For each subject, two horizontal brain slices taken parallel and above the inferior orbito-meatal line are shown, approximately 45 mm left side of the figure, and 90 mm right, respectively. For each individual slice, the right side corresponds to the right side of the brain, and the left to the left side, respectively. Compared to the healthy control subject, the patient with Alzheimer's disease shows reduction in cerebral glucose metabolism in the frontal, temporal, and parietal neocortical association areas, the patient with frontotemporal dementia in prefrontal and frontotemporal areas, and the patient suffering from the visual variant of Alzheimer's disease in occipitotemporal areas with a sparing of the most anterior portion of the brain. *Source: Adapted from Pietrini et al. (2000a).*

topographic distribution across individual patients, that is, some patients show a greater involvement of the left hemisphere whereas others may show more reductions in the right hemisphere. For instance, in a large sample of Alzheimer patients in the mild to moderate stages of dementia severity, a principal component analysis showed that the most common pattern involved metabolic reductions in superior and inferior parietal lobules and in the posterior medial temporal regions. A second subgroup had reduced glucose utilization in orbitofrontal and anterior cingulate areas, with a relative sparing of parietal regions. Metabolic reductions affected the left hemisphere more selectively in a third group of patients, and the fourth group had reduced metabolism in frontal, temporal, and parietal cortical areas (Grady et al., 1990).

4. *Patterns of cerebral metabolic alteration are related to patterns of cognitive impairment*. These patterns of metabolic alterations are related to and may even precede and predict the pattern of cognitive impairment in individual patient subgroups (Haxby et al., 1985, 1990). For example, the group of patients showing reduced metabolism in orbitofrontal cortex, a brain region known to be involved in the modulation of aggressive behavior (Pietrini et al., 2000d), showed agitation, anger outbursts, inappropriate social behavior, and personality and mood changes (Grady et al., 1990). Similarly, patients with visuospatial dysfunction showed greater right- than left-hemisphere hypometabolism while patients with language deficits had predominant left-hemisphere hypometabolism (Haxby et al., 1985, 1990; Kumar et al., 1991). In some cases, the pattern of cerebral hypometabolism could be detected several months before the appearance of the related picture of cognitive impairment.

   Furthermore, the relative pattern of regional distribution of metabolic alterations is maintained across progression of dementia severity, that is, patients who reveal a greater left- than right-hypometabolism in the early phases of the disease will show a relatively more severe left-hemisphere metabolic impairment also in the later/end stages, indicating that the pathological process maintains a relatively more selective effect on the same brain regions across the different stages of dementia progression (Grady et al., 1988; Haxby et al., 1988, 1990).
5. *Distinct cognitive and cerebral metabolic features characterize clinical subtypes of Alzheimer's disease*. Clinical subtypes of Alzheimer's disease are characterized by the predominant involvement as well as the relative sparing of selected cortical regions as compared to the classical form of Alzheimer's disease. For instance, patients with the so-called *visual variant of Alzheimer's disease* (Pietrini et al., 1996; Furey-Kurkjian et al., 1996) show a remarkable metabolic impairment of posterior cortical regions, including primary visual cortex—which is typically spared in Alzheimer's disease—in contrast with a peculiar sparing of the more anterior parts of the brain, including the entorhinal cortex and the limbic cortex which, on the contrary, are considered the hallmark feature in patients with classical Alzheimer's disease (Hof et al., 1993). Compared to the classical Alzheimer patients, the visual variant patients show early and prominent disturbances of visual consciousness, including visual agnosia and Balint's syndrome but retain awareness of their cognitive deficits until the end

stages of the disease, as we will discuss later (Pietrini et al., 1996; Furey-Kurkjian et al., 1996).

6. *Regional functional connectivity is altered in Alzheimer's disease*. The correlation coefficient between the regional cerebral metabolic rates for glucose (as well as between regional cerebral blood flow values) provides a measure for the functional association between distinct brain regions (Horwitz et al., 1987). The pattern of such interregional correlations reflects the integrated cerebral activity either at rest or during a specific cognitive task. Patients with Alzheimer's disease show abnormal patterns of interregional metabolic correlations both in the resting state and during the cognitive tasks (Salmon et al., 2007; Horwitz et al., 1987; Azari et al., 1992, 1993; Pietrini et al., 1993a; Grady et al., 2001; Rombouts et al., 2005; Wang et al., 2006; Allen et al., 2007). The alterations in functional connectivity may even precede the onset of significant reductions in regional glucose metabolism and indicate the progressive disruption of cerebral integrity in patients with Alzheimer's disease.

In summary, the dementing process in patients with Alzheimer's disease—as well as in patients with other forms of dementia, such as frontotemporal dementia or Lewy Body Disease, as we will discuss later—is associated with a heterogeneous and progressive disruption of the brain's functional integrity. These alterations can be measured in individual patients as dementia worsens, and the patterns of abnormal neural functioning can be related to distinct changes in cognition and consciousness. These observations can shed new light on the understanding of the brain's functional architecture that makes us aware of our surroundings and of ourselves.

HOW THE BRAIN GETS LOST IN DEGENERATIVE DEMENTIA

This disease is worse than cancer, is among the most frequent comments that a clinician may hear from family members of a patient with dementia. *Because it destroys the self*, is usually the explanation that follows. And indeed, this is what happens in patients with Alzheimer's disease or with another similar dementia syndrome. Patients become more and more unaware of the world and of themselves, until they eventually slide into a meaningless present with a fading past and no future. If this is the inevitable final destination for all patients who reach a severe stage, they may take different routes to arrive there. While these routes certainly share some way and intersect, they also present some distinctive features, so that by following step by step the descending march of patients along these pathways, scientists may begin to understand how the brain gets lost.

In degenerative diseases, the patients progressively lose not only their cognitive or behavioral abilities, but also the awareness of the functioning of these abilities, and frequently the awareness of their own incapacities. For example, patients with frontotemporal dementia may know that eating too much is bad for health (preserved common knowledge), but they cannot avoid eating quickly (impaired awareness of the application of common knowledge in society), and they do not see themselves as behaving abnormally (impaired awareness of self-behavior).

LOSS OF INSIGHT VERSUS LOSS OF SIGHT

Lack of awareness for the disease, anosognosia, or loss of insight are used interchangeably to indicate the patient's inability to properly recognize their clinical condition, which is frequently observed in patients with Alzheimer's disease or frontotemporal dementia (Salmon et al., 2005, 2006, 2008; Kalbe et al., 2005; Ruby et al., 2007). Anosognosia may be limited to some aspects of the disease and may be more pronounced for cognitive deficits than for behavioral dysfunction (Salmon et al., 2008; Kotler-Cope and Camp, 1995). Also, patients may be aware of their symptoms but not of their severity. In some patients with Alzheimer's disease, insight into the disease condition may be retained until the most advanced stages of dementia whereas in others may be lost since the early phases (Salmon et al., 2005, 2006; Pietrini et al., 1996), which may explain why correlations between loss of insight and dementia severity or illness duration in patients with Alzheimer's disease remain controversial (Sevush, 1999; Gil et al., 2001; Zanetti et al., 1999). In patients with frontal lobe dementia, the inability to accurately perceive changes in behavior and personality is indeed one of the core clinical features that lead to the diagnosis (O'Keeffe et al., 2007).

Recently, Salmon and colleagues (2006) investigated the neural basis of anosognosia for cognitive impairment in a large sample of patients with Alzheimer's disease in the mild to moderate range of dementia severity by examining the relation between regional cerebral glucose utilization at rest and two measures of anosognosia. They used a research questionnaire that covered 13 cognitive domains, including memory, attention, temporal and spatial orientation, abstract thinking, word finding, calculation, and others (Kalbe et al., 2005) and obtained three dependent variables: the caregiver evaluation of the patient's

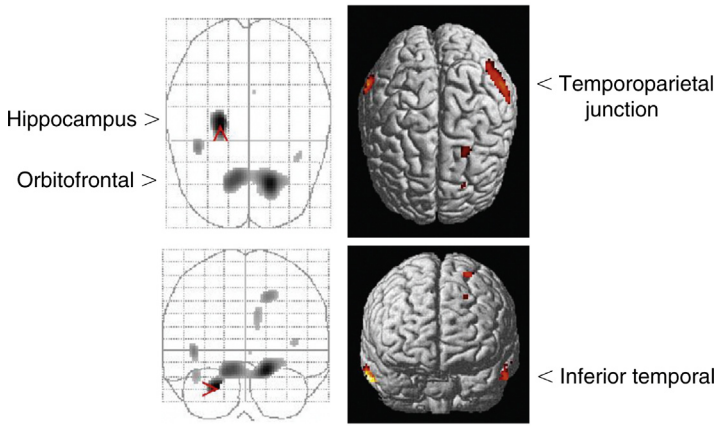

FIGURE 13.2 PET data showing brain region with a significant correlation between glucose metabolism and anosognosia for cognitive impairment in patients with Alzheimer's disease. Anosognosia was measured in 209 Alzheimer's disease patients either using patient's (erroneous) assessment of cognitive performances (on the left side) or by a discrepancy score between patient's and relative's assessment (on the right side). Correlations were obtained in cerebral glucose metabolic data measured in the resting state. *Source: Adapted from Salmon et al. (2006).*

cognitive dysfunction, the self-evaluation by the patient, and the discrepancy score between the caregiver's and the patient's evaluation. In this manner, the authors had two measures of anosognosia: the self-assessment of cognitive impairment by the patient and the discrepancy score between caregiver's and patent's evaluation (Cummings et al., 1995). The patient's self-assessment alone has the major limitation that a score indicating mild cognitive difficulties would be reported both by Alzheimer patients with truly mild cognitive deficit and by more severely demented patients with anosognosia. The discrepancy score, on the contrary, makes it possible to distinguish these two cases, as patients with anosognosia will receive a greater impairment score by their caregivers. It is interesting to note that a high discrepancy score, indicating greater informant than self-reported cognitive difficulties, in individuals with mild cognitive impairment (MCI) but no dementia may predict the risk of conversion to Alzheimer's disease (Tabert et al., 2002).

Correlation analyses showed that impaired self-evaluation was related to reduced cerebral glucose metabolism in the right parahippocampal cortex and in the orbitofrontal cortex. The discrepancy score was negatively correlated with glucose metabolism in the temporoparietal junction, inferior temporal cortex, and left superior frontal sulcus, that is, patients with greater lack of insight in their cognitive deficits had lower glucose utilization in these associative cortical regions (Salmon et al., 2006) (Figure 13.2). These findings are particularly robust, as the authors examined over 200 patients with Alzheimer's disease recruited at many European centers and the analyses took into consideration several potential confounding variables.

In another study, patients with Alzheimer's disease failed to activate the ventromedial prefrontal cortex as elderly controls did for assessing self-relevance of personality traits adjectives (Ruby et al., 2008). As a whole, these results indicate that anosognosia in Alzheimer's disease is associated with dysfunction in frontal and temporoparietal associative structures that subserve perspective taking on self and others (Frith and Frith, 2003). This observation is also consistent with data from patients with frontotemporal dementia who show an early loss of insight and have a selective functional damage in frontal and temporal cortical regions, with a relative sparing of the posterior parts of the brain, including the parietal lobes that are instead severely damaged in Alzheimer's disease (O'Keeffe et al., 2007; Salmon et al., 2003). In a recent study in a group of patients with frontotemporal dementia, the degree of metabolic activity in the left temporal pole was related to the severity of anosognosia for behavioral changes in social situations, in the sense that the greater was the lack of insight, the lower was glucose utilization in the temporal pole (Ruby et al., 2007) (Figure 13.3). Dysfunction of the left temporal pole would prevent patients with frontotemporal dementia accessing a script of their social behavior to correctly assess their personality.

On the other hand, demented patients with Alzheimer's disease who show a metabolic preservation of the frontal and temporal cortex maintain insight into their condition until the very late stages of dementia. This preservation can be appreciated particularly in a relatively rare subgroup of patients with the so-called visual variant of Alzheimer's disease (Pietrini et al., 1996; Levine et al., 1993; Graff-Radford et al., 1993). The peculiarities of the clinical, neuropsychological, and neurometabolic pictures make it possible to separate these patients from the classical Alzheimer patients. Unlike the classical Alzheimer patients,

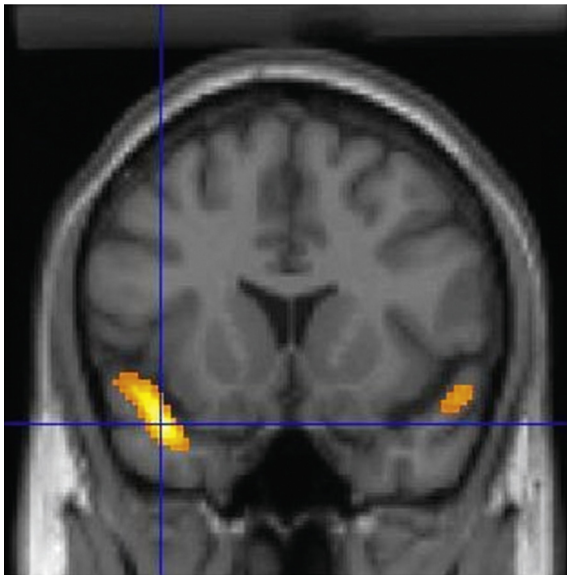

FIGURE 13.3 PET data showing a significant correlation between glucose metabolism in the superior temporal pole and anosognosia for behavioral changes in patients with frontotemporal dementia. Anosognosia was measured by a discrepancy score between 16 frontotemporal dementia patients' and their relative's assessment of social behavior. Correlations were obtained in cerebral glucose metabolic data measured in the resting state. *Source: Adapted from Ruby et al. (2007).*

patients with the visual variant of Alzheimer's disease show early and prominent disturbances of visual abilities in the absence of any memory difficulties. They often have difficulties driving, including being unable to drive in a straight line, to maintain the proper distance from other cars, or to make turns without hitting the curb (Levine et al., 1993; Graff-Radford et al., 1993). The clinical picture may progress to include difficulties in keeping track of a written line while reading, in reading an analog watch, decreased hand–eye coordination, alexia, agraphia, visual agnosia, and Balint's syndrome (oculomotor apraxia, optic ataxia, visual inattention, and simultagnosia). These visual difficulties are usually the first and only complaint for a long time and remain prominent also after the appearance of other cognitive deficits and until the end stages of the disease (Pietrini et al., 1993b, 1996; Furey-Kurkjian et al., 1996). From a brain metabolic point of view, patients with the visual variant of Alzheimer's disease show reduced cerebral glucose utilization bilaterally in primary and association visual cortices, posterior cingulate, parietal, superior and middle temporal areas, and sensorimotor cortex relative to matched healthy control subjects. In contrast, they have no reduction in frontal, inferior temporal, anterior and posterior medial temporal regions, or subcortical structures. In comparison to matched patients with the classical form of Alzheimer's disease, the visual variant patients show significantly reduced glucose utilization in bilateral occipital association cortex, and significantly higher metabolism bilaterally in frontal, anterior medial temporal and anterior cingulate regions, inferior temporal, and basal ganglia (Pietrini et al., 1996). Thus, in this pathology where the dementing process spares frontal and temporal cortex, patients do not lose awareness of their condition and of the severity of their cognitive deficits.

On the other hand, patients like those with the visual variant of Alzheimer's disease clearly show impairment in distinct aspects of consciousness, often from the initial phases of the disease. While these patients retain insight, moral judgement, abstract thinking, and even a sense of humor, they progressively lose the ability to visually perceive the surrounding world. They may describe one by one each detail of what they see in front of them, recognize the colors and even faces of people but be unable to grab the whole scene, so that a picture of a living room only becomes a boring list of pieces of furniture.

Neuropathological examinations of patients with the visual variant of Alzheimer's disease indicate a specific loss of functional connections between the primary visual cortex and regions in the posterior parietal cortex, whereas the connections between the primary visual cortex and the inferior temporal cortex do not appear more damaged than in typical Alzheimer's patients (Hof et al., 1990, 1993). Thus, the pattern of cerebral metabolism found in our sample of patients with the visual variant of Alzheimer's disease mirrors at a functional level, and extends to earlier stages of disease, the cerebral distribution of neurofibrillary tangles seen at autopsy (Hof et al., 1993) and indicates a more selective involvement of the dorsal visual pathway and a relative sparing of the ventral pathway. Considered the distinctive functional organization of the dorsal and ventral visual pathways in the human brain (Haxby et al., 1994, 2001), this preferential involvement of the dorsal visual pathway and the relative sparing of the ventral one may account for the visuospatial dysfunction shown by these patients and the preservation of their ability to perceive a face or a color (Pietrini et al., 1996).

While neuropathological examinations have confirmed the diagnosis of Alzheimer's disease in most patients with these prominent visual disturbances (Hof et al., 1993; Levine et al., 1993; Victoroff et al., 1994), other neurodegenerative disorders, such as Creutzfeldt–Jakob disease and subcortical gliosis, may give rise to similar patterns of visual impairment early in the course of the disease (Victoroff et al., 1994). These different dementia syndromes which preferentially affect the more posterior parts of the brain have in common also a much greater incidence of visual

hallucinations than that usually observed in patients with typical Alzheimer's disease, suggesting that visual hallucinations may be related to the prominent loss of integrity in the occipital-parietal visual cortical structures that occur in these patients (Holroyd and Sheldon-Keller, 1995; Holroyd et al., 2000).

HALLUCINATIONS IN DEMENTIA: WHERE DO THEY COME FROM?

Visual hallucinations are the most common type of hallucinations in patients with Alzheimer's disease and are significantly associated with disorders of the visual system, including decreased visual acuity and visual agnosia, and appear to be related to the neuropathological damage in the occipital cortex (Holroyd and Sheldon-Keller, 1995; Holroyd et al., 2000). A structural magnetic resonance imaging study showed a significantly reduced ratio of occipital volume to whole brain volume in Alzheimer patients with visual hallucinations as compared to age- and severity-matched Alzheimer patients without visual hallucinations (Holroyd et al., 2000). Alteration in visual association cortical areas (Brodmann area 18 and 19) rather than in primary calcarine cortex (BA 17) seems to be more relevant in the genesis of visual hallucinations. Indeed, complex visual hallucinations have been induced by the electrical stimulation of BA 19 but not BA 17 (Foerster, 1931) and, in patients with Alzheimer's disease, neurofibrillary tangles and neuritic plaques are 20–40 times more concentrated in visual association cortical areas than in calcarine cortex (Lewis et al., 1987).

Visual hallucinations, however, are also relatively frequent in Lewy Body Disease, the second most common form of dementia in the elderly, in which Lewy bodies, which are the hallmark neuropathological feature of Parkinson's disease, are found in the cortex and subcortical structures of the affected patients (Perry et al., 1990). Patients with Lewy Body Disease present a fluctuating cognitive impairment that affects memory and higher cognitive functions, recurrent visual hallucinations and Parkinsonian-like motor disturbances (McKeith et al., 1992). Disturbances of consciousness include mainly visual hallucinations associated in some instances with paranoid delusions. Auditory hallucinations are rare (Perry et al., 1990; Perry and Perry, 1995). These disturbances of consciousness have been found in up to 70% of patients with Lewy Body Disease, and thus are much more frequent than in patients with Alzheimer's disease who present these features only in 5–30% of the cases (Perry et al., 1990; Perry and Perry, 1995; Ropacki and Jeste, 2005). Typically, visual hallucinations are complex images with people and animals and may be very vivid and rich in detail. Neuropathological studies have found no correlation between visual hallucinations or the other mental disturbances and the distribution of Lewy bodies or senile plaques in the cortex of the affected patients (Perry and Perry, 1995). This lack of correlation is not surprising, as the fluctuating nature of the cognitive impairment and alteration of consciousness in these patients suggest that the true cause of visual hallucinations may be not at an anatomical level, but rather be linked to some other mechanisms than simply the prominent functional and anatomical disaggregation of visual cortical areas found in patients with the visual variant of Alzheimer's disease or similar dementing disorders.

Lewy Body Disease is associated with a remarkable impairment of the cholinergic neurotransmission due to the loss of acetyltransferase, the enzyme that synthetizes acetylcholine (Perry and Perry, 1995; Perry et al., 1993). The cholinergic impairment in the neocortex of patients with Lewy body dementia is greater than that found in patients with Alzheimer's disease, in which archicortical deficits (e.g., in the hippocampal regions) are more severe. A neurochemical study in patients with Lewy body dementia showed that acetyltransferase activity in the parietal and temporal cortex of patient with visual hallucinations was less than 20% of healthy control values whereas patients who did not experience visual hallucinations had values around 50% of the normal range (Perry et al., 1993).

Cholinergic activity in the cortex modulates signal-to-noise in neuronal firing, by increasing the firing of postsynaptic potentials and increasing their probability of being distinguished from background cortical activity (Drachman and Sahakian, 1979). In an fMRI study in young healthy subjects we showed that pharmacological potentiation of cholinergic neurotransmission by physostigmine, which inhibits the enzyme acetylcholinesterase, led to an improved processing of information in visual cortical areas as compared to the placebo condition during a visual working memory task (Furey et al., 2000). Specifically, neuronal activity, as measured by the fMRI-BOLD signal, during cholinergic enhancement was significantly greater in response to the target visual stimuli (faces to be remembered) than to the distractor (a nonsense scrambled picture). In contrast, during placebo, neural responses to the target and the distractor were identical (Furey et al., 2000) (Figure 13.4). Thus, cholinergic modulation appears to be important in allowing the brain to select relevant information from the background (Furey et al., 2008) (Figure 13.5).

It has been proposed that the visual hallucinations that occur in patients with impaired cholinergic neurotransmission may be due to an inability to suppress

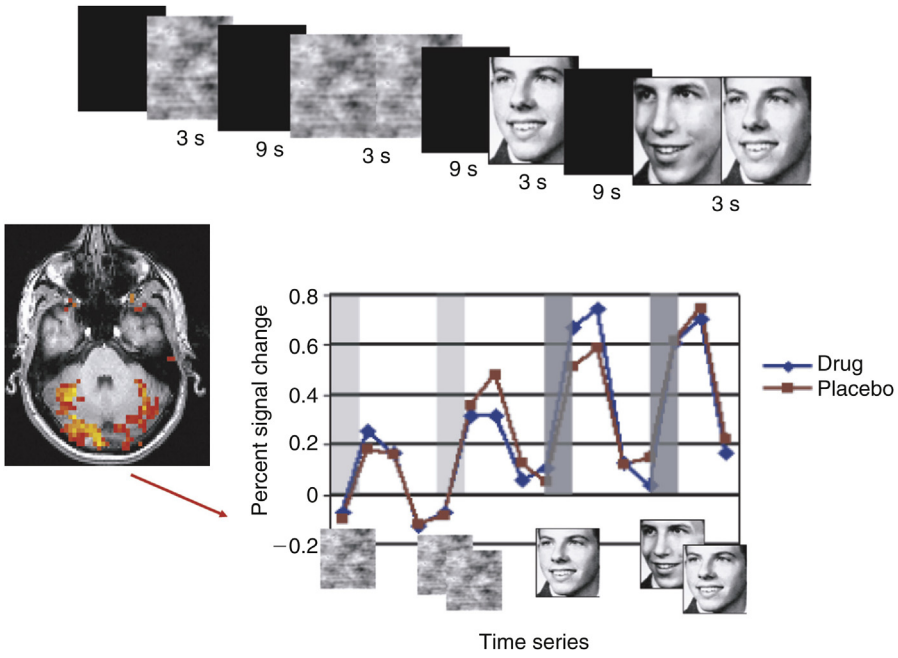

FIGURE 13.4 Effects of cholinergic potentiation on neural response in ventral extrastriate visual cortical areas that are activated in a visual working memory for faces task. (Top) For each scan series, subjects performed a task that alternated between a sensorimotor control item and a working memory item. For each working memory item, a picture of a face was presented for 3 s, followed by a 9-s delay, and by a 3-s presentation of two faces. Subjects indicated which of the two faces they had seen previously. For each sensorimotor control item, identical scrambled faces were presented to control for spatial frequency, brightness, and contrast, and subjects were instructed to press both buttons simultaneously when shown two scrambled faces. (Bottom) An axial slice of ventral occipital cortex from a single representative subject is reported with the voxels that showed a significant response to the task. The panel shows time series averaged across subjects, hemispheres, and all trials for the voxels that showed significant face-selectivity or encoding-selectivity. The figures show percent change in signal from baseline. The light gray bars indicate when the control stimuli (scrambled faces) were presented and the dark gray bars illustrate when the memory stimuli (faces) were presented. Data acquired during placebo (red) and during physostigmine (blue) are shown in each panel. Note the enhancement in signal-to-noise neuronal response during cholinergic potentiation as compared to the placebo condition. *Source: Adapted from Furey et al. (2000).*

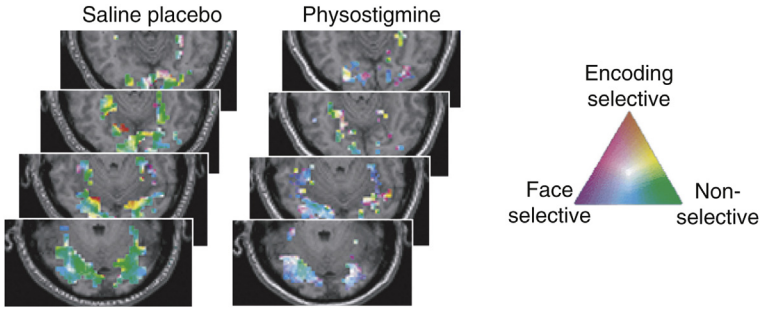

FIGURE 13.5 Improved signal-to-noise neuronal response during cholinergic enhancement. Axial slices of the ventral temporo-occipital cortex from representative subjects during a working memory for faces task during the administration either of placebo saline or physostigmine. Face-selective voxels are shown in blue, encoding-selective voxels in red, while non-selective voxels in green. Note the generalized increased selectivity of response across the ventral temporo-occipital cortex during cholinergic enhancement as compared to administration of placebo saline.

intrinsic cortical activity during perception (Perry and Perry, 1995). According to this hypothesis, when the cortical cholinergic modulation is diminished, there would be a failure to focus on the most relevant information and to maintain an appropriate conscious stream of awareness, with the intrusion of irrelevant information from the subconscious into consciousness (Perry and Perry, 1995). The role of the cholinergic deficit in the genesis of visual hallucinations is also supported by the evidence that the pharmacological blockade of muscarinic receptors results in complex and vivid visual hallucinations which resemble those

experienced by patients with Lewy body dementia (Perry and Perry, 1995). On the other hand, visual hallucinations respond, at least to some extent, to treatments with cholinergic potentiating drugs (Onofri et al., 2007; Nestor, 2007).

Considering that cholinergic terminals are spread across the whole cortex, one could speculate that the diffuse deficit in cholinergic activity may precipitate a functional impairment in those cortical regions that are more selectively targeted by the neuropathological process. Thus, in patients with a predominant compromission of the occipital and parietal association cortical areas, the lack of an efficient cholinergic modulation might lead to visual hallucinations (Nestor, 2007) whereas in others it might determine the appearance of different alterations of consciousness.

DELUSIONAL MISIDENTIFICATION SYNDROMES

The term delusional misidentification syndromes refers to a false belief in doubles and duplicates, and includes the syndromes of Capgras (Capgras and Reboul-Lachaux, 1923) and Fregoli, their variants, reduplicative paramnesia and other reduplicative phenomena.

Reduplication of person is the belief that a person has more than one identity, or that someone has been replaced by a close double. Patients with temporal reduplication are convinced that a current event or period of time has already taken place in the past, a sort of prolonged déjà fait experience. The first case of reduplicative paramnesia, reported by Pick (1903), was a woman with senile dementia who was convinced that there were two clinics in Prague, an "old" clinic and a "new" one, each directed by a Professor Pick. In the Capgras syndrome, the patient is convinced that a family member or a close friend is an impostor.

Delusional misidentification syndromes are frequently observed in patients with severe close head traumas and have been described also in association with vascular and neoplastic lesions and epilepsy, especially when affecting the frontal and temporal poles especially of the right hemisphere (Mentis et al., 1995).

Delusional misidentification syndromes are selective, that is, only a few people, places, or objects are misidentified, and also specific, that is, the misidentification always regards the same person and only that person. For instance, if a patient is convinced that her husband is an impostor, she will recognize him and only him as an impostor and will not misdesignate any other person.

From a brain functional point of view, demented patients with Alzheimer's disease and delusional misidentification syndrome showed a significant metabolic impairment in bilateral orbitofrontal and cingulate cortex and sensory association areas, including the superior temporal and inferior parietal cortex, as compared to severity-matched patients with Alzheimer's disease but no delusional syndrome (Mentis et al., 1995). The pattern of metabolic alterations is consistent with the hypothesis that delusional misidentification syndromes may be rooted in a disruption of the connections between multimodal cortical association areas and paralimbic and limbic structures (Price and Mesulam, 1985) that are thought to relate intermodal sensory information with emotional tone to validate experience (Pandya and Seltzer, 1982). This could result in a sensory–affective dissonance so that the patient perceives the stimulus but not its emotional significance and relevance to the self (Mentis et al., 1995). In the example cited above, the patient with Capgras delusion may recognize her husband but she does not feel that he is really her spouse.

Delusional misidentification syndromes are often associated with other delusions, anosognosia, environmental disorientation, depersonalization, and derealization, in which similar mechanisms of disrupted sensory–emotional connection may occur. As we discussed earlier, patients with anosognosia reveal a cerebral metabolic impairment that greatly overlaps with that found in patients with delusional misidentification syndrome.

IN DEMENTIA LOSING THE MIND MAY BE LOOSENING THE BRAIN

Impairments in cognitive and behavioral functions and disturbances of consciousness in patients with Alzheimer's disease or other neurodegenerative dementias are not only the consequence of the well-documented functional and morphological compromission of specific cortical regions but also of a breakdown in the brain functional connectivity. While most studies have used univariate analyses that considered each region separately and therefore could only determine specific metabolic alterations as compared to healthy control subjects, a few studies have employed a more sophisticated approach to examine the patterns of interregional metabolic correlations in the human brain and the alterations associated with the dementing process (Azari et al., 1992, 1993; Pietrini et al., 1993a; Grady et al., 2001; Allen et al., 2007; Greicius et al., 2004).

Overall, these studies have demonstrated that in the brain of patients with Alzheimer's disease there is a decrease in functional interactions among several brain regions, indicating a disconnection likely due to lesions

in the associative pathways. Alterations in the pattern of functional interactions have been showed between anterior and posterior cortical regions, between the right and the left hemisphere (Horwitz et al., 1987, 1995) and between medial temporal structures, including the hippocampus and the entorhinal cortex, and the posterior cingulate cortex (Greicius et al., 2004) as well as between the hippocampus and a number of regions in frontal, temporal, and parietal cortex (Grady et al., 2001; Wang et al., 2006). Because the medial temporal cortex typically is affected early and heavily in the course of dementia in patients with Alzheimer's disease, the disruption of functional connectivity between its neural structures and other cortical systems not only may account for the early and prominent memory deficits but might also contribute to some of the non-memory cognitive disturbances. From a neurometabolic viewpoint, reductions in glucose metabolism in several cortical association areas, including the posterior cingulate cortex, which is commonly affected since the initial stages in patients with Alzheimer's disease (Minoshima et al., 1994), could be the consequence, at least in part, of the altered connectivity with medial temporal structures (Grady et al., 2001; Greicius et al., 2004). This is supported by the observation that neurotoxic lesions in the entorhinal and perirhinal cortex in baboons determine a reduction in cerebral glucose metabolism in regions of the temporal, parietal and occipital association cortex and in the posterior cingulate cortex (Meguro et al., 1999). More recently, however, the posterior cingulate cortex was shown to be part of three principal components in patterns of cerebral metabolism obtained from 225 patients with Alzheimer's disease (Salmon et al., 2007). Posterior cingulate activity covaried not only with metabolism in the Papez's circuit, comprising the medial temporal lobe (PC2, 12% of the total variance), but it was also independently correlated with activity in the posterior cerebral cortices (PC1, 17% of the variance) and in frontal associative cortices (PC3, 9% of the variance), confirming a central role of the posterior cingulate region in Alzheimer's disease. Moreover, all principal components were correlated with controlled cognitive performances, suggesting that impaired interregional functional connectivity is related to decreased controlled (conscious) processes in Alzheimer's disease.

Disruption of the physiological functional connectivity in patients with Alzheimer's disease has been found not only in the default-mode network, that is, in the resting brain, but also while the brain is engaged in tasks that involve attention, perception, and memory (Grady et al., 2001; Horwitz et al., 1995; Bokde et al., 2006). Horwitz and colleagues (1995) found that during a face perception task healthy older control subjects showed a strong correlation between neural activity in the occipitotemporal region and in the right prefrontal cortex, whereas in the patients with Alzheimer's disease the activity in the right prefrontal area was correlated only with activity in other regions of the prefrontal cortex, indicating that the interaction between the face processing area in extrastriate visual cortex and the frontal cortex was disrupted. A similar loss of functional connectivity was found in patients with Alzheimer's disease when they were asked to perform a visual working memory for faces task in which memory delay was varied systematically (Grady et al., 2001). While healthy controls engaged a correlated functional network that included prefrontal, visual extrastriate and parietal areas and the hippocampus across the different memory delays, the Alzheimer patients failed to show any correlated activity between the prefrontal cortex and the hippocampus at any memory delay and had reduced correlations between the prefrontal cortex and visual cortical areas (Grady et al., 2001).

The results of these studies are consistent with and extend the observation of a disconnection between anterior and posterior cortical regions in the brain of patients with Alzheimer's disease found in the resting state (Horwitz et al., 1987; Azari et al., 1992; Greicius et al., 2004).

Moreover, in patients in the initial or even in the preclinical phases of Alzheimer's disease abnormal patterns in the brain interregional metabolic correlations may be detectable even before significant changes in the neural activity of any specific cortical or subcortical structure become evident (Azari et al., 1992, 1993; Pietrini et al., 1993a). This suggests that the earliest effects of the developing neuropathological process are those of loosening the brain's functional integrity which therefore affects the ability to rapidly integrate information that corresponds to the definition of consciousness itself (Tononi, 2001, 2005). In this respect, a recent fMRI study showed that the functional connectivity between the hippocampus of both the hemispheres and posterior cingulate cortex present in healthy elderly controls was absent in individuals with amnestic MCI, who have a high risk of developing Alzheimer's disease but do not have dementia (Sorg et al., 2007).

To conclude with a more positive note, we should say that the brain is not merely a passive bystander in the neuropathological process. So, if many cortical regions loosen their functional connections, other areas may tighten theirs in an attempt to compensate for the losses attributable to the degenerative process, at least temporarily. In a study of semantic and episodic memory, patients with Alzheimer's disease in the mild stage of dementia recruited a unique and more

extensive network of regions that included bilateral prefrontal and temporal cortex as compared to matched healthy subjects who showed a functional network between frontal and occipital areas in the left hemisphere (Grady et al., 2003). Of note, neural activity in this network of regions was correlated with the ability of patients to perform the memory tasks, indicating that this extended functional network may compensate for the disruption of the physiological network by facilitating the interactions among posterior storage regions and prefrontal areas that mediate executive and monitoring functions (Grady et al., 2003).

CONCLUSIONS

Awareness of what happens around us and of ourselves is rooted in the complexity of the functional and anatomical networks of the thalamocortical system that enables the brain to rapidly integrate information (Tononi, 2001, 2005). If the integrity of the thalamocortical connectivity is altered, cognition and consciousness are impaired as well. Patients with dementing disorders represent a precious model to investigate the effects of the disruption of different brain structures and networks on the distinct components of consciousness. In this chapter, we have reviewed work by our own labs and other groups that have combined clinical, neuropsychological, neurochemical and post-mortem examinations with *in vivo* brain functional and structural measures in patients with Alzheimer's disease and other dementia syndromes in the effort to gain novel insights in the neural mechanisms that sustain consciousness and its dysfunction.

We have shown that distinct components of consciousness may be affected or spared selectively in individual patients according to the differential development of the neuropathological process within the brain. Sophisticated functional brain imaging studies have proved that the earliest effects of the neuropathological process are the loosening of the connections that enable different parts of the cortex to communicate among themselves. This impairment of functional connectivity is detectable even before any specific cortical region may reveal any metabolic or functional sign of dysfunction. Impairments in cholinergic neurotransmission, as seen in patients with Alzheimer's disease or Lewy Body Disease, may compromise neuronal information processing by decreasing signal-to-noise.

Obviously, here we have considered only some aspects of the topic and several important issues have only been mentioned or even ignored, including evidence from other forms of dementia or other neurological disorders, the role of other neurotransmitter systems and so on. While many questions remain widely open, the journey that scientists have begun in the dementing brain is providing new stimulating insights on how the mind arises and falls (Pietrini, 2003).

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CHAPTER

14

Brain–Computer Interface Based Solutions for End-Users with Severe Communication Disorders

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OUTLINE

BRAIN–COMPUTER INTERFACES (BCI)—WHAT, WHY, AND WHERETO

Brain–computer interfaces (BCI) allow for interaction between the brain and artificial devices (for reviews see e.g., Kübler et al., 2001a; Wolpaw and Wolpaw, 2012a). They use brain activity "to change the ongoing interactions between the central nervous system and its environment" (Wolpaw and Wolpaw, 2012b, p. 5) (Box 14.1). Neuronal activity recorded with invasive or non-invasive technology (see Box 14.1) is sampled and processed in real-time and converted into commands to control an application for communication (Sellers et al., 2014; Zickler et al., 2011), gaming (Höhne et al., 2014; Holz et al., 2013a), painting (Holz et al., 2015; Zickler et al., 2013), Internet surfing (Bensch et al., 2007; Mugler et al., 2010), or neuroprosthetic control (Collinger et al., 2013; Rohm et al., 2013). In recent years, BCI-controlled treatment to improve diminished or lost function has received increased attention (Ang et al., 2014; De Vico Fallani et al., 2013; Kaiser et al., 2012; Ramos-Murguialday et al., 2013).

A variety of non-invasive technologies for monitoring brain activity may serve as the input signal for BCI. In addition to electroencephalography (EEG), these include magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and optical imaging (functional near infrared spectroscopy, fNIRS). As

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BOX 14.1

BRAIN–COMPUTER INTERFACES—UNLEASHING THE POTENTIAL OF THE BRAIN

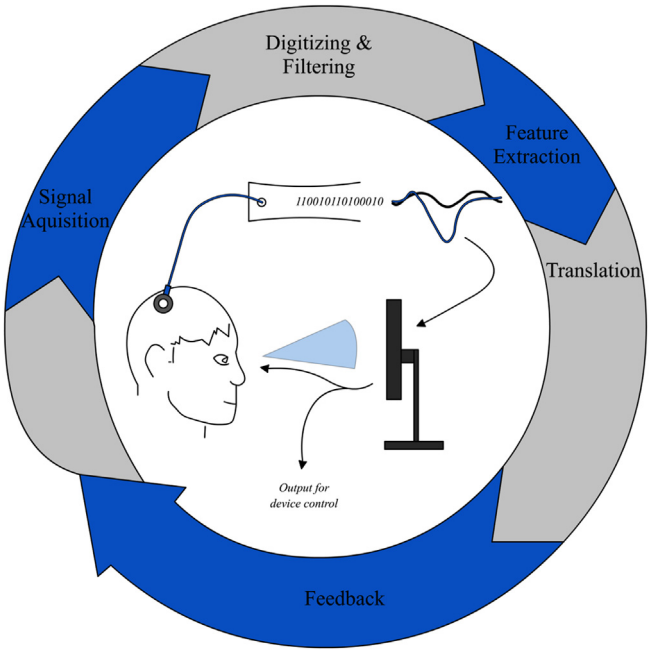
A BCI system can be depicted as a series of functional components (Kübler and Neumann, 2005; Mason and Birch, 2003). The starting point is the user, whose intent is coded in the neural activity of his or her brain (input). The end point is the device, which is controlled by the brain activity of the user (output) and provides him or her with feedback of the current brain activity (closed-loop systems).

Invasive recording methods allow us capturing action potentials of single neurons with electrodes containing neurotrophic factors inducing nerve growth into the glass tip (Kennedy and Bakay, 1998) or patterns of neural activity with few or multiple electrode arrays (Collinger et al., 2013; Hochberg et al., 2006, 2012). Electrocorticography uses electrode grids or strips sub- or epidurally and impressive spelling speed has been reported in a patient with epilepsy (Brunner et al., 2011), however, not those with SCD (Hill et al., 2006; Ramos-Murguialday et al., 2011); all invasive methods require surgery.

The *non-invasive recording* of the electroencephalogram (EEG) is the most frequently used method in BCI research. Components most often used are sensorimotor rhythms (Blankertz et al., 2007; Kübler et al., 2005; McFarland et al., 2010; Neuper et al., 2003; Wolpaw and McFarland, 2004) and event-related potentials as a response to sensory, auditory or tactile stimulation, namely the P300, a positive deflection in the EEG about 300 ms after presentation of rare target stimuli within a stream of frequent standard stimuli (Kaufmann et al., 2013b; McCane et al., 2014; Nijboer et al., 2008b), and steady state visually or tactually evoked potentials (Müller-Putz et al., 2005, 2006).

The acquired signals are digitized and subjected to a variety of feature extraction procedures, such as spatial filtering, amplitude measurement, spectral analysis, or single-neuron separation (Krusienski et al., 2012). In the following step a specific algorithm translates the extracted features into commands that represent the users' intent (McFarland and Krusienski, 2012). These commands can either control effectors directly such as robotic arms or indirectly via cursor movement on a computer screen to activate switches for interaction with the environment or to select items, words, or letters from a menu for communication or to surf the Internet.

Recently, the framework for possible applications of BCI has been extended beyond the so far dominating application to REPLACE lost function after injury or disease (Wolpaw and Wolpaw, 2012b). BCIs can be used to RESTORE lost function, for example, restoring grasp function via BCI-controlled functional electrical stimulation or decoding of motor patterns after high spinal cord injury (Collinger et al., 2013; Rohm et al., 2013); to ENHANCE behavior above the natural limits (Gruzelier et al., 2010, 2014); to SUPPLEMENT, that is, to provide an adjunctive means of action; and to IMPROVE impaired natural function, such as experienced after stroke or in children with attention deficit hyperactivity disorder (Arns et al., 2014; Ramos-Murguialday et al., 2013).



MEG and fMRI are demanding, tied to the laboratory, and expensive, these technologies are more suitable for addressing basic research questions, for short-term interventions to localize sources of brain activity, and for modifying brain activity in diseases with known neurobiological dysfunction. However, fMRI-driven BCIs have enabled proof-of-principle communication in patients diagnosed with vegetative state/unresponsive state (Monti et al., 2010). In contrast, EEG, fNIRS, and some invasive systems are portable, and thus may offer practical BCI for communication and control in daily life. In recent years, the concept of the so-called hybrid BCI has become more popular; the idea being to combine any available signal for communication

and interaction into an input for BCI (Lorenz et al., 2014; Müller-Putz et al., 2011; Riccio et al., 2015). Depending on the current state of the end-user (see Box 14.3), eye movement, residual speech, electrical muscular activity (as measured with electromyography, EMG), or different brain signals can be used to control assistive technology (AT).

In this chapter, we will give an overview of approaches to BCI with different input signals. Wherever possible, we will restrict our summary to studies with patients who are in potential need of a BCI for communication and interaction, that is, patients with a severe communication disorder (SCD). We will dedicate a section to non-visual BCIs, which are of particular relevance to the many SCD patients who may experience impaired vision. Further, we will outline the potential of BCI for increasing cognitive performance, which may also be relevant for SCD patients because such training may be applied prior to BCI-based interaction. If we are aiming at providing a useful assistive tool for patients who are otherwise unable to interact, the community must adopt a user-centered approach to research and development (Box 14.3), and valuable information has already been collected on the mandatory pre-requisites of BCI for daily usage. We will end our chapter with an outlook into the future.

BCI FOR COMMUNICATION AND CONTROL—TARGETED PATIENTS

A variety of neurological diseases with different neuropathologies may lead to the so-called locked-in state (LIS) in which only residual voluntary muscular control is possible. In "classic" LIS, vertical eye movement and eye blinks remain intact (Smith and Delargy, 2005). Incomplete LIS permits remnants of motion (Bauer et al., 1979) whereas in the complete locked-in state (CLIS), patients lose all ability to move and communicate (Kübler and Birbaumer, 2008). Hemorrhage or ischemic stroke in the ventral pons can cause a LIS, which includes tetraplegia and paralysis of cranial nerves (Chia, 1991). The syndrome can also occur due to traumatic brain stem injury (Smith and Delargy, 2005), encephalitis (Acharya et al., 2001), or tumor (Breen and Hannon, 2004). Other causes of the LIS are degenerative neurological diseases, the most frequent being amyotrophic lateral sclerosis (ALS), which involves a steadily progressive degeneration of central and peripheral motoneurons (Andersen et al., 2005).

In many studies, it has been shown that patients with severe motor impairment and LIS were able to achieve control over a BCI and to use this ability for communication (e.g., Birbaumer et al., 1999) or other interaction (Holz et al., 2015; Rohm et al., 2013). In all these patients, communication and control was restricted due to motor impairment and a BCI can provide a key for the conscious brain locked into a paralyzed body (Kübler and Neumann, 2005). Patients with disorders of consciousness (DOC) may be phenomenologically similar to LIS patients. The reason for their non-responsiveness is, however, quite different. In DOC, the connections between the brain and its motor effectors may be intact, yet the commanding centers and their interaction are disturbed or destroyed due to traumatic or non-traumatic brain injury (Laureys et al., 2004).

Many studies with DOC patients use passive stimulation paradigms to infer cortical processing (Bekinschtein et al., 2009; Kotchoubey et al., 2005). Patients are confronted with auditory or tactile stimulation and the related brain activity is recorded with EEG or fMRI. From a comparison with the brain activity seen in healthy volunteers with the same stimulation, it is deduced how much cerebral processing is maintained (King et al., 2013). Impressive abilities—in relation to the brain injury—were found in those studies, including semantic differentiation of auditorily presented sentences (Kotchoubey et al., 2013; Owen et al., 2005; Risetti et al., 2013). The question whether conscious and intentional processing is still possible and may not be expressed due to motor impairment, aphasia, akinesia, or disturbed arousal cannot be answered with such paradigms. For this purpose, so-called active paradigms are needed, which require from the subject active mental processing of the presented stimuli in order to elicit an expected brain response (Balconi et al., 2013; Herbert and Kübler, 2011; Owen et al., 2006). The final proof of conscious information processing can be achieved with BCI-driven interaction in which the subject gets involved in voluntary, goal-directed, and meaningful communication. The years between the first and second edition of this book have yielded significant insight into the problems and prospects of BCI application in this field, which will be addressed in the subsequent chapter.

Despite the variable disease etiology, the affected patients are very similar such that they can hardly communicate, have no control over limb movement, depend on intensive care, are artificially fed and often also ventilated. Taken together, the common denominator of these patients is their extreme difficulties to communicate and interact with their environment, that is, a SCD.

BRAIN–COMPUTER INTERFACING IN PATIENTS WITH SCD

In the following sections, we will give a summary of BCI research with patients. Work with BCI for purposes other than to replace and improve impaired or lost function (see Box 14.1), and with animals will not be included; the reader is referred to existing reviews

(e.g., Wolpaw and Wolpaw, 2012a). Work with healthy subjects will only be included to explain the history of the BCI and its application of interest. We will also focus on BCIs with potential for daily life application in SCD patients and all studies reported in more detail were conducted either at hospital, rehabilitation centers, or at home, that is, not in the laboratory, but in a real world environment adding to the external validity of the reported results. Although currently more relevant for neuroprosthetic control than for communication, and not anywhere near application in daily life, we will dedicate one short section to the invasive approach because it is a relevant field of BCI research. For end-users with SCD the most urgent need is a reliable, functional, and easy-to-use means of communication (Huggins et al., 2011; Zickler et al., 2009); BCIs for restoring lost limb function will only be mentioned when appropriate. Depending on the input signal, BCI control requires learning to modulate a specific component of the EEG. Neurofeedback, as provided with BCI, is a type of biofeedback that allows users to learn to regulate some aspects of their own brain activity measured with respective sensors that are connected to an output display (Kamiya, 1971; Sharon, 2013). In this respect, BCIs, especially those based on EEG signals, provide a powerful tool to inform the user about his or her own brain activity by real-time feedback, thus representing the technological substrate for learning mechanisms on how to manipulate one's own brain activity in a therapeutic manner (Huster et al., 2014).

Non-Invasive BCI for Replacing Lost Function

Non-invasive BCI use the electrical activity of the brain (EEG) recorded with single or multiple electrodes from the scalp surface as input signal for BCI control. Albeit reports exist about communication with SCD patients using fMRI as input signal (Monti et al., 2010), those approaches are not an option for practical BCIs in daily life. Participants are presented with stimuli or are required to perform specific mental tasks while the electrical activity of their brains is recorded. Relevant EEG features are extracted and can then be fed back to the user by the so-called closed-loop BCI (Box 14.1). Specific features of the EEG are either regulated by the BCI user (slow cortical potentials (SCP), sensorimotor rhythms (SMR)) or are elicited by sensory stimulation (event-related potentials (ERP)). Further, controlling an application with a BCI poses workload on the end-user because attention is required to produce or elicit the respective brain response and to control the application which requires deliberate, goal-directed behavior (Kübler and Neumann, 2005).

SCP as Input Signal for BCI (SCP-BCI)

The vertical arrangement of pyramidal cells in the cortex is essential for the generation of SCP. Most apical dendrites of pyramidal cells are located in cortical layers I and II. Depolarization (i.e., increased excitation) of the apical dendrites giving rise to SCP is dependent on sustained and synchronized afferent intracortical or thalamocortical input to layers I and II, and on simultaneous depolarization of large pools of pyramidal neurons (Birbaumer et al., 1990). The SCP amplitude recorded from the scalp depends upon the synchronicity and intensity of the afferent input to layers I and II. A strong relationship between self-induced changes in cortical negativity and reaction time, signal detection, and short-term memory performance has been reported in several studies in humans (Birbaumer et al., 1990).

SCD patients diagnosed with ALS, chronic Guillain-Barré Syndrome, muscular dystrophy, cerebral paresis, and post-anoxic encephalopathy were included in studies with the SCP-BCI (Kübler and Birbaumer, 2008). Significant control of the BCI was achieved within several training sessions and patients were able to use this ability for communication, which necessitated regulating the SCP amplitude with at least 70% accuracy (Kübler et al., 2001b). To learn regulation of the SCP amplitude, participants are usually required to "move" a cursor displayed on a screen in one of two targets. Movement in two directions is achieved with negative and positive SCP amplitude shifts as compared to an individual baseline (Kübler et al., 1999). The only instruction given is to closely watch and try to find the best strategy for the cursor movement by trial and error; successful cursor movement is reinforced at the end of each trial with a smiling face or otherwise salient reward thereby following operant conditioning principles (Kübler et al., 2004). Although the SCP-BCI takes quite a while until patients are able to communicate, messages of considerable length were communicated by SCD patients (Birbaumer et al., 1999; Neumann et al., 2003). The number of training sessions needed to achieve significant cursor control was moderately predictive for the time needed to achieve criterion level control (Kübler et al., 2004); other reliable predictors could not be found (Neumann and Birbaumer, 2003). Learning occurred in the early stages of training and patients remained stable around the performance level achieved in the first 10–20 training sessions (Kübler and Birbaumer, 2008; Kübler et al., 2004; Neumann and Birbaumer, 2003). Having predictors of BCI training outcome is desirable, because training with patients is a substantial effort for both patients and trainers.

In summary, regulation of the SCP-amplitude can be achieved by patients with SCD. SCP-BCI training may require a substantial amount of time, but has the

advantage that it can be initiated without the presence of an a priori classifiable brain response. Following a shaping schedule (Kübler et al., 2001b), every response in accordance with the task requirement has to be positively reinforced (operant conditioning). SCP-BCI was used for verbal communication and internet surfing: all the links of one website were assigned to either the top or bottom half of the screen. The number of links per half was divided after selection until a single link was presented for selection (Karim et al., 2006). The use of SCP as input signal is currently not implemented in BCI settings with patients due to the low information transfer rate, which takes into account the available number of possible selections and the time needed for a selection. However, a future BCI offering a variety of input signals to the end-user of which the best individually suitable can be selected, SCP may encounter a revival, specifically with respect to improving impaired function—we will refer to this option below.

SMR as Input Signal for BCI (SMR-BCI)

SMR include mu-rhythm usually with a frequency of 10 Hz (range 8–12 Hz) often mixed with a beta (around 20 Hz) and a gamma component (around 40 Hz) is recorded over sensorimotor cortices, most preferably over C3 and C4 (Chang et al., 2011). Spreading to parietal leads is frequent and is also seen in patients with ALS (Kübler et al., 2005). The SMR is related to the motor cortex with contributions of somatosensory areas such that the beta component arises from the motor, the alphoid mu-component from sensory cortex. SMR desynchronizes with movement, movement imagery, and movement preparation (event-related desynchronization—ERD), and increases or synchronizes (event-related synchronization—ERS) in the post-movement period or during relaxation (Pfurtscheller and Lopes da Silva, 2011). Thus, it is regarded as "idling" rhythm of the cortical sensory region.

Operant learning of SMR regulation is achieved through activation and deactivation of the central motor loops. To learn to modulate the power of SMR, patients are also presented with feedback, for example, cursor movement on a computer screen in one or two dimensions (Figure 14.1) (Pfurtscheller et al., 1997; Wolpaw and McFarland, 2004) and are instructed to imagine a movement of, for example, fingers or feet. To achieve localized ERD and ERS it is important to imagine the respective movement kinesthetically (Neuper et al., 2005). In a so-called screening session, the participants are required to imagine left hand, right hand, and foot movement to determine which imagery yields the best distinguishable neuronal patterns, albeit recently a calibration-free approach to SMR-BCI has been suggested (Kindermans et al., 2014). Here, the classifier is built while the subject is using the BCI and

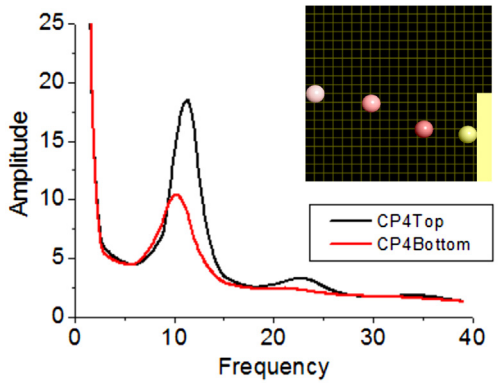


FIGURE 14.1 SMR-BCI: During each trial of one-dimensional control, end-users are presented with a target consisting, for example, of a red vertical bar that occupies the top or bottom half of the right edge of the screen and a cursor on the left edge (top). The cursor moves steadily across the screen, with its vertical movement controlled by the SMR amplitude. Patients' task is to move the cursor into the target which turns yellow when hit. Cursor movement is indicated by the circles during feedback of SMR amplitude, only one circle is visible. Low SMR amplitude following movement imagery moves the cursor to the bottom bar while high SMR amplitude following thinking of nothing in particular ("relaxation") moves the cursor toward the top bar. Cursor movement into different targets can also be achieved by different movement imagery (e.g., left vs. right hand or feet vs. hand movement). Bottom: Amplitude of the EEG as a function of frequency power spectrum averaged across 230 trials separated by task requirement (top vs. bottom target). Black line indicates frequency power spectrum when the cursor has to be moved toward the top target; red line when the cursor has to be moved toward the bottom target. A difference in amplitude can be clearly seen around the 10 Hz SMR peak.

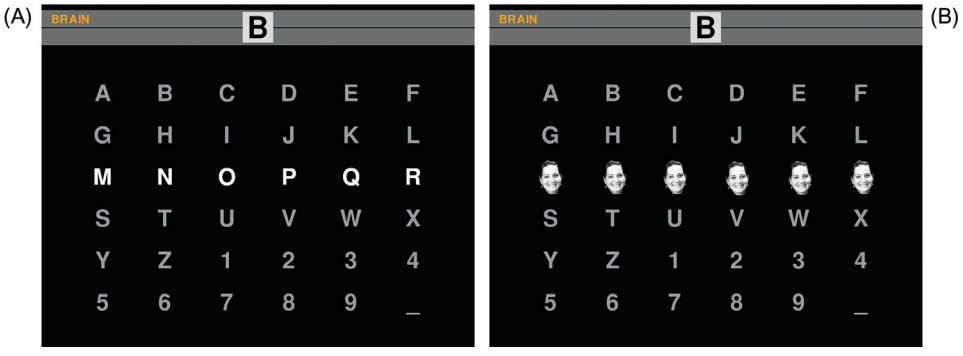
errors made at the beginning—due to a not yet individually adapted classifier—can be corrected post-hoc after the classifier has learned to distinguish the individual imagery related brain activation pattern. Using the SMR-BCI, it was shown that ALS patients were able to achieve SMR regulation of more than 75% accuracy within less than 20 training sessions (Kübler et al., 2005). Neuper and colleagues (2003) reported results of a patient with infantile cerebral paresis, who was trained over a period of several months with the SMR-BCI. The patient was trained with a two-target task. Eventually, the targets were replaced by letters and the patient could spell, using a so-called "virtual keyboard." The spelling rate varied between 0.2 and 2.5 letters per minute. Although this rate may seem slow, Neuper and colleagues showed for the first time that SMR-BCI could provide communication for patients with SCD. During training of this patient, a telemonitoring system was implemented allowing the experimenter to control and supervise BCI training from the laboratory (Müller et al., 2003). This is particularly important if patients wish to use a BCI for daily communication, and are located far away from the BCI laboratory (see Box 14.2).

Leeb and colleagues presented ten potential end-users of BCI with communication and interaction

BOX 14.2

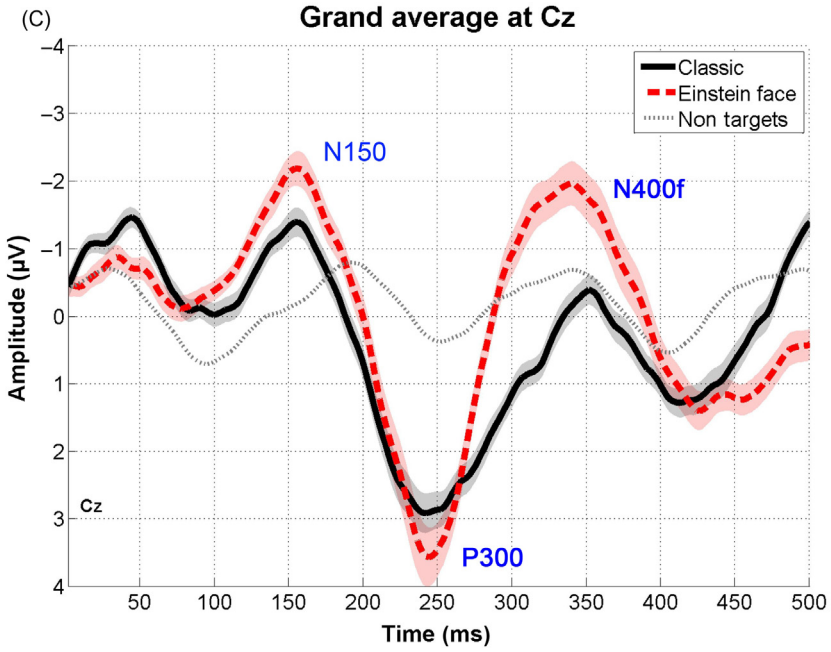
THE FACE SPELLER AND BRAIN PAINTING

ERP-BCI: for communication with an ERP-BCI, users are typically presented with matrices in which each of the matrix cell contains a character or a symbol. "A" depicts a 6×6 letter matrix. This design becomes an oddball paradigm by firstly, intensifying each row and column for 100 ms in random order and secondly, by instructing participants to attend to only one of the cells. In one sequence of flashes (one flash for each row and each column), the target cell will flash only twice constituting a rare event compared to the flashes of all other rows and columns and will therefore elicit a P300 (Farwell and Donchin, 1988). Selection occurs by detecting the row and column, which elicit the largest P300 (Krusienski et al., 2006). The ERP-BCI does not require self-regulation of the EEG. All that is required from the end-users is that they are able to focus their attention and gaze on the target letter albeit for a considerable amount of time. The better the ERPs to targets can be distinguished from the EEG in non-target trials, the faster the communication. Instead of intensifying rows and columns, face stimuli can be overlaid as shown in "B," leading to two additional ERPs, namely the N170 and N400f depicted in "C." These contribute to better classification and, thus, faster communication in healthy subjects and those with SCD alike (Holz et al., 2015; Kaufmann et al., 2013b). The face stimulation was also included in the so-called Brain Painting application that is controlled by an ERP-BCI. As seen in "D," the cells of the matrix provide commands for cursor position on the virtual canvas (were the object is to be placed), objects (square, circle, blob), opacity, grid size (determines the distances between objects), and colors. Several steps are necessary before the to-be-painted item appears on the virtual canvas. Objects, position, size, etc. have to be chosen, selecting the color transfers the object on the canvas. Despite quite some load, specifically on working memory, Brain Painting is used by two patients (HHEM, JT) with SCD at home without researches being present. "E" is an example of HHEM (with permission) called "Waiting for June," which she painted in spring 2013 for a visiting pregnant journalist who delivered in June 2013 "F" is the painting "Kling Klong" by JT (with permission). HHEM has had already two exhibitions with her paintings and her "The Brain of the Clairvoyant" was on the title page of Brain (http://brain.oxfordjournals.org/content/brain/136/6/local/front-matter.pdf). To date, HHEM painted for more than 400 and JT for more than 100 daily sessions of 1–2 h. For evaluation purposes, both end-users were asked to rate their satisfaction after each session. As can be seen in "G," in HHEM satisfaction increased with time, and lower satisfaction at the beginning of training was due to system failure, while in JT satisfaction was high from the beginning. The evaluation allows for immediate intervention if satisfaction is low, that is, the experts from the laboratory call the end-user and ask about the reason for dissatisfaction and provide support if necessary.

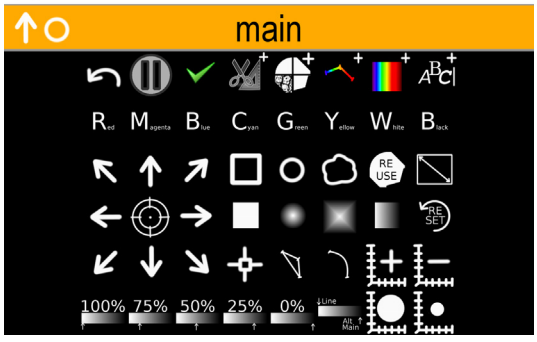


BOX 14.2 (*cont'd*)

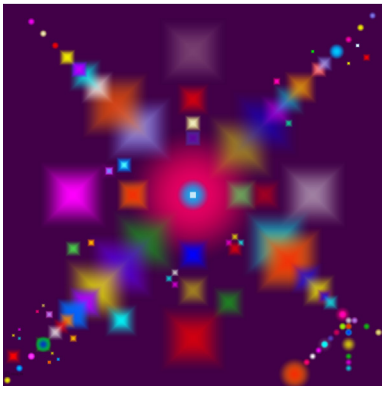
(C)



(D)

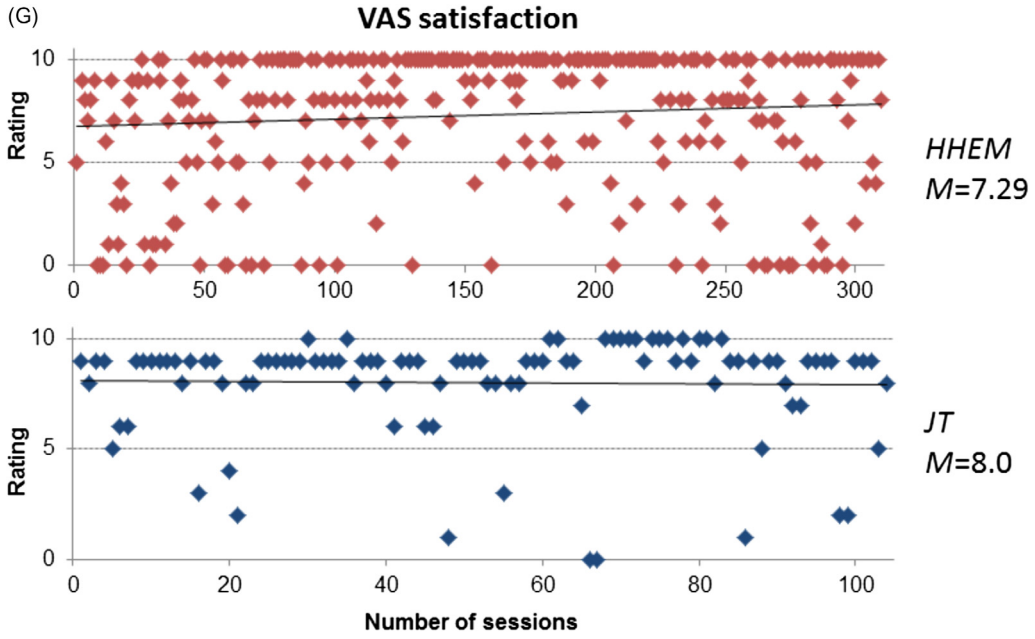


(E)



(F)

BOX 14.2 (*cont'd*)



applications; it is important to note that none of the patients could be classified as having a SCD, but nevertheless the majority of patients were severely motor disabled, such as incomplete LIS and tetraplegia after spinal cord injury. The BCI was operated in an asynchronous mode, which allows for better individual adaptation due to variable trial length, that is, the trial is terminated whenever the BCI identifies a specific brain activation pattern (Kus et al., 2012; Müller-Putz et al., 2010). As a means for exploring an environment, a telepresence robot "Robotino" was adapted to BCI control. By default, the Robotino moves forward and avoids obstacles; left and right turns are initiated by the BCI, which is controlled by two different motor imageries, for example, movement of the left and right hand. The task of the patients was to move the Robotino through a real, but remote environment, which they had never encountered before. Nine of ten patients were able to control the Robotino with high accuracy (Youden index (Youden, 1950) on average 0.87, lowest 0.7, highest 0.97 with 1 indicating perfect and 0 no control). In the future, such an application could enable SCD patients to join and participate in actions otherwise difficult or impossible. For communication, patients (five from the previous experiment) were confronted with a spelling program called "Brain Tree." In several selection steps, a single letter can be chosen and the program adapts letter presentation according to the underlying language model. The six patients who were able to control the spelling application achieved an average accuracy of 0.93 (Youden Index), but needed on average 1 min to spell two characters, which is slow as compared to the ERP-BCI that we will describe in the next section.

Modulation of SMR was also used to control a gaming application, namely the well-known "Connect 4," which was adapted to two class BCI control. It is a strategic game for two people who play against each other. Coins are placed in rows and columns with the goal to connect four coins in a row or column before the opponent can do so; the first to succeed wins the game. Four end-users with severe motor disability, two of them with SCD participated in an evaluation study. One of these was not at all able to control the BCI but for the others, performance varied between 60% and 80% of correct responses. This result is above chance level, but does not allow rapid control. Despite only moderate reliability and speed, end-users liked the game and were satisfied with the application (Holz et al., 2013a). In one SCD patient who has been in this state for 9 years after cerebral hemorrhage, communication with BCI was superior to that achieved with residual movement of his right thumb, which was often unreliable (Höhne et al., 2014).

Cruse and colleagues (2011) instructed their participants, 12 healthy volunteers and 16 diagnosed with vegetative state, to imagine toe or right-hand movement while 129-channel EEG was recorded. In nine

healthy participants the different imageries elicited a classifiable EEG pattern indicating the validity of the paradigm. In three of the 16 patients in vegetative state, toe and hand movement imagery could also be distinguished indicating that these patients were wrongly diagnosed as being in a vegetative state. In a follow-up study Cruse and colleagues (2012) instructed a patient in vegetative state for 12 years to imagine left or right-hand movement. With around 67%, offline classification of task related ERD/ERS was above chance level. Albeit, both were offline studies, that is, the loop for true BCI-based communication was not closed (see Box 14.1), they indicated the potential of EEG-based BCIs for the detection of consciousness in DOC patients. Yet, the value of this approach for active communication in patients with DOC remains to be demonstrated.

There is also some effort being made to find predictors of SMR-BCI control. Data from patients are sparse. In healthy subjects, physiological and behavioral predictors have been identified. The μ-rhythm amplitude recorded during 2 min of a relaxed state with eyes closed predicted 25% of subsequent performance (Blankertz et al., 2010). Likewise, the number of activated voxels in the middle frontal gyrus during observation and imagination of movement predicted 35% of later performance (Halder et al., 2011). Halder and colleagues divided their sample in high and low aptitude BCI users according their correct response rate. From the white matter fractional anisotropy in the cingulum/hippocampal area, 94% of the subjects could be correctly assigned to their group and around 30% of the variance in SMR-BCI performance could be explained (Halder et al., 2013c). On the behavioral level, visuo-motor coordination ability repeatedly predicted SMR-BCI performance (Hammer et al., 2012, 2014). Motivation has also been positively associated with SMR-BCI performance in healthy subjects (Kleih et al., 2013; Nijboer et al., 2008a) and SCD patients alike (Kleih et al., 2013; Nijboer et al., 2010) such that higher motivation was linked to better performance.

In summary, SMR-BCI has been successfully tested in patients with severe motor impairment and SCD and may provide control of application aiming at communication, gaming, and environmental exploration.

ERP as Input Signals for BCI (ERP-BCI)

ERP are electrocortical potentials that can be measured in the EEG before, during, or after a sensory, motor, or psychological event. They have a fixed time delay to the stimulus and their amplitude is usually much smaller than the ongoing spontaneous, EEG activity. To detect ERP, averaging techniques are used. An averaged ERP is composed of a series of large, biphasic potential shifts, lasting a total of 100–1000 ms. Several components of the ERP (e.g., N200, P300, N400) can be evoked in an oddball paradigm.

The P300 is a positive deflection in the EEG time-locked to stimuli presentation. It is typically seen when participants are required to attend to rare target stimuli presented within a stream of frequent standard stimuli, an experimental design referred to as an oddball paradigm (Fabiani et al., 1987). It is mostly observed in central and parietal regions. It is seen as a correlate of an extinction process in short-term memory when new stimuli require an update of representations (Polich, 2007).

Although the prototype of a P300-BCI (Box 14.2) was published in 1988 (Farwell and Donchin, 1988), it was not until the early years of the new millennium that ERP were tested and used in BCI for paralyzed patients (see Kleih et al., 2011). Nijboer and colleagues (2008b) were the first showing that patients with ALS can use the P300-BCI for free communication. To date, the P300 response has been demonstrated to remain stable in ALS patients over years (Holz et al., 2015; Sellers et al., 2010). Sellers and Donchin (2006) introduced a visual and auditory four-choice spelling system, which allowed patients yes/no communication, which was also tested with SCD patients diagnosed as being in a vegetative state, a minimally conscious state (MCS) or LIS. However, only one of two LIS patients achieved significant online control and for one of 13 MCS patients offline classification reached significance (Lulé et al., 2013). Obviously, the selection speed and reliability of the ERP-BCI depends on the signal-to-noise ratio, which is better the higher the amplitude and the higher number of ERPs that can be detected for classification. Thus, much effort has been invested in changing the presentation of items in the matrix (Box 14.2). For example, Sellers and colleagues introduced the so-called checkerboard mode of flashing which exposes the end-user to a random flashing of items, and, importantly, avoids flashing of adjacent items (Townsend et al., 2012). It has long been shown that most errors in the ERP-BCI are selections of items in the neighborhood of the target item. Further, the effect of the flashing rate and of flashing groups of letters instead of rows and columns has been investigated (McFarland et al., 2011). All these approaches, which were mostly tested with healthy subjects, improve performance, but no effort has yet been undertaken to integrate these results into a device that could be used with patients. A major step to improve spelling speed and reliability has been achieved when increasing the number of ERPs by introducing face stimuli (Jin et al., 2012; Kaufmann et al., 2011) (Box 14.2). Instead of simply flashing letters, a face appears which elicits the face-specific N400f (Eimer, 2000). Not only healthy participants but

also those with neurodegenerative disease of different etiology were significantly faster in spelling with the "face speller." Specifically, two end-users with disease who were unable to control the "classic" letter matrix achieved 100% control after the introduction of faces (Figure 3a in Kaufmann et al., 2013b). In a few studies, patients with SCD after brain stem stroke were provided with ERP-BCI controlled applications. The SCD patient of Schreuder and colleagues (2013) achieved 100% accuracy with a BCI-controlled photobrowser. Very recently, Sellers and colleagues (2014) could also demonstrate, in a long-term (13 months) single-case study, that the ERP-BCI can be used for communication with a spelling program. However, in another patient, the visual ERP-BCI could not be operated, probably due to nystagmus (Kaufmann et al., 2013a).

The ERP-BCI was implemented into commercially available software enabling end-users, also those with SCD, to enter text, write emails and surf the Internet (Zickler et al., 2011). Evaluation following the user-centered design (UCD; see below and Box 14.3) revealed that communication speed of the BCI was perceived too low, albeit reliability was rated as being high. Thus, to improve this prototype, the hybrid concept was introduced such that wrong selections could be corrected with an EMG switch. Location for the EMG sensors was individually chosen and patients could double their information transfer rate (Holz et al., 2013b; Riccio et al., 2015).

To enable SCD patients not only to communicate but also to express themselves creatively, the so-called Brain Painting was implemented into the ERP-BCI (Box 14.2). Instead of letters forms, opacity, cursor position, colors and other functions can be chosen from the matrix (Kübler et al., 2008; Münßinger et al., 2010). Following the UCD, the usability for this entertainment application has also been evaluated by a sample of patients with severe disease including those with SCD (Zickler et al., 2013). Despite low speed and sometimes low perceived control, participants enjoyed Brain Painting and could imagine using it in their daily life. Brain Painting was installed at the home of two patients with SCD (both locked-in due to ALS). Performance can be supervised remotely and caregivers were trained to set up the system (Holz et al., 2015). To date, patient 1 (enrolled for more than 2 years) has been painting for more than 400 daily sessions and patient 2 (enrolled for 1 year) for more than 100 and, in both patients, the BCI-controlled Brain Painting improved their quality of life (Holz et al., 2014, 2015). These results clearly indicate that if a BCI-controlled application meets the end-users needs it will be used despite obstacles such as the EEG cap, cables and low speed. Due to the importance of addressing the end-users' needs, we will dwell on this issue in the section on the UCD and Box 14.3.

Specifically in patients with neurodegenerative disease, the question arises whether control of BCI deteriorates with disease progression. Piccione and colleagues (2006) found that paralyzed patients' performance (68.6%) was worse than that of healthy participants (76.2%). In particular, those patients who were more impaired performed worse, whereas there was no difference between less impaired patients and healthy participants. However, in a long-term study from the same group and with a sample of 21 patients with ALS, a deterioration of performance with disease progression could not be confirmed (Silvoni et al., 2009). Likewise, Nijboer and colleagues (2008b) could not confirm a relationship between ERP-BCI performance and physical impairment. In long-term studies including patients who are using the Brain Painting application, no deterioration of performance occurred in a period of more than 1 year (Holz et al., 2015; Nijboer et al., 2010; Sellers et al., 2014). This result is important and encouraging considering long-term independent home use by SCD patients. Furthermore, with the "face speller" patients with severe disease and SCD achieved the same performance as healthy participants (Kaufmann et al., 2013b).

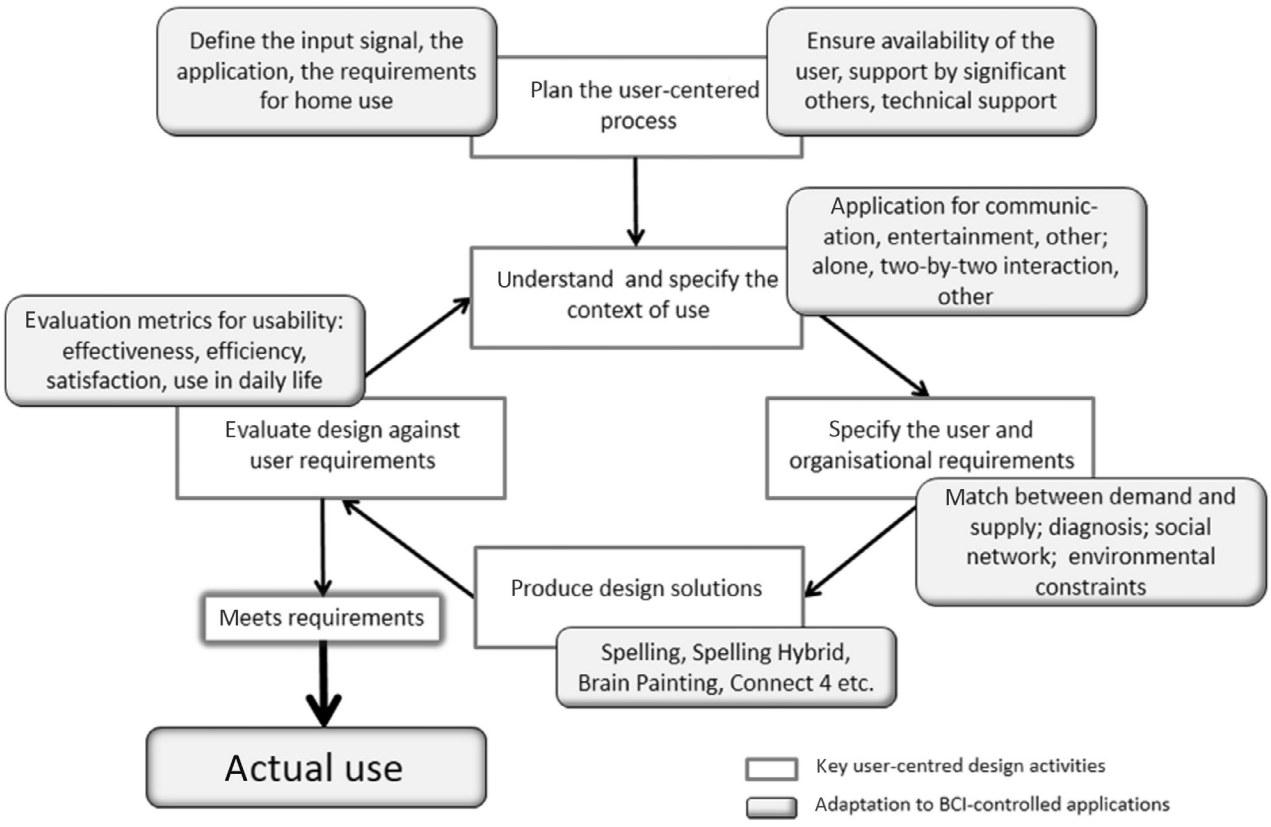
Recently BCI based on steady state visually evoked potentials (SSVEP) has also been explored in SCD patients. This approach takes advantage of the visual cortex' response to repetitive stimulation such as flickering lights. Visual stimulation with a specific frequency leads to SSVEP of the same frequency and their harmonics (Müller-Putz et al., 2005). Thus, from the frequency of the SSVEP, the BCI can deduce which flickering item on a computer screen is selected by the end-user. Combaz and colleagues (2013) compared performance with the 6×6 P300 spelling matrix and letter selection with SSVEP; in the SSVEP paradigm letters and symbols were presented in four matrices each flickering with a different frequency. After selection, the respective matrix was subdivided in four matrices and so once again, such that three selections were necessary to select a single item. Six of 11 SCD patients in the LIS tested both approaches. Patients performed better with SSVEP and judged the workload as being lower.

Pan and colleagues (2014) combined SSVEP and P300 into a hybrid approach. Two photographs were presented to the participants: their own face and an unknown face. The photographs flickered with different frequency to elicit an SSVEP while simultaneously the frame flashed at a lower frequency to elicit a P300. The task was to focus gaze on one's own photo and to count how often the frame flashed. All healthy subjects (4), one of four patients in vegetative state and one of three in minimally conscious state and one LIS performed well above chance level in all three runs. While the results indicate that patients with

BOX 14.3

THE USER-CENTERED DESIGN—BRINGING BCI TO END-USERS

The user-centered design places the end-user in the center of an iterative process of feedback and development, which implies understanding the user, the task and environmental requirements. The early and active involvement of users is encouraged and the process is driven and refined by user-centered evaluation. The whole user experience needs to be addressed preferably by a multidisciplinary team. These principles are realized in a four stages process, which implies understanding and specifying the context of use and the user requirements, producing design solutions to meet these requirements, and evaluating the designs against the requirements. This process was adapted to BCI research and development and is depicted below (Figure 5 from Kübler et al., 2014). To assess the usability of a BCI driven application, metrics for effectiveness, efficiency, and satisfaction were suggested. Effectiveness refers to how accurate and complete users can accomplish the task at hand and is expressed with accuracy, that is, how often the end-user is able to select the intended item or induce the intended command with a BCI. Often accuracy is expressed as number or percentage of correct responses. Efficiency relates the invested costs to effectiveness. The users' invested costs and time was operationalized as information transfer rated for an objective and the experienced workload as a subjective measure. User satisfaction entails the perceived comfort and acceptability while using the product and can be measured with questionnaires and visual analog scales. In a comparable large sample recently summarized by Kübler and colleagues, it was demonstrated that the user-centered design can be implemented in research and development with SCD patients (Kübler et al., 2014).



SCD may be able to control such a hybrid BCI, it remains to be demonstrated that it can be used for active communication.

All the described ERP-BCI approaches to communication require gaze control. To avoid such restriction, Acqualagna and Blankertz (2013) presented healthy participants items for selection serially and rapidly in the center of a monitor and letter selection was possible with 95% accuracy. Oken and colleagues (2014) combined this approach with a language model for letter prediction and six of nine patients with SCD of different etiology were able to select letters, but performed less well and sustained compared to healthy volunteers; unfortunately it is not specified whether the one patient diagnosed as being in CLIS was among the drop outs. Lesenfants and colleagues (2014) realized a gaze-independent SSVEP approach to accommodate for impaired eye movement and presented participants with a checkerboard like arrangement of red and yellow squares flickering at 10 and 14 Hz. Eight of 12 healthy participants and one of four patients in the LIS succeeded to communicate online.

As for the SCP- and SMR-BCI, predictors of performance have been investigated for the ERP-BCI, and here, even data with patients are available. To operate all BCI, it is necessary to focus attention for a considerable amount of time, that is, attentional resources have to be allocated to task execution. Focusing on a task while ignoring distractors requires self-regulatory capacities, and a physiological measure of such capacity is heart rate variability (HRV). This measure indicates the varying length of inter-beat intervals and is linked to parasympathetic influence on the heart rate. Within the central autonomous network, the nervus vagus connects the heart to subcortical and prefrontal areas of the brain (Thayer and Lane, 2009). Higher HRV is associated with higher flexibility to adapt to environmental and psychological requirements and better health (Thayer et al., 2012). In a sample of healthy participants, higher HRV was associated with better performance in the ERP-BCI (Kaufmann et al., 2012a). The ability to filter and focus on relevant information was linked to better performance and higher P300 amplitude in a sample of patients diagnosed with ALS (Riccio et al., 2013). Higher motivation has been linked to higher P300 amplitude and better performance in healthy participants (Brown et al., 2013; Kleih, et al., 2010), as well as in patients (Kleih and Kübler, 2014; Nijboer et al., 2010), albeit results are inconsistent, in that some studies do not find any effect of motivation (Kleih and Kübler, 2013). The amplitude of ERP, namely the N200 and P200, elicited in a simple auditory oddball task, was strongly correlated to later performance in healthy subjects and patients with severe motor impairment and those with SCD alike (Halder et al., 2013b).

Taken together, to achieve control of the SCP- and SMR-BCI is more time consuming than that of the ERP-BCI, because the latter requires no learning to regulate the EEG. With the ERP-BCI, specifically when introducing faces as stimuli, 100% accuracy and selection rates of up to 15 items per minute were achieved in healthy subjects, and most importantly, in SCD patients alike. If classifiable ERP can be detected, the ERP-BCI is the method of choice for communication and control and thus, it is the ERP-BCI, which has been used for implementation into commercially available off-the-shelf AT and for independent home use of BCI (Kübler et al., 2014).

Invasive BCI for Replacing Lost Function

Invasive recording methods have advantages in terms of signal quality and dimensionality, but issues of long-term stability of implants and protection from infection arise. Intracortical recording methods require electrodes that penetrate the brain whereas electrode grids for electrocorticography remain on the cortical surface.

Intracortical Signals as Input for BCI

Studies with invasive recordings for the purpose of communication and control with a BCI are still sparse. Kennedy and Bakay showed in few ALS patients that humans were able to modulate the action potential firing rate when provided with feedback (Kennedy and Bakay, 1998; Kennedy et al., 2000). Hochberg and colleagues (2006) implanted a multi-electrode array in the hand motor area of two patients with tetraplegia following spinal cord. Neural activity from field potentials was translated into movement of a robotic arm and continuous mouse movement on a computer monitor. Recently Hochberg and his colleagues reported on two people with a long-standing tetraplegia with no functional arm control due to brain stem stroke using an implantable BCI to perform a point-to-point reach and grasp with a robotic arm within the natural human arm workspace (Hochberg et al., 2012). The control signals were decoded from a small, local population of neurons within the motor cortex (M1) recoded from a 96-channel microelectrode array.

The Electrocorticogram as Input Signal for BCI (ECoG-BCI)

The ECoG is measured with strips or arrays epidurally or subdurally from the cortical surface. ECoG-BCI has been tested with epilepsy patients in whom electrode grids were implanted for the purpose of future brain surgery to treat epilepsy. In two SCD patients with ALS in CLIS, the instruction to imagine a movement did not lead to any classifiable signal

(Hill et al., 2006; Ramos-Murguialday et al., 2011). In the last 2 years, incremental evidence has been accumulated on the feasibility of ECoG-brain interfaces to control assistive devices. Wang and colleagues (2013) reported on a person with tetraplegia due to cervical (C4 level) spinal cord injury who was able to achieve control of a 3D cursor motion with 80% final success rate by using signals recorded with 32 electrode grid positioned subdurally, over the left sensorimotor areas. The decoding of control signals relied on the modulation of high frequency oscillations in the gamma band and SMR, occurring during the attempted movements of the right hand and arm. No side effects were reported after 28 days of the grid implantation. Further advancement in signal decoding from the sensorimotor cortex was obtained with a different approach by Bleichner and colleagues (2014). In their work, the authors postulated that neuronal activity associated with hand gestures could be reliable signals for implantable BCI as they are used in sign language. Two patients implanted with subdural ECoG electrodes for epilepsy diagnostic purposes were recorded during actual execution of hand gestures during "finger-spelling" the letters D, F, V, and Y. Offline analysis of associated signals from the contralateral hand-knob area revealed a classification of four hand gestures with accuracy of 97% and 74% (Bleichner et al., 2014).

Kapeller and colleagues (2014) proposed voluntary task related modulation of brain rhythmical oscillations. The authors focused on BCI based on visual evoked potentials and its capability as a continuous control interface for augmentation of video applications. The feasibility of this approach was tested with the participation of a patient with intractable epilepsy, during her temporarily implantation of subdural grid for therapeutic purposes. The task was to select one out of four visual targets, while each was flickering with a code sequence. The patient was able to select the established target (so-called "copy mode") with an accuracy of 99.2%.

Albeit these findings are encouraging, additional data regarding safety, reliability, longevity, and utility issues are essential in order to claim that implantable BCIs are suitable to maintain communication and control in patients with SCD.

NON-VISUAL BCI FOR RESTORING LOST FUNCTION

Almost all approaches to BCI rely on vision. Intact gaze and reliable control of eye movement are the prerequisite for all these BCI, which may render them unsuitable for SCD patients. BCI based on auditory and tactile information presentation may provide a solution to this problem. In recent years, significant effort has been devoted to improving non-visual BCIs and first data with SCD patients are available. In the following, we will present studies with auditory and tactile BCI, and with the so-called "gaze-independent" visual BCI, which still requires vision, albeit all stimuli are presented in the center of the screen; again, wherever possible, we will focus on studies that involved patients.

The first studies about auditory feedback focused on learning to regulate the SCP amplitude of the EEG. BCI control could be achieved with auditory feedback, but performance was below that of control with visual feedback (Pham et al., 2005). The superiority of visual over auditory feedback was also found in the first study that used auditory feedback of SMR (Nijboer et al., 2008a). SMR desynchronization was represented by bongo sounds and synchronization by harp sounds. With auditory feedback, healthy participants started at chance level indicating that they had no control over their SMR amplitude. After three training sessions, however, performance was the same as with visual feedback. Thus, auditory feedback required more training, but led to approximately the same level of performance at the end of training. The authors concluded that a two-choice BCI based on auditory feedback of SMR is feasible for communication, if sufficient time is provided for learning to regulate SMR. Wilson and colleagues (2012) provided tactile feedback of SMR to the tip of the tongue via a small grid with stimulators. Subjects achieved an accuracy of about 76% which was not different from performance with visual feedback.

With the accumulating evidence of higher performance with the ERP-BCI and the possibility of immediate control, that is, without a long-lasting learning procedure, research focused on non-visual ERP-based BCI (Kleih et al., 2011). Sellers and Donchin tested healthy volunteers and patients with ALS with a four-choice ERP-BCI ("four-choice speller"). Patients were presented either visually or auditorily or both with the words "yes," "no," "pass," and "end." The patients' task was to focus their attention on either "yes" or "no" and a P300 was reliably elicited (Sellers and Donchin, 2006). This paradigm was also applied to SCD patients including those with DOC, namely two in the LIS after brain stem stroke, 13 in minimally conscious state, and three in vegetative state, and participants were not only asked to select "yes" or "no," but also to answer questions. In all subjects the ERP-BCI classifier could be trained on the basis of the calibration data, indicating differential responses to standard and target stimuli. However, significant control was only achieved by one LIS patient. Offline, significant performance could be detected in one minimally conscious patient who showed no bedside command following at the time of the measurement (Lulé et al., 2013). Furdea and colleagues (2009) directly

transferred the visual speller with its letter matrix into an auditory speller. Rows and columns of the matrix were coded with numbers from one to ten and letter selection required focusing attention on the two numbers representing a letter, which imposes a high load on attention and working memory. Three patients with SCD were tested and achieved significant control, yet far below the accuracy necessary for meaningful communication (Kübler et al., 2009).

In further studies, letters were grouped, those groups were encoded by spatially distributed sounds and different sounds were applied (Käthner et al., 2013; Schreuder et al., 2011). Kleih and colleagues grouped letters such that they formed meaningful words, which are easier to memorize as no stimulus-letter association has to be learned, and severely motor impaired patients two with SCD were involved in the feasibility study. One SCD patient had a "textbook" P300 and was able to spell with 100% accuracy while the other performed above chance level yet was not sufficiently accurate to control a BCI (Kleih et al., 2014a). Halder and colleagues (2013a) coded the grouped letters with animal sounds. SCD patients were able to control the respective spelling application and, importantly, became better with training indicating a learning effect for ERP-based BCIs. A patient with SCD due to hemorrhage in the brain stem and cerebellum could operate the auditory (and tactile) BCI, but control was not stable (Halder et al., 2014). In an attempt to further simplify stimulus presentation for SCD patients, specifically those with DOC who very likely have only a short attention span, a two-stream auditory oddball paradigm was implemented. Two different tone streams with different oddballs were presented to each ear via headphones in a group of 12 patients in minimally conscious state. Online it could not be discriminated between standard and deviant tones. However, when averaging across trials offline, differential ERP-responses to standards and deviants could be detected in nine patients. These results indicate in this patient group, specific difficulties in single trial online classification, which is, however, necessary for BCI-based interaction (Pokorny et al., 2013).

Vibrotactile feedback of SMR was realized by Cincotti and colleagues (2007) and accuracy for six healthy participants was between 56% and 77%. Like for the auditory approach, the ERP-BCI appeared to be more promising. In 2010, Brouwer and van Erp transferred the oddball based BCI paradigm to the tactile modality and demonstrated that the P300 could be elicited and significantly classified in healthy subjects. Healthy subjects were also able to steer a wheelchair in a virtual building by focusing attention on tactile stimulators that represented movement directions (Kaufmann et al., 2014). Severens and colleagues (2014) applied tactile stimulation to three finger tips of healthy subjects and patients with ALS. Both groups performed equally well above chance level, but too low for BCI control (>70% accuracy Kübler et al., 2001b). These results are particularly important with respect to end-users with ALS because the skin alterations seen in such patients (Ono, 2000) did not prevent detection of tactually evoked ERPs; however, all the patients were in the earlier stages (<3 years) of the disease and, thus, had no SCD.

There is one study available that investigated a tactile ERP-BCI in a group of six SCD patients in the LIS after brain stem stroke, (Lugo et al., 2014). Tactile stimulators were placed on the left- and right-hand wrist and on the neck; the left hand was linked to "No" and the right hand to "Yes," the neck stimulator served as standard stimulus as required in an oddball paradigm. The participants had to answer questions with "Yes" or "No" and four patients achieved an accuracy of 100%. Albeit these results are encouraging, the reliability of the responses needs to be investigated.

Kaufmann and colleagues (2014) presented an SCD patient who was in a LIS after brain stem stroke, with visual, auditory, and tactile stimulation, and tactually ERP proved to be best discriminable, yet communication could not be realized due to a lack of training possibility, which indicates that BCI use does not only depend on a classifiable input signal, but also on the circumstances of the patient and the researcher. Further, albeit this patient was able to view the entire monitor on which the visual matrix was presented, accuracies achieved with any type of visual presentation of stimuli was either at chance level or below the necessary level for controlling a BCI (>70% accuracy). This included the so-called gaze-independent speller in which all stimuli are presented in the center of the screen (Acqualagna and Blankertz, 2013). Although Acqualagna and Blankertz state that this approach "...can be considered as a valid paradigm in applications with patients for impaired oculo-motor control" (p. 901), validation studies with SCD patients who may have impaired vision are lacking. There is one study with patients diagnosed with ALS who could select items, which were displayed around a central fixation cross, while focusing their gaze on the center of the screen where directional cues were presented. However, these patients were in earlier stages of the disease and still able to control their gaze (Marchetti et al., 2013). Thus, the feasibility of such "gaze-independent" visual paradigms remains to be proven with SCD patients.

Taken together, the auditory and tactile modes of stimulus presentation were implemented in BCI that used SCP, SMR, and ERP as input signal. Regulation of SCP and SMR were possible and classifiable ERPs

were elicited with the respective stimulation. Few studies with patients exist and ERPs could be elicited albeit not in all patients; in some patients with SCD even accuracies up to 100% were achieved (Lugo et al., 2014) indicating that BCIs with tactually or acoustically evoked ERPs may be feasible for SCD patients. However, the implementation for control of applications relevant for activities of daily living and the long-term stability of the ERPs, that is, the reliability, remain to be demonstrated.

BCI TO IMPROVE IMPAIRED FUNCTION

When conceiving BCI for improving brain function, that is, after stroke, traumatic brain injury and other acquired neurological disorders, the fundamental elements of BCI are maintained as in BCI for communication and control applications, that is, replacing lost function (Box 14.1). The main difference is that these systems aim at directly modifying the brain activity in order to improve some aspects of function such as motor or cognitive. In this context, the BCIs must be designed to have an appropriate feedback to either altering the ongoing brain activity or inducing or facilitating the brain plasticity phenomena, or both (Dobkin, 2007; Grosse-Wentrup et al., 2011; Pichiorri et al., 2011).

In the following section, we will provide a brief overview of the current approaches based on non-invasive BCI technology in the field of rehabilitation with special regard to motor and cognitive impairment after stroke. The major focus in post-stroke rehabilitation research has been on motor recovery of hemiplegic limbs, being the most common and disabling consequence of stroke (Langhorne et al., 2009). Present therapies mainly consist of the repeated practice of motor tasks, with the expectation that this task-specific training and practice will induce neural plastic changes and thus improve function (Zeiler and Krakauer, 2013). In this respect, BCI technology can encourage motor training and practice by offering online feedback about brain signals associated with mental practice, motor intention or attempt, or both and other neural recruitment strategies, and thus helping to guide neuroplasticity to improve recovery (Shih et al., 2012). The potential of BCI systems to improve functional motor recovery after stroke has been tested in several studies (Cincotti et al., 2012; Rea et al., 2014). In all these studies, the intentional modulation of brain signals recorded with different techniques such as EEG, MEG and fNIRS, was demonstrated to be feasible in chronic stroke patients. Up to date, the BCI technology based on volitional modulation of the EEG SMR has been the most extensively applied in combination with motor imagery (MI) practice (Prasad et al., 2010), robotic training (Ang et al., 2014) and with functional electrical stimulation (Do et al., 2012). Although most of the available results are from proof-of-concept studies, they consistently show a promising role of BCI as a strategy to enhance motor recovery after stroke. Two randomized, controlled trials (RCT) have demonstrated significant clinical advantages in large sample of severely affected chronic stroke patients when BCI was combined with robotic therapy and added on to intensive physiotherapy (Ang et al., 2014; Ramos-Murguialday et al., 2013). In a recent RCT, Pichiorri and colleagues demonstrated the efficacy of BCI-monitored MI practice as add-on intervention to usual rehabilitation care in subacute stroke patients, in terms of better hand motor functional outcome. Moreover, the observed motor functional improvement correlated with a post-training increase of the ipsilesional intrahemispheric connectivity specifically in the SMR frequency (Pichiorri et al., 2015).

To effectively encourage training and practice, the BCI design should follow the UCD and incorporate principles of current rehabilitative settings, apt to stimulate patients' engagement during a given exercise (Box 14.3). Morone and colleagues (2015) used an SMR-BCI to support the practice of MI in hospitalized subacute stroke patients that was designed and implemented according to the UCD iterative process with end-users which included rehabilitators and patients. The authors evaluated the usability of the system based on patients' psychological assessment and showed that patients ranked their motivation and satisfaction high; also their experience in being exposed to the BCI-based training was interesting and not over-challenging. Moreover, professionals positively acknowledged the opportunity offered by a BCI-assisted training to measure patients' adherence to rehabilitation, as emerged during a focus group including them, the researchers and the patients. This pilot study on usability allowed the system to be installed in the ward and to launch a large RCT to establish the efficacy on the outcome of motor recovery as an add-on intervention during the subacute post-stroke stage.

Although cognitive deficits are estimated to be present in more than 35% of patients 3 months after stroke (Hoffmann et al., 2010), little is known about the possibility of using neurofeedback procedures to promote cognitive recovery after stroke (Barker-Collo et al., 2009). Attentional deficits can be seen in more than 80% of stroke patients (Makin et al., 2013). Furthermore, a significant number of stroke patients are affected by memory and learning disabilities, visuo-spatial impairments including neglect phenomena and other cognitive disorders (Cumming et al., 2013). The state of the art treatment in most cases is reduced to a more or less individually planned cognitive retraining procedure (Cicerone et al., 2011).

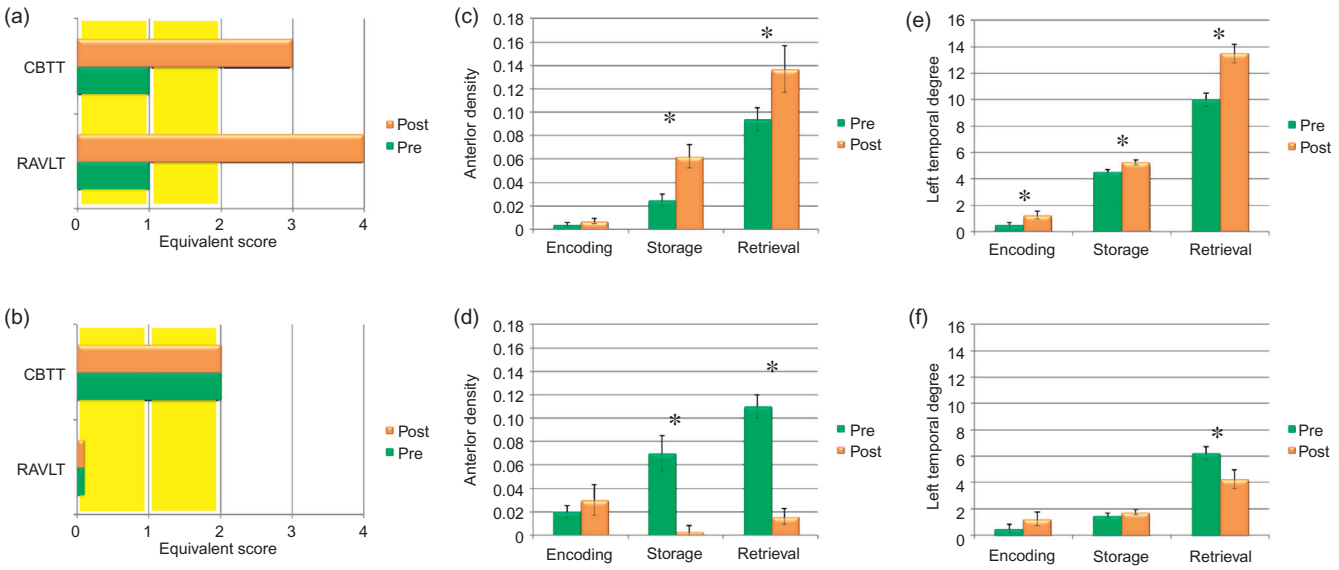


FIGURE 14.2 Neurofeedback-based intervention to target post-stroke memory disorders. Data form 2 exemplary stroke patients are illustrated. The training protocol consisted of 10 training sessions in which the patients were instructed to voluntarily increase their SMR amplitude over an established threshold. Each time the SMR amplitude exceeded the threshold for ≥ 250 ms, the participant was rewarded with points. The threshold was automatically adapted after each run on the basis of all previous runs. Cz was used as feedback electrode. Each training session lasted 25 min. Before (PRE) and after (POST) intervention, EEG scalp signals were recorded with 64 channels while patients were performing a memory task, comprising encoding, storage and retrieval phases. Patients' declarative memory and visuo-spatial short-term memory were assessed before and after the training with the Rey Auditory Verbal Learning Test (RAVLT) and the Corsi Block Tapping Test (CBTT), respectively. Time-varying effective connectivity networks were estimated for each memory phase and frequency band (defined according to individual alpha frequency) and the corresponding salient properties were derived by means of graph theory approach (Real et al., 2014; Toppi et al., 2014a). Patient A was able to learn the modulation of her SMR as indicated by the increase of SMR amplitude from 7.7 to 8.4 μV across the 10 training sessions while Patient B did not show such changes. In panels (a) and (b), the bar diagrams report the equivalent scores achieved for RAVLT and CBTT before (PRE, green bars) and after (POST, orange bars) the SMR training. Equivalent scores below 2 (in yellow) indicate a pathological condition. The panels (c)–(f), illustrate the changes in the Anterior Density and Left Temporal Degree indices (estimated in alpha band in PRE—green bars—and POST—orange bars—sessions) observed in Patient A (panels (c) and (e)) and B (panels (d) and (f)). The symbol (*) denotes a significant difference between PRE and POST session scores. Importantly, only in Patient A, who responded to the BCI training, brain network indices increased, as did behavioral performance. In both patients, thus, a concordance between physiological and behavioral results could be observed.

Gruzelier has recently reviewed a number of studies performed on the potential of (EEG-based) neurofeedback to preserve or improve cognitive function in normal and pathological aging. The conclusion was that cognitive improvement in several aspects of attention and memory function do occur following a neurofeedback training (Gruzelier, 2014). This knowledge awaits to be transferred into the field of cognitive rehabilitation after stroke. A solid step toward this application of neurofeedback was made by the EU-funded project CONTRAST (www.contrast-project.eu). The research conducted by a multidisciplinary team stems from the application of the user-centered approach to design, implement and evaluate a novel technology (Box 14.3) aiming at improving cognitive function after stroke that embeds a set of EEG-based training modules targeting attention, memory, and inhibitory control (Kober et al., 2015); a semiautomatic algorithm to provide clinicians with a tool to support the decision making in terms of planning the best possible cognitive module training for an individual stroke patient (Kleih et al., 2014b); and easy-to-use and wearable features to foster the use of such system at home (Risetti et al., 2014). Preliminary findings collected by means of a multicenter clinical study, clearly indicate that training cognitive function with specific EEG neurofeedback modules for working memory based on SMR modulation and general attention based on SCP modulation is feasible in stroke patients even during the subacute post-stroke stage (Figure 14.2) (Real et al., 2014; Toppi et al., 2014a). Further, an initial pilot study on the evaluation of the efficacy of the SMR-based training module revealed that after 1 month of training, subacute stroke patients improved their memory function as assessed by neuropsychological routine examination (Toppi et al., 2014a). This behavioral improvement was associated with specific changes in the EEG-derived brain network state elicited during a memory task execution, thus suggesting that neurofeedback training has the potential to affect brain network re-organization occurring after stroke (Astolfi et al., 2013; Toppi et al., 2014b).

Neurofeedback was also applied for cognitive rehabilitation after traumatic brain injury. According to

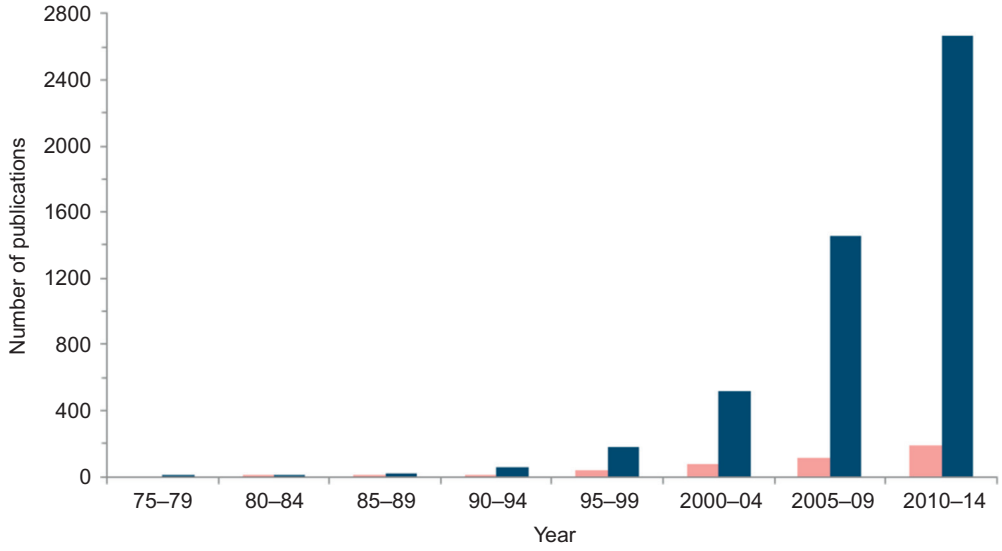


FIGURE 14.3 Number of BCI related publications per 5-year-period. Results of a coarse screening for BCI papers in pubmed. Search term was "brain AND computer AND interface*" (blue bars); for patients "AND patient*" was added (magenta bars). Columns represent simple counts per respective time period, that is, the papers were neither validated for involvement of genuine BCI for communication and control or other purposes nor for true patient participation (or simple mentioning that BCI are being developed for patients). While the overall number of BCI related publications is high and is almost exponentially increasing, those including or referring to patients are around tenfold lower, but also increasing.

May and colleagues (2013), two studies with control groups exist. Keller and colleagues (2001) provided a group of patients with mild head injury with feedback of beta activity and found significantly improved attentional capacities. Likewise, in a group of patients with mild traumatic brain injury who received individually adapted EEG frequency feedback, improvement of attention and verbal learning was found in the experimental but not in the control group (Tinius and Tinius, 2000). No studies exist which tried to implement cognitive rehabilitation with neurofeedback in SCD.

PRACTICAL BCI FOR SCD—PROBLEMS AND SOLUTIONS

BCI research has increased almost exponentially in the past 20 years while studies including end-users with disease and SCD increase only slowly from a comparably low level (Figure 14.3), owing to difficulties with access to patients, time to acquire data, reduced signal quality and artifacts, costs and the vulnerability of the target group (Kübler et al., 2014). To overcome these difficulties, the end-users of BCI technology have to be clearly defined and selected accordingly for participation in application-oriented studies. Figure 14.4 depicts a decision algorithm, which was suggested recently for such selection. Importantly, it takes into account not only the end-user but also the environment (Kübler et al., 2014). A major effort toward more precise description of potential end-user groups and the respective BCI-controlled application is currently undertaken within the EU-funded coordinating support action BNCI Horizon 2020 (http://bnci-horizon-2020.eu/). Importantly, an application cannot be developed and improved without involving the end-users. The UCD is an established procedure for developing technology for human-machine interaction which was recently adapted to BCI (Kübler et al., 2014) (Box 14.3). The UCD focuses on usability, that is, how well a specific technology suits its purpose and meets the needs and requirements of the targeted end-users. According to end-users, the most important aspects for AT are functionality, independent use, and ease of use (Zickler et al., 2009). To address these aspects, the ERP-BCI was integrated into commercially available software (Zickler et al., 2011), and the hybrid approach was adopted such that errors could be corrected with an EMG switch (Riccio et al., 2015). The calibration procedure necessary to adapt the BCI to the individual end-user and launching of the software were simplified enabling independent home use as realized with the Brain Painting application (Box 14.2) (Holz et al., 2015; Kaufmann et al., 2012b). Metrics have been suggested that allow us to assess the usability of each application in a standardized manner (Kübler et al., 2014) (Box 14.3).

For patients with SCD, specifically those with DOC, a BCI for monitoring the current state of vigilance would be desirable. Ideally, such a BCI would be constantly attached to the patient and allow for interaction whenever the patients' are sufficiently alert. For this purpose, passive and active paradigms that elicit well-established physiological responses have to be

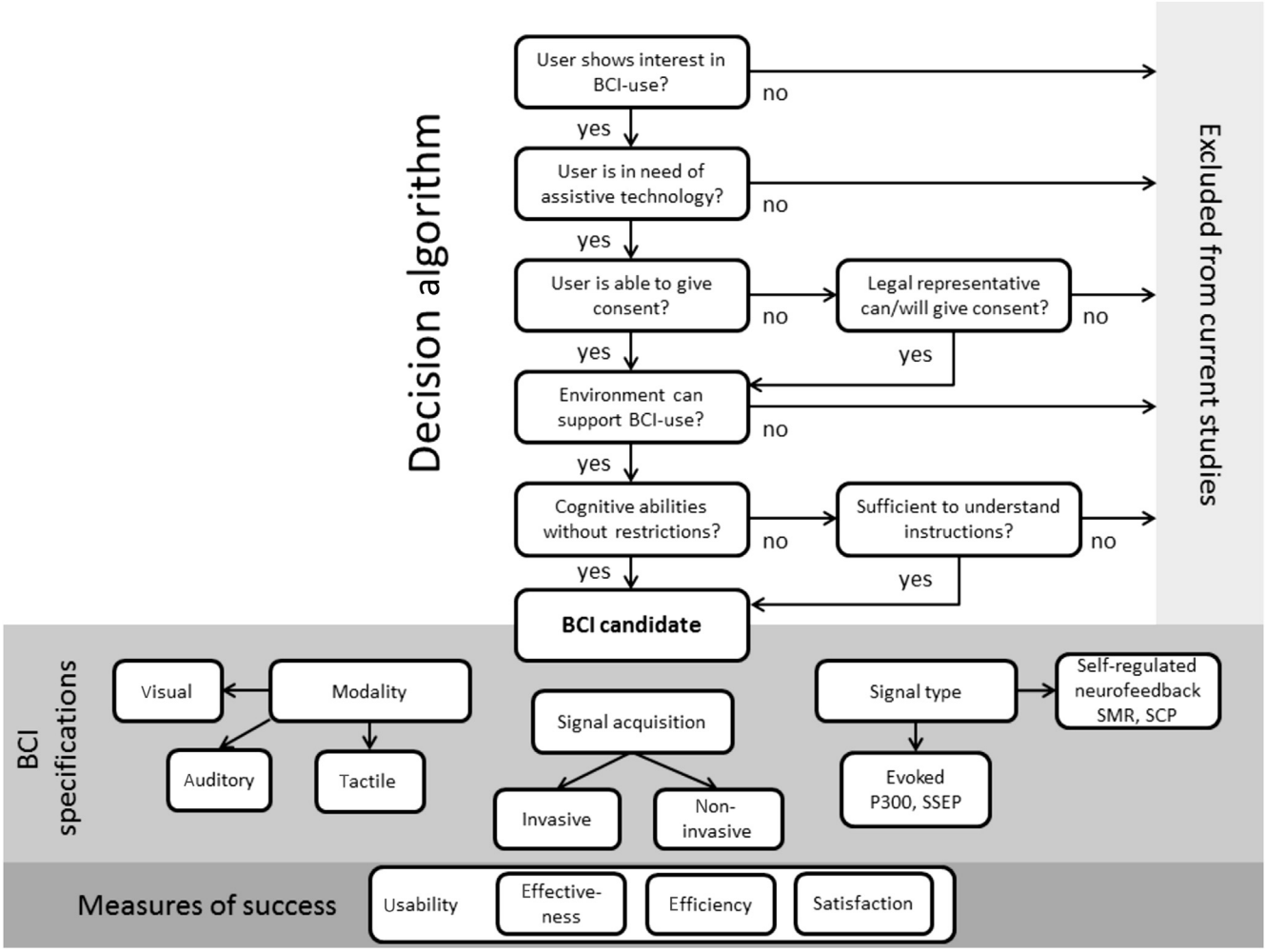


FIGURE 14.4 Decision tree for optimal selection of BCI candidates to participate in validation studies for BCI-controlled applications. *Source: From Kübler et al. (2015) with permission.*

integrated in a BCI and thoroughly evaluated with the targeted end-users. The BCI needs to allow for deliberate non-use and recognize involuntary decrease of vigilance, that is, a stand-by mode is required from which the BCI can be re-activated by the end-user without help of a third person. All available signals at any moment in time, may it be EEG changes or residual muscular movement, must serve as possible input for BCI which can be realized within the hybrid approach. Such a BCI for passive monitoring and active interaction might also prove to be a valuable tool for improving diagnosis in patients with SCD including those with DOC.

CONCLUSION

BCIs do indeed offer a tool for intervention and interaction with SCD patients, but with limitations that need to be resolved in the future. Those include the trade off between time required for data acquisition, limited attention span and the lack of practical, of-the-self solutions. The development of non-visual BCI may render BCI technology feasible for patients who lost control of eye movement due to disease progression or injury, however, this hypothesis has to be confirmed with SCD patients. The BCI needs to be individually adaptable and embrace all remaining capacities for communication and interaction as realized with the hybrid approach. This also includes signals from large neuronal networks or few cells which are recorded epi- or subdurally or intracortically. In proof-of-principle studies including patients with epilepsy and after high spinal cord injury fast item selection (Brunner et al., 2011) and control of a robotic arm (Collinger et al., 2013) were demonstrated. However, these approaches await implementation in real life situations. Ideally, an individual end-user could choose from a variety of applications and different

input signals would be tested for BCI control such that the end-user would be enabled to make an informed decision. BCI-controlled neurofeedback to improve impaired function as experienced, for example, after stroke, will become increasingly important provided the respective randomized clinical trials are conducted and confirm its superiority to treatment as usual.

The UCD appears to be a useful tool for the development of BCIs that control applications which precisely meet the needs and wishes of the end-users. If researchers and developers adhere to the UCD, we may be able to specify which type of BCI and which application may be most appropriate for which group of end-users, i.e., differential indication. We envision a future in which BCI-controlled applications are an established tool for replacing and improving lost or impaired function in people with disease including those with SCD.

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CHAPTER

15

Neuroethics and Disorders of Consciousness: A Pragmatic Approach to Neuropalliative Care

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OUTLINE

INTRODUCTION

The world is not ready for the potential discoveries and innovations described in this collection. Unraveling the mysteries of consciousness, lost and regained, and novel intervention so as to prompt recovery are possibilities for which neither the clinical nor the lay community are prepared. The list of recent progress is breathtaking and includes the use of deep brain stimulation in the minimally conscious state (MCS) (Schiff et al., 2007), drugs like amantadine and zolpidem to accelerate and foster recovery (Giacino et al., 2012; Whyte and Myers, 2009) and enhanced rehabilitative strategies (Nakase-Richardson et al., 2012). Collectively these interventions have begun to alter the clinical landscape and the possibilities for recovery (Giacino et al., 2014). But as much as things change, despite the progress that has been made, patients and families encounter an uncertain clinical context, where static views about brain injury persist, despite two decades of progress (Fins, 2013, 2015; Fins and Hersh, 2011).

While these developments should shake existing expectations about severe brain damage, their potential to positively inform clinical care remain uncertain because of a still ambivalent clinical context and a complex regulatory environment has the potential to imperil it (Fins, 2003a,b, 2009; Fins and Suppes, 2011). Added to the complexity of the scientific challenges that must be overcome is the societal context in which

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these investigations must occur. Research on human consciousness goes to the heart of our humanity and asks us to grapple with fundamental questions about the self (Fins, 2004a). Added to this is the regulatory complexity of research on subjects who may be unable to provide their own consent because of impaired decision-making capacity, itself a function of altered or impaired consciousness. These factors can lead to a restrictive view of research that can favor risk aversion over discovery.

In this chapter, I will attempt to explain systematically some of these challenges. I will suggest that some of the resistance might be tempered if we view the needs of patients with severe brain injury through the prism of palliative care (Fins, 2005a; Fins and Pohl, in press; Fins and Master, in press). To make this argument I will draw upon the American pragmatic tradition and utilize *clinical pragmatism*, a method of moral problem solving that I have developed with colleagues for clinical care and research (Fins and Bacchetta, 1995; Fins, 1996, 1998; Fins et al., 1997; Miller et al., 1997). Finally, I will argue that the care of these patients is nothing less than a human rights issue (Fins, 2010). That if one is conscious, one's consciousness should be properly respected, diagnosed and restored so as to maximally reintegrate patients into their family and society.

CLINICAL PRAGMATISM

Clinical pragmatism has its philosophical roots in the American pragmatic and the work of John Dewey (1859–1952) in particular (Menand, 2001; Dewey, 1988, 1991a,b). Dewey was a leading American philosopher of the first half of the twentieth century as well as a psychologist, democratic theorist, and education reformer (Ryan, 1995; Hook, 1995; Miller et al., 1996; Fins, 1999a). Deweyan pragmatism is an appealing philosophical method to assess the novel ethical challenges posed by neuroscience because Dewey sought to use the scientific method as a means to inductively address normative questions (Dewey, 1997, 1998; Miller and Fins, 2006).

As a method of moral problem solving, clinical pragmatism begins with the recognition of the problematic situation. This prompts a process of enquiry which includes the collection of medical, narrative and contextual data. This information leads to the articulation of an ethics differential diagnosis. These speculations in turn inform a negotiation with stakeholders about a plan of action with this consensus leading to an intervention (Table 15.1) (Fins and Miller, 2000a). This process is completed with a periodic review that will foster experiential learning (Fins, 2006a).

TABLE 15.1 Clinical Pragmatism and Inquiry

I.	Recognition of the problematic situation and the need for inquiry
II.	Data collection: medical, narrative, contextual
	1. Medical facts
	2. Patient/surrogate preferences
	3. Family dynamics
	4. Institutional arrangements
	5. Broader societal issues and norms
III.	Interpretation (ethics differential diagnosis)
IV.	Negotiation
V.	Intervention
VI.	Periodic review/experiential learning

Source: Modified from Fins and Miller (2000a).

CLINICAL PRAGMATISM AND DISORDERS OF CONSCIOUSNESS

The Problematic Situation

The very clinical context of care encountered by patients with disorders of consciousness is a problematic situation, which generally goes unrecognized. I have previously characterized this as a *neglect syndrome*, borrowing the diagnostic category from clinical neurology (Fins, 2003a). Although notable exceptions exist among highly dedicated neurologists, neurosurgeons and rehabilitation specialists, the vast majority of patients with disorders of consciousness are a population who remain out of our gaze.

Without careful consideration or an evidence base, it is taken for granted that patients who have sustained severe brain damage are beyond hope of any remediation. This leads to a clinical context marked by errors of omission and a sense that ethically, nothing can or should be done for patients with catastrophic brain dysfunction. These prevailing sentiments have undermined the usual intellectual curiosity that marks other areas of practice. Surveys of neurologists' knowledge of diagnostic categories related to disorders of consciousness are rife with errors that would be intolerable elsewhere in practice (Childs et al., 1993), though they are tolerated here because of the sense that diagnostic clarity in the face of one form of futility or another just does not matter.

This is indeed paradoxical because while most in the clinical context are dismissive of these patients, questions related to consciousness are among the most fascinating topics in science and society (Sacks, 1994; Edelman, 2004; Crick, 1994; Searle, 2002; Koch, 2004). Despite this interest outside of medicine, within the clinic disinterest and lack of intellectual curiosity have marked the clinical context. Even diagnostic rigor is lacking (Fins and Plum, 2004). It is not uncommon for the same patient with impaired consciousness to be described as nearly brain-dead, vegetative, or comatose.

These practices can create a problematic situation that can go unrecognized because such attitudes become so pervasive so as to become the norm. The potential recovery of a brain damaged patient goes unexamined because it is assumed that the intellectual consequences will be dire. Even survivors with intact cognitive abilities, like Jean Dominique Bauby—the author of *The Diving Bell and the Butterfly* a memoir of the Locked-in-State (LIS)—comments, "But improved resuscitation techniques have prolonged the agony" (Bauby, 1997, p. 4). These perceptions prevail despite the fact that evidence-based outcomes demonstrate a wide variety of outcomes depending upon a range of patient variables.

Although one would think that absence of careful diagnosis and informed prognostication would be an obvious deficit calling out for more precise assessment, confident pronouncements that there is "no hope for meaningful recovery" are taken for granted, unexamined and without the requisite skepticism that marks prudential medicine. Meaningful to whom? The neurologist? The patient? Their family? (Fins, 2005b) It is also critical to appreciate that notions of the life that might be worth living can evolve as disability is confronted. Quality of life considerations can also be informed by perspective (Uhlmann et al., 1988; Uhlmann and Pearlman, 1991).

Another unarticulated problem which informs the care provided to these patients are the norms that inform decisions about life-sustaining therapy. Our views on do-not-resuscitate orders and decisions to withdraw life-sustaining therapies have grown out of our experience in intensive care units and the provision of acute care (Zussman, 1992). In that setting the loss of consciousness may be taken as the ethical predicate to withdraw life-sustaining therapy because it signals the end-stage of a disease process. This is in contradistinction to the loss of consciousness that occurs at the outset of severe brain injury (Fins, 2007a).

This is the context of care for critically ill patients who have sustained brain damage, where clinical routines can become an excuse for unreflective practice. It is a setting with decisional constructs that operate in days and weeks, not months. And these contextual factors lead to a paradox that also informs the problematic situation: decisions about withholding and forgoing life-sustaining therapy are made prematurely for patients with disorders of consciousness because options for withdrawals are increasingly abridged as the patient moves from the acute to chronic stage of illness, even though these decisions may become more justifiable once the prognosis becomes clearer.

As has been noted elsewhere in this book, the course of recovery from the vegetative states can take from 3 to 12 months, depending upon whether the etiology of the insult was anoxic or traumatic (Kobylarz and Schiff, 2004; Jennett, 2002). Thus, to fully know whether recovery from the vegetative state is possible, a patient with traumatic brain injury might have to be observed for 12 months. By then he will have become *medically* stable and been extubated (Winslade, 1998). His only life-sustaining therapy might be his percutaneous gastrostomy tube and hence the paradox. While the legal and ethical norms clearly view a ventilator as an extraordinary measure that can be withdrawn within weeks of an injury, the ethical (and theological consensus) on decisions to withdraw artificial nutrition and hydration is less clear even after a patient is irreversibly in a permanent vegetative state.

These difficulties, coupled with the culture of the intensive care, lead to decisions to remove life-sustaining therapy while it remains feasible even though the dimensions of the patient's recovery remain unknown. This can lead to pronouncements about expected outcomes that may reflect personal biases and fall short on the evidence (Fins, 2005b). A better approach would be to be transparent with families and explain to them that the patient's prognosis and hope for recovery of consciousness will become clearer within weeks and months. Although we should not compel families to continue to treat patients who are persistently but not permanently vegetative in order to develop greater prognostic clarity, it seems prudent and ethically within the norm of informed consent *and* refusal, to be intellectually honest about what can be predicted so early in the course of care. At the very least clinicians need to be careful about making expedient claims that there is "no hope for meaningful recovery" when the evidence is lacking in order to "scientifically" justify decisions to forgo life-sustaining therapy.

Data Collection

Clarifying the Medical Facts: Brain Damage and the Challenge of Diagnosis and Prognosis

The first issue that will be seen as immediately different in the care of patients with disorders of consciousness is the fact that it may be difficult to clarify the medical facts. The diagnostic categories that inform practice in this area—the vegetative and MCS (Giacino et al., 2002)—remain *descriptive*. Diagnoses are just on the cusp of becoming more physiologic and precise utilizing advanced imaging techniques and sophisticated electroencephalography, but our state of knowledge remains rudimentary compared with other domains in medicine.

A colleague suggested that our state of knowledge is just a bit more evolved from the time when

infectious diseases were termed "the fevers" (Barondess, 2003). A review of the history of medicine from Hippocrates and Galen to Osler and beyond indicates how etiology and prognostication evolved from rudimentary observations and theoretical speculations concerning fever (Wilson, 1997). Asserting that patients had a pattern of fevers carried less diagnostic and prognostic precision than linking these empirical manifestations of illness to an actual pathogen.

The state of affairs in neurological diagnosis, because of the complexity of the object of study, *is less evolved than other areas of medicine*. Families depend upon diagnostic clarity to make life-altering and family-defining choices, but even this basic element of decision making may be lacking clarity in disorders of consciousness. We take some semblance of diagnostic clarity elsewhere in medicine for granted. Clinicians counseling families about disorders of consciousness need to be careful to be as precise as possible and to acknowledge the limitations of what is currently known and predictable.

Although progress has been made since Jennett and Plum described the vegetative state as "a syndrome in search of a name" (Jennett and Plum, 1972), descriptive brain states are only now being refined in sub-categories such as the persistent and permanent vegetative states and the MCS based on correlations between clinical observation neuropathological studies and neuroimaging studies (Jennett, 2002; Jennett et al., 2001; Schiff et al., 2002, 2003, 2005; Menon et al., 1998; Schiff and Plum, 1999; Laureys et al., 2000, 2002, 2004; Voss et al., 2006; Owen et al., 2006; Wilson et al., 2001).

But as noteworthy as this work is, these efforts are rudimentary and fundamentally still descriptive with patients with variable injuries and outcomes clumped together into broad inclusive categories. This imprecision can lead to disorders of consciousness of different etiologies being clinically indistinguishable, although their causes and potential course are dramatically different, making prediction and prognostication so difficult. Such diagnostic questions are further confounded by diagnostic error.

These issues create a challenging problem for clinical care which may be unique to this area in medicine, namely the difficulty of providing patients and families with a clear and meaningful diagnosis, which is an essential element of any ethical analysis about care. Families accustomed to diagnostic precision in other disciplines have similar expectations when a loved one has a disorder of consciousness. They expect precision and could easily mistake a magnetic resonance imaging scan as meeting their expectations or misconstrue meanings of investigational work, such as the report by Owen et al. (2006) of a neuroimaging response in a patient who was behaviorally in the vegetative state.

This potential for misconstrual is heightened by popular articles on neuroethics, increasingly a mode of technological critique versus a scholarly discipline, that warn of imaging studies that might be able to read your mind and monitor your thoughts (The Economist, 2004; Farah and Wolpe, 2004; Fins, 2005c, 2007b; Moreno, 2006). If that is the case, they might logically ask, why can't my child's neurologist tell me if he is going to come out of his coma (Fins, 2005c)?

And when we do return from the realm of science fiction to the less promising confines of the clinic, we appreciate how crude our categories are. Here families also encounter a profession and society that has yet to reach a clear consensus on emerging diagnostic domains, as demonstrated by the controversy over the status of the MCS. Minimally *contentious* to some, there is the scientific critique about the use of a consensus panel to create such categories (Cranford, 1998; Shewmon, 2002), as well as the political concerns of advocates asserting disability rights and the right to die. Some disability advocates have been wary of MCS because they fear that this diagnostic category could equate patients with higher functioning to those in the vegetative state and lead to the devaluation of their lives (Coleman, 2002). Conversely, right to die advocates fear that this category may open Pandora's box by suggesting that patients with impaired consciousness might be candidates for treatment and more aggressive care (Cranford, 1998). If they are, these advocates worry, will this erode society's willingness to accept withdrawal of care?

Despite the forces that might conspire to rob patients of the most accurate diagnosis currently available, establishing the medical facts and the diagnosis is a critical and necessary step in making ethical choices about patient care. This becomes clear if we consider the exceptional case of Terry Wallis who was misdiagnosed, or perhaps simply ignored, while in the MCS (Schiff and Fins, 2003). In 1984, Wallis was an unrestrained passenger in a motor vehicle accident and suffered severe head trauma. He received acute medical care, survived and was discharged to a nursing home only months after his injury (Giacino, 2004). He carried the diagnosis of the persistent vegetative state. But on July 11, 2003, he had what has been described as a miracle awakening while in "custodial care" in a nursing home. He spoke tentatively, single words at a time like "Mom" and "Pepsi." As the weeks passed, he spoke still haltingly but with greater fluency. In his mind he had never aged, and Reagan was still President.

Although Wallis had been labeled as being in the persistent vegetative state, the behaviors noted by family members—evidence of episodic but unreliable demonstrations of awareness and consciousness—went

unheeded by the nursing home staff. Their views about him were codified by his diagnosis on transfer. He had been and would always remain vegetative. The family had requested that a neurologist reassess him during this period and were refused, so certain or indifferent were the staff to the question of his diagnosis. This neglect of Wallis was all the more poignant because subsequent diffusion tensor imaging revealed what was described as the "sprouting" of new axonal connections. It was hypothesized that these new connections between surviving neurons might have played a role in the evolution of his brain state and his recovery (Voss et al., 2006). Although these findings generated worldwide media attention, before his emergence from MCS, Mr. Wallis went nearly two decades without a neurological assessment because he failed to demonstrate overt clinical improvement, a health policy question of great import (Fins et al., 2007). It is critical to remember that brains recover by biological mechanisms and not by reimbursement criteria. Given this, we need to have funding policies that reflect this underlying truism (Fins, 2012) and which takes proper account of the time course of recovery (Fins, 2015; Pohl and Fins, 2014).

The failure to provide rehabilitation is a generic problem because patients who fail to meet medical necessity or demonstrate improvement with rehabilitative interventions are transferred to what is ungraciously described as "custodial care," where assessment is rare and incomplete. Given the exigencies of discharge planning, it is quite possible for a patient to be discharged while still in the persistent vegetative state and moved to MCS once transferred to a nursing home within the first year of traumatic injury. If this occurs in an inattentive or disinterested setting, crossing this diagnostic demarcation may go unnoticed to the detriment of the patient and family.

Another pressure that makes the usually routine task of diagnosis so difficult is that these diagnoses have become so value laden. If we recall the Terri Schiavo case in Florida, we are reminded of how the objective process of diagnosis can be eroded by ideology (Fins, 2006b). That these diagnoses are prone to becoming so value laden has the potential to further complicate family counseling. Though each of us can place a different moral valuation on life in a vegetative state, we should not let these values turn the objective clinical evidence into something that it is not. Moral valuation should follow *upon* the clinical facts and *not transmute them* to meet political or ideological needs. Diagnostic clarity, or its distortion, has consequences beyond the patient. It also has implications for other patients and society in general (Fins and Plum, 2004). Asserting by executive or legislative fiat, that Terri Schiavo was conscious when she was not obscures material differences between patients like Schiavo and Wallis. Such conflations have the potential to further the neglect of patients who retain residual elements of consciousness and who should be the object of intense study and clinical concern.

Patient and Surrogate Preferences

Once the medical facts have been clarified it is time to turn to the narrative dimensions of the case. Most patients do not engage in advance planning, that is talking with family and friends about their wishes in the event of decisional incapacity (The SUPPORT Investigators, 1995). Of those who do, even fewer envision a cognitively altered state while still a young person, the demographic most affected by traumatic brain injury. Nonetheless strong views persist about cognitive impairment from Alzheimer's disease or following stroke later in life. In a study we concluded using structured vignettes to assess patient and proxy views on end-of-life decision-making, respondents were averse to continued life support following a stroke which left the patient with "no hope for meaningful recovery" (Fins, 2005b), a phrase as we have noted that is in the common prognostic discourse in the clinical setting. It is important to be cautious about these *background* views about impaired consciousness when they are analogized from the geriatric context and the setting of degenerative diseases to disorders of consciousness which are traumatic, occurring in an otherwise healthy younger patient cohort. Although analogic reasoning is how we often analyze difficult choices, it is important to appreciate the salient differences between various types of cognitive impairment throughout the life cycle and make these potential biases explicit.

Parents of young adults considering their own views about cognitive impairment later in life or in their parents may erroneously generalize these preferences to a context, which is biologically and developmentally quite different, at the risk of being too pessimistic about hopes for some modicum of recovery. It is worth remembering and counseling surrogates that recovery from brain damage is more variable than the inexorable decline that follows a diagnosis of Alzheimer's disease. And as the compelling account of the Central Park jogger's account of her experience shows, though statistically unusual, even patients who have a grim Glasgow Coma Scale of 4–5 have the potential to recover cognitive function, as Meli's account indicates (Meli, 2003).

In addition to pre-existing views of cognitive impairment analogized from other contexts, families will also bring their religious and cultural traditions to bear upon these deliberations. Life in the persistent vegetative state may look different to a family from a more fundamentalist religious tradition that holds that

life itself is precious and which does not sanction quality of life distinctions. Such a vitalist approach, that any life is worth preserving, is often accompanied by an obligation to provide what, in the Catholic tradition, is called ordinary care such as artificial nutrition, hydration (Beauchamp and Childress, 1994). As has been noted, this becomes a critical point because late withdrawals will not likely involve ventilator support but simple feeding tubes, the subject of a 2004 Papal discourse (Fins, 2005b; Paul, 2004).

If surrogates are looking to forgo life-prolonging therapies, the process should be analogous to the process of an informed consent discussion, although in this context it would be an informed refusal of care. The practitioner should avoid value-laden statements that can engineer outcomes and preclude choice and provide surrogate decision-makers with the best available evidence of the patient's outcome as well as its time course and any burdens associated with continued treatment. The patient's ability to perceive pain and experience suffering should be discussed and efforts to provide symptomatic relief should be reviewed (Paul, 2004).

Given the potential for confusion about the sequence of recovery, clinicians should carefully explain how a patient who is comatose, who neither dies nor regains consciousness, moves into the "wakeful unresponsiveness" of the vegetative state after a couple of weeks. Clinicians should appreciate that families may perceive that eye opening is an improvement over the eyes-closed state of coma. This misconstrual needs to be clarified and families made aware that the failure to recover consciousness and awareness coming out of coma is a negative prognostic sign. The move into the vegetative state, though, needs to be tempered with information that a persistent vegetative state is not yet permanent and that prospects for the MCS and subsequent emergence can remain for months depending upon the etiology of injury. These discussions become even more complex if the patient recovers and is able to communicate preferences.

When the patient is able to participate in these decisions they are confronted with the challenge of being an altered self. Paradoxically an improvement in awareness and self-awareness may also bring a greater appreciation of how devastating an injury has been and how much farther one has to travel to regain skills and the ability for independent living (Schiff, 1999).

Is the goal to recapture former self or approximate a reasonable facsimile? The literature is rife with narratives of brain injury survivors who provide first-hand accounts of this very private journey. Theirs are an admixture of physiology and psychology in which the nature of their injury determines *what* their deficits will be while their personal narratives will determine *who* they will now become. Claudia Osborn, a physician who sustained head trauma and lost much of her executive function characterized the psychological evolution necessitated by her injury (Bauby, 1997; Meli, 2003; Osborn, 1998).

The challenge of crafting a new future becomes even more formidable when the body has been paralyzed but the mind remains intact as in the LIS. In these cases it becomes especially important *to speak with the patient* using assistive devices or rudimentary efforts at blinking (Morris, 2004). Indeed, if we take self-determination seriously, we need to ensure that those trapped in a lifeless body are not robbed of the opportunity to direct their care by turning to surrogates for guidance. Contrary to the expectations held by the able-bodied and anecdotal reports (Powell and Lowenstein, 1996), a systematic assessment of the quality of life of patients in the LIS indicate that they can maintain a quality of life, enjoy social intercourse, and that depression is not the norm (Leon-Carrion et al., 2002a).

Finally, it is important to appreciate that views about an acceptable existence are plastic. They evolve over time, often accommodating an increasing burden of disability. Studies have shown that patients are willing to continue treatments that physicians think are burdensome. Physician and patient views about quality of life can be discordant. These valuations can inform the clinicians' view of "appropriate" end-of-life decisions even though patients may see things differently (Uhlmann et al., 1988; Uhlmann and Pearlman, 1991). Physicians must recognize these potential biases so as to enable neutral counseling about what might constitute proportionate care (Leon-Carrion et al., 2002a).

Family Dynamics

Thrown into this mix is the impact of care on the family (Fins, 2013, 2015; Fins and Hersh, 2011). Having a family member with severe brain damage can lead to social isolation, or as one commentator put it, "of the loneliness of the long-term care giver" (Fins, 1992a). Relationships change with the patient when the person has changed but one's marital status has not. For better or worse takes on a new connotation when one spouse no longer recognizes the other or when a frontal head injury has led to disinhibition and dramatic change in personality and temperament. When this occurs love can turn to compassion and compassion might turn to resentment. Spouses can feel as trapped as the patient, burdened by loving vows that may seem impossible to fill and tethering. It is important to appreciate the stress that families operate under when challenged by brain damage in a loved one. The patient's

dependency, indeed fragility, becomes the epicenter of family life, altering roles and obligations.

Institutional Arrangements

Whatever the family dynamic, it will be played out within an institutional setting (Fins, 2015). For the most part, these institutions will not be geared to the chronic care needs of patients with severe head injury but rather to the provision of acute or what has been euphemistically called "custodial care" (Winslade, 1998). These contextual factors can distort decision-making and engineer outcomes that may not be in the patient or family's best interest.

We have already described how the time frame of end-of-life decisions are discordant with the pace of recovery from head injury. Similar economic pressures exist, at least in the North American context, to discharge patients from acute care if they do not demonstrate what has been termed "medical necessity" or more colloquially, show improvement. Although it is appreciated that recovery from brain damage can take months and that the trajectory of improvement may not be linear, the prevailing bureaucracy regulates length of stay in ways that may truncate admissions and deprive patients of adequate diagnostic assessment and proper placement in appropriate rehabilitation settings.

The pace of discharge from hospital, and the sequestration of the acute and rehabilitative medical communities, can lead to distortions among the former about what may be achievable with continued treatment over time. Because acute-academic and rehabilitative care centers are generally geographically separate, acute care practitioners can have a distorted view about patient outcomes. They suffer from what has been described as a "bureaucratization of prognosis" (Christakis, 1999; Fins, 2002).

At its worst, institutional perceptions about what might constitute futile care can become objectionable. Consider the conflicting goals of caring for patients with severe brain damage and the need to obtain organs for transplantation. The contemporary example of organ procurement practices has historical roots that also inform our utilitarian views about severely brain injured and our societal obligations. In 1968, the diagnosis of brain death was justified by the greater good that might come from organ harvesting (Stevens, 1995; Beecher, 1968). These powerful perspectives have expanded to those who are still not brain dead and today it is not uncommon for organ procurement personnel to urge referrals of patients with Glasgow Coma Scales of 3–5 for assessment as potential donors, even though these patients may yet harbor the potential for recovery (Meli, 2003). My goal is not to undermine laudable transplantation efforts but rather to illustrate how views about the viability and potential of patients with severe brain injury can be shaped by institutional practices that may go unexamined.

Societal Issues and Norms

All of the above factors are occurring against a broader societal backdrop as illustrated by the impact of cases like Schiavo and Wallis. I have addressed this broader context elsewhere at great length (Fins, 2003a, 2006a,b; Fins and Plum, 2004), suffice it to say here that our collective views about disorders of consciousness are informed by the tangled history of brain damage and the evolution of the right to die in modern medical ethics. American bioethics since the 1960s has been predicated upon the evolution of self-determination and autonomy. This right evolved as the right to be left alone and to have life-sustaining therapy withdrawn. The important right to die, to direct one's care at the end of life autonomously, was founded upon a number of landmark cases involving patients in the vegetative state, most notably Quinlan and Cruzan (Cantor, 2001; Cruzan, 1990). This is critical because the test cases to establish this *negative* right were in vegetative patients whose society concluded were beyond hope and beyond care. Further treatment in their case was, in a sense, the paradigmatic case of medical futility (Cranford, 1994) simply geared at the preservation of vegetative functions and not as the Quinlan court put it a, "cognitive sapient state" (Annas, 1996).

By considering the potential for recovery we are now asking society to intervene in a population which resembles those in whom the negative right to be left alone was first established. This has created a bit of cognitive dissonance—an oxymoron if you will—seen so dramatically in the cases of Schiavo and Wallis, in which the laudable goals of *preserving the right to die* and *affirming the right to care* have come into conflict (Fins, 2006a).

Interpretation (Ethics Differential Diagnosis): Towards a Palliative Neuroethics

In considering how to reconcile these two conflicting obligations—preserving the hard-won right to direct care at the end of life and to care for those who may be helped—I would like to suggest that there may be a value in viewing these cases through the ethos of palliative care. The World Health Organization (WHO) defines palliative care as "... the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual support is paramount. The goal of palliative care is the achievement of the best quality of life for patients and their families" (World Health Organization, 1990, pp. 11–12).

Conceptually palliative care can accommodate the oxymoron of affirming the right to die and preserving the right to care in patients with disorders of consciousness. Clinically, it does not preclude active care but at the same time it attends to symptom management and quality-of-life issues when the patient has eluded cure.

Palliation is an especially good metaphor to describe interventional strategies being developed for patients with disorders of consciousness. If we consider the philological origins of palliation we are reminded that to palliate means to cloak or disguise (Fins, 1992b). This is precisely what will occur if deep brain stimulation can restore impaired consciousness or (Fins, 2004b) if brain–computer interfaces can help LIS patients communicate (Leon-Carrion et al., 2002b). Neither of these interventions are curative but rather assistive devices that palliate by *cloaking* or placing a *veneer* over underlying disability which remains. (Such is the case of deep brain stimulation in the MCS, making it a mosaic blend of the curative and palliative.) (Schiff et al., 2007).

But more fundamentally palliative medicine is concerned with questions of meaning and suffering. At the most fundamental level disorders of consciousness are about the endangered and altered self, raising the possibility the potential for suffering as the patient contemplates what has been lost, what remains and what still might be. What aspect of the self-matters? Is the goal of care restoration or personal identity or a tolerable facsimile? Or is it the restoration of affect, memory and executive function? These are both empirical questions that will be relevant to emerging therapies such as DBS (Schiff et al., 2007; Fins, 2000).

It is vital that practitioners attend to this alteration of the self and appreciate that there are indeed psychological connections between the patient before and after injury. Although some philosophers, like Parfit (1987), maintain that there is a discontinuity between the former and current self, this is more a theoretical argument than a pragmatic one as there is indeed continuity of memory and affect. Though these linkages may be tenuous at the margins, they do remain and inform relationships with intimates.

These sentiments remind us of the importance of appreciating that even as we distinguish differing brain states from another, there is a unique psychological element at each bedside, even when there are disorders of consciousness. Consciousness is about questions of meaning and though physiologically based, is psychological in its expression.

Negotiation and Intervention

In the absence of a particular patient narrative, it is difficult to script how to negotiate a plan of care with patients or their surrogates, but as a rule it is helpful to suggest plausible and achievable goals of care. Surrogates confronted with the specter of a loved one with brain damage may want to precipitously withdraw care or cling to hope when there is none. These emotional responses may reflect more about their preconceptions about brain injury than the clinical reality that they face. To temper these responses and help to ensure that surrogates are adequately informed, it is essential that surrogates understand the patient's diagnosis, prognosis, and prospects for recovery. It is important to avoid misconstruals that might distort the surrogate's thinking and help ensure that they appreciate the likelihood and time course of recovery, its scope and the foreseeable burdens that might be imposed by on-going care. This information needs to be conveyed empathically and with compassion, appreciating that most of us never consider the prospect of brain injury touching our families or close friends.

A palliative approach may help frame the goals of care by acknowledging both the right to die and the right to care while seeking an optimal quality of life through the mitigation of the patient's symptom burden. Palliative care, however, should be carefully introduced into the discourse, because it is generally associated with end-of-life care. To avoid this potential confusion, it may be best not to explicitly label care as "palliative." It would be more effective to be descriptive about the *elements* of palliative care including the right to withhold or withdraw life-sustaining therapies.

When offering palliation, or any other care strategy, it is important that the appropriate surrogate decision-maker retains the ability to direct care. Ultimately, any decision-making authority resides in the patient's surrogate. This moral authority is based on what they know about the patient's preferences or values and their pre-existing relationship (Fins, 1999b). The practitioner's task is to help weave a consensus with the surrogate that takes account of the medical facts and the patient and surrogate's values and balances burdens and benefits.

Once a care plan has been agreed upon, it is helpful to suggest a *time trial* to see how and if the patient improves, leaving open the possibility that the goals of care can evolve as the situation changes. Time trials are also an important way to achieve a consensus and balance the power dynamic between clinician and family. They are essential to the *process of negotiation* and provide time for the surrogates to accommodate themselves to the sudden and often tragic reality of severe brain damage. Most importantly, they help safeguard the surrogate's authority and help them make decisions without being dictated to by the clinical team.

Periodic Review

The final step in the process of clinical pragmatism is periodic review. This is a critical step because it allows for the reassessment of decisions made in particular cases and modification of a course of action. As critically, this process allows us to organize empirical observations to reform practice and public policy. Public policy that governs research with individuals with disorders of consciousness is one critical issue that calls for reassessment in the wake of this consideration of the clinical care of such patients.

It is beyond the scope of this chapter to address fully the challenge of engaging in clinical research with subjects who have decisional incapacity (National Bioethics Advisory Commission, 1998; Fins and Miller, 2000b). These subjects are rightly considered a vulnerable population and subject to special protections because they are unable to provide their autonomous consent for enrollment in clinical trials. Although their next-of-kin or surrogates may authorize therapeutic procedures with demonstrated benefit, surrogates' ability to authorize enrollment in research is constrained when it has yet to demonstrate medical benefit, unless it was authorized prospectively by the patient before decisional incapacity. This severely limits the potential for phase I research in individuals who cannot provide consent (Fins, 2000, 2003b; Miller and Fins, 1999, 2005, 2006; Michels, 1999; Fins et al., 2006).

But unlike other vulnerable populations, the disorder that precludes autonomous consent is the object of the intervention when trying to restore consciousness. A compelling argument emerges that clinical trials to restore consciousness would be ethically proportionate, even with the challenges posed by surrogate consent, when we appreciate this critical distinction and the burdens imposed on these patients and families (Schiff et al., 2007; Fins, 2000).

While those with disorders of consciousness should be protected from harm, balancing and specifying the ethical principles of respect for persons, beneficence, and justice compel us to craft a responsible and responsive research ethic geared, for now, towards the pursuit of palliation (Fins, 2003a; National Bioethics Advisory Commission, 1998). This becomes a fiduciary obligation grounded in a justice claim to meet the needs of patients society has so misunderstood and historically neglected (Fins, 2003a).

More fundamentally, society needs to appreciate that patients who are conscious must be accorded their basic human rights. Long sequestered from society, misdiagnosed and ignored, these individuals make a moral claim on us for more humane care that distinguishes the vegetative patient from one who is minimally conscious. Once this is discerned, the goal becomes one of seeking to restore functional communication, which is the key to reintegration into one's family and society. This is more than a medical imperative or simply a disability rights issues. It is an ethical one which recognizes the personhood of those patients who are liminally conscious, and values and affirms their humanity. Only then can we ensure that these individuals are viewed as citizens worthy of the protections of the law, such as those articulated in disability conventions.

History is full of examples of the expansion of civil rights to marginalized individuals: the enfranchisement of women as voters; the right to vote for those excluded by the color of their skin; and the right of people in love to marry, irrespective of their sexual preference. To this list of advances, society must now add the fuller inclusion of individuals with disorders of consciousness into civil society. In the face of what neuroscience has taught us over the past decade, it is no longer acceptable to plead ignorance or to conflate the moral status of brain states like the permanent vegetative state with the MCS. This is a diagnostic distinction that makes a difference. An individual who is conscious, albeit minimally so, must be properly diagnosed and maximally treated so as to allow their fullest integration into our shared human community. Nothing less is acceptable if we seek to affirm our collective respect for persons and the commonweal we comprise together.

CONCLUSION

The *terra nova* of neuroscience exploring disorders of consciousness is, to invoke an over-used phrase, paradigm breaking (Kuhn, 1996). This line of enquiry will challenge assumptions, stir up misconceptions and engender both unrestrained hopes and unsubstantiated fears. If we are to grapple with the promise and peril of this work, it is critical to engage in a deliberative process of enquiry that allows us to see all sides of the argument, identify the range of stakeholders who may be affected by clinical and scientific developments, and to reach a societal consensus on how these efforts will proceed. An inductive approach which is reminiscent of diagnostics, clinical pragmatism can help constructively apply ethical principles to the context of care (Miller and Fins, 1999) and bring principled reasoning to complex ethical questions posed by cognitive neuroscience, reasoning which ultimately will expand human rights protections those in the MCS (Fins, 2015).

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CHAPTER

16

Epilepsy and Consciousness

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OUTLINE

INTRODUCTION

Consciousness is something that every child understands, but that scientists and philosophers still struggle to explain. We are all intimately acquainted with what it means to be conscious or unconscious as we wake up in the morning, doze off briefly during a lecture, drive somewhere without thinking about the route, or engage in a stimulating discussion requiring full awareness. Consciousness provides an important, human quality to our life experience, and we depend on consciousness as an efficient way to organize and prioritize our memories and actions (Koch, 2004; Dehaene, 2014). In epilepsy, consciousness is suddenly and involuntarily taken away. During seizures, patients experience lapses in consciousness, which can have major negative impact including injuries, social stigma, and lost time.

Up until recently, the mechanisms for impaired consciousness in epilepsy were not known. Much work has been done, and is ongoing to elucidate the mechanisms of normal consciousness, and impaired consciousness in disease states (see other chapters in this volume). With advances in functional neuroimaging and neurophysiology it is now possible, for the first time, to identify specific networks that are affected in the brain during epileptic unconsciousness. Recent investigations suggest that epilepsy, like other disorders of consciousness, disrupts a core network of anatomical structures critical for the maintenance of normal consciousness, referred to as the consciousness system (see Chapter 1). Because epileptic seizures cause transient, dynamic, deficits in consciousness which can range from mild impairment of attention to complete behavioral unresponsiveness, the study of seizures provides an opportunity to functionally localize specific aspects of consciousness in the brain. Impaired consciousness in epilepsy also has major practical significance, since most negative consequences of seizures including driving accidents, falls, burns, social stigma, work-related disability, and sudden unexpected death in epilepsy (SUDEP) are directly related to loss of consciousness.

Epileptic seizures are usually classified as either focal—meaning that they involve localized regions of the brain, or generalized—meaning that they involve widespread regions of the brain bilaterally (ILAE, 1981; Berg et al., 2010; Blumenfeld and Jackson, 2013). Interestingly, impaired consciousness can be seen in both focal and generalized seizures. Thus, impaired consciousness is seen in generalized seizure types such as absence (petit mal) and tonic–clonic (grand mal)

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TABLE 16.1 Seizures Associated with Impaired Consciousness

	Absence seizure (petit mal)	Generalized tonic–clonic seizure (grand mal)	Focal impaired consciousness seizure (FICS; complex partial)[a]
Classification	Generalized	Generalized	Focal
Typical behavior	Motionless stare, unresponsive, often with eyelid flutter, and minor hand movements	Bilateral tonic limb rigidity and extension lasting 10–20 s, then rhythmic bilateral clonic limb jerks for ~1 min	Aura (vague premonition, fear, rising epigastric feeling, etc.), then stare, unresponsive, chewing or lip smacking, contralateral limb dystonia, ipsilateral repetitive automatisms (rubbing, picking, etc.)
Duration	Less than 10 s	1–2 min	1–2 min
Postictal deficits	None	Sleepy or sleeping, weakness, confused	Confused
Scalp EEG	Generalized 3–4 Hz spike-wave discharge	**Tonic phase:**	**Ictal:**
		Generalized high frequency polyspike discharge	5–7 Hz rhythmic temporal discharge, with some bilateral slowing
		Clonic phase:	**Postictal:**
		Generalized polyspike-and-wave discharge	Generalized slowing
		Postictal:	
		Generalized suppression or generalized slowing	

[a]*Temporal lobe seizures are the most common type of FICS so are described in this table, but features of other FICS may differ slightly based on region of onset.*

seizures, as well as in focal impaired consciousness (complex partial) seizures (Table 16.1). These three types of seizures differ dramatically in terms of their usual causes, behavioral manifestations, and brain electrical activity (Table 16.1).

However, despite the differences between absence, tonic–clonic and focal impaired consciousness seizures (FICS), they all share a common thread of disordered consciousness and affect the same specific brain networks. As discussed elsewhere in this volume (Chapter 1), consciousness depends on a specialized network of cortical and subcortical structures referred to as the "consciousness system" (Blumenfeld, 2010). The consciousness system is directly involved in controlling the level of consciousness, including the alert state, attention, and awareness of self and the environment (mnemonic AAA). Therefore, the consciousness system at minimum includes regions of the frontal and parietal association cortex, cingulate gyrus, precuneus, thalamus (especially the medial, midline, and intralaminar nuclei), and multiple activating systems located in the basal forebrain, hypothalamus, midbrain, and upper pons.

In this chapter we will review recent findings which suggest that absence seizures, generalized tonic–clonic seizures, and FICS all involve the same general anatomical regions of the consciousness system (see Figure 1.2 in Chapter 1). Recent neuroimaging studies have shown that all three types of seizures cause abnormal increases in activity in the upper brainstem and medial thalamus. Changes in the medial and lateral frontoparietal association cortex are also anatomically similar in these three seizure types. However, the direction of changes is more complicated. Absence seizures show increases followed by prominent decreases in cortical functional magnetic resonance imaging (fMRI) signals, differing in relative magnitude depending on the region. Generalized tonic–clonic seizures show cerebral blood flow (CBF) increases in most regions of the frontal and parietal association cortex during seizures, except for the medial frontal and cingulate cortex which shows prominent decreases. These same regions all show decreases in the postictal period following tonic–clonic seizures, when consciousness usually remains severely impaired. Temporal lobe seizures are the most common type of FICS, and these show ictal CBF decreases and slow wave activity in the frontal and parietal association cortex, which persist along with impaired consciousness in the postictal period.

The shared anatomical regions but different directions of changes for these three seizure types causing loss of consciousness arise through different physiological mechanisms in each case, as we will discuss in greater detail in this chapter. Improved understanding of the specific brain regions and mechanisms involved in epileptic unconsciousness may allow therapeutic interventions, such as deep brain stimulation, or targeted medical therapies to be developed which will

prevent this serious consequence of epilepsy. In addition, since the impaired consciousness in epilepsy is variable, careful study of specific deficits and involved brain areas during seizures may allow a greater understanding of the anatomy of consciousness. In this chapter we will review the three main types of seizures causing impaired consciousness, and discuss each in turn, emphasizing recent neuroimaging and other results that shed light on the mechanisms for impaired consciousness. Finally, we will discuss practical applications, and future directions for work on impaired consciousness in epilepsy.

ABSENCE SEIZURES

In absence seizures, as the name implies, awareness briefly vanishes. Typical absence seizures consist of staring and unresponsiveness, often accompanied by subtle eyelid fluttering or mild myoclonic jerks. Duration is usually less than 10 s (Table 16.1). Absence seizures occur most commonly in childhood, and are accompanied by bilateral, frontal predominant 3–4 Hz spike-wave discharges on electroencephalography (EEG) (Weir, 1965; Rodin and Ancheta, 1987). Both human and animal studies support the role of corticothalamic network oscillations in generating absence seizures (Williams, 1953; Avoli et al., 1990; Blumenfeld and McCormick, 2000; Kostopoulos, 2001; McCormick and Contreras, 2001; Blumenfeld, 2002, 2003, 2005b; Crunelli and Leresche, 2002).

Because motor manifestations are relatively mild, absence can be considered the purest form of impaired consciousness in epilepsy. Patients appear as if someone has pushed the "pause button" on their stream of consciousness, briefly interrupting their ongoing behavior, and then resuming approximately where they left off without significant postictal deficits. More behavioral studies of impaired consciousness have been performed with absence seizures than any other seizure type. This is, most likely, because absence seizures can occur in susceptible individuals up to several hundred times per day. These behavioral studies were performed mostly in the 1930s through 1970s, before functional neuroimaging was available, and were reviewed in Blumenfeld (2005a). Based on these behavioral studies, it can be concluded that: (i) Impaired consciousness during spike-wave seizures varies from one patient to the next, and even within individual patients. (ii) The severity of impairment also varies with the specific task used for testing. For example, patients often perform better during absence seizures with simple repetitive motor tasks, and have the most difficulty with tasks that require complex decision making or a verbal response (Goldie and Green, 1961; Mirsky and Van Buren, 1965; Goode et al., 1970; Browne et al., 1974). (iii) Atypical, irregular, or slow (~2 Hz or less) spike-wave discharges, and prolonged absence status epilepticus in some cases causes little or no impairment of consciousness (Gokygit and Caliskan, 1995; Vuilleumier et al., 2000).

Although considered a form of generalized epilepsy, there is ample evidence based on both human and animal studies that the so-called "generalized" spike-wave discharges in fact arise from specific corticothalamic networks which are most intensely involved, while other regions are relatively spared (Blumenfeld, 2005b). The specific brain regions involved during absence seizures may have important implications for explaining why these seizures cause relatively selective impairment of consciousness.

Human EEG recordings during absence seizures have long shown that the spike-wave discharges are of largest amplitude in the frontal midline regions (Weir, 1965; Rodin and Ancheta, 1987; Holmes et al., 2004). Animal models have also supported focal involvement of bilateral anterior cortical and subcortical brain regions during spike-wave discharges, based on electrophysiology (Vergnes et al., 1990; Meeren et al., 2002; Manning et al., 2004; Nersesyan et al., 2004b; van Luijtelaar and Sitnikova, 2006), molecular changes (Klein et al., 2004), and more recently, neuroimaging with fMRI (Nersesyan et al., 2004a; David et al., 2008; Mishra et al., 2011). These investigations suggest that spike-wave seizures, which appear fairly generalized on scalp EEG recordings, in fact may intensely involve some corticothalamic networks, while other brain regions are relatively spared.

Early human imaging studies during absence seizures produced highly variable results, with some studies showing global increases in cerebral metabolism or blood flow (Engel et al., 1982, 1985; Theodore et al., 1985; Prevett et al., 1995; Yeni et al., 2000), and others showing no change, biphasic changes, or generalized decreases (Theodore et al., 1985; Ochs et al., 1987; Diehl et al., 1998). Some of this variability may reflect technical limitations of the methods used. For example, Doppler flow studies have limited spatial resolution, and imaging methods such as positron emission tomography or single photon emission computed tomography (SPECT) have limited temporal resolution relative to absence seizure duration. However, the variable results could at least in part also reflect the variable nature of absence seizures themselves. For example, even typical absence seizures have varying EEG amplitude, duration, and rhythmicity; and larger amplitude often fluctuates between the right and left side (Mirsky and Van Buren, 1965; Ebersole and Pedley, 2003).

The availability of simultaneous EEG-fMRI has greatly improved the spatial and temporal resolution

of neuroimaging during spike-wave seizures. Several recent studies have investigated the fMRI changes during spike-wave seizures (Archer et al., 2003; Salek-Haddadi et al., 2003; Aghakhani et al., 2004; Gotman et al., 2005; Labate et al., 2005; Hamandi et al., 2006; Laufs et al., 2006), some of which were performed in children with absence epilepsy (Labate et al., 2005; Moeller et al., 2008; Bai et al., 2010; Berman et al., 2010). These studies have shown bilateral fMRI changes in the consciousness system described above, including the medial and lateral frontoparietal association cortex and the thalamus (Figure 16.1). It is important to note that the fMRI changes during absence seizures are best appreciated by examining the full time course in all regions as has been done recently by several groups (Bai et al., 2010; Carney et al., 2010; Moeller et al., 2010b). Simplified hemodynamic modeling at one time point can miss crucial changes in some regions particularly in the frontal cortex (Bai et al., 2010).

Very few studies have attempted to directly relate fMRI or EEG changes during individual absence seizures to impaired consciousness. Some early studies reported that impaired consciousness in absence seizures is associated with specific EEG features including spike-wave amplitude, duration, rhythmicity, frontocentral distribution, and generalization (Jus and Jus, 1960; Mirsky and Van Buren, 1965; Browne et al., 1974), but others claimed that there is no relation between EEG and absence behavioral severity (Gastaut, 1954; Boudin et al., 1958; Davidoff and Johnson, 1964). A few studies based on limited numbers of seizures also suggest that fMRI changes may be greater for absence seizures with impaired consciousness (Li et al., 2009; Berman et al., 2010; Moeller et al., 2010a). Recent work based on a relatively large sample size suggests that absence seizures can be separated behaviorally into those with or without impaired consciousness, and that absence seizures with impaired

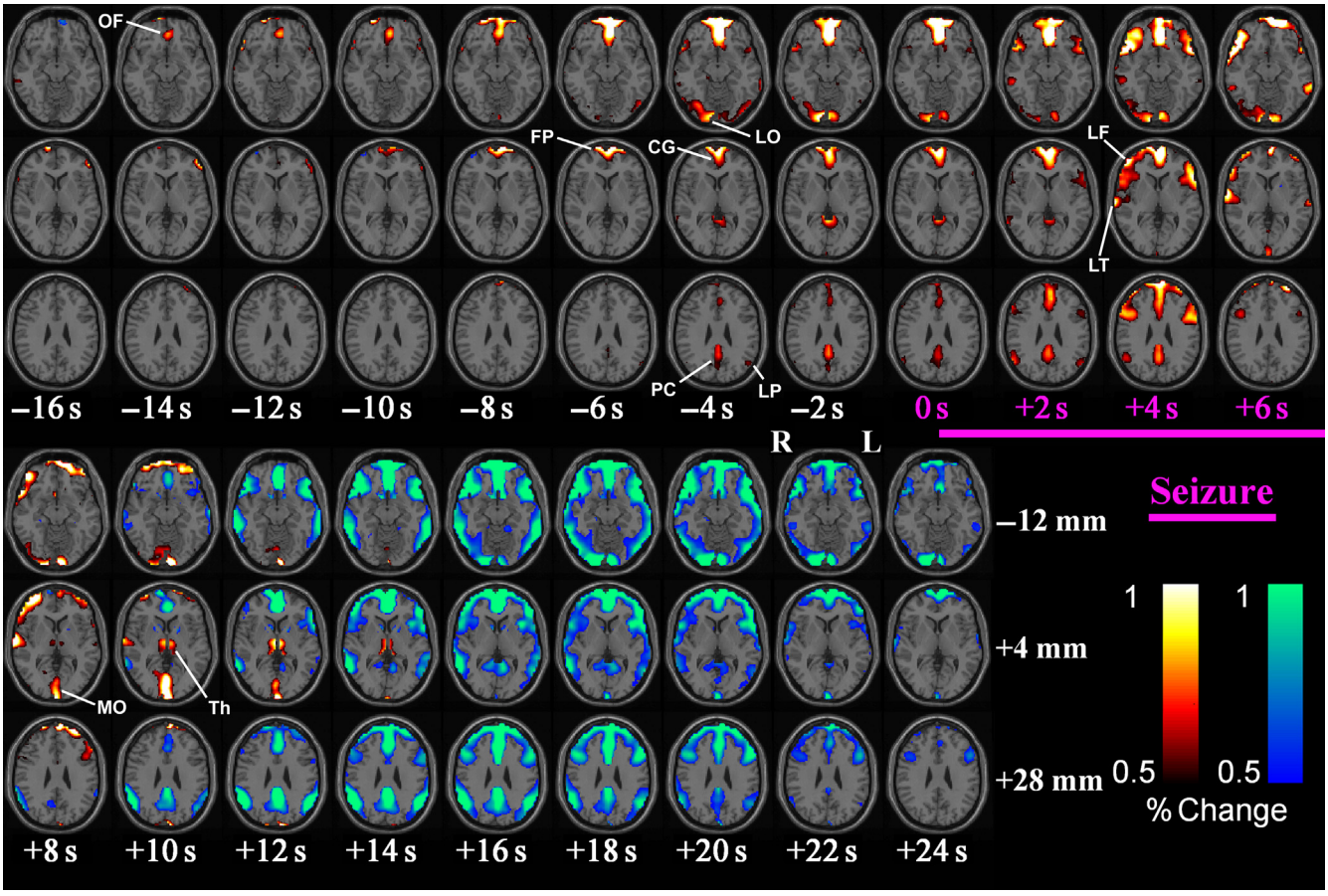

FIGURE 16.1 fMRI changes in absence seizures involve the consciousness system. Sequential increases (warm colors) and decreases (cool colors) are seen in bilateral frontoparietal association cortex and thalamus (Th), as well as other regions including medial orbital frontal (OF), frontal polar (FP), cingulate (CG), lateral parietal (LP), precuneus (PC), lateral occipital (LO), lateral frontal (LF), lateral temporal (LT), and medial occipital (MO) cortex. Prolonged fMRI decreases follow seizures. Percentage fMRI signal changes are shown from group analysis of 51 seizures in eight patients, with a display threshold of 0.5%. The ictal time period of seizures was scaled to 6.6 s (mean seizure duration), and the preictal, ictal, and postictal time periods temporally aligned across all seizures to seizure onset (0 s). *Source: Reproduced with permission from Bai et al. (2010).*

consciousness exhibit larger amplitude fMRI and EEG changes in widespread brain networks including the consciousness system (Guo et al., 2014).

GENERALIZED TONIC–CLONIC SEIZURES

Like absence seizures, grand mal (tonic–clonic) seizures are classified as "generalized" (Table 16.1). Although it may appear obvious that generalized tonic–clonic seizures cause impaired consciousness through involvement of widespread brain regions, surprisingly little research has been done to investigate this claim. It is natural to ask whether, like in absence seizures, impaired consciousness in the so-called "generalized" tonic–clonic seizures may depend on abnormal activity in specific brain regions. Generalized tonic–clonic seizures are subdivided into primarily generalized, in which there is no obvious focal onset, and secondarily generalized, in which seizures begin in a focal brain region and then spread. In the tonic phase, there are sustained muscle contractions accompanied by high frequency activity on EEG recordings lasting 10–20 s (Table 16.1). This is followed by a variable vibratory stage and then rhythmic clonic contractions of the limbs accompanied by polyspike-and-wave EEG discharges (Theodore et al., 1994; Jobst et al., 2001; Blumenfeld et al., 2009; Varghese et al., 2009). After 1–2 min, clinical and EEG seizure activity usually abruptly stops, and the patient remains deeply lethargic, unresponsive, and with markedly suppressed EEG amplitude for a variable time in the postictal period. In the ictal and postictal periods, patients are deeply unresponsive to even basic tasks such as ball grasp, visual tracking or blink to visual threat (McPherson et al., 2012). Although amnesia commonly occurs for events around the time of generalized tonic–clonic seizures, in rare cases patients remain conscious and can reliably describe their experiences afterwards, possibly when seizures remain relatively confined to bilateral frontal regions (Botez et al., 1966; Weinberger and Lusins, 1973; Bell et al., 1997).

Some previous studies, including those using electrophysiological, blood flow, and metabolic mapping, suggest that the entire brain may be homogeneously involved in generalized tonic–clonic seizures (Matsumoto and Marsan, 1964; Engel et al., 1978, 1982; Handforth and Treiman, 1995; McCown et al., 1995; Andre et al., 2002). However, other animal studies show more regional changes (Ackermann et al., 1986; McIntyre et al., 1991; DeSalvo et al., 2010). Furthermore, secondarily generalized tonic–clonic seizures in humans often cause focal postictal deficits, reflecting impaired function in the regions of seizure onset (Rolak et al., 1992; Blumenfeld et al., 2003b). SPECT imaging studies of CBF in secondarily generalized tonic–clonic seizures have shown focal involvement as well, often in regions of seizure onset (Lee et al., 1987; Green and Buchhalter, 1993; Koc et al., 1997; Shin et al., 2002; Blumenfeld et al., 2009; Varghese et al., 2009). These findings suggest that secondarily generalized, and possibly also primary generalized tonic–clonic seizures do not involve the entire brain homogenously, but may instead affect certain regions most intensely. Like in absence seizures, identifying the specific regions involved may be important for understanding how generalized tonic–clonic seizures cause impaired consciousness.

SPECT ictal-interictal difference imaging is a useful method for investigating brain regions involved in human generalized tonic–clonic seizures, because this method can be used even when patients move during seizures (Blumenfeld et al., 2003b, 2009; Varghese et al., 2009). This is because the SPECT radiopharmaceutical is injected during the seizure, but the actual imaging can be done later, when the patient is stable. The imaging done later reflects blood flow at the time of the injection, not at the time of imaging. Using this approach, we have imaged spontaneous secondarily generalized tonic–clonic seizures in patients with epilepsy (Blumenfeld et al., 2003b, 2009; Varghese et al., 2009), and generalized tonic–clonic seizures induced by electroconvulsive therapy (ECT) for treatment of refractory depression (in patients without epilepsy) (Blumenfeld et al., 2003a,b; McNally and Blumenfeld, 2004; Enev et al., 2007). In both spontaneous and induced generalized tonic–clonic seizures we saw CBF increases that were most intense in specific focal brain regions. The regions most intensely involved were again in the consciousness system described above. During seizures, there were CBF increases in the thalamus and upper brainstem, and decreases in the cingulate gyrus. In the lateral frontal and parietal cortex there were large CBF increases during seizures. In the postictal period, when patients remain unconscious, there were large CBF decreases in the lateral frontal and parietal cortex, along with continued decreases in the anterior and posterior cingulate.

More recent work has shown that these brain regions undergo a complex sequence of changes at different times during and after generalized tonic–clonic seizures. For example, early on in bilateral ECT-induced seizures, focal increases are seen in the frontotemporal association cortex, near the region of the stimulating electrodes, along with increases in the thalamus (Enev et al., 2007). Thirty seconds later, large increases are seen in the bilateral parietal cortex, along with decreases in the cingulate gyrus (Enev et al., 2007). In the postictal period, study of spontaneous secondarily generalized

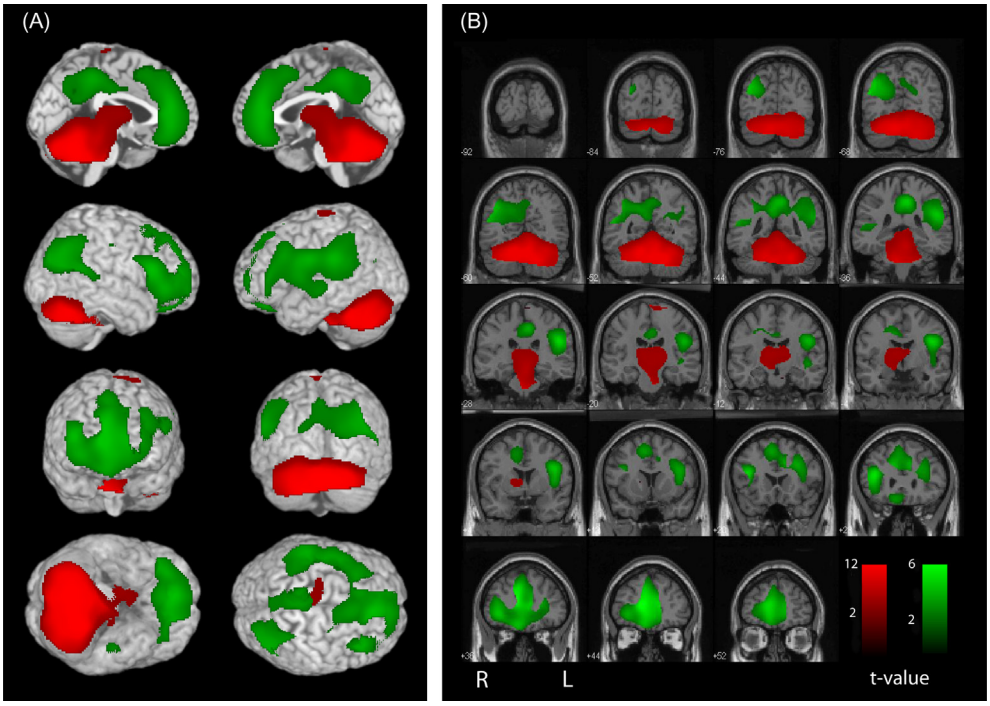

FIGURE 16.2 Consciousness system changes in generalized tonic–clonic seizures correlate with the cerebellum. (A) Surface rendering and (B) coronal sections. Significant positive correlations are seen for cerebellar blood flow changes and those in the upper brainstem tegmentum and thalamus. Negative correlations are seen with changes in the bilateral frontoparietal association cortex, the anterior and posterior cingulate, and the precuneus. Statistical parametric mapping analysis was across ictal-interictal SPECT imaging in 59 patients, with extent threshold $k = 125$ voxels (voxel size 2 mm × 2 mm × 2 mm), and height threshold $p = 0.01$. *Source: Reproduced with permission from Blumenfeld et al. (2009).*

tonic–clonic seizures has shown an interesting progression of CBF increases in the cerebellum (Blumenfeld et al., 2009). Cerebellar CBF increases in the late ictal and early postictal periods are correlated with increases in the thalamus, and with profound CBF *decreases* in frontal and parietal cortex (Figure 16.2). These findings suggest a possible role for inhibitory cerebellar outputs in seizure termination, as well as in ictal and postictal depression of consciousness (Salgado-Benitez et al., 1982; Norden and Blumenfeld, 2002).

It is interesting that the regions most intensely involved in CBF increases during generalized tonic–clonic seizures were the bilateral frontal and parietal association cortex, while intervening regions were relatively spared (Blumenfeld et al., 2003b; Enev et al., 2007). Seizure propagation between frontal and parietal association cortex could occur through long association fiber pathways such as the superior longitudinal fasciculus (Schwartz et al., 1991; Makris et al., 2005), or through cortical-thalamic-cortical interactions (Guillery and Sherman, 2002; Weisman et al., 2003). Sparing of motor cortex supports the notion that the motor manifestations of generalized tonic–clonic seizures may be mediated primarily by brainstem circuitry (Browning, 1985; Velasco et al., 1985; Gale, 1992; Faingold, 1999).

Additional work is needed to better understand the electrophysiological correlates of imaging changes seen during generalized tonic–clonic seizures. It has been shown, for example, that paradoxical imaging changes can occur during tonic–clonic seizures, which do not always accurately reflect the underlying electrical activity (Schridde et al., 2008). It will, therefore, be crucial to further verify neuroimaging findings during tonic–clonic seizures with direct electrical recordings from patients or animals models.

FOCAL IMPAIRED CONSCIOUSNESS SEIZURES

While it is logical that absence and tonic–clonic seizures impair consciousness by involving the brain bilaterally, it has been more difficult to explain how a focal seizure, which involves a unilateral region such as the temporal lobe, can cause impaired consciousness. Traditionally focal seizures with spared consciousness were called simple partial seizures, and those with impaired consciousness were called complex partial seizures (ILAE, 1981). Recently more descriptive terminology has been recommended (Berg et al., 2010), which we have abbreviated as focal aware conscious seizures (FACS) and focal imparied consciousness seizures (FICS) (Blumenfeld and Jackson, 2013). Impaired consciousness in FICS is less severe than in generalized

tonic–clonic seizures, and in many ways resembles sleep parasomnias, encephalopathy or the minimally conscious state in which simple automatic behaviors such as grasping a ball or visual tracking may be spared (Blumenfeld, 2011; McPherson et al., 2012), but higher cognitive functions requiring more purposeful responses or decision making are severely impaired. FICS most often arise from the temporal lobe, and are frequently accompanied by pathological changes referred to as mesial temporal sclerosis (Engel Jr., 1987; Williamson et al., 1993). Temporal lobe seizures typically begin with localized phenomena such as fear, rising epigastric sensation, an indescribable premonition, or lip smacking automatisms (Park et al., 2001; Janszky et al., 2003) (Table 16.1). Although consciousness may be spared initially, progression to impaired consciousness is common during temporal lobe seizures. In addition to impaired responsiveness and amnesia, temporal lobe FICS are often accompanied by automaton-like movements referred to by Penfield as "automatisms," dystonic posturing of the limbs (Marks and Laxer, 1998), and neuroendocrine changes (Bauer, 2001; Quigg et al., 2002). Temporal lobe FICS usually last 1–2 min, and electrographically show 5–7 Hz rhythmic temporal lobe activity on scalp EEG recordings, with some bilateral slowing (Table 16.1). Impaired consciousness can persist for up to several minutes after the seizure has ended (postictal period).

The diverse behavioral repertoire of temporal lobe seizures, and prior human and animal investigations, suggest that more widespread neural networks beyond the temporal lobe are recruited during these events (Newton et al., 1992; Cassidy and Gale, 1998; Shin et al., 2001; Lee et al., 2002; Norden and Blumenfeld, 2002; Zhang and Bertram, 2002). Based on EEG studies, it has been suggested that bilateral temporal lobe involvement is important for loss of consciousness (Gloor et al., 1980; Munari et al., 1980; Bancaud et al., 1994; Inoue and Mihara, 1998; Lux et al., 2002). However, while bilateral temporal lobe dysfunction may cause amnesia (Milner, 1972), it is unclear why this would cause impaired consciousness, manifested as loss of responsiveness and awareness during seizures.

To explain how impaired consciousness could occur with focal temporal lobe seizures, we proposed a "network inhibition hypothesis" (Figure 16.3) (Norden and Blumenfeld, 2002; Blumenfeld and Taylor, 2003; Blumenfeld, 2012). According to this model, impaired consciousness occurs due to spread of temporal lobe seizures to midline subcortical structures (Figure 16.3B, C). These include regions rich in GABAergic neurons such as the lateral septal nuclei and anterior hypothalamus which may inhibit subcortical arousal structures, causing bilateral cortical suppression and impaired consciousness (Figure 16.4D).

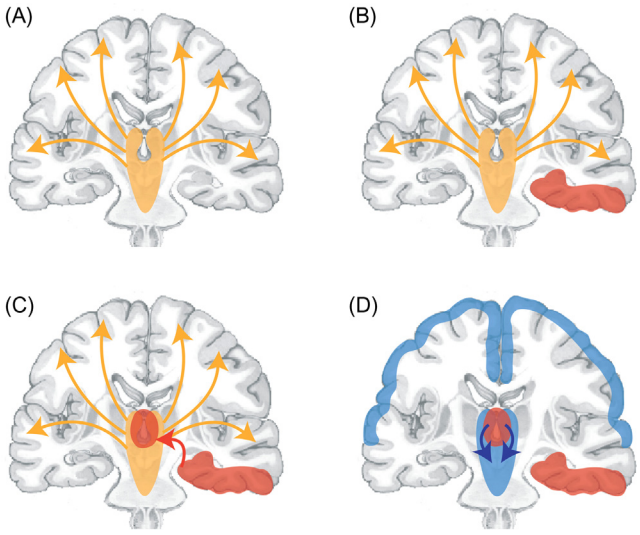

FIGURE 16.3 Network inhibition hypothesis for impaired consciousness in temporal lobe FICS. (A) Under normal conditions, the upper brainstem-diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness (yellow represents normal activity). (B) A focal seizure (red) involving the mesial temporal lobe unilaterally. If the seizure remains confined, a focal seizure without impairment of consciousness will occur. (C) Seizure activity often spreads from the temporal lobe to midline subcortical structures and propagation may also extend to the contralateral mesial temporal lobe (not shown). (D) Inhibition of subcortical activating systems (blue) leads to depressed activity in bilateral frontoparietal association cortex (blue) and to loss of consciousness. *Source: Modified with permission from Englot et al. (2010).*

Recent behavioral studies of focal seizures support a network switching mechanism of the kind proposed by the network inhibition hypothesis. With this mechanism, seizure propagation to subcortical structures is expected to cause a relatively abrupt and global transition in arousal state, severely impairing all higher-order cognitive functions. Indeed, using prospective testing batteries (Yang et al., 2012; Bauerschmidt et al., 2013) focal seizures were found to either impair or spare multiple cognitive functions, leading to a bimodal distribution of deficits (Figure 16.4), unlike other disorders of consciousness in which the severity of deficits lies more on a continuum (Cunningham et al., 2014).

More definitive support for the network inhibition hypothesis comes from functional neuroimaging studies and electrophysiology in both human patients and fundamental animal models. Involvement of the medial thalamus and upper brainstem on ictal SPECT in temporal lobe epilepsy was initially reported by Mayanagi and colleagues (Mayanagi et al., 1996). Lee et al. subsequently found an association between medial thalamic and upper brainstem involvement on SPECT imaging during seizures, and loss of consciousness (Lee et al., 2002). In addition to midline subcortical involvement, SPECT imaging has also identified

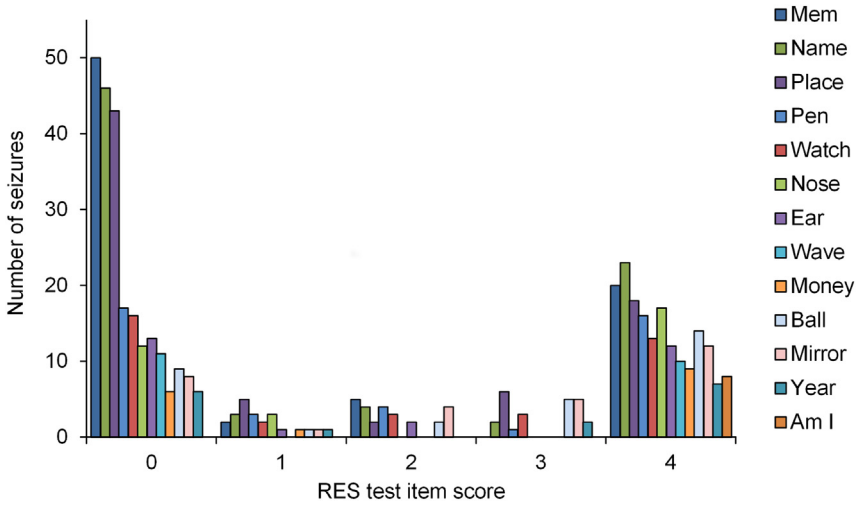

FIGURE 16.4 Bimodal distribution of impaired consciousness in focal seizures. Impairment on behavioral tasks is bimodally distributed, suggesting that propagation to key subcortical structures may cause an abrupt and relatively global change in performance. In support of this, most focal seizures can readily be separated into those with overall impairment (left cluster in the histogram) versus those without overall impairment (right cluster). Multiple standardized behavioral tasks (indicated on right), including both verbal and non-verbal items, were administered prospectively during focal seizures and scored based on video/EEG review. Scores show a bimodal distribution, with the large majority receiving a score of either "0" (no response whatsoever) or "4" (normal, unimpaired response). Data are from 83 focal seizures in 30 patients. A bimodal pattern has not been observed with similar testing items in other disorders of consciousness (Giacino et al., 2004). *Source: Reproduced with permission from Cunningham et al. (2014).*

frontal or parietal hypoperfusion during temporal lobe seizures (Rabinowicz et al., 1997; Menzel et al., 1998; Chang et al., 2002; Van Paesschen et al., 2003). In studying patients with temporal lobe epilepsy who had impaired consciousness during seizures, we found widespread changes outside the temporal lobe on ictal SPECT imaging, especially involving bilateral frontoparietal and midline subcortical regions of the consciousness system (Blumenfeld et al., 2004b) (Figure 16.5). Increased CBF was present in the upper brainstem and medial thalamus. Interestingly, the increases in the medial thalamus were correlated with decreases in the anterior and posterior interhemispheric regions, and in the frontoparietal association cortex (Figure 16.5) (Blumenfeld et al., 2004b). In contrast, temporal lobe seizures in which consciousness was spared were associated with more focal changes confined to the temporal lobes, and did not show frontoparietal or midline subcortical changes. Several additional studies have shown similar involvement of midline subcortical structures on SPECT imaging during temporal lobe seizures (Kaiboriboon et al., 2005; Tae et al., 2005; Kim et al., 2007).

These neuroimaging findings suggest that loss of consciousness during temporal lobe seizures may be caused by abnormal activity in the midline subcortical structures and depressed function of the frontoparietal association cortex. What are the physiological changes underlying the decreased CBF in the frontoparietal cortex? Interestingly, human intracranial EEG studies have shown slow waves in the association cortex during temporal lobe seizures (Lieb et al., 1991; Mayanagi et al., 1996; Blumenfeld et al., 2004a). Some have interpreted this as "propagation" of seizure activity outside the temporal lobe; however, unlike the high frequency seizure discharges seen in the temporal lobe, the activity in the frontoparietal association cortex consists of slow waves, without spike or sharp components (Figure 16.6A–D) (Blumenfeld et al., 2004a). We have argued that this slow rhythm on intracranial recordings does not represent seizure activity, but instead more closely resembles the EEG patterns seen in sleep, coma, or encephalopathy (Blumenfeld et al., 2004a). Further support for this has come from quantitative studies of intracranial EEG in temporal lobe epilepsy, confirming distinct patterns of high frequency activity in the temporal lobe and low frequency activity in the association cortex. Importantly, temporal lobe seizures with impaired consciousness show greater bilateral frontoparietal slow wave activity (as well as temporal lobe fast activity) compared to seizures without impaired consciousness (Figure 16.6E–H) (Englot et al., 2010). Increased thalamocortical synchrony, particularly in the slower frequency ranges, has also been reported in FICS (Guye et al., 2006; Arthuis et al., 2009; Bartolomei, 2012; Lambert et al., 2012).

Recent work in an animal model of temporal lobe seizures further supports the following two conclusions: (i) ictal neocortical slow wave activity is a distinct state of depressed cortical function that is different

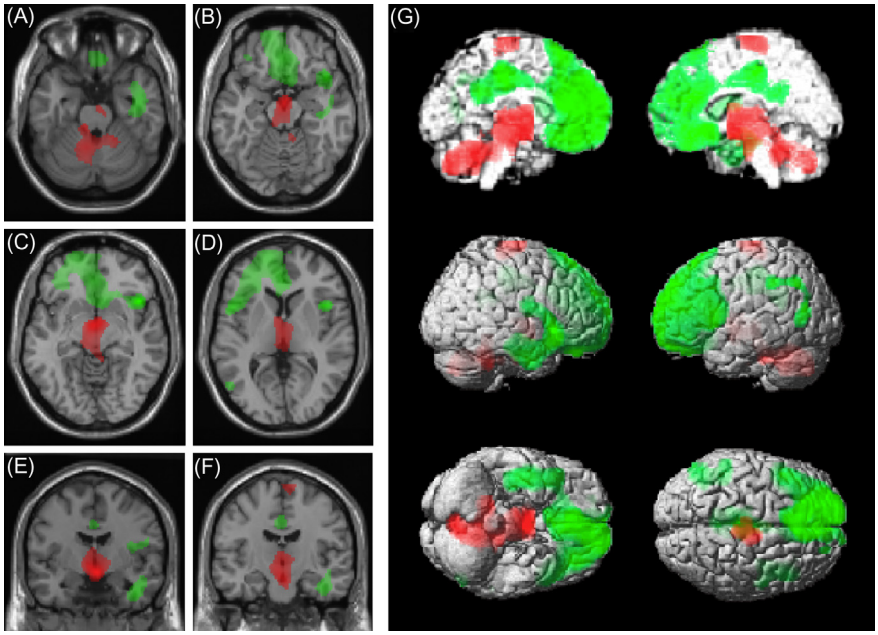

FIGURE 16.5 Cerebral blood flow imaging in temporal lobe seizures with impaired consciousness. FICS arising from the temporal lobe are associated with significant cerebral blood flow increases and decreases in widespread brain regions. Statistical parametric maps depict SPECT increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain (combining patients with left and right onset seizures, $n = 10$). Data are from >90 s after seizure onset, when consciousness was markedly impaired. Note that at earlier times there were SPECT increases in the ipsilateral mesial temporal lobe (not shown). (A)–(D) Horizontal sections progressing from inferior to superior, and (E) and (F) coronal sections progressing from anterior to posterior showing blood flow increases in the bilateral midbrain, hypothalamus, medial thalamus, and midbrain. Decreases are seen in the bilateral association cortex. (G) 3-dimensional surface renderings show increases mainly in the bilateral medial diencephalon, upper brainstem and medial cerebellum, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (same data as (A)–(F)). Extent threshold, $k = 125$ voxels (voxel size = 2 mm × 2 mm × 2 mm). Height threshold, $p = 0.01$. *Source: Reproduced with permission from Blumenfeld et al. (2004b).*

physiologically from seizures, and more closely resembles coma, slow wave sleep, or encephalopathy; (ii) as proposed in the network inhibition hypothesis (Figure 16.3), focal limbic (hippocampal or temporal lobe) seizures propagate to inhibitory subcortical regions, which in turn depress subcortical arousal systems, leading to cortical slow wave activity and impaired consciousness. The first conclusion is based on recordings during focal limbic hippocampal seizures in rats, which demonstrate slow wave activity in the frontal cortex, accompanied by decreased neuronal firing and decreased CBF which closely resembles deep anesthesia in the same model (Englot et al., 2008). The physiology of ictal cortical slow waves further differs from seizure activity and resembles deep sleep or anesthesia based on the presence of decreased BOLD fMRI signals, decreased cerebral blood volume, and decreased cortical metabolic rate of oxygen consumption (Englot et al., 2008). Together, these findings suggest that focal seizure activity in the temporal lobe may put the cortex into a sleep-like state, resulting in loss of consciousness.

Support for the second conclusion, and for the network inhibition hypothesis as a mechanism for impaired consciousness in focal limbic seizures comes from the following additional experiments in the animal model: (i) fMRI during seizures demonstrates increases in subcortical inhibitory regions such as the lateral septal nuclei and anterior hypothalamus, along with decreases in arousal regions such as the thalamic intralaminar nuclei and midbrain reticular formation, as well as in the frontoparietal cortex (Englot et al., 2008, 2009; Motelow et al., 2015); (ii) cutting the fornix prevents propagation of seizure activity into subcortical inhibitory structures such as the lateral septum, and also prevents ictal cortical slow wave activity and behavioral arrest (Englot et al., 2009); (iii) stimulation of the lateral septum can mimic the effect of seizures (without seizure activity) by inducing cortical slow waves, behavioral arrest, and decreased cortical cholinergic neurotransmission (Englot et al., 2009; Li et al., 2015); (iv) focal limbic seizures cause decreased firing of cholinergic neurons in the brainstem pedunculopontine tegmental nucleus and in the basal forebrain, as well as decreased firing of serotonergic neurons in the raphe nuclei (Zhan et al., 2014; Motelow et al., 2015); (v) focal limbic seizures cause decreased cholinergic

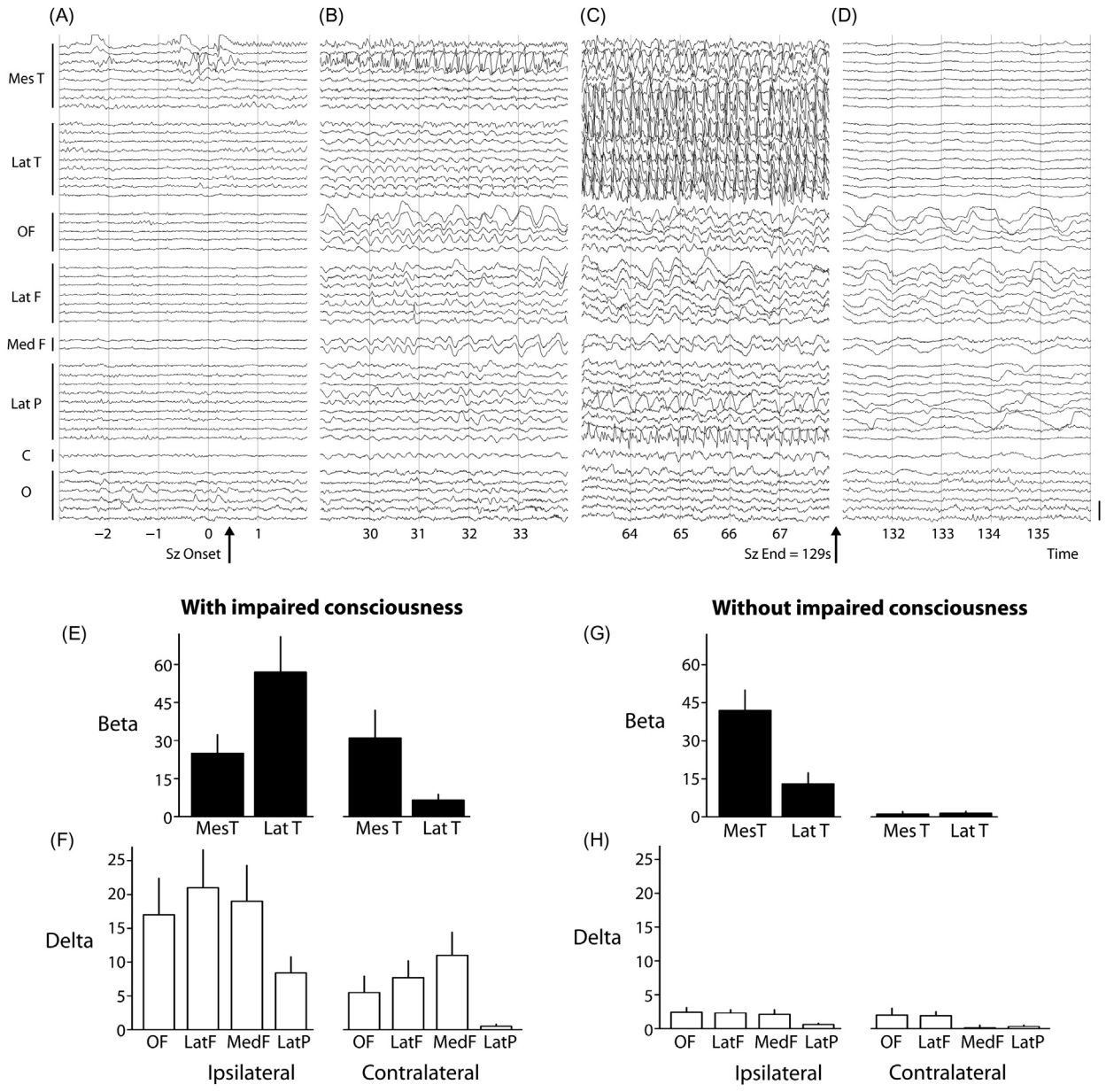

FIGURE 16.6 EEG in temporal lobe seizures with impaired consciousness shows cortical slow wave activity. (A)–(D) Time course of intracranial EEG changes during typical temporal lobe seizure with impaired consciousness. Only ipsilateral contacts are shown. Bars along left margin indicate electrode contacts from different strips, rows, or depth electrodes in the indicated brain regions. A subset of representative electrodes are shown of the 128 studied in this patient. Calibration bar on right is 3 mV. Montage is referential to mastoid. (A) Seizure onset with low-voltage fast activity emerging from periodic spiking in the mesial temporal contacts. (B) Sample of EEG from early seizure. Rhythmic polyspike and sharp wave activity develops in the mesial temporal lobe, while the frontal and parietal contacts show large-amplitude irregular slow activity. (C) Sample of EEG from mid-seizure. Polyspike-and-wave activity is present in the mesial and lateral temporal lobe contacts, with ongoing slow waves in the association cortex. Para-central Rolandic and occipital contacts are relatively spared. (D) Postictal suppression is seen in temporal lobe contacts, with continued irregular slowing in the frontoparietal neocortex. (E)–(H) Group data. Focal temporal lobe seizures with impaired consciousness have bilateral increases in temporal beta frequency and frontoparietal delta frequency activity, while seizures without impaired consciousness show mainly increases in ipsilateral temporal lobe beta. Mean fractional changes ($\pm$SEM) in intracranial EEG power compared to 60 s pre-seizure baseline. (E) Temporal lobe beta in seizures with impaired consciousness. (F) Neocortical delta in seizures with impaired consciousness. (G) Temporal lobe beta in seizures without impaired consciousness. (H) Neocortical delta in seizures without impaired consciousness.

Bilateral temporal lobe beta activity and frontoparietal delta activity were significantly higher in seizures with versus without impaired consciousness ($p < 0.05$, Mann Whitney U test; $n = 38$ seizures with impaired consciousness and 25 seizures without impaired consciousness in 26 patients). Mes T, mesial temporal; Lat T, lateral temporal; OF, orbital frontal; Lat F, lateral frontal; Med F, medial frontal; Lat P, lateral parietal; C, perirolandic pre- and post-central gyri; O, occipital. *Source: Reproduced with permission from Englot et al. (2010).*

neurotransmission in the intralaminar thalamus and in the frontal cortex measured by biosensor probes (Motelow et al., 2015); (vi) optogenetic stimulation of cholinergic brainstem pedunculopontine tegmental nucleus neurons during seizures abolishes cortical slow wave activity (Furman et al., 2013); (vii) electrical stimulation of thalamic intralaminar nuclei in the postictal period abolishes slow wave activity and increases normal arousal and behavioral responsiveness (Gummadavelli et al., 2015).

These exciting findings have advanced the mechanistic understanding of impaired consciousness in focal seizures, and raise the possibility of therapeutic interventions to improve behavioral arousal in patients with uncontrolled seizures.

SUMMARY AND PRACTICAL IMPLICATIONS

We have seen that diverse seizure types cause impaired consciousness through involvement of common structures in the consciousness system, including the thalamus, basal forebrain and upper brainstem, interhemispheric regions (medial frontal cortex, cingulate, and precuneus), and lateral frontal and parietal association cortex. Absence seizures, generalized tonic–clonic seizures, and temporal lobe FICS all converge on the same anatomical regions when consciousness is impaired. The physiological mechanisms differ, however. Absence seizures cause widespread increases followed by decreases in activity throughout consciousness system networks. Generalized tonic–clonic seizures cause increases and decreases in cortical networks extending into the postictal period that correlate with cerebellar increases. Temporal lobe FICS cause depressed subcortical-cortical arousal affecting the consciousness system in the ictal and postictal periods.

There is much remaining work to be done to more fully understand the mechanisms of impaired consciousness in epilepsy. In all three seizure types, direct electrophysiological recordings are needed to better interpret the meaning of neuroimaging signals. For example, it is not known whether regions showing fMRI decreases during absence seizures will exhibit spike-wave discharges, relative silence, or some other pattern on electrophysiological measurements.

Impaired consciousness in epilepsy has a major negative effect on patient quality of life. The amount of time that patients spend before returning to normal after seizures has been shown to have a strong correlation with reduced quality of life (Vickrey et al., 2000). Impaired quality of life in patients with epilepsy includes a shorter life expectancy, and greater risk of injuries than the general population (Vickrey et al., 2000; Sperling, 2004; Theodore et al., 2006). Epilepsy-related injuries such as burns, falls, and motor vehicle accidents are often caused by impaired consciousness during seizures. In addition, impaired postictal arousal may prevent patients from safely recovering from mechanical airway obstruction (e.g., when lying face-down) leading in some cases to suffocation and SUDEP (Buchanan et al., 2013; Ryvlin et al., 2013; Sowers et al., 2013; Massey et al., 2014).

Patients with seizures causing impaired consciousness are not permitted to drive, which often has a large effect on self-esteem, and employability, contributing to the economic impact of epilepsy (Begley and Beghi, 2002; Begley et al., 2002). Risk of motor vehicle accidents, including those causing death, is increased in patients with epilepsy (Hansotia and Broste, 1991; Taylor et al., 1996; Krauss et al., 1999; Sheth et al., 2004). Motor vehicle accident risk is highest in seizures causing impaired consciousness such as generalized tonic–clonic seizures and FICS, less in FACS (Gastaut and Zifkin, 1987; Berkovic, 2000; Chen et al., 2014). Prospective testing of patients with driving simulators during seizures has provided additional insights into the hazards of driving during seizures associated with impaired consciousness (Yang et al., 2010; Chen et al., 2013). The stigma of suddenly losing conscious control of one's actions in public also has a large adverse effect (Jacoby et al., 2005). In addition, another negative consequence of impaired consciousness during seizures is that it may result in under-reporting of seizure occurrence to health care providers, leading to challenges in knowing how to best adjust seizure medications (Ezeani et al., 2012; Detyniecki and Blumenfeld, 2014).

With a greater understanding of the mechanisms of impaired consciousness in epilepsy it may be possible to devise new treatments to prevent these adverse consequences. Although the first goal is to stop all seizures, including both those do and do not cause impaired consciousness, in many cases this is not possible. Often a large improvement would be made if the seizures causing impaired consciousness could be stopped, even if some seizures without impaired consciousness remained. Implantation of deep brain stimulators is a growing field both for the treatment of epilepsy (Murphy and Patil, 2003; Theodore and Fisher, 2004; Morrell, 2006; Heck et al., 2014), and disorders of consciousness (Yamamoto and Katayama, 2005; Schiff et al., 2007). It may be possible to devise stimulation protocols or electrode locations that if, unable to fully block seizures, will at least prevent impaired consciousness. Knowledge of the specific brain networks, and underlying biological changes in the regions causing impaired consciousness in epilepsy may also allow the targeting of improved medications to these regions. New drugs which help patients retain

consciousness during seizures would be a very welcome addition for patients with medically refractory epilepsy.

In conclusion, investigation of impaired consciousness in epilepsy may have a large impact on improving quality of life in this disorder. In addition, by understanding the specific anatomical brain regions that are crucial for changes in consciousness, and how patterns of neuronal activity during seizures alter information flow, we may also gain important insights into normal mechanisms for human consciousness.

Acknowledgments

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CHAPTER

17

Split-Brain, Split-Mind

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OUTLINE

Decades of research on split-brain patients have shown that splitting the corpus callosum splits the conscious mind as well. The corpus callosum enables interhemispheric communication and consists of approximately 200–250 million axons that project from the cerebral cortex of one hemisphere to the other (Aboitiz et al., 1992; Nolte, 2009). In some cases of intractable epilepsy, the corpus callosum is severed to reduce the frequency and severity of patients' seizures. This surgical procedure blocks the hemispheric transfer of sensory, motor, perceptual, and semantic information (Gazzaniga, 2000, 2005). Despite their anatomical and functional disconnection, however, extensive experimentation has shown that both hemispheres of a split-brain patient are conscious—at least conscious in the sense that both hemispheres can recognize words and objects, create and retrieve memories, initiate voluntary behaviors, and possess a sense of self. Additionally, each hemisphere of a split-brain patient cannot access the thoughts, intentions, or conscious experience of the opposite hemisphere, much as we cannot access the mental states of other individuals (Gazzaniga, 2000; Sperry, 1984). Since it appears that each hemisphere of a split-brain patient is conscious, and the conscious experience of each hemisphere is private and independent of the other hemisphere, we argue that consciousness is divisible. Split-brain patients demonstrate that disconnecting the two cerebral hemispheres creates two distinct—though not identical—conscious entities.

The divided consciousness of split-brain patients supports the idea that consciousness is an emergent property that arises out of the dynamic interaction of many specialized cognitive systems, or modules. As has been widely shown, the brain consists of numerous local neural circuits that perform specialized computations on specific inputs (Gazzaniga, 1989; Kanwisher, 2001). These specialized systems vie for attention, which serves to boost the neural activity in the attended system (Dehaene and Naccache, 2001; Gazzaley et al., 2005). When any one cognitive module becomes sufficiently activated, we suggest it enters conscious awareness, where it remains until the activity of another cognitive system supersedes it. In this view, the brain consists of hundreds of localized, competing circuits that bubble up into conscious awareness and the content of consciousness at any given moment is determined by what cognitive module is most active. Conscious experience, therefore, is contingent on the characteristics of localized neural circuits: any processing biases at the local level will affect consciousness on the global, hemispheric level. Since the two

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hemispheres contain unique sets of specialized neural systems, one would expect the conscious experiences of the hemispheres to differ following split-brain surgery. Split-brain studies suggest that the conscious experiences of the two disconnected hemispheres do indeed differ. As we will see, the manifestations of these differences can range from the complete lateralization of a particular cognitive function, such as language, to subtle differences in cognitive strategies and biases.

In this chapter, we review evidence that both hemispheres of a split-brain patient are conscious, even though the consciousness of the right hemisphere may be less enriched than the left. We also review instances in which the behavior and cognitive styles of the hemispheres vary, presumably because each hemisphere is comprised of a different set of specialized cognitive modules. Finally, we offer several explanations as to why split-brain patients feel unified despite having disconnected conscious experiences, and we discuss the implications of split-brain research on current theories of consciousness.

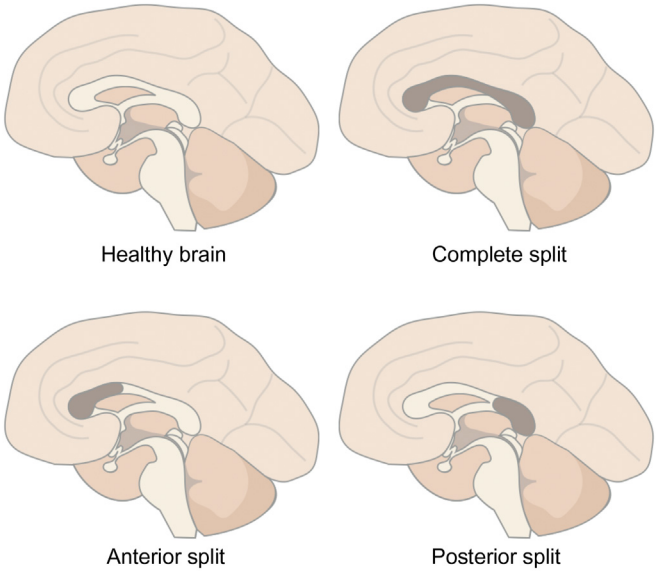

FIGURE 17.1 Brain anatomy of a healthy individual with an intact corpus callous (top left), a split-brain patient with a complete callosotomy (top right), a split-brain patient with an anterior callosotomy (bottom left), and a split-brain patient with a posterior callosotomy (bottom right).

TWO CONSCIOUS HEMISPHERES

In the 1930s, the neurosurgeon Willam Van Wagenen observed that epileptic patients with tumors that encroached on the corpus callosum appeared to be relieved of their severe seizures. So, across a 4-month period in 1939, Van Wagenen, along with his colleague Yorke Herren at the Strong Memorial Hospital in Rochester, NY, conducted a surgical procedure on ten patients with intractable epilepsy with the intention of severing the corpus callosum, either partially or completely (Van Wagenen and Herren, 1940) (Figure 17.1). Van Wagenen seemed quite pleased with the results and commented in the published report that "as a rule, consciousness is not lost when the spread of the epileptic wave is not great or *when it is limited to one cerebral cortex*" (p. 740, emphasis ours).

There was concern, however, that disconnecting the two hemispheres might create two dueling psyches, each fighting for control of the body. Van Wagenen's colleague, the psychiatrist Andrew Akelaitis, took the opportunity to test this idea in the 1940s with Van Wagenen's new "split-brain" patients and conducted a series of studies on their visual, motor, and language abilities (Akelaitis, 1941, 1943, 1945). Remarkably, he found them to be quite normal and mentally unaffected by the surgeries; "The observation that some of these patients were able to perform highly complex synchronous bilateral activity as piano-playing, typewriting by means of the touch systems and dancing postoperatively suggests strongly that commissural pathways other than the corpus callosum are being utilized" (Akelaitis, 1943, p. 259).

But the neurosurgeon Joseph Bogen suggested decades later that Akelaitis's observations may have been the result of incomplete corpus callosotomies (Bogen, 1997).[1] Indeed, Bogen was intrigued by the result of the surgeries of Van Wagenen, and re-introduced a more complete surgical procedure over two decades after Van Wagenen's surgeries (Bogen et al., 1965). In the 1960s at Cal Tech, Bogen teamed up with Roger Sperry and Michael Gazzaniga to study the effects of the callosotomy surgeries he was performing and found that, besides initial difficulties with language and movement, split-brain patients did not evince any obvious psychological or behavioral abnormalities (Gazzaniga et al., 1962; Sperry, 1961).

Despite concerns that severing the corpus callosum might create two dueling minds, patients who underwent callosotomy appeared normal and healthy. In fact, it was not until lateralized testing procedures were implemented that the psychological side effects of callosotomy were detected (Gazzaniga et al., 1962). Lateralized procedures involve selectively presenting stimuli to, and recording responses from, one hemisphere (Figure 17.2). Lateralized testing procedures exploit the fact that each hemisphere controls the opposite side of space: the left hemisphere receives visual input from the right side of space and primarily

[1]Years later Dr. Bogen, then a resident of Van Wagenen, made the same point to one of us (MSG).

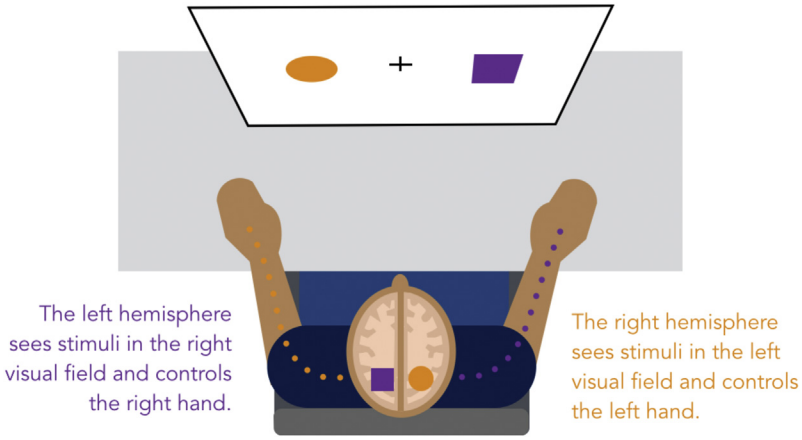

FIGURE 17.2 Lateralization procedure used in split-brain studies. As patients fixate on a central cross, stimuli are presented in patients' left or right visual fields. The right hemisphere processes stimuli presented in the left visual field and controls the left hand. The left hemisphere processes stimuli presented in the right visual field and controls the right hand. Since language is largely lateralized to the left hemisphere, patients' verbal responses originate from the left hemisphere.

controls the right hand, while the right hemisphere receives visual input from the left side of space and controls the left hand (Gazzaniga, 2000). By presenting stimuli to the left half of the visual field and asking patients to respond with their left hand, researchers can selectively probe the contents of the right hemisphere, and vice versa. Thus, lateralized testing on split-brain patients allows one hemisphere to be assessed in isolation from the other hemisphere.

Prominent differences between the hemispheres emerged after the implementation of lateralized experimental procedures. The most notable difference between the two hemispheres involves their capacity for language, with the language skills of the left hemisphere far surpassing those of the right. For example, when asked to identify objects with his left or right hand, one split-brain patient performed normally when using his right hand, but exhibited severe agnosia, anomia, and agraphia when using his left hand (Gazzaniga et al., 1962). Similarly, the patient could identify visual stimuli that were presented to the right half of his visual field, but not the left. These results suggest that the left hemisphere can easily recognize and name objects while the right hemisphere is severely impaired at doing so. Further experimentation on split-brain patients has shown that the semantic system of the left hemisphere is more complex and organized than the right (Baynes et al., 1992; Gazzaniga, 1983, 2000; Gazzaniga and Miller, 1989; Gazzaniga et al., 1984a; Reuter-Lorenz and Baynes, 1992) and only the left hemisphere can convert graphemes to phonemes (Benson and Zaidel, 1985; Zaidel and Peters, 1981), a skill necessary for sub-lexical reading (Ehri, 2005; Joubert and Lecours, 2000). Split-brain studies have also shown that the left hemisphere exclusively produces complex spoken language and the verbal IQ of the disconnected left hemisphere is comparable to the patients' verbal IQ prior to surgery (Nass and Gazzaniga, 1987). The sophisticated linguistic abilities of the disconnected left hemisphere suggest that it possesses a rich consciousness that may be comparable to the consciousness of normal individuals. In addition to its superior language capabilities, the left hemisphere also retains normal problem-solving skills (Ledoux et al., 1977) and reasoning abilities (Roser et al., 2005; Wolford et al., 2000) following callosotomy. The cognitive and linguistic abilities of the isolated left hemisphere are comparable to those of a healthy individual with an intact corpus callosum, suggesting that the left hemisphere retains a rich, human-like consciousness following split-brain surgery. Indeed, split-brain patients appear so normal because of the extraordinary capabilities of the speaking left hemisphere.

There is little doubt that the left hemisphere of a split-brain patient is conscious, but what about the right hemisphere? Although the abilities of the right hemisphere are not as numerous or complex as the left, we argue the right hemisphere is indeed conscious. Split-brain studies indicate that the right hemisphere's capacity for language is variable among split-brain patients and may gradually increase following surgery (Baynes, 1990; Gazzaniga et al., 1984b). Although language in the right hemisphere is limited, the right hemisphere can read whole words and access their semantic content (Benson and Zaidel, 1985; Gazzaniga and Sperry, 1967; Gazzaniga and Smylie, 1984; Zaidel and Peters, 1981) and, in some cases, can understand syntax and produce simple speech (Gazzaniga et al., 1984b). The right hemisphere can also understand and follow a variety of task instructions, which requires at least some language comprehension. Additionally, the right hemisphere outperforms the left in several domains, such as perception, spatial processing, facial recognition, and recognition memory. Compared to the left hemisphere, the right hemisphere is better at perceiving illusory contours (Corballis et al., 1999a), completing amodal boundaries (Corballis et al., 1999a), and detecting apparent motion (Forster et al., 2000). The right hemisphere also excels at spatial tasks involving mental rotation (Corballis and Sergent, 1988), spatial matching

(Corballis et al., 1999b), part-whole relations (Nebes, 1972), spatial relationships (Nebes, 1973), and mirror image discrimination (Funnell et al., 1999). Finally, the right hemisphere is specialized for detecting and recognizing faces (Gazzaniga and Smylie, 1983; Gazzaniga, 1989; Levy et al., 1972; Miller et al., 2002) and has a more accurate memory than the left (Metcalfe et al., 1995; Phelps and Gazzaniga, 1992).

Most importantly, the right hemisphere satisfies the defining attributes of consciousness, which include possessing a sense of self and initiating purposeful behavior (Damasio and Meyer, 2009). In a split-brain experiment designed to assess the consciousness of each hemisphere, a series of open-ended questions were presented selectively to each hemisphere of a split-brain patient and the patient used two sets of Scrabble tiles to spell out his answers to the questions (LeDoux et al., 1977). The experiment revealed that the right hemisphere has feelings, a sense of self, likes and dislikes, a sense of time, and future goals and aspirations—all indications of consciousness. Furthermore, the right hemisphere conveyed its answers with lettered tiles that could be arranged in an infinite number of ways, suggesting the right hemisphere can behave in an unconstrained, complex, and goal-directed manner. In the same experiment, words were presented to each hemisphere individually and the patient reported how much he liked or disliked the word or how good or bad the word was. The experimenters found that the judgments of the left and right hemispheres were similar for some items, but differed substantially for others. This suggests that each hemisphere can assign subjective values to external stimuli, and these assignments may differ between hemispheres. In another experiment, the right hemisphere was found to possess "a well developed sense of self and social awareness" (Sperry et al., 1979, p. 163); patients' right hemispheres could identify their relatives, pets, and belongings, and demonstrated semantic knowledge of historical figures, politicians, and celebrities. Furthermore, the right hemisphere appropriately assigned subjective ratings to stimuli. For example, the right hemisphere of one split-brain patient gave "thumbs-down" signals to pictures of Hitler, Castro, and a war scene, and "thumbs-up" signals to Johnny Carson, Churchill, and pretty girls. Although these studies suggest the right hemisphere possesses a sense of self, it is important to note that the right hemisphere's responses may instead simply reflect conditioned associates; that is, it is possible that right hemisphere can access episodic and semantic information, along with any related associations, but nonetheless lacks a subjective sense of self. Experiments designed to assess the right hemisphere's sense of self more directly are currently underway and will hopefully shed light on the subjective experience of the disconnected right hemisphere. In sum, numerous split-brain studies suggest that both hemispheres are indeed conscious, although the conscious experience of the right hemisphere may be more limited or impoverished than the left.

TWO CONSCIOUS HEMISPHERES WITH DIFFERENT CONSCIOUS EXPERIENCES

Although each hemisphere of a split-brain patient is conscious, the conscious experiences of the hemispheres differ substantially because they contain unique sets of specialized cognitive modules (Figure 17.3). Some specialized local circuits, such as those that produce and understand complex language, are completely lateralized to one hemisphere, which results in drastically different

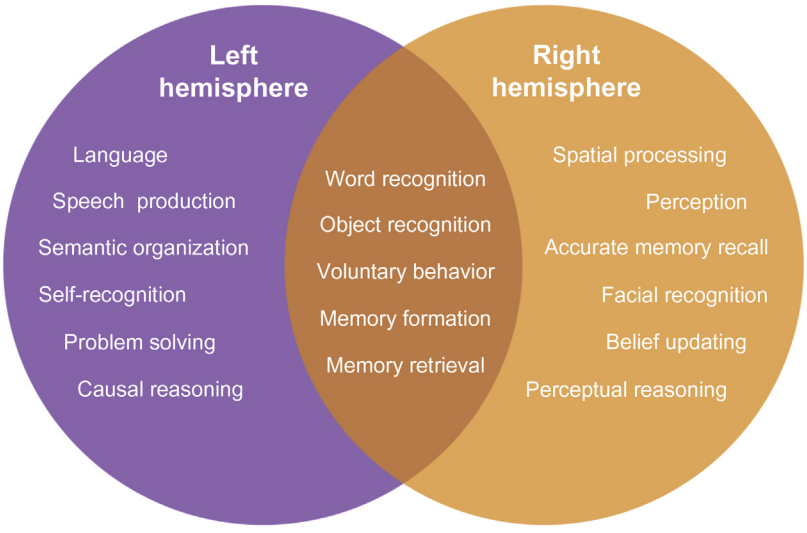

FIGURE 17.3 Cognitive processes that the left hemisphere (purple) or right hemisphere (orange) excel at. Cognitive processes that are strongly bilateral are depicted in dark orange.

hemispheric conscious experiences. Other cognitive modules are present in both hemispheres but exhibit different processing characteristics. In these cases, the differences in each hemisphere's conscious experience may be subtle, and may take the form of cognitive biases or strategies. We have already examined how the hemispheres' capacities for language, spatial processing, and perception differ. Here, we briefly review how the hemispheres diverge in regards to memory, reasoning, and the self.

Though both hemispheres can create and retrieve memories, the right hemisphere tends to recall material more accurately than the left (Metcalfe et al., 1995; Phelps and Gazzaniga, 1992). In one experiment, split-brain patients were shown visual scenes with a common theme, such as getting ready for work (Phelps and Gazzaniga, 1992). After a period of time, each hemisphere was tested for its memory of the scenes. Both hemispheres recognized most of the presented scenes, but the left hemisphere tended to also falsely recognize scenes that were not presented previously but nonetheless fit the scenes' theme. The tendency for the left hemisphere to falsely recognize items that fit a gist has since been replicated (Metcalfe et al., 1995) and is also observed in patients with unilateral right hemisphere brain damage (Braun, 2007). The memory of each hemisphere also differs depending on what stimuli are used; the left hemisphere has superior memory for verbal stimuli whereas the right hemisphere has superior memory for visual stimuli, such as faces (Miller et al., 2002).

The hemispheres also differ in their abilities to make inferences and update beliefs (Marinsek et al., 2014). Unlike the right hemisphere, the left hemisphere can infer casual relationships between objects (Gazzaniga and Smylie, 1984), infer rules based on a series of causal events (Roser et al., 2005), and create a cognitive model or hypothesis to predict future events (Wolford et al., 2000). Although the right hemisphere is impaired at creating higher-order inferences, there is evidence that it may play a prominent role in perceptually-based inference making. The right hemisphere can create a cognitive model to predict future events when faces are used as stimuli (Miller and Valsangkar-Smyth, 2005) and can skillfully judge the causality of perceptual events, such as two balls colliding (Roser et al., 2005). The right hemisphere may also play a role in updating inappropriate beliefs or hypotheses. In a recent study, split-brain patients made verbal moral judgments about scenarios that featured characters with helpful or cruel intentions and that resulted in either neutral or harmful outcomes (Miller et al., 2010). The responses of the split-brain patients' left hemispheres are consistent with the idea that the left hemisphere based its judgment on the initial set up of the scenario (which revealed the potential danger of the situation), and failed to update its initial judgment when new evidence about the characters' intentions was provided.

Finally, the left hemisphere may have a more enriched sense of self than the right hemisphere. Turk et al. (2002) tested each hemisphere's capacity for self-recognition by presenting a series of morphed faces to each hemisphere of a split-brain patient and asking the patient to judge whether the face was his own or a familiar other's. Each face consisted of a graded combination of the patient's face and the face of a familiar other (e.g., the experimenter or the president), and ranged from 100% of the patient's face to 100% of the familiar other's face. They found that the patient's left hemisphere was biased toward making self-judgments and his right hemisphere was biased toward making familiar-other-judgments; that is, the left hemisphere was more likely to consider a morphed face his own and the right hemisphere was more likely to consider it someone else's.

A SPLIT-BRAIN CONUNDRUM AND THE LEFT HEMISPHERE INTERPRETER

The most remarkable and perplexing finding to emerge from split-brain research is the fact that, despite evidence that split-brain patients have a divided consciousness, these patients feel unified. As Zaidel writes, "Their walk is coordinated, their stride is purposeful, they perform old unilateral and bilateral skills, converse fluently and to the point, remember long-term events occurring before surgery, are friendly, kind, generous, and thoughtful to the people they know, have a sense of humor, and so on down a whole gamut of what it takes to be human" (Zaidel, 1994, p. 9–10). After complete commissurotomy, split-brain patients do not exhibit distress or internal conflict, nor do they report any subjective feelings associated with a dual consciousness. So then, if both hemispheres are conscious and the conscious experiences of the two hemispheres differ, why do split-brain patients *feel* united?

One possibility is that the consciousness of the hemispheres is not completely split. As Roger Sperry (1984) suggested, the consciousness of split-brain patients may be Y-shaped; that is, consciousness may be divided at the hemispheric level but not at the subcortical level. Subcortical connections may help unify the conscious experiences of the hemispheres by supporting the subcortical transfer of some types of information, such as emotional valence or mood (Gazzaniga, 2000). Similar inputs to the two hemispheres may also help unify their conscious experiences. Bilateral afferents, such as facial sensation, audition, pain, temperature, pressure, and proprioception, provide identical information to each hemisphere, which may lead to the recruitment of similar

cognitive processes (Sperry, 1984). In non-experimental settings, the two hemispheres also receive similar visual information since patients can freely explore their environments. Additionally, the two hemispheres of split-brain patients can communicate with each other via external cueing, such as by using hand gestures or language, for example. All of these facts may compensate for the lack of interhemispheric communication due to commissurotomy and may serve to lessen the division between the conscious experiences of the two disconnected hemispheres of a split-brain patient (Gazzaniga, 2012).

Alternatively, split-brain patients may not feel conflicted because the left hemisphere plays a dominant role in cognition. As we have seen, the language and problem-solving abilities of left hemisphere far surpass those of the right. The relatively impoverished consciousness of the right hemisphere may prevent it from exerting control, which may in turn contribute to the feeling of a unified consciousness. However, we would expect that the right hemisphere would at least occasionally disagree with the intents and actions of the left hemisphere. Since emotions have been shown to transfer to the opposite hemisphere subcortically (Gazzaniga, 2000), the dominant left hemisphere should be able to detect the discomfort of the right hemisphere in these cases. In one series of experiments, researchers instructed a split-brain patient's disconnected hemispheres to make subjective judgments about a list of words (LeDoux et al., 1977). They found that "on a day that this boy's left and right hemispheres equally valued himself, his friends, and other matters, he was calm, tractable, and appealing. On a day when testing indicated that the right and left sides disagreed on these evaluations, the boy became difficult to manage behaviorally" (p. 420). Although this finding is limited to one patient, it suggests that conflicting conscious experiences, goals, and intentions may produce noticeable subjective feelings. However, these feelings may be wrongly interpreted as a change in mood or temperament.

Finally, and perhaps most importantly, the left-brain interpreter may preserve the subjective unity of split-brain patients. The left-brain interpreter refers to a cognitive system that is exclusive to the left hemisphere. The interpreter "makes sense of all the information bombarding the brain, interpreting our responses—cognitive or emotional—to what we encounter in our environment, asking how one thing relates to another, making hypotheses, bring order out of chaos, creating a running narrative of our actions, emotions, thoughts and dreams. The interpreter is the glue that keeps our story unified and creates our sense of being into a coherent, rational agent" (Gazzaniga, 2008). The interpreter may serve to reconcile salient conflicts or feelings of disunity between the hemispheres. For example, in one experiment the left hemisphere was shown a picture of a chicken claw and right hemisphere was shown a picture of snow scene (Gazzaniga, 2000). Next, the split-brain patient was asked to point, with each hand, to a card that was related to the picture it just saw. With his right hand, the patient pointed to a chicken, which matched the chicken claw, and with his left hand he point to a shovel, which matched the snow scene. When the experimenter asked the patient why he selected each item, the patient's speaking left hemisphere rightly reported that the chicken matched the chicken claw but said, "You need the shovel to clean out the chicken shed." The left hemisphere made an explanation for the actions of the right hemisphere based on the information that was available to it. By doing so, the patient could maintain the illusions that his actions were willful and his mind was unified and in control. On another occasion, experimenters commanded the right hemisphere of a split-brain patient to stand. The patient stood and the experimenter asked him why he did so. Again, the speaking left hemisphere created an explanation for his behavior, explaining he was thirsty and wanted to get a drink. The left hemisphere interpreter extinguishes conflict and uncertainty and, in doing so, maintains the feelings of unity and willful control.

The left hemisphere interpreter may not only rationalize behavior, but may also rationalize any distress signals it receives from the right hemisphere. If so, we may expect that, even if the right hemisphere feels distress and the emotional valence of the distress crosses over to the dominant left hemisphere, the left hemisphere interpreter may attribute the discomfort to some external cause.

WHAT SPLIT-BRAIN PATIENTS TELL US ABOUT CONSCIOUSNESS

Split-brain patients demonstrate that an intact corpus callosum and, correspondingly, interhemispheric communication are not essential for consciousness. Considering the great abundance of interhemispheric functional connections in the healthy brain (Doron et al., 2012; Salvador et al., 2005), it is surprising that consciousness survives callosotomy, in which nearly all interhemispheric communication is lost. But it does—the two disconnected hemispheres of a split-brain patient appear to possess all of the defining attributes of consciousness (Damasio and Meyer, 2009), such as wakefulness, emotion, attention, and purposeful behavior (Gazzaniga, 2000; LeDoux et al., 1977). However, although consciousness persists after hemispheric disconnection, the conscious experience of split-brain patients may differ from that of healthy individuals since each disconnected hemisphere (especially the right) possesses only a subset of the intact brain's gamut of cognitive functions.

One possible explanation for the preserved consciousness of split-brain patients is that each hemisphere's thalamocortical connections remain intact following commissurotomy. Several theories of consciousness, such as the global workspace model (Newman et al., 1997) or dynamic core model (Tononi and Edelman, 1998), posit that consciousness arises through reentrant neural activity of thalamocortical loops (Llinas et al., 1998; Newman et al., 1997; Tononi and Koch, 2008; Tononi, 2004; Ward, 2011). In line with these theories, each hemisphere of a split-brain patient may remain conscious following commissurotomy because the connections between the cortex and thalamus in each hemisphere remain intact. In a related vein, each hemisphere may remain conscious following surgery because of spared cortico-cortical connections. In support of this view, recent fMRI (Monti et al., 2013) and EEG (Boly et al., 2012) studies have shown that loss of consciousness is associated with a decrease in cortico-cortical connectivity, even when thalamocortical connectivity remains unchanged. Spared subcortical and cortico-cortical connections may enable bilateral functional connectivity after split-brain surgery (Uddin et al., 2008). In a recent study, O'Reilly et al. (2013) measured rhesus monkeys' resting state functional connectivity with fMRI before and after callosotomy. They found that corpus callosum sectioning abolished nearly all interhemispheric functional connectivity, but these effects were mitigated if the anterior commissure was spared. In sum, these theories suggest that both hemispheres of a split-brain patient are conscious because subcortical and intra-hemispheric cortico-cortical connections remain intact following commissurotomy.

Another possible explanation for the preserved consciousness of split-brain patients stems from Giulio Tononi's integrated information theory (IIT) of consciousness, which posits that consciousness is proportional to the capacity of a system to integrate information, such that greater information integration produces richer conscious experiences (Tononi and Edelman, 1998; Tononi, 2004, 2008; Oizumi et al., 2014). Integrated information, denoted by phi, is determined by a system's degree of differentiation (a measure of possible conscious experiences) and integration (the degree to which information across modules is unified). According to the theory, the human brain has a large phi—and therefore a rich conscious experience—because it consists of many specialized modules (high differentiation) that can form countless functional assemblies (high integration). The brain's capacity to integrate information decreases after commissurotomy because interhemispheric connections are lost (less integration) and each hemisphere has fewer specialized modules and possible conscious states than an intact brain (less differentiation). Therefore, according to IIT, the consciousness of each hemisphere should correspondingly decrease. In a computation model of split-brain patients' capacity for information integration, Tononi (2004) estimates that phi equals 72 in the united brain but only 61 in each disconnected hemisphere. The model predicts that phi decreases after commissurotomy, but not drastically so, because many cognitive functions are present in both cerebral hemispheres. The model is consistent with research on split-brain patients, with one exception: as we have seen, both hemispheres appear to be conscious following commissurotomy, but the conscious experience of the left hemisphere is superior to that of the right. In relation to the integrated information model, these findings may suggest that the disconnected left hemisphere has a greater capacity to integrate information—and therefore a greater phi—than the right hemisphere.

SUMMARY

In this chapter, we reviewed evidence from split-brain research that suggests consciousness can be divided. Both hemispheres of a split-brain patient appear conscious even though nearly all interhemispheric communication is blocked following commissurotomy. As we have also seen, the conscious experiences of the two hemispheres differ, such that the consciousness of the left hemisphere is more enriched and human-like than the right. Although it is possible that the conscious experience of the left hemisphere only *appears* more enriched than the right because the left hemisphere can report its subjective experience while the right hemisphere cannot, several split-brain studies suggest that the superior conscious experience of the left hemisphere extends beyond language. Generally, the abilities of the left hemisphere are more sophisticated and differentiated than the right; for example, the left hemisphere can reason causally, create explanations, think more abstractly, and it may have a richer subjective sense of self. We argue that the different conscious experiences of the divided hemispheres can be explained by the fact that they contain different specialized cognitive modules. We suggest that consciousness emerges from the interaction of countless specialized cognitive modules, and the content of consciousness at any given moment is determined by what module, or coalition of modules, is most active. Therefore, the difference between the conscious experiences of the divided left and right hemispheres can be attributed to the different specialized cognitive modules that they contain.

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CHAPTER

18

Visual Consciousness: A "Re-Updated" Neurological Tour*

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OUTLINE

INTRODUCTION

The scientific investigation of consciousness has recently stimulated experimental research in healthy human subjects, in neurological and psychiatric patients, and in some animal models. Although this major ongoing effort does not yet provide us with a detailed and explicit neural theory of this remarkable mental faculty, we already have access to a vast collection of results acting as a set of constraints on what should be a scientific model of consciousness. There are many ways to summarize and present this set of "consciousness principles." One may either use a chronological or a domain-specific strategy. Here, I deliberately adopt a narrative approach driven by a neurological perspective. This approach allows an emphasis of the crucial role played by the observation of brain-lesioned patients affected by neuropsychological syndromes. I argue that, as in other fields of cognitive neuroscience, clinical neuropsychology often offers profound and precious insights leading to the discovery of neural principles governing distinct aspects of the physiology of consciousness (Ramachandran and Blakeslee, 1998). Most importantly, many of these principles also prove to be relevant and to generalize to the cognition of healthy human subjects. In a schematic

*This chapter re-updates a previous paper (Naccache, 2008), which itself updated the original version of this review paper (Naccache, 2005).

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manner, the "borderline cases" provided by clinical neurology have the power to specifically illustrate a single property of consciousness by showing the consequences of its impairment. This magnifying effect makes it easier to isolate and delineate this property, and then to take it into account in more complex situations where it is functioning in concert with other processes.

I will focus our interest on a selected number of these properties, and will limit our investigation to visual phenomenal consciousness, which is by far the most experimentally investigated aspect of consciousness.

CONSCIOUS REPORTABILITY

Following the psychologist Larry Weiskrantz (1997) our criteria to establish subject's conscious perception of a stimulus will be the "reportability" criteria: the ability to report explicitly to oneself or to somebody else the object of our perception: *I see the word consciousness printed in black on this page*. This criteria is fully operational, and can be easily confronted to other sources of information (external reality, functional brain-imaging data…), therefore paving the way to an objective evaluation of subjective data, a scientific program called "heterophenomenology" by Daniel Dennett (1992). It is important not to confuse subjective self-reports with behavioral reports of these subjective states: for instance a paralyzed but conscious patient (e.g., patients suffering from the "locked-in syndrome") do have subjective self-reports while having difficulty in communicating them through behaviors. It can be argued, however, that reportability might be a biased measure underestimating subjects' conscious state, and that forced-choice tasks using signal detection theory parameters (e.g., d-prime measure of objective discriminability) might be preferable (Holender, 1986). However, discrediting reportability on these grounds in favor of purely objective measures is far from satisfying. Firstly, unconscious perception of a stimulus might have an impact on objective measures, as illustrated in many unconscious perception situations such as masked priming paradigms (Merikle et al., 2001). Secondly, to ignore subjective reports is somewhat of a counterproductive approach, because it may lead to simply giving up the original project of investigating consciousness. Finally, some authors contest the criteria of reportability by establishing differences between phenomenal consciousness and access consciousness, claiming that we are actually "phenomenally" conscious of much more information than we can access and report (Block, 1995). The key problem with this definition of phenomenal consciousness lies in the way it can be established: How can we infer that subjects are phenomenally conscious of far more information than they can report? By taking at face value another of their conscious reports, related to their strong belief of visual completeness: "I see everything present in the visual scene." In other words, the problem with this definition of phenomenality is the incontrovertible need to rely on conscious reports to establish it: a form of logical circularity (Naccache and Dehaene, 2007). If one wants to define phenomenal consciousness differently from conscious reportability, then one should resist the temptation to make use of subjects' reports to credit the existence of phenomenal consciousness. We will tackle again this interesting issue when discussing the fictionalization property of conscious processing. Note also that a conscious report is not a "cut and paste" copy of a visual scene, but rather a conscious comment on an inner mental representation. This representation can originate from perceptual systems at multiple levels, but ultimately it results from their redescription by evaluative and interpretative systems. Valuably, conscious reports can be non-verbal and observable in disconnected right hemispheres of split-brain patients, in some aphasic patients or even become entirely covert, due to motor system impairments (Gazzaniga et al., 1977; Laureys et al., 2005).

Thus far, I have justified our adoption of the "reportability" criteria to diagnose conscious perception in subjects. How then may we use it to specify a scientific program to investigate systematically the neural basis of visual consciousness? By first recalling a basic but essential "Kantian" statement: when we report being conscious of seeing an object, strictly speaking we are not conscious of this object belonging to external reality, rather we are conscious of some of the visual representations elaborated in our visual brain areas and participating to the flow of our visual phenomenal consciousness, as masterly expressed by the Belgian Surrealist Painter, René Magritte in his famous painting "This is not a pipe" ("Ceci n'est pas une pipe" or "La trahison des images," 1928–1929). This simple evocation of the concept of representation foreshadows the two fundamental stages in the search of the "neural correlates of visual consciousness" (Frith et al., 1999): (i) make a detailed inventory of the multiple representations of the visual world elaborated by different visual brain areas (from retina and lateral geniculate nuclei to ventral occipito-temporal and dorsal occipito-parietal pathways described by Ungerleider and Mishkin (1982), in addition to superior colliculus mediated visual pathways); (ii) identify among these different forms of visual coding which participate in visual phenomenal consciousness, and in these cases, specify the precise conditions governing the contribution of these representations to the flow of phenomenal consciousness. One may date the beginning of this scientific program with the

influential publication of Crick and Koch (1995) who proposed, mainly on the basis of neuro-anatomical data, that neural activity in area V1 does not contribute to the content of our phenomenal consciousness.

BLINDSIGHT: HIGHLIGHTING THE ROLE OF VISUAL CORTEX

Some patients affected by visual scotoma secondary to primary visual cortex lesions display striking dissociations when presented with visual stimuli at the location of their scotoma. While claiming to have no conscious perception of these stimuli, they perform better than chance on forced-choice visual and visuo-motor tasks such as stimulus discrimination, stimulus detection or orientation to stimulus spatial source by visual saccades. This phenomenon, discovered in the early seventies (Poppel et al., 1973; Weiskrantz et al., 1974; Perenin and Jeannerod, 1975), has been coined "blindsight" by Weiskrantz. Compelling evidence supports the idea that such unconscious perceptual processes are subserved by the activity of sub-cortical visual pathways including the superior colliculus and by-passing primary visual cortex (Cowey and Stoerig, 1991). In a subsequent study, de Gelder and Weiskrantz enlarged the range of unconscious perceptual processes accessible to blindsight patients by showing that patient G.Y., whose fame is comparable to that of patient H.M. in the field of medial temporal lobe amnesia, was able to discriminate better than chance emotional facial expressions on forced-choice tasks (de Gelder et al., 1999). This unconscious processing of fear faces in patient G.Y. was also found to interact with the perception of conscious emotional faces and voices (de Gelder et al., 2005). Taking advantage of this behavioral result, the authors used functional magnetic resonance imaging (fMRI) to demonstrate that this affective blindsight performance correlated with activity in an extra-geniculo-striate colliculo-thalamo-amygdala pathway independently of both the striate cortex and fusiform face area located in the ventral pathway (Morris et al., 2001). In fact, this unconscious visual process discovered in blindsight subjects is also active in healthy human subjects free of any visual cortex lesions. One way to observe it consists of using paradigms of masked or "subliminal" visual stimulation in which a stimulus is briefly flashed foveally for tens of milliseconds, then immediately followed by a second stimulus, suppressing conscious perception of the former. Whalen and colleagues used such a paradigm to mask a first fearful or neutral face presented during 33 ms by a second neutral face presented for a longer duration (167 ms). While subjects did not consciously perceive the first masked face, fMRI revealed an increase of neural activity in the amygdala on masked fearful face trials as compared to masked neutral face trials (Whalen et al., 1998). This interesting result has been replicated and enriched by a set of elegant studies conducted by Morris et al. (1998, 1999). However, Pessoa et al. (2006) challenged this view in normal controls by arguing that under strict conditions of unconscious processing, as assessed by objective discrimination measures, no residual activation of the amygdala could be observed. The Pessoa et al. (2002) study capitalized on a previous experiment demonstrating that under conditions of high attentional load, a briefly presented fearful face did not activate the amygdala. Beyond the risk of *throwing the baby out with the bath water*, frequently encountered in the area of subliminal perception, this set of criticisms certainly call for methodological improvements in the assessment of masked faces visibility. Such a methodological process occurred in the close area of masked word perception, driven by a seminal criticism of masked word visibility (Holender, 1986). This work stimulated the use of more stringent masking conditions and led to the production of a rich literature describing perceptual, cognitive and motor processing of unconsciously perceived masked words (see Kouider and Dehaene, 2007 for a review).

The blindsight model and its extension in healthy subjects via visual masking procedures underlines the importance of the neocortex in conscious visual processing by revealing that a sub-cortical pathway is able to process visual information in the absence of phenomenal consciousness. In other words, these data are in close agreement with Jackson's (1932) hierarchical conception (formulated in particular in the third and fourth principles of his "Croonian lectures on the evolution and dissolution of the nervous system") attributing the more complex cognitive processes, including consciousness, to the activity of neocortex. Nevertheless, should we generalize the importance shown here for the primary visual cortex—the integrity of which seems to be a pre-requisite for visual consciousness—to the whole visual cortex?

VISUAL FORM AGNOSIA, OPTIC ATAXIA, AND VISUAL HALLUCINATIONS: THE KEY ROLE OF THE VENTRAL PATHWAY

As a result of the seminal work of Ungerleider and Mishkin (1982), visual cortex anatomy is considered to be composed of two parallel and interconnected pathways both supplied by primary visual cortex area V1: the occipito-temporal or "ventral" pathway and the occipito-parietal or "dorsal" pathway. The dorsal pathway mainly subserves visuo-motor transformations (Andersen, 1997), while ventral pathway neurons represent information from low-level features to more

and more abstract stages of identity processing, thus subserving object identification. This "what pathway" is organized according to a posterior-anterior gradient of abstraction, the most anterior neurons located in infero-temporal cortex coding for object-based representations free from physical parameters such as retinal position, object size or orientation (Lueschow et al., 1994; Ito et al., 1995; Grill-Spector et al., 1999; Cohen et al., 2000). Goodale and Milner reported a puzzling dissociation in patient D.F. suffering from severe visual form agnosia due to carbon monoxide poisoning (Goodale et al., 1991). As initially defined by Benson and Greenberg (1969), this patient not only had great difficulties in recognizing and identifying common objects, but she was also unable to discriminate even simple geometric forms and line orientations. Anatomically, bilateral ventral visual pathways were extensively lesioned, while primary visual cortices and dorsal visual pathways were spared. Goodale and Milner presented this patient with a custom "mail-box," the slot of which could be rotated in the vertical plane. When asked to report slot orientation verbally or manually patient D.F. performed at chance level, thus confirming her persistent visual agnosia. However, when asked to post a letter into this slot she unexpectedly performed almost perfectly, while still being unable to report slot orientation consciously. This spectacular observation demonstrates how spared dorsal pathway involved in visuo-motor transformations was still processing visual information but without contributing to patient D.F.'s phenomenal conscious content. This case suggests that some representations elaborated in this "how pathway" are operating unconsciously while ventral pathway activity subserves our phenomenal visual consciousness. Since this influential paper, many studies have tested this hypothesis in healthy subjects using visual illusions (Aglioti et al., 1995; Gentilucci et al., 1996; Daprati and Gentilucci, 1997). For instance, Aglioti and colleagues (1995) engaged subjects in a Titchener-Ebbinghaus circles illusion task in which a given circle surrounded by larger circles appears smaller than the very same circle surrounded by smaller circles. While subjects consciously reported this cognitively impenetrable illusion, when asked to grip the central circle, online measures of their thumb-index distance showed that their visuo-motor response was free of the perceptual illusion and was adapted to the objective size of the circle.[1]

An inverse dissociation supporting the same general principle was reported by Pisella and colleagues (2000) who demonstrated the existence of an unconscious "automatic pilot" located in the dorsal pathway. Their patient I.G. presented important stroke lesions affecting dorsal pathways in both hemispheres, while sparing primary visual cortices and bilateral ventral pathways. They designed a subtle task manipulating online motor corrections of pointing movements on a tactile screen on which visual targets appeared and could unexpectedly jump from one position to another. While normal subjects were capable of extremely fast and automatic visuo-motor corrections in this task, patient I.G. could only rely on very slow strategic and conscious corrections. Crucially, when tested in a more complex condition in which subjects had to inhibit an initiated pointing correction on some trials, patient I.G. committed far fewer errors than controls who were unable to inhibit very fast motor corrections and who reported being astonished by their own uncontrollable behavior.

Taken together, these results are currently interpreted as dissociations between visuo-motor processes subserved by the activity of the dorsal visual pathway, the computations of which do not participate to our phenomenal consciousness,[2] and other visual processes relying on ventral pathway activity, which supplies our conscious perception. The strong version of this theoretical position is defended in particular by authors such as Goodale and Milner. The latter claims for instance that "we have two (largely) separate visual systems. One of them is dedicated to the rapid and accurate guidance of our movements. . ., and yet it lies outside the realm of our conscious visual awareness. The other seems to provide our perceptual phenomenology" (Milner, 1998). Additional data originating from behavioral measures of subliminal priming, and functional brain-imaging data support this thesis (Bar and Biederman, 1999; Bar et al., 2001).

Lastly a functional brain-imaging study of consciously reportable visual hallucinations observed in patients with Charles-Bonnet syndrome[3] reinforces this conception, by revealing correlations between color, face, texture, and object hallucinations and increased levels of cerebral blood flow in the corresponding specialized visual areas located in the ventral visual pathway (Ffytche et al., 1998).

UNILATERAL SPATIAL NEGLECT: THE NECESSITY OF ATTENTIONAL ALLOCATION

The proposal of a cerebral substrate of visual consciousness through the distinction drawn between dorsal ("unconscious") and ventral ("conscious") pathways still bears some similarity to Jackson's conception since it relies on a similar anatomical partition between some sectors of the visual system which would supply the flow of our phenomenal consciousness, and other sectors which would process information out of our conscious awareness. However, we may posit a further question: Does visual information represented in the

ventral pathway depends on some additional conditions to be consciously accessible and reportable? In other words, are we necessarily conscious of all visual information represented in the ventral pathway? A key answer to this question comes from unilateral spatial neglect (USN), a very frequent neuropsychological syndrome clinically characterized by the inability to perceive or respond to stimuli presented to the side contralateral to the site of lesion, despite the absence of significant sensory or motor deficits. USN has two interesting characteristics: Firstly, most USN patients display impaired visual phenomenal consciousness for objects located on their left side.[4] Some neglect patients even present a very pure symptom named "visual extinction," and defined by the specific loss of phenomenal consciousness for left-sided stimuli presented in competition with right-sided stimuli, while the same left-sided stimuli presented in the absence of contralateral competing stimuli are available to conscious report. Secondly, USN syndrome is usually observed with lesions affecting the spatial attentional network—most often right parietal or superior temporal gyrus (Karnath et al., 2001) cortices or fronto-parietal white matter pathways (Thiebaut de Schotten et al., 2005), but also right thalamic or right frontal lesions—sparing primary visual cortex and the whole ventral visual pathway. Behavioral and functional brain-imaging studies have reliably shown that this spared visual ventral pathway still represents the neglected visual information at multiple levels of processing culminating in highly abstract forms of coding (McGlinchey-Berroth, 1997; Driver and Mattingley, 1998; Driver and Vuilleumier, 2001). For instance, McGlinchey-Berroth et al. (1993) demonstrated that left-sided neglected object pictures could be represented up to a semantic stage, as revealed by significant behavioral priming effects on the subsequent processing of consciously perceived semantically related words. Rees et al. (2000) have shown that an unconsciously perceived extinguished visual stimulus still activates corresponding retinotopic regions of primary visual cortex and several extra-striate ventral pathway areas. In the same vein, we showed that a neglected number could be processed up to the stage of semantic coding using a masked priming paradigm (Sackur et al., 2008). These results demonstrate that ventral pathway activation constitutes a necessary but not sufficient condition to perceive consciously visual stimuli. The additional mechanism, defective in USN patients and mandatory to conscious perception, seems to be the top-down attentional amplification supplied by the activity of the spatial attention network (Mesulam, 1981).

We have been able to generalize this principle demonstrated by USN patients to healthy subjects, by investigating neural correlates of unconsciously perceived words using a visual masking procedure (Dehaene et al., 2001). Using both fMRI and event related potential (ERP) recordings we observed significant activations of a left ventral pathway—the visual word form area, previously identified as the first non-retinotopic area responding to letter string stimuli (Cohen et al., 2000)—by unconsciously perceived masked words. In a second experiment, we tested the specificity of these activations by using a masked priming paradigm: on each trial subjects consciously perceived a target word and classified it either as man-made or as a natural object. Subjects responded faster to visible words immediately preceded by that same masked word (e.g., table/table) than to different prime-target pairs (e.g., radio/table). This repetition priming effect was correlated to specific reductions of the fMRI signal in the visual word form area on repeated word trials as compared to non-repeated word trials. This repetition suppression effect is strongly suggestive of the activation of common neurons sharing the same response tuning properties by unconsciously perceived masked words and by unmasked words (Naccache and Dehaene, 2001a,b).

This work enabled us to compare brain activations elicited by briefly (29 ms) flashed words depending on whether it was consciously perceived or not. On masked trials a backward mask suppressed conscious perception of the word, while words flashed for the very same duration but not backward masked were consciously perceived and reported. When consciously perceiving a word, corresponding neural activity is hugely amplified and temporally sustained in ventral visual pathway by comparison with neural activity elicited by masked words. Moreover, conscious perception is systematically accompanied by the co-activation of a long-range distributed network, the epicenters of which involve prefrontal, anterior cingulate, and parietal cortices.

SOURCE AND EFFECTS OF TOP-DOWN ATTENTIONAL EFFECTS: ATTENTION IS NOT CONSCIOUSNESS

The crucial role of top-down attentional amplification on the perceptual fate of stimuli is likely to occur recursively at multiple stages of processing all along the ventral visual pathway, allowing large modulations of activation patterns elicited by the same stimulus according to the task being presently performed. The rich plasticity of visual representations observed in conscious strategical processing leads to the following question: are unconscious visual representations impermeable to such top-down effects? Indeed, in

most current theories of human cognition, unconscious processes are considered as automatic processes that do not require attention (Posner and Snyder, 1975; Schneider and Shiffrin, 1977; Eysenck, 1984).

Kentridge et al. (1999, 2004) questioned this conception by testing the efficacy of several visual cues on the forced-detection of targets in the hemianopic scotoma of the blindsight patient G.Y. They found that a central, consciously perceived arrow pointing toward the region of the scotoma where the target would appear could enhance G.Y.'s performance, although the target remained inaccessible to conscious report.[5] In normal subjects, using a visual masking procedure, Lachter et al. (2004) reported that unconscious repetition priming in a lexical decision task occurred only if the masked primes appeared at spatially attended locations.

We also investigated a similar issue related to the impact of temporal attention on visual masked priming effects (Naccache et al., 2002). In previous studies, we showed that masked numerical primes can be processed all the way up to quantity coding (Naccache and Dehaene, 2001a,b) and motor response stages (Dehaene et al., 1998b). When subjects had to compare target numbers to a fixed reference of 5, they were faster when the prime and target numbers fell on the same side of 5, and therefore called for the same motor response, than when they did not (i.e., response-congruity effect). They were also faster when the same number was repeated as prime and target (i.e., repetition priming effect). In three experiments manipulating target temporal expectancy, we were able to then demonstrate that the occurrence of unconscious priming in a number comparison task is determined by the allocation of temporal attention to the time window during which the prime-target pair is presented. Both response-congruity priming and physical repetition priming totally vanish when temporal attention is focused away from this time window. We proposed that when subjects focus their attention on the predicted time of appearance of the target, they open a temporal window of attention for a few hundreds of milliseconds. This temporal attention then benefits unconscious primes that are presented temporally close to the targets.

Taken together these findings are inconsistent with the concept of a purely automatic spreading of activation during masked priming and refute the view that unconscious cognitive processes are necessarily rigid and automatic. While several paradigms, such as inattentional blindness (Mack and Rock, 1998) or the attentional blink (Raymond et al., 1992) suggest that conscious perception cannot occur without attention (Posner, 1994), our findings indicate that attention also has a determining impact on unconscious processing. Thus, attention cannot be identified with consciousness. One of the key criteria for automaticity is independence from top-down influences. However, these results suggest that, by this criterion, masked priming effects or unconscious blindsight effects cannot be considered as automatic. We propose that the definition of automaticity may have to be refined in order to separate the source of conscious strategic control from its effects. Processing of masked primes is automatic inasmuch as it cannot serve as a *source* of information for the subsequent definition of an explicit strategy (e.g., see Merikle et al., 1995). However, this does not imply that it is impermeable to the *effects* of top-down strategic control, for example originating from instructions or task context. As a matter of fact, I retrospectively found an explicit formulation of this principle 30 years ago by Daniel Kahneman and Anne Treisman (1984):

> . . .a dissociation between perception and consciousness is not necessarily equivalent to a dissociation between perception and attention. (. . .) To establish that the presentation is subliminal, the experimenter ensures that the subjective experience of a display that includes a word cannot be discriminated from the experience produced by the mask on its own. The mask, however, is focally attended. Any demonstration that an undetected aspect of an attended stimulus can be semantically encoded is theoretically important, but a proof of complete automaticity would require more. Specifically, the priming effects of a masked stimulus should be the same regardless of whether or not that stimulus is attended. (. . .). These predictions have yet to be tested.

This fundamental distinction drawn between attention and consciousness is also crucial for experimental investigations aiming at delineating the scope and limits of unconscious processing. Reconsidering the set of studies by Pessoa and colleagues refuting previous results of unconscious processing of masked faces (see above), their negative result could well be the consequence of two distinct factors: (i) the contamination of previous studies by some consciously visible faces, (ii) a stronger attentional engagement on masked faces in previous studies (reinforced if some faces were visible and could attract spatial and temporal attention to masked faces). If so, in order to maximize sensibility to detect genuine unconscious processing, faces have to be strongly masked but subject attention also has to be maximally engaged on those stimuli. Note that some authors propose a full dissociation between attention and consciousness (Lamme, 2003; Schurger et al., 2008; Wyart and Tallon-Baudry, 2008) (Koch and Tsuchiya, 2007; and see Tsuchiya and Koch chapter in the present book).

This original impact of the conscious posture on non-conscious processing has been generalized behaviorally to a large variety of tasks and conditions

(Naccache, 2008), and confirmed in several brain-imaging studies. For instance, Nakamura et al. (2007) explored the modulation of masked repetition priming effects by the current task being performed consciously on visible words (reading aloud vs. semantic categorization) with fMRI. They found that top-down influences of task sets have a strong impact on the neural fate of masked words through the entire cerebral circuitry for reading. Another study showed that the threshold for conscious perception of masked visual stimuli was largely increased in patients suffering from prefrontal cortex lesions, typically considered outside the traditional visual pathways (Del Cul et al., 2009). This result again suggests a causal role of executive networks on the conscious access of visual representations, and strengthens this idea that some non-conscious cognitive processes can be amplified by top-down effects. Sergent and colleagues revisited the classical iconic memory paradigm (Sperling, 1960), and could even show that short-lived unconscious visual representations elicited by subliminal visual targets could still be consciously accessed after target disappearance by means of top-down cueing (Sergent et al., 2013). Such a "retro-cueing" effect demonstrates that conscious perception can be triggered by an external event several hundred milliseconds after stimulus offset, underlining unsuspected temporal flexibility in conscious perception.

ARE THERE LIMITS TO NON-CONSCIOUS COGNITIVE CONTROL?

Once the very existence of conscious top-down effects on unconscious representations were discovered, a dedicated domain of research rapidly emerged driven by the following question: which facets of cognitive control can operate unconsciously? A first set of studies advocated the view that inhibition, spontaneity, and flexibility of cognitive control were highly dependent on conscious processing of the relevant piece of visual information (Dehaene and Naccache, 2001). For instance, Persaud and Cowey (2008) elegantly showed that while blindsight patient G.Y. was able to indicate better than chance level on which side a visual stimulus was flashed (a typical Jacobi's inclusion task (Jacoby, 1991)), he could indicate the contralateral side (exclusion task) exclusively for consciously perceived stimuli presented in the spared visual field. For unconsciously perceived stimuli the patient could not override an inclusion response. This dissociation strongly supports the idea that inhibitory cognitive processes could be specific to conscious processing. A large set of studies originating from such various fields as episodic memory (conscious forgetting (Anderson and Green, 2001; Anderson et al., 2004)) and decision-making (originating from Libet's seminal experiments (Libet et al., 1983)) converge on this tight relation between conscious processing and inhibition. In the same vein, Merikle and his colleagues used an adapted version of the Stroop task to demonstrate that controls could strategically set up an optimal chain of processing only for consciously visible stimuli, whereas masked stimuli were processed automatically (Merikle et al., 1995). We recently observed similar findings, but note that subjects typically have poor introspection of these strategic changes (El Karoui et al., 2013). In many similar experimental situations, behavioral results suggest that there could exist a class of cognitive processes requiring conscious access to the critical piece of information necessary to initiate the strategic change, but that this strategic change could occur in the absence of conscious agentivity. We recently observed such an effect in a posterior split-brain patient (Naccache et al., 2014). We designed a matching-to-sample visual task during which this patient was randomly presented with two successive numerical targets (T1 and T2) flashed with either a short or a long stimulus-onset asynchrony (SOA), each presented within one visual hemi-field (HF). Intra-hemispheric processing of visual stimuli was essentially preserved. In sharp contrast, patient's performance was massively impaired during inter-HFs trials with a short-SOA, confirming the lack of fast inter-hemispheric transfer. Crucially, this patient spontaneously improved his performance in inter-HFs trials with a long-SOA. This behavioral improvement was correlated with a mid-frontal ERP effect occurring during the T1−T2 interval, concomitant with an increase of functional connectivity of this region with distant areas including occipital regions. These results bring to light a slow, non-automatic, and frontally mediated route of inter-hemispheric transfer dependent on top-down control. Note however, as we mentioned above about the Merikle paradigm, that this patient did not consciously report any agentivity of this strategic change. In addition to inhibition and strategy, it is noteworthy to mention that no intentional behavior seems to be triggered by a stimulus processed unconsciously. Inhibition, strategic processing and intentionality seem to be exclusive property of visual stimuli consciously processed by conscious agents. In other terms, the long-standing philosophical challenge of distinguishing a "zombie" (a non-conscious agent behaving like a conscious agent) from a conscious subject may find here a possible solution.

However, another group of studies complicated the story by demonstrating that non-consciously visible stimuli may still trigger some forms of cognitive control processes. Notably, Van Gaal used the Go/No-Go

paradigm to show that a masked No-Go signal could trigger behavioral inhibitory control processes, and that this inhibitory effect was associated with neural activity in the fronto-central region of the prefrontal cortex (van Gaal et al., 2008). In the same vein, Lau and Passingham (2007) detected an activation of mid-dorsolateral prefrontal cortex with fMRI contemporary with a conflict triggered by a subliminal stimulus escaping from conscious perception. Each trial began with the presentation of a visible cue instructing subjects to perform either a phonological judgment or a semantic judgment on an upcoming target word. On some trials a masked cue was presented before the visible cue target word, which could prime for the correct or incorrect task. A clear subliminal priming effect was observed both on behavioral data (increase of response times for incongruent trials) and on fMRI patterns, suggesting that this subliminal cue could modulate brain activation within task-related areas. Moreover, a prefrontal area associated with cognitive control was more activated during incongruent trials than during congruent ones. Other studies have shown that unconscious stimuli can also bias spatial attention (Woodman and Luck, 2003).

However, two important arguments invite us to caution when interpreting these results: first, unconscious processing can actually reach parietal and frontal areas in some specific instances, although such unconsciously driven frontal or parietal activity seem much more focal and evanescent than during conscious processing (van Gaal et al., 2008, 2009, 2011; Cohen et al., 2009). Second, while conscious processing allows for fast, flexible, and strategic dynamic modifications of behavior which can occur after a single critical trial, the vast majority of reported findings during unconscious processing require a long training with usually small effects sizes, and they show a limited range of flexibility and generalization (Dehaene and Naccache, 2001; Kunde, 2003; van Gaal et al., 2012; Chiu and Aron, 2014).

CONSCIOUSNESS IS A WORLD OF (NEURO)SCIENCE-FICTIONS

What is the subjective status of conscious perceptual representations? Are they more of less accurate "cut and paste" copies of a visual scene, or could they be constructs marked by the systematic presence of interpretative processes, rationalizations and beliefs? Beyond the broad range of philosophical traditions proposing distinct frameworks to theorize the links prevailing between external reality and mental representations, from Plato to Pyrrhon, Descartes, Spinoza, Husserl, and Wittgenstein, clinical neuropsychology of vision offers unique sources of empirical knowledge to address this fundamental issue.

Consider for instance Capgras syndrome (Capgras and Reboul-Lachaux, 1923), a rare clinical situation during which a patient recognizes faces of familiar individuals, but elaborates an odd and very strong delusion inaccessible to criticism, claiming that the owner of this face is a look-alike imposter. While considered for a long-time as an enigmatic psychotic phenomenon, cognitive neuroscience of vision offered a simple mechanistic scenario of this strange syndrome (Ellis and Lewis, 2001). Capgras patients do explicitly and consciously recognize faces or other visual stimuli, in sharp contrast for instance with prosopagnosic patients. However, when looking at a familiar face patients affected by Capgras syndrome do not exhibit the emotional response normally observed such as autonomic skin conductance responses (Ellis et al., 1997; Hirstein and Ramachandran, 1997). This dissociation between a preserved recognition of face exemplar identity and an impaired familiarity coding would trigger a non-conscious interpretation identifying this stimulus as a "look alike." It is important to mention that patients are not the conscious agents of this interpretation. In other terms, they do not reason on the basis of this dissociation, which they ignore, to infer that such a subject could be a look alike. Rather, when they consciously access to this face, they irrepressibly access to this interpretation, and then show strong difficulties to criticize it, probably due to the presence of a second cognitive impairment affecting the "belief evaluation system" dependent on the activity of right prefrontal cortex areas (Feinberg and Keenan, 2005; Coltheart et al., 2010).

The case of Capgras delusion illustrates that perceptual representations seem to incorporate interpretative processes or fictions. A fiction is not necessarily false, but a fiction is a belief and not a pure description of reality. This piece of evidence described here for Capgras patients is actually extremely frequent in several neuropsychological syndromes which do not exclusively concern visual perception: amnesic confabulations of Korsakov patients, reduplicative paramnesia, foreign-limb syndromes such as those observed in asomatognosic patients, or split-brain patients fictive interpretations. All these situations share a common principle: various conscious representations of these patients are characterized by a strong and obviously erroneous belief: false belief of remembrance, false belief of location, false belief of owns actions causality, false belief of limb ownership… The fiction and belief nature of these representations strikes us because of their obvious fallacy. However, beyond the fallacy present in several neuropsychological syndromes, I would argue that many aspects of conscious visual representations of the neurologically healthy subject share this general

fictionalization property (Naccache, 2006). Indeed, one of the most powerful perceptual beliefs is the visual completeness illusion: when we open our eyes on a visual scene, we have the phenomenal sensation of seeing everything present in our visual field. Change or inattentional blindness paradigms demonstrated the fallacy of this belief: it is possible to change major components of an ecological visual scene (removing a building from a picture, inserting a gorilla crossing slowly a basket ball field in a short movie…) while the perceiver does not detect this change: we do not consciously access to every component of a visual scene (O'Regan et al., 1999; Simons and Rensink, 2005). Another elegant illustration of this visual completeness illusion was provided by Rayner and Bertera (1979). They presented subjects with a window of readable text moving in synchrony with the eye, while parafoveal information was replaced by strings of X's. Subjective reports were characterized by the impression of seeing a whole page of text during the whole experiment. Visual iconic memory experiments also illustrate the fallacy nature of this visual completeness belief. The classical experiment by Sperling (1960) demonstrates that when an array of 12 letters if briefly presented (∼half a second), subject have the ability to consciously report only a subset of letters. However, they claim that they have a strong phenomenal sensation of having seen each of the letters.

Taken together, this set of apparently different clinical or experimental situations point toward a massive aspect of conscious vision: when consciously perceiving a visual scene, we do not merely build an "objective" representation of it, but we systematically fill it with interpretations, significations and beliefs. In a word, our conscious perception incorporates a process of fictionalization.

A THEORETICAL SKETCH OF CONSCIOUSNESS

Thus far, our non-exhaustive review has allowed us to isolate four general principles governing the physiology of visual consciousness. Firstly, a large number of processes coded in some sectors of the visual system—such as the sub-cortical colliculus mediated pathway, or some areas of the dorsal visual pathway—never participate in conscious visual representations. Secondly, a visual representation is reportable only if coded by the visual ventral pathway. Thirdly, this anatomical constraint is necessary but clearly not sufficient, as is nicely demonstrated in visual neglect. Top-down attentional amplification seems to be the additional and necessary condition for a visual representation coded in the ventral pathway to reach conscious content. Finally, inspired by Posner's (1994) distinctions between the *source* and the *effects* of a top-down attentional process, we propose that only conscious representations can be used as sources of strategic top-down attention, while some unconscious representations are highly sensitive to the effects of such attention. These principles help to better delineate the properties of conscious visual perceptions, and also argue for a distinction between two categories of non-conscious processes: those which never contribute to conscious content, and those which can potentially contribute to it.

These principles can be accounted for within the "global neuronal workspace" theoretical framework developed by Dehaene, Changeux, Naccache, and colleagues (Dehaene et al., 1998a, 2003; Dehaene and Naccache, 2001). This model, in part inspired from Bernard Baars' (1989) theory, proposes that at any given time many modular cerebral networks are active in parallel and process information in an unconscious manner. Information becomes conscious, however, if the corresponding neural population is mobilized by top-down attentional amplification into a self-sustained brain-scale state of coherent activity that involves many neurons distributed throughout the brain. The long-distance connectivity of these "workspace neurons" can, when they are active for a minimal duration, make the information available to a variety of processes including perceptual categorization, long-term memorization, evaluation, and intentional action. We postulate that this global availability of information through the workspace is what we subjectively experience as a conscious state. Neurophysiological, anatomical, and brain-imaging data strongly argue for a major role of prefrontal cortex, anterior cingulate, and the areas that connect to them, in creating the postulated brain-scale workspace. We could empirically confirm some major predictions of this model, and precise key aspects of the oscillatory processes at work during conscious access. For instance, we compared conscious and non-conscious processing of briefly flashed words using a visual masking procedure while recording intracranial electroencephalogram (iEEG) in 10 epileptic patients (Gaillard et al., 2009). Non-conscious processing of masked words was observed in multiple cortical areas, mostly within an early time window (<300 ms), accompanied by induced gamma-band activity, but without coherent long-distance neural activity, suggesting a quickly dissipating feed-forward wave. In contrast, conscious processing of unmasked words was characterized by the convergence of four distinct neurophysiological markers: sustained voltage changes (P3b previously associated with conscious access (Luck et al., 1996; Sergent et al., 2005)), particularly in prefrontal cortex, large increases in spectral power in the gamma band, increases in long-distance phase synchrony in the

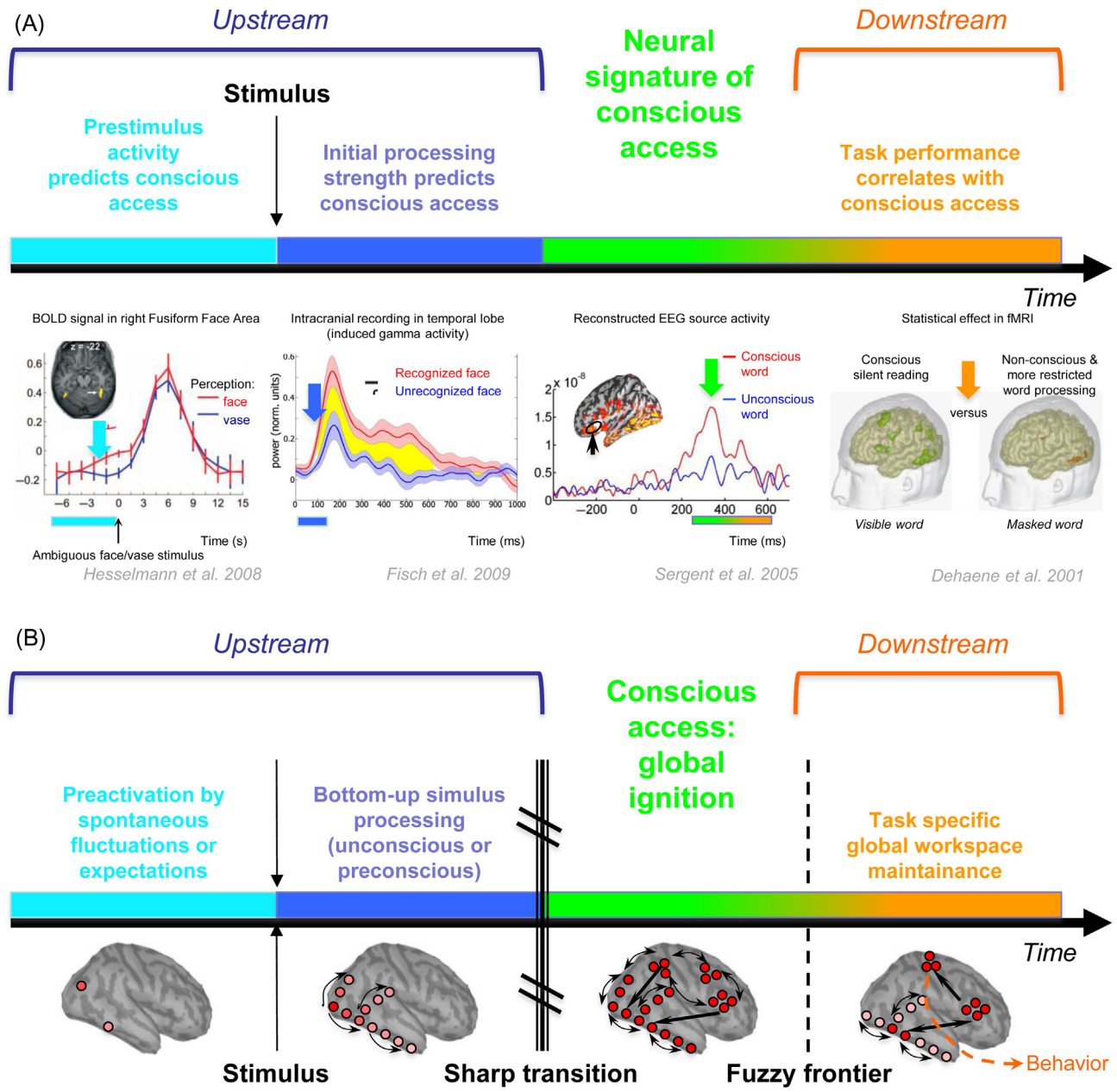

FIGURE 18.1 Distinguishing different categories of neural correlates of consciousness in time: "upstream," "neural signature," and "downstream." (A) Shows how this classification applies to various classes of empirical data on the neural correlates of consciousness. (B) Shows the proposed underlying neuronal mechanisms associated with each stage within the Global Neuronal Workspace theoretical framework. *Source: Reproduced from Sergent and Naccache (2012).*

alpha-beta range, and increases in long-range Granger causality. We could recently generalize most of these iEEG results to the auditory modality when contrasting the mismatch negativity component and P3b responses to violations of auditory regularities (El Karoui et al., 2014). Interestingly, this late and sustained P3b signature of conscious access seems very specific when probing conscious processing in non-communicating patients. Only conscious or minimally conscious patients show such a signature (Bekinschtein et al., 2009; Faugeras et al., 2012), and the single two vegetative state patients in whom it was observed recovered clinical signs of consciousness in the next 3–4 days (Faugeras et al., 2011).

Note, however, that if this neural signature seems to specifically index conscious access, it is extremely difficult to disentangle it from a correlate occurring after conscious access ("downstream" neural correlate of consciousness, see Figure 18.1) (Aru et al., 2012; Sergent and Naccache, 2012). Indeed, a strong correlate of conscious perception can occur before conscious

access ("upstream" correlate), and even before stimulus onset, or after conscious access ("downstream" correlate). Therefore the identification of a neural correlate of conscious access does not guarantee that its timing allows a direct timing of conscious access. For instance, Pitts and colleagues (2014) reported experimental evidence suggesting that conscious access was not systematically associated with the P3 component. However, in this interesting work these authors may have missed a delayed P3 due to a psychological refractory period effect the presence of which is plausible in the experimental paradigm they used (Sigman and Dehaene, 2005; Hesselmann et al., 2013). Another important issue concerns the variability of conscious access timing. Indeed, Melloni et al. (2011) found that stimulus expectation shortened the delay of a potential signature of conscious access from 300 to 200 ms after stimulus onset. Moreover, one has to be careful about the methodology used to probe conscious access. When a behavioral report (e.g., button press, verbal act) is required to identify subjective self-reports, it is important to be aware that such a task could increase conscious access per se by focusing attention and executive control over a specific perceptual content, and that it could include post-perceptual processes occurring after conscious perception, as compared to passive viewing during which subjects are not asked to explicitly report their conscious perception. Indeed, in a recent fMRI study, Frassle and colleagues replicated the classical frontal lobe activity associated with conscious access during binocular rivalry (Lumer et al., 1998) when subjects had to communicate their self-reports, but showed that when subjects underwent binocular rivalry alternations in a passive condition no such frontal activity was present. During passive viewing, the authors inferred alternations of conscious perception through the continuous monitoring of pupil dilation and optokinetic nystagmus. Note that in the auditory task we used to probe conscious access to violations of regularities (see above), we could replicate the P3b event both in active and passive versions of the task (Wacongne et al., 2012). Interestingly, the similarity of the neural signatures we observed for visual and conscious access (similar electrophysiological properties, including timing, spatial distribution) across sensory modalities, tasks and contexts suggests the existence of a common neural mechanism at work during conscious access, as predicted by the global neuronal workspace theory.

Within this framework, the different unconscious visual processes reviewed in this chapter can be distinguished and explained. The activity of sub-cortical visual processors such as the superior colliculus, which do not possess the reciprocal connections to this global neuronal workspace which are postulated to be necessary for top-down amplification, cannot access or contribute to our conscious content, as revealed by blindsight.[6] Moreover, the activity of other visual processors anatomically connected to this global workspace by reciprocal connections can still escape the content of consciousness due to top-down attentional failure. This "attentional failure" may result from a direct lesion of the attentional network (such as in USN), from stringent conditions of visual presentation (such as in visual masking), or even from the evanescence of some cortical visual representations too brief to allow top-down amplification processes (such as the parietal "automatic pilot" revealed by optic ataxia patients[7]). This model also predicts that once a stream of processing is prepared consciously by the instructions and context, an unconscious stimulus may benefit from this conscious setting, and therefore show attentional amplification, such as in blindsight.

CONCLUSION

This theoretical sketch will of course necessitate further developments and revisions, but its set of predictions can already be submitted to experimentation. For instance, this model predicts that a piece of unconscious information cannot itself be used as a source of control to modify a choice of processing steps. Another prediction is to extend the sensitivity of some blindsight effects to top-down attention to other paradigms or relevant clinical syndromes, such as USN, attentional blink or inattentional blindness.

Most notably, the fictionalization process inherent to conscious perception should stimulate intense theoretical efforts during the next decades. A potential track could be to incorporate and adapt in our models a concept proposed by Dennett in his "multiple drafts" theory of consciousness (Dennett, 1992). Rather than being a pure broadcasting process of a locally coded unconscious representation, conscious access could also incorporate transcriptional and editing processes creating new versions of the representation. This introduces the possibility for biases, interpretations, and beliefs, which are subtending this fictionalization dimension of conscious contents.

As a conclusion, I have tried in the present chapter to describe how the observation of neurological patients has played a major role in the discovery of several important principles related to the neural bases of visual consciousness. However, this description is not written as a record of an heroic past era of brain sciences. Clinical neuropsychologists and their patients are not dinosaurs, and we did not adopt here a "paleontologist attitude." On the contrary, this audacious neuropsychology of consciousness will provide us

with exciting and unexpected observations, enabling us to tackle the most complex and enigmatic aspects of visual consciousness.

NOTES

1. Since these first reports, Franz and colleagues (Franz et al., 2000; Franz, 2001) challenged this interpretation by showing that when task difficulty was equated between perceptual and grasping tasks, action was not resisting to the illusion. However, studies taking into account these possible confounds reproduced the dissociation between perceptual and action performances (for a detailed review see Kwok and Braddick, 2003).
2. Area MT or V5, located within the dorsal pathway, is an important exception to this principle because: (i) its activity correlates directly with conscious reports of genuine or illusory visual motion (Tootell et al., 1995), (ii) when lesioned (Zeki, 1991) or transiently inactivated by transcranial magnetic stimulation (Beckers and Homberg, 1992) it results in akinetopsia (i.e., the inability to report visual motion), and (iii) microstimulation within this area influences motion orientation discrimination in monkeys (Salzman et al., 1990).
3. This syndrome is characterized by vivid visual hallucinations in elderly patients with peripheral visual deficits. Charles Bonnet, a Swiss philosopher, first described this condition in the 1760s when he noticed his grandfather, who was blinded by cataract, described seeing birds and buildings, which were not there.
4. An exact definition of "left side" remains the subject of many investigations, as visual neglect has been reliably observed at several distinct spatial frames of reference such as different subject-centered or "egocentric" frames, and multiple environment or object-centered "allocentric" frames (Mesulam, 1999).
5. This very elegant demonstration in patient G.Y. will require further investigations in additional blindsight patients, given that G.Y.'s residual vision has been interpreted in terms of low-level phenomenal vision through a set of subtle experiments manipulating visual presentations in both the spared visual field and within the scotoma (Stoerig and Barth, 2001).
6. Indeed neurons located in the superficial visual layers of superior colliculus receive direct input from parietal areas while projecting indirectly to intraparietal cortex through a thalamic synapse (Sparks, 1986; Clower et al., 2001).
7. Within the global workspace model only explicit—or active—neural representations coded in the firing of one or several neuronal assemblies are able to reach conscious content. Therefore, a third class of unconscious processes can be described, those resulting from the neural architecture (fibers lengths and connections, synapses, synaptic weights) in which information is not explicitly coded. This type of unconscious information is also postulated to never participate to conscious content.

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CHAPTER

19

Self-Awareness Disorders in Conversion Hysteria

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OUTLINE

INTRODUCTION

Patients who experience physical or intellectual disorders without any evidence for an underlying organic illness have puzzled both physicians and for more than 20 centuries. Today, despite the tremendous improvements in medical knowledge, such cases remain frequent and perplexing in clinical practice. Across different times and different theories, this condition has raised many questions on the relationships between mind and body, either when it is considered as an effect of obscure somatic anomalies on psychic functions or, vice versa, when it is conceived as the impact of strong passions or beliefs on bodily functions. Historically, scientific interest in these phenomena is intimately connected with the emergence of modern concepts of diseases in neurology and psychiatry. However, as these two disciplines have diverged during the last hundred years, these patients and their symptoms still remain today in a largely uncharted frontier territory of both clinical medicine and science.

This intriguing condition was initially called "hysteria" by the ancient Egyptian and Greek physicians, who thought that it resulted from some dysfunction of the uterus in women (through its wandering in the body). In recent psychiatry classification systems, the term "hysteria" has been replaced by "conversion" disorder because of the recognition of important psychoemotional factors and the influence of psychoanalytical theories following Freud (Freud and Breuer, 1895). Yet, the psychological processes and the neurobiological underpinnings of this condition remain poorly understood by physicians and scientists alike, continuing to raise fundamental questions on mechanisms of self-consciousness, and still lying in a gray zone at the border between psychiatry and neurology. To acknowledge this historical legacy and the lack of a single explanatory framework, terms such as "hysterical conversion" or "conversion hysteria" are often used in the literature, and will be employed interchangeably in this review. The term "functional symptoms" is also often advocated in clinical practice.

According to the most recent DSM-5 criteria, conversion hysteria is defined as a somatoform disorder characterized by a pseudoneurological deficit (e.g., paralysis or anesthesia) that is not explained by organic lesions

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and may arise in relation to psychological stress or conflict, without a deliberate intention to feign the deficit (see Box 19.1). This deficit may involve a loss or distortion in elementary neurological functions, including not only motor or sensory symptoms, but also blindness or deafness, as well as gait problems, dystonia, aphonia, pseudo-seizures, or disturbances in higher-level functions such as amnesia or pseudo-dementia (Ganser

BOX 19.1

DIFFERENT DIAGNOSTIC CRITERIA FOR CONVERSION AND DISSOCIATION

The definition of *conversion disorder* in the new DSM-5 classification (shown below) has recently changed from its previous DSM-IV-TR version as it now acknowledges the importance of positive clinical findings during examination (criteria B) in establishing the diagnosis, rather than only exclusion criteria. By stating that "Clinical findings *provide evidence* of..." it is understood that the neurological examination should determine the presence of classical "positive signs," such as a Hoover sign for example (for reviews of positive signs see Daum et al., 2015; Syed et al., 2011). Another new addition to the DSM-5 was also the term "functional" in bracket in the title of the disorder, as many experts advocate the use of such a neutral term, rather than the previous terms of psychogenic, conversion or dissociation, all suggesting a precise and unique mechanistic/etiological interpretation (which actually remains unknown), whereas the term "functional" is merely descriptive.

Conversion Disorder (Functional Neurological Symptom Disorder) (F44.x)

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type:

- With weakness or paralysis (F44.4)
- With abnormal movements (F44.4)
- With swallowing problem (F44.4)
- With speech problem (e.g., dysphonia, slurred speech) (F44.4)
- With attacks or seizures (F44.5)
- With anesthesia or sensory loss (F44.6)
- With special sensory symptom (e.g., visual, olfactory, hearing) (F44.6)
- With mixed symptoms (F44.7).

Specify if:

- *Acute episode*: symptoms present for less than 6 months
- *Persistent*: symptoms occurring for 6 months or more.

Specify if:

- *With psychological stressor* (specify stressor)
- *Without psychological stressor*.

On the other hand, *somatization disorders* are classified as a broader category within the somatoform disorders, with the following criteria:

A. A history of many physical complaints beginning before age 30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.
B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:
  1. four pain symptoms
  2. two gastrointestinal symptoms other than pain
  3. one sexual or reproductive symptom other than pain
  4. one pseudoneurological symptom other than pain (conversion or dissociative symptoms such as amnesia).

By contrast, the International Classification of Diseases (ICD-10) of the World Health Organization includes conversion hysteria among dissociative disorders, and requires the following criteria:

A. No evidence of a physical disorder that can explain the symptoms that characterize the disorder (but physical disorders may be present that give rise to other symptoms).
B. Convincing associations in time between the symptoms of the disorder and stressful events, problems or needs.

BOX 19.1 (*cont'd*)

C. In addition, for specific disorders:

Dissociative motor loss includes either (1) or (2):

1. Complete or partial loss of the ability to perform movements that are normally under voluntary control (including speech).
2. Various or variable degrees of incoordination or ataxia or inability to stand unaided.

Dissociative anesthesia and sensory loss include either (1) or (2):

1. Partial or complete loss of any or all of the normal cutaneous sensations over part or all of the body (specify: touch, pin prick, vibration, heat, cold).
2. Partial or complete loss of vision, hearing, or smell.

Note that only disorders of physical functions normally under voluntary control and loss of sensations are included in these categories. Disorders involving pain and other complex physical sensations related to the autonomic nervous system or visceral functions are categorized under the somatization disorders. Moreover, the traditional reference to unconscious or non-intentional mechanisms in the diagnosis of conversion (present in the DSM-4 but not DSM-5) may not only differentiate such disorders from the willed and conscious production of symptoms in simulation or malingering, but also raises the question of how conscious awareness can be objectively defined in the patient. Likewise, the reference to stressful events (highlighted by the ICD-10) is often faced with difficulties that their presence in the medical history, exact temporal relation with symptoms, and true emotional significance for the patient, are difficult to establish with certainty and dependent on the physician's appreciation.

syndrome). However, due to the lack of a coherent theoretical model, the current psychiatry classifications are somewhat inconsistent (Cloninger, 2001): hysterical memory loss is categorized as a form of dissociative disorder in DSM-5, distinct from somatoform disorders, even though memory is clearly a neurological function. By contrast, both somatic conversion and hysterical amnesia are included among dissociative conditions in the ICD-10 classification. This discrepancy highlights the fact that current theories fail to capture all aspects of conversion hysteria satisfactorily (Brown et al., 2007). Therefore, more empirical work combining psychological and biological perspectives may not only be useful to better understand the mechanisms by which psychological stressors or conflict can affect the conscious experience of movements, sensations, or memories, but also to clarify the possible commonalities between different kinds of conversion symptoms and their relationships to dissociative phenomena.

Advances in neuroimaging techniques provide new opportunities to investigate changes in brain activity associated with psychiatric disorders, because they may offer useful hints about cognitive and affective processes implicated in conversion hysteria. However, to date, relatively few imaging studies have attempted to identify specific neurobiological correlates for hysterical symptoms (for review see Cojan and Vuilleumier, 2011; Voon, 2014; Vuilleumier, 2005, 2014). This stands in sharp contrast with abundant imaging research conducted in other psychiatric conditions such as depression, anxiety, schizophrenia, etc. This also seems all the more striking given that the "functional" deficits of conversion hysteria, without any visible organic lesions, would logically lend themselves to functional neurobiological investigations using brain imaging techniques. However, over the last 15 years, an increasing number of studies have used functional neuroimaging tools such as SPECT (single-photon emission computerized tomography), PET (positron emission tomography), or fMRI (functional magnetic resonance imaging) in order to investigate conversion disorders, although often in small samples of patients. A few earlier attempts in the 1970s and 1980s also employed other neurophysiological techniques such as EEG or MEG. The goal of the current review is to present a general summary of this imaging work, and discuss possible implications for neurobiological theories of conversion hysteria, focusing specifically on unexplained neurological symptoms in motor and sensory functions that are most common in neurology practice. Psychogenic memory loss may also occasionally arise (Markowitsch, 2003) but will be only briefly mentioned here. Other symptoms such as non-epileptic seizures (Devinsky et al., 2001; Reuber and Elger, 2003) will not be discussed, because little is known about their possible functional neural correlates (but see Ding et al., 2014; Pillai et al., 2015). However, a complete model of conversion hysteria would eventually need to account for both negative and positive manifestations of this inherently proteiform condition. In any case, new findings

from functional neuroimaging are not only likely to provide important constraints for future theories of conversion hysteria, but are also more generally apt to offer unique insights on the cerebral mechanisms of self-awareness.

CLINICAL PRESENTATION AND DIAGNOSIS

Conversion hysteria is a common and difficult problem in medical practice. Several studies conducted at different time periods in different countries converge to indicate an incidence of 5–10/100,000 in the general population, while it is thought to represent approximately 1% of consultations in a general hospital, and up to 4–9% of patients seen by neurologists or psychiatrists (Carson et al., 2000; Krem, 2004). However, the type of symptoms and clinical presentation may vary across different cultures and different medical settings. Poor socio-economic status and immigration conditions are common risk factors for the development and persistence of conversion symptoms.

A major issue is that in practice, the diagnosis of conversion hysteria is challenging, because it essentially rests on clinical findings and no gold-standard paraclinical tests exist to confirm the diagnosis (see Box 19.1) (Krem, 2004). Thus, in the clinic, this diagnosis is suspected when the symptoms and physical signs are not consistent with basic anatomical or physiological principles of the nervous system (e.g., sensory or motor losses that do not respect anatomical boundaries of normal innervation, paralysis with intact reflexes, etc.); when symptoms change or evolve erratically over time; and when radiological or electrophysiological tests show normal results.

A number of "positive" clinical signs have been described, but only a few of them have a proper validation (Daum et al., 2014; Syed et al., 2011). Following Babinski, who described his classic sign of toe extension to distinguish organic from hysterical hemiparesis, several other clinical maneuvers may be used to bring out dissociation between subjective symptoms and objective motor functions (Okun and Koehler, 2004). For instance, in patients with hysterical paralysis, preserved strength in the affected limb can be observed during postural adjustment or locomotion while movements involving the same muscles are impossible to execute with voluntary commands (Karnik and Hussain, 2000); this has been designated as a positive "motor inconsistency" sign. Similarly, in patients with unilateral leg paralysis, discrepancy can be observed between weak voluntary hip flexion (tested by asking the patient to press against the examiner's hand while lying in bed) and preserved strength for involuntary hip flexion (when the patients focuses on contralateral hip flexion against resistance). When such a difference is observed, it constitutes a positive Hoovers' sign, which has been shown to be highly reliable in distinguishing stroke patients from conversion patients (McWhirter et al., 2011). The value of several other positive sensorimotor signs has recently been evaluated (Daum and Aybek, 2013; Daum et al., 2015) (see Table 19.1). Likewise, patients with hysterical blindness may fail to reach their own index finger with the other hand (which is easily done by truly blind persons

TABLE 19.1 Classification of "Positive" Sensory-Motor Clinical Signs

Highly reliable signs	Reliable signs	Suggestive signs
Motor/sensory	*Motor/sensory*	*Motor/sensory*
Giveway weakness	Spinal Injury test (SIC)	Irregular drift (arm stabil.)
Drift without pronation	Sternocleidomastoid-test	Non digiti quinti sign
Co-contraction	Collapsing weakness	
Splitting the midline	Non-concavity of the palm	
Splitting of vibration sense	Inconsistence of direction	
Hoover's sign[a]	Mingazzini: irregular drift	
	Systematic failure	
	Non-anatomical sensory loss	
	Gait	*Gait*
	Leg dragging	Falls always towards support
	Hesitation	Non-economic posture
	Psychogenic Romberg	Sudden knee buckling
	Bizarre excursion trunk	Tremulousness
	General sign	
	Expressive behavior	

[a]*The Hoover sign can be considered a highly reliable sign because it fulfills all criteria and had a strong validation in several studies, although no interrater validation has been performed.*

Highly reliable signs defined by (i) previous validation in other samples *and* (ii) significant difference between groups in the study by Daum et al. (Fisher $p < 0.05$) *and* (iii) good to excellent interrater reliability (kappa > 0.6).
Reliable signs defined by (i) previous validation in other samples *or* (ii) significant difference between groups in the study by Daum et al. (Fisher $p < 0.05$) **AND** (iii) moderate to excellent interrater reliability (kappa > 0.4).
Suggestive signs defined by (i) high individual specificity >95% *and* (ii) moderate to excellent interrater reliability (kappa > 0.4).
Source: Adapted from Daum et al. (2014, 2015).

using proprioception), or may still manifest normal stereoscopic vision despite an apparent monocular loss (Chen et al., 2007). Nevertheless, although these clinical signs are useful indices of preserved neurological functions, it is worth recalling that striking dissociations between conscious subjective experience and actual objective performance can also be observed in some cases with clearly organic brain disorders such as blindsight, neglect, or amnesia (Driver and Vuilleumier, 2001; Weiskrantz, 2004). Conversely, some patients with brain damage may present with obvious neurological deficits, yet remain unaware of these and even deny them (a syndrome called "anosognosia" (Vuilleumier, 2004)). Altogether, such phenomena suggest that the conscious experience associated with some behavioral abilities may dissociate from actual abilities themselves, and that such dissociation may result from either neurological brain lesions or certain psychological or emotional conditions. Moreover, these situations are also reminiscent of dissociative phenomena observed during hypnosis, a condition that has often been compared to hysteria since the time of Charcot (e.g., see Oakley, 1999; Spiegel, 1991)—although the classic relationships between hypnotic susceptibility and conversion is only relative (Roelofs et al., 2002a) and still unclear both clinically (Foong et al., 1997a; Persinger, 1994; Van Dyck and Hoogduin, 1989) and neurally (Cojan and Vuilleumier, 2011; Vuilleumier, 2014).

Another "classic" positive sign described in conversion hysteria is "la belle indifference," which implies a lack of appropriate emotional response or no apparent worry for the deficit and its consequences (Stone et al., 2006). However, this feature is also inconstant and unspecific. Moreover, a similar attitude may be seen in patients with organic neurological disorders and anosognosia (i.e., anosodiaphoria) (Vuilleumier, 2000). Some authors have emphasized instead that conversion symptoms are often characterized by more affective expressions as compared with true organic symptoms (Schuepbach et al., 2002), and thus seem to reflect a greater "concern" rather than indifference from the patient. Nevertheless, conversion patients have lower abilities identifying emotions on an alexithymia questionnaire relative to patients with organic neurologic disease or healthy controls (Demartini et al., 2014). Another study used a conversational analysis to examine how patients reported their medical history (Schwabe et al., 2007) and found that conversion patients had difficulties providing details of their symptoms and avoided subjective feeling descriptions. However, it can also be argued that such "vague" statements about their illness can wrongly be attributed by the examiner to a lack of concern but may in fact reflect a poor memory of these episodes when patients are clinically symptomatic and dissociated.

Other clinical signs may stem from the psychological causal factors underlying conversion hysteria. These factors are a key feature of the Freudian interpretations of conversion, and still constitute an important criterion for diagnosis according to some of the current clinical definitions (such as ICD-10, see Box 19.1). Yet, the role of specific stressors or conflicts for triggering hysterical symptoms is often problematic. Even though it is generally accepted that stressful situations or emotional factors are frequently preceding the onset of hysterical symptoms (Binzer et al., 1997; Roelofs et al., 2005), the importance of such factors and their relation to the symptoms often involve highly subjective judgments by the clinicians. It is not unusual that psychiatrists invoke a stressor that precedes the onset of symptoms by several years, whereas a more immediate effect of certain events or situations is noted in other patients. Their impact or even their existence may be difficult to ascertain. Moreover, in itself, the occurrence of "psychological stress" or "adverse life events" does not always seem sufficiently specific to distinguish conversion from other disorders such as somatization, malingering, or depression (Krem, 2004). In addition, many patients with conversion hysteria do not report the occurrence of stressors, or perhaps do not easily reckon or admit these. Conversely, many patients with organic neurological diseases may also report stressful conditions preceding the initiation or exacerbation of their illness. For instance, an increased incidence of stress or adverse life events is commonly reported prior to the onset of truly neurological disorders such as stroke (House et al., 1990) or multiple sclerosis (Mohr et al., 2004). Among psychological stress factors associated with conversion, a history of sexual abuse is often mentioned, and particularly emphasized in early Freudian theories (Freud and Breuer, 1895). However, recent studies have shown that although this may be relevant in some patients (Roelofs et al., 2002b), childhood trauma are by far not found in all cases (Binzer and Eisemann, 1998). Therefore, both the nature of the critical psychological stress responsible for conversion hysteria, and the temporal dynamics of its influences on behavior, often remain elusive. It is likely that the type, context, or personal significance of these events is critical in determining conversion (Roelofs et al., 2005), but their exact characteristics, as well as their exact impact on mental, emotional, or physiological processes are still poorly defined. For these reasons, the new DSM-5 criteria now state that two subtypes of conversion disorder may occur; one with an identified psychological stressor (when the clinical evaluation provide strong arguments to link such stressor with the appearance of symptoms) and one without identified psychological stressor (in other cases).

More objective signs of stress can also be obtained. Early studies have described anomalies in the hypothalamic-pituitary-adrenal axis that regulate neuroendocrine responses to stress, with impaired cortisol suppression test in patients with conversion hysteria (Tunca et al., 1996). High cortisol levels have also been reported in patients with psychogenic non-epileptic seizures, correlating with sensitivity to emotional challenges (Bakvis et al., 2010, 2011). Other studies have reported higher responses and reduced habituation in skin-conductance responses, indicative of higher autonomic sensitivity to novelty (Horvath et al., 1980). However, similar anomalies may be observed in other psychiatric disorders such as depression, anxiety, or post-traumatic stress disorder. Abnormal cortisol activity is also linked with chronic fatigue syndrome or burnout (Pruessner et al., 1999). Hence, such anomalies may not be specific to conversion disorders, although they could reflect heightened reactivity to stressful events.

In addition, conversion hysteria is associated with an important comorbidity and overlaps with several other psychiatric conditions, including depression, fatigue, or somatization. In particular, many patients recovering from conversion symptoms eventually suffer from depression at a later stage (Michael Binzer and Kullgren, 1998; Crimlisk et al., 1998), and a history of depression is an important risk factor for poor prognosis and persistent conversion symptoms (Carson et al., 2003). A recent case-control study (Stone et al., 2010) showed that, compared to patients with organic paralysis, patients with conversion paralysis have a significantly higher frequency of major depression (32% vs. 7%), generalized anxiety disorder (21% vs. 2%), panic disorder (36% vs. 13%), and somatization disorder (27% vs. 0%). Such intricate relations raise a number of questions about the boundaries between these different diagnostic categories. In this perspective, it is likely that a better understanding of the functional neuroanatomy underlying conversion hysteria might also contribute to clarify its relationships with other psychiatry conditions.

CONVERSION HYSTERIA AND BRAIN DISEASES

Although by definition conversion hysteria reflects psychogenic symptoms without any organic medical cause, it may occasionally arise in patients suffering from a true cerebral disease. In such cases, conversion symptoms cannot be directly explained by the visible lesions alone, but may add to or modify the clinical complaints of the patient. Moreover, it was suggested by some neurologists more than a century ago that hysteria could sometimes constitute a "complication" of organic brain disease (Gowers, 1893; Reynolds, 1869), and Schilder (1936) wrote that brain dysfunction could sometimes induce "organic neurotic attitudes" leading to stereotyped reactions and behaviors, including hysteria or anosognosia.

Another study by Eames (1992) reported that "hysteria-like" behavior was observed in 30% of patients seen in a rehabilitation ward after various types of brain injuries, as evaluated by systematic ratings of the caregivers. While the latter study may be limited by methodology issues, other authors reported that 12% of patients suffering from a neurological condition also had an additional component to their complaint that was "unexplained by an organic condition," a clinical observation sometimes referred to as "functional overlay" (Stone et al., 2012). Interestingly, not all types of patients presented hysteria-like symptoms. In the study by Eames (1992) such behaviors were more frequent after diffuse brain lesions (e.g., closed injuries, anoxia, encephalitis) than after focal lesions (e.g., stroke), and after subcortical more than cortical lesions, suggesting a possible predisposition by dysfunctions affecting distributed brain networks. Similarly, Gould et al. (1986) reported that "atypical" deficits suspected to have non-organic origin (such as fluctuating symptoms, patchy sensory loss, or "give-away" weakness) were seen in 20% of patients who were admitted for an acute hemispheric stroke. Furthermore, a combination of both "organic" and "psychogenic" manifestations is sometimes observed in other diseases with diffuse brain anomalies, such as multiple sclerosis (Nicolson and Feinstein, 1994) and epilepsy (Devinsky et al., 2001). In the latter cases, truly "organic" manifestations (e.g., seizures) may be difficult to distinguish from non-organic manifestations (pseudo-seizures), and some patients may present with both types of phenomena.

Although these occasional associations between conversion hysteria and neurological diseases might occur purely by coincidence due to the high frequency of each kind of disorders, they challenge a too simple "dichotomous" diagnostic strategy. Furthermore, they might provide valuable clues about the neurocognitive mechanisms underlying an impaired awareness of bodily functions in these patients. Indeed, some brain lesions might affect mental processes contributing to self-awareness or self-monitoring functions that are potentially also implicated in conversion hysteria. As such functions presumably rely on distributed brain networks, they might be more likely to be disrupted by diffuse or subcortical damage (Eames, 1992; Nicolson and Feinstein, 1994), and perhaps more likely

to involve circuits that are not amenable to volitional conscious control (Devinsky et al., 2001; Markowitsch, 2003; Vuilleumier, 2014; Vuilleumier et al., 2001).

On the other hand, a misdiagnosis of organic illness erroneously taken as conversion is a rare possibility. Although a few early studies suggested that patients with hysteria often developed a truly neurological disorder after several years of follow-up, more recent reviews have clearly established that less than 5% of conversion symptoms are falsely diagnosed at the time of onset and then turn into an organic disease 5–10 years later (Stone et al., 2003, 2005). A prospective follow-up of more than a thousand patients revealed a possible misdiagnosis in only 0.4% of cases (Stone et al., 2009). This misdiagnosis rate is similar or even lower than many other medical disorders. Yet, the lack of standard diagnostic tests and the absence of a universally accepted set of diagnostic criteria still constitute a major complication for clinical management of these patients, as well as for scientific approaches to the underlying neural and cognitive mechanisms.

NEUROBIOLOGICAL HYPOTHESES

In parallel to the dominant psychodynamic theory of conversion proposed by Freud and his successors, several neurobiological accounts have been put forward during the last two centuries (for review, see Crommelinck, 2014). While Freudian theory assumed that affective conflicts or stress can be "converted" into physical symptoms, it did not offer any precise mechanism to produce this conversion. By contrast, biological accounts have sought to elucidate the possible cerebral systems underlying the distortion of self-awareness in conversion patients; that is, how the mind may take control over the body. However, until recently, most of the neurobiological hypotheses relied on speculations or analogies with various other conditions, rather than on empirical data about brain function in patients with hysteria (for review, see Kozlowska, 2005; Vuilleumier, 2005).

Prior to Freudian theory, neurologists such as Charcot (1892), Reynolds (1869), or Babinski (Babinski and Dagnan-Bouveret, 1912) suggested that particular beliefs or strong emotions could somehow modify the functioning of neurological pathways and produce abnormal states leading to hysterical disorders (including negative effects like paralysis, as well as positive effects like convulsions). Charcot classified hysteria among "neuroses," that is, diseases characterized by functional disturbances in the nervous systems without structural disturbances (a category that also included epilepsy and Parkinson's disease, for which no visible substrate was known at the time). Babinski proposed replacing the term of hysteria by "pithiatism" in order to emphasize the role of suggestion for inducing and reversing the symptoms, and he argued that emotion and individual predisposition were two important causal factors. At the same time, Janet (1894) insisted more on the internal psychological or cognitive mechanisms by suggesting that hysteria might involve a "limitation of the field of consciousness" which precluded a full control on "strong impressions" or "strong ideas," so that the latter could then govern actions and thoughts of the individual through mechanisms operating a lower, unconscious level. This introduced an important notion of dissociation between conscious and unconscious domains in mental processes. But Janet offered no specific hints about the possible neural pathways by which such dissociation might arise, although he speculated that physiologically distinct systems might mediate conscious and unconscious functions (e.g., with selective dysfunction of higher attentive binocular visual centers, but sparing of lower reflexive monocular visual centers in cases with hysterical blindness).

Many subsequent hypotheses have revisited the same issues, borrowing various concepts from neuropsychology or neuroscience but generally without direct empirical evidence. Different kinds of neural mechanisms have been considered to explain conversion hysteria, which focus on different features of the disorder but are not mutually exclusive. Overall, the putative neurobiological mechanisms most commonly associated with the production of conversion symptoms include inhibitory processes, attentional filtering, functional dissociation, interhemispheric disconnection, impaired representations of self-agency, as well as phylogenetic reactions elicited by stress- or affect-related processes.

Inhibition theories derive from the psychodynamic notion of repression and generally postulate an active suppression of bodily function by inhibitory signals, imposed by cognitive or emotional processes on the dysfunctional system. Following Pavlov (1941) who first proposed that such inhibition might be triggered in the cortex by over-activity in subcortical centers, several authors suggested that "corticofugal inputs" could inhibit or gate sensory, motor, or memory function via the thalamus or brainstem reticular formation (Ludwig, 1972; Sackeim et al., 1979; Whitlock, 1967). This inhibition has variably been ascribed to impaired attention or vigilance (Whitlock, 1967), motivation states (Sackeim et al., 1979), or particular kinds of stress or fears (Ludwig, 1972). Early neurophysiology studies using somatosensory potentials provided indirect evidence for such inhibition (Hernandez Peon

et al., 1963). More recently, inhibitory mechanisms mediated by ventromedial prefrontal cortex (VMPFC) have also been suggested to account for reduced motor activation in a neuroimaging study of motor conversion (Marshall et al., 1997). However, there is still little direct evidence for active inhibition being a primary cause of hysterical deficits (Cojan and Vuilleumier, 2011; Vuilleumier, 2014).

Likewise, attention theories propose that conversion hysteria might involve a selective filtering of sensory or motor information, preventing access to higher cortical processing stages associated with conscious awareness, while residual unconscious processing might still take place at lower stages. Such filtering by attention mechanisms has been suspected to arise not only at the level of subcortical nuclei (Whitlock, 1967) but also in anterior cingulate cortex (Spiegel, 1991) or parietal cortex (Ramasubbu, 2002; Sierra and Berrios, 1999). At first sight, impaired awareness of motor or sensory performance due to inattention for the affected function or body part (e.g., moving a left "paralyzed" arm) may appear consistent with deficits in awareness caused by neurological damage to attentional systems within the right hemisphere (i.e., neglect syndrome), but it seems less consistent with clinical observations that patients with conversion or somatization may often exhibit increased attention to physical symptoms or bodily sensations, rather than actual "neglect" or "unawareness" of affected body parts. Moreover, hysterical symptoms are often reduced by distraction or inattention, or sometimes even reversed by using "narco-analysis" (Hurwitz, 2004). Motor conversion patients perform poorly when performing an explicit motor task (requiring selective attention to motor action), whereas they do as well as controls in an implicit motor condition where an attentive mode is not required (Parees et al., 2013). However, these findings accord with the notion of deficient integration between consciously controlled and more automatically driven processes in (motor) behavior, converging with earlier dissociation views proposed by Janet (1894).

Dissociation theories partly overlap with attention and disconnection models of conversion but refer to more complex cognitive architectures of information processing. These theories generally postulate that motor or perceptual representations formed in functional modules at low-level within the nervous system might become disconnected from the higher-level executive control or monitoring systems, which are presumably subserved by prefrontal cortical areas and responsible for conscious awareness (Brown, 2004; Kihlstrom, 1994; Oakley, 1999). Thus, motor or perceptual representations might fail to be represented or integrated with each other within consciousness (Oakley, 1999), or they might be abnormally or incompletely represented in consciousness, incorporating some erroneous information that is distorted by current state or retrieved from other sources, such as memory or past experiences (Brown, 2004). Other theorists did not refer to dissociation within executive control systems but similarly proposed that conversion symptoms might result from abnormal representations of body state, formed in higher somatosensory cortical areas (such as SII or insula) under the influence of certain attentional or emotional states (Damasio, 2003; Miller, 1984). According to Damasio, "somatic markers" are generated by the brain to anticipate the outcome of perceived or imagined events through the use of an "as-if" loop, which simulates bodily states and feelings associated with these events or their consequence, prior to their occurrence. Thus, it might be possible that a false representation could be activated by this "as-if system" in patients with conversion hysteria, somehow corrupting or parasitizing their internal body maps (Kozlowska, 2005). A recent study (Parees et al., 2012) provided indirect evidence for such dissociation between the subjective feeling of abnormal movements (conversion tremor) and the objective amount of tremor. Patients wore an actigraph for several hours, measuring objectively the percentage of time with tremor during the day, while a subjective report of tremor duration was obtained from the patients through a diary questionnaire. Patients overestimated the time of tremor by 65%, which demonstrate that (i) they did not intentionally produce their tremor—as they would than have been able to report adequately the percentage of abnormal movement as they knew they were being monitored and (ii) that they have an abnormal biases sense of their abnormal movements.

A variant of such accounts, more specifically focusing on motor deficits, argues that conversion symptoms might reflect impaired sense of action agency, due to impaired binding of motor commands with internal signals that compare executed actions with intentions and thus monitor self-initiated movements (Kranick et al., 2013; Voon et al., 2010b). For example, an elegant experiment by Kranick and colleagues (2013) showed that patients had difficulties in integrating the timing of their own actions with the timing of a perceptual consequence of this action (i.e., a sound produced by their key press), a deficit not seen in individuals with depressive symptoms. Such an account relating motor conversion to impaired mechanisms of self-agency echoes similar hypotheses put forward to explain anosognosia for hemiplegia after brain damage (Frith et al., 2000; Spinazzola et al., 2008), which is characterized by the "mirror" phenomenon of unawareness for motor loss despite real paralysis (Saj et al., 2014; Vuilleumier, 2004).

Disconnection theories emphasize more specific anatomical substrates by which motor or sensory information might fail to be normally transmitted between the two hemispheres (Galin et al., 1977; Stern, 1983) or between different cortical regions (Ballmaier and Schmidt, 2005; Flor-Henry et al., 1981). Thus, impaired transfer of inputs from the right hemisphere (involved in emotion and interoception) to the left hemisphere (involved in language and symbolic communication) might lead to distorted awareness for one hemibody and explain a more frequent occurrence of conversion symptoms on the left side (Galin et al., 1977). However, this asymmetry was questioned by more recent systematic reviews (Roelofs et al., 2000; Stone et al., 2002), and some conversion symptoms may affect both sides of the body (e.g., paraparesis). Impaired cross-talk between medial and lateral prefrontal areas has also been proposed to account for anomalies in intentional control of action or thoughts (Ballmaier and Schmidt, 2005). These disconnection hypotheses have not been supported by direct evidence so far, although some neuroimaging results are consistent with changes in functional connectivity between frontal and motor pathways (basal ganglia) (Vuilleumier et al., 2001) or between limbic and motor cortical areas (Cojan and Vuilleumier, 2011; Cojan et al., 2009a; de Lange et al., 2010; Voon et al., 2010a) during conversion symptoms.

Phylogenetic reaction theories do not directly refer to specific brain systems, but invoke evolutionary or ethological approaches to behavior to propose that conversion hysteria may result from adaptive biological mechanisms that determine stereotyped responses to particular kinds of stress or threat (Demaret, 1994; Kozlowska, 2005; Kretschmer, 1948). Such responses might stem from partly hard-wired neural substrates inherited among various animal species including humans. For instance, Kretschmer (1948) argued that two basic patterns of reflexive behavior mediate instinctive reactions of self-preservation and potentially relate to conversion hysteria: motor immobilization (freezing) or motor agitation (flurry). Thus, hysterical paralysis might be viewed as instinctive reactions similar to those manifested by animals who simulate a broken limb or wing when exposed to danger (injury-feigning behavior) or maintain prolonged immobility after stressful restraint (arrest behavior). Likewise, hysterical convulsion might correspond to the frantic struggle of a prey to escape when attacked or captured. In humans, more complex aspects might also relate to social communication and illness behavior (so-called "sick role"), by which symptoms develop to call for attention and elicit care from others (Merskey, 1995; Miller, 1987).

Although the cerebral mechanisms for these instinctive behaviors are incompletely elucidated and their relation to conversion remains entirely speculative, phylogenetic models offer intriguing cues in order to explain not only defective (negative) but also excessive (positive) components of hysterical disorders. In addition, similar analogies have been drawn between animal self-preservation reactions to threat and some of the characteristics of other dissociative disorders (Nijenhuis et al., 1998), consistent with the presumed parallels between conversion and dissociation (Brown et al., 2007). Furthermore, neural circuits responsible for stereotyped behavioral arrest responses to stress or threat have been related to dopaminergic networks in striatum, thalamus, and brainstem (Klemm, 2001), whereas catatonic immobilization during certain emotional states is thought to involve a modulation of functional interactions between basal ganglia and prefrontal cortex (Moskowitz, 2004; Northoff, 2002). Interestingly, similar subcortical circuits have been implicated in some neuroimaging studies of hysterical paralysis (Atmaca et al., 2006; Vuilleumier et al., 2001). Exaggerated avoidance reactions, as measured by a facilitation of arm movements made away rather toward oneself in response to emotional stimuli, has also been reported in patients with psychogenic nonepileptic seizures (Bakvis et al., 2011). However, it remains to be determined whether such mechanisms may also apply to other types of conversion symptoms, such as hysterical blindness or amnesia. Moreover, phylogenetic or evolutionary perspectives are generally consistent with putative biological mechanisms related to inhibition, attention, or dissociation, as proposed by other theories mentioned above.

After several decades during which these different accounts have rested on speculative grounds or indirect neuropsychological evidence, the past decade has witnessed an increasing number of studies using functional brain imaging techniques to probe for the role of specific neural mechanisms in the production of conversion hysteria, and to test more directly the hypotheses made by different theoretical accounts.

BRAIN IMAGING STUDIES OF CONVERSION

Several studies have used neurophysiology or neuroimaging methods to investigate the neural correlates of various types of conversion disorders, such as motor paralysis, anesthesia, or blindness (for review see Black et al., 2004; Broome, 2004; Vuilleumier, 2005, 2014). A better understanding of changes in brain function during such disorders would not only be useful to shed light on puzzling conditions of altered self-awareness, but also help physicians to obtain new "positive signs" of conversion. Ideally, this might

ameliorate the management of these patients who typically reject a purely psychological diagnosis, by avoiding unnecessary "exclusion" diagnostic tests whose negative results often exacerbate anxiety in patients and frustration in physicians. However, although neuroimaging approaches have already expanded our knowledge of conversion, the current data remain inconclusive due to a great heterogeneity of patients and symptoms, important differences in paradigms, and small samples of cases in most of these studies.

Many early studies employed EEG and event-related potentials (ERPs) to probe for neurophysiological anomalies associated with conversion. Most of these studies have typically reported a normal pattern of results for elementary sensory or motor components (e.g., Howard and Dorfman, 1986). MEG studies also reported normal activation of SI and SII by tactile stimulation in patients with hysterical anesthesia (Hoechstetter et al., 2002). Only a few studies using non-clinical protocols have described subtle changes in somatosensory ERPs, such as reduced responses to tactile stimuli close to detection threshold despite normal responses to supra-threshold stimuli (Levy and Mushin, 1973); slower rate of habituation to repeated stimuli (Moldofsky and England, 1975); or suppression of the P300 response to deviant stimuli within a continuous stream of touches on the affected limb (Lorenz et al., 1998; Luaute et al., 2010). Mild reductions of P300 responses were also reported for visual stimuli in hysterical blindness (Towle et al., 1985) and for auditory stimuli in hysterical deafness (Fukuda et al., 1996).

In the motor domain, some anomalies have been noted for the contingent negative variation preceding movement execution (Drake, 1990) and for a N2 component elicited by responses with the affected hand in conflict/interference conditions (Roelofs et al., 2006). An elegant investigation of motor preparation and execution (Blakemore et al., 2013) found reduced N1 in response to preparatory cues for both hands but exaggerated P3 for the affected hand only, which were attributed respectively to reduced engagement of attention to movements on both sides, and enhanced emotional engagement and active suppression of motor circuits on the affected side. Interestingly, a similar P3 enhancement has been observed during motor inhibition in a no-go task (Cojan et al., 2013). However, further systematic studies comparing EEG activity for voluntary and involuntary motor performance are needed (Scott and Anson, 2009). Finally, TMS over motor cortex has shown either normal (Meyer et al., 1992) or reduced (Foong et al., 1997b) excitability, particularly when TMS is delivered during covert motor imagery (Liepert et al., 2008, 2011). Taken together, these findings are consistent with intact activation of early stages of sensory or motor pathways, but point to some anomalies at higher stages involving attentional and cognitive control processes that presumably integrate sensory-motor functions with more complex representations related to goals, motivation, and self-relevance. However, most of these studies remain isolated and need further replication. Moreover, EEG and MEG methods have inherent limitations in anatomical resolution, precluding a more precise delineation of distributed neural networks that are presumably implicated in conversion disorders.

Other brain imaging studies have used hemodynamic or metabolic measures such as SPECT, PET, or fMRI (see Table 19.2). A large majority focused on motor conversion disorders. A first pioneer study was carried by Tiihonen et al. (1995) who performed SPECT scans in a patient with left hemiparesis and numbness during sensory stimulation of the left arm, and reported relative decreases in right parietal lobe and increases in right frontal lobe, which returned to normal after recovery. Conversion symptoms were

TABLE 19.2 Summary of Functional Neuroimaging Studies in Conversion Hysteria

Authors	Patients	Symptoms	Duration	Other psychiatric symptoms	Method	Protocol	Neuroimaging findings
MOTOR LOSS							
Tiihonen et al. (1995)	1 F	L hemiplegia and paresthesia	1 week	Panic attacks, major depression	SPECT	Left median nerve stim during symptoms and after recovery	↓ R parietal + ↑ R frontal during symptoms
Marshall et al. (1997)	1 F	L leg paralysis	2.5 years	Major depression	PET	Preparation or execution of mvts with either leg	N activation in DLFC and cerebellum during preparation ↓ motor cx + ↑ R ACC and OFC during attempted mvts

(*Continued*)

TABLE 19.2 (Continued)

Authors	Patients	Symptoms	Duration	Other psychiatric symptoms	Method	Protocol	Neuroimaging findings
Yazici and Kostakoglu (1998)	3F, 2M	bilateral gait symptoms (astasia abasia)	1–24 weeks	N/A	SPECT	Resting state	↓ in L temporal and parietal lobes
Spence et al. (2000)	3 M patients 10 M healthy	2 L + 1 R arm weakness; 4 controls who feign paralysis 6 controls who move normally	6–15 months	Past depression in all patients	PET	Attempt to move joystick at fixed pace	↓ L DLPFC in conversion ↓ R ant MFG in feigners (irrespective of hand side)
Vuilleumier et al. (2001)	6 F, 1 M	4 L + 3 R hemiparesis and paresthesia	<2 months	Mild depression in 5, personality disorder in 1	SPECT	Resting state + vibratory stim of both hands during and after symptoms	N activation of motor and somatosensory cx ↓ contra thalamus, putamen, caudate + coupling of basal ganglia with IFG + OFC
Burgmer et al. (2006)	4 M patients 4 M, 3 F healthy	3 L, 1 R hemiparesis	1–8 months	Depression in 1	fMRI	Observation of movies showing L/R hand mvts and execution of L/R mvts	N (or ↓) contra motor cx during execution + ↓ contra motor cx during observation in patients
de Lange et al. (2007)	5 F, 1 M	4 L, 4 R arm paresis	3–41 months	Depression in 1, anxiety and panic attack in 1	fMRI	Laterality decision on pictures of L/R hand	N contra motor cx and IPS for increasing mental rotation ↑ OFC, STG
Stone et al. (2007)	3 F, 1 M patient 3 F, 1 M healthy	2 L + 2 R leg weakness 2 L + 2 R feigners	9–30 months	Depression and anxiety in 3 patients	fMRI	Mvts of ankle on either side	↓ R MFG and OFC + ↑ extent in motor cx + ↑ IFG, insula, putamen, SPL, and visual cx in patients ↑ SMA in feigners
Kanaan et al. (2007)	1 F	R hemiparesis	15 months	Conduct disorder	fMRI	Cued recall of adverse life events and neutral personal events	↓ L primary motor cx ↑ R amygdala, medial temporal cortex, IFG, ACC
SENSORY LOSS							
Mailis-Gagnon et al. (2003)	3 F, 1 M	1 L, 2 R, 1 bilat hypo/anesthesia and pain	1–9 years	Multiple (developmental or traumatic stress factors)	fMRI	Tactile (brush) and painful stim (von Frey probes)	↓ SI, SII, thalamus, insula, inferior frontal, and posterior cingulate for all stim when non-perceived ↑ rostral ACC to painful stim when unperceived
Ghaffar et al. (2006)	3 F	2 L foot, 1 L hand numbness	4 months–9 years	N/A	fMRI	L, R, or bilateral vibrotactile stim	↓ activation SI contra to symptoms during unilateral stim + N activation SI during bilateral stim ↓ OFC, striatum, and thalamus in 2/3 during unilateral stim
VISUAL LOSS							
Werring et al. (2004)	4 F, 1 M patient 4 F, 3M healthy control	Reduced visual field or acuity	2–10 years	1 minor depression, 1 grief reaction	fMRI	Periodic visual stim (8 Hz), each eye separately	↓ primary and secondary visual cx, bilateral ↓ R ant cingulate ↑ L IFG, insula, striatum, thalamus, post cingulate, uncus

Abbreviations: ACC, anterior cingulate cortex; cx, cortex; F, female; IFG, inferior frontal gyrus; L, left; M, male; M1, primary motor cortex; MFG, middle frontal gyrus; mvts, movements; OFC, orbitofrontal cortex; R, right; SI, primary somatosensory cortex; SII, primary somatosensory cortex; SMA, supplementary motor area; STG, superior temporal gyrus; stim, stimulation.

attributed to an inhibition of parietal areas due to frontal activation subsequent to stressful events. A similar interpretation was suggested in a later study by Marshall et al. (1997), who used PET in a woman with left leg paralysis while she either prepared to move one leg or the other, moved her intact right leg, or attempted to move her paralyzed left leg. Although preparation to move activated dorsolateral frontal areas and cerebellum for both legs (suggesting preserved motor intention), attempted movements of the left leg did not activate contralateral motor areas (consistent with the absence of movement) but instead produced increases in the right anterior cingulate (ACC) and orbitofrontal cortex (OFC)—unlike right leg movements that normally activated contralateral motor cortex only (Figure 19.1). These findings were taken to support the idea that motor volition and preparation were preserved but actively suppressed by emotional signals from cingulate and orbitofrontal areas. Two subsequent PET studies in healthy subjects who performed the same task but after hypnotic suggestion of unilateral paralysis also reported increases in ACC (Halligan et al., 2000) or OFC (Ward et al., 2003) during movement attempts with the "paralyzed" leg. However, activation of frontal and cingulate areas in this condition might potentially also reflect other cognitive processes such as effort (Paus et al., 1998), conflict (Badre and Wagner, 2004), or increased self-monitoring and anxiety (de Lange et al., 2007; Roelofs et al., 2006).

An fMRI study by Stone et al. (2007) also compared attempted movements with affected or normal leg in four patients with conversion, as well as in four controls who feigned weakness. But these authors found reduced activation in orbitofrontal and mediofrontal areas in patients during movements with the weak limb, together with bilateral increases in inferior frontal gyri and insula. In addition, motor cortex and basal ganglia showed more diffuse activation in conversion patients than in feigners (Figure 19.2). While these data suggest some impairment in motor control, perhaps reflecting effortful and uncoordinated movements with the affected limb, other changes in fronto-limbic regions also indicate anomalies in affective and motivational functions. Moreover, regions in inferior frontal gyri showing increases in conversion patients are known to be engaged in monitoring and inhibition processes (Robbins, 2007; Xue et al., 2008). However, unlike previous results of Marshall and colleagues (1997), here OFC was deactivated rather than hyperactivated.

In contrast to the proposal of an active inhibition by ACC or OFC on planned movements, other imaging findings suggest a dysfunction in motor preparation or intention. Spence (1999) found that patients with motor conversion activated the left prefrontal cortex less during paced movements made with the weak hand, relative to both feigners and healthy controls. This reduction was attributed to a disorder in motor generation processes that normally mediate willed action and selectively rely on the left frontal lobe (Spence et al., 2000). Unlike conversion patients, feigners showed less activation of the right prefrontal cortex in the same task. These data converge with other results to indicate that changes in brain activity in conversion hysteria differ from the pattern observed during conscious simulation (Cojan et al., 2009a; Stone et al., 2007;

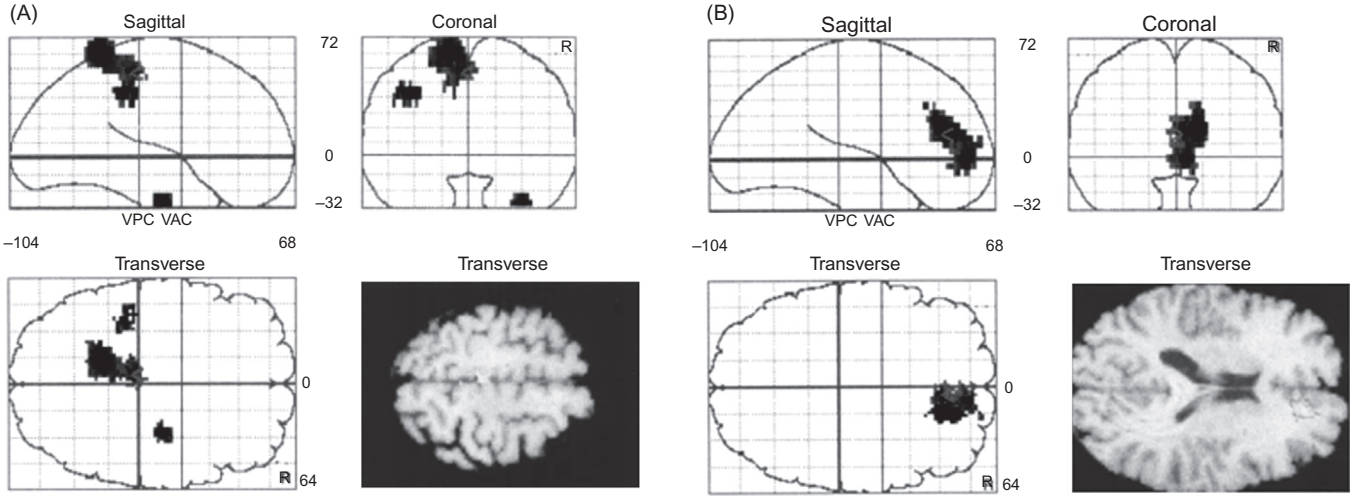

FIGURE 19.1 PET results in a patient with hysterical paralysis of the left leg, shown on a standard anatomical template in stereotactic space. (*Source*: Adapted from Marshall et al., 1997). (A) Activation during movement of the right (good) leg, compared to right motor preparation, showing increases centered in contralateral (left) primary motor and sensory cortex, plus left parietal and right inferior temporal cortex. (B) Activation during attempted movement of the left (affected) leg, compared to left motor preparation, showing no increases in contralateral sensorimotor areas, but selective activation of the right anterior cingulate and right orbitofrontal cortex.

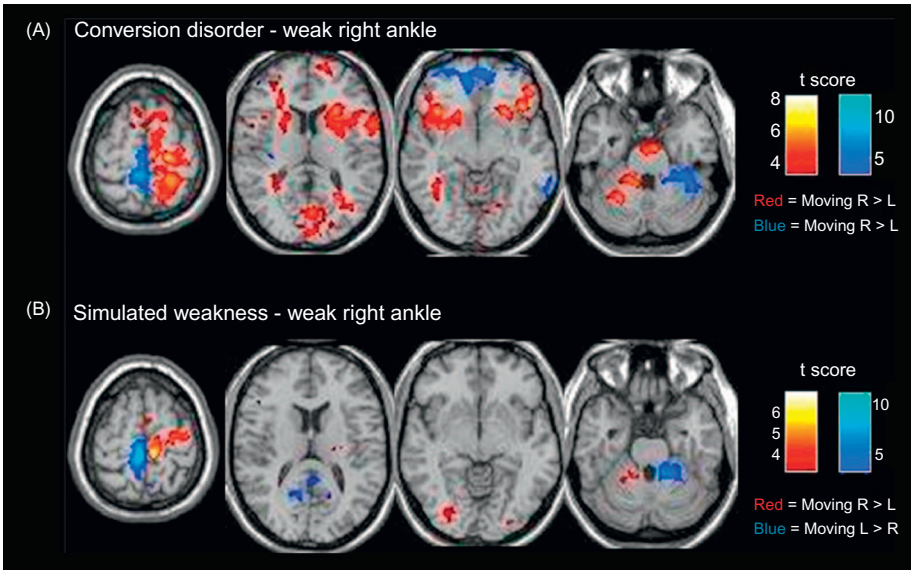

FIGURE 19.2 Functional MRI results in four patients with unilateral ankle weakness due to conversion hysteria and four healthy controls simulating unilateral weakness (group data), shown on transverse brain slices with images flipped to correspond with right-side ankle weakness. (*Source*: Adapted from Stone et al., 2007). Red color depicts areas more active during right than left movements, whereas blue color depicts areas more active during left than right leg movements (left hemisphere shown on the right). (A) Conversion patients showed weaker and more diffuse activation in motor areas contralateral to the weak limb than in motor areas contralateral to the normal limb, together with additional activation in a wide network of including bilateral basal ganglia, inferior frontal gyrus, left insula, and left visual cortex, while they showed relative deactivation in right middle frontal and orbitofrontal cortices. (B) Healthy controls simulating weakness activated primary motor areas contralateral to the moving limb, with additional activation in supplementary motor area only for the weak relative to the normal limb.

Ward et al., 2003). However, reduced activation in left frontal regions are also commonly associated with depression (Drevets, 2000) and might reflect nonspecific comorbid anomalies in these patients. Variable changes in left frontal, temporal, and parietal regions were also often observed in other imaging studies of conversion patients (de Lange et al., 2007; Yazici and Kostakoglu, 1998).

A recent study (Cojan et al., 2009a) used a go-no-go paradigm combined with cued motor preparation in order to directly test the two alternative hypotheses above, that is, deficient intention or active inhibition of motor action. Participants were cued to prepare a movement with either the right or left hand based on a corresponding hand picture presented on the screen, which could then turn green (75% of trials) to summon the subject to press a button (go) or red (25% of trials) to require inhibition of the prepared movement (no-go). The no-go condition activated the right inferior frontal gyrus (IFG) in healthy controls (Figure 19.3A and B), as expected given the role of this region in inhibitory control (Robbins, 2007; Xue et al., 2008). The right IFG was also activated in the go condition when subjects were instructed to feign a paralysis, but this was not the case in two patients with motor conversion (Cojan et al., 2009a; Luaute et al., 2010). Instead, conversion paralysis was associated with a selective activation of the VMPFC and precuneus on trials requiring movement preparation and execution with the affected hand (Figure 19.3C and D), together with increased functional connectivity between VMPFC and primary motor cortex. Such changes were not seen when unilateral hand paralysis was induced by hypnosis during the same go-no-go paradigm (Cojan et al., 2009b). On the other hand, primary motor cortex was normally activated when subjects were instructed to prepare a movement with the affected hand, during both conversion (Cojan et al., 2009a) and hypnosis (Cojan et al., 2009b), indicating normal intention-related activity. Likewise, a group of patients with unilateral conversion paralysis showed symmetrical activation in primary motor cortex and parietal areas during a motor imagery task requiring mental rotation of either right or left hands from pictures with different orientations (de Lange et al., 2007), consistent with previous results of behavioral studies on covert motor planning (Maruff and Velakoulis, 2000; Roelofs et al., 2002c). Increased activity of the VMPFC and abnormal connectivity were also observed in patients during the hand rotation imagery study (de Lange et al., 2007, 2008).

However, some fMRI data have pointed to a possible impairment in the generation of intentional motor representations during motor conversion (Burgmer

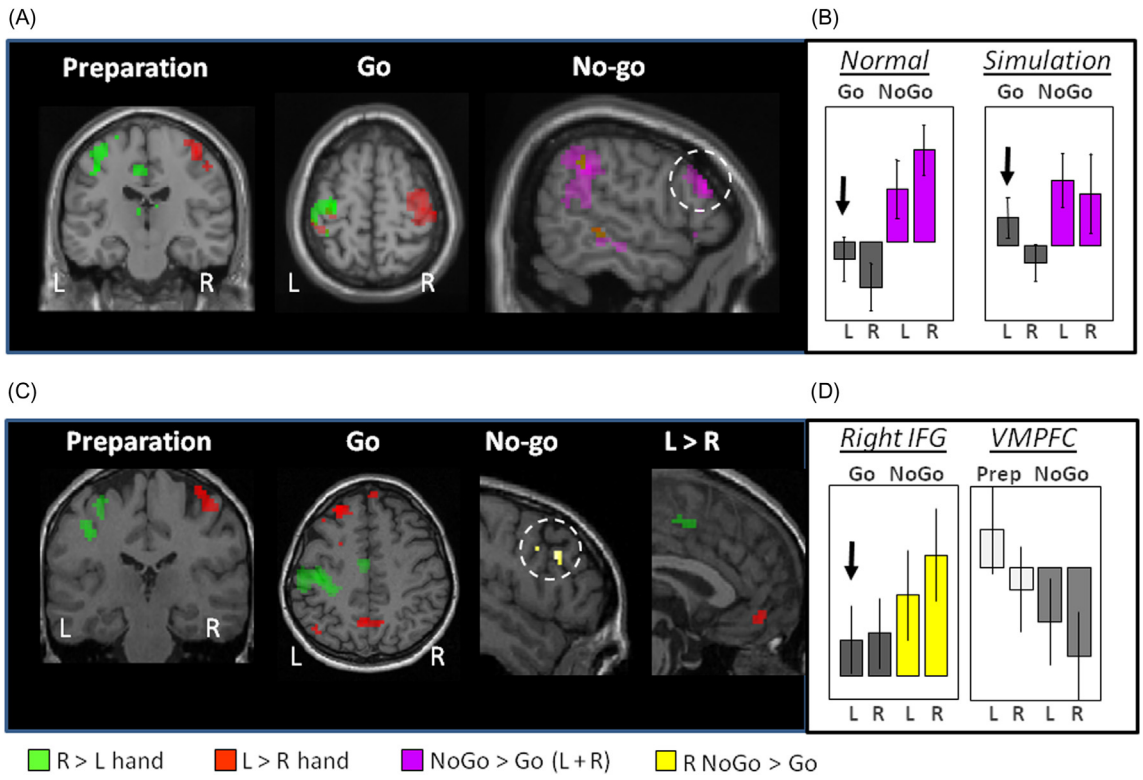

FIGURE 19.3 Brain activity in different stages of a go-no-go task. (*Source*: Adapted from Cojan et al. 2009a,b) (A) results in healthy controls, showing activation in contralateral M1 during preparation and execution (go), and activation in right IFG during inhibition (no-go) for both hands. (B) Activity in right IFG during normal condition and during voluntary simulation of left paralysis, showing that simulation was associated with increases in right IFG and produced by voluntary inhibition. (C) Results in a patient with left conversion paralysis, showing normal activation of contralateral M1 during preparation but lack of activation of right M1 during paralysis, together with increases in precuneus and VMPFC. (D) In the patient, activity in right IFG showed that left paralysis was not associated with increases as seen during voluntary inhibition of simulation; whereas activation in VMPFC was selective for preparing or attempting to move the left/paralyzed hand.

et al., 2006): patients showed no activation in their motor cortex when they observed actions made by others with the same hand as their affected limb, unlike the observation of actions involving the healthy hand (Figure 19.4). This lack of covert motor imitation was found despite a normal activation of the motor cortex during attempts to execute real movements with the affected hand. This therefore contrasts with other studies reporting normal recruitment of primary motor cortex (Cojan et al., 2009a; de Lange et al., 2007). Altogether, these data might suggest that internal motor plans can still be generated, but their execution may fail or be abnormally modulated by motivational factors (Cojan et al., 2009a; Roelofs et al., 2006).

In keeping with this idea, motivational and emotional signals might also influence subcortical sites within motor pathways such as the basal ganglia, which control the initiation and execution of motor commands generated in cortex, and presumably integrate these motor commands with contextual factors coded in other brain regions. Reduced activation in the striatum (caudate and putamen) as well as the thalamus contralateral to motor symptoms was found by a SPECT study (Vuilleumier et al., 2001) in seven patients with unilateral weakness and mild sensory symptoms, while they underwent passive stimulation by vibration of both limbs (affected and unaffected). Brain SPECT with bilateral stimulation was performed first during motor symptoms and then repeated a few months later after recovery. The asymmetry of activation in basal ganglia and thalamus disappeared after recovery (Figure 19.5A and B). Furthermore, the magnitude of hypoactivation in caudate nucleus observed at the time of symptoms predicted their duration until recovery. By contrast, activation of primary sensorimotor areas contralateral to the affected limb was enhanced during symptoms relative to the later recovery stage (Figure 19.5C). In addition, functional network analyses showed that functional decreases in striato-thalamic circuits were correlated

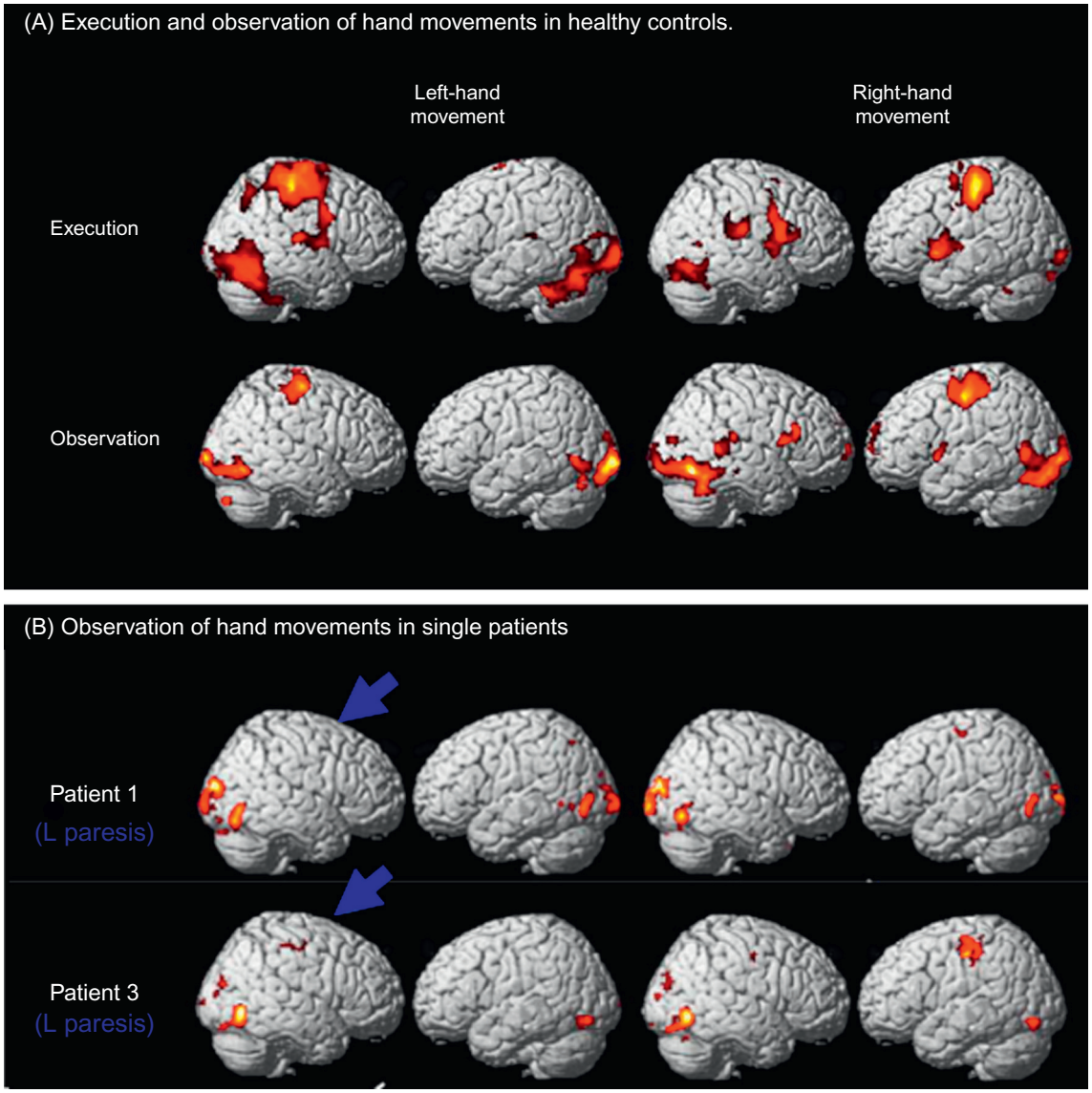

FIGURE 19.4 Functional MRI results during execution or observation of unilateral hand movements. (*Source*: Adapted from Burgmer et al., 2006). (A) Activations in healthy subjects during execution and observation of movements made with either the right or the left hand (group data), showing an activation of contralateral motor cortex during both execution or observation. (B) Activations in two representative patients with left hysterical paresis during observation of left- or right- hand movements, showing normal increases contralateral to the intact (right) hand but no increases contralateral to the affected (left) hand. The arrows mark the expected localization of activation in the motor areas during observation of hand movements for the affected side.

with concomitant changes in inferior and ventromedial prefrontal areas (BA 44/45 and BA 11) in the same hemisphere, contralateral to the motor symptoms (Table 19.3). Moreover, a recent structural volumetric MRI study reported that patients with motor conversion had generally smaller gray-matter density in their right caudate and right thalamus as compared with a group of healthy individuals (Atmaca et al., 2006), while another study found smaller left thalamus in patients (Nicholson et al., 2014). However, no correlation with the type and duration of symptoms was provided in these studies, preventing any interpretation in terms of causal mechanisms or instead consequences of the motor disorder.

Abnormal activation of striato-thalamic circuits typically occurs during Parkinson disease (i.e., decreases due to dopamine loss) or during Tourette syndrome (i.e., increases due to probable genetic anomalies), which entail opposite dissociations between conscious volition and actual execution of movements. Thus,

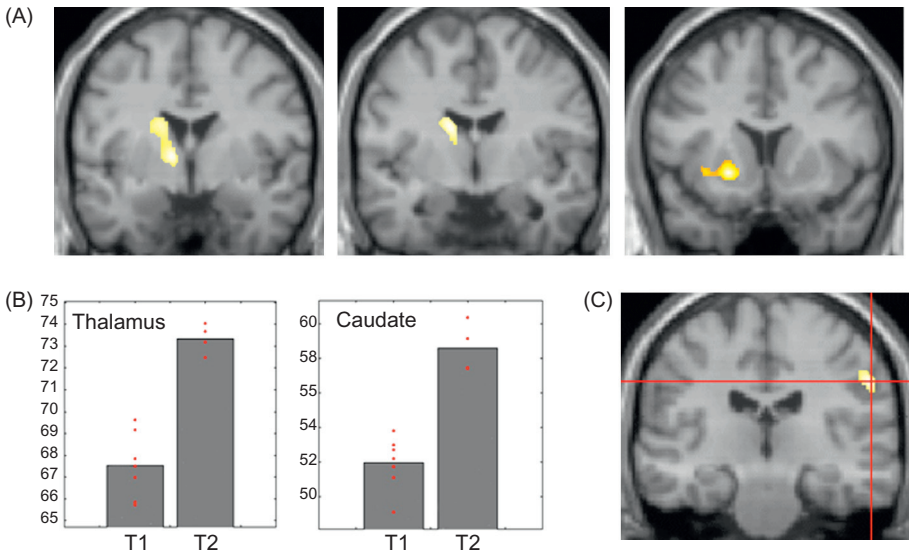

FIGURE 19.5 SPECT results in seven patients with unilateral weakness and hypoesthesia due to conversion hysteria (group data), during passive vibrotactile stimulation applied to both hands simultaneously. (*Source*: Adapted from Vuilleumier et al., 2001). (A) Activation was increased in caudate, putamen, and thalamus contralateral to the symptoms when vibrotactile stimulation after recovery was compared to stimulation during symptoms. (B) Parameters of activity in thalamus and caudate during symptoms (T1) and after recovery (T2). (C) Conversely, activation was increased in somatosensory areas contralateral to the symptoms when vibrotactile stimulation during symptoms was compared to stimulation after recovery.

Parkinson patients experience a subjective blocking of actions despite their intention to move, whereas Tourette patients experience an irrepressible urge to move without purpose. These subcortical anomalies can variably reduce or enhance activation of motor cortical regions depending on experimental conditions (Dagher and Nagano-Saito, 2007). Focal lesions in basal ganglia or thalamus (such as produced by stroke) may also produce "intentional neglect," characterized by a failure to use the contralesional limb despite normal motor strength (von Giesen et al., 1994). The basal ganglia have a unique position within motor pathways in that their activity is strongly modulated by environmental context and motivational cues (Delgado et al., 2004; Mogenson and Yang, 1991), and such influences may operate without consciousness (Pessiglione et al., 2007). The caudate nucleus receives prominent limbic inputs from the amygdala and orbitofrontal cortex, encoding emotional significance of events in relation to past experience, and may thus contribute to eliciting or suppressing specific patterns of motor behavior in response to emotional states (Mogenson and Yang, 1991). Inputs from amygdala and orbitofrontal cortex may also act on thalamic nuclei to modulate activation of striato-cortical loops based on affective signals. Moreover, in animals, alert states with inhibition of motor behavior or protective limb immobility after injury are also known to implicate inhibitory processes mediated by striatal and thalamic pathways (De Ceballos et al., 1986; Klemm, 2001).

A role of these subcortical regulatory circuits in motor conversion would therefore accord with phylogenetic theories that suggest a psychobiological adaptive role of hysteria behavior, with self-preservation value in the context of perceived threats (Demaret, 1994; Kretschmer, 1948; Miller, 1987). Hysterical paralysis could thus involve a suppression of motor readiness or initiation through a modulation of specific basal ganglia and thalamo-cortical systems, under the influence of emotional signals from limbic brain regions such as the amygdala, orbitofrontal cortex, or anterior cingulate gyrus (Vuilleumier et al., 2001). The VMPFC might also play a key role due to its privileged position for the integration of personally-relevant and affectively laden information in autobiographic memory (D'Argembeau, 2013; Gusnard et al., 2001). This neural network might enable emotional states or unconscious memory associations to affect motor, sensory, or even cognitive processing, perhaps also partly owing to previous experiences and particular attentional states of the individual (Brown, 2004; Kozlowska, 2005; Oakley, 1999; Vuilleumier, 2014). Such changes might in turn modulate the degree of activation of primary motor cortex during initiation or preparation of movements, producing either decreases (Burgmer et al., 2006; Marshall et al., 1997), increases (Stone et al., 2007; Vuilleumier et al., 2001), or no changes (Defayolle et al., 1963) depending on the task conditions.

Indirect evidence in support of emotional influences on motor function in conversion was provided by fMRI studies that investigated brain activation to short narratives concerning personal stressful events (Aybek et al., 2014; Kanaan et al., 2007). In one study (Aybek et al., 2014), events judged to be relevant to the occurrence of symptoms (called "escape events," where illness could alter the negative impact of a real life event: e.g., if the spouse threatens to leave, illness of the partner could

TABLE 19.3 Brain Network Analysis During Motor Conversion Using Scaled Subprofile Model (SSM)

	Factor 1	Factor 2	Factor 3
Eigenvalue	5.46	2.24	2.14
Variance explained (%)	45.5	18.6	17.9
(A) BRAIN AREAS			
BA 4	0.84		
BA 6	0.90		
BA 8		0.88	
BA 9-44		−0.65	
BA 44-45		−0.58	0.66
BA 46			
BA 10	−0.75		
BA 11			0.66
ACC		0.70	
BA 1-2-3	0.87		
BA 5-7	0.97		
BA 39-40	0.57	0.68	
BA 37	−0.53	0.76	
BA17-18			
BA 22		−0.72	
BA 20-21	−0.75		
BA 38	−0.55	−0.82	
Caudate			0.68
Lenticular	−0.92		
Thalamus			0.72
(B) SCAN ACQUISITIONS			
T1—contra	0.43	−0.06	**0.58**
T1—ipsi	**0.59**	**0.37**	0.21
T2—contra	**0.77**	−0.07	−0.24
T2—ipsi	**0.80**	−0.11	−0.26

SSM is a modified principal component analysis used to identify networks of regions that form significant covarying patterns (topographic profiles) associated with a specific state (see Alexander and Moeller, 1994). SSM was performed on 20 anatomically defined regions of interest (ROIs) in the SPECT study of Vuilleumier et al. (2001), for both hemispheres contralateral and ipsilateral to motor symptoms, with bilateral vibrotactile stimulation during symptoms (T1) and after recovery (T2). Factors indicate overlapping functional networks of brain areas whose activity was found to covary across subjects and scans. Coefficients indicate the degree to which brain regions (A) and individual hemispheres (B) contribute to (or "weigh" in) each topographical profile. For clarity, factor loadings <0.5 in topographical profiles are not shown. Values in bold indicate scans (sessions and hemisphere) where these networks were significantly expressed. The first two factors reveal a network of sensorimotor cortical areas (factor 1) and attentional areas (factor 2), which were activated by vibrotactile stimulation during both T1 and T2, but with reduced expression in the hemisphere contralateral to symptoms when these are present (factor 1 at T1). Factor three reveal a network of subcortical & frontal areas, including ventral-orbital regions (BA 11 and BA 44/45), which were associated with the presence of symptoms and expressed in the hemisphere contralateral to symptoms when these are present (T1).

change or delay this decision) were compared with other stressful events (called "severe events," where the illness could not influence the outcome of the event: e.g., if the spouse is admitted to hospital for a heart attack, illness of the partner would have no influence on the outcome). Results showed that "escape events" elicited greater activity in patients as compared to healthy controls in the supplementary motor area (SMA) and in the right temporo-parietal junction, two regions involved in motor control and agency, even though the task involved no motor or sensory components. These activations may reflect the particular functional impact of emotionally relevant information on sensory and motor pathways and be potentially related to the production of conversion symptoms; yet the exact nature and mechanisms of such impact remains to be better understood. Further evidence linking abnormal limbic-motor interaction in conversion patients comes from a study showing enhanced functional connectivity between the amygdala and the SMA in patients while they viewed emotional faces (Voon et al., 2010a), a functional connectivity pattern also observed in the previous autobiography memory study (Aybek et al., 2014). Abnormal connectivity between motor cortex, SMA, and caudate nucleus has also been found with methods testing for the functional network organization using independent component analysis of the motor go-no-go task (Cojan and Vuilleumier, 2011; Vuilleumier, 2014).

A few other studies focused on mechanisms of self-agency. While behavioral findings suggest that conversion patients may have an abnormal sense of intention (Edwards et al., 2011), an fMRI study by Voon et al. (2010a,b) observed hypoactivity in the right temporo-parietal junction, a region involved in self-agency monitoring, while patients experienced their involuntary psychogenic tremor as compared with when they intentionally produced a similar tremor (i.e., mimicking their symptoms). This hypoactivity was attributed to abnormal integration between the planned action (feedforward) and the actual action (feedback), leading to an abnormal sense of agency in the patients.

Fewer imaging investigations have been performed in patients with somatosensory hysterical symptoms, such as hemianesthesia or functional pain disorders. Ghaffar et al. (2006) compared brain activation to vibrotactile stimulation applied unilaterally or bilaterally in three patients with hysterical anesthesia of one limb. Results showed a reduced activation of the primary (and to a lesser extent secondary) areas of somatosensory cortex only during unilateral stimulation of the affected limb, while bilateral stimulation produced symmetrical activations in both hemispheres. A similar pattern was found in OFC for all three patients, as well as in the striatum and thalamus

for two patients. These different responses to unilateral and bilateral stimulation were attributed to a reversible functional suppression of sensory processing due to attentional mechanisms. Another fMRI study (Mailis-Gagnon et al., 2003) reported a complex pattern of changes in four patients with chronic sensory loss and pain in one or more limbs. Non-noxious or noxious tactile stimulation were applied to both the affected and unaffected limbs. Different patterns of responses were found in different brain areas. First, unlike stimulation on the normal side (which was always perceived and reported), noxious and non-noxious stimulation on the affected limb (which were not perceived or not reported) did not activate the thalamus, insula, inferior frontal, and posterior cingulate regions. Second, some areas activated by perceived stimuli on the intact limb were deactivated during stimulation on the affected limb (relative to a baseline without any stimulation), including contralateral SI and SII, as well as bilateral prefrontal areas. It is unclear whether such deactivation by stimulation may reflect inhibitory effects, or greater activation in the baseline condition. Third, ACC and VMPFC showed selective increases during unperceived/unreported stimulation on the affected limb than during perceived stimulation on the unaffected side. These complex changes across a wide brain network were interpreted as the result of attentional and emotional processes triggered by stressful or painful conditions, perhaps exacerbated by individual predispositions or developmental factors (Mailis-Gagnon et al., 2003). Moreover, EEG and MEG findings in patients with hysterical anesthesia also suggest that early neural responses in SI and SII are normal, while later responses associated with cognitive or affective processes might be disturbed (Hoechstetter et al., 2002; Lorenz et al., 1998). Other unpublished fMRI results from our group also showed preserved (and even enhanced) responses to tactile stimuli in a patient with hemianesthesia due to conversion (Figure 19.6).

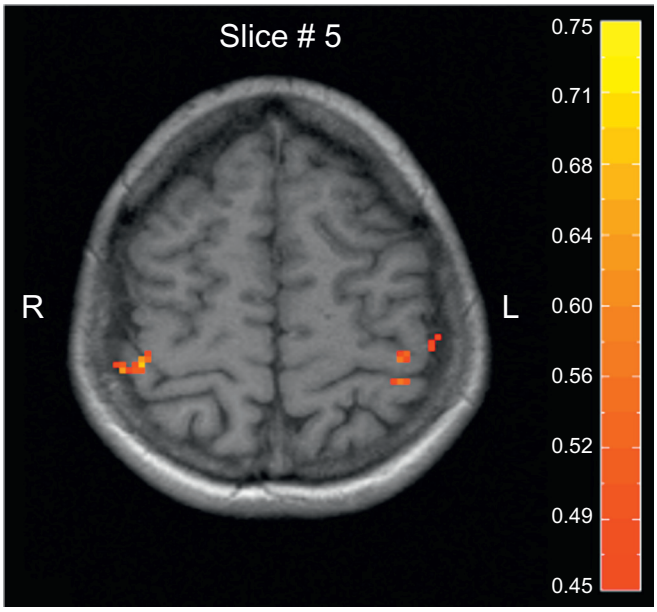

FIGURE 19.6 Functional MRI results in a patient (19-year-old right-handed woman) with left hemianesthesia due to conversion hysteria (normal MRI of the brain and spine, and normal sensory and motor evoked potentials), following a minor car accident (Vuilleumier and Assal, unpublished data). Activation during blocks of bilateral tactile stimulation showed bilateral increases in somatosensory cortex, but stronger in the contralateral than ipsilateral hemisphere.

Although the findings above may not generalize due to the small sample and heterogeneity of patients, it is notable that increased activity arose in the rostral cingulate and ventral prefrontal regions during stimulation of the limb affected by somatosensory conversion symptoms (Mailis-Gagnon et al., 2003), in keeping with similar activations in several studies of motor conversion (Cojan et al., 2009a; de Lange et al., 2007; Marshall et al., 1997; Stone et al., 2007). Abnormal activations in these areas were also reported in two studies of hysterical visual loss. In one study (Werring et al., 2004), occipital cortical areas showed reduced responses to visual stimulation by whole-field color flickers, accompanied by decreased (rather than increased) activation in ACC. Increased activity was observed in several regions including posterior cingulate, insula, temporal poles, as well as the thalamus and striatum on both sides. In another study (Becker et al., 2013), occipital cortex showed normal responses to simple geometric stimulation but markedly decreased responses to faces, together with selective increases in VMPFC. Functional connectivity analysis also revealed increased coupling between VPMFC and occipital areas during blindness episodes. In both cases, results were interpreted as reflecting abnormal modulation of sensory visual processing due to emotional influences from VMPFC, consistent with previous findings in motor conversion (Cojan et al., 2009a; Marshall et al., 1997). Visual neglect symptoms due to conversion have also been observed, accompanied by activation of ACC in addition to parietal areas during a line bisection task (Saj et al., 2009).

Finally, psychogenic amnesia is another type of hysterical deficit without organic cause that has been increasingly investigated by neuropsychological and neuroimaging approaches in recent years (e.g., Markowitsch, 2003). Although a detailed review of this syndrome is beyond the scope of this chapter, and it is considered as a separate category of dissociative disorders in DSM-IV classification, it is noteworthy that psychogenic amnesia shares some clinical features with conversion reactions, including its frequent occurrence after stressful situations and

BOX 19.2

PSYCHOGENIC AMNESIA AND DISSOCIATION

Some patients may present with memory impairments without a discernable neurological cause, typically after one or more stressful life events. This type of "psychogenic" or "dissociative" amnesia differs from the classic amnesic syndromes caused by brain lesions in that autobiographic retrograde memory is predominantly affected with no or more variable problems in memory for new information (Kopelman and Kapur, 2001). This may be accompanied by other dissociative or depersonalization phenomena, such as fugue disorders. The dissociative disorders were once classified together with other conversion disorders as forms of hysteria, but are now considered separately despite some commonalities. Cognitive and brain imaging research has begun to reveal some of the cerebral mechanisms underlying psychogenic amnesia, borrowing from the well-known architecture of memory systems. Single-case studies have shown decreases in activation of medial temporal lobe and basal forebrain region during such episodes (Markowitsch et al., 1998; Yasuno et al., 2000), while some regions in right amygdala and right anterior temporal lobe may still respond more to familiar than unfamiliar material despite a lack of explicit recognition. Abnormal activations in anterior cingulate, prefrontal areas, and caudate have also been found (Glisky et al., 2004; Yasuno et al., 2000). Markowitsch (2003) proposed that such memory deficits may result from a functional suppression or disconnection between frontal and temporal areas within the right hemisphere, triggered by intense environmental stress or psychological trauma, or brain injuries in some cases, leading to a subsequent inability to retrieve affectively-laden information that is stored with personal autobiographical memories. This, in turn, would disrupt the subjective experience of selfhood in memory retrieval. By contrast, semantic information stored in left hemisphere might remain more accessible and allow preserved anterograde learning. Furthermore, it was proposed that this "mnestic blockade" might be facilitated by the release of steroids (cortisol) due to stress or depression, which can exert suppressive effects on hippocampal function and memory (Markowitsch, 1999). Although it is unclear how such hormonal factors could affect limbic circuits in the right hemisphere more than in the left hemisphere, a right hemisphere predominance would also be consistent with other asymmetries associated with sensorimotor conversion (Stern, 1983) and pseudoseizure disorders (Devinsky et al., 2001).

occasional mixture with organic factors such as mild brain injury (concussion). While functional neuroimaging studies also point to anomalies in frontal and limbic regions potentially associated with emotion and self-attribution processes, together with changes in medial temporal lobe regions associated with memory, it remains to be determined whether the "mnestic blockade" of psychogenic amnesia involves neural processes regulating awareness of memory function that are at least partly common to neural processes regulating awareness of motor or sensory functions (see Box 19.2). Further studies elucidating the commonalities and differences between the functional neuroanatomy of these different types of psychogenic reactions might contribute to better understand the relationships between conversion and dissociation disorders (Brown et al., 2007).

CONCLUSIONS

In spite of decades of interest in conversion hysteria, a number of important aspects concerning its causal factors and clinical manifestations still remain to be clarified; and recent attempts to identify specific cerebral correlates for conversion symptoms by using neurophysiology or neuroimaging techniques still remain conflicting. However, significant progress has been made in recent years and may now begin to provide new clues about the possible biological and cognitive underpinnings of these disorders. Despite some divergence in specific findings between studies, and despite a large heterogeneity between patients and symptoms, the results obtained from functional neuroimaging have contributed to delineate a network of brain areas including ventromedial and inferior frontal cortex, basal ganglia, thalamus, amygdala as well as higher-level associative sensory or motor regions (SMA and temporo-parietal junction), which all appear critically implicated and abnormally interacting with each other in conversion hysteria. On the one hand, most fMRI and PET studies have found changes in activity arising within brain regions involved in the affected, motor, sensory, or mnemonic functions (e.g., during motor, somatic, or amnesic symptoms, respectively), typically with concomitant changes in limbic

regions associated with emotional and motivational regulation such as orbitofrontal and medial prefrontal areas. The latter areas most often exhibit increases (Becker et al., 2013; Cojan et al., 2009a; de Lange et al., 2007; Mailis-Gagnon et al., 2003; Marshall et al., 1997), but sometimes selective decreases (Ghaffar et al., 2006; Stone et al., 2007; Werring et al., 2004), or changes in functional coupling (Becker et al., 2013; Vuilleumier et al., 2001), accompanied by variable changes in other subcortical regions such as amygdala or striatum. On the other hand, most neurophysiology studies using EEG or MEG have found normal activation of primary motor or sensory cortical areas, with occasional anomalies in later components such as P300, consistent with a lack of damage to low-level sensorimotor pathways but more complex anomalies in higher-level modulatory or integrative processes.

Whether observed changes in the activity of these brain areas reflect causes, consequences, comorbidity markers, or compensatory mechanisms is, however, still unclear at present. Studies testing brain responses directly related to impaired function (e.g., movement attempts during hysterical paralysis (Marshall et al., 1997; Spence et al., 2000; Stone et al., 2007)) may not only disclose activation reflecting not only this function alone but also vary as a function of actual performance (failure, attempt, or reduced), and in addition yield a mixture of other activations related to intentional, emotional, executive, or monitoring processes that might be engaged by the task and the context. Alternative approaches testing brain responses to more passive stimulation in order to elicit covert activation of cognitive or emotional pathways (Burgmer et al., 2006; de Lange et al., 2007; Kanaan et al., 2007) might provide useful information to characterize functional neural changes associated with conversion hysteria across different types or degrees of clinical deficits. However, these approaches may require a precise model of the tested function and of the normal effects of such indirect paradigms in order to interpret the findings in an informative manner. For instance, the role of specific mechanisms putatively involved in the generation of conversion symptoms (e.g., inhibition, attention, or disconnection) might be tested using paradigms borrowed from current neurobiological models of sensorimotor, emotion, or memory processing.

A key role of orbitofrontal and ventromedial prefrontal areas in hysteria conversion, as suggested by imaging studies, would be consistent with a major function of these areas in integrating the emotional significance of external events with past experiences and self-representations (D'Argembeau, 2013; Gusnard et al., 2001), and in forming expectancies about the outcome associated with these events based on sensory and mnemonic cues (Roesch and Schoenbaum, 2006). OFC and VMPFC are likely to be activated in response to stressful situations and personally relevant affective signals that may trigger conversion hysteria, perhaps under the influence of other limbic regions such as the amygdala (Vuilleumier, 2014). Such activation might then promote the generation of abnormal functional states in motor or sensory networks, involving either a stereotyped adaptive mode of response (e.g., to perceived threat, as postulated by phylogenetic theories) or some reinstatement of past associations or memories (e.g., acquired by personal experience or observations, as proposed by some dissociation theories). Whether these functional changes involve an inhibition of normal processing or an impairment in the normal readiness or responsiveness of specific neural pathways still remains to be determined; but these different neural mechanisms may not necessarily be exclusive. Moreover, because emotional responses in limbic areas and their influences on connected brain regions can arise without awareness (and even without any direct emotional experience) (Dolan and Vuilleumier, 2003), such effects might generate conversion behavior without intentional control and thus enter awareness of the patient as a distorted experience of motor will or self-perception (Vuilleumier, 2014). Chronic or acute stress may further contribute to promote the retrieval of representations and behaviors mediated by limbic circuits such as amygdala, while reducing those mediated by cortical and hippocampal regions (Tsoory et al., 2007). Likewise, a disruption in the dynamic integration between awareness of agency and immediate sensation, and the control of bodily function or memory retrieval, might also underlie some aspects of other dissociative disorders subsequent to emotional stressors.

Finally, it is essential that modern neuroimaging approaches to conversion hysteria should not constitute a simple return to the purely neurogenic models that preceded Freudian psychodynamic accounts, but rather yield more testable predictions about both psychological and neurobiological mechanisms underlying the clinical concept of "conversion" in hysteria. A better understanding of these common but still enigmatic disorders will not only offer precious insights into cerebral processes mediating self-awareness, but will also help refine the clinical diagnosis and management of patients. Just as conversion hysteria has too often been seen as a disease of imagination, neurobiological accounts have too often rested on pure speculation, without sufficient positive evidence to support them. However, thanks to the development of functional neuroimaging and current advances in cognitive and affective neurosciences, the time seems now ripe to

gain a much deeper knowledge into one of the most ancient and most physical reactions of the human mind to perceived stress and distress.

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CHAPTER

20

Leaving Body and Life Behind: Out-of-Body and Near-Death Experience

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OUTLINE

Out-of-body experiences (OBEs) and near-death experiences (NDEs) have accompanied and fascinated humanity since times immemorial and have long been the province of circles interested in the occult. Many authors have even argued that either experience provides evidence for the mind being separate or independent from processes in the body and brain or the persistence of life after death. The neurology of OBEs and NDEs takes a different—empirical and neuroscientific—stance studying the brain mechanisms that are associated behaviorally and neurally with these experiences. Accordingly, OBEs have been studied by neurologists and cognitive scientists investigating the functional and neural mechanisms of bodily awareness

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and self-consciousness in specific brain regions. In the present chapter we will review these recent neuroscientific data on OBEs. The situation is quite different for NDEs. Although many different theories have been proposed about brain processes, neurologists and cognitive neuroscientists have paid little attention to these experiences. This is unfortunate, because the scientific study of NDEs could provide insights into the functional and neural mechanisms of many facets of human experience such as beliefs, concepts, personality, spirituality, magical thinking, and self. Moreover, as we will review, there is a frequent association of OBEs and NDEs, to the point that they are frequently confused with each other or unwarrantedly cross-referenced (e.g., Formatting Citation). This is probably due to the fact that OBEs are often associated with NDE, if not one of the NDE key elements (Ring, 1982; Sabom, 1982; Moody, 2001). In the following, we will describe OBEs and NDEs, providing definitions, incidences, key phenomenological features, and reviewing some of the underlying psychological and neurocognitive mechanisms.

OUT-OF-BODY EXPERIENCES

Definition

In an OBE, people seem to be awake and feel that their "self," or center of experience, is located outside of the physical body (disembodiment). They report seeing their body and the world from an elevated extracorporeal location (Green, 1968; Blackmore, 1992; Brugger, 2002; Blanke et al., 2004; Bünning and Blanke, 2005). The subject's reported perceptions are organized in such a way as to be consistent with this elevated visuo-spatial perspective. The following example (Irwin, 1985, case 1) illustrates what individuals commonly experience during an OBE: "I was in bed and about to fall asleep when I had the distinct impression that "I" was at the ceiling level looking down at my body in the bed. I was very startled and frightened; immediately [afterwards] I felt that I was consciously back in the bed again." We have defined an OBE by the presence of the following three phenomenological elements: the feeling of being outside one's physical body (or disembodiment); the perceived location of the self at a distanced and elevated visuo-spatial perspective (or perspective); and the experience of seeing one's own body (or autoscopy) from this elevated perspective (Bünning and Blanke, 2005). In other proposed definitions of OBEs it suffices to experience disembodiment, and OBEs are thus defined as "experiences in which the sense of self or the center of awareness is felt to be located outside of the physical body" (Alvarado, 2000, p. 331; see also Alvarado, 2001) or as experiences in which "the center of consciousness appears to occupy temporarily a position which is spatially remote from his/her body" (Irwin, 1985). Another definition requires disembodiment and a distanced visuo-spatial perspective: "the feeling of a spatial separation of the observing self from the body" (Brugger, 2002). OBEs constitute a challenge to the experienced spatial unity of self and body under normal conditions, that is the feeling that there is a "real me" that resides in my body and is both the subject and agent of my experiences (Blackmore, 2013; Zahavi, 2005). Probably for this reason, OBEs have attracted the attention of philosophers (Metzinger, 2004, 2005), psychologists (Blackmore, 1992; Irwin, 1985; Palmer, 1978), and neurologists (Blanke et al., 2004; Devinsky et al., 1989; Grüsser and Landis, 1991; Brugger et al., 1997) that have conceptualized OBEs as experiences due to deviant bodily self-consciousness arising from abnormal brain processes that code for the feeling of embodiment under normal conditions.

Incidence

How common are OBEs in the general population? This question is still difficult to answer as the relevant studies vary in several respects: (i) the different investigators have asked quite different questions about the presence of an OBE and (ii) have asked the questions either by mail, over the phone, or by interviewing subjects personally. Depending on the questions asked, how they are asked, and how an OBE is defined, the results are very likely to differ. In addition, (iii) most studies have been carried out in younger populations, mostly college students, mostly in Anglo-Saxon psychology departments. Accordingly, it is not surprising that questionnaire studies have estimated the OBE incidence differently (8–34%; reviewed in Blackmore, 1992). Also the two key elements (autoscopy and distanced visuo-spatial perspective) as used in neurobiologically motivated studies (see below) were not necessary OBE elements in most of these studies. We thus agree with Blackmore (1992) that incidences above 10% are very likely overestimates and suggest that ~5% of the general population have experienced an OBE. Finally, OBEs seem to occur across many cultures in the world, although to date only one study has investigated this interesting issue (Sheils, 1978).

Phenomenology

OBEs have to be distinguished from two other phenomena that also involve autoscopy: autoscopic hallucinations and heautoscopy. Whereas there is no disembodiment in autoscopic hallucinations and always disembodiment in OBEs, many subjects with heautoscopy generally do not report clear disembodiment,

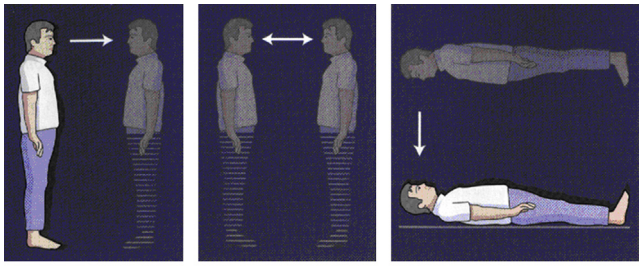

FIGURE 20.1 Illustration of three types of autoscopic phenomena (from Blanke and Mohr (2005)). In this figure the phenomenology of (A) autoscopic hallucination (AH), (B) heautoscopy (HAS), and (C) out-of-body experience (OBE) is represented schematically. The experienced position and posture of the physical body for each autoscopic phenomenon is indicated by full lines and the experienced position and posture of the disembodied body (OBE) or autoscopic body (AH, HAS) in blurred lines. The finding that AH and HAS were mainly reported from a sitting/standing position and OBE in a supine position is integrated into the figure. The experienced visuo-spatial perspective during the autoscopic phenomenon is indicated by the arrow pointing away from the location in space from which the patient has the impression to see (AH: from the physical body; OBE: from a disembodied body or location; HAS: alternating or simultaneously from either the fashion between physical and the autoscopic body). *Source: Modified from Blanke et al. (2004), with permission from Oxford University Press.*

but are not able to localize their self unambiguously (self-location may alternate between an embodied location and an extracorporeal one, or they might feel "localized" at both positions at the same time). Accordingly, the visuo-spatial perspective is body-centered in autoscopic hallucinations, extracorporeal in the OBE, and at different extracorporeal and corporeal positions in heautoscopy, with the impression of seeing one's own body (autoscopy) present in all three forms of autoscopic phenomena (Figure 20.1, for further details see Brugger, 2002; Blanke et al., 2004; Brugger et al., 1997; Blanke and Mohr, 2005; Blanke and Arzy, 2005).

OBEs have been the province of esoteric circles for much of their history. From this literature one may nevertheless find abundant phenomenological details and varieties of OBEs (e.g., Muldoon and Carrington, 1969; Yram, 1972; Monroe, 1977; for review see Blackmore, 1992). In addition, subjects with repeated OBEs (so-called "astral travelers") have not just given detailed accounts of their OBEs, but also proposed several procedures to induce OBEs that might be approached more systematically by researchers. These authors also reported about the phenomenological characteristics of the disembodied body, its location with respect to the physical body, the appearance of the autoscopic body, and the vestibular and bodily sensations associated with the experience (see Lippman, 1953). Yet, only a small minority of subjects with OBEs experience more than one or two in a lifetime. Most commonly, OBEs are therefore difficult to study because they generally are of short duration, happen only once or twice in a lifetime (Green, 1968; Blackmore, 1992) and occur under a wide variety of circumstances that we will review next.

Precipitating Factors

Several precipitating factors of OBEs have been identified. We review findings from neurology, psychiatry, drugs, and general anesthesia. OBEs will also be discussed in the context of NDEs (see "Out-of-Body Experiences" subsection).

Neurology

Only few neurological cases with OBEs have been reported in the last 50 years (Lippman, 1953, cases 1 and 2; Hécaen and Green, 1957, case 3; Daly, 1958, case 5; Lunn, 1970, case 1). Further more recent cases have been reported (Devinsky et al., 1989, cases 1, 2, 3, 6, 10; Maillard et al., 2004, case 1; Blanke et al., 2004, cases 1, 2a, 3) (see also Greyson et al., 2014). OBEs have been observed predominantly in patients with epilepsy, but also in patients with migraine (Green, 1968; Lippman, 1953); see also Jürgens et al. (2014). In his seminal study, Orin Devinsky et al. (1989) described many neurological OBE patients and reported patients whose OBEs were associated with non-lesional epilepsy (cases 6 and 10), with epilepsy due to an arteriovenous malformation (cases 2 and 3), or associated to posttraumatic brain damage (case 1). In another study (Blanke et al., 2004), OBEs were due to a dysembryoplastic tumor (cases 1 and 2a) and in one patient induced by focal electrical stimulation (case 3). Epileptic OBEs were also reported in a patient with focal cortical dysplasia (Maillard et al., 2004, case 1; see also Greyson et al., 2014; Ionta et al., 2011).

Whereas many authors (e.g., Devinsky et al., 1989) observed the frequent association of vestibular sensations and OBEs, Grüsser and Landis (1991) proposed that a paroxysmal vestibular dysfunction might be an important mechanism for the generation of OBEs. In another study (Blanke et al., 2004), the importance of vestibular dysfunction was underlined by their presence in all patients with OBEs and by the fact that vestibular sensations were evoked in a patient at the same cortical site where higher currents induced an OBE (Blanke et al., 2002). In more detail, it has been suggested that OBEs are associated with specific vestibular sensations, namely graviceptive, otholithic, or vestibular sensations (Blanke et al., 2004; Lopez et al., 2008). Otholithic sensations are characterized by a variety of sensations including feelings of elevation and floating, as well as a 180° inversions of one's body and visuo-spatial perspective in extrapersonal space. They may be associated with brain damage (Smith, 1960;

Brandt, 1999), but also occur in healthy subjects during orbital and parabolic flight during space missions or the microgravity phase of parabolic flights (Lackner, 1992; Mittelstaedt and Glasauer, 1993). Interestingly, responses to microgravity may either be experienced as an inversion of the subject's body and visuo-spatial perspective in extrapersonal space (inversion illusion) or as an inversion of the entire extrapersonal visual space that seems inverted by 180° to the stable observer (room-tilt illusion). Based on these functional similarities it was suggested that an otholithic dysfunction might not only be an important causal factor for room-tilt illusion and inversion illusion, but also for OBE (for further details see Blanke et al., 2004; Lackner, 1992; Blanke, 2012).

In addition to vestibular disturbances, it has been reported that OBE patients may also experience paroxysmal visual body-part illusions such as phantom limbs, supernumerary phantom limbs, and illusory limb transformations either during the OBE or during other periods related to epilepsy or migraine (Blanke et al., 2002, 2004; Devinsky et al., 1989; Lunn, 1970; Hécaen and de Ajuriaguerra, 1952). A patient was reported in whom OBEs and visual body-part illusions were induced by electrical stimulation at the right temporo-parietal junction (TPJ) (Blanke et al., 2002). In this patient an OBE was induced repetitively by electrical stimulation whenever the patient looked straight ahead (without fixation of any specific object). If she fixated her arms or legs that were stretched out, she had the impression that the inspected body part was transformed leading to the illusory, but very realistic, visual perception of limb shortening and illusory limb movement if the limbs were bent at the elbow or knee. Finally, with closed eyes the patient did have neither an OBE nor a visual body-part illusion, but perceived her upper body as moving towards her legs (Blanke et al., 2002). These data suggest that visual illusions of body parts and visual illusions of the entire body such as autoscopic phenomena might depend on similar neural structures as argued by previous authors (Brugger et al., 1997; Hécaen and de Ajuriaguerra, 1952). These data (Blanke et al., 2002) also show that visual body-part illusions and OBEs are influenced differently by the behavioral state of the subject.

Another functional link between OBE and disturbed own body perception is suggested by the fact that OBEs and autoscopic hallucinations (and heautoscopy) depend differently on the patient's position prior to the experience. This suggests that proprioceptive and tactile mechanisms influence both phenomena differently. Thus, during neurological OBEs patients are in supine position (Blanke et al., 2004; Blanke and Mohr, 2005) as was found by Green (1968) in 75% of OBEs in healthy subjects. Interestingly, most techniques that are used to deliberately induce OBEs recommend a supine and relaxed position (Blackmore, 1992; Irwin, 1985). This contrasts with the observation that subjects with autoscopic hallucination or heautoscopy are either standing or sitting at the time of their experience (Blanke et al., 2004; Blanke and Mohr, 2005; Dening and Berrios, 1994). It thus seems that OBEs depend on the subject's position prior or during the experience and that these differential proprioceptive, vestibular, and tactile mechanisms differentiate them from other types of autoscopic phenomena (see "Summary" section). The observation of OBEs during general anesthesia and sleep (see "General Anesthesia" section and Bünning and Blanke, 2005) also corroborates the notion that OBEs are facilitated by the sensory signals predominating in supine body position. Moreover, rapid bodily position changes such as brutal accelerations and decelerations have been associated with OBEs. This has long been reported by mountain climbers who unexpectedly fell (Heim, 1892; Ravenhill, 1913; Brugger et al., 1999; Firth and Bolay, 2004), as well as in car accidents (Devinsky et al., 1989; Muldoon and Carrington, 1969) and in the so-called "break-off phenomenon" experienced by airplane pilots (Benson, 1999). In this last case, a pilot might initially fail to sense correctly the position, motion or tilt of the aircraft as well as his own body position with respect to the surface of the earth and the gravitational "earth-vertical." These feelings can lead to several experiences grouped under the term "break-off phenomenon" that is characterized by feelings of physical separation from the earth, lightness, and an altered sense of the pilot's own orientation with respect to the ground and the aircraft (Benson, 1999; Clark and Graybiel, 1957; Sours, 1965). Some pilots have even described a feeling of detachment, isolation, and remoteness from their immediate surroundings which they sometimes describe as an OBE with disembodiment, elevated visuo-spatial perspective, and autoscopy (Benson, 1999; Tormes and Guedry, 1974). At the extreme, pilots feel being all of a sudden *outside* the aircraft watching themselves while flying, and being "broken off from reality." These OBEs are most often experienced by jet aviators flying alone, especially at high altitudes (above 10,000 m), although helicopter pilots can experience this phenomenon at altitudes of only 1500–3000 m (Benson, 1999; Tormes and Guedry, 1974). These OBEs seem facilitated by mental absorption (the pilot is unoccupied with flight details) and by the length and visual monotony of the mission (Benson, 1999). Monotony and absorption coupled with physical exhaustion might also be sufficient to trigger OBEs, as reported by long-distance runners (Morgan, 2002).

With respect to the underlying neuroanatomy, only few neurological OBE patients with circumscribed

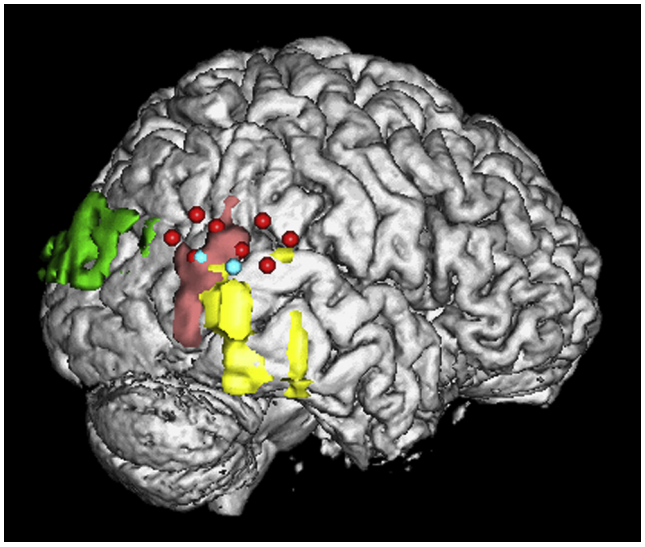

FIGURE 20.2 Lesion analysis of patients with documented brain anomalies and OBE. Mean lesion overlap analysis of five neurological patients with OBE in whom a lesion could be defined (Patients 1, 2, 3, 5, and 6 from Blanke et al. (2004)). The MRI of all patients was transformed into Talairach space and projected on the MRI of one patient. Each color represents a different OBE patient. Mean overlap analysis centered on the TPJ. For details, see Blanke et al. (2004), Blanke and Arzy (2005). *Source: Modified from Blanke et al. (2004), reproduced with permission from Oxford University Press.*

brain damage have been described. In some patients with OBEs, the seizure focus was estimated only by EEG recordings and localized to the temporal lobe or posterior temporal region (standard magnetic resonance imaging (MRI) or computer tomography was normal in most patients) (Devinsky et al., 1989). Yet, in one patient the lesion was found in the temporal lobe and in another patient in frontal and temporal lobe (Devinsky et al., 1989). Others (Lunn, 1970) described an OBE patient with posttraumatic brain damage in the parietal lobe, as well as an OBE patient with damage to the temporal lobe (Daly, 1958). More recent MRI-based analysis revealed a predominant involvement of the right TPJ in patients with OBEs (Blanke et al., 2004; Blanke and Mohr, 2005; Maillard et al., 2004; see Ionta et al., 2011 for more recent analysis). It has also been shown that electrical stimulation of the TPJ leads to OBEs, providing additional causal evidence for the importance of this region in the generation of OBEs (Blanke and Mohr, 2005) (Figure 20.2).

Psychiatry

While reports of autoscopic hallucinations and heautoscopy are not rare in patients suffering from schizophrenia, depression, and personality disorders (Blanke et al., 2004; Devinsky et al., 1989; Brugger et al., 1997; Hécaen and de Ajuriaguerra, 1952; Menninger-Lerchenthal, 1946; Lhermitte, 1998); others (Bünning and Blanke, 2005) found only two cases of OBE in psychiatric patients. One had severe depression (Hécaen and Green, 1957) and the other patient was undiagnosed (Zutt, 1953). Two questionnaire surveys have investigated OBEs in schizophrenia (Blackmore, 1986; Röhricht and Priebe, 1997) and found a similar incidence and phenomenology as in healthy subjects. A study in psychiatric patients suffering from posttraumatic stress disorder found a fourfold increase in prevalence as compared to healthy subjects (Reynolds and Brewin, 1999). Moreover, the personality measure of schizotypy is positively correlated with OBEs in healthy subjects and has also been shown to relate behaviorally and neurally (at the TPJ) to OBEs (Mohr et al., 2006; Arzy et al., 2007). As this trait reflects a continuum between healthy subjects and schizophrenic patients, these data suggest that OBEs are very likely more frequent in schizophrenic patients than currently thought. In addition, other personality traits such as individuals' somatoform (Murray and Fox, 2005a,b) but not general dissociative (Arzy et al., 2007) tendencies, body dissatisfaction (Murray and Fox, 2005a), or dissociative alterations in one's body image during a mirror-gazing task (Terhune, 2009) have also been linked to OBEs. Finally, in a questionnaire-based investigation, healthy individuals who experienced OBEs reported significantly more perceptual anomalies (e.g., body-distortion) and the tendency to be more hallucinatory-prone relative to individuals with no OBE (Braithwaite et al., 2011).

Drugs

The administration of different pharmacological substances has presumably been used since immemorial times in ritual practices to induce abnormal experiences including OBEs (Sheils, 1978). These include marijuana, opium, heroin, mescaline, ketamine, and lysergic acid diethylamide (LSD) (Blackmore, 1992; Grüsser and Landis, 1991; Lhermitte, 1998; Tart, 1971; Aizenberg and Modai, 1985). Concerning marijuana, Tart (1971) found that OBEs occurred in 44% of a sample of 150 college students who used this drug (see also Bünning and Blanke, 2005), that is, a much higher frequency than in the general population. However, a majority of the subjects with OBEs in this study frequently used other drugs such as LSD. It is thus not clear whether the higher frequency of OBEs is due to marijuana consumption or the consumption of other drugs. Experiences related to OBEs such as a feeling of floating or of being dissociated from one's body, have also been induced under controlled conditions by marijuana administration compared with placebo administration (Siegel, 1977), although similar data with respect to OBEs or other autoscopic phenomena are lacking. Moreover, the intake of therapeutic marijuana was shown to induce

OBE in a patient with tetraplegia and severe somatosensory loss due to large lesions in the cervical spinal cord (Overney et al., 2009). Recently, an online survey investigated the strength of the association of OBEs with ketamine use relative to other common substances (Wilkins et al., 2011). The results suggest that both lifetime frequency of ketamine use and OBEs during ketamine intoxication were more strongly related to the frequency of OBEs than other drugs, and that the apparent effects of other drugs could largely be explained by associated ketamine use. In another survey (Corazza and Schifano, 2010), the large majority (90%) of NDEs with a strong sense of disembodiment were also reported to occur during first instances of ketamine use. These authors proposed that by impacting NMDA receptors (Jansen, 1997) ketamine may affect the availability and integration of multisensory signals, including those mediated by the temporo-parietal junction (TPJ) (see below).

General Anesthesia

It has long been known that conscious perceptions may occur under general anesthesia: "Awareness during anesthesia is as old as the specialty itself" (Spitellie et al., 2002). Insufficient levels of anesthesia combined with the application of muscle relaxants seem to be the main cause of this preserved awareness. Another pathophysiological factor might be related to hemodynamic cerebral deficits, most notably in anesthesized patients undergoing cardiac and posttraumatic surgery (Sandin, 2003; Sandin et al., 2000). OBEs in association with general anesthesia have been described in retrospective case collections (Muldoon and Carrington, 1969; Crookall, 1964), but also in more recent patient studies (Ranta et al., 1998, patient 3, Cobcroft and Forsdick, 1993, 4 of 187 patients). Such a patient reports: "I had the strangest [...] sensation of coming out of my self; of being up at the ceiling looking down on the proceedings [of the operation]. After the initial realization that I couldn't communicate at all, came the feeling of acceptance... of being aware of having one hell of an experience" (Cobcroft and Forsdick, 1993). Several patients reported that they "left their body during the operation at some point" (Osterman et al., 2001). Although OBEs are quite rare during general anesthesia, this is probably linked to the relative infrequency of visual awareness during general anesthesia, and the much higher frequency of auditory perceptions (89%), sensations of paralysis (85%), motor illusions and bodily transformations (30–40%), and pain (39%). Visual perceptions were reported in only 27% of patients (Moerman et al., 1993; see also Cobcroft and Forsdick, 1993). Yet, among patients with visual perceptions, many reported disembodiment and seeing the surgeon and other people or surroundings of the operating theater during the actual operation. Thus, if analyzed only with respect to the presence of visual awareness and experiences in the context of general anesthesia, OBEs and OB-like experiences are not so rare. This is of special interest because paralysis, complex own body perceptions, and supine position are not only frequent during general anesthesia with preserved awareness, but also frequently reported by subjects with OBEs of spontaneous or neurological origin (Blackmore, 1992; Blanke et al., 2004; Blanke and Mohr, 2005; Irwin, 1999). Concerning hemodynamic cerebral deficits that have been shown to be associated with an increased incidence of awareness during anesthesia (Bünning and Blanke, 2005), it is interesting to note that they may lead to rather selective and initially focal decreases in cerebral blood flow and as a consequence induce transient or manifest brain infarctions that frequently include the TPJ (Ringelstein and Zunker, 1998) suggesting that OBEs under general anesthesia might be related to the functional and anatomical pathomechanisms as described in neurological patients with epilepsy, migraine, and cerebrovascular disease.

Experimental Induction of OBE States

Besides pathological conditions and drug studies, researchers can now simulate out-of-body illusions in healthy volunteers using video, virtual reality, or robotic devices (Ionta et al., 2011; Ehrsson, 2007; Lenggenhager et al., 2007; for a review see Blanke, 2012). In these studies, full-body (or "out-of-body") illusions are generally induced by the application of multisensory conflicts between a visual stimulus and a tactile, vestibular, or cardiac one. For instance, a tactile stroking stimulus is repeatedly applied to the back (Lenggenhager et al., 2007) or chest (Ehrsson, 2007) of a participant who is filmed, and simultaneously sees a human body being stroked at corresponding body parts. As in classical OBEs, participants view an image of their own body (the "virtual body") from an "outside," third-person perspective while feeling tactile stimulations on their skin. Under such conditions, a multisensory conflict arises, as what is seen (i.e., one's avatar being stroked) does not match what is felt (one's back being stroked). The illusion vanishes when a temporal delay is added between the visual and tactile stimulus (i.e., asynchronous visuo-tactile condition). Out-of-body and full-body illusions are usually associated with changes in self-location and self-identification. Indeed, as compared to asynchronous visuo-tactile conditions, participants in synchronous visuo-tactile conditions self-identify more strongly with the seen virtual body, judge their self-location as closer to it, and feel that the tactile stimulus emanates from it. These subjective changes support the idea that self-identification and self-location are based on the

integration of multisensory signals. In addition, experimental alterations of bodily self-consciousness are also associated with changes at the physiological level (i.e., skin conductance response to a threat directed towards the virtual body (Ehrsson, 2007; Petkova and Ehrsson, 2008); body temperature (Salomon et al., 2013); nociceptive thresholds (Hänsell et al., 2011)). This suggests that changes in bodily self-consciousness induced by exteroceptive multisensory conflicts (e.g., visuo-tactile) interact with the interoceptive homeostatic systems. Consistent with this idea, the level of interoceptive sensitivity (e.g., as measured in a heartbeat counting task) can be used as a predictor of changes in self-other boundaries in response to multisensory stimulation (Tsakiris, 2010; Tajadura-Jiménez and Tsakiris, 2014).

To what extent are interoceptive bodily signals themselves relevant for bodily self-consciousness, and how do they interact with external bodily signals? While the large majority of cited studies manipulated exteroceptive signals (i.e., vision and touch) in order to manipulate bodily self-consciousness, behavioral, imaging, and neurological results also suggest that the brain's representations of internal bodily states (Critchley et al., 2004) are primordial for the self (Damasio and Dolan, 1999; Craig, 2009). Accordingly, modulations of bodily consciousness due to conflicts between an interoceptive signal (e.g., the heartbeat) and an exteroceptive one (e.g., a visual stimulus) have been documented. Aspell and colleagues (2013) showed that a colored silhouette surrounding the virtual body and flashing in synchrony with respect to the participant's heartbeats also induced changes in self-identification and self-location. Importantly, changes in bodily self-consciousness under these conditions were of similar magnitude to those that stemmed from purely exteroceptive conflicts (i.e., visuo-tactile; for related work with a rubber hand illusion, see Suzuki et al., 2013). These findings are compatible with proposals that both exteroceptive and interoceptive signals are important for bodily self-consciousness (see also Seth et al., 2011). As integrated interoceptive and exteroceptive signals show to be potent modulators of bodily self-consciousness, it may be argued that central processing of signals from the inside and the outside of the human body form an integrated cortical system for bodily self-consciousness, and thus might be important factors in OBEs.

Brain regions involved in the processing of interoceptive signals like the insula (Critchley et al., 2004) are likely to be crucial components of this system. A few neuroimaging studies on bodily self-consciousness have linked self-identification and self-location to several brain regions using different paradigms and techniques. The role of insula is supported by functional connectivity analysis during the full-body illusion (Petkova et al., 2011) and neurological data in patients suffering from heautoscopy (Brugger, 2002; Heydrich and Blanke, 2013). Moreover, changes in self-identification were shown to be associated with activity in bilateral ventral premotor cortex, left posterior parietal cortex, and the left putamen (Petkova et al., 2011). In another study, Ionta and colleagues (2014) found that self-identification with a virtual body was associated with activation in the right middle-inferior temporal cortex (partially overlapping with the extrastriate body area), a region that is, like the premotor cortex, involved in the multisensory processing of human bodies (Downing et al., 2001; Grossman and Blake, 2002; Astafiev et al., 2004). Importantly, activity in bilateral temporo-parietal cortex (in proximity with the lesion overlap zone associated with OBEs of neurological origin by Ionta et al., 2011) differed between synchronous and asynchronous visuo-tactile conditions, and depended on the experienced direction of the first-person perspective (i.e., seeing a virtual body from an elevated or lowered perspective while laying down in a supine position). More recent experimental data suggested that these subjective changes in the first-person perspective are associated with inter-individual differences in visuo-vestibular integration (Pfeiffer et al., 2013). The influence of vestibular signals on first-person perspective and bodily self-consciousness is notably supported by the proximity of the vestibular cortex to TPJ (Lopez and Blanke, 2011), and the frequent vestibular disturbances that occur during OBEs of neurogical origin. Accordingly, we argue that changes in the experienced direction of the first-person perspective are due to abnormal signal integration of vestibular and visual cues (see Blanke, 2012 for review). Taken together, the reviewed brain imaging studies implicate brain areas that integrate multisensory bodily signals and thus provide further evidence for the link between multisensory body representations, bodily self-consciousness, and OBEs, in particular in bilateral temporo-parietal cortex.

Summary

The reviewed data point to an important involvement of bilateral, but in particular the right TPJ in OBEs and related processing with respect to bodily self-consciousness. The observation that electrical stimulation of this area may induce OBEs and other altered own body perceptions further suggests that during OBEs the integration of proprioceptive, tactile, visual, and vestibular information of one's body is altered due to discrepant central own body representations. Blanke and colleagues have suggested (Blanke et al., 2004; Blanke and Mohr, 2005) that autoscopic phenomena (including OBEs) result from a failure to integrate

multisensory bodily information and proposed that they result from a disintegration in bodily or personal space (due to conflicting tactile, proprioceptive, kinesthetic, and visual signals) and a second disintegration between personal and extrapersonal space (due to conflicting visual and vestibular signals caused by a vestibular otolithic dysfunction). While disintegration in personal space is present in all three forms of autoscopic phenomena (see also Heydrich and Blanke, 2013), differences between the different forms of autoscopic phenomena are mainly due to differences in strength and type of the vestibular dysfunction. Following this model, OBEs were associated with a strong otolithic vestibular disturbance, whereas heautoscopy was associated with a moderate and more variable vestibular disturbance (and the association with interoceptive signals (Heydrich and Blanke, 2013)), and autoscopic hallucinations without any vestibular disturbance. Neuroimaging studies have revealed the important role of the TPJ in vestibular processing, multisensory integration as well as the perception of human bodies or body parts and the self (see Bünning and Blanke, 2005; Blanke and Arzy, 2005). Multisensory stimulation and involvement of the temporo-parietal cortex in OBEs and related out-of-body illusions has recently also been confirmed in healthy subjects (Ionta et al., 2011) and previously in a study using high-density electroencephalography and transcranial magnetic stimulation (Arzy et al., 2007). Taken together, these results (Blanke and Arzy, 2005, see also Arzy et al., 2006, 2007) suggest that the TPJ and an associated larger network are crucial structures for OBEs and for the conscious experience of the self-characterized by spatial unity of self and body.

NEAR-DEATH EXPERIENCES

Definition

In different life-threatening situations, people can sometimes experience vivid illusions and hallucinations as well as strong mystical and emotional feelings often grouped under the term near-death experience (NDE). These medical situations seem to involve cardiac arrest, perioperative or postpartum complications, septic or anaphylactic shock, electrocution, coma resulting from traumatic brain damage, intracerebral hemorrhage or cerebral infarction, hypoglycemia, asphyxia, and apnea. To this date, systematic studies on the incidence of NDEs in verified medical conditions only exist for cardiac arrest patients (Van Lommel et al., 2001; Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003; Parnia et al., 2014). Other situations that are merely *experienced* as life-threatening have also been reported to be associated with NDEs, although they often are not objectively life-threatening (mild or not life endangering diseases, depression, minor accidents, falls, and other circumstances (Van Lommel et al., 2001)).

Several definitions have been attempted for NDEs. Moody (2001) coined the term NDE defining it as "any conscious perceptual experience which takes place during… an event in which a person could very easily die or be killed […] but nonetheless survives" (Moody, 1977, p. 124). Irwin (1999) defined NDEs as "a transcendental experience precipitated by a confrontation with death" and Nelson et al. (2006) state that "NDEs are responses to life-threatening crisis characterized by a combination of dissociation from the physical body, euphoria, and transcendental or mystical elements." Greyson (2005) proposed that NDEs are "profound subjective experiences with transcendental or mystical elements, in which persons close to death may believe they have left their physical bodies and transcended the boundaries of the ego and the confines of space and time." Many more such broad definitions of the NDE have been given (Smith, 1991; Greyson, 1999) rendering their scientific study difficult. They seem to include a large variety of phenomena and not all researchers may agree that the investigated phenomenon (or assembly of phenomena) of a given study, may actually concern NDEs or "typical" NDEs. Below, we have reviewed the most frequent and characteristic perceptual elements of NDEs (see "Phenomenology" section). To complicate matters NDEs (as OBEs) are difficult to study as their occurrence is unpredictable and they are generally not reported at their moment of occurrence, but days, months, or even only years later.

Incidence

Early studies about the incidence of NDEs among survivors of cardiac arrest, traumatic accidents, suicide attempts, and other life-threatening situations estimated an incidence of 48% (Ring, 1982) or 42% (Sabom, 1982). Greyson (1998) suggested that this rate is probably too high as these studies were retrospective, often carried out many years after the NDE occurred, were using self-selected populations, and lacked appropriate control populations. He rather estimated the incidence of NDEs between 9% and 18%. More recent and better controlled prospective studies focused on cardiac arrest patients and confirmed lower estimations, with values ranging between 6% and 12%. These found an incidence of 6.3% (Parnia et al., 2001), 10% (Greyson, 2003), and 12% (Van Lommel et al., 2001). Yet, as indicated in the section on OBEs, in the absence of a clear and widely accepted definition of NDEs, it will remain difficult to define their exact incidence (Smith, 1991; Greyson, 1998, 1999, 2005). In order to avoid this problem most recent

TABLE 20.1 Phenomenological Features of NDEs According to Several Authors

Moody (1975)	Ring (1982)	Greyson (1983)
Identified 15 common elements in NDEs based on a sample of 150 reports. No statistics were provided. 1. Ineffability 2. Hearing oneself pronounced dead 3. Feelings of peace and quiet 4. Hearing unusual noises 5. Seeing a dark tunnel 6. Being "out of the body" 7. Meeting "spiritual beings" 8. Experiencing a bright light as a "being of light" 9. Panoramic life review 10. Experiencing a realm in which all knowledge exists 11. Experiencing cities of light 12. Experiencing a realm of bewildered spirits 13. Experiencing a "supernatural rescue" 14. Sensing a boarder or limit 15. Coming back "into the body."	Identified five stages of a "core experience," based on structured interviews and a measurement scale (WCEI: weighted core experience index) administered to 102 individuals who have been near death, 48% of whom reported a NDE. These stages tended to appear in sequence, with the earlier ones being more frequent and the latter ones indicating the "depth" of the experience. 1. Peace and well-being, reported by 60% 2. Separation from the physical body (OBE), reported by 37% (half of whom had an autoscopic OBE) 3. Entering a tunnel-like region of darkness, reported by 25% 4. Seeing a brilliant light, reported by 16% 5. Through the light, entering another realm, reported in 10%.	Devised a typology of NDEs based on his development of the 16-item NDE scale. On the basis of cluster analysis, he arrived at one's four categories of NDEs each comprising four features. 1. Cognitive features a. time distortion b. thought acceleration c. life review d. revelation 2. Affective a. peace b. joy c. cosmic unity d. encounter with light 3. Paranormal a. vivid sensory events b. apparent extrasensory perception c. precognitive visions d. OBEs 4. Transcendental a. sense of an "otherworldy" environment b. sense of a mystical entity c. sense of deceased/religious spirits d. sense of border/"point of no return."
Sabom (1982)	**Noyes and Slymen (1984)**	**Lundahl (1992)**
Proposed from his investigation of 48 subjects with NDE three main types of experiences. 1. "Autoscopic" (i.e., the NDE is essentially an OBE) 2. Transcendental (apparently entering another "dimension" through a tunnel and meeting a personified light) 3. Combined (involving an OBE and transcendental features).	Conducted a factor analysis of questionnaire responses from 189 victims of life-threatening accidents, and found the following three factors of subjective effects that accounted for 41% of the variance. 1. Depersonalization (loss of emotion, separation from the body and feelings of strangeness or unreality) 2. Hyperalertness (vivid and rapid thoughts, sharper vision and hearing) 3. Mystical consciousness (feeling of great understanding, vivid images, life review).	Summarized the NDE literature and extracted what he saw as the ten main stages. 1. Peace 2. Bodily separation 3. Sense of being dead 4. Entering the darkness 5. Seeing the light 6. Entering another world 7. Meeting others 8. Life review 9. Deciding to or being told to return to life 10. Returning to the body.

studies have used a score above a certain value on a frequently used scale (Greyson, 1983, see below).

Early studies failed to find demographic correlates of the NDE. Neither age, nor gender, race, occupational status, marital status, religiosity seemed to predict the probability of reporting an NDE (Ring, 1982; Sabom, 1982). More recently, two studies (Van Lommel et al., 2001; Greyson, 2003) found that young age is associated with a higher probability of NDEs in cardiac arrest patients, although this finding might be confounded by increased medical recovery rates in younger cardiac arrest patients. Another finding is that women tend to have more intense NDEs than men (Ring, 1982; Van Lommel et al., 2001) an observation that might partly be related to suggestions (Moody, 2001) that women might be less afraid to report NDEs or the fact that women have been found to score generally higher on anomalous-perception questionnaires than male subjects (Mohr et al., 2006). It is possible that having had a NDE facilitates the re-occurrence of such experiences, as 10% of subjects reported multiple NDEs (Van Lommel et al., 2001). NDEs have been described in many different cultures and times. Although some consistency can be found in cross-cultural reports, the specific phenomenology (i.e., the structure and the contents of the experience) may nevertheless vary (Osis and Harraldsson, 1977; Zaleski, 1988; Walker and Serdahely, 1990; Groth-Marnat, 1994).

Phenomenology

Moody (1977, 2001) initially listed 15 key features in NDEs (see Table 20.1). Yet, not one single NDE in his sample included all 15 NDE features. Moreover, none of these 15 NDE features was present in all reported NDEs, and no invariable temporal sequence

of features could be established. Due to these difficulties, standardized questionnaires have subsequently been developed to identify and measure more precisely the occurrence of NDEs and their intensity (or depth). Ring (1982) developed the Weighted Core Experience Index on the basis of structured interviews of 102 persons who reported a NDE. The scale is based on ten features that he gathered from the literature as well as interviews with people with NDEs. His ten features were: the subjective feeling of being dead, feelings of peace, bodily separation, entering a dark region, encountering a presence or hearing a voice, life review, seeing or being enveloped in light, seeing beautiful colors, entering into the light, and encountering visible spirits. According to the presence or absence of each of these features, the score ranges between 0 and 29. This scale has been criticized because it is largely based on arbitrary selected and weighted features, and seemed to contain several uncommon features of NDEs as estimated by other authors. Ring (1982) also elaborated a sequence of five NDE-stages, the presence of which he considered to be representative of the "core NDE" (see Table 20.1). To address the aforementioned limitations, Greyson (1983) developed a NDE scale that has been used by many recent investigators. He began by selecting 80 features from the existing literature on NDEs and subsequently reduced these to 33 features. He further arrived at a final 16-item scale with a maximum score of 32. This questionnaire has been shown to have several advantages as compared to other questionnaires, especially good test-retest reliability (even for a follow-up at 20 years; Greyson, 2007) and item score consistency (Lange et al., 2004). In the original study (Greyson, 1983), four NDE components were defined—cognitive, affective, paranormal, and transcendental—which were later reduced to a classification of three main types of NDEs, according to the specific dominance of the phenomenological components: cognitive, affective, and transcendental types (Greyson, 1985) (see Table 20.1). In the following we describe the main phenomena that characterize NDEs.

Out-of-Body Experiences

OBEs are considered a key element of NDEs, although their frequency was found to vary greatly between the different studies. Ring (1982) found that 37% of subjects with a NDE experienced disembodiment ("being detached from their body") of whom about half also experienced autoscopy (no detailed data were reported on elevation or visuo-spatial perspective). Others (Greyson and Stevenson, 1980) found an incidence of 75% of disembodiment (without detailing the presence of autoscopy or elevated visuo-spatial perspective) or reported a "sense of bodily separation" in 99% (Sabom, 1982), whereas still others reported disembodiment in only 24% (Van Lommel et al., 2001). Disembodiment during NDEs has been reported to be accompanied by auditory and somatosensory sensations (Irwin, 1999). NDE subjects with OBEs characterized by disembodiment and elevated visuo-spatial perspective often report seeing the scene of the accident or operating room. A 26 year-old patient with pulmonary embolism reported: "I (the real me, the soul, the spirit, or whatever) drifted out of the body and hovered near the ceiling. I viewed the activity in the room from this vantage point. The hospital room was to my right and below me. It confused me that the doctors and nurses in the room were so concerned about the body they had lifted to the bed. I looked at my body and it meant nothing to me. I tried to tell them I was not in the body (p. 393)" (Greyson, 1993). We argue that future studies on OBEs during NDEs should characterize OBEs with respect to recently defined phenomenological characteristics and inquire systematically about the associated sensations as done in neurological patients (such as visual, auditory, bodily, or vestibular sensations) as well as the presence of disembodiment, autoscopy, elevated perspective permitting to distinguish between autoscopic hallucination, heautoscopy, and OBE. This will allow describing the phenomenology of OBEs during NDEs in more detail and allow relating these data to recent neurological and neurobiological observations on OBEs. Not much is known about whether OBEs that are associated with NDEs differ from OBEs without NDE elements or whether NDEs with or without OBEs differ. Alvarado found (Alvarado, 2001) that OBEs in subjects who believed themselves to be close to death were phenomenologically richer than for those who did not, with more feelings of passing through a tunnel, hearing unusual sounds, seeing spiritual entities, as well as seeing one's physical body and seeing lights (see also Gabbard et al., 1981). Of course, it might be the case that due to the presence of these features these subjects *believed* they had been close to death (no medical data were reported). Further links might exist between rare, the so-called supernaturalistic, OBEs (Irwin, 1985) and OBEs during NDEs. Accordingly, other authors have compared the phenomenology of NDEs in subjects being medically close to death with NDEs where subjects only *believed* to be close to death (as established from medical records) and found that the former group reported more often seeing lights and enhanced cognition than the latter group (Owens et al., 1990). There were no significant differences between both groups in seeing tunnels (see below), having OBEs and experiencing a life review (see below). However, a more recent study failed to find differences in the intensity and content of NDEs

of varied etiologies occurring during life-threatening ("real NDEs") and non-life-threatening ("NDE-like") events (Charland-Verville et al., 2014). In another study, 76% of subjects with NDEs were reported to also experience an OBE (Nelson et al., 2007). Around 40% of these patients had their OBE only as part of the NDE episode, ~33% also had OBEs in other circumstances, and ~26% had an OBE only in other circumstances, i.e., not associated with the NDE. This last number was significantly higher than non-NDE-related OBEs in an aged-matched control group of healthy subjects (Nelson et al., 2007). Collectively, these data suggest that OBEs and NDEs may share important functional and brain mechanisms, but clearly point towards distinct mechanisms as well.

The Tunnel and the Light

Experiencing a passage through some darkness or a tunnel is experienced by ~25% of subjects with NDEs (Ring, 1982; Sabom, 1982; Van Lommel et al., 2001). This may be associated with the sensation of movement of one's own body such as forward vection, flying, or falling, at varying speeds. Some (Owens et al., 1990; Drab, 1981) suggest that the experience of a tunnel is associated with the presence of severe medical conditions (such as cardiac arrest, drowning, trauma, profuse blood loss), as opposed to mild injuries, fear, or fatigue. Here is one example: "After I had floated close to the ceiling for a short time, I was sucked into a tunnel.... It was black and dark around me, somewhat frightening, but this did not last long: at the end of the tunnel I saw a clear light towards which I traveled" (p. 211) (Woerlee, 2005). The tunnel experience or darkness may thus be associated with the experience of intense light. This was found to be the case in half of the subjects with NDEs (Drab, 1981), whereas others found that 30% (Ring, 1982; Sabom, 1982) or 23% (Van Lommel et al., 2001) reported seeing a light (but did not investigate how frequently this was associated with the experience of a tunnel). It is usually white or yellow, very bright, but not experienced as painful. The light seems to cover a larger area in the visual field when subjects experience vection (Drab, 1981).

The Life Review

The life review has been defined as the perception of "unusually vivid, almost instantaneous visual images of either the person's whole life or a few selected highlights of it" (Irwin, 1999, p. 204). Heim (1892) reports the following life review during a fall during mountaineering: "...I saw my whole past life take places in many images, as though on a stage at some distance from me. I saw myself as the chief character in the performance. Everything was transfigured as though by a heavenly light and everything was beautiful without grief, without anxiety, and without pain." Life reviews were found in 13–30% of subjects with NDEs (Ring, 1982; Van Lommel et al., 2001; Greyson, 1983; Greyson and Stevenson, 1980; Noyes and Kletti, 1976). In an analysis of 122 subjects with NDEs it was found that the number of distinct life memories may range from few images (one or two) to the impression of a rapid flow of countless images depicting their entire life (Stevenson and Cook, 1995). Some subjects reported that the life review unfolds with an infinite number of images, simultaneously ("all at once"). The life review is usually experienced very vividly, associated with bright colors and can occur as moving in chronological order or in the opposite order (i.e., ending or starting with childhood (Blackmore, 1993)). It can also purportedly involve elements of the future (Groth-Marnat, 1994). Two studies speculated that life reviews are especially frequent in drowning victims, as compared to other situations (Noyes and Kletti, 1976; Dlin, 1980). Conversely, it seems that suicide survivors (Rosen, 1975) and children (Morse et al., 1986; Serdahely, 1990) rarely report life reviews during NDEs.

Meeting of Spirits

People often report seeing or feeling different entities or people during NDEs. Here is an example from a man with cardiac disease: "...he experienced an apparent encounter with his deceased mother and brother-in-law, who communicated to him, without speaking, that he should return to his body" (Greyson, 2000, p. 315). The encounters are sometimes identified as supreme beings, pure energy, spiritual guides, angels, helpers, or familiar people, but also as demons or tormentors (Judson and Wiltshaw, 1983; Lundahl, 1992; Kelly, 2001). These encounters are reported frequently during NDEs (40% (Ring, 1982); 52% (Greyson, 2003): "sense of deceased/religious spirits," see Table 20.1). Sometimes subjects report to feel (rather than see) the presence of an unfamiliar person, a mystical, or a supreme entity (reported by 26% of NDE subjects (Greyson, 2003)). The seen or felt person may also be familiar, but is most often a deceased relative or friend. Ring (1982) and Kelly (2001) respectively found that 8% and 13% of seen or felt persons were dead relatives, whereas others ((Fenwick and Fenwick, 1997) 39%; (Van Lommel et al., 2001) 32%) found this more frequently. This feature was further analyzed by comparing 74 people with NDEs who reported to have perceived one or more deceased relatives with 200 people with NDE who did not (Kelly, 2001). It was found that deceased relatives are more frequently reported than deceased friends or children (in this study only 4% of people with NDEs reported

seeing persons that were alive at the time of the NDE (Kelly, 2001)). Encounters with dead relatives have long been reported in the occult literature as "apparitions" and are supposed to be frequent in the so-called "death-bed visions" (Osis and Harraldsson, 1977; Barrett, 1926). Sometimes verbal or thought communication (often described as "telepathic") has been reported to take place between the subject and the encounters. Physical interactions such as touch or embraces are sometimes described as well (Greyson, 2000). Some of these features have also been reported in neurological patients with heautoscopy (Blanke and Mohr, 2005).

Positive and Negative Emotions

NDE reports often consist of feelings of peace and calm (and sometimes ecstasy), despite the experienced severity of the situation. Whereas Ring (1982) found that 60% of subjects with a NDE reported feelings of peace (56% in Van Lommel et al., 2001), others (Sabom, 1982) noted such feelings in all subjects with NDE. Analyzing feelings of peace and joy separately, the presence of peace was found in 85% and joy in 67% (Greyson, 2003). A related feature might be the loss of pain sensations as subjects with NDE often report to be relieved from the unbearable pain they were enduring minutes earlier. Heim (1892) reports his own experience when falling from a cliff: "There was no anxiety, no trace of despair, nor pain; but rather calm seriousness, profound acceptance, and a dominant mental quickness and sense of surety…" (see also Ernest Hemingway's account of his own painless NDE, despite suffering from multiple shrapnel wounds (Dieguez, 2010)). Many subjects also report feelings of absolute love, all encompassing acceptation, often by a supreme entity, which is associated with a radiant light. Nevertheless, NDEs may also be associated with negative emotions, with "hell"-like features, encounters with tormentors or frightfully devoid of any meaning (Greyson and Bush, 1992). The exact incidence of such negative NDEs is not known, but it is assumed to be rather low (Greyson, 2000).

Other Features

In this section we have listed other NDE features about which less is known concerning their phenomenology, frequency, and association with other features. These features are realness, mental clarity, sense of time, mystical elements, and the experience of border and return.

Realness and Mental Clarity

Although NDEs are often described as highly realistic sensations, we were not able to find detailed estimates. In the literature we found reports that NDEs are often experienced as "real" or "realer than real" (Potts, 2002). Some authors have argued that NDEs are qualitatively different from dreams or drug-induced hallucinations (e.g., Moody, 2001). As one subject wrote: "For many years, it was the most real thing that ever happened to me. Yes, far more real and vivid than any real-life incident. It was so real, detailed and so vivid and consistent…; in fact, so totally un-dream-like!" (Blackmore, 1993, p. 137). Thus, many subjects with NDEs believe them to be an *actual* disembodiment, meeting of spirits, seeing of lights, or of being in the afterworld rather than mere experiences thereof. These subjects are often reluctant to refer to NDEs in psychological or neurophysiological terms (Schwaninger et al., 2002). A recent study compared NDE memories to real and imagined memories, including non-NDE coma memories. It was found that NDE memories had richer content than all other types of memories, including better clarity and more self-referential and emotional information, suggesting that memories of NDEs are more akin to flashbulb memories and hallucinatory experiences than imagined events. These characteristics seem related to the content of the memory *per se*, rather than medical factors or actual closeness to death, and help understand why such experiences are often perceived as "super real," even more so than real recent events (Thonnard et al., 2013). Realness is sometimes also reported as mental clarity or cognitive enhancement. The report of clear experience, perception, and cognition was more frequent in subjects who suffered serious life-threatening conditions than those who only thought themselves in great biological danger (Owens et al., 1990). Others found that 44% of NDE subjects reported accelerated thought with their NDE (Greyson, 2000). Heim (1892) refers to this aspect during a mountain fall: "All my thoughts and ideas were coherent and very clear, and in no way susceptible, as are dreams, to obliteration…The relationship of events and their probable outcomes were viewed with objective clarity, no confusion entered at all."

Sense of Time

A distorted sense of time is a frequent feature of NDEs, but has not been described in detail in statistical and phenomenological terms. Already Heim (1892) reported that "time became greatly expanded" during his fall. More recent investigators (Greyson, 2000) found that 67% of NDE subjects reported an alteration of the sense of time, whereas this was much less frequent in a control group of subjects without NDEs (4%). Based on the reviewed phenomenology we suggest that the presence of a distorted sense of time, mental clarity, and life review might co-occur in subjects with NDEs.

Mystical and Transcendental Elements

A feeling of "oneness" with the universe or of "cosmic unity" was present in 52% of subjects with NDEs (Greyson, 2000). Other studies reported that 20% (Ring, 1982) or 54% (Sabom, 1982) of the questioned NDE subjects reported the "visit" of a supernaturalistic environment. This value is considerably smaller in people reporting OBEs (~1%; Irwin, 1985), but more frequent in subjects who report multiple OBEs. Descriptions here vary considerably, but most often seem to involve the experience of seeing pleasant sights like cities of light, green and flowered meadows, and vivid colors. Sometimes, images reminiscent of religious iconography are perceived (Irwin, 1987).

Border and Return

A symbolic or concretely perceived limit or border is sometimes reported by subjects with NDEs. Greyson (2000) found this in 41% and Van Lommel et al. (2001) in 8%. NDEs (and OBEs) are often reported to end abruptly without the experience of intentional control (Irwin, 1999). A patient, resuscitated by electrical defibrillation after an anterior myocardial infarction, reported: "It appeared to me…that I had a choice to re-enter my body and take the chances of them [the medical staff] bringing me around or I could just go ahead and die, if I wasn't already dead. I knew I was going to be perfectly safe, whether my body died or not. They thumped me a second time. I re-entered my body just like that (quoted in Rogo, 1986, p. 65)." The immediate aftermath is frequently the return of pain and the realization that one is alive (similar observations have also been reported in neurological patients with OBEs and related experiences such as heautoscopy; see below and Blanke et al., 2004, case 4).

Folk-Psychological Accounts and Psychological Aspects

Following psychoanalytic theory, several researchers consider NDEs as a defense mechanism unfolding in a hopeless, life-threatening situation. Noyes and Kletti (1976, 1977) were influential with their suggestion that the experience during a NDE may reflect a form of depersonalization, whereby the endangered subject "separates" from the body and the current events in order to be "separated" from the intolerable consequences of death and pain. Following Albert Heim's (1892) report of NDEs in fall survivors, Oskar Pfister suggested that "persons faced with potentially inescapable danger attempt to exclude this unpleasant reality from consciousness and "replace" it with pleasurable fantasies which protect them from being paralyzed by emotional shock" (Pfister, 1930 quoted in Grosso, 1983, p. 613). By this process, it was then argued that subjects "split" into an observing self and a body. The OBE component of many NDEs, in particular, has been seen as the prototypic experiential correlate of this detachment (Menz, 1984; Ehrenwald, 1974) (for critique see Gabbard and Twemlow, 1984; Irwin, 1993). Psychological authors suggested that NDEs are the consequence of a human tendency to deny death (Menz, 1984; Ehrenwald, 1974), the release of archetypical concepts of death (Grosso, 1983), or the (symbolic or literal) regression to the experience of coming to life (Grof and Halifax, 1978; Sagan, 1980; but see Blackmore, 1993). These approaches of NDEs suffer from the same methodological and scientific concerns as psychoanalytical propositions.

More quantitative approaches have proposed to analyze psychological variables of people with NDEs, as estimated by interviews and questionnaire surveys. However, in comparison to OBEs, no clear psychopathological features have yet been found (Greyson, 2000; Gabbard and Twemlow, 1984). Also subjects with NDEs and without NDEs were not found to differ with respect to measures of intelligence, extraversion, neuroticism, or anxiety. Unfortunately, only a small number of subjects with NDEs have been studied in this systematic manner (Locke and Shontz, 1983; Twemlow and Gabbard, 1984). However, people with NDEs were found to report the so-called paranormal experiences prior to their NDE more often (Greyson, 2003; Groth-Marnat, 1994), as well as other complex experiences such as OBEs, feelings of being united with the universe, feeling the presence of God and other wordly entities, or having past-life memories (Osis and Harraldsson, 1977). It was also noted that people with NDEs tend to report repeated OBEs and higher interest in dreams, past-lives, and meditation (Kohr, 1983), suggesting that subjects with NDEs might differ from other subjects in being more open to unusual experiences (and also willing to report these) and being attentive to the so-called inner-states (Roberts and Owen, 1988). It might also be that this personality trait is linked to the larger concept of "magical thinking," which has been shown to depend on right hemispheric activity and affinity to "paranormal" thought (Brugger and Taylor, 2003). People with NDEs as well as people with OBEs (Irwin, 1985) also score higher than control subjects on absorption (a measure that refers to the tendency to immerse in imagination and internal states) and the related trait of fantasy proneness (a tendency to have vivid hallucinations, blurred distinction between reality and imagination, enhanced sensory experiences, and heightened visual imagery) (Greyson, 2000; Twemlow and Gabbard, 1984). The fact that this personality factor is shared among subjects with OBEs and NDEs again suggests common predisposing factors. On a related

note, Ring (1992) suggested that subjects with NDEs are more likely to have suffered abuse, stress, illness, and social problems during childhood than a control group (see also Irwin, 1993). Measures of dissociation (and depersonalization) have also been associated with NDEs. Subjects with NDEs scored higher than controls, but were below the range of pathological conditions on this measure (Greyson, 2000). Others also found significantly higher scores in a group of NDE subjects on the Dissociative Experiences Scale than in their control group (again these scores were different between both groups, but within the normal range) (Britton and Bootzin, 2004).

Neurology of NDEs

Although several authors have speculated on the neurology of NDEs, there is an almost complete absence of neurological data. Medical and neurological conditions that have been associated with NDEs and that are associated with brain interference or brain damage are cardiac arrest, general anesthesia, temporal lobe epilepsy, electrical brain stimulation, and sleep abnormalities (e.g., REM intrusions). As more systematic studies have focused on the investigation of the frequency and intensity of NDEs in cardiac arrest patients (Van Lommel et al., 2001; Parnia et al., 2001; Schwaninger et al., 2002; Greyson, 2003) we will start by reviewing these studies with respect to potential neurological mechanisms (see also French, 2005).

Brain Anoxia in Cardiac Arrest Patients

The data reported in a large prospective study (Van Lommel et al., 2001) describe several clinical characteristics of patients that are likely to report a NDE after cardiac arrest. In most of these patients cardiac arrest occurred in the hospital ($n = 234$; 68%) and resuscitation was initiated within 2 min after this ($n = 190$; 81%). Loss of consciousness lasted less than 5 min ($n = 187$; 80%). Yet, loss of consciousness was defined independent of a neurological examination as well as electroencephalographic (EEG) records and estimated only by electrocardiogram records. We therefore do not have detailed neurological data about brain function in the critical clinical period that is frequently assumed to be associated with NDEs. This is likely due to the medical emergency situation and lack of time to evaluate neurological function during resuscitation. Accordingly, the authors (Van Lommel et al., 2001) "defined clinical death [independent of neurological data] as a period of unconsciousness caused by insufficient blood supply to the brain because of inadequate blood circulation, breathing, or both." The remaining patients were resuscitated outside the hospital ($n = 101$; 29%) and likely suffered from longer periods of cardiac arrest ($n = 88$; 80%) and unconsciousness for more than 10 min ($n = 62$; 56%). Among all investigated patients, 36% ($n = 123$) were unconscious, as defined above, for longer than an estimated period of 60 min.

Twelve percent of the total of 344 patients investigated in that study (Van Lommel et al., 2001) reported an NDE. The data showed that younger patients with a first myocardial infarction and with a previous NDE reported NDEs more frequently, while prolonged reanimation was associated with less frequent NDEs. Moreover, male patients and patients who were reanimated outside the hospital reported less NDE elements. The authors (Van Lommel et al., 2001) argue that the diminished frequency of NDEs in patients with prolonged reanimation might be due to memory loss or deficient short-term memory in these patients. This statement seems premature since no quantitative neurological or neuropsychological assessment on short- or long-term memory were carried out (or reported) in the acute or later phases of the study. Furthermore, no EEG records and neuroimaging examinations (MRI or computer tomography) were studied and compared between cardiac arrest patients with and without NDEs. We believe that neurological and neuropsychological data as well as EEG and neuroimaging data in cardiac arrest patients with NDEs will be crucial in describing eventually some of the neurocognitive mechanisms of NDEs.

Several recent studies have reported neurological data about brain function and brain damage in patients suffering from more serious consequences of cardiac arrest such as prolonged loss of consciousness in coma, vegetative state, minimally conscious state, as well as milder associated neurological conditions (see Chapter 3). Unfortunately, we were not able to find similar studies reporting such data for cardiac arrest patients with NDEs, who are most often considered to have maintained pre-morbid brain functions (although this was not confirmed by neuropsychological testing). Given the common etiological origin, we suggest that patients with NDEs following cardiac arrest may suffer from brain damage that is milder, but anatomically similar, to the brain damage reported in patients with mild forms of postanoxic brain damage of cardiac or pulmonary origin (Ammermann et al., 2007). Data reported in the latter study showed that brain damage in such patients is symmetrical and predominantly affects gray and white matter in several cortical and subcortical regions without affecting the brainstem (Figure 20.3). These regions include the frontal and occipital cortex (including the optic radiation) as well as the hippocampus, the basal ganglia and the thalamus confirming earlier results that have also revealed damage to watershed regions such as the TPJ (Kinney and Samuels, 1994;

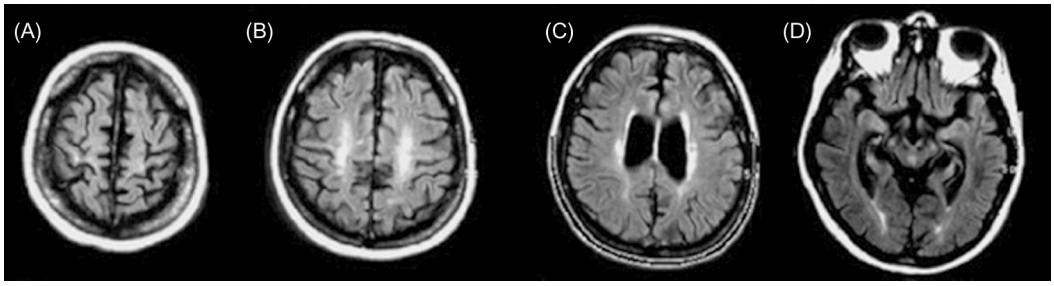

FIGURE 20.3 MRI of the brain of a cardiac arrest patient with excellent recovery. MRI reveals a distinct pattern of brain damage including white matter damage in three brain areas: in proximity of the primary motor and premotor cortex (A and B), periventricular white matter lesions (C), and in proximity of primary visual cortex including the optic radiation (D). *Source: Modified from Ammermann et al. (2007) reproduced with permission from Elsevier.*

Adams et al., 2000; Chalela et al., 2001). Importantly, damage or interference with these regions may be linked to several key features of NDEs (see below).

Another, smaller prospective study on NDEs in cardiac arrest survivors (Parnia et al., 2001) also failed to present any neuroimaging data or results of neurological, neuropsychological, or EEG examinations. We reiterate that EEG records during or immediately after the cardiac arrest period will be important as well as multi-channel EEG recordings during later periods allowing detection or exclusion of more subtle potential abnormalities and their correlation with potential neurological, neuropsychological, and neuroimaging abnormalities. In addition, the patient sample was small and only four cardiac arrest patients (6%) reported NDEs (as defined by the NDE scale described in Greyson, 1983). A third study (Schwaninger et al., 2002) not only found that NDEs occurred with a frequency of 23% in the same clinical population, but also did not report neurological, neuropsychological, EEG, or neuroimaging data. A final study (Greyson, 2003) found a frequency of 10% and found no differences in cognitive functions between cardiac arrest patients with and without NDEs. For the cognitive examination the investigators applied the mini mental status that is often used for brief clinical pre-evaluations of patients with dementia (Folstein et al., 1975). Although the latter test revealed normal performance in cardiac arrest patients with and without NDEs (score of $\sim$27) this examination does not permit detailed testing of memory, language, spatial thought, visual, auditory, attention, and executive functions as is done with standard neuropsychological examinations. Despite the variability in frequency estimations of NDEs in cardiac arrest survivors in these four studies the two larger studies seem to agree on 10–12%, but unfortunately do not provide any empirical data on the neurology of NDEs.

Other MRI-based techniques might allow describing potential brain damage in cardiac arrest patients with NDEs. Thus, diffusion-weighted MRI allows the detection of focal cerebral infarctions in the acute phase (Moseley et al., 1990; Röther et al., 1996), due to its sensitivity for ischemia-induced changes in water diffusion (Fiehler et al., 2002). Els et al. (2004) have shown that diffusion-weighted MRI may allow to reveal correlates of cerebral anoxia in cardiac arrest patients independent of severity of anoxia, that is, even in patients who recover very well (Figure 20.4). Moreover, standard T1 and T2 weighted MRI may not always reveal brain damage in these patients. It thus seems that different techniques of MRI in the acute as well as the chronic phase in such patients will be necessary to reveal potential functional and structural lesions causing distinct features of NDEs.

Several authors have argued that brain anoxia may account for the auditory, visual, and memory aspects of NDEs (heard noises, perceived lights and tunnels, life review, encounters). The mechanisms involved have been proposed to occur as a cascade of events, beginning by a neuronal disinhibition in early visual cortex spreading to other cortical areas leading to NDE features such as tunnel vision and lights (Woerlee, 2005; Blackmore, 1993; Rodin, 1980; Saavedra-Aguilar and Gómez-Jeria, 1989). However, the actual sequence of NDE features remains an unexplored area. Based on the reviewed data, it seems clinically plausible that cardiac arrest patients with NDEs may suffer from acute or chronic damage or interference with a subset of widespread cortical and subcortical areas, including gray and white matter, that have been described in cardiac arrest patients. Especially, damage to bilateral occipital cortex and the optic radiation (Figures 20.3D and 20.4C) may lead to the visual features of NDEs such as seeing the tunnel or surrounding darkness (i.e., bilateral peripheral visual field loss) and lights (damage to the optic radiation is often associated with macular sparing and hence centrally preserved vision), whereas interference with the hippocampus may lead to heightened emotional experiences and experiential phenomena due to epileptogenic interference,

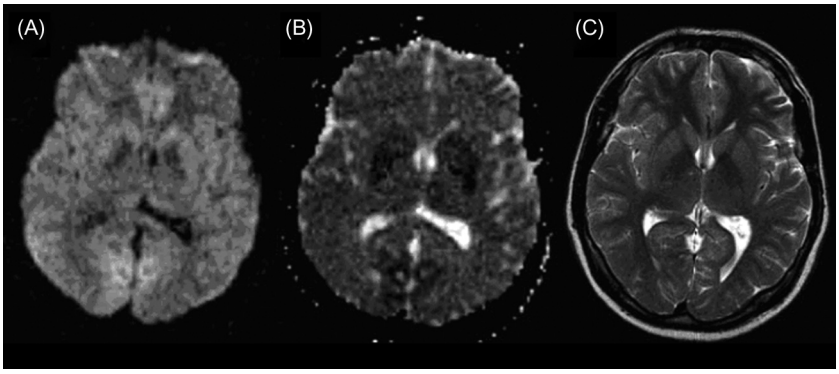

FIGURE 20.4 MRI of the brain of a cardiac arrest patient with excellent recovery. Whereas standard T2-weighted MRI (Figure 20.4C; compare to Figure 20.3) did not reveal any abnormalities, diffusion-weighted MRI in the acute phase (15 h after resuscitation) revealed MRI abnormalities that are compatible with bilateral brain damage. These are shown in Figure 20.4A and consist of bilateral hyperintense damage in proximity to primary visual cortex and the optic radiation (compare also with Figure 20.3D). In addition, the apparent diffusion coefficient (ADC; Figure 20.4B) maps showed prominent signal decrease in the same locations as DWI, compatible with ischemic brain damage. *Source: Modified from Els et al. (2004) with permission from Blackwell Publishing.*

including memory flashbacks and the life review (see below). Moreover, interference with the right TPJ may lead to OBEs (Blanke et al., 2002, 2004; Blanke and Mohr, 2005) whereas interference with the left TPJ may cause the feeling of a presence and meeting of spirits, and heautoscopy (Arzy et al., 2006; Brugger et al., 1996). This proposition extends previous postanoxic accounts of NDEs by linking the different features to different brain regions that may be damaged in cardiac arrest patients with rapid recovery of consciousness and neuropsychological functioning. These speculations have to be regarded with caution, as to date, no neurological, neuropsychological, and neuroimaging data exist to corroborate this claim empirically. We also note that models only based on the pathophysiology of brain anoxia do not account for NDEs occurring in situations that are not related to cardiac arrest such as polytraumatism, general anesthesia, and hypoglycemia. Nor do they account for NDEs occurring during mountain falls as well as other fearful situations leading to NDEs (Blackmore, 1993; Roberts and Owen, 1988). As stated by Blackmore (1993), brain anoxia is probably one of several, related, mechanisms that lead to NDEs.

Experimental Brain Hypoxia in Healthy Subjects

Lempert et al. (1994) induced syncopes in 42 healthy subjects using cardiovascular manipulations (hyperventilation, orthostasis, Valsalva maneuvers) with the aim of investigating the symptoms of transient cerebral hypoxia. They found that many of their subjects reported NDE-like sensations: 16% had OBEs, 35% feelings of peace and painlessness, 17% saw lights, 47% reported entering another world, 20% encountered unfamiliar beings and 8% had a tunnel experience. Two subjects were even reminded of previous spontaneous NDEs. These data suggest that NDEs may be approached experimentally in healthy subjects although anxiety, vagal effects, as well as other non-hypoxia related mechanisms may also play an important role (Lempert et al., 1994).

General Anesthesia

NDEs may also occur during general anesthesia. Thus, Cobcroft and Forsdick (1993) have reported patients who experienced OBEs during general anesthesia as well as sensations of moving in a tunnel, seeing people and operating theater details, and seeing bright lights, and surrounding whiteness. This was found in 4% of a large sample of patients having undergone general anesthesia and was confirmed by other investigators (Parnia et al., 2001; Schwaninger et al., 2002). There is also a report of a NDE in a 12-year-old boy (known for mild cerebral palsy) who underwent general anesthesia for elective uncomplicated surgery (Lopez et al., 2006). Monitoring during general anesthesia did not reveal any signs of awakening, hypoxia, ischemia, or hypoglycemia. Yet, this young patient, who did not know about NDEs, reported the following "strange dream": "I was sleeping and suddenly I felt awake and had the impression that I was leaving my body… I could see from above my whole body lying on the back on the operating table … and surrounded by many doctors … I felt as being above my physical body … I was like a spirit … and I was floating under the ceiling of the room. … but then I had a sensation of lightness … and I felt relaxed and comfortable… I had the impression that everything was real … I then saw a dark tunnel in front of me … and I felt attracted to it … I passed through the tunnel very fast and at its end I saw … a bright light … I heard noises …[and] voices …."

Interestingly, anesthetic agents such as propofol (as applied in this patient) are known to have neuroexcitatory effects (Walder et al., 2002) inducing in some patients seizure-like activity and decreased metabolism in the dorsolateral prefrontal cortex, posterior parietal cortex (including the TPJ), and temporal lobe (Veselis et al., 2002). Lopez et al. (2006) speculated accordingly that interferences of anesthetic agents in these areas may lead to the induction of some features of NDE, such as OBEs, feelings of a presence, and meeting of spirits.

Independent of general anesthesia, substances such as ketamine, LSD, and cannabinoids, as well as many others (Jansen, 1997; Carr, 1982; Saavedra-Aguilar and Gómez-Jeria, 1989) may also lead to experiences resembling some of the NDE features, like the feelings of joy and bliss, visual hallucinations (including tunnels, lights, and people), transcendental elements (Jansen, 1997; Siegel, 1980), and OBEs (Bünning and Blanke, 2005; Tart, 1971). Feelings that the experience is veridical are not rare when using such substances, as well as the impression of "mental clarity" and enhanced cognition (Jansen, 1997). Other authors argued that drug administration, instead of facilitating NDEs, may also diminish their frequency (Ring, 1982; Sabom, 1982) or have no effect on the frequency of NDEs (in cardiac arrest patients; Van Lommel et al., 2001; Greyson, 2003).

Epilepsy and Brain Stimulation

Many observations link NDEs to epilepsy and especially to complex partial seizures. This evidence includes (i) interictal EEG signs (spikes and spike-waves) in subjects with NDEs, (ii) interictal manifestations such as the interictal temporal lobe syndrome, (iii) similarity of NDEs with several known sensory and cognitive ictal symptoms, (iv) experimental induction of some of these symptoms by electrical cortical stimulation in awake humans, (v) and frequent damage to the hippocampus, a major epileptogenic region, in cardiac arrest patients.

Whereas the neurological examination is frequently normal in patients with temporal lobe epilepsy, neuropsychological examinations often reveal mild to moderate memory impairments characterized by deficits in learning, recognition, delayed recall, or fluency tasks either for verbal or visuo-spatial material (Pegna et al., 1998; Flügel et al., 2006). Moreover, these distinct memory deficits have been correlated with hippocampal sclerosis, decreased volume, and metabolic changes of this structure, as shown by functional MRI, magnetic resonance volumetry, and magnetic resonance spectroscopy (Pegna et al., 2002; Zubler et al., 2003). Such examinations in cardiac arrest patients with NDEs might thus reveal similar circumscribed deficits and brain damage, at least in some of these patients.

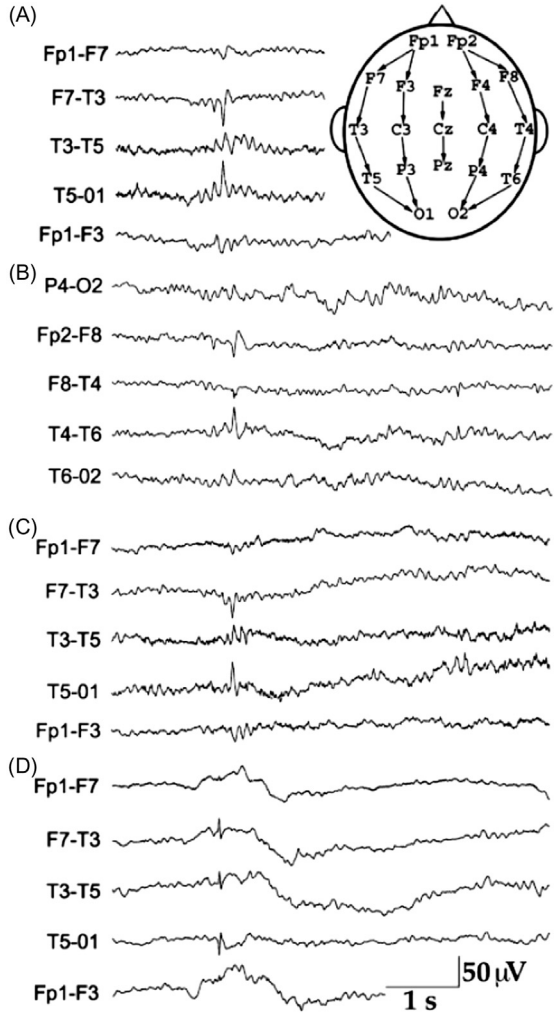

FIGURE 20.5 Examples of interictal epileptiform discharges in the temporal lobe of subjects with NDE. (A)–(C) Stage 2 sleep; (D) REM sleep. The illustration of the head shows the placement of the electrodes in the 10–20 system with an anterior–posterior bipolar reference scheme. Each tracing shows the localized brain activity from the area of the two electrodes indicated. *Source: From Britton and Bootzin (2004); with permission from Blackwell Publishing.*

EEG recordings in healthy subjects who have reported NDE previously have been carried out and suggested the presence of abnormal epileptic interictal EEG activity over the left mid-temporal region in 22% of subjects (one subject had bilateral abnormal activity) (Britton and Bootzin, 2004). No epileptic seizures were recorded or reported by any of the subjects. Abnormal activity was most prominent over mid-temporal regions and characterized by spikes and spike-waves, as well as sharp waves (Figure 20.5). The authors added that subjects with NDE also reported more often than the control group several temporal lobe symptoms (Figure 20.6) compatible with the interictal temporal lobe syndrome (Waxman and Geschwind, 1975). These include deepened emotionality, nascent

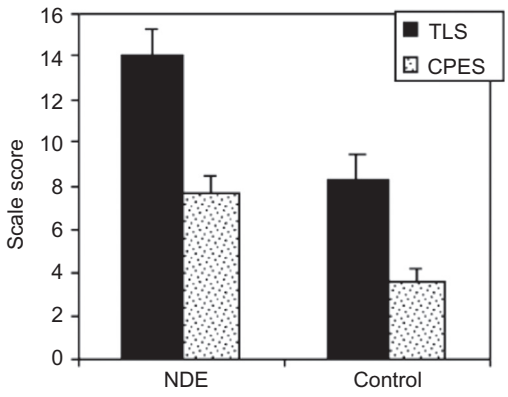

FIGURE 20.6 Symptoms evocative of interictal and ictal temporal lobe syndrome in subjects with NDE. Scores on the temporal lobe symptoms (TLS) and complex partial epileptic signs (CPES) subscales of the Personal Philosophy Inventory (Persinger, 1983) in subjects with NDE and a control group of age and gender matched participants with no history of life-threatening event. Items include experiences of sleepwalking, olfactory hypersensitivity, hypergraphia, feelings of intense personal significance, and unusual perceptions. *Source: From Britton and Bootzin (2004); with permission from Blackwell Publishing.*

religious interest, enhanced philosophical preoccupation, moralism, sense of personal destiny, as well as others (although patients with temporal lobe epilepsy may not always show these signs (Blumer, 1998; Schomer et al., 2000; Trimble and Freeman, 2006)). Finally, abnormal epileptic activity in subjects with previous NDEs (Britton and Bootzin, 2004) was correlated with their score on an NDE scale (Greyson, 1983), but not with trauma-related measures such as posttraumatic stress disorder, dissociation, or previous head trauma.

Many features of the NDE have been described as symptoms of epileptic seizures and have also been induced in a controlled fashion by electrical cortical stimulation. Thus, direct electrical cortical stimulation (Blanke et al., 2002; Penfield, 1955) and focal epileptic activity at the TPJ (Blanke et al., 2004; Devinsky et al., 1989) may induce OBEs as well as vestibular sensations (Blanke et al., 2002, 2004; Penfield, 1955; Kahane et al., 2003). Interestingly, in a small study (Hoepner et al., 2013), five patients with OBE and autoscopy of ictal origin involving the TPJ or adjacent regions reported significantly higher scores on Greyson's NDE Questionnaire than a control group of 12 patients with temporal lobe seizure preceded by aura, but no ictal autoscopy phenomena, involving mesio-temporal pathologies. Notably, all ictal autoscopy patients, but no patients in the control group, reported scores equal or higher to the cut-off defining the NDE. It thus seems that current measures are unable to distinguish OBEs of ictal origin from NDEs, which suggests common mechanisms between both conditions. Memory flashbacks and life reviews have long been known to occur as a symptom of temporal lobe epilepsy and are generally referred to as experiential phenomena (Penfield and Jasper, 1954; Halgren et al., 1978; Gloor, 1990; Bancaud et al., 1994). Experiential phenomena have also been induced by electrical cortical stimulation of the temporal lobe, the hippocampus, and the amygdala (Halgren et al., 1978; Gloor, 1990; Bancaud et al., 1994; Gloor et al., 1982), as well as the frontal cortex (Bancaud and Talairach, 1991; Chauvel et al., 1995; Blanke et al., 2000). One of Hughlings Jackson's (1888) patients with temporal lobe epilepsy describes an ictal life review: "The past is as if present, a blending of past ideas with present. . .a peculiar train of ideas of the reminiscence of a former life, or rather, perhaps, of a former psychologic state" (quoted in Hogan and Kaiboriboon, 2003, p. 1741). More recently, Vignal et al. (2007) re-investigated memory flashbacks and life reviews in patients with pharmacoresistant epilepsy during spontaneous seizures and by electrical cortical stimulation with intracranial electrodes. Among a population of 180 subjects, they found 17 patients that described 55 memory flashbacks. These were quite variable, but could be repeatedly evoked in a given subject by the electrical stimulation of specific areas. Within the temporal cortex, Vignal et al. (2007) evoked memory flashbacks and life reviews by electrical stimulation of the amygdala, the hippocampus and the parahippocampal gyrus. One evoked memory flashback was: ". . .it is always thoughts from childhood, it is always visual, it is a place behind the house, the field were my father put his car, near a lake. . .Yes, it is pleasant because we were going to get the car from behind the house, it is a happy memory, it is never unpleasant" (Vignal et al., 2007, p. 92). Similar observations have been reported earlier by Penfield and Jaspers (1954) by electrical stimulation of the lateral temporal cortex. This suggests that both the stimulation of medial and lateral temporal structures can be at the origin of experiential phenomena including memory flashbacks and life review. Another feature of the NDE that can be observed in epileptic seizures and by electrical cortical stimulation is the feeling of a presence, namely the experience of feeling and believing that someone is nearby, without being able to see this person (Brugger et al., 1996; Jasper, 1913; Lhermitte, 1951; Critchley, 1979; Blanke et al., 2003) In one patient with pharmacoresistant epilepsy (Arzy et al., 2006), the feeling of a presence was induced by electrical cortical stimulation during presurgical epilepsy evaluation. The patient reported an "illusory shadow," who mimicked her body position and posture when her left TPJ was stimulated. She also reported a negative feeling about the experience, sensing hostile intentions from this unfamiliar "shadow." The feeling of a presence (in neurological or psychiatric patients) may also be quite elaborated and the felt person may be identified or interpreted as a

mystical or supreme entity, or guardian angel (Blanke et al., 2004 (case 5); Lunn, 1970; Brugger et al., 1996; for a more recent study see Blanke et al., 2014). The seen double during heautoscopy has also been linked to the left TPJ and may also be experienced as a mystical or supreme entity (Blanke et al., 2004; case 4; Blanke and Mohr, 2005). The experience of such a heautoscopic double may be of great emotional and personal relevance (Brugger, 2002; Brugger et al., 1996), as witnessed by the frequent inclusion of similar experiences in romantic and gothic literature (Dieguez, 2013). Also, heautoscopy is often associated with the experience of sharing of thoughts, words, or actions with the double or other people. Thus, patients with heautoscopy (but not OBEs) experience to hear the autoscopic body talk to them (Brugger et al., 1994) or experience that they communicate with the illusory body by thought (Blanke et al., 2004; case 5) a finding reminiscent of people reporting about the meeting of spirits during NDEs. Other patients with heautoscopy stated that the autoscopic body is performing the actions they were supposed to do (Devinsky et al., 1989; case 9) or fights with other people that could be of potential danger to the patient (Devinsky et al., 1989; case 5).

To summarize, the NDE features OBE, feeling of presence, meeting with spirits, memory flashbacks and life review are well-known symptoms of epileptic discharge or electrical stimulation of hippocampus, amygdala, and parahippocampal gyrus as well as more lateral, neocortical temporal areas including the TPJ. The most common cause of temporal lobe epilepsy is hippocampal dysplasia and sclerosis following brain anoxia, as the hippocampus is one of the most anoxia-sensitive brain regions in humans, and is damaged in almost all patients with cardiac arrest (as well as the TPJ which is a classical watershed region). Although more empirical investigations on this issue are needed, interference and damage to hippocampus and TPJ and consequently clinical and subclinical partial epileptic seizures manifestations thus seem likely candidates as major mechanisms of NDEs.

Sleep Abnormalities and Brainstem Mechanisms

Recently it has been suggested that subjects with NDEs report more frequently symptoms that might be associated with a sleep disorder associated with REM intrusions as compared to age-matched control subjects without NDEs (Nelson et al., 2006, 2007) (see Chapter 8 for more details on REM sleep). This was especially the case in subjects who had NDEs with OBEs (whether as part of their NDE or occurring at a different time (Nelson et al., 2007)). REM intrusions were estimated based on questions such as "Just before falling asleep or just after awakening, have you ever seen things, objects or people that others cannot see?" and "Have you ever awakened and found that you were unable to move or felt paralyzed?." Both items were reported significantly more often in subjects with NDEs. Visual and auditory hallucinations were also reported to be more frequent in subjects with OBEs during NDEs. The authors (Nelson et al., 2006, 2007) suggest that NDEs and OBEs may be related to muscular atonia during REM intrusions due to abnormal brainstem processing. REM intrusions are relatively frequent in the normal population and associated with sleep paralysis (a temporary paralysis of the body during sleep-wake transitions) in about 6% of the population. Symptoms similar to NDEs are also found in other medical conditions involving sleep or brainstem disturbances such as narcolepsy (a disorder involving excessive daytime sleepiness; Overeem et al., 2001), peduncular hallucinations (Manford and Andermann, 1998), hypnagogic and hypnopompic hallucinations (Takata et al., 1998), as well as sleep paralysis (Cheyne, 2005). Finally, patients with Guillain-Barré syndrome (an acute autoimmune disturbance of the peripheral nervous system leading in some cases to severe peripheral sensorimotor deficits that may require intensive care) have also been reported to have OBEs as well as NDE-like features (Cochen et al., 2005). In a series of 139 such patients, mental disturbances have been found in 31% and included vivid and unusual dreams, visual illusions and hallucinations, as well as paranoid delusions. The investigators did not inquire about OBEs directly, but patients reported related phenomena such as vivid or dreamlike sensations of losing the sense of one's body, meeting people, hovering or floating weightlessly over their body, or having the impression to have left one's body. Moreover, patients with the Guillain-Barré syndrome also reported complex own body illusions that have been linked functionally to OBEs such as illusory body-part dislocations, the inversion illusion, and room-tilt illusion (Blanke et al., 2004; Lopez and Blanke, 2007).

COGNITIVE NEUROSCIENCE OF NDE PHENOMENA

The reviewed data suggest that many functional and neural mechanisms are involved in the generation of the wide range of phenomena grouped under the term NDE. These mechanisms include mainly visual, vestibular, multisensory, memory, and motor mechanisms. Concerning brain regions the reviewed studies suggested damage to or interference with different cortical, subcortical, and brainstem areas, as well as the peripheral nervous system. Interference with the functioning of this extended network also seems to occur in situations characterized by stress, physical

exhaustion, rapid accelerations or decelerations, and deliberate relaxation. Although the neural mechanisms of many illusions and hallucinations have been described in detail, there are—at this stage—only preliminary data on the neurology of the different phenomena associated with NDEs. Systematic neurological research is needed to fill this gap as has already been done for related experiences (such as the OBE) or related medical conditions in cardiac arrest patients (coma, vegetative state, minimally conscious states). Although abnormalities in brainstem and peripheral nervous system may lead to NDE phenomena, we argue that major insights into these experiences will be gained by applying research techniques from cognitive neurology and cognitive neuroscience in order to reveal their cortical and subcortical mechanisms. We have reviewed evidence that suggests that some NDE phenomena can be linked to distinct brain mechanisms. This was shown for the OBE (damage to right TPJ), tunnel vision and seeing of foveal lights (bilateral occipital damage including the optic radiation with macular sparing or foveal hallucinations), feeling of a presence and meeting of spirits (damage to left TPJ), as well as memory flashbacks, life review, and enhanced emotions (hippocampal and amygdala damage). All structures have been shown to be frequently damaged in those cardiac arrest patients that show excellent recovery and who are so far the best studied patient group with NDE phenomena.

Based on the selective sites of brain damage in cardiac arrest patients (with excellent recovery) and the associations of key NDE phenomena to some of these same areas we would like to suggest that two main types of NDEs exist, depending of the predominantly affected hemisphere. We propose that type 1 NDEs are due to bilateral frontal and occipital, but predominantly right hemispheric brain damage affecting the right TPJ and characterized by OBEs, altered sense of time, sensations of flying, lightness, vection and silence. Type 2 NDEs are also due to bilateral frontal and occipital, but predominantly left hemispheric brain damage affecting the left TPJ and characterized by feeling of a presence, meeting of and communication with spirits, seeing of glowing bodies, as well as voices, sounds, and music without vection. We expect emotions and life review (damage to unilateral or bilateral temporal lobe structures such as the hippocampus and amygdala) as well as lights and tunnel vision (damage to bilateral occipital cortex) to be associated with type 1 and type 2 NDEs alike. Unfortunately, the few existing empirical studies on NDEs in patients with well-defined medical conditions lack neurological, neuropsychological, neuroimaging, and EEG data and to our knowledge no phenomenological analysis of case collections has tried to differentiate the two different types of NDEs in the way we are proposing here. Our proposition remains therefore speculative. We are confident that future neuroscientific studies in cardiac arrest patients with NDEs are likely to reveal the functional neuroanatomy of several NDE phenomena, likely implicating distributed bilateral cortical and subcortical brain mechanisms. There are also the promising experimental results and earlier suggestions (Britton and Bootzin, 2004; Persinger, 1994) that link NDE phenomena to symptoms of temporal lobe epilepsy. We therefore also expect additional insights into the neural and neuropsychological mechanisms of NDE phenomena through studies investigating the incidence of NDE phenomena (by carrying out detailed interviews and questionnaires) in patients with focal epilepsies as well as other neurological patients suffering from focal brain damage.

CONCLUSION

The present chapter has summarized findings on the functional and neural mechanisms of OBEs and NDEs. Whereas OBEs and their underlying brain mechanisms are currently investigated by several research groups and point to the importance of bodily multisensory integration at the right TPJ, the data on the neural mechanisms of NDEs are extremely sparse or altogether absent. We have argued above that the investigation of NDEs in cardiac arrest patients as well as neurological patients may be one possibility to start investigating the functional and neural mechanisms of NDEs. We agree with Christopher French (2005) who suggested that "given the heterogenous nature of the NDE ... [t]here is no reason to assume that a single comprehensive theory will explain the entire phenomenon." We add that there is also no reason to assume that an NDE is just one phenomenon, but rather a group of loosely associated experiences due to interference with different brain functions and brain mechanisms. Yet, after countless speculations that have focused on "life after life" and "survival of bodily death" in "survivors" of life-threatening situations, we propose that future studies on NDEs may want to focus on the functional and neural mechanisms of NDE phenomena in patient populations as well as healthy subjects. This might eventually lead to the demystification of NDEs, at least partly. More importantly, the scientific study of these varied complex experiences may allow studying the functional and neural mechanisms of beliefs, personality, spirituality, and self that have and will continue to intrigue scientists, scholars, and laymen alike.

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CHAPTER

21

The Hippocampus, Memory, and Consciousness

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OUTLINE

PROLOGUE: ROAD TRIP

In past decades, one of the privileges afforded graduate students at MIT's Behavioral Neuroscience Laboratory was the opportunity to transport the renowned amnesic patient H.M. from and to his home, a handful of hours distant, for his roughly semiannual research visits.[1] His renown derived from the profound influence that the study of his global amnesia, first described by Scoville and Milner (1957), had had on the neuroscience and psychology of memory. For example, it had provided the impetus for lesion studies of the role of the hippocampus and adjacent structures in learning and memory in rodents, nonhuman primates, and humans (Squire, 1987), for electrophysiological studies of long-term potentiation (Bliss and Lomo, 1973; Bliss et al., 2003), for the idea of the hippocampus as a cognitive map (O'Keefe and Nadel, 1978), and for many theoretical models of learning and memory (Tulving and Craik, 2000).

The convention for H.M.'s transport was for the designated graduate student to travel with a companion, and there was never a shortage of volunteers (typically a fellow student or a postdoc) eager to take a "road trip" with this famous patient. On one such trip the two scientists-in-training and their charge sought to pass the time by playing a game in which each player selects a color—on this occasion, green, blue, and white—and accumulates a point for each car painted in his or her color that passes in the opposite direction on the

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highway. Each player counts aloud, and the gaps between passing cars are typically filled with cheering and good-natured banter. H.M. participated fully in the game, selecting his color, accurately keeping track of his running total, and participating in the debate about whether a teal-colored car should be scored as blue, green, or neither. Indeed, on this occasion H.M. won, accruing a score of 20 first. A round of congratulations was exchanged, followed by a lull as the car rolled through the undulating central Massachusetts countryside. A few minutes later, the guest traveler, eager to maximize his once-in-a-lifetime opportunity to gain first-hand insight from this famous patient, asked "Henry, what are you thinking about right now?" H.M. replied that his count of white cars had now increased to 36.

The driver and guest were both impressed that this patient, famously incapable of remembering virtually anything that had occurred in his life since his 1953 surgery, had accurately maintained and updated a running count of arbitrarily selected "target stimuli" across a span of several minutes, with no evident source of external support or reinforcement. The three travelers commented on this before the guest traveler redirected the conversation to a line of questions that was typical of these trips: *Do you know what today's date is? Do you know who the current President is? Do you know who we are; where we're going today?* H.M. complied with good-natured responses, as always, although he couldn't answer any of the questions. Very quickly, however, he initiated another typical element in the driving-with-H.M. script, by steering the conversation toward a reminiscence from his youth, the portion of his life that was still mentally accessible after his surgery. (The story, about riding the Silver Meteor passenger train on a multi-day trip to visit an Aunt in Florida, had already been told several times at that point in the trip, a product of the teller not remembering the previous tellings.)

At that point, sensing a "teachable moment," the driver of the car interjected with a question of his own:

> Henry, do you remember what game we were playing a few minutes ago?
>
> *No, he didn't.*
>
> It involved counting cars of different colors; do you remember what your color was?
>
> *No.*
>
> The three colors were green, blue, and white; do you remember which was yours?
>
> *No, the cues didn't help.*
>
> Do you remember who won the game?
>
> *No recollection even of the triumph that had, only a few minutes before, produced in H.M. a modest chuckle and satisfied smile.*

This vignette illustrates several points about the cognitive profile and conscious phenomenology of medial temporal-lobe (MTL) amnesia that will be taken up in this chapter: the selectivity of the memory deficit vis-à-vis other cognitive functions; the selectivity of the deficit, within the myriad abilities that can be called mnemonic, to the conscious accessing of information experienced post trauma; the seeming normalcy of many aspects of the patient's conscious experience; and, yet, the severe constraints that damage to the MTL places on the candidate information and qualia that can make up the contents of consciousness for the MTL amnesic patient.

BACKGROUND

The study of patients with anterograde amnesia resulting from damage to the hippocampus and adjacent structures of the MTL has contributed enormously to our understanding of the organization of memory, of its relation to other aspects of cognition and behavior, and of its neural bases. Perhaps the most important principle to derive from the study of anterograde amnesia is that it is inaccurate to depict *memory* as a unitary domain of cognition, in the way that one might characterize *vision* or *language*. Indeed, a hallmark of a "pure" case of anterograde amnesia is the inability to encode (or learn) new information, despite relatively intact abilities to retrieve premorbid memories,[2] to remember a small amount of information, such as a phone number, for tens of seconds or even longer, and to demonstrate the improvements that accompany repeated performance of routine behaviors or repeated exposure to stimuli. Also spared in anterograde amnesia is every other major domain of cognition—sensory perception, language comprehension and production, motor control, intelligence, and so on. Because this condition produces so circumscribed a deficit of cognition, it provides an interesting case with which to examine the relation of consciousness to memory versus other domains of cognition. The analysis in this chapter will begin with a review of the neurological exam and its implications, followed by the anatomical and physiological profile of the amnesic brain, followed by considerations of cognitive effects of damage to the MTL. It will end with a consideration of phenomenology (Box 21.1).

THE NEUROLOGICAL EXAM AND ITS IMPLICATIONS FOR CONSCIOUSNESS

Anterograde amnesia is diagnosed when a neurological exam and neuropsychological testing reveal a specific deficit in the ability to learn new information, as assessed by poor performance on subsequent tests

BOX 21.1

ANTEROGRADE VERSUS RETROGRADE MEMORY

Although the severity of anterograde amnesia can differ across patients as a function of the nature and size of the lesion, it remains stable within a patient for the remainder of his or her life. This is illustrated by case H. M., who has been tested numerous times, across a span of greater than 25 years, on his ability to identify from photographs people who were famous during specific decades (e.g., Oliver North from the 1980s, John L. Lewis from the 1940s, Warren G. Harding from the 1920s, and so on). On each occasion that he was tested on this Famous Faces test (Marslen-Wilson and Teuber, 1975)—in 1974, 1977, 1980, 1988, 1989, 1990, 1994, 1997, and 2000—his performance never varied from between 0%-to-20% correct for photos taken after the onset of his amnesia (i.e., portraying people from the 1950s to 1980s). For stimuli assessing premorbid knowledge, in contrast, H.M.'s performance never varied from between 50%-to-75% correct for photos from the 1940s and 1930s, and it dropped off to between 15% and 50% for photos from the 1920s, the decade in which he was born. By contrast, the mean performance of 19 age- and education-matched control subjects starts high and declines steadily, and nearly monotonically, from approximately 75% correct for the 1980s to 30% for the 1920s (Kensinger and Corkin, 2000). (It is interesting to note that, for items from the 1940s and 1930s, H.M.'s performance exceeds the control group's mean performance of approximately 40% correct. This is perhaps because the remote memories of the neurologically healthy group have endured more interference over the years than have those of H.M.) A more detailed consideration of retrograde amnesia is provided in Box 21.4.

of memory for this new information. In a case described by Mega (2003), for example, the patient had a normal general medical exam. She could, upon hearing a spoken list of digits, correctly recite lists of six in the forward order, and lists of five when instructed to recall them in reverse order. On the Mini Mental State Exam, a dementia screen that evaluates knowledge of where one is and when it is (year, season, month, date, day of the week) at the time of testing, counting backward from 100 by sevens, and following simple instructions, she responded correctly to 28 out of 30 questions, missing only two that required recall of information provided earlier in the exam. Her vocabulary was intact, as assessed by the ability to name 59 of 60 black-and-white drawings of objects from the Boston Naming Test. When asked to name as many animals as possible within a minute, an index of retrieval from semantic memory and, particularly, the control of this retrieval, she named 19. Executive function was intact, as assessed by tests evaluating the ability to perform mental arithmetic, to change strategy after covert changes of the rule in the Wisconsin Card Sorting Test, and to withhold responses on a speeded responding test. Finally, and perhaps most striking for one not familiar with such cases, her full-scale intelligence quotient (IQ) as assessed by the Wechsler Adult Intelligence Scale-Revised was within the normal range.

Against this backdrop of normal functioning, however, the patient exhibited marked impairment on several formal tests of recall and recognition. For example, she demonstrated marked impairments on tests requiring recall of a list of 16 words several minutes after she had heard them (California Verbal Learning Test), requiring recall of the content of two short stories 30 min after they had been read aloud (Wechsler Memory Scale (WMS) delayed paragraph recall), and requiring recall of a complex nonsense figure 30 min after she had first seen it and successfully copied it (Rey-Osterrieth complex figure recall).[3] One concise (if overly simplistic) way to summarize this patient's clinical profile, which is characteristic of anterograde amnesia, is that she displayed a normal full-scale IQ but an abnormally low *memory quotient* (as assessed by the WMS). Another important distinction revealed here is between long-term memory (LTM) and short-term memory (STM). Although these terms can have different meanings in different contexts, to the cognitive neuroscientist the former refers to memory for information that has not been in conscious awareness for at least several tens of seconds (but possibly for as long as several decades) prior to its retrieval, whereas the latter refers to the temporary retention of a limited amount of information beginning the moment that this information is no longer accessible to the senses. (Thus, for example, your memory for what time you woke up today is an example of LTM, not STM. Skeptics of this convention need only consider the penultimate vignette that concludes this chapter.)

From this profile we see that many domains of mental function remain intact after the onset of anterograde

amnesia. One can infer from these results that this patient can, when prompted, call into conscious awareness much of the impressively vast amount of knowledge that she (like most typically developing humans) has acquired during her life (such as the names of a plethora of different kinds of animals and common objects, facts about political history, knowledge about numbers and their mathematical manipulation, etc.); consciously recite to herself lists of digits and think about how to reverse their order; consciously reason about what the rules of a novel card-sorting game might be, come to the realization that the rules have changed, and think about what the new rule might be; and so on. As an interim conclusion, then, we might infer that many aspects of consciousness are largely unaffected by anterograde amnesia. This conclusion is also consistent with the impression that one might draw from the vignette that opened this chapter. Next we will consider how the evidence about the damage sustained by the amnesic brain, as well as the effects of this damage on the brain's functioning, informs our understanding of the conscious phenomenology of the anterograde amnesic patient.

THE IMPLICATIONS OF MTL DAMAGE FOR NEUROANATOMICAL AND NEUROPHYSIOLOGICAL CORRELATES OF CONSCIOUSNESS

Patients demonstrating the classic neuropsychological profile of a pure anterograde amnesia, such as the patient profiled in the preceding section, invariably have sustained damage that is largely confined to one or more elements of the *medial temporal lobe-diencephalic memory system*, which comprises the hippocampal complex (dentate gyrus, cornu Ammonus (a.k.a., the hippocampus proper), and subiculum), and adjacent structures of the MTL—the parahippocampal, perirhinal, and entorhinal cortices—and two closely anatomically linked structures—the mammillary bodies of the hypothalamus and the anterior thalamic nuclei. Also important to the MTL memory system is the fornix, a bundle of fibers leaving the hippocampal complex that synapse on the mammillary bodies and on neurons of the basal forebrain. A postmortem examination of the brain of Mega's patient revealed bilateral hippocampal sclerosis—cell loss in the CA1 fields of the hippocampus accompanied by gliotic change—and an absence of pathological changes in cortex. Importantly, there was no evidence of the widespread cortical damage that is associated with such neurodegenerative disorders as dementia of the Alzheimer's type[4] (Mega, 2003). The possible etiology of this damage was not considered. (In contrast, a retrieval deficit, as considered in Box 21.2, would be associated with damage to the dorsolateral prefrontal cortex (PFC) (Mega, 2003).)

The bilateral damage to H.M.'s MTL, produced by surgical aspiration intended to treat his intractable epilepsy (Scoville and Milner, 1957), was considerably more extensive. Detailed structural imaging with magnetic resonance imaging (MRI) indicates that H.M.'s lesion is bilaterally symmetrical, and includes the medial temporal polar cortex, most of the amygdaloid complex, most of the entorhinal cortex, and the rostral half of the hippocampus proper (Figure 21.1). The caudal half of the hippocampus (approximately 2 cm in length), although intact, is atrophic. The mammillary nuclei are shrunken. In addition, the cerebellum demonstrates marked atrophy (a finding assumed to have resulted not from the surgery, but rather from the patient's decades-long history of taking anticonvulsant medication (Corkin, 2002)). Importantly, the lateral temporal, frontal, parietal, and occipital lobe cortices appeared normal for a 66 year-old individual (Corkin et al., 1997).

When we contrast the lesions of these two patients, one quite circumscribed and the other considerably more extensive, we see that they do not invade the brain regions whose function is implicated in waking consciousness. The brain regions whose level of activation differentiates conscious from unconscious mental states include lateral and medial frontal and parietal cortex, and thalamus (for more detail, see the chapter by Laureys in this volume, and Fiset et al., 1999; Laureys, 2005; Maquet, 2000). Similarly, the lesions of these MTL amnesic patients largely spare the territories of the so-called "default network" of cortical regions that display elevated levels of activity when subjects are at rest: medial posterior cingulate and dorso- and ventromedial frontal cortex; lateral inferior parietal cortex; and medial and lateral aspects of temporal polar cortex. (Portions of this latter area were resected during H.M.'s surgery.) Ideas about functional significance of activity in this network include "unconstrained, spontaneous cognition—[e.g.,] daydreams," maintaining balance within neural networks and systems, and "instantiat[ing] the maintenance of information for interpreting, responding to, and even predicting environmental demands" (Raichle, 2006, pp. 1249–1250).

Turning to the functioning of the brain of MTL amnesics, there is a surprising paucity of published information on this topic (this despite an abundance of data for patients with, for example, mild cognitive impairment and with Alzheimer's disease). H.M. has undergone a brain scan with single photon emission computed tomography, a method that can measure blood flow in tissue. In comparison to the scan of a

BOX 21.2

LOST FOREVER OR TEMPORARILY MISPLACED?[a]

The presence of anterograde amnesia, alone, does not permit one to distinguish between a "consolidation block" (i.e., impaired encoding) account versus disordered storage or disordered retrieval accounts of hippocampal function. In the years following the report of case H.M. Scoville and Milner (1957), which launched the modern study of the MTL and of amnesia, the emphasis was on "the central role of the learning impairment" (Milner et al., 1968, p. 233). By the late 1960s, however, accumulating evidence that many kinds of learning could be spared in amnesic patients (e.g., Milner et al., 1968; Warrington and Weiskrantz, 1968) led to the alternative proposal that the amnesic syndrome was best characterized not as a disorder of encoding, but rather as one of storage or retrieval (Warrington and Weiskrantz, 1970). For example, when Warrington and Weiskrantz (1974) tested amnesic subjects and neurologically healthy control subjects 10-min after reading 16 words, the patients performed as well as control subjects on what the authors termed a "cued recall" task, but were markedly impaired on a test of Yes/No recognition. (The cued recall task from ref. Warrington and Weiskrantz (1974) used a procedure that came to be known as word-stem completion, in which the first three letters of a studied word were presented and the subject was "required to identify the stimulus word" (p. 420). It will be revisited in Box 21.3). These results, together with evidence of disproportionate sensitivity to interference from items presented prior to or after the critical information, were taken as evidence for "altered control of information in storage" (p. 419) in amnesia, and against the consolidation block account.

These early studies illustrated that the study of amnesia could provide powerful insight into the organization of human memory, and the 1970s witnessed an explosion of LTM research, in both memory-impaired and normal populations. One result of this development was increased understanding of the differences between anterograde and retrograde memory (Box 21.1), which led to a convincing refutation of strong versions of storage- and retrieval-based accounts of anterograde amnesia (Marslen-Wilson and Teuber, 1975; Squire, 2006).

The ambiguity of whether the patient's deficit is one of encoding versus one of retrieval also has implications for the clinic, in that, for example, evidence of impaired recall of recently presented information, alone, cannot distinguish an isolated deficit in *learning* new information from a deficit in *retrieving* it. To differentially diagnose anterograde amnesia from a retrieval deficit, it is important to follow up a finding of poor 10-min recall with retrieval cues. If the availability of cues produces a marked improvement in performance, the diagnosis of a retrieval deficit is indicated (Mega, 2003).

[a]A more thorough treatment of this question can be found in Squire (2006), from which the title of this box was appropriated.

healthy, age- and education-matched control subject, H.M.'s thalamus and cortical mantle appear to show normal levels of blood flow, with the exception of the MTL, from which no signal is detected (Corkin, personal communication). Other evidence for normal cortical functioning in H.M. comes from a functional MRI scan acquired while he performed a novel picture encoding task. This scan revealed task-related activity in a portion of caudal MTL that was spared by the surgeon, an effect that was comparable to what was seen in control subjects (Corkin, 2002). This rather thin set of observations from the human is supplemented, however, by controlled studies in experimental animals. In baboons with surgically produced neurotoxic lesions of entorhinal and perirhinal cortex, positron emission tomography (PET) scans revealed pre-to-postoperative hypometabolic changes in several brain regions, including inferior parietal, posterior cingulate, sensorimotor, posterior temporal, and rostral occipital regions, as well as in thalamus. No differences were observed in lateral prefrontal, anterior cingulate, anterior temporal, or insular cortex (Meguro et al., 1999). (These rhinal cortex lesions produced significant impairment of recognition memory (Chavoix et al., 2002).) A study in rats that used a similar procedure found significant hypometabolism (as measured by PET) in bilateral frontal, parietal, and temporal regions 4 days after unilateral chemical lesion of entorhinal cortex, an effect that persisted 4 weeks later only in temporal cortex (Hayashi et al., 1999).

This summary of the structural damage associated with relatively pure cases of anterograde amnesia, and its physiological sequelae, leaves equivocal the question of whether the lesions that are sufficient to produce anterograde amnesia would be expected to affect directly the phenomenological consciousness of these patients. Considering data from amnesic patients themselves, it is clear that their lesions do not directly

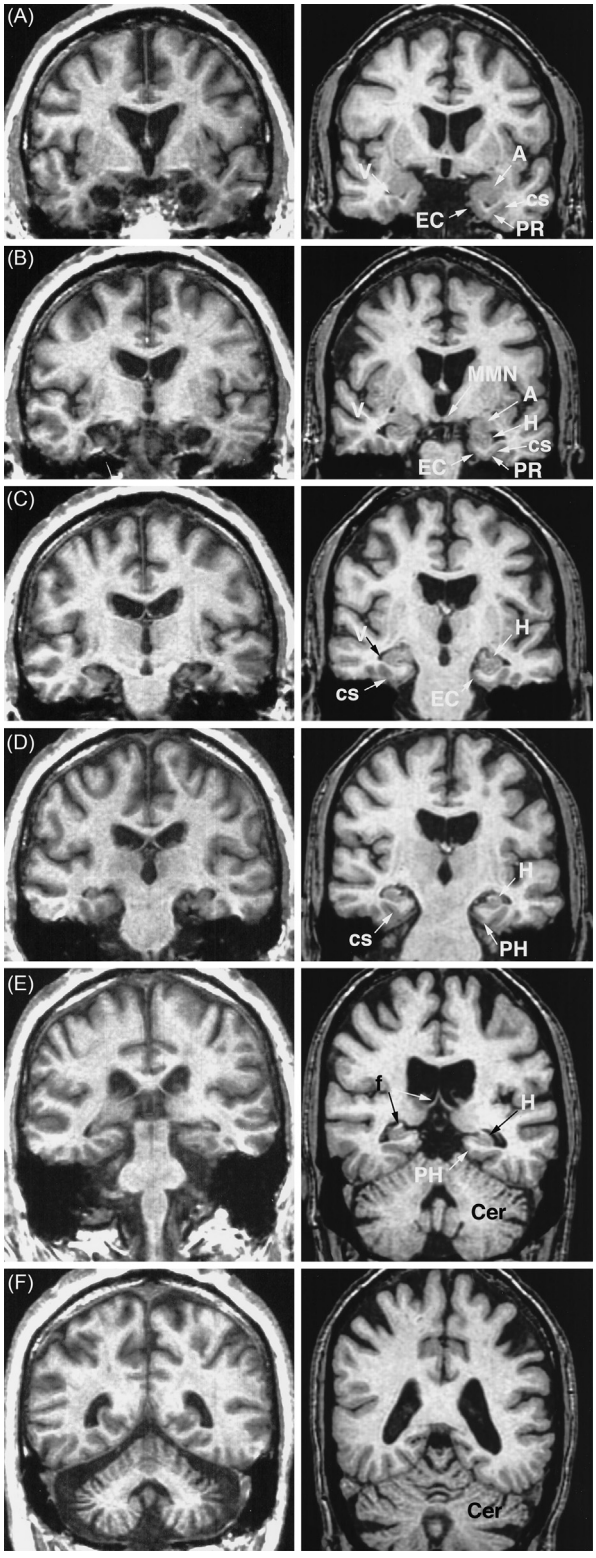

FIGURE 21.1 T1-weighted MR images of the brain of H.M. (left side) and an age- and education-matched control subject (right side). Labels on the control images identify regions that are damaged or missing in H.M. (A, amygdala; CS, collateral sulcus; EC, entorhinal cortex; PR, perirhinal cortex; MMN, medial mammillary nuclei; H, hippocampus; V, ventricle). *Source: Adapted from Corkin et al. (1997).*

invade brain regions known to be necessary for conscious awareness. Additionally, the scant amount of information available from case H.M. does not show any obvious alterations in the physiology of consciousness-related regions. In the baboon, however, bilateral damage to entorhinal cortex produced lasting alterations in many cortical and subcortical regions, some of which may correspond to regions that, in the human, contribute importantly to conscious awareness. An analogous effect may be more transient in rats, although the lesion in this case was unilateral. Finally, it is worth noting that the lesions in the animal studies, although targeting portions of the MTL memory system, spared the hippocampus proper. Thus, at this point in our exploration we have found, at best, only indirect hints that conscious awareness may be altered in patients with MTL amnesia. We shall see in the next section, however, that targeted evaluation of specific cognitive functions in these patients uncovers deficits that are not readily evident from standard clinical and neuroradiological exams.

THE EFFECTS OF MTL DAMAGE ON VARIOUS MENTAL FUNCTIONS AND THEIR IMPLICATIONS FOR CONSCIOUSNESS

Long-Term Memory

The Quality of Remote Autobiographical Memories

By far the most influential framework for thinking of the relations between consciousness and memory has been Tulving's distinction between *autonoetic*, *noetic*, and *anoetic* states of awareness with respect to memory retrieval (Tulving, 1985). Derived from a Greek word appropriated by philosophers to refer to "mind" or "intellect," the term "noetic" in this context roughly corresponds to "knowing." Thus autonoetic (or "self-knowing") awareness refers to an instance of memory retrieval that "is not only an objective account of what has happened or what has been seen or heard . . . [but also] necessarily involves the feeling that the present recollection is a reexperience of something that has happened before" (Wheeler, 2000, p. 597). "At the core of autonoetic memory," writes Moscovitch (2000), "is a sense of personal self and the subjective experiences associated with that self or ascribed to it" (p. 611). In relation to the structure of memory, autonoetic awareness is the defining feature of episodic memory, the subcategory of declarative memory corresponding to events that one has personally experienced. Noetic ("knowing") awareness, in contrast, "occurs when one thinks about something that one knows, such as a mathematical, geographical, or even

BOX 21.3

"MEMORY WITHOUT AWARENESS"

A second major focus of memory research beginning in the 1970s was what came to be known as *implicit* or *nondeclarative* memory (for reviews, see Schacter, 1987; Squire et al., 1993). The consequent development of theoretical and methodological sophistication in this domain led to a more nuanced interpretation of some of the earlier reports of intact performance by amnesic subjects. With word-stem completion, for example, it was shown that the performance of amnesic subjects relative to age- and education-matched control subjects depended on the precise phrasing of instructions about how to process the three-letter stem: When subjects were instructed to complete the three-letter stem to "the first word that comes to mind," and no reference was made to the prior study episode, amnesic patients often generated target words at a level that was comparable to that of control subjects (i.e., they exhibited intact *repetition priming*); when, in contrast, they were instructed to use the three-letter stem as a cue with which to retrieve an item from the studied list, amnesic patients were typically impaired (e.g., Gabrieli et al., 1994). (The former procedure, which most closely resembles that from Warrington and Weiskrantz (1974), came to be know as word-stem completion *priming*, the latter as word-stem *cued recall*.) Thus, the intact performance of amnesic patients in Warrington and Weiskrantz (1974) came to be reinterpreted as an early demonstration of intact performance by amnesic subjects on a priming task, a phenomenon that fell under the rubric of *nondeclarative memory*.

In parallel to this research in nondeclarative memory, by the late 1980s, the dominant neuropsychologically inspired view was that memory was organized into distinct systems, with the principal distinction being between MTL-dependent declarative memory and MTL-independent nondeclarative memory.[a] From this perspective, the function of the *MTL memory system* was one of encoding information that is active in the subjective present (e.g., the products of the visual and auditory perception of an event, together with the emotions that they engendered) and effecting its "transition from perception to memory" (Squire and Zola-Morgan, 1991, p. 1384) by binding together its anatomically discrete representations (in our example, visual, auditory, and affective). Only by undergoing this process of MTL-mediated *consolidation* could a memory later be called back into conscious awareness via volitional retrieval processes.

[a]In parallel with the development of memory-systems models were transfer appropriate-processing models, which appealed to the overlap of mental processes engaged at study versus test as the critical factor in determining memory performance. However, because this development emerged largely via the study of neurological healthy, its application to the amnesic syndrome has been only indirect. A comprehensive overview of recent theoretical developments in human memory research can be found in Tulving and Craik (2000).

personal fact, without reexperiencing or reliving the past in which that knowledge was acquired" (Moscovitch, 2000, p. 611). Noetic awareness characterizes the phenomenology associated with retrieving information from semantic memory, the other subcategory of declarative memory. Finally the concept of anoetic ("not knowing") awareness captures the fact that nondeclarative memory can be expressed without the individual's awareness that his or her performance is being influenced by a prior experience (see Box 21.3). For example, when H.M.'s performance on the completion of three-letter word stems or on the identification of briefly flashed words displays a robust level of influence of a prior study session (Postle and Corkin, 1998), it does so despite an apparent lack of awareness on the part of the patient that there even was a study session 5 min prior to the test, let alone that his performance reflects the influence of that session. (Thus, perhaps "anoetic performance" would be a better term.) There exists a large and complex literature, extending back even before Tulving's seminal paper (Tulving, 1985), that grapples with the question of how to determine precisely the level of awareness that accompanies performance on different memory tasks. This literature is reviewed comprehensively elsewhere (Moscovitch, 2000; Roediger et al., 2007), and the remainder of this section will draw on it only to the extent that it addresses directly the goals of this chapter.

The standard neuropsychological model of the MTL memory system, the development of which is sketched in Boxes 21.2–21.4, includes two important tenets that we will examine in detail. One is the time-limited role for MTL-mediated consolidation, a feature necessitated by the temporal gradient that typifies retrograde amnesia following damage to the MTL (Box 21.4, Squire, 1992). The second is the hierarchical arrangement of the elements in the MTL memory system, with memory formation depending on the funneling of

BOX 21.4

RETROGRADE MEMORY AND CONSOLIDATION

Retrograde memory refers to memory for information encountered prior to the insult to the MTL. Were one to start from a strict assumption that the hippocampus is an engine of encoding, one might expect that memory for an event that occurred the day before the MTL insult would be as strong as (if not stronger than) memory for an event that occurred years earlier. However, no such cases of anterograde amnesia accompanied by the absence of any retrograde memory impairment have ever been reported. Instead, irreversible damage to the MTL invariably also produces some retrograde memory loss. However, there are marked differences in the effects of MTL damage on anterograde versus retrograde memory. Whereas the former is stable across time, the latter is more variable, perhaps, as we shall see below, in systematic ways.

The strength and duration of retrograde amnesia can be sensitive to the amount of tissue damaged (particularly cortical tissue outside the MTL), the patient's age at the time of MTL trauma, and other factors (Squire and Bayley, 2007). For case H.M., his retrograde memory has been estimated to extend back to 11 years prior to his surgery (Sagar et al., 1985). Unlike anterograde amnesia, however, many studies suggest that retrograde amnesia can be characterized by a temporal gradient, such that memory for events that occurred shortly prior to the MTL trauma is worse than is memory for events that occurred several years earlier. Quantitative studies of this phenomenon, carried out in amnesic patients (Squire et al., 1989), in psychiatric patients undergoing electroconvulsive therapy (Squire et al., 1975), in a variety of animal preparations (Squire, 1992), and in formal computational modeling (Alvarez and Squire, 1994), indicate that this gradient takes the form of a monotonic function. Such a replicable, systematic pattern of results requires an explanation at the level of memory processing, and the explanation that has made its way into the textbooks is *consolidation*. More a description than a detailed account of a process, the concept of consolidation captures the logic that the MTL must continue to play a role in memory processing after the initial encoding of information, but that this role is time limited. Thus, memory for information that was encoded shortly before MTL damage was incurred is vulnerable to disruption, because consolidation of that memory is still underway. Memory for information that was encoded long before the trauma, in contrast, is more likely to be preserved, because the "process" of consolidation had been completed. (A thorough summary of retrograde memory research, including an intriguing phenomenon known as "reconsolidation," can be found in a special section of the journal *Learning & Memory* (2006, vol. 13, issue 5) that is devoted to this topic.)

activity from nonmnemonic cortical regions first into perirhinal or parahippocampal cortex, then into entorhinal cortex, and finally "up" to hippocampus ("up" in the sense of the apex of the hierarchy) (Broadbent et al., 2002). Recently, questions have been raised about both of these tenets of the standard neuropsychological model that have important implications for the neurobiology of consciousness.

A challenge to the idea of a time-limited role for the hippocampus in memory consolidation has come in the form of the *multiple trace theory* (MTT) of hippocampal function (Nadel and Moscovitch, 1997). MTT posits that each instance of memory retrieval also prompts the encoding by the hippocampus of a new memory trace, such that over time a single memory comes to be stored as multiple traces. To the extent that elements of these traces overlap, this process leads to the development of semantic knowledge that is independent of the episodes in which the information was learned. So, for example, if learning about US presidents in primary school and taking a family trip to Washington DC both create traces representing the proposition that "Thomas Jefferson was the third President of the United States," repeated iterations of this process create a representation that can be retrieved independently of any reference to any one of the contexts in which this information was encountered. In this way, the memory that *Thomas Jefferson was the third President of the United States* becomes a *semantic* memory. Should damage to the hippocampus be sustained several years after the learning took place, the patient would nonetheless be able to retrieve this knowledge. On this prediction, the MTT and the standard neuropsychological model are in accord. The specific memory of the visit to the Jefferson Memorial during the family trip to Washington DC, however, remains an *autobiographical episodic* memory that is dependent on the hippocampus for the remainder of the subject's life. Thus, MTT would predict that access to this autobiographical episodic memory would be severely compromised, if not completely impossible, after extensive damage to the MTL (particularly to the

hippocampus). The standard neuropsychological model, in contrast, would hold that autonoetic awareness for remote autobiographical episodic memories can be comparable to that experienced by neurologically intact individuals when recalling a memory of the same vintage. Detailed theoretical accounts of these models can be found at Moscovitch et al. (2006), Squire and Bayley (2007), and are nicely summarized in Yassa and Reagh (2013). The latter also offers an attempt to reconcile these two perspectives with a *competitive trace theory*, whereby each retrieval episode results in a "recontextualization" of the original cortically based memory with information about the context at the time of retrieval. By this view, repeated retrieval episodes result in greater tendency toward "decontextualization" (i.e., semanticization) of a memory, or toward "recontextualization," whereby "illusory" details deriving from retrieval-related context outcompetes and, thus, replaces the original context (Yassa and Reagh, 2013).

The introduction of MTT has prompted a reevaluation of the quality of H.M.'s conscious experience when retrieving premorbid autobiographical memories. As Corkin recounts it in her book,

> At first, Scoville and Milner believed that Henry's amnesia was fairly straightforward—he could not remember any new information after the surgery, but had clear recall of things that had happened earlier in his life... As remote memory testing became more standardized and sophisticated, we realized that our early impressions were incorrect. ***Corkin (2013, pp. 215–216)***

In particular, a careful study of the quality of H.M.'s remote memories (Steinvorth et al., 2005) provided

> a breakthrough in our evaluation of Henry's memory, show[ing] that his recollections from the time before his operation were sketchier than initially believed. He could conjure up memories that relied on general knowledge—for example, that his father was from the South—but could not recall anything that relied on personal experience, such as a specific Christmas gift his father had given him. He retained only the gist of personally experienced events, plain facts, but no recollection of specific episodes. ***Corkin (2013, pp. 215–216)***

Further consideration of the implications of the findings from Steinvorth et al. (2005) for the standard neuropsychological model versus MTT can be found in Squire (2009) and in Chapter 10 of Corkin (2013).

Single- Versus Dual-Process Models of LTM Retrieval

A second debate currently underway in the memory community relates to the retrieval of episodic memory, and can be thought of, for our present purposes, as a debate as to whether there are distinct processes corresponding to the autonoetic versus noetic awareness that can accompany memory retrieval. No one disputes that recognition can either be accompanied by an autonoetic sense that *"yes, I've seen this person before and I recall distinctly when and where it was that I first encountered her"* or by a noetic "feeling of familiarity" such that *"I know that I've seen this person before, but I don't recall who she is, or where or when it was that I first encountered her."* What is contentious, however, is whether there exist two processes—*recollection* and *familiarity*—that underlie these two phenomenological experiences. The alternative is simply that memories of different strengths can give rise to different phenomenological experiences, in this case autonoetic versus noetic awareness, but that the actual underlying process of memory retrieval is the same in both cases. The details of this debate in the cognitive psychology community (e.g., Wixted and Stretch, 2004; Yonelinas, 2002) are beyond the scope of this chapter. What is relevant to our current interest, however, are reports that these two putative processes may be neurobiologically dissociable.

Results from functional MRI (fMRI) in humans (e.g., Yonelinas et al., 2005) and lesion studies in humans (e.g., Aggleton et al., 2005; Bastin et al., 2004; Yonelinas et al., 1998, 2002) and rats (Fortin et al., 2004), have been interpreted as evidence that recollection is differentially supported by the hippocampus, whereas familiarity is supported by nonhippocampal elements of the MTL memory system, of which the perirhinal cortex is particularly emphasized (Brown and Aggleton, 2001). An implication of this "dual processes" account is that autonoetic awareness at the time of retrieval may depend on the hippocampus proper, whereas noetic awareness may be supported by nonhippocampal elements of the MTL. In contrast, the standard neuropsychological model would hold that any differences in retrieval-related phenomenology associated with damage to different elements of MTL memory system would be quantitative, rather than qualitative, because it denies the possibility that different elements of this system differentially support discrete memory-related processes. (Indeed, one account of this view aligns itself with "single process" theories from cognitive psychology that deny a fundamental difference between recollection and familiarity (Wais et al., 2006).)

Short-Term Memory

STM can be understood as the retention of recently presented, or recently cued, information that is not accessible to the senses, but that is needed to guide

behavior. One example would be being asked to dial a telephone number, then holding in mind that set of digits, in that specific order, while searching the house for one's telephone. As we shall see here, it represents yet another case in which received wisdom about the mnemonic functions of the hippocampus has come under reappraisal. In this instance, however, a function previously believed to be independent of the integrity of the hippocampus is now being shown, under some conditions, to depend on it. As we saw in the earlier section on the neurological exam, anterograde amnesia is characterized by a preserved ability to prehend a spoken list of items (in this case, digits) and to recite it back to the speaker. Formal demonstrations of this (e.g., Baddeley and Warrington, 1970; Drachman and Stahl, 1966; Teuber et al., 1968; Wickelgren, 1968) contributed to the development of cognitive models specifying a fundamental distinction between STM and LTM (Baddeley and Hitch, 2007), as well as to the idea that STM is independent of the MTL memory system. (To be thoroughly precise, therefore, this name would need to be expanded to "MTL *declarative long-term* memory system.")

Alternative Models of Hippocampal Function

Relational Memory Theory

The recent reconsideration of the dependence of STM on the MTL, alluded to in the previous subsection, has its roots in a detailed theory of what might be the specific operations performed by the hippocampus that give it its privileged function with respect to the formation of LTM. In brief, this *relational memory theory* holds that the hippocampus effects the operation of representing and learning the relationships between items in the environment. This might include the arbitrary rule for written English of "*i* before *e*, except after *c*," or the concrete spatial content of "Zidane struck the free kick from the left side of the field, lofting the ball over the heads of the Brazilian defenders and into the right side of the goal box, where Henry, running in unmarked, volleyed it into the back of the net." (Incidentally, Eichenbaum (1999) has argued that the demonstration of a necessary role for the hippocampus for nondeclarative memory for the relationships between stimuli (e.g., learning cue-context relationships embedded in a visual search task (Chun and Phelps, 1999)) rules out the view that the hippocampus "could be a 'gateway' for awareness to enter into memory" (p. 775).) Motivated by this "relational binding" model, recent studies have demonstrated that patients with hippocampal damage are impaired on tests of STM, with lags as short as 1 s, for spatial relationships between items in a display (Hannula et al., 2006; Olson et al., 2006b). This suggests that one qualitative effect of hippocampal damage on phenomenological consciousness is to disrupt the ability to represent the relationships between discrete objects.[5]

A Processing-Based Model of Memory Function

This recently articulated perspective argues that "consciousness seems to be a poor criterion for differentiating between declarative (or explicit) and nondeclarative (or implicit) types of memory" (Henke, 2010, p. 523). It draws on much of the literature summarized previously in this section, as well as on many demonstrations that "unconscious episodic memory" either recruits the hippocampus in activation studies or is impaired in MTL amnesics. Examples include impaired performance of these patients on tests with implicit contextual information (Chun and Phelps, 1999) or requiring implicit associative learning (e.g., Hannula et al., 2007; Verfaellie et al., 2006). The resultant *processing-based model* holds that mnemonic functions are best construed as organized into three categories: the rapid encoding of flexible associations (hippocampal-dependent); the slow encoding of rigid associations (hippocampal-independent); and the rapid encoding of single or unitized items (Henke, 2010).

Imagining New Experiences, and Scene Construction

One question that arises from both *relational memory theory* and the *processing-based model*, as summarized in the "Alternative Models of Hippocampal Function" section, is whether the disruption of the mental operations that they hold to be dependent on the hippocampus might also affect real-time cognition (i.e., thinking) in situations that do not make explicit demands on memory retrieval. This would include the perception and experience of complex scenes, and the class of mentation referred to as "mental time travel."

The debates summarized in "Long-Term Memory" section relate to whether the hippocampus is necessary for autonoetic awareness during memory retrieval. But what about thinking about experiences that have never actually occurred, such as might happen when one daydreams, or when one thinks about what might happen at an upcoming event? One group has reasoned that because these phenomenological experiences would seem to draw on many of the same psychological processes required for autonoetic awareness of an episodic memory (e.g., mental imagery, a sense of "being there," maintenance of a narrative structure), the ability to imagine new experiences might also be dependent on the hippocampus. (This line of reasoning depends on many precepts of the MTT.) In one experiment they asked patients with bilateral hippocampal damage to construct new imagined experiences, such as "Imagine you are

lying on a white sandy beach in a beautiful tropical bay," and "Imagine that you are sitting in the main hall of a museum containing many exhibits." The results indicated that the imagined experiences of the patients contained markedly less experiential richness than did those of healthy control subjects. A more detailed analysis also revealed lower "spatial coherence" (a measure of the contiguousness and spatial integrity of an imagined scene) in the performance of the patients, and the authors speculated that this might be at the root of the overall poor performance of the patients (Hassabis et al., 2007).

The work reviewed here has contributed to the articulation of *scene construction theory*, whereby scenes are held to be "the primary currency of the hippocampus. For many of us," Maguire and Mullally (2013) posit, "scenes are the language of thought, and we argue that the hippocampus actively and automatically predicts and constructs the scenes we need to fuel our cognition" (p. 1187). From the perspective of this theory, an implication of the importance of scene construction for the quality of conscious awareness is illustrated in the report of an MTL amnesic patient trying to imagine a scene:

> There is no scene in front of me here. It's frustrating because I feel like there should be. I feel like I'm listening to the radio instead of watching it on the TV. I'm trying to imagine different things happening, but there's no visual scene opening out in front of me... It's hard trying to get the space, it keeps getting squashed. ***Mullally et al. (2012, p. 266)***

To summarize "The Effects of MTL Damage on Various Mental Functions and Their Implications for Consciousness" section, many recent developments in research on memory and on the functions of the hippocampus, although some of them still controversial, point to the possibility that the contributions of the hippocampus to phenomenological consciousness may extend beyond the processing of the present so that the events of the present can later be revisited. They suggest that the hippocampus may also be necessary for rich autonoetic awareness, as well as for spatially coherent thinking about the very recent past, the present, and even the future.

WHAT IT IS LIKE TO BE AMNESIC?

The first two analytic sections of this chapter established that many quantitatively measurable correlates of the conscious experience of the MTL amnesic patient are not appreciably changed from what they must have been prior to the neurological insult. This might justify what is arguably the most direct approach to investigating the phenomenal consciousness that is characteristic of MTL amnesia-interrogating patients. We have already done this in the context of scene construction theory (see "Imagining New Experiences, and Scene Construction" section), but before further pursuing this approach, a brief review of a few concepts from the philosophy of consciousness will prove to be useful. Within the tradition of phenomenology, the *stream of consciousness* is held to provide coherence and continuity to conscious experience. As summarized by Thompson and Zahavi (2007), "Phenomenological analyses point to the 'width' or 'depth' of the 'living present' of consciousness: our experience of temporal[ly] enduring objects and events, as well as our experience of change and succession, would be impossible were we conscious only of that which is given in a punctual now and were our stream of consciousness composed of a series of isolated now points, like a string of pearls. According to Husserl (1991), the basic unit of temporality is not a 'knife-edge' present, but a 'duration block' ..." (p. 77). The relevance of this concept to anterograde amnesia is clear, and is further bolstered by empirical evidence that relates to H.M.'s perception of the passage of time. In his experiment, Richards (1973) asked "Without the normal recall for events, how fast does time pass for H.M.? Does one hour, one day or one year seem just as long to this unique individual as to us?" (p. 279). The results indicated that whereas time reproduction (and thus, by inference, the experienced passage of time) was normal for intervals less than 20 s, it was grossly distorted for longer intervals. In answer to his passage-of-time question, Richards concluded by extrapolating from the data that "one hour to us is like 3 minutes to H.M.; one day is like 15 minutes; and one year is equivalent to 3 hours for H.M." (p. 281). Thus, for H.M., the width of his "living present" may, in fact, be best characterized as a knife edge.

A second concept from philosophy that is germane to our pursuit is that of *fringe consciousness* (Hassabis et al., 2007), summarized by Seager (2007) as "the background of awareness which sets the context for experience ... [a]n example is our sense of orientation or rightness in a familiar environment" (p. 10). Fringe consciousness situates a person, preventing the feeling that one has simply popped into the world at that moment.

Moving on, then, to the interrogation, self-report from H.M. suggests that one phenomenological quality of anterograde amnesia is a pervasive anxiety about what may have happened just beyond the edge of the truncated duration block of the living present:

> Right now, I'm wondering, have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? ... It's like waking from a dream; I just don't remember ... Every day is alone, in itself. Whatever enjoyment I've had, whatever sorrow I've had. ***Hilts (1995, p. 138)***

On another occasion, during an exchange between H.M. and researcher William Marslen-Wilson (relayed by Hilts, 1995) the patient confessed to worrying about giving the wrong answer, whether during formal testing or just in conversation.

> It is a constant effort, Henry said. You must always "wonder how is it going to affect others? Is that the way to do it? Is it the right way?" ... Asked if he worried about these things a lot, struggled with his thought to get right answers, he said yes, all the time. "But why?" "I don't know," said Henry (p. 140).

The experience of disordered fringe consciousness is evident in amnesic patient Clive Wearing, a distinguished British musicologist, conductor, and keyboardist whose amnesia resulted from herpes encephalitis, a condition that can produce severe damage to the hippocampus while leaving the rest of the brain relatively unscathed. Wearing has been featured in several television documentaries, one of which, at the time of this writing, can be viewed on the World Wide Web.[6] The video clip opens with the camera panning in on Wearing and his wife sitting in a city park.

Wife:	"Do you know how we got here?"
Wearing:	"No."
Wife:	"You don't remember sitting down?"
Wearing:	"No."
Wife:	"I reckon we've been here about 10 min at least."
Wearing:	"Well, I've no knowledge of it. My eyes only started working now ..."
Wife:	"And do you feel absolutely normal?"
Wearing:	"Not absolutely normal, no. I'm completely confused."
Wife:	"Confused?"
Wearing (agitatedly):	"Yes. If you've never eaten anything, never tasted anything, never touched anything, never smelled something, what right have you to assume you're alive?"
Wife:	"Hmm. But you are."
Wearing:	"Apparently, yes. But I'd like to know what the hell's been going on!"

(In making these pronouncements about his senses, it is clear that Wearing is speaking figuratively, not literally.) Thus, for Wearing, too, each waking moment feels as though he is just waking up from sleep. The journal that he keeps is filled with multiple entries that all contain variants of the same message. For example, directly under the entry "10:49 am I AM TOTALLY AWAKE—FIRST TIME," which appears on the first line of a page, is a second entry "11:05 am I AM PERFECTLY AWAKE—FIRST TIME," and so on. When left alone in his room, the patient fills entire pages in this way with entries made at intervals ranging from 5 to 45 min.

These anecdotes capture an essential quality of the conscious phenomenology of the MTL amnesic patient, the near-continual experience of just having awakened from unconscious sleep. The plight of the MTL amnesic patient, then, is to be fully cognizant of, if not preoccupied by, the fact that one is not cognizant of the daily events of one's life.

CONCLUSIONS

The contributions of the hippocampus to conscious awareness were once thought to be minimal, in that its strong association with LTM encoding would have seemed to contribute little to the ongoing operations that comprise the contents of our moment-to-moment conscious awareness—perception, retrieval and contemplation of semantic knowledge, language processing (receptive and productive), social interactions, and so on. More recently, however, a growing body of evidence suggests that hippocampus may contribute importantly to the quality of conscious experience, via a putative role in such operations as relational processing, the rapid encoding of flexible associations, and scene construction. Further, there is a fundamental role for the hippocampus in determining the width of the stream of consciousness and the integrity of fringe consciousness. This chapter has highlighted several important questions that remain to be resolved. Physiologically, what are the contributions of the MTL to the quality and quantity of activity in the main complex of brain structures whose activity underlies awareness (Laureys, 2005; Tononi, 2004)? Psychologically, what explains the phenomenological difference between autonoetic and noetic awareness? Empirically, are the recent findings that suggest a necessary role for the MTL in some kinds of STM and in the ability to imagine new experiences replicable and generalizeable?

EPILOGUE: A FINAL WORD

> "What happened to you? ... " asked researcher Marslen-Wilson. "Well," said Henry, "I think of an operation. I have an argument with myself right there—did the knife slip a little? Or was it a thing that's naturally caused when you have this kind of operation?" "That caused what?" Marslen-Wilson asked. "The loss of memory, but not of reality," Henry said.
> ***Hilts (1995, pp. 139–140)***

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NOTES

1. Anecdotes relating to H.M.'s life as a celebrated patient can be found in Corkin (2013).
2. As we shall see, although there is ongoing controversy about the quality of some types of premorbid memories in these patients, neurologists find it "clinically useful to describe amnesia as a failure to learn new information, which is distinct from a retrieval deficit" (Mega, 2003, p. 41).
3. Details about the testing procedures for each of the tests listed here, as well as the brain systems and mental abilities that they are intended to measure, can be found in Lezak (1995).
4. *Dementia* is distinguished from *amnesia* by the clinical presentation, along with a memory impairment, of marked impairment of one or more nonmnemonic domains of behavior, including perception, receptive or productive language, executive control, and motor control.
5. Another study has described a deficit in MTL patients in 4-s delayed recognition of visually presented stimuli that impose no explicit relational binding requirements (location of squares, face identity, color identity, Olson et al., 2006a). However, in view of the small number of amnesic subjects tested (three) and the heterogeneity of their lesions, it would be premature to draw strong conclusions about the implications of this one study for our understanding of the role of the MTL in STM.
6. http://www.youtube.com/watch?v=OmkiMlvLKto&mode=related&search=.

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CHAPTER

22

Syndromes of Transient Amnesia

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OUTLINE

For most of us, transient lapses of memory are a minor and, at worst, irritating feature of everyday life. They are usually brief, item specific, and alleviated by a pertinent cue. Occasionally, we find ourselves with no recollection for longer periods of activity. Some such experiences raise intriguing questions about the relation between consciousness and memory. When the long-distance truck driver suddenly "comes to," realizing that he remembers nothing of the last 10 miles driven, has he merely failed to form long-term memories during that period, or was his consciousness in some way impaired throughout?

Clinical syndromes of transient amnesia are more dramatic. The patient typically presents with a story of sudden onset but self-limiting memory impairment, during which he was unable to retain new information (anterograde amnesia) or remember past events (retrograde amnesia). Despite this, he was able to carry out complex, purposeful actions and engage in conversation. He appeared, in other words, despite his memory loss, to be fully "conscious," at least in the neurosurgical sense of the term—able to respond to events in the well-integrated fashion most of us can manage while awake. But what of the contents of his consciousness? In some sense, his awareness, and self-awareness, were undoubtedly affected by his amnesia during the attack. How does memory loss impact on our experience?

In this chapter, we first describe features of the principle clinical syndromes of transient amnesia—transient global amnesia (TGA), transient epileptic amnesia (TEA), and psychogenic amnesia—and then discuss several interactions between amnesia and consciousness: (i) the effect of transient amnesia on consciousness in its key senses of wakefulness and awareness, (ii) its effect, specifically, on the consciousness of self, (iii) the distinction between conscious but unremembered behavior and the complex "unconscious" behaviors known as automatisms.

TRANSIENT GLOBAL AMNESIA

TGA is a striking clinical syndrome, characterized by the abrupt onset of a profound but transient

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anterograde amnesia, together with a variable degree of retrograde amnesia. The name was coined in 1964 by Fisher and Adams in a paper describing the clinical features of 17 patients (Fisher and Adams, 1964), although several authors published accounts of similar cases using different terminology at around the same time (Bender, 1960; Poser and Ziegler, 1960; Guyotat and Courjon, 1956; Evans, 1966). It has been suggested (Hodges, 1991) that, prior to this period, the syndrome remained buried within the literature on psychogenic, or hysterical amnesia.

> A 63 year-old, recently retired teacher was brought to the Accident and Emergency department by her husband. One hour earlier, she had telephoned him from the local gym where she had just finished her daily workout and said: "I don't know where I am. What's happening? Where am I?" Despite his reassurances, she had continued to repeat the same questions. On examination, she was disoriented in time and place, had no recollection for events of the previous week and was unable to retain new information—including the identity of the attending doctor. Besides the amnesia, there were no other neurological signs or symptoms. A CT scan of the head was normal. Over the following 6 hours, her memory deficit gradually resolved although she was left with a dense "gap" for the episode of transient amnesia itself and for the preceding trip to the gym.

Clinical Features

The most widely accepted diagnostic criteria for TGA were introduced by Hodges and Warlow (1990a):

1. attacks must be witnessed and information available from a capable observer who was present for most of the attack
2. there must be a clear-cut anterograde amnesia during the attack
3. clouding of consciousness and loss of personal identity must be absent, and the cognitive deficit must be limited to amnesia (i.e., no aphasia, apraxia, etc.)
4. there should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards
5. epileptic features must be absent
6. attacks must resolve within 24 h
7. patients with recent head injury or active epilepsy (i.e., remaining on medication or one seizure in the past 2 years) are excluded.

TGA is a relatively infrequent occurrence, with an annual incidence of between 3 and 10 per 100,000 (Hodges, 1991). Nonetheless, it has attracted considerable attention in the scientific literature and well over 1500 cases have been described (Quinette et al., 2006). The mean age of onset is 62 years (Hodges, 1991) and the condition occurs almost exclusively in individuals between the ages of 40 and 80. In younger people, a similar phenomenon may occur following head injury (Haas and Ross, 1986) but this is usually excluded from the rubric of TGA. A review of all literature cases (Quinette et al., 2006) failed to find any significant difference in frequency between the sexes.

Ever since the early reports, it has been noticed that TGA is often preceded by a period of intense emotional or physical stress. Frequently reported triggers include immersion in cold water, sexual intercourse, receipt of distressing news or a heated argument. The onset of anterograde amnesia is betrayed by repetitive questioning, often related to attempts at self-orientation such as "What day is it?" or "What am I doing here?" Although a small amount of information can be retained for a few seconds, it is rapidly lost when the patient's attention shifts. The retrograde amnesia may cover a few hours prior to the attack onset or be much more extensive. Witnesses usually describe the patient as "confused," but careful examination reveals that there is no impairment of conscious level or of other cognitive functions such as attention, language or perception. In contrast to psychogenic forms of amnesia, knowledge of personal identity is always retained. Non-specific symptoms such as headache, nausea or dizziness may be present, but there are no focal neurological deficits. Symptoms usually resolve gradually over 4–10 h, with recovery of retrograde memory occurring more rapidly than anterograde memory (Kapur et al., 1998). The majority of patients, therefore, do not present to a neurologist in the acute phase. After recovery, a dense amnesic gap for the attack itself persists. There is no clinically significant, long-term cognitive impairment, although more subtle deficits have been reported. Recurrence is rare and occurs at a rate of around 6–10% (Quinette et al., 2006; Bartsch and Deuschl, 2010) per year.

Etiology

Ever since the first descriptions of TGA, there has been considerable debate about its etiology and this debate remains unresolved. TGA-like attacks have been reported in association with brain tumors, sodium amobarbital injection, high altitude, herpes simplex encephalitis, and the use of marijuana. This suggests that TGA could be a "final common pathway" with numerous potential triggers.

Epilepsy: Fisher and Adams believed that the most likely explanation for TGA was cerebral seizure activity and several other early authors also maintained this position (Godlewski, 1968; Lou, 1968; Tharp, 1969; Cantor, 1971; Gilbert, 1978; Rowan and Protass, 1979; Deisenhammer, 1981). This idea has now largely fallen out of favor for a number of reasons. Epilepsy is, by definition, a recurrent condition whereas patients

usually experience one or two episodes of TGA in their lifetime. The duration of most TGA attacks is also uncharacteristically long for epileptic seizures. Other common features of generalized or partial epilepsy are absent during the attack. Finally, EEG recordings during or after a TGA attack are almost invariably normal or show only minor non-specific abnormalities (Miller et al., 1987; Jacome, 1989). However, in a series of 114 patients followed up over a mean of 34 months following TGA, Hodges and Warlow (1990b) identified a small subset (7%) that subsequently developed epilepsy. These patients, in keeping with more recent descriptions of TEA (see below), typically had briefer and recurrent amnesic episodes.

Migraine: Several authors have proposed a causal link between migraine and TGA (Gilbert and Benson, 1972; Laplane and Truelle, 1974; Olivarius and Jensen, 1979; Caplan, 1981). A past history of migraine has been reported in up to 30% of patients with TGA (Hodges and Warlow, 1990a), a significantly higher proportion than in controls, and migrainous features, particularly headache and nausea, accompany about 20% of TGA attacks (Hodges, 1991). A large cohort study in Taiwan recently found that the relative risk of TGA over a 3-year period was 2.5 times higher amongst 158,000 migraineurs than in a matched, control cohort (Lin et al., 2014). Olesen and Jorgensen (1986) suggested that the underlying pathological mechanism behind both TGA and migraine might be the experimentally observed phenomenon of spreading depression. A range of stimuli, applied directly to the cortex, may induce a wave of depolarization that spreads at a rate of 3–5 mm/min and reduces cerebral blood flow for a period of about 1 h. Spreading depression can be elicited in the hippocampus of experimental animals, in which it provokes a transient period of amnesia. According to the migraine hypothesis, emotional or physical stressors lead to the release of glutamate in the hippocampus triggering spreading depression and hippocampal dysfunction. Critics argue that the migraine hypothesis does not readily account for the age range of TGA or its low recurrence rate.

Arterial ischemia: Permanent amnesia can result from stroke, most frequently when involving the thalamus bilaterally (Schmahmann, 2003). It is, therefore, reasonable to ask whether TGA is a form of transient ischemic attack (TIA). A number of studies have, however, shown that patients with TGA have fewer vascular risk factors than control subjects with TIA and a more favorable prognosis in terms of mortality and cerebrovascular events (Hodges and Warlow, 1990a; Quinette et al., 2006; Mangla et al., 2014). Recent imaging studies (below) have shown changes in the hippocampus in the days following attacks but the features are not typical of standard ischemic stroke.

Venous ischemia: Another theory, originated by Lewis (1998), postulates that the well-recognized triggers of TGA lead to an increase in central venous pressure. In susceptible individuals, this could cause venous ischemia in medial temporal and diencephalic brain regions. Support for this idea comes from reports of jugular valve insufficiency leading to retrograde venous flow during a Valsalva-like maneuver in 73.4% of TGA patients compared with 35.7% of controls (Sander and Sander, 2005).

Psychological: Emotional stress as a trigger for TGA is well recognized. It has been reported that TGA patients are more likely to have phobic personality traits (Inzitari et al., 1997) and a past history and family history of psychiatric disease (Pantoni et al., 2005) than normal control subjects and patients with transient ischemic attacks. These authors propose that, in such individuals, hyperventilation in response to a stressful situation leads to a reduction of cerebral blood flow in medial temporal regions and consequent transient amnesia (Pantoni et al., 2000).

Neuroimaging

For many years, structural brain imaging was thought to be entirely normal in the majority of TGA cases. However, with the development of more sensitive techniques, a number of studies has now shown that, in the period immediately following a TGA attack (within 24–72 h of onset), diffusion weighted magnetic resonance imaging can detect small (1–2 mm), punctate hippocampal lesions, indicating areas of restricted diffusion, in about 70% of patients (Bartsch et al., 2006). These lesions are most frequently found in the CA1 subfield of the hippocampus, a region known to be particularly sensitive to hypoxic injury, and may be unilateral or bilateral (see Figure 22.1). At repeat scanning 4–6 months later, the lesions are no longer detectable and memory function has returned to normal. The pathophysiology of these abnormalities remains unclear although they have been used to support hypotheses of both arterial and venous etiologies (Sander and Sander, 2005; Winbeck et al., 2005).

It seems unlikely that these very small, and often unilateral hippocampal lesions could be the sole pathological disturbance in TGA, and result in such profound memory disturbance. After all, the surgical excision of an entire hippocampus is sometimes used to treat epilepsy and usually results in no, or only a minor, decline in memory function. A recent study (Peer et al., 2014) used functional magnetic resonance imaging (fMRI) of the resting state to examine changes in connectivity between different brain regions in 12 patients in the throes of TGA. During the amnesic

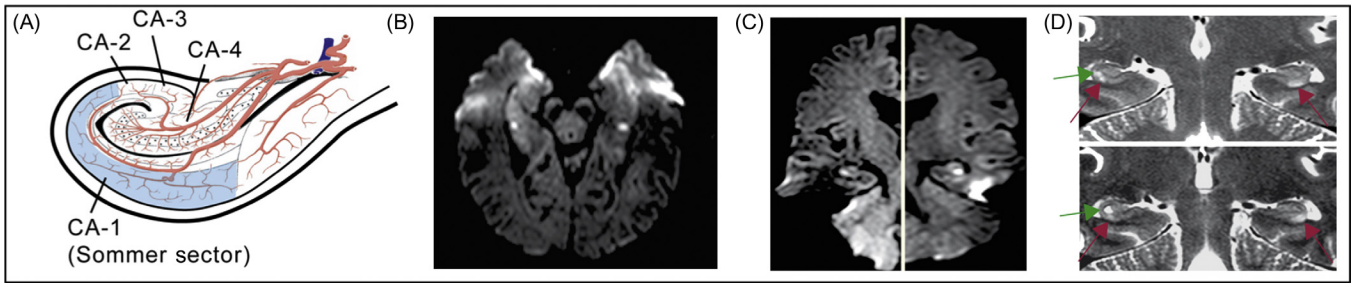

FIGURE 22.1 Magnetic resonance imaging in transient global amnesia. (A) Hippocampal subfields; (B)–(D) Typical lesions seen in the hippocampus within 48 h after onset on axial and coronal diffusion weighted and T2 weighted sequences, respectively. Note in this case the bilateral T2 lesions in the CA-1 sector of the cornu ammonis (red arrow) extending over 4–5 mm (slice thickness 2 mm) which are clearly separated from the cavity of the pre-existing vestigial hippocampal sulcus (green arrow) located in deeper subcortical layers in the vicinity of the gyrus dentatus (Bartsch et al., 2006). *Source: Reproduced with permission of Oxford University Press.*

attack, the coherence of activation levels across a wide "episodic memory network" (including the medial temporal lobes, thalamus, posterior cingulate cortex, orbitofrontal cortex, and several other structures) was greatly reduced compared with that observed in healthy controls. This indicates that the functional disturbance underlying TGA extends much further than the hippocampus. Importantly, however, the authors failed to detect any disruption of connectivity across other functional brain networks, including those involved in motor and language processing. Patients in the immediately post-acute phase of TGA ($n = 7$) showed a milder disruption of functional connectivity. These abnormalities appeared to have entirely recovered in a subgroup of patients who were rescanned several months later.

Neuropsychology

Formal neuropsychological testing during a TGA attack bears out the clinical impression. The patient is able to hold and manipulate information normally in working memory as tested, for example, by backward digit span (Quinette et al., 2003). However, on tests of long-term anterograde memory, such as delayed recall of a word list, story or complex figure performance is at floor (Hodges, 1991). Interestingly, despite having no recollection of stimuli encountered during the attack, patients nonetheless demonstrate perceptual priming (Kapur et al., 1996). Perceptual priming occurs when the perception of a stimulus is affected by the prior, conscious or unconscious, presentation of another stimulus. This result suggests that, as in the case of permanent amnesia from medial temporal lobe or diencephalic damage, implicit memory remains intact.

During the episode, patients also lose access to memories acquired prior to the onset of the attack (retrograde amnesia) to some degree. The initial acquisition of such memories is, of course, beyond the reach of experimental manipulation, so assessment of retrograde amnesia can be difficult. In the acute and recovery phase of TGA, probes of memory for both personal and public facts and events have revealed variable patterns of impairment across individuals. In general, accounts of personally experienced episodes are "curiously empty and lacking in color, as if reduced to the bare bones of memory" (Hodges and Ward, 1989). They lack what has been called "autonoetic consciousness"—the feeling of having experienced the past episode oneself (Wheeler et al., 1997). Retrograde amnesia may affect memories from across the lifespan (Guillery-Girard et al., 2004) or from a more limited time period prior to the attack (Kritchevsky, 1997).

During the recovery phase, retrograde memory improves more rapidly than anterograde memory. In some cases, memories are recovered in chronological order whereas in others more salient, detailed memories return first no matter what age they are (Kapur et al., 1998; Guillery-Girard et al., 2004). Anterograde memory impairment lasts much longer than is clinically apparent. Deficits, particularly in story recall, can be demonstrated several days and, in some cases, several months later. Following recovery from TGA, patients are left with complete amnesia for events that occurred during the attack. There is also usually a short, permanent retrograde amnesia for events that occurred in the 1–2 h leading up to the attack (Hodges, 1991).

TRANSIENT EPILEPTIC AMNESIA

Amnesia is a cardinal feature of the majority of epileptic seizures, particularly generalized and complex partial seizures. This amnesia is usually only one manifestation of a wide disruption of cerebral function that results in loss or alteration of consciousness during the ictus. However, it has been recognized for over a century that, occasionally, memory impairment may the sole feature

of epileptic seizures. In 1888, the renowned British neurologist Hughlings-Jackson described the case of Dr. Z, a medical practitioner who suffered from an unusual variety of epilepsy (Hughlings-Jackson, 1888). During seizures, he retained consciousness and was able to engage in complex, purposeful behavior for which he was later amnesic. On one occasion he felt the onset of a seizure when just about to examine a patient. During this attack, he correctly diagnosed pneumonia, prescribed treatment and wrote in the patient's notes, but later had no recollection of having done so.

When Fisher and Adams first described the syndrome of TGA (Fisher and Adams, 1964), they concluded that it was most likely due to cerebral seizure activity. It is now clear that this is not true for the majority of TGA attacks (see above). However, despite using stringent diagnostic criteria for TGA, Hodges and Warlow discovered that a significant minority (7%) of the patients in their series went on to develop complex partial seizures (Hodges and Warlow, 1990a). This observation, together with a steady trickle of case reports in the literature, has led to increasing interest in the syndrome of TEA—a term, introduced by Kapur (Kapur and Markowitsch, 1990), which emphasizes the similarity to, but also the differences from TGA.

> A 58-year old carpet fitter experienced 28 episodes of transient amnesia over 18 months. All occurred upon waking in the night and lasted about 20 minutes. He repetitively questioned his wife, but was responsive and coherent throughout. During one attack he was unable to recall the death of his brother a few days earlier. Routine EEG and MRI were normal. Lamotrigine abolished the attacks but they briefly returned, with associated olfactory hallucinations, during a period of non-compliance, and ceased again when he restarted the medication. At interview, he described rapid forgetting of recently acquired memories, patchy loss of salient autobiographical memories from the past 30 years, such as his wife's abdominal surgery and the wedding of his son, and significant new difficulties navigating around his local area.

The diagnosis of TEA is made when a patient meets the following diagnostic criteria (Zeman et al., 1998; Butler et al., 2007):

1. a history of recurrent witnessed episodes of transient amnesia
2. cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
3. evidence for a diagnosis of epilepsy based on one or more of the following:
   - **a.** epileptiform abnormalities on electroencephalography
   - **b.** the concurrent onset of other clinical features of epilepsy (e.g., lip-smacking, olfactory hallucinations)
   - **c.** a clear-cut response to anticonvulsant therapy.

Clinical Features

Review of the literature and our detailed study of 50 cases (Zeman et al., 1998; Butler et al., 2007; Butler and Zeman, 2008), reveal TEA to have many consistent features. As with TGA, TEA typically begins in late middle to old age (mean 62 years). Why this age group should be particularly susceptible to both conditions remains uncertain. The amnestic attacks are characterized by a mixed anterograde and retrograde amnesia. In comparison with TGA, there is considerable variation in the relative extent of these two components. Some patients, for example, have incomplete anterograde amnesia and are later able to "remember not having been able to remember." Other patients have minimal or no obvious retrograde amnesia and only realize they have had an attack when they are later unable to recall part of their day. The preservation of other cognitive functions such as attention, perception, language, and executive function is revealed by the patient's continued ability to respond appropriately to conversation and act in a purposeful manner. In our series, there were reports of patients driving, winning a hand at bridge, sight-reading piano pieces and translating text from French into English. Certain additional features may accompany the amnesia. Most commonly (in almost half the cases in our series), patients experience hallucinations of smell or taste which are usually unpleasant—"like burning rubber," "metallic," "rotten." The attack typically lasts around 30 min to 1 h. However, much longer episodes, even persisting for several days, have been reported and may reflect non-convulsive status epilepticus (Lee et al., 1992; Vuilleumier et al., 1996). Whereas TGA is often a one-off event, patients with TEA experience recurrent attacks of memory loss, with an average frequency of around 13 per year (Butler et al., 2007).

There is a close and intriguing relationship between TEA and sleep. Approximately three quarters of patients will have at least one amnesic attack upon waking and one quarter only ever experience amnesia in this context (Butler et al., 2007). Some have described such attacks as very similar to, only more persistent than, the disorientation many of us have briefly felt upon waking in an unfamiliar place. One patient noted in his journal: "Woke up at 3.30 am—had no idea where I was. After stumbling around to find a light switch, found that I was in a small room in the P... Hotel in Milan. Initially had no idea why I was here. Found documents in room with my itinerary...Gradually began to recall that I was on a trip to attend meetings in Milan and Lugano." The reason for the relationship between sleep and TEA is not yet clear. It may be that the transition from sleep to waking acts as a trigger to an epileptogenic area in

memory-related brain regions. Alternatively, amnesia upon waking may reflect persistent postictal dysfunction of such brain regions following a seizure during sleep. In one case, for example, morning amnesia was always preceded by a brief arousal at around 2 am when the patient sat up in bed, staring and said "Oh, the smell, the smell" before going straight back to sleep.

Given the apparent similarity between TEA attacks and the amnesia observed in TGA and other forms of medial temporal lobe amnesia, it can expected that TEA results from disruption of function in the hippocampus and related structures. Certain clinical features, including the frequent co-occurrence of olfactory hallucinosis and the predominance of temporal lobe epileptiform abnormalities on the EEG, would support this hypothesis. One patient, who was admitted to hospital during a very prolonged episode of epileptic amnesia, underwent ictal FDG-PET scanning which revealed focal hypermetabolism in the left anterior hippocampus (see Figure 22.2). One month later, this abnormality had resolved. Structural magnetic resonance imaging reveals that, in comparison with matched, healthy control subjects, TEA patients have a reduction in volume of the hippocampus bilaterally of about 8% (Butler et al., 2009). There is also volume loss in nearby brain regions including the perirhinal and orbitofrontal cortices (Butler et al., 2013). This evidence of subtle focal pathology in memory-related structures corresponds to mild, interictal decrements in performance on standardized tests of anterograde memory (Butler et al., 2009, 2013). Importantly, however, patients usually still perform well within the normal range on these memory tasks.

In common with other forms of late-onset epilepsy, TEA generally responds well to a low dose of anticonvulsant medication. Nevertheless, despite complete cessation of acute amnesic attacks, the patient often complains of ongoing memory difficulties. Two problems are particularly common.

Accelerated Long-Term Forgetting (ALF)

About 50% of patients with TEA report that, although they are able to retain new information over the short-term, these memories evaporate over a few days or weeks. For example, immediately after returning from holiday in the Rhineland, a patient gave an intricately narrated slide presentation to his family. However, 2 months later he had no recollection of his trip to Germany or of the slideshow. This problem can be extremely debilitating, and led to the early retirement of a number of patients in our series. However, it falls under the radar of standard neuropsychological tests, which typically assess retention of information over a period of less than 1 h. Since TEA patients usually perform very well on such tests, their difficulties are sometimes mislabeled as "psychological."

However, if memory for a story, a list of words, a series of designs or for real-life events is tested at longer intervals, a clear difference emerges between TEA patients and neurologically normal control subjects (see Figure 22.3) (Butler et al., 2007; Muhlert et al., 2010). This difference is typically detected over intervals of days or weeks, but recent evidence suggests that it may become apparent over as little as a few hours after learning (Atherton et al., 2014; Hoefeijzers et al., 2015). The cause of ALF is not yet known. It may be related to seizure activity (presumably sub-clinical, since frank seizures were no longer present in the patients tested) or to underlying structural pathology in memory-related brain areas. With regard to current models of memory, ALF has been interpreted by some as representing a deficit in long-term "systems"

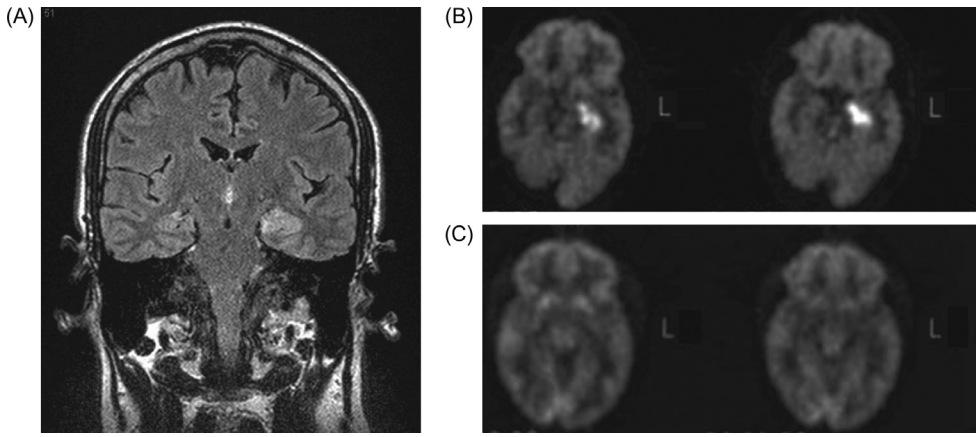

FIGURE 22.2 Neuroimaging during a prolonged episode of transient epileptic amnesia. (A) FLAIR MRI scanning during a prolonged episode of transient epileptic amnesia revealed hyperintensity in the left hippocampus. (B) FDG-PET scanning during the same episode showed hypermetabolism localized to the left anterior hippocampus. (C) This region had returned to normal 1 month later.

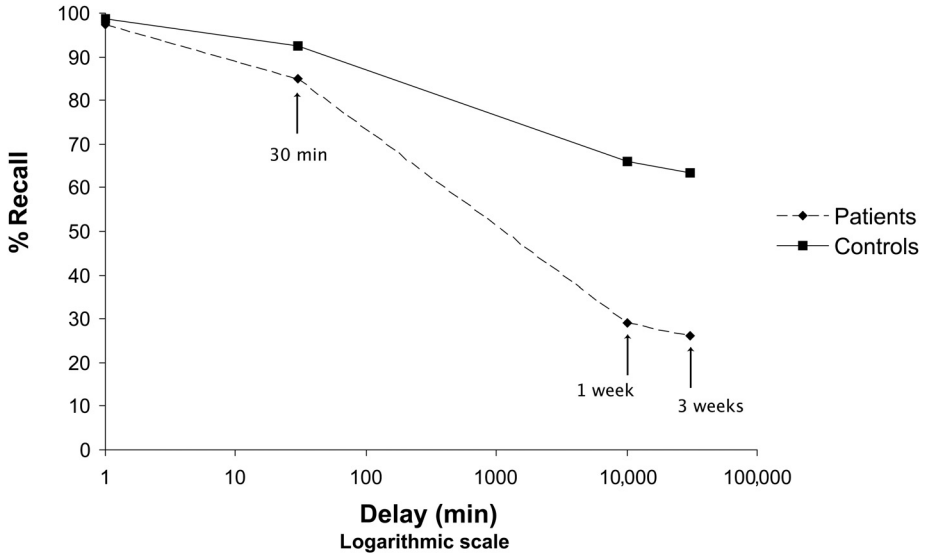

FIGURE 22.3 Accelerated Long-Term Forgetting in transient epileptic amnesia. 24 patients with transient epileptic amnesia and 24 normal controls learnt a list of 15 words. Despite normal learning and initial recall, patients showed accelerated forgetting over 3 weeks (Butler et al., 2007). *Source: Reproduced with permission from John Wiley and Sons Inc.*

consolidation, a hypothetical process by which memory traces are reorganized in the brain over time and thus become more resistant to disruption.

Autobiographical Memory Loss

Even more common amongst TEA patients is the complaint, in about 70%, of a patchy loss of remote, salient autobiographical memories, often extending back over many decades of their life. They frequently report, for example, being unable to remember family holidays or weddings from the past 20 to 30 years, even when prompted with photographs. As mentioned above, autobiographical memory is difficult to assess formally since the original encoding episode is beyond the control of the experimenter. This problem is enhanced in TEA by the patchy nature of the memory loss. However, using semi-structured interviews in which subjects are requested to provide detailed episodic memories for each decade of their lives, we have exposed significant differences between patients and controls in the quality of memories for events that occurred even 30 or 40 years prior to testing (see Figure 22.4) (Butler et al., 2007; Milton et al., 2010).

Remote memory loss in the absence of significant impairment of anterograde memory on standard tests has been termed "focal retrograde amnesia." Some authorities have questioned whether this can ever be caused by purely "organic" brain disease, rather than primarily "psychogenic" mechanisms (Kopelman, 2000), and its pathophysiological basis is still far from clear. Neuroimaging studies in healthy volunteers have identified an "autobiographical memory network" of brain regions (including the hippocampus, the parahippocampal gyrus, the lateral temporal lobes, the posterior cingulate, the temporoparietal junction, the cerebellum, and diverse areas of the frontal lobes including the medial prefrontal cortex) that typically engages when an individual is recollecting salient personal events from his or her past (Milton et al., 2012). This network overlaps substantially with the so-called "default mode network" that activates during quiet rest (Svoboda et al., 2006). An fMRI study examining autobiographical memory in TEA patients revealed hypoactivation in parts of this autobiographical memory network, particularly the right parahippocampal cortex, and altered effective connectivity between network regions (see Figure 22.5) (Buckner et al., 2008). Further exploration of remote memory loss in TEA is needed, but the phenomenon certainly has potential to reveal much about the brain processes behind autobiographical recollection.

A third interictal problem occurs in some patients. In our series, 18/50 patients complained of impairment of topographical memory—difficulty in recognizing familiar landmarks and in navigating previously familiar routes.

PSYCHOGENIC AMNESIA

Cases of transient amnesia straddle the border between psychiatry and neurology, and highlight just how artificial and misleading the traditional distinction between these two disciplines can be (Zeman, 2014). As discussed above, TGA, generally thought of as a "neurological" condition with hints of pathology in the

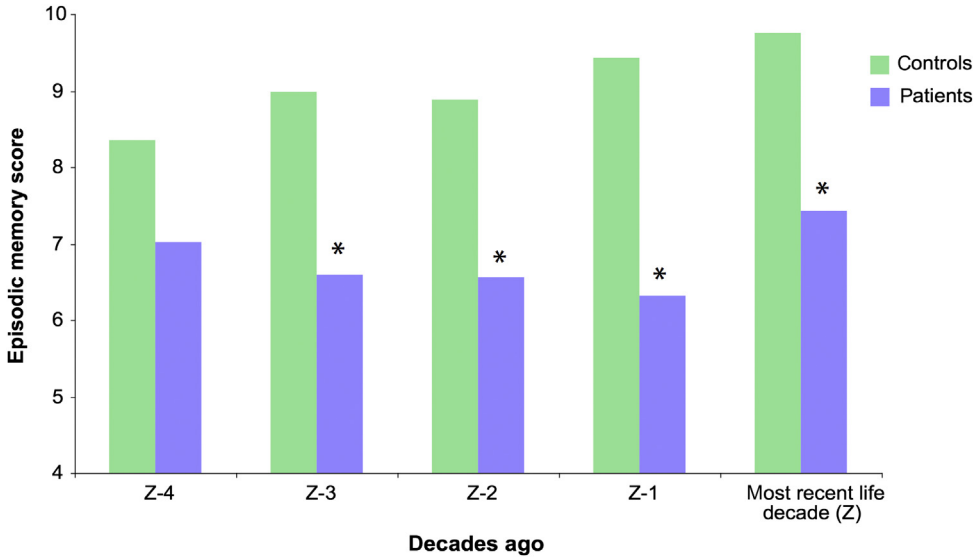

FIGURE 22.4 Autobiographical memory impairment in transient epileptic amnesia. Mean scores of transient epileptic amnesia patients ($n = 22$) and matched control subjects ($n = 18$) on the episodic memory component of the Modified Autobiographical Memory Interview ($^*p < 0.001$) (Butler et al., 2007). *Source: Reproduced with permission from John Wiley and Sons Inc.*

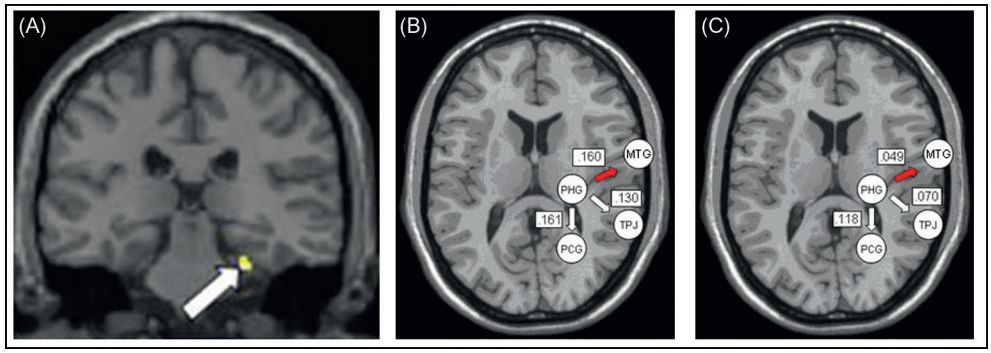

FIGURE 22.5 Functional imaging of autobiographical memory retrieval in transient epileptic amnesia. (A) Within a medial temporal lobe region of interest, patients with transient epileptic amnesia showed reduced activation in the right parahippocampal cortex while retrieving autobiographical memories. Direct causal modeling in healthy controls (B) and TEA patients (C) revealed the patients to have reduced effective connectivity between the parahippocampal gyrus (PHG) and the middle temporal gyrus (MTG) in the right hemisphere, two key regions in the autobiographical memory network (Milton et al., 2012). Other abbreviations: TPJ, temporoparietal junction; PCG, posterior cingulate gyrus.

medial temporal lobes, can be triggered by psychological stressors and may even be more common among people with certain personality traits. Other instances of transient amnesia, in which there is no obvious neuropathological explanation, may be more easily explained in primarily psychological terms. Such cases, variably termed "psychogenic amnesia," "functional amnesia," "dissociative amnesia," or "hysterical amnesia," are characterized by:

> a memory loss that is attributable to an instigating event or process that does not result in insult, injury or disease affecting brain tissue, but that produces more forgetting than would normally occur in the absence of that instigating event or process. ***Schacter and Kihlstrom (1989)***

Psychogenic amnesia may be divided into two main subtypes after Kopelman et al. (2002): situation-specific psychogenic amnesia and global psychogenic amnesia. In the former, there is a temporally circumscribed amnesia for a specific and usually emotionally charged event such as a criminal offense. The degree of amnesia is proportional to the violence of the offense, and up to 30% of convicted homicide cases claim amnesia at trial (Pyszora et al., 2003). Rates are higher in the so-called "crimes of passion," where a murder is unpremeditated and associated with extreme emotional arousal, and if alcohol or drug intoxication is involved. Although the mechanism of this type of amnesia is unclear, it is unlikely to be due to malingering, or

"putting it on," and in many legal systems, amnesia does not in itself constitute a defense. On occasions, the defendant may claim decreased responsibility for a crime on account of an "intrinsic" brain disorder such as epilepsy, sleepwalking, or hypoglycemia. Although such conditions are only very rarely implicated in violent crime, they can result in amnesia and pose considerable diagnostic challenges.

Global psychogenic amnesia is not restricted to a single event but involves memory loss for a large swathe of the patient's life.

> A 43-year old construction worker was brought to hospital by colleagues. That morning, he had suffered a minor head injury when his fork-lift truck collided, at low speed, with an earth bank. Since then, he had a "complete loss of memory," with no recollection of any past events. He was unable to remember his own name and failed to recognize his colleagues or, when she arrived, his recently estranged wife. Despite this, there was no apparent difficulty in learning new information—he could recount in detail the events following his arrival at hospital. MRI of the brain was normal. It later emerged that, since an acrimonious separation from his wife, he had been showing signs of depression and drinking heavily. He had suffered a period of concussion following a motorcycle accident in his 20s.

The onset typically follows a stressful experience, such as a marital or financial crisis, and there is often a background of depression or alcohol abuse (Kritchevsky et al., 2004). There is frequently a history of "organic" transient amnesia (Berrington et al., 1956). Knowledge of personal identity is often impaired: this is not a feature of organic amnesia. There may be a period of wandering, "psychogenic fugue" that typically lasts for a few hours or days. There is usually a relative preservation of anterograde memory, so that patients are able to "relearn" about themselves, although they may complain that such memories lack the experiential aspect, or "autonoetic consciousness," that defines true episodic memory. Recovery is frequently protracted and incomplete. The brain mechanisms responsible for psychogenic amnesia are unknown. It has been proposed that there is a functional disconnection between memory storage and retrieval mechanisms in the frontal and temporal lobes (Markowitsch, 2003) and functional neuroimaging studies have revealed decreased brain metabolism, at baseline and during attempted memory retrieval, in the right frontal cortex (Markowitsch, 1999).

HEAD INJURY

Following closed head injury, there is often a period of posttraumatic amnesia (PTA) during which new learning is grossly impaired and there is retrograde memory loss for events leading up to the head injury. This can occur even in mild injuries which produce no coma. The retrograde amnesia gradually shrinks until the patient can recall all but the brief instant preceding the head injury. The duration of the anterograde amnesia is predictive of the final neuropsychological outcome (Levin et al., 1979). The memory deficits are usually accompanied by a variety of other cognitive and behavioral problems including impaired attention, agitation, lethargy and disinhibited behavior. The pathological mechanisms underlying PTA may be a combination of focal contusions, characteristically in the frontal or temporal lobes, diffuse axonal injury and secondary effects of hypoxia or ischemia. Sometimes, a mild head injury such as sustained during sport, may trigger an episode of typical TGA with repetitive questioning. This tends to occur in people below the usual age range for TGA, and may be recurrent (Haas and Ross, 1986).

DRUGS

A period of transient memory impairment can also result from administration of several types of drug including benzodiazepines, anticholinergics, ketamine (an NMDA receptor antagonist), and alcohol. Benzodiazepines, particularly midazolam, are widely used in clinical practice as an adjunct to or even a replacement for anesthesia. The resultant, short-lived and predominantly anterograde amnesia is thought to result from specific impairment of memory encoding, not just a generalized reduction in alertness (Curran and Birch, 1991). Retrograde memory is unaffected. Benzodiazepines act as agonists at inhibitory $GABA_A$ receptors and the specificity of the cognitive deficit may be partially due to the abundance of these receptors in the hippocampal complex. Declarative, conscious memories appear to be specifically targeted: certain types of procedural memory and perceptual priming have been shown to remain intact (Thomas-Antérion et al., 1999; Arndt et al., 2004).

TRANSIENT AMNESIA AND CONSCIOUSNESS

The amnesic syndrome, in both its permanent and transient forms, offers insights into the relationships between memory and consciousness. In this closing section, we will explore these with regard to transient amnesia. Neither "memory" nor "consciousness" are straightforward, unitary concepts so an initial clarification of terms is required (Zeman, 2002). We will then consider three aspects of their relationships: (i) the effect of transient amnesia on consciousness, in the

senses of "wakefulness" and "awareness"; (ii) the effect of transient amnesia on the consciousness of self; (iii) the distinction between conscious but unremembered behavior and "automatism."

The syndromes we have described in this chapter affect the ability to form or retrieve long-term declarative memories, but leave the following kinds of memory intact: working or "short-term" memory (the ability to hold information "in mind" and to manipulate it mentally); perceptual memory (underlying the processes of perceptual classification that allow us, for example, to identify glimpses of the same object from different views); semantic memory (our database of explicit knowledge about language and the world); and procedural memory (a collective term used to refer to memories that guide behavior without requirement for explicit recollection—like memories for motor skills and conditioned responses). The key senses of "consciousness" we need to consider here are wakefulness, as conscious *state*, and "awareness," or "experience," the current *contents* of consciousness.

(i) *The effect of transient amnesia on consciousness*: Consciousness in the sense of "wakefulness" is unaffected by transient amnesia of the kinds we have discussed in this chapter. Correspondingly, the abilities, normally on line during ordinary wakefulness, to perform complex, goal-directed actions, and to monitor their execution, are also unaffected, at least over short periods. We have seen that patients with transient amnesia are able to walk, use objects, talk, and drive; during episodes of TGA patients have been reported variously to persevere with carpentry, put together the alternator of a car, row a small dingy to the seashore, perform a complex bell ringing routine, and engage in ballroom dancing (Hodges, 1991). Patients with TEA whom we have studied have managed, during attacks, to sight read piano pieces, translate between languages and win a hand of cards. Of course, their performance is liable to falter if they forget what they are meant to be doing: presumably in the cases just noted the activity itself provided a continuing series of cues that kept the performer on task.

What of these patients' awareness, the contents of their experience, during attacks? To judge by their own reports, patients are indeed aware of themselves and their surroundings during episodes of transient amnesia, but this awareness is altered in various ways. Thus, sufferers usually recognize and are perplexed by their inability to remember events from a few minutes ago, if anterograde memory is disabled, or from the more distant past, if retrograde memory is affected. The quality of recollection, more generally, may be altered in patients with an associated impairment of "autonoetic consciousness," whose remote memories lose their color and detail. It is possible, though this has not so far been investigated, that during episodes of transient amnesia there is a subtle but pervasive alteration of experience of the present, if this depends to some extent on the operation of structures in the limbic system involved in memory formation and retrieval (Lee et al., 2005; Zeman et al., 2013).

(ii) *The effect of transient amnesia on the consciousness of self*: Patients sometimes become distressed during episodes of transient amnesia because of their inability to situate their current experience in a coherent context. Failing to recognize his son or his new bungalow during an episode of TEA, our patient RG was found in tears by his wife. He explained: "I can't remember anything, it feels horrible."

The abilities to contextualize our experience, to interpret it through a personal narrative and incorporate it in our autobiography, are important elements in our consciousness of self. Antonio Damasio has contrasted this "extended consciousness" to the "core consciousness" that normally confers ". . . a consciousness of oneself as an immediate subject of experience, unextended in time" (Gallagher, 2000): it is ". . . a transient entity, ceaselessly re-created for each and every object with which the brain interacts" (Damasio, 1999). In transient amnesia the core self is intact: sufferers are in no doubt about the ownership of their experiences, but the extended self, rooted in the past and reaching towards the future, is imperiled by the loss of access to personally significant memories. The theme of the interdependence of the self and autobiographical memory is echoed in other contemporary theories of self-knowledge (Conway, 2005).

In TEA, specifically, the temporary loss of access to remote memories that occurs during the attack is accompanied, between attacks, by a persistent, patchy, but dense loss of memories for some salient autobiographical events, often extending back for several decades. Like the transient loss of access, this depletion of autobiographical memory is sometimes distressing. Its tempo and mechanism, its impact on the sense of self, and the role of anticonvulsant drugs in preventing its progression are all uncertain at present.

(iii) *The distinction between conscious but unremembered behavior and "automatism"*: The diagnosis of TGA

or TEA requires evidence from a witness that the patient was "conscious" at the time of the episode—that is to say, able to behave normally in all respects other than those governed by the memory dysfunction. Sometimes, however, there is no witness to clarify this point. We may then be left in a quandary as to whether awareness itself, or merely memory, was impaired at the time. This important, but potentially problematic, distinction was underlined by Dr. Z, Hughlings-Jackson's physician–patient with epileptic amnesia, who wrote in his diary, on the occasion mentioned earlier in this chapter, of his "unconscious—or perhaps I should say unremembered—diagnosis." In this case, Dr. Z's preserved abilities to converse with his patient, examine him and record the correct diagnosis demonstrate that he was conscious at the time, beyond all reasonable doubt, even if he was amnesic for the process afterwards. But what of those occasions, familiar to most of us, when we have no recollection of an episode of apparently well-integrated but relatively simple behavior—for example, of a 20 min drive down a familiar road—in the absence of a witness? Are episodes like these due to transient amnesia without impairment of awareness at the time? Or might awareness be disengaged as well as memory? These questions raise a further fascinating, fundamental, issue: how complex must behavior be to provide clear evidence for awareness? Although this draws us away from the main subject of the chapter, we shall address the question briefly.

In general, we tend to regard behavior that is clearly purposeful, and that demonstrates flexible selection of means appropriate to an agent's ends, as evidence for awareness. The ability to converse intelligently and responsively, for example, is normally taken to be conclusive evidence for awareness as it involves just this kind of cognitive flexibility. Automatisms—complex behaviors in the absence of conscious awareness or volitional intent—provide test cases for our understanding of the role of awareness in action. The most familiar examples come from realms of sleep and epilepsy.

Sleepwalkers navigate around their surroundings with some, but often insufficient, care, running a real risk of inadvertent injury. They are usually unable to give an account of themselves and remember little or nothing about episodes afterwards. They are thought to be "unconscious" during episodes—both asleep and unaware—and, indeed, they do not normally exhibit the capacity for flexible and appropriate selection of means to ends. But there are difficult intermediate cases. Sleepwalking is occasionally associated with quite elaborate, and apparently goal-directed behavior that is nevertheless entirely or largely unremembered afterwards and unintended by the perpetrator in his normal waking state. In a well-known Canadian case, for example, a man was acquitted of the murder of his mother-in-law, an act he had committed after driving 12 km to his in-laws' home, on the grounds that he was sleepwalking (Broughton et al., 1994). The intuitive notion that the brains of people who sleepwalk are in a twilight state between sleep and waking is borne out by a study that demonstrated activity at waking levels in regions of the brain controlling movement while activity in other regions of the cortex, particularly frontal cortex, remains at sleeping levels (Bassetti et al., 2000).

Hughlings-Jackson referred to "all kinds of doings after epileptic fits" under the rubric of automatisms. Contemporary epileptologists recognize five categories of epileptic automatism, "more or less coordinated adapted epileptic activity occurring during the state of clouding of consciousness ... and usually followed by amnesia for the event": (i) oropharyngeal, for example lip-smacking or chewing movements; (ii) expression of emotion, most often fear; (iii) gestural, such as tapping, rubbing, fidgeting or flag-waving movements; (iv) ambulatory, including walking, running, or bicycling movements; (v) verbal, usually single words or short phrases (Oxbury et al., 2000). As a rule, patients are unaware of these behaviors, in the sense that they cannot interact with others or report their behavior at the time, though this is not always the case even for the types of automatism just listed.

In TEA, as we have seen, patients can interact normally and describe their experiences during attacks despite their subsequent amnesia: for these reasons we would not regard these episodes—like Dr. Z's during his unremembered consultation—as automatisms. However, the observation that epileptic activity can disable some but not other psychological capacities complicates the understanding of automatisms: for example, a focal frontal lobe seizure might selectively impair decision-making capacities, interfering with "volitional intent" but not with perception or memory. Whether a resulting crime is the result of an automatism may be a question for lawyers rather than for scientists.

Finally what of that drive along a familiar road of which we cannot recall a single detail? The cause of the amnesia in such cases is open to investigation, at least in principle. It could be that we had normal awareness of events throughout, but failed to lay down a permanent record of them because they were so mundane. If so, reaction times and accuracy of response should be normal at the time. It could be that the subsequent amnesia reflects a redirection of attention—towards the music on the radio, an internal dialog, a daydream. If so, questioning at such times should allow report of the

TABLE 22.1 Distinguishing Clinical Features of the Transient Amnesic Syndromes

	Transient global amnesia	Transient epileptic amnesia	Psychogenic amnesia
Typical age	50–70 years	50–70 years	Also younger
Past medical history	Migraine	Nil	"Organic" transient amnesia, substance abuse, psychiatric illness
Precipitants	Cold water, physical exertion, psychological stress	Waking	Minor head injury, stress, depression
Ictal memory profile	Profound anterograde amnesia with repetitive questioning; variable retrograde amnesia; non-declarative memory intact	Variable anterograde and retrograde amnesia (may later partially recall attack); non-declarative memory intact	Highly variable: often profound retrograde amnesia with loss of personal identity; relatively preserved anterograde memory; procedural memory may be impaired
Other features	Headache/nausea may be present	Sometimes: olfactory hallucinations; oroalimentary automatisms; brief loss of responsiveness	Focal "neurological" symptoms or signs, e.g., hemiparesis may be present
Duration	Typically 4–10 h	Usually <1 h but may last much longer (days)	Days or months
Recurrence	Rare	Mean frequency = 13/year	Rare
Postictal/interictal memory	Grossly intact, but subtle deficits may persist for months	Accelerated forgetting, remote autobiographical memory loss and topographical amnesia	Variable: may "relearn" the past causing memories to lack "autonoetic consciousness"

current focus of attention; reaction times and accuracy measures are likely to reflect our relative absorption in matters other than driving. If—and this seems highly unlikely—the amnesia is the result of true loss of awareness, probing should once again be revealing, and potentially lifesaving!

CONCLUSION

The syndromes of transient amnesia are characterized by a temporary loss of conscious access to knowledge of the past and an inability to lay down new, consciously accessible memories. TGA, TEA, and psychogenic amnesia have distinct clinical and neuropsychological features, which are summarized in Table 22.1. These syndromes raise interesting questions about the relationship between memory and consciousness, and provide an arena in which to investigate them further. Patients with transient amnesia are able to act as their own control subjects, and thus eliminate some of the interindividual variation that plagues many lesion studies. Future work should address the status of perceptual experience during transient amnesia, and examine whether implicit memory is truly spared—to test, for example, the hypothesis that the hallmark of the deficit in amnesia is not so much conscious access to memory but relational processing (Ryan et al., 2000; Eichenbaum and Cohen, 2001). In addition, the persistent autobiographical memory deficits in patients with TEA offer an ideal opportunity to investigate the contentious issue of focal retrograde amnesia, and examine its effect upon that philosophically slippery creature—the self.

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CHAPTER

23

Consciousness and Aphasia

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OUTLINE

INTRODUCTION

One aspect of consciousness (Bisiach, 1988) refers to the availability of mental representations for use in other cognitive processes. Mental states are conscious if they can be reported, reasoned about, voluntarily acted on, or recollected. Block (1995) describes such states and their content as access-conscious, i.e., other cognitive processes have access to them. This chapter will deal with this aspect of consciousness.

In a clinical setting one can be said to be conscious or aware of something whenever a verbal or a nonverbal description can be provided of the object of that awareness. Aphasic patients can hardly provide precise verbal descriptions of what they see, feel, want, and think. Furthermore, they might have altered comprehension or associated cognitive deficits severe enough to impair their ability with nonverbal descriptions. In order not to underestimate the mental representations they have access to (the "content" of their consciousness) one has to look carefully for alternative means to obtain controlled responses or indirect evidence of what the aphasic patient is aware of.

In this chapter I will explore the issue of the mental representation available to aphasic patients by using the Baddeley's model of working memory (Repovs and Baddeley, 2006). Within this framework I will analyze the relationships between inner speech, working memory, and different aphasic syndromes. Related to the question of mental representations available to aphasic patients is the question of the relationship between thinking and aphasia. According to some authors certain forms of reasoning can only take place in explicit (i.e., conscious) sentences of a natural language: I will examine this issue by analyzing the special case of retained "Theory of Mind (ToM)" understanding in

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patients with severe agrammatism. I will consider consciousness in its monitoring component and review the topics of language output monitoring and anosognosia of aphasia. Lastly, I will analyze the problem of assessing language impairment in patients with disorders of consciousness both at the behavioral level and by means of different neurophysiological paradigms.

CONSCIOUSNESS AND WORKING MEMORY

The concept of working memory refers to a limited capacity system allowing the temporary storage and manipulation of information necessary for complex tasks as comprehension, learning, and reasoning. Working memory has been classically coupled with conscious awareness. However, recent data (Soto and Silvanto, 2014) have demonstrated that working memory processes can be engaged without awareness due to the interaction of varying factors (e.g., attention, intention, motivation).

Although the basic model of working memory was first proposed 40 years ago, it has continued to develop and to stimulate research and debate. Baddeley's initial model (Baddeley and Hitch, 1974) proposed the existence of three functional components of working memory: an attentional control system (the "central executive"), aided by two subsidiary slave systems, the "phonological loop" and the "visuospatial sketchpad." The two slave systems are assumed to hold respectively phonological and visuospatial information. A fourth component, the "episodic buffer," was subsequently added (Baddeley, 2000) on the basis of a number of empirical findings. The episodic buffer is assumed to be a limited capacity store retaining integrated units of visual, spatial, and verbal information marked for temporal occurrence. It provides a temporary interface between the slave systems and long-term memory (LTM). It is controlled by the central executive, which is responsible for binding information from a number of sources into coherent episodes.

Retrieval of such episodes is based on conscious awareness. Figure 23.1 shows the components of the "crystallized"[1] cognitive systems (shaded area), capable of accumulating long-term knowledge (e.g., language and semantic knowledge) and the "fluid"[1] capacities of working memory (subserving attention and temporary storage) that are unchanged by learning other than indirectly, via the crystallized system (Baddeley, 2000).

It is argued that some components of the model have a modular organization (Vallar and Papagno, 2002). However, this would not be the case for the biological mechanism of the episodic buffer (the binding), for which the process of synchronous firing (Singer, 1999) is assumed to be the most promising hypothesis (Baddeley, 2000).

Within the working memory model, short-term storage and manipulation of verbal material is accomplished by the "slave system" called the "phonological loop" (Baddeley, 1986). In turn, the phonological loop is conceived as a modular system. The main characteristic of this system is the distinction of two separate components: a phonological non-articulatory short-term store (Salamè and Baddeley, 1982) and an articulatory

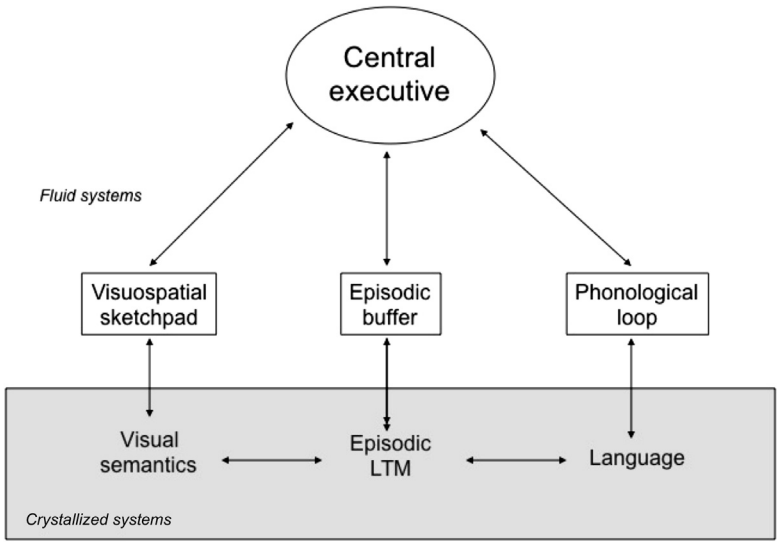

FIGURE 23.1 The current version of Baddeley's multi-component working memory model. The episodic buffer is assumed to form a temporary storage that allows information from the subsystem to be combined with data from long-term memory into integrated chunks. This system is assumed to form a basis for conscious awareness. *Source: Based on Baddeley (2003).*

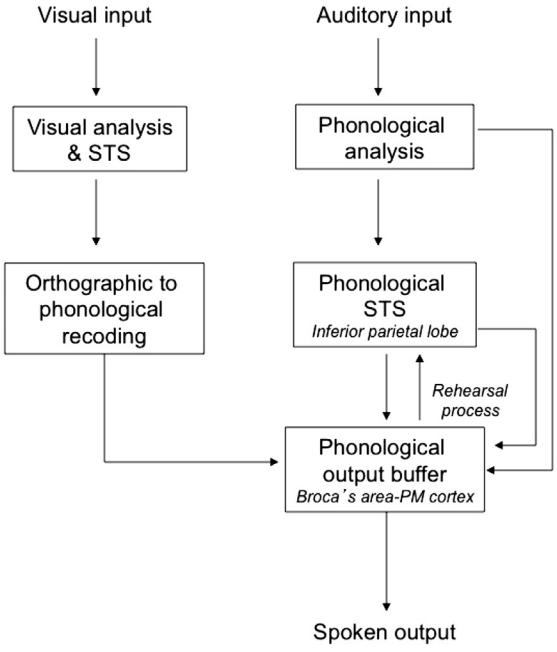

FIGURE 23.2 The proposed model for the phonological loop. Auditory information is analyzed and fed into a phonological short-term store. From this system, information can either pass into the phonological output buffer or be rehearsed, both overtly and subvocally. Visually presented stimuli are transferred from an orthographic to a phonological code and thereby registered within the phonological output buffer. *Source: Based on Baddeley (2003).*

rehearsal mechanism (Vallar and Baddeley, 1984). The phonological store consists of auditory memory traces that are subject to rapid decay. The articulatory rehearsal mechanism is an active process that can refresh the content of the phonological store, thus preventing trace decay. Auditory material is registered directly in the phonological store while visually presented verbal information is transformed into phonological code by silent articulation and thereby encoded into the phonological store.

The notion of such a model (Figure 23.2) is supported by the following findings:

1. *The phonological similarity effect*. Immediate memory is poorer for phonologically similar items (e.g., P, T, C, V, B) than for with dissimilar items (e.g., R, W, Y, Z, Q). Semantic similarity has comparatively little effect (Conrad, 1964).
2. *The word length effect*. Immediate memory span is better with short than with long words. This is explained by the fact that short words can be articulated faster, so that more words can be silently articulated before they decay (Baddeley et al., 1975).
3. *The effect of articulatory suppression*. Memory for verbal material is impaired when people are asked to say something irrelevant aloud. This is assumed to block the articulatory rehearsal process, thereby leaving memory traces in the phonological loop to decay. With visually presented items the information is transferred from a visual to an auditory code. Articulatory suppression prevents this transfer, and in that case the phonological similarity effect disappears. On the contrary, with auditory presentation concurrent articulation suppresses the word length effect but not the phonological similarity effect (Baddeley et al., 1984): it is therefore assumed that the word-length effect is due to the articulatory rehearsal mechanism, while the phonological similarity effect reflects the process going on within the phonological store, which directly receives auditory information but needs the mediation of the articulatory rehearsal mechanism to be fed by visual information.

WHAT IS INNER SPEECH?

Some authors have proposed that inner speech mediates self-awareness (Morin and Michaud, 2007). Indeed, the term inner speech has been used in many ways. First, it refers to the subjective phenomenon of talking to oneself, of developing an auditory-articulatory image of speech without uttering a sound. This is the abstract inner speech, also called "the language of the mind." The relationship between inner speech and thought was extensively investigated by earlier works based on introspection (reviewed in Sokolov, 1972). Second, it refers to the objectively measurable ability to appreciate the auditory-articulatory structure of speech irrespective of its meaning (Levine et al., 1982). Third, it refers to any measurable effect of covert speech on the content of verbal short-term memory.

In subjects with left-side language dominance, inner speech has been consistently demonstrated to depend on the activation of the left inferior frontal gyrus (LIFG, or Broca's area; Brodmann's area 44, 45, and 47; left frontal operculum; left ventrolateral prefrontal cortex), as it is active when participants are asked to silently articulate sentences (McGuire et al., 1996a) or single words (McGuire et al., 1996b).

In a extensive review of 59 studies measuring brain activity during processing of self-information, Morin and Michaud (2007) showed that LIFG activated in 55.9% of all studies included in the review, and more frequently during conceptual tasks than during perceptual tasks, thus supporting the view of an involvement of inner speech in self-reflective processes.

INNER SPEECH AND ANARTHRIA

Pure anarthria is a rare disorder commonly defined as a total inability to articulate speech in the absence of

TABLE 23.1 Summary of the Characteristics of Different Types of Aphasia

Type of aphasia	Fluency	Repetition	Naming	Comprehension
Broca's aphasia	Non-fluent	Impaired	Impaired	Relatively good[a]
Wernicke's aphasia	Fluent	Impaired	Impaired	Impaired
Conduction aphasia	Fluent	Impaired	Impaired	Good
Transcortical sensory aphasia	Fluent	Good	Impaired	Impaired
Transcortical motor aphasia	Non-fluent	Good	Impaired	Good
Transcortical mixed aphasia	Non-fluent	Good	Impaired	Impaired
Anomic aphasia	Fluent	Good	Impaired	Good
Global aphasia	Non-fluent	Impaired	Impaired	Impaired

[a]*In patients with Broca's aphasia auditory comprehension is relatively preserved. However, patients' ability to understand grammar is often affected.*

any deficit both of auditory comprehension and of written language. It can follow either cortical, subcortical, or brain stem lesions. Anarthria should be kept separate from mutism (inability or unwillingness to speak in the absence of any brain lesion capable of affect the articulatory planning), as well as from dysarthria (a speech disorder due to weakness or incoordination of speech muscles).

Some anarthric patients (see for instance the patient described by Levine et al., 1982) subjectively report that they do not speak silently. Yet, several authors have claimed that anarthria does not affect covert articulation: they based this assumption on the finding that anarthric patients perform short-term memory tasks differently from normal subjects who are prevented from articulating (Baddeley and Wilson, 1985; Bishops and Robson, 1989; Vallar and Baddeley, 1987). However, Cubelli and Nichelli (1992) showed that anarthric patients perform short-term memory tasks differently also from normal subjects who are allowed to subvocally rehearse as one would expect if they could use covert articulation. For example, while in tasks of short-term memory normal subjects, when allowed to rehearse, show both phonological and word-length effects with auditory and visual stimuli, anarthric patients cannot demonstrate a word length effect with visually presented words.

Furthermore, anarthric patients' performance demonstrates dissociation between patients with pontine lesions and patients with frontal opercular lesions (Cubelli and Nichelli, 1992). Pontine patients (i.e., patients with "locked-in" syndrome) do not show a word length effect with both auditory and visual stimuli but they do show a phonological similarity effect with visual stimuli. On the other hand, patients with fronto-opercular anarthria do show a word length effect with auditory but not with visual stimuli (Cubelli and Nichelli, 1992). In a further study Cubelli et al. (1993) demonstrated that anarthric patients score in the lower bounds of the performance of normal subjects suppressing articulation at a task of subvocal counting (e.g., when they are requested to count the number of times a stimulus appears in the center of a computer screen). These results have been interpreted as due to the impaired functioning of a circuit dependent on supplementary motor area (SMA) in the case of the locked-in syndrome and to the impairment of multiple afferent and efferent connections of the lateral premotor system in the case of cortical anarthria. In conclusion, anarthric patients' performance with tasks involving subvocal rehearsal demonstrates that they are not simply "mute," as their inability on overt articulation is associated with a more subtle impairment of covert articulation. It appears therefore that inner speech (in this case the "inner voice") is dependent for its operation on brain mechanisms involved in "overt" speech.

INNER SPEECH AND APHASIA

Aphasia is the common name that is given to a number of different language disorders that can follow damage to the brain, most commonly of the left hemisphere. The different types of aphasia can be divided in two categories (fluent and non-fluent aphasia). The main characteristics of the different aphasic syndrome are listed in Table 23.1.

Henseler et al. (2014) have recently provided a careful account of the anatomical correlates of Broca's and Wernicke's aphasia and of the site of the lesions determining impairment of different linguistic modalities (e.g., articulation, phonemic structure, etc.) or impaired performance at different tasks (e.g., repetition, picture naming, etc.) (Figure 23.3).

Inner and overt speech can dissociate in aphasia. Aphasic patients sometimes complain there is poor

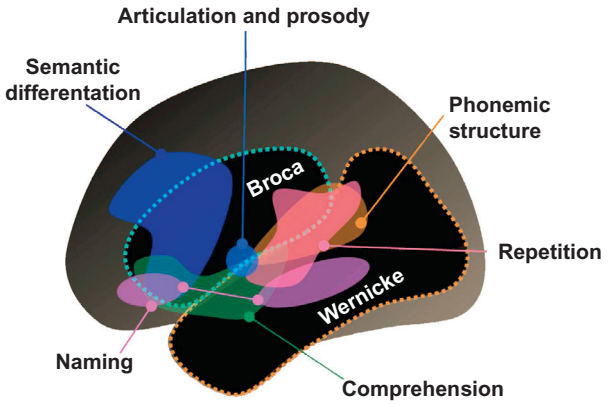

FIGURE 23.3 Lesion correlates of different profiles in aphasia: comparison of syndrome-, modality-, and symptom-based analyses. *Source: Figure based on Henseler et al. (2014).*

correspondence between the words they intend to say (inner speech) and those they are able to produce aloud (overt speech) (Marshall et al., 1994). Geva et al. (2011a) studied a group of 27 patients with chronic post-stroke aphasia, using tests for language abilities, speech apraxia and inner speech (homophone and rhyme judgments, using both words and pictures). They demonstrated that while for most patients with aphasia there is a high correlation between inner and overt speech abilities, some show preserved inner speech with a marked deficit in overt speech, while others show impaired inner speech despite intact overt speech. In a lesion study, using voxel-based morphometry, Geva et al. (2011b) demonstrated that inner speech abilities (investigated by means of rhyme and homophone judgments) were affected by lesions of the left pars opercularis in the LIFG (Brodmann's area 44) and to the white matter adjacent to the left supramarginal gyrus, over and above overt speech production and working memory. These results suggest that inner speech can be, at least in some cases, dissociated from overt speech, and that is not simply overt speech without a motor component.

INNER SPEECH IN CONDUCTION APHASIA

Conduction aphasia is a language disorder characterized by selective defect of oral repetition of words or sentences in the presence of relative preservation of auditory comprehension. The general level of articulation, rate of speech, and use of grammatical elements is fluent, but speech output is usually disrupted by phonemic paraphasias (e.g., errors like "lelephone" for telephone or "papple" for apple)[2] and anomias (i.e., word finding difficulty causing hesitancy or circumlocutions).

Kurt Goldstein (1948) suggested that conduction aphasia is a disturbance of inner speech, a central language process mediating between nonverbal thought and overt speech. Feinberg et al. (1986) hypothesized that if that assumption was correct, patients with conduction aphasia should fail on tasks requiring the generation of phonological representation of words even when no overt speech is required. They tested this hypothesis in five patients who had conduction aphasia with similar speech disturbances. The patients were presented with pictures and were required to perform, without overt vocalization, comparisons of word length and homophonic and rhyming matches. Four patients successfully performed such judgments on words they could not vocalize, but one patient could not. The findings provided evidence for heterogeneity within the class of conduction aphasia and suggested that inner speech might be impaired only in a subgroup of conduction aphasics.

Further studies (Bartha and Benke, 2003) have demonstrated that a majority of patients with conduction aphasia also shows a selective deficit in verbal short-term memory. One Italian patient, P.V., with a very pure and specific deficit in auditory short-term memory, was extensively tested to determine whether her deficit could be explained within the working memory framework (Vallar and Baddeley, 1984). She appeared to be intellectually entirely normal, with a high level of verbal and performance I.Q., and excellent LTM (Basso et al., 1982). Her immediate memory span was no more than two items with auditory presentation and about three to four items with visual presentation. Her performance was affected by phonological similarity with spoken but not with visual presentation, as if she had a phonological store but was not using the articulatory rehearsal process to feed it. That this was indeed the case was also confirmed by lack of the usual deleterious effect of articulatory suppression on the span of visually presented items. However, she also showed a defective phonological store, as demonstrated by the progressive impairment at a task of shadowing spoken words by presenting them at various rates. While she was able to perform this task at slow rates, her performance fell behind that of controls as speed increased and phonological store was needed as a buffer to avoid temporary overload (Baddeley, 1986).

A particularly interesting observation concerns P.V.'s ability at learning: while she was very good at learning lists of meaningful words, Baddeley et al. (1988) demonstrated that she could not learn unfamiliar words, such as the vocabulary of a foreign language. Within the framework of the Baddeley's working memory model such a deficit of the phonological loop prevented the episodic buffer to build association between new words and semantic nodes to be stored in LTM.

INNER SPEECH AND DYNAMIC APHASIA

In 1885 Lichteim reported a patient with a striking dissociation between his inability to talk or write spontaneously and his ability to name objects, repeat words and phrases, and read and write under dictation. This pattern of speech disturbance was termed "transcortical motor aphasia" and subsequently subdivided in two types, both sharing the common characteristic of preserved word repetition. One type is characterized by effortful non-fluent spontaneous speech in which phonemic paraphasic errors were common. The second type, named by Luria (1970) "dynamic aphasia" is characterized by sparsely produced but normally articulated spontaneous speech. Luria and Tsveskova (1967) provided the first analytic investigation of dynamic aphasia. They hypothesized that "inner speech with its predicative function which takes part in forming the structure or scheme of a sentence is disturbed in cases of dynamic aphasia." In this framework inner speech is defined as "a mechanism used by the subjects for the transition from a preliminary idea to the extended verbal proposition" and provides the so-called "linear schema of the sentence."

Costello and Warrington (1987) reported a patient, who, after a left frontal lobe tumor, manifested a selective speech disorder with all the hallmarks of a dynamic aphasia. His speech was very sparse, with long response latencies and, on many occasions, with a complete absence of response. At the same time there was no evidence of impaired comprehension or naming difficulties. His repetition was excellent and his literacy skill (reading and spelling) satisfactory. On the few occasions that he did use speech spontaneously there was no evidence of paraphasic errors and his speech was grammatically correct, with normal articulation and prosody. His ability to generate sentences was significantly better given a pictorial context than a verbal context. Although he could order a sequence of pictures, he had the greatest difficulty in ordering the constituent words of a sentence. Based on these findings, Luria's hypothesis that dynamic aphasia was due to an impairment of inner speech, which provides "the linear scheme of a sentence" was disconfirmed. It was concluded that dynamic aphasia does not reflect a deficit of language processing but rather the selective impairment of verbal planning.

In a more recent case report and review of dynamic aphasia literature Robinson et al. (2006) suggested two subtypes of dynamic aphasia. The first subtype is characterized by a propositional language impairment resulting in inability to generate a single response to stimuli, which activate many competing verbal responses. This deficit is specific to language production and is associated with left posterior frontal damage (Brodmann area 45). On the basis of a computational model of prefrontal cortex functioning, Robinson et al. (1998) proposed that this type of dynamic aphasia might be the result of damage to a "context" module containing units responsible for selection of verbal response options. The second subtype, associated with bilateral frontal and subcortical involvement, is characterized by a propositional language impairment resulting in inability to generate a fluent sequence of novel thought on discourse level generation tasks in the context of preserved ability to generate a single response on word and sentence level generation tasks.

In his influential theoretical model of speech production, Levelt (1989) proposed that conceptual preparation processes are responsible for the generation of new conceptual structures or messages that are subsequently realized in overt speech. Several linguistic theories (Levelt, 1999; Grosz and Sidner, 1986; McKeown, 1992) highlighted the importance of focusing and attention as key properties of discourse structure, whereby "focusing" is defined as a process of directing attention to a particular set of concepts or topic in conversation. According to Robinson et al. (2006) dynamic aphasia patients of the first type might be impaired at one of the mechanisms involved at the stage of conceptual preparation (selecting a single response option among competitors), while patients of the second type might be impaired in generating multiple potential messages that are intended to be communicated and in focusing attention on a specific message to be expressed.

While speaking is fluent, one is not aware of antecedent inner speech, probably because it so quickly becomes overt (Kinsbourne, 2000). When a brain damage blocks phonological plans, aphasic patients might become aware of preverbal thoughts that usually are not experienced by normal speakers. Dynamic aphasia offers a window to explore the interface between thought and language. Careful neuropsychological investigation of patients with dynamic aphasia is just beginning to disentangle the processes that are involved in the transition between thinking and speaking.

ToM IN AGRAMMATISM

The thoughts that precede language are generally not conscious. However, upon introspection, we sometimes seem to think and to reason in the language we speak. According to some theories (Carruthers, 1996; Segal, 1996) certain forms of reasoning can only take place in explicit sentences of a natural language. Other investigators (Clark, 1998) have proposed that

propositions support thinking by providing a sequential structure to brain processes that are massively parallel. ToM is the ability to attribute mental states (e.g., beliefs, intents, desires, pretending, knowledge) to oneself and others and to understand that others have beliefs, desires, and intentions that are different from one's own (Premack and Woodruff, 1978). Some features of ToM involve eye gaze and emotion interpretation: they are viewed to be language independent (Tiger-Flusberg and Sullivan, 2000). In contrast, it has been claimed that ToM reasoning, such as reasoning on a "changed content task," depends upon language, specifically upon the possession of syntactic structures such as those that allow embedding false proposition within true statements. In a typical changed content task the experimenter shows to Anne a chocolate box with an unusual content (e.g., a set of color pencils). Then the box is closed and Anne is requested to say what a person who has not seen the contents would say is inside the box. Varley and Siegal (2000) have reported the case of a patient with agrammatic aphasia of such severity that language proposition was not apparently available at an explicit processing level in any modality of language use. Despite the severe grammatical impairment, he displayed ToM understanding and simple causal reasoning. This observation, along with a few similar case studies (Varley et al., 2001), demonstrates that reasoning about causes and beliefs involve processes that are independent of propositional language.

ERROR MONITORING AND ANOSOGNOSIA IN APHASIC PATIENTS

There are few opportunities to know the subjective experience of being affected by aphasia associated with severe comprehension deficit. Among the few available anecdotal reports, I found particularly interesting the book by neuroanatomist Dr. Jill Bolte Taylor, who in 1996 suffered a brain hemorrhage from a left hemisphere arteriovenous malformation which led to severe aphasia associated with inner speech deterioration and later on, after recovering from this accident, published a book in which she related her experience (Taylor, 2006).

From her report it is clear that, from the beginning, she was perfectly aware of what was going on: that she was having a stroke, that she was unable to speak and that she was producing meaningless utterances. At the same time she clearly noted a disturbance in her inner speech ("my brain chatter began to disintegrate"). Alain Morin (2009) noted that in the early phase of her stroke there were several examples of remnants of inner speech that she refers to as "moments of clarity." However, once completely deteriorated, inner speech was gone for 5 weeks and replaced by imagery. Based on J.B. Taylor's account, Morin (2009) put forward the hypothesis that loss of the ability to converse with herself led to self-awareness deficit not to consciousness disruption as indicated by her retained ability to focus her attention toward the environment and to process incoming external stimuli. However, Mitchell (2009) has argued that in normal subjects inner speech pops up all sporadically, that self-awareness of a sort can be experienced without inner speech, and that Taylor continued to experience it.

Lazar et al. (2000) provided a more systematic and controlled account of the experience from the viewpoint of the patient. During angiography, they induced a transient Wernicke's aphasia in a patient with left frontal arteriovenous malformation by super selective injection of anesthetics (amobarbital sodium and lidocaine) exclusively into the lower division of the left middle cerebral artery. During the procedure the patient underwent examination of fluency, comprehension, naming, repetition, and oral reading. At baseline and 15 min after anesthetic injection all aspects of language function were entirely normal. After the procedure, the patient had no recollection of some of the tasks that had been administered to him. By his account, however, there was a more systematic attempt to respond appropriately than could be inferred from his overt behavior. His description indicated not only that he could think, but also that he could recall afterwards what it was he was trying to do.

Yet, not all aphasic patients seem aware of their deficits while they are aphasics. The phenomenon of anosognosia for aphasia presents a particularly striking failure of the normal monitoring functions for speech and, in some cases, seems to require the postulation of a more fundamental alteration of consciousness of the language-processing systems (Rubens and Garret, 1991). Several sorts of language monitoring processes have been suggested, including those internal to the production system itself and those that depend on comprehension system (Levelt, 1989; Postma, 2000; Hartsuiker et al., 2005). Note that normal speakers (and listeners), not only aphasic patients, are often "unaware" of their language errors, so that extremely focused attention may be necessary to pick up certain phonological and syntactic deviations (Cutler, 1981). Indeed, insensitivity to language errors in normal subjects depends on the circumstances and priorities: perceptual correction mechanisms are often necessary to automatically penetrate the haze of false starts, repetitions, and occasional ungrammaticalities that are on the surface of most well formed intended messages (Foster, 1979).

Schlenck et al. (1987) looked for two types of speech behavior in aphasic patients: repairs and anticipatory adjustments ("prepairs"). They found that repairs occurred far less frequently than "prepairs," which indicates impaired postarticulatory as opposed to intact prearticulatory monitoring. "Prepairs" were found to be most frequent in patients with relatively good comprehension, in patients with poor production, and in those who had both good comprehension and poor production. This finding indicates that good comprehension may be related to successful anticipation of production difficulties. Also, the relatively low frequency of repairs in all aphasics' groups may also point out to poor functioning of monitoring relying on comprehension abilities. Oomen et al. (2001) found that, contrary to normal controls, Broca's aphasic patients were not impaired in a noise-masked condition, such confirming the greater reliance of Broca's aphasics on prearticulatory rather that on postarticulatory monitoring.

Anosognosia of linguistic deficit is present whenever an aphasic patient does not attempt to correct an error and, confronted with that error, denies its occurrence. Such unawareness of language disturbance is most often associated to specific forms of abnormal speech such as jargon, stereotypy, or echolalia. Typically, patients with anosognosia for aphasia produce a great amount of meaningless utterance, phonemic and semantic paraphasias, and neologisms. They show few of the hesitations, pauses, and self-correction found in most of the aphasic patients. However, there are also several patients with severe auditory comprehension deficit and blatant jargon aphasia who seem perfectly aware that they are aphasics (Lecours and Joanette, 1980; Rubens and Garret, 1991). On the opposite side, there has been also reports of lack of error awareness in a patient with relatively preserved auditory comprehension (Maher et al., 1994).

There are several possible theories to account for anosognosia for aphasia. Some authors argued for a psychodynamic explanation (Weinstein and Lyerly, 1976). However, the observation that lack of awareness often does not extend to the accompanying motor disorders strongly argues against this hypothesis. Furthermore, double dissociation between jargon aphasia and awareness of the deficit indicates that simple monitoring failure cannot provide a general account of this kind of anosognosia.

Shuren et al. (1995) have also reported an anosognosic aphasic patient that, although apparently unaware of his production errors, could detect his own speech errors when played back. The authors explained this dissociation as caused by the patient's inability to perform speaking and listening at the same time, due to a reduced attentional capacity. However, the patient described by Maher et al. (1994) not only recognized more of his errors in a recording of his voice than he did while speaking, but he also recognized more errors in a recording of the examiner making errors than he did when listening to the recordings of his own speech, a dissociation that cannot be accounted by reduced attentional capacity. With a series of experiments on four patients with jargon aphasia Marshall et al. (1998) ruled out explanation of monitoring failure in jargon aphasia based on deficit of auditory feed-back or to resource limitation which prevents concurrent speaking and monitoring. The authors demonstrated that, at least for one of the four patients, monitoring difficulties arose when he was accessing phonology from semantics. They concluded that monitoring failure could arise from deficits within the production process, which preclude comparison of actual with intended output. However, while this theory might explain monitoring failure in jargon aphasic, it cannot account for double dissociation between jargon aphasia and anosognosia for aphasia.

In conclusion, there is clearly the need of a more systematic study of error monitoring in aphasia. However, while most aphasic patients have difficulty speaking and monitoring their own speech, lack of awareness of speech deficit (i.e., anosognosia) seems to go beyond speech monitoring. As suggested by Rubens and Garret (1991) this points to the need to develop an account of monitoring processes that treat different classes of language structure as having distinct access to conscious report. The possibility that the ability for flexible attentional focus can decline during the act of speaking as well as the effect of familiarity of one's own voice should also taken into account.

THE ASSESSMENT OF APHASIA IN PATIENTS WITH IMPAIRED CONSCIOUSNESS

Language is a fundamental window to examine disorders of consciousness and detecting the presence of aphasia is of utmost importance to avoid underestimation of the patient' level of consciousness.

Clinical Assessment of Language in Patients with Impaired Consciousness

At the behavioral level, in patents in—or emerging from—a Minimally Conscious State (MCS), language should be examined using customized bedside screening batteries including tests aimed at assessing language comprehension, repetition, and production.

Language comprehension is the most difficult function to test in this group of patients. Assessing language begins with simple commands requiring a straightforward motor response (such as "close your eyes" or "raise your arm"). If the patient can follow simple instructions then the examiner can use commands more complex at the semantic level (e.g., "point to the ceiling"), at the syntactic level (e.g., "if this is a coin, then point to the key") or for their increased short-term memory requirements (e.g., "with your right index finger touch first your nose, then your lower lip"). I would suggest particular caution in using yes/no response to situational orientation questions to examine verbal comprehension in patients with MCS. Indeed, to rule out chance responses, this procedure would require consistent yes/no accuracy in different sessions, which—due to diminished attention and motivation—is uncommon among patients in early recovery from brain injury, especially dependent from trauma (Nakase-Richardson et al., 2008). Furthermore, language-processing demands associated with yes-no questions are more complex than those required for following simple commands. Repetition tests usually start with single, short, high frequency words (e.g., mom, dad, bed) and then proceed with short sentences. Language production can be examined starting from automatic series (e.g., counting days of the week or months of the year). I would suggest prompting patients with the first members of the series and then asking them to proceed with those following. Then, one can test propositional language with a naming task, using objects, from more to less common ones. Presentation modality should also be varied as dissociation between written and auditory language processing has been frequently reported in the aphasia literature and there have been occasional reports of patients with locked-in syndrome and associated central deafness (Keane, 1985; Smart et al., 2008).

There are several test batteries for diagnosing aphasia. However, there is an unmeet need of developing new diagnostic tools especially devised for detecting language deficits in patients with consciousness disorders and to differentiate these deficits from disturbance of consciousness (Schnakers et al., 2015).

Functional Neuroimaging of Language in Consciousness Disorders

Given the difficulty of assessing language deficits in patients with altered states of consciousness, a number of investigators have tried different approaches. Several authors have used different functional imaging techniques (e.g., $H_2{}^{15}O$-PET and fMRI) and protocols to examine the integrity of language networks in MCS and in patients with unresponsive wakefulness syndrome (UWS, previously labeled vegetative state) (Laureys et al., 2010). Using $H_2{}^{15}O$-PET or fMRI Laureys et al. (Laureys et al. 2000, 2004; Boly et al., 2004; Di et al., 2007) presented auditory stimuli with emotional valence (infant cries and the patient's own name) and observed that, compared to meaningless noise, these stimuli were associated with more robust activation not only of the primary auditory cortex but also of higher order associative temporal areas involved in language-processing. Such activation was observed in patients with MCS and also in a few patients with UWS, interestingly those who recovered to an MCS within 3 months after scanning. However, one must be careful in interpreting these experiments. As noted by Cole (2007) in controls recognition of a face or a name presumably does mean that this person is recognized to be oneself. But in a subject with UWS is it possible that a previously frequently met name or face is recognized differently without necessarily it being known that it is "me."

Further investigations have demonstrated the integrity of language-processing areas in patients with altered state of consciousness by contrasting fMRI activation related to meaningful and unintelligible (digitally reversed) speech (Schiff et al., 2005). Comparing fMRI activation related to sentences that were made difficult to understand by the presence of words that were semantically ambiguous to matched low-ambiguity sentences, Coleman et al. (2007, 2009) demonstrated some evidence of preserved speech processing in three patients with a clinical diagnosis of UWS and that fMRI correlates of speech comprehension had no association with patient's behavioral assessment at the moment of scanning but were strongly related with patient's subsequent recovery at 6 months after the scan.

Using the same paradigm, the same authors (Davis et al., 2007) had showed that normal subjects lightly (or deeply) sedated with anesthetic agent propofol cannot activate brain regions associated with semantic processes critical for comprehending ambiguous sentences (i.e., left inferior frontal gyrus and left inferior temporal gyrus). Accordingly, previous studies had demonstrated that neural responses to speech in the absence of awareness, as during sleep (Portas et al., 2000), or for non-attended presentations (Scott et al., 2004) are confined to superior temporal gyrus, while activity in prefrontal and premotor regions is directly associated with awareness of speech.

Owen et al. (2006) proposed a different method to investigate speech comprehension in patients with altered states of consciousness: they asked subjects, via verbal instructions, to perform two mental imagery

tasks (imagining playing tennis and imagining going around the rooms of their house). During the former, normal subjects activate the SMA, while, during the latter, a wider network of regions is activated including the parahippocampal gyrus and the lateral premotor cortices. They found a patient in UWS who, when asked to perform the two imagery tasks, showed the same activations as controls, thus demonstrating that she retained ability to understand spoken commands and to respond to them through intentional brain activity. In a further study (Monti et al., 2010) the same imagery tasks were administered to a larger cohort of patients. Of the 54 patients enrolled in the study (including 23 in a UWS and 31 in a MCS), 5 were able to willfully modulate their brain activity. In three of these patients additional bedside examination revealed some signs of awareness but, in the other two patients, no voluntary behavior could be detected by means of clinical assessment. One of the patients was even able to use modulation of brain activity to communicate yes-or-no answers to simple questions, but it remained impossible to establish any form of communication with him at the bedside.

Conceivably, these experiments provoked a heated debate. Nachev and Husain (2007) claimed that the presence of brain activation is not sufficient evidence for a consciously mediated behavior, unless one has also demonstrated that the same activation cannot occur without it. According to Greenberg (2007) brain activity might have been unconsciously triggered by the last word of the instruction, which always referred to the item to be imagined. However, a control experiment (Owen et al., 2007) found no evidence for such widespread and different cortical activation determined by the simple exposure to sentences containing the target words "house" and "tennis." Indeed, the most likely explanation is that these patients were consciously aware and willfully following the instructions given to them, despite their diagnosis being in a MCS or even in a UWS. This drives two considerations: that in a small number of cases, patients who meet the behavioral criteria for UWS have residual cognitive functions and conscious awareness and that obtaining indirect evidence of language comprehension abilities in patients with altered states of consciousness is of paramount importance. There is no doubt that the prospect of not knowing that the person that we believe is in a UWS can understand what we say but has no way to communicate with us is horrifying. It has been claimed that fMRI should become a routine tool to aid the clinical diagnosis of patients with disorders of consciousness and to avoid this situation (Coleman et al., 2009). However, many authors have emphasized the limitations and the pitfalls of obtaining and interpreting fMRI data in these patients. FMRI is not widely available and difficult to employ with uncooperative patients that cannot inhibit head motion. Indeed, when patients produce substantial head motion it might be hard, or even impossible, to interpret their data. Furthermore, only positive findings can be interpreted and an absent response cannot imply that the same patient, at another time, might not respond to the same task.

Assessment of Language Comprehension via Neurophysiological Measures

Neurophysiological paradigms, using event-related potentials (ERP) measuring the electrical correlate of neural activity in response to specific stimuli, might overcome some of these limitations and provide further helpful information (Majerus et al., 2009). Different ERP paradigms have been developed to capture the functioning of perceptual, lexical, and semantic processes. To study acoustic and phonological processes a sensitive component of ERP is the so-called mismatch negativity (MMN). It is a negative amplitude potential, occurring 100–200 ms after stimulus onset, related to an odd stimulus occurring in a sequence of repetitive stimuli (e.g., ba, ba, ba, ba, da). The odd sound can differ from the repetitive ones in acoustical or phonological features (Ylinen et al., 2006) and, notably, MMN can be elicited without paying attention to the odd stimulus, that is, in conditions where conscious awareness of the target stimulus is not necessary (Naatanen, 1990). The MMN has been also used to study speech perception processes in preconscious neonates and infants. Patients with MCS or UWS often fail to present an MMN response to odd stimuli differing at the acoustic, phonetic or phonological level: this may suggest that linguistic information is not accurately processed at these levels (Holler et al., 2011). However, Qin et al. (2008) have demonstrated that the subject's own name, an emotion relevant self-referential stimulus, is effective to evoke MMN and might even have a prognostic value in predicting recovery of consciousness. Similar results were obtained with different protocols by Wijnen et al. (2007) and by Fisher et al (2010).

Later occurring potentials, such as the positive peak at 300 ms (P300) and the negative peak at 400 ms (N400) have been used to investigate lexical and semantic processes. In a study on 50 patients in Intensive Care Unit, who remained comatose for more than 24 h after coma onset, Fisher et al. (2008) demonstrated that the use of novelty P3, a component assumed to reflect aspects of the orienting response (Friedman et al., 2001), increases the prognostic value of MMN alone and improves the assessment of high-level cognitive

functions in comatose patients. The negative potential at 400 ms (N400) has been used in normal subjects to study higher-level language processes, such as semantic plausibility of sentences (e.g., a N400 wave is observed when a sentence ends with a semantically inappropriate word (Kutas and Hillyard, 1980)). The observation of abnormal P300 and N400 in aphasic patients with lexico-semantic impairment confirms their relation with higher-level language processes (Hagoort et al., 1996; Pulvermuller et al., 2004). Although the paradigms used to elicit N400 components are attentional demanding, they have been reliably observed in 90% of MCS patients and even in 12% of UWS patients (Schoenle and Witzke, 2004). In a recent study of a large cohort of UWS and MCS patients followed up between 2 and 14 years after discharge Steppacher et al. (2013) demonstrated a highly significant relationship between N400, but not P300, presence and subsequent recovery of communicative capabilities.

Indeed, language is an important window to explore consciousness. The possibility to use ERP as surrogate markers of aphasia (and of residual language abilities) in patients with disorders of consciousness rests on a multidisciplinary effort that could get standardized procedures and reliable comparisons between performance at behavioral and at neurophysiological testing in aware patients with different aphasic syndromes, and different degree of impairments. A better understanding of the significance of language related ERP in patients with disorders of consciousness could also benefit from studies on subjects under general anesthesia: indeed, language processing is not diagnostic of normal consciousness, as some aspects of language can be processed without awareness.

CONCLUSIONS

Most of the neuropsychological literature on aphasia has been focused more on demonstrating the independence of thinking form language rather than on studying the effects of different language impairments on the functioning of working memory. More recent studies have demonstrated that language can be processed at various levels outside conscious awareness (Sklar et al., 2012; Axelrod et al., 2014). Language is a powerful window to examine patients with consciousness disorders. However, we should be careful to infer the level of consciousness impairment based on residual language capabilities. On the contrary, it would be very important to develop independent and reliable neurophysiologic measures of consciousness and of residual language processing capabilities in patients with severe trauma and brain anoxia, which potentially can cause both aphasia and severe consciousness disorders.

NOTES

1. The notion of "crystallized" and "fluid" was originally proposed by Raymond Cattel in reference to general intelligence. Crystallized intelligence is conceived as the ability to use skill, knowledge and experience. Fluid intelligence is the capacity to solve problems in a novel situation, independent of acquired knowledge.
2. Phonemic (or phonological) paraphasias are defined as substitutions of a word with a pseudoword that preserves at least half of the segments and number of syllables of the intended word.

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CHAPTER

24

Blindness and Consciousness: New Light from the Dark

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OUTLINE

If we could splice the nerves so that the excitation of the ear fed the brain center concerned with seeing, and vice versa, we would "hear the lightning and see the thunder."
William James (1890)

WHAT CAN WE LEARN ABOUT CONSCIOUSNESS FROM THE BLIND BRAIN?

The study of brain function in individuals with congenital blindness provides a powerful approach to understanding how consciousness develops in the absence of sight. Classically, sight has always been regarded as the most important sense for humans to interact with the environment. Let us not forget that in the ancient Greek language the verb "to know" (oi\da) was the past tense of the verb "to see" (oJravw), that is, *I saw and thus I know*. The relevance of sight is also clearly reflected in the mental attitude senses of the lexicon of vision. Consider everyday linguistic uses such as *can you see my point?*, *I see what you mean*, etc. At the same time, the brain surface devoted to visual function in primates is quite remarkable, accounting for almost one-third of the whole cortex.

These few considerations are sufficient to raise some critical questions. How do individuals with congenital blindness form a conscious representation of a world that they have never seen? How do their brains behave? What happens to visual-devoted brain structures in individuals who are born deprived of sight or who lose vision at different ages? What does the study of blind individuals teach us about the functional organization of the brain in physiological conditions?

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In this chapter we review evidence from studies conducted in animals and in humans in an attempt to shed new light on these questions.

STUDIES IN ANIMALS

The cerebral cortex has a remarkable capacity for plasticity and reorganization, both in animals and humans (Kaas, 2002; Pascual-Leone et al., 2005). Following loss of a particular sense, input from other modalities invades the cortical area that is deprived of its normal inputs. These intermodal connections result from a phenomenon called cross-modal plasticity. As early as 1977, Rebillard and colleagues reported that the primary auditory cortex can be driven by visual stimuli in congenitally deaf cats. Conversely, studies on the microphthalmic mole rat (*Spalax ehrenbergi*) have shown that auditory stimulations can drive cells in the primary visual cortex (Bronchti et al., 2002). Cells in the primary visual cortex of visually deprived cats, rats, or mice can be driven by somatosensory or auditory inputs, suggesting cross-modal reorganization (Toldi et al., 1994). Peripheral inputs play a pivotal role in the organization of the neocortex, as cortical territories usually involved in visual processing are invaded by the auditory and somatosensory system. It seems therefore that the visual cortex is capable of rewiring in order to accommodate these non-visual inputs. However, in the case of early brain damage, abnormal neuronal connectivity patterns can be produced and an alternative approach to study cross-modal plasticity resides in the tampering with "blue prints" during prenatal development. Relevant to this approach are the numerous studies on "rewiring" in hamsters (Ptito and Desgent, 2006) and in ferrets (reviewed in Lyckman and Sur, 2002).

When the Brain of Hamsters is "Rewired"

If brain damage occurs during development, abnormal neuronal connectivity patterns can be produced. It is thus possible to induce, by lesioning central retinal targets, the formation of new and permanent retinofugal projections into non-visual thalamic sites such as the auditory nucleus (Frost and Metin, 1985; Ptito et al., 2001) (Figure 24.1A). These surgically induced retinal projections are retinotopically organized and make functional synapses (Metin and Frost, 1989). Neurons in the somatosensory cortex (SI) of animals with ectopic retinal projections have visual response properties similar to

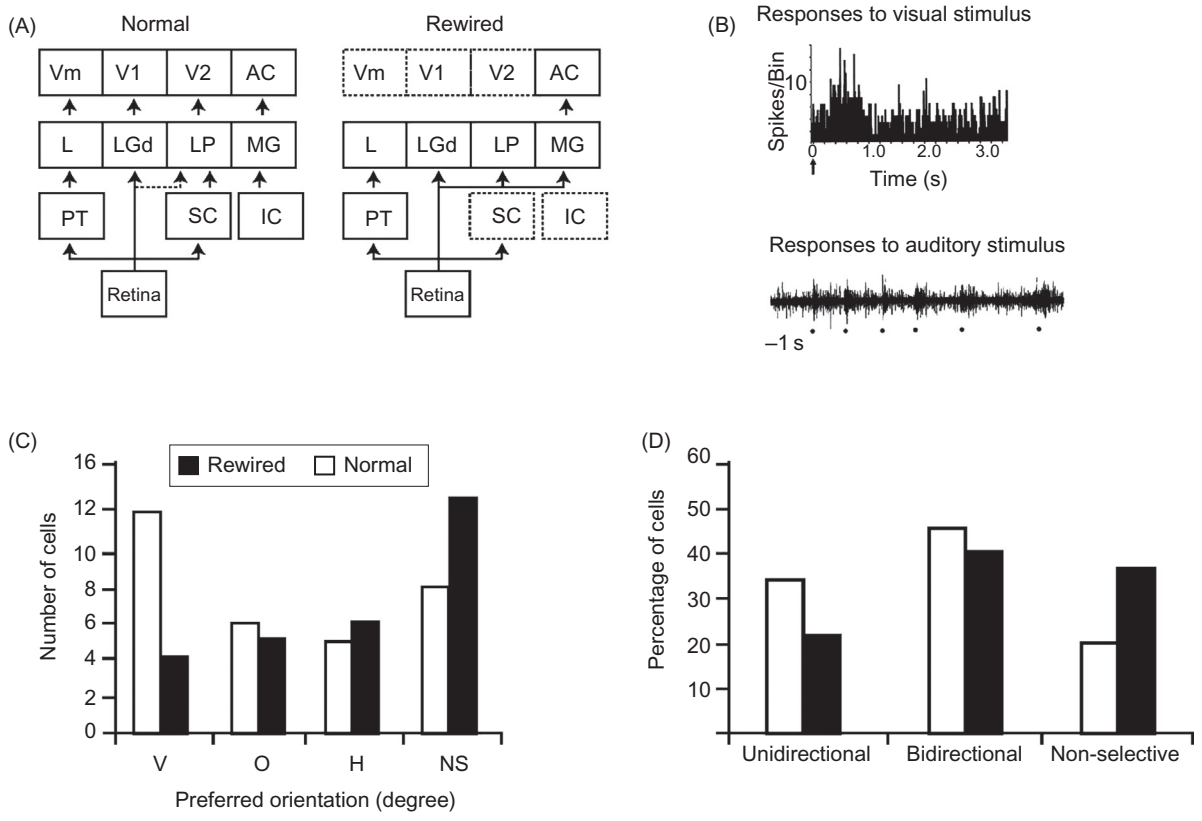

FIGURE 24.1 Visual properties of cells in the auditory cortex of rewired hamsters. (A) The visual system of normal and rewired hamsters. Examples of receptive field properties: (B) a bimodal neuron (audio-visual), (C) orientation, and (D) direction selectivity.

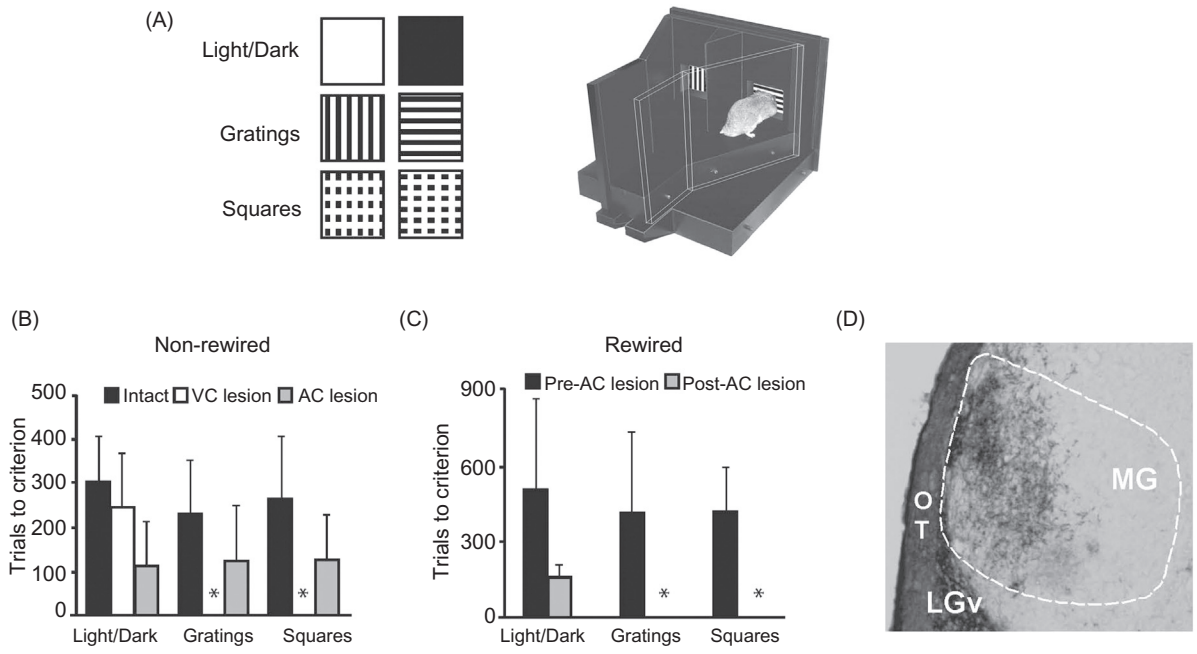

FIGURE 24.2 Visually guided behavior of rewired hamsters. (A) Stimuli and apparatus. (B) Histograms showing trials to criterion on the visual discrimination tasks in non-rewired hamsters before and after ablation of visual (VC) and auditory (AC) cortices. *: Means and standard deviations cannot be calculated because only one animal learned the grating discrimination and none learned the squares discrimination. (C) Behavior of rewired hamsters before and after AC lesions. * indicates that no animals with complete VC lesions learned the grating or squares discriminations when the AC was also ablated. (D) Video micrograph showing retino-MG projections in rewired hamsters. LGv, ventral lateral geniculate nucleus.

those of neurons in the primary visual cortex of normal animals (Metin and Frost, 1989). Ferrets with retinofugal projections to the auditory thalamus but no visual cortex appear to perceive light stimuli as visual (Von Melchner et al., 2000). The question concerning the parallelism between a different brain organization (produced by lesions) and a behavioral recovery is still debated although recent experiments both in rewired ferrets and hamsters seem to indicate a large degree of recovery in visual functions (reviewed in Ptito et al., 2001). For example, responses to visual stimuli have been observed in the auditory cortex of hamsters with robust and permanent projections to the auditory thalamic nucleus (medial geniculate nucleus) lacking a visual cortex. Single neurons in the auditory cortex of these animals respond to visual stimuli and some of them respond equally well to visual as to auditory stimuli (Figure 24.1B). Moreover, cells responding to visual stimuli show orientation selectivity (Figure 24.1C), and motion and direction sensitivity (Figure 24.1D). These receptive field properties compare favorably well with those obtained from cells in the visual cortex of normal hamsters.

At the behavioral level, rewired hamsters can learn visual discrimination tasks as well as normal animals and a lesion of the auditory cortex abolishes this function (Figure 24.2) (Frost et al., 2000). In fact, rewired hamsters with auditory cortex lesions exhibit cortical blindness similar to non-rewired hamsters with visual cortex lesions.

These results provide strong evidence for sensory substitution where a given sensory modality acquires the functional properties of a missing one. Most brain imaging studies in humans have addressed the question of cross-modal plasticity by studying Braille reading or sound perception in the blind. These studies have shown in a convincing manner that early blind subjects show augmented activity in the visual cortex evoked by tactile or auditory tasks compared to late blind or normal seeing subjects. Brain imaging studies in Braille readers have concluded that the brain of the blind is not only functionally reorganized (see reviews by Ptito and Desgent, 2006; Sathian, 2005; Merabet et al., 2005; Sadato et al., 1996) but also anatomically (Shimony et al., 2006; Liu et al., 2007; Noppeney et al., 2005; Ptito et al., 2008b). This raises questions about plastic mechanisms that take place in both the visually deprived and the normal brain as well as about the subjective character associated with activity in these "rewired" areas.

STUDIES IN SIGHTED AND BLIND HUMAN SUBJECTS

How Do We Make Sense of the External World?

If we look around us, no matter how many different things unfold in front of our eyes, we are able to

recognize all of them, to perceive their moving up and down or side by side, to distinguish even the more subtle shadows of color and so on. That is, we seem to have the ability to recognize an infinite number of distinct objects. How this may happen has been a matter of fascinating debates for philosophers and scientists since the early days. Even if the "visual brain" is widely distributed, the cortical surface responsible for integrating all the pieces of information and for recognizing all these object categories is rather limited. Single-cell recording in non-human primates and functional brain imaging studies in humans have suggested the existence of a "fusiform face area" and of a "parahippocampal place area" (Kanwisher et al., 1997; McCarthy et al., 1997). While for these categories, and perhaps a few more, one could even speculate that evolution might have led to the selection of specialized subgroups of neurons given the biological relevance that both face and place recognition have for survival, this certainly cannot be true for the vast majority of object categories. According to an alternative model, different areas in the extrastriate ventro-temporal cortex are specialized for different types of perceptual processes. For instance, the fusiform face area would be responsible for expert recognition of items from any category, not merely faces (Gauthier et al., 1999, 2000). Thus, the peak response to faces shown by this region would be due to the fact that all of us are "face-experts" as we begin to look at faces since the very first days after birth. A few years ago, Haxby and colleagues (2001) proposed a third model, called *Object Form Topology*, that may explain how a limited portion of the brain, such as the extrastriate visual cortex in the inferior surface of the temporal lobe, is capable of distinguishing an infinite number of object categories. The authors examined brain responses by using functional magnetic resonance imaging (fMRI) in a group of healthy young subjects while they viewed items from different object categories, including human faces, cats, houses and man-made objects such as bottles and shoes. The authors found that neural responses to the different object categories were not restricted to specific subregions within the extrastriate ventro-temporal cortex but were rather widely distributed and overlapping. That is, there was not such a thing as a specific response to a given category, say human faces or chairs, limited to a specific neuronal group. Rather, it looked as if most of this cortical area contributed to the elaboration of any of the object categories taken into exam. The authors reasoned that the specificity of the response was not due to the all-or-none activation of a given group of cells, but rather to the specificity of the whole pattern of neural activity elicited by that given category. In other words, this area of the cortex would be able to produce an infinite number of neural response patterns specific for each category of objects being viewed. Indeed, response patterns were so specific that they made it possible to predict what the subject was actually looking at. Moreover, the specificity of the patterns changed only minimally even when the voxels with the maximal response to a given category had been removed from the analysis. On the other hand, all the voxels with maximal response to a given category also responded to the presentation of the other categories. That is, the specificity of the response was not driven by smaller subgroups with the strongest activation within a wider cortical region, but was rather linked to the whole distributed pattern of neural activity (Haxby et al., 2001). Object form topology provides an explicit account for how the ventral temporal cortex can generate unique patterns of neural responses for a virtually unlimited number of categories.

Is Visual Cortex Just for Vision?

The demonstration that the representation of a face or object occurs through the concerted neural activity in a widely distributed cortical area within the ventral temporal cortex raises further questions. Is object form topology in these cortical areas strictly visual or does it represent a more abstract, supramodal functional organization? Furthermore, is visual experience a necessary prerequisite for this functional organization to develop?

Tactile Recognition Studies

We addressed this question in a new series of fMRI studies in sighted and congenitally blind individuals, using finger tactile recognition of the same object categories (Haxby et al., 2001) or tactile recognition of geometric shapes through electrotactile stimulation of the tongue (Matteau et al., 2008). In the first series of studies, we tested whether the response patterns elicited by tactile recognition of face-masks and man-made objects of daily use (plastic bottles and shoes) in blindfolded sighted young subjects are distinct and to what extent response patterns during tactile recognition are similar to those elicited by visual recognition of the same object categories (Pietrini et al., 2004). In the second series of experiments, we evaluated the ability of sighted and blind individuals to recognize shapes designed on their tongue in the form of electrotactile pulses delivered by a tongue display unit (TDU) (Matteau et al., 2008; Ptito et al., 2005).

Tactile recognition activated a large distributed cerebral network that included visual extrastriate regions in the inferior temporal and the ventral temporal cortices.

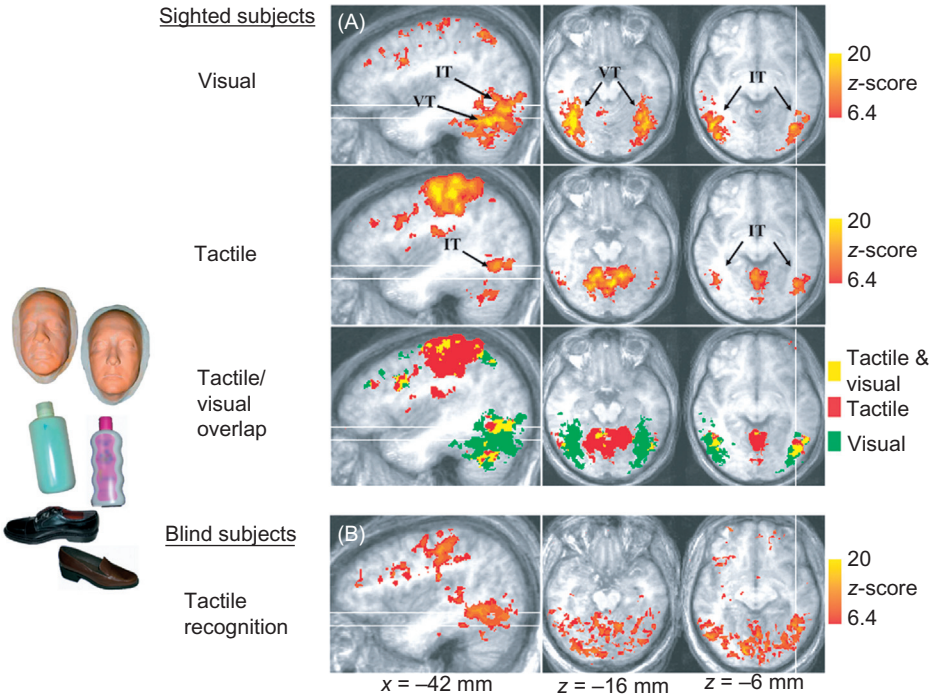

FIGURE 24.3 Supramodal neural response in extrastriate ventral temporal cortex in the human brain. On the left, examples of stimuli (life masks of faces, plastic bottles, and shoes) used during tactile and visual recognition of different object categories in sighted (A) and congenitally blind (B) subjects. On the right side, brain areas that responded during tactile and/or visual object perception in sighted subjects and during tactile perception in blind individuals. The inferior temporal (IT) and ventral temporal (VT) regions activated by tactile and visual object perception are indicated. The tactile/visual overlap map shows the areas activated by both tactile and visual perception (shown in yellow), as well as the areas activated only by tactile (red) and visual (green) perception. The white lines correspond to the locations of the sagittal and axial slices. *Source: Modified from Pietrini et al. (2004).*

In sighted subjects, the temporal areas activated by tactile recognition were also activated by visual recognition of the same object categories and the neural response patterns in these extrastriate cortical regions were category specific (Figure 24.3A). Furthermore, the neural response patterns elicited by tactile perception of bottles or shoes were significantly correlated with the response patterns evoked by visual perception of the same object category, indicating that neural responses for these objects categories in those cortical regions are supramodal in nature; that is, that they are not merely restricted to visual perception (Pietrini et al., 2004). Interestingly, the response pattern during tactile recognition of face-masks was not related to the response pattern evoked by visual recognition of faces. This is likely due to the fact that during tactile recognition subjects were not able to form an image of the whole face but rather focused on single features, such as the chin or nose. This suggests that during tactile recognition of face-masks, subjects processed the faces more like other objects than like holistic face configurations (Kilgour and Lederman, 2002). Even within the visual modality, face inversion compromises configural face processing (Yin, 1969) and is associated with neural activation in extrastriate cortical regions that respond more to non-face objects than to faces (Haxby et al., 1999).

Our results in sighted subjects confirm and extend the finding from other laboratories that visual and tactile object perception activate the dorsal part of the lateral occipital cortex (LO proper) (Amedi et al., 2001, 2002; James et al., 2002) by showing a cross-modal correlation of response patterns between the two sensory modalities. Although findings in normal subjects cannot rule out the possibility that activation in the ventral temporal extrastriate cortex in blindfolded sighted individuals is due to visual imagery during tactile object recognition, this possibility is certainly less likely in congenitally blind individuals who never experienced sight. In this respect, the results of our fMRI study with a sensory substitution device deserve attention (Matteau et al., 2006). This study showed that congenitally blind subjects trained in tactile shape recognition with a tactile-to-vision sensory substitution device activate the inferotemporal cortex during a tactile object recognition task.

Is Vision Necessary to See What We Perceive?

Independent studies have shown that seeing an object or recalling the image of that object through visual imagery leads to similar responses in the brain (Ishai et al., 2000; O'Craven and Kanwisher, 2000). To determine the potential role of visual imagery in the activation of area LO during haptic object exploration, we examined brain responses to tactile recognition of the same object categories in congenitally blind or early blind subjects with no recollection of visual experience who, by definition, do not have any visually based imagery (though they do have imagery!).

Congenital/early blind subjects showed similar category-specific neural response patterns in the

temporal extrastriate cortex as our sighted controls (Figure 24.3B). These findings are crucial in demonstrating that activation evoked by tactile recognition of distinct object categories in ventral temporal extrastriate cortex cannot be explained by visual imagery (Matteau et al., 2008; James et al., 2002; Ishai et al., 2000; Sathian and Zangaladze, 2002). These results also suggest that the development of topographically-organized, category-related representations in the extrastriate visual cortex does not require visual experience. Experience with objects acquired through other sensory modalities appears to be sufficient to support the development of these patterns.

Supramodal Cortical Organization Extends Beyond the Ventral Stream

Visual functions in the brain of human and non-human primates are primarily subdivided into a ventral "what" pathway devoted to recognition of different object categories and a dorsal "where" pathway that is responsible for spatial processing (Ungerleider and Mishkin, 1982; Haxby et al., 1994). The converging evidence discussed above favoring a supramodal functional organization in the ventral temporal cortex of the "what" pathway in the brain has prompted us to ask whether a similar supramodal organization also exists in the "where" pathway of the dorsal stream.

To answer this question, we have studied brain responses to tasks known to activate areas within the dorsal visual pathway, including spatial working memory, mental rotation and perception of translational motion and optic flow. *Optic flow* results from the perception of coherent changes in visual images caused by object or viewer movement (Gibson, 1950). *Tactile flow* involves analogous changes in tactile stimuli caused by object or subject movement. Both optic and tactile motion provide information about object form, position, orientation, consistency and movement, as well as information about the position and movement of the self in the environment (Bicchi et al., 2008). Perception of visual motion activates the human extrastriate cortical region, hMT+ (Ptito et al., 2001; Watson et al., 1993). Perception of tactile motion also results in the activation of hMT+ (Hagen et al., 2002; Blake et al., 2004), suggesting that this area is not merely visual but plays a more general role in the supramodal representation of sensory flow. Since mental imagery of visual movement also activates the hMT+ complex (Goebel et al., 1998), the question arises again whether activation during tactile motion perception is mediated by visual mental imagery.

We therefore compared brain responses in sighted subjects and in individuals with congenital or early blindness during passive perception of visual or tactile motion. Optic motion stimuli consisted of gray dots on a black background whereas tactile motion stimuli were made of raised dots on a plastic surface moving horizontally or rotationally (Ricciardi et al., 2007). In sighted subjects, optic flow perception induced activation in the hMT+ complex in the posterior inferior temporal cortex bilaterally. Tactile flow perception activated the anterior part but deactivated a more posterior part of the hMT+ complex. In blind subjects, tactile flow perception activated a much more extensive region in the inferior temporal cortex that also included the more posterior part of the hMT+ complex, which was activated by visual motion and deactivated by tactile motion in sighted subjects (Figure 24.4). Similarly, using motion detection and motion discrimination tasks in positron emission tomography (PET) and fMRI studies, we were able to demonstrate that motion stimuli applied to the tongue resulted in a significant activation of the dorsal visual pathway, specifically area middle temporal (MT) (Cortex) (Matteau et al., 2006; Kupers et al., 2006) (Figure 24.5).

The observation that the hMT+ complex can be activated by perception of tactile motion even in subjects with congenital blindness demonstrates that recruitment of the hMT+ cortex is not mediated by visual-based mental imagery and that visual experience is not necessary for the development of this cortical system. Visual experience, however, seems to play a crucial role in determining the functional segregation of hMT+ into a more anterior part that is involved in the representation of both optic and tactile motion and a more posterior part that is uniquely involved in the representation of optic flow. If the case that hMT+ develops in the absence of visual experience, the entire structure is involved in the representation of tactile motion. These results suggest that competitive interactions between visual and tactile inputs in normal development lead to functional specialization in hMT+ that does not develop without visual input.

Recently, hMT+ activation was shown in both sighted and congenitally blind individuals also while they listened to auditory stimuli that elicited the apparent perception of sounds moving right-to-left, front-to-back, and self-rotating (Poirier et al., 2006; Ricciardi et al., 2006b).

This supramodal organization extends beyond area MT in the dorsal pathway. Indeed, spatial working memory and mental rotation tasks with visually or tactilely prompted stimuli evoked neural activity in the posterior parietal cortex in sighted subjects (Prather et al., 2004; Reed et al., 2005; Ricciardi et al.,

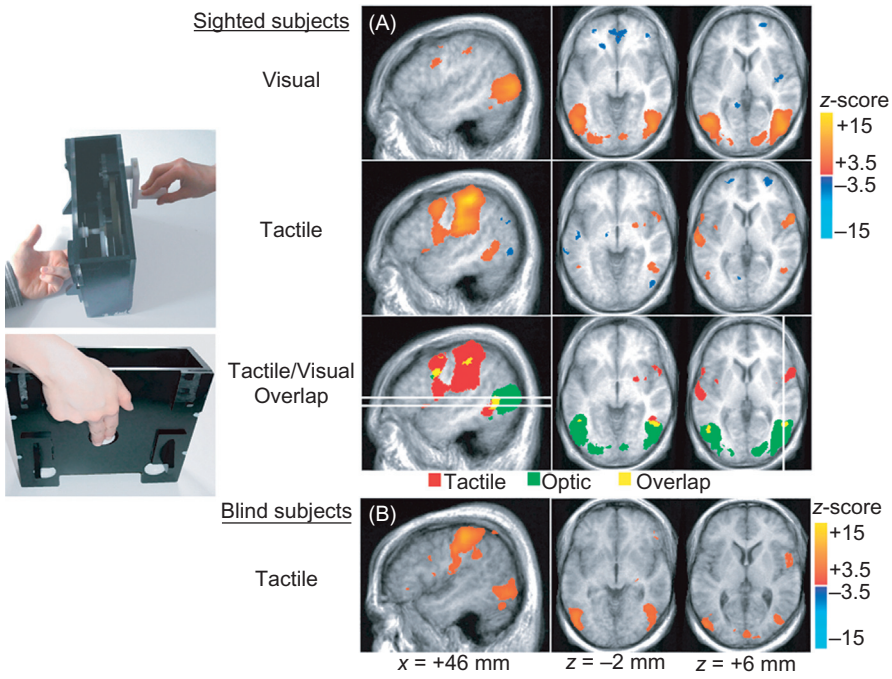

FIGURE 24.4 Supramodal neural response in hMT+ cortex in the human brain. Braille-like dot patterns moved on a plastic surface to provide translational and rotational tactile flow stimulation. Subjects' hands lay on the table with the index and middle fingers touching the plastic surface with dot patterns, as shown in the pictures on the left side. Brain areas are shown that responded during tactile or optic flow perception in sighted subjects (A) and during tactile flow perception in blind (B) subjects. The tactile/visual overlap map shows the areas activated by both tactile and optic flow perception (shown in yellow), as well as the areas activated only by tactile (red) and optic (green) perception. *Source: Modified from Ricciardi et al. (2007).*

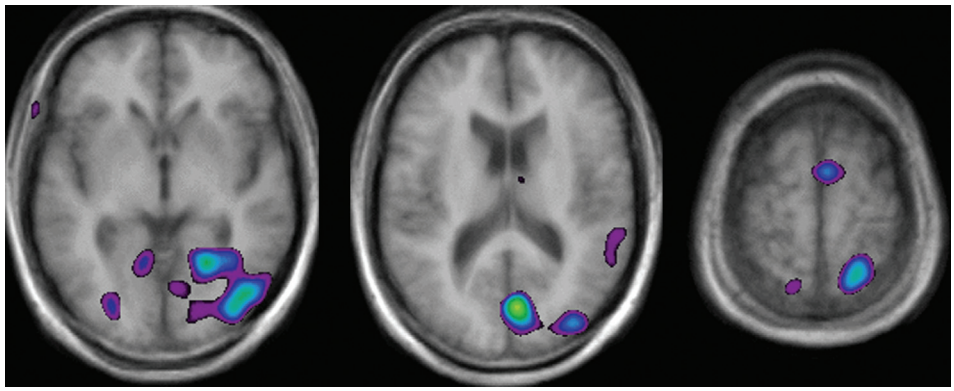

FIGURE 24.5 PET images showing activation of the dorsal visual pathway in congenital blind subjects during a motion direction discrimination task.

2006a; Zhang et al., 2005) as well as in individuals with congenital or early blindness (Bonino et al., 2005). In the latter study, we measured brain activity while sighted and congenital/early blind subjects performed a one-back spatial discrimination task of visually and/or tactilely presented matrices. Tactile matrices were wooden squares and cubes with three or five Velcro-covered target squares/cubes. White squares and rotating cubes with three or five black target squares/cubes represented the two- and three-dimensional visual stimuli. During both the visual and tactile spatial detection tasks, sighted subjects recruited a common fronto-parietal network that extended bilaterally from dorsolateral prefrontal and anterior cingulate cortex towards fronto-parietal sensorimotor and posterior parietal cortices, including precuneus and intraparietal sulci. During the tactile spatial discrimination task, the blind individuals showed a similar cortical activation pattern extending from the fronto-parietal network towards the sensorimotor cortex, the lateral occipito-temporal cortex, and the cerebellum.

Given that spatial visual perception and visual imagery activate common cortical areas in the parietal lobes, we addressed the question whether spatial imagery might also rely on supramodal neural mechanisms. We studied brain activity in a group of sighted and congenital/early blind subjects while they performed a modified version of the mental clock task in three distinct conditions: auditory imagery, tactile discrimination and, for the sighted subjects, visual discrimination (Bonino et al., 2007). During the auditory imagery condition, subjects were asked to imagine two analog clock faces showing the times that were indicated verbally by the examiner, and to judge in which

case the clock hands formed the wider angle. During the visual and tactile angle discrimination conditions, participants compared pairs of clock faces visually or tactilely to decide which hand set formed the wider angle. During the auditory imagery condition, both sighted and congenitally blind individuals activated posterior parietal areas, including the intraparietal sulcus and the inferior parietal lobule. The same areas were activated during the tactile and visual angle discrimination conditions. These findings therefore demonstrate that spatial imagery representation occurs in the posterior parietal extrastriate cortex also when spatial stimuli are not visual in nature.

Altogether, the results of these studies strongly indicate that "visual" association cortical regions are capable of processing and interpreting information carried by non-visual sensory modalities. This is not merely the consequence of a phenomenon of plastic functional reorganization in the brain of subjects deprived of sight since birth or soon afterwards, as this ability also exists in sighted subjects. Not surprisingly, however, sighted and congenitally blind individuals do show differences in the extension and magnitude of the activation of the recruited areas that are likely due to the effects of rearrangements that follow the lack of sight, as discussed in detail below. The supramodal nature of this functional cortical organization may explain how individuals who have never had any visual experience are able to acquire normal knowledge about objects and their position in space, form mental representations of and interact effectively with the external world (Pietrini et al., 2004).

UNDERSTANDING WITHOUT SEEING

Understanding actions carried out by other individuals is crucial for survival and for social organization in human and non-human primates. A particular class of visuomotor neurons, originally discovered in area F5 of the monkey premotor cortex and called *mirror neurons*, discharge both when an animal performs a goal-directed action and observes another individual performing the same or a similar action (Gallese et al., 1996). The fact that this mirror neuron system is able to transform visual information into motor knowledge raises the hypothesis that this system may also have a significant role in action understanding. This has been confirmed by several animal studies showing that the mirror neuron system is recruited when monkeys receive a sufficient number of non-visual clues that allow them to understand the meaning, and create a mental representation of the occurring actions, such as when listening to sounds of actions (Kohler et al., 2002). In fact, a subclass of auditory–visual mirror neurons responds both while monkeys perform hand or mouth actions and while they listen to sounds of similar actions.

Neurophysiological, behavioral and brain functional studies strongly support the existence of an observation–execution matching system in humans similar to the monkey mirror neuron system, that may enable humans not only to understand the actions of others but also to learn by imitation (Rizzolatti and Craighero, 2004). The human mirror neuron system is activated during the observation of actions done by others and recruits a complex network formed by occipital, temporal and parietal areas, and the inferior frontal gyrus. Auditory–visual mirror neurons that allow to understand the actions of others by hearing their sound have been described also in humans (Gazzola et al., 2006).

We recently asked whether an efficient mirror neuron system exists in individuals who have never had any visual experience, and whether this action recognition-oriented network shares common neural patterns in sighted and blind individuals. We measured neural response patterns in congenitally or early blind and sighted volunteers during the auditory presentation of hand-executed action or environmental sounds. Preliminary fMRI findings show that a left premotor–temporo-parietal network subserves action recognition through hearing in blind individuals, and that this network clearly overlaps with the left-lateralized network of the auditory mirror neuron system in sighted subjects (Ricciardi et al., 2008). These findings indicate that visual experience is not a necessary precondition for the functional development of the mirror neuron system and that a more abstract representation of actions done by others may take place also through non-visual sensory modalities. This may help to explain the ability of congenitally blind individuals to learn by imitation of others.

SUBJECTIVE EXPERIENCE ASSOCIATED WITH ACTIVATION OF THE VISUAL CORTEX

We next addressed the question of the subjective character of this visual cortex activation in the blind, by studying the subjective responses induced by transcranial magnetic stimulation (TMS) of the visually deprived and cross-modally responsive occipital cortex. In a first study, we exploited a tactile-to-vision sensory substitution model to examine the subjective character of experience associated with the activation of occipital cortex before and after the establishment of cross-modal plasticity (Kupers et al., 2006). More specifically,

we wanted to test the possibility of whether stimulation of the occipital cortex can induce subjective sensations or qualia associated with the new (tactile) input. We stimulated the occipital cortex with TMS in a systematic manner before and after training with the TDU in a group of blind and blindfolded seeing control subjects. The TDU is a device that captures a visual image, taken by a camera, and translates it into electrotactile stimulation which is applied to the tongue (Bach-y-Rita and Kercel, 2003). With sufficient training, subjects learn to use the TDU to discriminate orientation, detect motion and form. As expected, TMS of the occipital cortex in control subjects only elicited phosphenes. Only two late blind subjects but none of the early blind subjects reported some fugitive central sparks following occipital TMS (Cowey and Walsh, 2000). In sharp contrast, following a 1-week training period with the TDU, some blind subjects reported "tactile sensations" on the tongue following occipital TMS. These tactile sensations were described as short-lasting experiences of distinct tingling, varying in intensity, extent, and topography depending on the locus of the occipital cortex which was stimulated (Figure 24.6).

None of the trained blindfolded subjects reported TMS-induced tactile sensations on the tongue. TMS over the primary SI did not induce any subjective sensations, neither in blind nor in control subjects. Only few reports have described TMS-induced tactile sensations when stimulating SI (Sugishita and Takayama, 1993; Tegenthoff et al., 2005). This may be explained by the fact that excitation of the post-central gyrus requires prolonged repetitive stimulation for accessing the perceptual system (Libet et al., 1964). Not all blind subjects reported TMS-induced tactile sensations following training with the TDU. Although we have no definitive explanation for this intersubject variability, we found a positive correlation between the amount of occipital cortex activated in the PET study during a sensory substitution task and the number of occipital sites from which TMS-induced tactile sensations could be induced.

If tactile sensations referred to the tongue can be induced by stimulating the occipital cortex already following a one-week training period with the TDU, what about TMS-induced tactile sensations in blind subjects who read Braille since childhood? Should not a daily experience with Braille reading also induce tactile sensations referred to the fingertips in proficient Braille readers? An anecdotal observation by Cohen and co-workers (1997) already mentioned that TMS over the occipital cortex in blind Braille readers was able to induce occasional distorted somatosensory perceptions (missing dots, extra dots…) during Braille reading. We therefore addressed the question of remapping of the fingers onto the visual cortex in a subsequent study (Ptito et al., 2008a). Participants were blind subjects who all read Braille on a daily basis and Braille-naive normal sighted controls. Like in the previous study, TMS of the occipital cortex in control subjects evoked only phosphenes. As predicted, blind subjects reported tactile sensations in the fingers that were described as short-lasting tingling sensations, varying in intensity, extent and topography depending on the stimulated locus of the occipital cortex (Figure 24.6). We found again important interindividual differences with respect to the number of sites from which tactile sensations could be induced and in the topography of the referred sensations. The blind subjects with paresthesiae in the fingers following occipital TMS where the ones with the highest amount of Braille reading hours/day and with the highest word reading speed. Like in the previous study, no subjective sensations were produced by TMS over SI in any of the subjects.

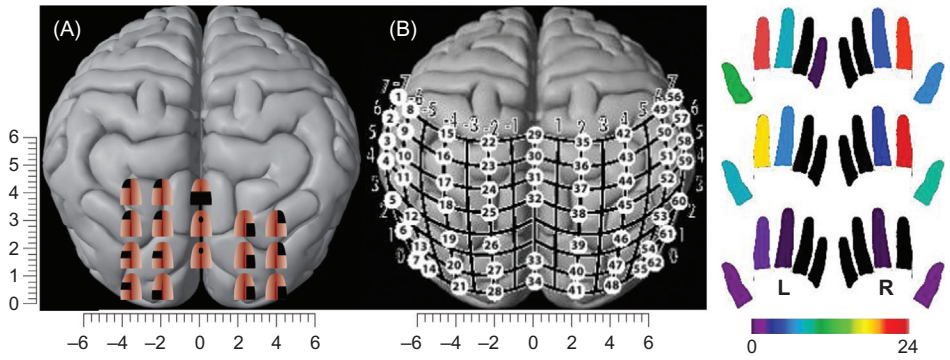

FIGURE 24.6 TMS of the visual cortex in congenitally blind subjects induces tactile sensations. (A) TMS-induced tactile sensations referred to the tongue in a congenitally blind subject following a 1-week training with the TDU. (B) TMS-induced tactile sensations referred to the fingertips in a congenitally blind proficient Braille reader. The color map to the right indicates the fingers in which the subject experienced TMS-induced tactile sensations. The number of visual cortex sites from which paresthesiae could be induced in a particular finger is color coded. On the color scale, red indicates the highest number of cortical sites that induced paresthesiae in a particular finger and purple the lowest number.

Cortical Reorganization or Unmasking?

The results of the experiments described above constitute the first direct demonstration that the subjective experience of activity in the visual cortex after sensory remapping is tactile, not visual. These results provide new insights into the long-established scientific debate on cortical dominance or deference (James, 1890; Hurley and Noë, 2003). What is the experience of a subject in whom areas of cortex receive input from sensory sources not normally project to those areas? Our studies suggest that the qualitative character of the subject's experience is not determined by the area of cortex that is active (cortical dominance), but by the source of input to it (cortical deference). Our results are also in line with recent evidence that sensory cortical areas receive input from multiple sensory modalities early in development (Wallace et al., 2004; Falchier et al., 2002; Rockland and Ojima, 2003). What is the neural mechanism driving this type of cross-modal plasticity? Two competing hypotheses have been put forward. According to the *cortical reorganization* hypothesis, cross-modal brain responses are mediated by the formation of new pathways in the sensory-deprived brain. When the brain is deprived of visual input at an early age, tactile (and other non-visual) information is rerouted to visual cortex. For instance, electrophysiological recording studies in behaving monkeys following early visual deprivation showed that neurons in visual cortical area 19 respond to somatic inputs such as manipulating the experimenter's hand to search for food (Hyvarinen et al., 1991). This is in sharp contrast with the findings obtained in normal seeing animals, in which area 19 neurons respond exclusively to visual inputs. This implies that following early visual deprivation, tactile information reaches the visual cortex. This claim is largely supported by results of functional brain imaging studies showing activation of visual cortex in early blind subjects during Braille reading (Sadato et al., 1996; Buchel et al., 1998; Burton et al., 2002; Gizewski et al., 2003) and other forms of tactile stimulation (Ptito et al., 2005; Burton et al., 2004). The importance of visual deprivation early in early life is further underscored by the observation that brain activity patterns in occipital cortex evoked by tactile stimulation are significantly stronger in early blind compared to late blind subjects (Burton et al., 2002; Cohen et al., 1999). According to the *unmasking* hypothesis, loss of a sensory input induces unmasking and strengthening of existing neuronal connections. Although the results of the second experiment are compatible with both hypotheses, the rapid onset of cross-modal responses in the TDU experiments (within 1 week) excludes the possibility of mediation by the establishment of new anatomical connections and therefore favors the unmasking hypothesis. One possibility is that training unmasks and strengthens pre-existing connections between the parietal and the occipital cortices. There is indeed electrophysiological (Fishman and Michael, 1973) and anatomical (Falchier et al., 2002; Rockland and Ojima, 2003) evidence that primary visual cortex in normal mammals receives input not only from the visual thalamus, but also from somatosensory and auditory modalities. Single unit recordings in the visual cortex in unanesthetized cats have shown that neurons in areas 17 and 18 receive both visual and auditory input (Fishman and Michael, 1973). Anatomical tracing studies have further shown that there are direct projections from the auditory cortex to area 17 of the macaque monkey (Falchier et al., 2002). Direct projections from parietal association areas to areas V1 and V2 in the calcarine fissure have also been described (Rockland and Ojima, 2003). These non-visual inputs conveying tactile and auditory inputs to occipital cortex may modulate the processing of visual information (Macaluso et al., 2000), while not giving rise to subjective non-visual sensations under normal circumstances due to masking by the dominant visual input. In this respect it is interesting to mention the results of a TMS study which showed that disrupting the function of the visual cortex by TMS impairs tactile discrimination of grating orientation in normal seeing subjects (Zangaladze et al., 1999). This confirms that although the visual cortex receives tactile input, this normally does not lead to subjective tactile sensations. Thus, in our trained control subjects, TMS over occipital cortex produced only phosphenes, without tactile sensations. However, under certain circumstances, non-visual processing in the occipital cortex can be strengthened or unmasked. In line with the dynamic sensorimotor hypothesis, training with the TDU device results in new highly specific learned dynamic interaction patterns between sensory stimulation and active movement (O'Regan and Noe, 2001), thereby further strengthening and unmasking existing connections between the parietal and occipital cortices.

HOW BLINDNESS SHAPES THE BRAIN

What is the effect of visual deprivation on the gross anatomical organization of the brain and by which pathways does non-visual information reach the occipital cortex in the visually deprived brain? In recent years, modern brain imaging tools such as voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and diffusion tensor tractography (DTT) have been used to investigate alterations in gray and white matter of the brain of the blind *in vivo*

(Shimony et al., 2006; Noppeney et al., 2005; Ptito et al., 2008b; Pan et al., 2007; Chebat et al., 2007). The results of these studies seem to concur that there is a significant atrophy of all structures belonging to the visual pathways, including the lateral geniculate and the posterior pulvinar nuclei (Ptito et al., 2008b), the striate and extrastriate visual areas (Noppeney et al., 2005; Ptito et al., 2008b; Pan et al., 2007), and the inferior temporal gyrus and lateral orbital cortex, areas that are part of the ventral stream which is involved in object recognition (Ptito et al., 2008b). Reductions also occur in non-visual structures such as the posterior hippocampus (Ptito et al., 2008b; Chebat et al., 2007). Changes in white matter include atrophy of the optic tracts and optic chiasm, the optic radiations, the splenium of the corpus callosum (Shimony et al., 2006; Noppeney et al., 2005; Ptito et al., 2008b; O'Regan and Noe, 2001) and the inferior longitudinal fasciculus, a fiber bundle that connects the occipital cortex with the temporal lobe (Ptito et al., 2008b). The latter pathway is involved in several visual functions and lesions of it may induce visual agnosia, prosopagnosia, and disturbances in visual recent memory (Tusa and Ungerleider, 1985; Catani et al., 2003). In general, no studies reported direct evidence for the establishment of new pathways but only volume increases in existing cortico-cortical pathways. We reported a significant enlargement of the occipito-frontal fasciculus, the superior longitudinal fasciculus and the anterior portion (genu) of the corpus callosum (Figure 24.7). However, there seems to be indirect evidence for increased functional connectivity between parietal and visual areas in the blind.

For instance, a combined TMS–PET study reported that TMS of SI induces a significant blood flow increase in the occipital cortex in early blind but not in blindfolded control subjects (Wittenberg et al., 2004). In addition, we showed that functional connectivity between the dorsal intraparietal sulcal area and the cuneus is increased in blind (but not in control) subjects trained with the TDU (Ptito et al., 2005). Moreover, somatosensory evoked potentials induced by electrical stimulation of the tongue after training with the TDU revealed in addition to the short latency (13–18 ms) N1–P1 complex over the parietal cortex, a second peak over the occipital cortex after 48–60 ms, suggesting a mediation by a cortico-cortical pathway (Kupers et al., 2006). Taken together, since no additional tracts have been demonstrated so far in early blind subjects, the data suggest that cross-modal functionality of the visual cortex in early blindness is primarily mediated by preserved or strengthened cortico-cortical connections. These cortico-cortical connections involve a pathway from SI to either VIP (ventral intraparietal area) or area 7 (or both), then to areas MT and V3 to finally reach the visual cortex.

A DARWINIAN STRUGGLE FOR SURVIVAL?

Although the majority of the studies have focused on the rerouting of tactile input to the visual cortex, the occipital cortex in the blind is involved in many more functions than just tactile processing. There is now a wealth of data showing that this cortex is activated in tasks involving lexical and phonological processing (Röder et al., 2002; Burton et al., 2003), verbal memory (Amedi et al., 2004; Raz et al., 2005), repetition priming (Kupers et al., 2007), auditory discrimination (Weeks et al., 2000; Gougoux et al., 2005), and selective attention (Stevens et al., 2007). This seems to suggest that the visually deprived occipital cortex is involved in a bewilderingly diverse compensatory plasticity. How to understand this multiplicity of cognitive functions of the occipital cortex in the blind? Does it reflect some kind of Darwinian principle of struggle for survival? As humans, we are living in a very visual world. This is already reflected by the fact that the visual cortex in primates covers about 30% of

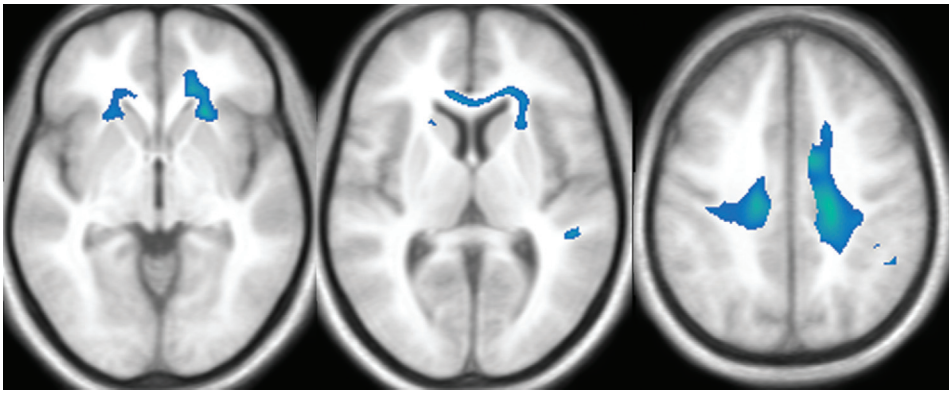

FIGURE 24.7 Increases in the white matter in the brain of congenitally blind subjects as revealed by VBM.

the total cortical surface. Therefore, the loss of vision is one of the most incapacitating events that can happen to a person. In order to survive in our very visual world, blind subjects have to rely on other senses and develop these in a supranormal manner. As a result, they develop superior tactile and auditory discriminatory capacities as well as superior verbal memory functions to compensate for their loss of vision. Many functional brain imaging studies have shown that enhanced practice leads to an enlargement of cortical representations (Draganski et al., 2004; Bengtsson, 2005). In the normal brain, this is always reflected by an enlargement of the cortex that is normally involved in the execution of the task (e.g., an expansion of the motor cortex in musicians (Bengtsson, 2005; Lotze et al., 2003)) and not by the recruitment of novel cortex. In case of loss of a sensory input, the opposite occurs. Rather than getting an expansion of the cortex proper for the execution of the task, the brain recruits *de novo* cortex which is normally not involved in execution of this particular task. This may represent a Darwinian reflex for survival. Recruitment of the visually deprived occipital cortex is a much more cost-effective computational solution since it does not put extra demands on the cortex which is normally used for executing this task, thereby leaving sufficient resources available for situations of increased demand. The pathways through which this occurs are available since birth but in the normal brain, activity is masked by the dominant specific afferent input to a particular cortical region.

How does the rewired cortex cope with this multitude of new inputs? Is there some kind of segregation of functions or does the visually deprived cortex become genuinely multimodal? It is difficult to answer this question since most studies only investigated one or at best a few cognitive functions in the same subjects. One of the few studies that investigated the cortical representation of multiple cognitive functions in the occipital cortex of the blind suggest that different functions may indeed be segregated anatomically (Amedi et al., 2003). However, more studies are needed to confirm these preliminary findings. The idea that different functions are anatomically segregated in the cortex of the blind may also provide an answer to a prominent question raised by our TMS studies. How is it possible that TMS of the occipital cortex induces tactile sensations referred to the tongue after a one-week training period and in the fingertips in Braille readers but that it never evoked any auditory sensations or lexical or semantic thoughts? A possible explanation is that these rewired functions are located more anteriorly and hence further away from the TMS coil which makes them more difficult to evoke by stimulating at submaximal intensities.

FINAL CONSIDERATIONS

The study, in animals and in humans, of the dark-reared brain has shed a bright light on many questions regarding not only the plastic rearrangements that take place when vision is absent but also on the functional organization of the sighted brain itself. In this respect, the availability of novel non-invasive methodologies for the functional exploration of the brain in the past 25 years has made it possible to begin to understand the neural mechanisms that enable awareness of the surrounding world and make sense of it (Pietrini, 2003). In this chapter, we have reviewed and discussed some new findings from studies from our own labs as well as from others. We are well aware that the issues that we have considered are only a few among the many more that an ambitious topic such as the relation between blindness and consciousness may raise. For instance, we have completely omitted to discuss cortical blindness, as well as the effects of congenital blindness versus blindness acquired at different ages, or the effects of monocular vision. Moreover, we have only briefly touched upon the "blind social brain," a topic that merits a whole book by itself, not to mention emotional life and its disturbances. As was shown in this chapter, we have already learned a lot and we can still learn much more about the sighted brain by observing the blind brain.

A final important thought prompted by the many different findings from studies in animal and humans is that the blind brain should not be considered as a "disabled" brain but rather as a truly "differentially able" brain.

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CHAPTER

25

The Neurology of Consciousness: An Overview

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OUTLINE

Many chapters of this book present a composite picture of the relationship between consciousness and the brain, as seen from several different angles by many different authors. Can one discern, from such a fragmented perspective, the contours of the neural process underlying consciousness, the ghost in the machine? Not yet, a skeptical reader casting a cold eye on this book might conclude; or perhaps something is beginning to emerge, though dimly. But at least, this volume should have made clear that neurological investigations, often forgotten by philosophers and neuroscientists alike because what they offer is often rough, dirty, and idiosyncratic, still provide the fundamental empirical evidence concerning the physical substrate of consciousness: it is by examining how human consciousness is drastically changed by anatomical or functional changes in the brain, and conversely by considering which changes in brain structure and dynamics do not seem to affect consciousness

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much, that over the past 100 years or so we have been learning the lay of the land.

This final chapter attempts to provide the reader with an overview of the neurological and neurobiological literature, stating what seems to be reasonably established and what is instead still open or unknown. First, the chapter reviews the evidence suggesting that consciousness can be dissociated from other brain functions, such as responsiveness to sensory inputs, motor control, attention, language, memory, reflection, spatial frames of reference, the body and perhaps even the self. The chapter then summarizes what has been learned by studying global changes in the level of consciousness, such as sleep, anesthesia, seizures, and post-comatose states. Next, it asks what can be said at this point about the neuroanatomy and the neurophysiology of consciousness. The chapter ends by briefly considering how a theoretical analysis of the fundamental properties of consciousness can complement neurobiological studies.

CONSCIOUSNESS AND OTHER BRAIN FUNCTIONS

Many suggestions have been ventured in the hope of alleviating the puzzle of subjective experience. Perhaps consciousness emerges somehow when an organism is immersed in some complex sensorimotor loop that includes the environment. Another common idea is that consciousness may arise when one part of the brain, acting as the "subject" (typically the front), looks upon another part as its object (typically the back), and evaluates or reflects upon its activity. It is often thought that in the end consciousness may be reduced to attention and its brain mechanisms, since we are usually conscious of what we attend. Much could be said about each of these suggestions. Here, we consider some recent results (and some very old evidence) indicating that consciousness—in the sense of having an experience—does not require sensorimotor loops involving the body and the world, does not require language, introspection, or reflection, can do without spatial frames of reference and perhaps even without a sense of the body and the self, and does not reduce to attention or memory. Likewise, consciousness must not be confounded with processes that directly precede or follow experience itself, such as expectation, task planning, self-monitoring, unconscious stimulus processing, or giving a report (Revonsuo, 2000; Hohwy, 2009; Aru et al., 2012b; de Graaf et al., 2012; Miller, 2014). Due to space limitations, we will not discuss the relationship between consciousness and time, between consciousness and emotion, or the notion of conscious access.

Consciousness and Sensory Input/Motor Output

We are usually conscious of what goes on around us, and occasionally of what goes on within our body. So it is only natural to think that consciousness may be tightly linked to the ongoing interaction we maintain with the world and the body. However, there are many examples to the contrary. We are conscious of our thoughts, which do not seem to correspond to anything out there; we can also imagine things that are not out there. When we do so, sensory areas can be activated from the inside (Kosslyn et al., 2001), though there are some differences (Amedi et al., 2005). Also, stimulus-independent consciousness is associated with its own patterns of activation within cortex and thalamus (Mason et al., 2007). During dreams, we are virtually disconnected from the environment (Hobson et al., 2000)—hardly anything of what happens around us enters consciousness, and our muscles are paralyzed (except for eye muscles and diaphragm). Nevertheless, we are vividly conscious: all that seems to matter is that the corticothalamic system continues to function more or less like in wakefulness, as shown by unit recording, electroencephalography (EEG), transcranial magnetic stimulation (TMS), and functional neuroimaging studies performed during rapid eye movement (REM) sleep, when dreams are most intense (Maquet et al., 1996; Braun et al., 1997; Massimini et al., 2010; Siclari et al., 2014b) (Chapter 7). Interestingly, certain regions of the corticothalamic systems, such as dorsolateral prefrontal cortex, are deactivated in REM sleep, which likely accounts for some peculiarities of dreaming experiences, such as the reduction of voluntary control. Recently, it has been shown that these brain areas are reactivated during lucid dreaming, when one knows that one is dreaming and is able to control their dream (Dresler et al., 2012).

Neurological evidence also indicates that neither sensory inputs nor motor outputs are needed to generate consciousness. For instance, retinally blind people can both imagine and dream visually if they become blind after 6–7 years of age or so (Hollins, 1985; Buchel et al., 1998) (Chapter 24). Patients with the locked-in syndrome can be almost completely paralyzed, and yet they are just as conscious as healthy subjects (Laureys et al., 2005; Lule et al., 2009) (Chapter 12) and can compose eloquent accounts of their condition (Bauby, 1997). A transient form of paralysis is one of the characteristic features of narcolepsy. Severe cataplectic attacks can last for minutes and leave the patient collapsed on the floor, utterly unable to move or to signal, but fully aware of their surroundings (Guilleminault, 1976; Siegel, 2000). Drug addicts known as *frozen addicts* who show symptoms of severe Parkinson's disease due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced damage to

the dopaminergic system are also fully conscious, yet unable to move or speak (Langston and Palfreman, 1995, 2014). Thus, consciousness here and now seems to depend on what certain parts of the brain are doing, without requiring any obligatory interaction with the environment or the body.

Consciousness and Language

There have been claims that consciousness only emerges with language (Macphail, 1998), though it seems preposterous to suggest that infants and animals are unconscious automata. Neurological evidence from adult humans can help settle the issue by asking whether consciousness is preserved in patients with aphasia. Nichelli (Chapter 23) reviews the evidence indicating that even deep aphasia does not seem to interrupt the flow of experience, though it may alter or abolish certain aspects of it, such as inner speech. He points to the remarkable interview with Dr. Jill Bolte-Taylor, a neuroanatomist who was struck with a left hemisphere hemorrhage. Over the course of 3–4 h, she lost her inner speech, became hemiparetic, and soon realized that her utterances did not make sense, nor did those of others. In her retrospective recall of that time, she experienced the loss of function of a good part of the left hemisphere, language included, and remained fully conscious, though things felt differently from a "right hemisphere perspective." Her account not only confirms that consciousness continues in the absence of language—or at least left hemisphere specializations having to do with comprehension and production, but that thought and self-reflection continue too. Another extraordinary report is from a patient who underwent an anesthetic injection (Wada test) into the lower division of the left middle anterior artery. The anesthetic presumably led to the inactivation of posterior temporal, inferior parietal, and lateral temporo-occipital region of the left hemisphere, and caused as expected a deep Wernicke aphasia indistinguishable from that due to strokes, except that it was temporary (a few minutes) and fully reversible (Lazar et al., 2000). From the patient's recollections of the experience, it is clear not only that he was conscious and thinking, but that he also had a much better understanding of the situation than appeared from the language tests being administered. Moreover, he could usually recall what happened and what he was trying to do, especially when presented with pictures rather than with spoken or written material. For instance, he recalled that he was desperately trying to identify the picture of a tennis racket, of which he was fully aware, but all that came out was "perkbull." He wanted to add that he owned one, but thought he had said instead that he had just bought one—in reality, he had said nothing. These examples leave little doubt that experience continues after the loss of the left hemisphere's language functions.

Consciousness and Introspection/Reflection

Consciousness is usually evaluated by verbal reports. Questions about consciousness ("Did you see anything on the screen?") are answered by "looking inside" retrospectively and reporting what one has just experienced. So it is perhaps natural to suggest that consciousness may arise through the ability to reflect on our own perceptions: our brain would form a scene of what it sees, but we would become conscious of it—experience it subjectively—only when we, as a subject of experience, watch that scene from the inside. This suggestion is often framed in a neurobiological context by assuming that patterns of activity corresponding to "unconscious" or "subconscious" percepts form in posterior regions of the cerebral cortex involved in the categorization/association of sensory stimuli. These percepts then become conscious when mainly anterior prefrontal and cingulate regions involved in self-representations interact with posterior cortex, perhaps by reading in signals through forward connections and selectively amplifying them through back-connections (more on this later).

There is of course no doubt that the brain categorizes its own patterns of activity, in the sense that neurons respond mainly to the activity of other neurons, so the brain is constantly "looking at itself." However, this is not necessarily in terms of a "subject" (the front) looking at an "object" represented in sensory cortices (the back). Leaving aside the mystery of why reflecting on something should make it conscious, this scenario is made less plausible by a common observation: when we become absorbed in some intense perceptual task, for example watching an engrossing movie, playing a fast-paced video game, or rushing through the woods at high speed, we are vividly conscious—we are immersed in the rapid flow of experience—without any need for reflection or introspection. Often, we become so immersed in such flow that we may lose the sense of self, the inner voice. Perhaps the habit of thinking about consciousness makes the experts forget that much of experience is unreflective.

A neuroimaging study throws some interesting light on these old observations (Goldberg et al., 2006). Subjects were scanned with functional magnetic resonance imaging (fMRI) in three conditions (Figure 25.1). In the slow categorization task, subjects were asked to categorize pictures into animal/no-animal categories. During the introspective task, subjects viewed the images and then self-introspected about their emotional response (strong/neutral). Finally, the fast categorization task was identical to the "slow" condition but at

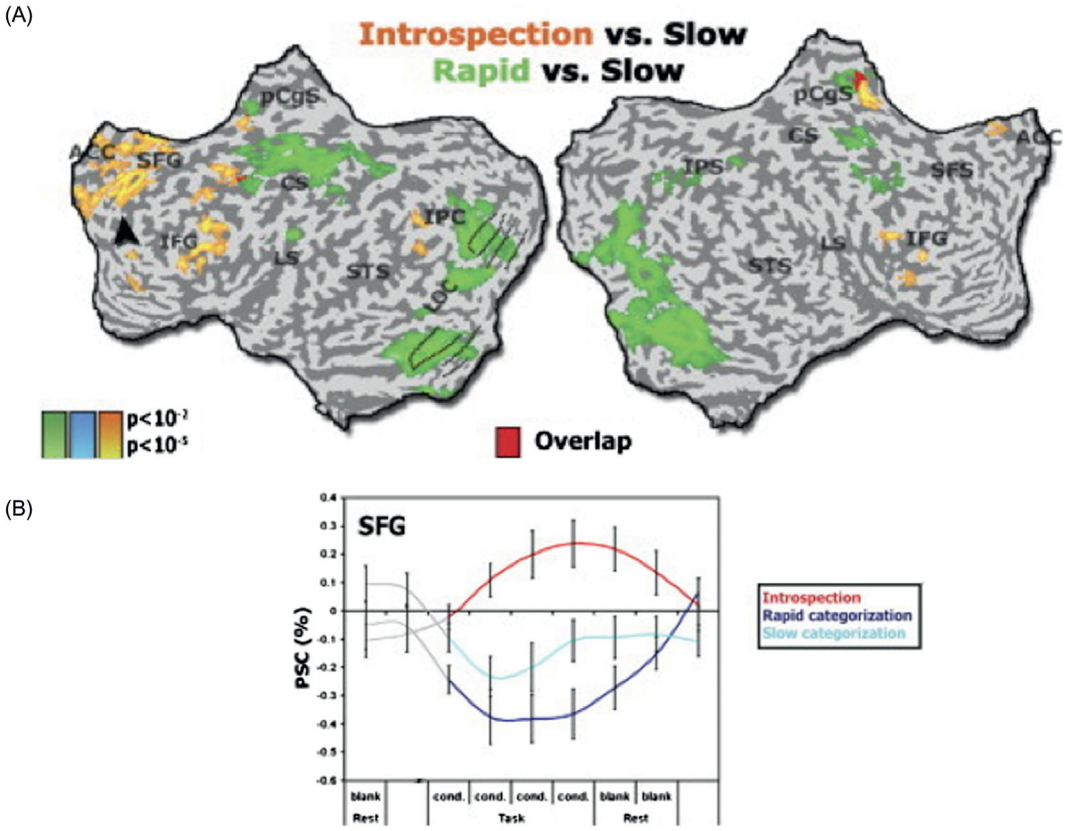

FIGURE 25.1 Introspection versus sensorimotor activation. (A) Main activation for introspection (versus slow categorization) is in prefrontal areas and lateralized to the left hemisphere (yellow-orange) whereas main activation for rapid categorization (versus slow categorization) is in the left motor and bilateral premotor regions (green). (B) Averaged time courses from the left superior frontal gyrus (SFG) during introspection (red), rapid (dark blue), and slow (light blue) categorization conditions. Only introspection showed a positive response in this area. ACC, anterior cingulate cortex; CS, central sulcus; IFG, inferior frontal gyrus; IPC, inferior parietal cortex; IPS, intraparietal sulcus; LOC, lateral occipital complex; LS, lateral sulcus; pCgS, paracingulate sulcus; SFG, superior frontal gyrus; SFS, superior frontal sulcus; STS, superior temporal sulcus. *Source: Adapted from Goldberg et al. (2006).*

triple the stimulation rate. Thus, "slow" and "introspection" conditions were identical in terms of sensory stimuli and motor output but differed in the cognitive task. On the other hand, "slow" and "rapid" conditions were similar in the cognitive task but differed in the sensorimotor processing and attentional loads. Behavioral measurements confirmed that self-awareness was high during the introspection task, and virtually abolished during rapid categorization. The neuroimaging results were clear: during introspection task there was an activation of prefrontal regions, whereas sensory cortex was strongly activated during rapid categorization (Figure 25.1). Crucially, during the rapid categorization task self-related cortex was deactivated below the rest condition (Chapter 6). This deactivation of prefrontal regions was thus the neural correlate of "losing oneself" in the categorization task. To the extent that these prefrontal regions were indeed involved in self-representation, these findings suggest that their activation is not necessary for the emergence of perceptual consciousness, but only to reflect upon it and report it to others. Indeed, it appears that self-related activity is actually shut off during highly demanding sensory tasks (Goldberg et al., 2006). A recent fMRI study of binocular rivalry employing optokinetic nystagmus and pupil size also showed that frontal activity relates to introspection and report rather than to conscious perception (Frässle et al., 2014).

Consciousness and Attention

Attention and consciousness often go hand-in-hand: when we pay attention to an object, our experience of it becomes more vivid, and when we shift our attention, it fades from consciousness. Attention can be bottom-up, as when a salient stimulus—say a flash or a sound turn our gaze or a colored letter in the middle of a black text pops out at us, capturing attention. Top-down attention instead is willingly deployed toward a particular position in space, a particular feature, or a particular object. It is often assumed that attention is a necessary prerequisite for consciousness. For

example, if we do not attend to it, we may fail to see a large, stable stimulus at the very center of the visual display—the phenomenon known as inattentional blindness (Mack and Rock, 1998). This view had led many authors to think that consciousness and attention are indistinguishably intertwined, if not identical (Chun and Wolfe, 2000; De Brigard and Prinz, 2010; Cohen and Dennett, 2011; Marchetti, 2012). However, already Wundt and James argued that attention was a mechanism for selecting within consciousness, and many studies since have reinforced this view (Baars, 1997; Lamme, 2003; Koch and Tsuchiya, 2007, 2012).

Tsuchiya and Koch make an especially strong case for a double dissociation between visual attention and visual consciousness (Koch and Tsuchiya, 2007, 2012) (Chapter 5). For example, paying attention to a stimulus decreases the duration of its afterimage, whereas seeing the stimulus consciously increases the afterimage duration, suggesting that attention and consciousness have contrasting effects (van Boxtel et al., 2010). The tip-of-the-tongue phenomenon may be a familiar demonstration that attention may actually interfere with consciousness. There are by now many reports, both in blindsight patients and healthy subjects, indicating that attention can facilitate responses to unseen stimuli (Kentridge et al., 1999, 2008; Zhang et al., 2012; Kentridge, 2013). For instance, a recent study using continuous flash suppression showed that a pop-out target can capture attention even when the stimulus itself is invisible (Hsieh et al., 2011). Another recent study reported that post-cued attention can retrospectively trigger the conscious perception of a stimulus that would otherwise have remained unconscious, and this effect lasts up to 400 ms after stimulus presentation (Sergent et al., 2013). Attention without consciousness has now been demonstrated in more than 40 experiments manipulating bottom-up as well as top-down spatial, temporal, feature-based, and object-based attention (Dehaene et al., 2006; van Boxtel et al., 2010; Cohen et al., 2012). Some neurophysiological and neuroimaging evidence also seems consistent with this view. For instance, an event-related potential component (N2pc) that appears to be a correlate of top-down attention can be elicited by stimuli that remain invisible (Woodman and Luck, 2003); also, attention to an invisible stimulus can increase the activation of primary visual cortex (Bahrami et al., 2007). Finally, a magnetoencephalography study showed that consciously seen stimuli induced increased mid-frequency gamma-band activity over contralateral visual cortex whether attended or not, whereas spatial attention modulated high-frequency gamma-band activity in response to both consciously seen and unseen stimuli (Wyart and Tallon-Baudry, 2008). In summary, attention can be deployed to stimuli that remain unconscious, selective attention does not necessarily result in conscious experience, and may even be counterproductive.

The complementary dissociation—consciousness without attention—is more controversial. When we contemplate an empty blue sky, there is no need for selective attention, and yet the experience is vivid. Conversely, when we attend intensely onto something, the world outside the focus of attention does not disappear from consciousness: we still experience the gist or context of the overall visual scene that faces us. Indeed, as observed by Tsuchiya and Koch, gist is immune from inattentional blindness (Mack and Rock, 1998)—when a photograph covering the entire background is briefly and unexpectedly flashed onto the screen, subjects can accurately report a summary of its content. In the 30 ms necessary to apprehend the gist of a scene, top-down attention cannot play much of a role. Similarly, a subject engaged in a task that requires focusing attention on the center of the visual field, can still perceive the difference between a background scene containing an animal or a vehicle from one that does not. Of course, while the gist of a scene may be experienced vividly, it is also coarse (Campana and Tallon-Baudry, 2013). For example, outside the focus of attention subjects cannot differentiate between a red-green bisected disk and a green-red one (Li et al., 2002). Or consider what happens when one is driving home on a familiar segment of the highway while attending to an engaging radio program. While we are not attending the familiar and monotonous road, does it mean that we do not experience at all, or is rather that we do not need to form explicit memories (see below)? Finally, as indicated by neuroimaging studies mentioned above, consciousness without attention and consciousness with attention may have different neural correlates: Victor Lamme has suggested that consciousness without attention could be generated by interactions among posterior regions of the cortex, whereas when top-down attention boosts conscious experience prefrontal cortex enters the game through reentrant interactions with posterior cortex (Lamme, 2006). We will return to this distinction when considering the role of the front versus the back of the brain in generating consciousness.

Consciousness and Memory

Considerations similar to those just reviewed for attention are likely to apply to working memory—the ability to keep things in mind for a few seconds. Indeed, attention and working memory are closely related and may be conceptualized as two different aspects of the same process (Olivers, 2008): attention selects some aspects of an existing scene, whereas working memory

selects the same aspects in the absence of the stimulus. Moreover, the neural structures subserving working memory and top-down attention overlap to a large degree both anatomically and functionally (Mayer et al., 2007). Should one then expect a double dissociation also between working memory and consciousness? This question is complicated by the need to distinguish between the targets of attention, working memory, and imagery, typically located in posterior cortex, where activity is either enhanced in response to a stimulus, or else maintained or even generated in its absence; and control mechanisms, typically located in anterior cortex, which are responsible for directing attention, manipulating contents of working memory, and generate images (Postle, 2006).

Nevertheless, recent studies indicate that working memory can be engaged without awareness (Hassin et al., 2009; Soto and Silvanto, 2014). For instance, subjects can maintain in memory some visual cues during a delay period filled with similar distractors and perform above chance level even though they are not conscious of the cues, as shown by an awareness rating scale (Soto et al., 2011). Also, perceptual processing of unseen stimuli can be biased top-down by working memory (Pan et al., 2014). Moreover, arithmetic problems involving working memory can be solved based on information that remains unconscious (Ric and Muller, 2012; Sklar et al., 2012). Finally, monkeys who had their primary visual cortex removed can make accurate saccades to a target presented in the blind field even after the target has disappeared from the screen (Takaura et al., 2011). Conversely, it is undisputable that one can be conscious of something without exercising working memory, as when we follow the rapid flow of images in a movie. Indeed, when photographs or line drawings are flashed at a rapid rate, subjects are very poor at remembering a particular picture at a later time, yet they have no trouble seeing it—and detecting it—if they are cued prior to the experiment (at 110−333 ms/picture, the experience is one of "grasping and losing large amounts of information within moments") (Intraub, 1999). Also, several examples of inattentional blindness may actually be cases of *inattentional amnesia* (Wolfe, 1999). The latter may be the rule for low-level features, partly because these features should be reset every time the image changes, and partly because it seems neither possible nor particularly useful to store a detailed snapshot of every fleeting activation pattern in low-level visual areas. Finally, there are disorders, typically associated with prefrontal lesions, in which working memory is severely compromised but consciousness is clearly preserved (Muller and Knight, 2006).

The relationship between consciousness and episodic memory (also known as autonoetic memory) is complex, but there is little doubt that consciousness can be present even when episodic memory is impaired (the converse would seem to be out of the question). In syndromes of transient amnesia, patients are obviously conscious—they engage in conversations, carry out complex tasks, but later show no memory of what they did (anterograde amnesia) (Bartsch and Deuschl, 2010) (Chapter 22). Butler and Zeman discuss a case described by Hughlings-Jackson in which a doctor suffering from epileptic transient amnesia visited a patient, correctly diagnosed pneumonia, and wrote down prescriptions and notes without remembering anything about the episode. Perhaps the amnesia for a stretch of familiar highway is a normal example of the same dissociation: under normal circumstances, if our attention is engaged elsewhere, and if there is no particular reason to engage it on the scene we face when driving, we may simply not burden hippocampal circuits to lay down useless memories. In transient amnesia, the hippocampus may not be capable of laying down memories, either due to some kind of trauma (transient global amnesia) or because it is preempted by seizure activity (transient epileptic amnesia). When damage to the hippocampal formation is permanent, as with the bitemporal resection suffered by H.M. and similar patients, anterograde amnesia is permanent, and the patient is limited to the immediate present and to the content of his working memory (Squire, 2009; Corkin, 2013). Yet as described by Postle (Chapter 21), when interacting with H.M. there was little doubt that he was conscious.

On the other hand, when amnesia is deep, consciousness is altered in peculiar ways. Usually, patients with transient amnesia appear to be confused and uncertain about the past (retrograde amnesia). H. M. and other patients recounted by Postle (Chapter 21) describe an unsettling feeling of entering the world as from deep sleep, when we may be briefly unsure about who we are and where we are, except that feeling in their case is permanent. Possibly, this deficit may also reduce the window of time over which the conscious present flows. Moreover, several studies have shown that patients with damage to the hippocampal formation also show a deficit in imagination, not just in memory, and their account of the world, both remembered, experienced in the present, and imagined, appears to be less rich, lacking in color, detail, and spatial coherence (Lee et al., 2005a; Barense et al., 2007; Hassabis et al., 2007; Mullally et al., 2012). This view fits nicely with evidence for a role of the hippocampal formation in responding to as well as storing relations among objects in a context-dependent (episodic) manner (Hannula et al., 2006). Over time and over multiple episodes of retrieval the memory is transformed to one that is more schematic (semantic) and independent of the hippocampus (Nadel and Moscovitch, 1997; Winocur et al., 2007). Thus, while consciousness

remains in the absence of episodic memory and of the hippocampal formation, it does seem to lose not just an external sketchpad for writing down memories, but actually a part of itself.

Consciousness and Space

We all have the strong impression that much of experience is situated in an outside, external space. In turn, this external space is centered on an internal space, that of the body. And, whenever we think about our own experience, nothing is stronger than the feeling that it is centered somewhere within the head, roughly between the eyes. Can consciousness even exist without any representation of space, or of our own body, or without our "first-person" perspective, centered somewhere behind the eyes? These questions are hard to answer on the basis of neurological evidence because maps of space and of the body are widespread, and lesions that eliminate all such maps would have to be so wide as to make any firm conclusion unwarranted. Nevertheless, a few lessons can still be learned.

Neurophysiological studies have demonstrated that the brain employs multiple maps of external space, some unimodal, some multimodal, many in the cerebral cortex, especially but not exclusively in parietal lobes, but some also in thalamus and colliculi. Parietal areas receive converging visual, auditory, and touch inputs, as well as proprioceptive and vestibular signals about the position of the eyes, head, and limbs. These maps implement different frames of reference, so there are eye-centered, head-centered, and body-centered maps, maps for distant space and maps for peri-personal space (Robertson, 2004). Attention can rapidly shift between one frame of reference and the other, and there are indications that more global frames of reference may be a specialty of right hemisphere maps, whereas more local maps are a specialty of the left. It is also clear that, under normal conditions, many different maps are kept in register for smooth functioning, and that posterior parietal cortex, especially on the right side, is important in coordinating these various maps, perhaps through what has been called a master map. Indeed, studies in monkeys have identified neurons that respond only to the stimulus that is being selected as the current target for attention—a kind of a winner-takes-all principle over space, and do so in a stable manner, in line with the need of a stable perceptual representation of a target for action (Andersen et al., 2014). This fits with the finding that parietal neurons are involved not only in multimodal spatial integration of sensory input, but also in the early stages of planning spatial movements. Multimodal neurons in different parietal areas are also well-suited to mediate smooth transformations between different frames of reference, showing responses to one stimulus modality (e.g., visual) that are influenced in a multiplicative manner by stimuli in other modalities (e.g., proprioceptive or vestibular)—an effect called gain modulation (Cohen and Andersen, 2002).

How much of the information about external space that is constantly being updated within and across these many maps leads to experience, and how much instead remains unconscious? Conscious experience of space is so pervasive that it seems to provide a general framework for much of what we experience, at least in the visual and auditory domains. In fact, Kant thought that space was an essential substrate for all experience. For the same reason, it is difficult to evaluate neuropsychological evidence to address the question whether consciousness could persist in the absence of spatial concepts and a spatial frame of reference. Patients with hemianopia due to occipito-parietal strokes are often unaware of their deficit (Celesia et al., 1997; Baier et al., 2015), suggesting that one can lose awareness of part of space. Patients with simultagnosia—a classic component of Balint's syndrome (together with optic ataxia and apraxia of gaze) (Robertson, 2004), have an extremely narrow "window of attention" (Dalrymple et al., 2013): at any given time they only experience one particular object, the one that happens to grab their fixation point, at the exclusion of everything else. Moreover, while they can easily recognize and describe the object they are experiencing, they have no idea of *where* it might be in space: left, right, up, and down are impossible for them to say, and especially spatial relationships among objects are out of the question. They also have a problem binding colors with shapes, as indicated by frequent illusory conjunctions, in which the color of another object is mistakenly attributed to the one they are experiencing. In the few cases studied in detail, the site of the lesion was bilateral inferior parietal cortex, centered around the angular gyrus (area 39). As usual with attention and consciousness, it is difficult to decide whether the problem with simultagnosia is primarily one of narrow attention, which makes it impossible for them to be aware of *where* things are in visual (or auditory) space. Yet simultagnosics still seem to know that space exists and contains objects they cannot see (see Robertson, 2004, p. 159), they still experience space in reference to their own body, as well as within a single, spatially extended object. In this sense, simultagnosia would be an extreme form of *extinction*, in which the object they are attending extinguishes any other object in the visual field (see Robertson, 2004, p. 159). The inability to locate the single perceived object in extrapersonal space might then be due not to unawareness of space per se, but to a disconnection (unbinding) of ventral stream neurons specifying position-invariant concepts of the object from the dorsal

stream neurons specifying spatial locations, due to a lesion of some of the maps that link the two streams.

While simultagnosia is exceedingly rare, presumably because it involves bilateral, symmetric parietal lesions, neglect is a common occurrence, especially early on after acute brain lesions on the right side (Chapter 18). A patient with hemispatial neglect acts as if he is inattentive to one half of the world—most often the left half. He may not notice people and objects on the left side, may read only the right side of a map, may eat only the right side of the food on his plate, or shave only one side of his face. Neglect can occur in sensory modalities besides vision, including audition, touch, proprioception, and smell, and it can affect various aspects of space, from one's own body (personal space) to nearby objects (peri-personal space) to distant objects. For example, one patient may neglect objects on the left side that are out of reach but not objects nearby, another one may neglect only objects that are within reach, and yet another may neglect his own left face. Or a patient may ignore his left arm and leg, trying to climb out of bed without them even though he is not at all paralyzed. Finally, some patients may show predominantly motor neglect, in that their eye or hand movements are biased toward the right. In the clinic, hemispatial neglect can be revealed by simple paper-and-pencil tests. For example, asked to mark all lines on a page, the patient marks only those on the right side. Asked to mark the middle of a line, he errs toward the right side. Asked to draw a figure, he leaves out the left side of it. Nevertheless, a typical neglect patient is definitely not blind: if an isolated object is shown on the left, the patient can see it and pick it up. Indeed, neglect is most apparent in competitive situations, a phenomenon called "*extinction*." The same stimulus on the left side that is reported if presented alone, is ignored if presented simultaneously with a stimulus on the right side. Importantly, patients may also show neglect for imagined or remembered left space: asked to imagine the buildings lining the main piazza in Milan, a patient would only recall those on the right side of where he imagined himself standing (Bisiach and Luzzatti, 1978). In short, a patient with neglect behaves as if his attention were pathologically attracted to events and things on the right side and pathologically insensitive to events and things on the left side. The spatial bias of attention that causes neglect is thought to depend on an imbalance between the left and right dorsal attention networks. These frontoparietal networks, which include the frontal eye field and the intraparietal sulcus, contain multiple maps of space, including maps for directing attention, eye movements, and arm movements directed toward contralateral space. Normally, activity in the two sets of maps in right and left hemispheres is kept in a delicate push-pull balance through mutual inhibitory interactions.

A constellation of symptoms that usually accompanies hemispatial neglect is a reduction in arousal and vigilance, as well as an inability to maintain sustained attention. These functions, together with the reorienting of attention, are supported by the ventral attention network, which is lateralized to the right hemisphere and may receive preferential innervation from brainstem and subcortical systems that promote arousal (Corbetta and Shulman, 2011; Corbetta, 2014; Gazzaniga et al., 2014). The ventral attention network includes ventral frontal cortex and insula, the temporoparietal junction and the superior temporal gyrus.

Over the past several years, an extensive set of anatomical and functional studies has led to a comprehensive model of hemispatial neglect (Corbetta and Shulman, 2011; Corbetta, 2014; Gazzaniga et al., 2014). Right cortical lesions causing neglect tend to occur in the ventral attention network and in the underlying white matter, especially the superior longitudinal fasciculus, thus explaining the problems with arousal, vigilance and sustained attention. However, these right ventral lesions also cause large-scale changes of functional connectivity within and between bilateral dorsal frontoparietal networks, in their interactions with default mode and control networks, and in their interactions with the basal ganglia (Baldassarre et al., 2014). Changes in functional connectivity and, presumably, excitability may lead to a reduced activation of the right dorsal attention network, impairing the normal interhemispheric balance between the left and right side, thereby accounting for hemispatial neglect (Corbetta et al., 2005). Moreover, the reduced activation of many spatial maps on the right side indirectly affects sensory regions, at least in the acute stage of neglect (Corbetta et al., 2005). This conclusion is supported by the partial, short-lasting recovery of neglect that can be achieved by increasing arousal and the degree of activation of the right hemisphere, for example by galvanic or caloric stimulation of the ear.

Consciousness, Body, and Self

Can consciousness exist in the absence of a sense of self or of a body? The self is a multilayered concept, and different people or disciplines tend to conceptualize it in very different ways. In a neurological context, it is useful to keep a few distinctions in mind. First and foremost is the *narrative, autobiographical self*—the one that characterizes in a fundamental sense who we are. As important as this self may be for each of us, it seems clear that an autobiographical self is not a prerequisite for experience—just think of how it may take some time

to reconnect with it when awakening in the morning, though experience is already present.

Then there is the *feeling of agency*: experiencing that one is the source of one's actions There is a growing neurological literature about the neural substrate of agency, and about how agency may be altered in pathological conditions (Ruby and Decety, 2001; Frith, 2002; Farrer et al., 2003; David et al., 2006). Again, however, it seems that experience of agency is not necessary for consciousness—one can be completely passive and still experience the flow of images.

At a more basic level then there is the *feeling of ownership*—the knowledge that your body and its parts are indeed yours. The body is heavily represented in the brain, and not only in the cerebral cortex. There are maps of the body already in the brainstem, in the thalamus, and in multiple cortical areas, especially primary and secondary somatosensory cortex, right posterior insular cortex, and portions of the parieto-temporal junction. The representations deal with touch, proprioception, and vestibular signals, which very soon become integrated into multimodal maps. The hypothalamus and brainstem have access to many other inputs from the body and the viscera, although much of what is recorded there does not seem to make it to consciousness.

Like the experience of external space, the experience of our own body might appear as an integral aspect of all experience. Usually, awareness of the body is discrete and stays in the background, perhaps because it is always there and is relatively stable compared to the awareness of external circumstances. But is a complete loss of body awareness impossible, perhaps even unconceivable? A few intriguing phenomena may speak to the issue.

Recent experiments, exploiting for instance the so-called rubber hand illusion, have shown that our sense of ownership can be altered, and we may feel like we own a hand that is not ours (Tsakiris et al., 2007). The sense that our body is ours appears to depend on neural circuits centered in right posterior insula. Then there is asomatognosia, a condition in which patients may claim that the left arm and leg may be missing, or that it may disappear. In such cases the site of lesions is usually in right posterior parietal areas, though premotor cortex may also play a role (Arzy et al., 2006a). Asomatognosia suggests that certain brain lesions may selectively eliminate awareness of the body without compromising consciousness. However, asomatognosia is usually for just a part of the body, so firm conclusions are not possible.

A more global phenomenon is the out-of-body experience (Lenggenhager et al., 2006) (Chapter 20). In its full manifestation, a subject may feel that he is disembodied, that is, he does not feel located within his own body. Instead, the subject feels that he—his experiencing self—is located or centered somewhere else with respect to his body, typically hovering over it at some distance. Moreover, he may be able to contemplate his own body from this new perspective (autoscopy). Out-of-body experiences, which can be triggered by brain lesions, seizures, anesthesia and some drugs, and sometimes occur when falling asleep, are associated with an altered functioning of the temporo-parietal junction, including the insula, especially on the right side. This brain region combines tactile, proprioceptive, and visual signals in a coordinated reference frame, and receives abundant vestibular projections. It is activated when subjects imagine to change perspective and see the world from somewhere else (e.g., Vogeley et al., 2004). Compellingly, focal electrical stimulation in the same area can produce full-fledged out-of-body experiences (Blanke et al., 2005). Clinical data and a further electrical stimulation study in humans suggest that disembodiment and autoscopy (and change in perspective) can be dissociated: disembodiment would be due to perturbations of the junction between right supramarginal and angular gyri, leading to somatosensory-vestibular disintegration, whereas autoscopy/change in perspective would be obtained by perturbing a slightly more posterior region of the right angular gyrus involving visual pathways (De Ridder et al., 2007). An extrastriate body areas is also thought to be involved in perception of the body (Downing et al., 2001; Arzy et al., 2006b). It remains to be clarified whether disembodiment can indeed be construed as a true lack of experience of the body, or rather as a dislocation of such experience. But altogether, asomatognosia and out-of-body experiences suggest that it may be possible to lose one's bodily self without losing consciousness.

What seems to be left if we take away the bodily self is the centeredness of any experience: even in the out-of body experience, experience seems to be localized somewhere behind the eyes, even if such disembodied self is not associated with any physical simulacrum. But it is centered somewhere. One could argue that what is centered in this case is just the visual experience of space—since subjects report seeing their own body from such altered first-person perspective. Conceivably, however, one could have an out-of-body experience induced in a patient with Balint's syndrome, in which case there would be simultagnosia—the loss of a spatial reference frame for experience, together with a loss of a reference to the body. What kind of experience would this be, or would experience vanish? Though such thought experiments are always dangerous, a reasonable guess would be that experience would still persists: like a Balint patient, one would experience a single object, or say an intense smell, not located in space, and not associated to a body. Perhaps states achieved thorough transcendental meditation

techniques can approximate a loss of awareness of space, body, and self: experts reports a feeling of silence, no bodily feelings, unboundedness (no space, and possibly no self), and no time. Even in such cases, though, the experience would still be happening to one particular entity—it would be "centered," if you wish, but not in the conventional spatial sense. This last sense of "self," which we may call the "intrinsic" or "subjective" self—would be one and the same as the experience, not further dissociable.

Consciousness, Perception, Imagination, and Absolute Agnosia

Neuropsychology provides perhaps the most compelling evidence concerning which brain areas are *necessary* for experiencing particular conscious modalities. In principle, compiling a list of the areas whose lesion eliminates the experience of colors, shapes, visual motion, faces, places and so on, should yield the anatomical substrate of conscious vision. Completing the list for other modalities and submodalities would yield the anatomical substrate of consciousness in its entirety. However, such a list is hard to come by, and not just because brain lesions are rarely selective and symptoms change with time: a more fundamental reason is that, to ascertain that the neural substrate of a conscious modality, say a sensory modality, has truly been eliminated, one must be able to demonstrate a complete loss of: (i) the corresponding sensory experiences; (ii) the ability to imagine, remember, or dream any such experience; (iii) the first-hand understanding of what is missing.

To see why, consider first a simple thought experiment concerning a hypothetical sixth sense—let's say echolocation. Obviously, we are not endowed with neural hardware appropriate for generating echolocation qualia. Not surprisingly, when we move around our house, we do not experience any echolocation-like quale. But it is not just a matter of not having the appropriate sensors or sensory pathways: we cannot even imagine what such a quale would feel like, or dream that we are echolocating. Finally, we do not really understand first-hand what we are missing, even though we may know a lot about how bats, for example, make use of echolocation, and some of us can talk about echolocation in great detail. Equipping us with a bat-like sonar (say with a visual or auditory output) might help us to navigate in the dark, but it would not generate echolocation qualia.

To make things a bit more concrete, consider a conscious submodality we are familiar with, namely color. Assume that a cortical area C is the one actually responsible for providing us with color qualia (in association with other areas that ensure a proper level of consciousness); another cortical area A provides "processed" sensory input to area C—say by computing color constancy—so that the appropriate activity patterns are triggered in C when a surface of a certain reflectance is viewed; finally, a cortical area B can generate similar patterns (maybe less effectively) in C in a top-down manner, implementing the ability to imagine colors.

Given such a scenario, a lesion of area A would lead to what might be called pure achromatopsia: a patient would not be able to discriminate among colors and would not experience colors when presented with colored stimuli. However, the patient would still be able to imagine, remember, or dream of colors. Moreover, he would be perfectly aware that he is missing color, that is, things would look strangely black and white. Such patients have indeed been described (Shuren et al., 1996; Bartolomeo et al., 1997). For example, E.H. (Shuren et al., 1996) was impaired at color perception: he could not recognize colored characters in the Ishihara pseudoisochromatic plates, could not arrange patches in terms of their hue, and could not match objects with the proper colored swatch. On the other hand, he could imagine colored objects and say the appropriate color, and respond correctly if asked, for example, which of a plum and an eggplant had more red in it.

By contrast, a lesion of area B would lead to the isolated loss of the ability to imagine colors, with no deficit in color perception, and a preserved understanding of what color means. Again, such patients have been described (De Vreese, 1991, case II; Goldenberg, 1992, case KQu; Luzzatti and Davidoff, 1994, see also Bartolomeo, 2002). An especially selective example is that of patient QP (Jakobson et al., 2008), who had an isolated deficit in color imagery and color memory secondary to a concussive episode. QP had normal color perception, would properly name colors, could even dream in color, but since the time of the injury she had trouble imagining colors or remembering most colors, both short and long-term (intriguingly, she had little problem with shades of blue).

Continuing along these lines, a combined lesion of both areas A and B (or of their connections) would produce a patient who not only does not experience the color of objects but, in addition, cannot imagine or remember color. However, he would be fully aware that his world has turned black and white, and would complain about missing color. Such achromatopsic patients with no color imagery have also been described. For example, the painter I., recounted by Oliver Sacks (1995), described his symptoms after a car accident thus: "My vision was such that everything appeared to me as a black and white television screen

. . . I can see a worm wiggling a block away. . . But—I AM TOTALLY COLOUR-BLIND." To him it made no difference if he was looking with his eyes open, or attempting to imagine colors, or remembering scenes that he knew had color or whether he was dreaming—he only saw "awful and disgusting" shades of grey. Being a painter, he could discuss the 256 colors of the Pantone chart and the finer aspects of hues without being able to see them. Obviously, patient I. understood perfectly what colors meant, and was overwhelmed by its loss. In such cases, one could speculate that area C, being deafferented from areas A and B, would have no opportunity to become activated, but it would still be functional (for example, direct stimulation with transcranial magnetic stimulation (TMS) might produce colored phosphenes). The inactivity of area C would then constantly signal to upstream areas that the current visual input is achromatic, just as when watching black and white movies.

However, feeling of an absence is not the same as an absence of feeling—having a functional but inactive area C is very different from not having it at all. Indeed, with damage to area C, there should be a complete loss of color consciousness, whether seen, imagined, remembered or dreamt and, crucially, the patient would not understand first-hand what color really means (just as we do not understand echolocation first-hand) and what he is missing. Nevertheless, he could certainly talk about color second-hand, just as we can talk about echolocation. A patient possibly similar to this ideal case has also been described (van Zandvoort et al., 2007). Patient MAH seems to have a pure form of color agnosia: he cannot name the color of colored pencils (though he has no problem with color naming *per se*), and he cannot tell whether an object is shown with its proper color (as opposed to, say, a purple banana). Moreover, he fails to group colored tokens according to their color, and is clearly not sure about what he is trying to do. When asked to color line drawings of common objects, he produced an orange cherry with a purple stick, or a blue meadow with pink daffodils. On the other hand, MAH can respond to color unconsciously, as demonstrated by priming tasks and a Stroop task, and he performed flawlessly and rapidly on the Ishihara test (he could easily see the characters as being different from the background). He could also discriminate between different hues, although slowly and with little confidence about what he was doing. But when asked about the color of a bright green bag, he hesitated, and then said it was a bright color, perhaps yellow or orange. His condition was apparently congenital (and possibly hereditary, as his mother and one of his daughters showed similar deficits), and he had no relevant neurological problem. MAH is highly educated and knows about the physics of color, but it would seem that he knows about color second-hand, as a biologist may know about echolocation. Uneasily, he admits that he may be color blind "or something like that," though occasionally he claims to like colors (especially Fauve paintings). It may be that, though he does see differences between differently colored objects, these may be in terms of brightness or other achromatic attributes, and that he may lack color qualia. In that case, he may not really understand color first-hand the way normal subjects do, or the way pure achromatopsic patients do: we might call his condition one of *absolute agnosia* for color. Absolute agnosia would automatically imply loss of conscious perception for that modality, as well as loss of imagery, memory, and dreaming. What MAH is missing, then, would truly be the neural substrate for the qualia pertaining to the color submodality, due to the absence of the relevant circuits. Recently, another patient has been identified who, during the initial phase after a stroke, had an absolute agnosia for color: he could not discriminate colors and, in addition, he had no idea of what he was missing (von Arx et al., 2010) (Figure 25.2). Thus, at least in principle, identifying patients with absolute agnosia for different modalities and submodalities of consciousness, as well as the underlying dysfunction (the equivalent of "area C") would reveal the true neural substrate of the corresponding qualia.

Consciousness and Anosognosia

Given the above definition of absolute agnosia (lack of first-hand understanding) as essential to the lack of consciousness in a given modality, it is natural to ask whether examples of anosognosia (unawareness of deficit) in the neuropsychological literature (Vuilleumier, 2000, 2004; Prigatano, 2009) may represent a similar lack of first-hand understanding, and thus of consciousness for that modality. Patients with anosognosia often seem to deny their loss without understanding what they are talking about. For instance, patients with Anton's syndrome can be completely blind due to cortical lesions (to the point that they may not be able to tell whether the light is on or off), yet they insist that they do see, and make up excuses as to why they fail in the simplest visual tasks. It could be that such patients, besides being blind, have indeed absolute agnosia for vision, having lost all sense of what seeing (and not seeing) means: they may merely resort to vision-related words and memories without actually being able to experience anything visual, not even in their imagination or their dreams.

Examples of selective anosognosia are hard to come by, but there are examples of selective unawareness of

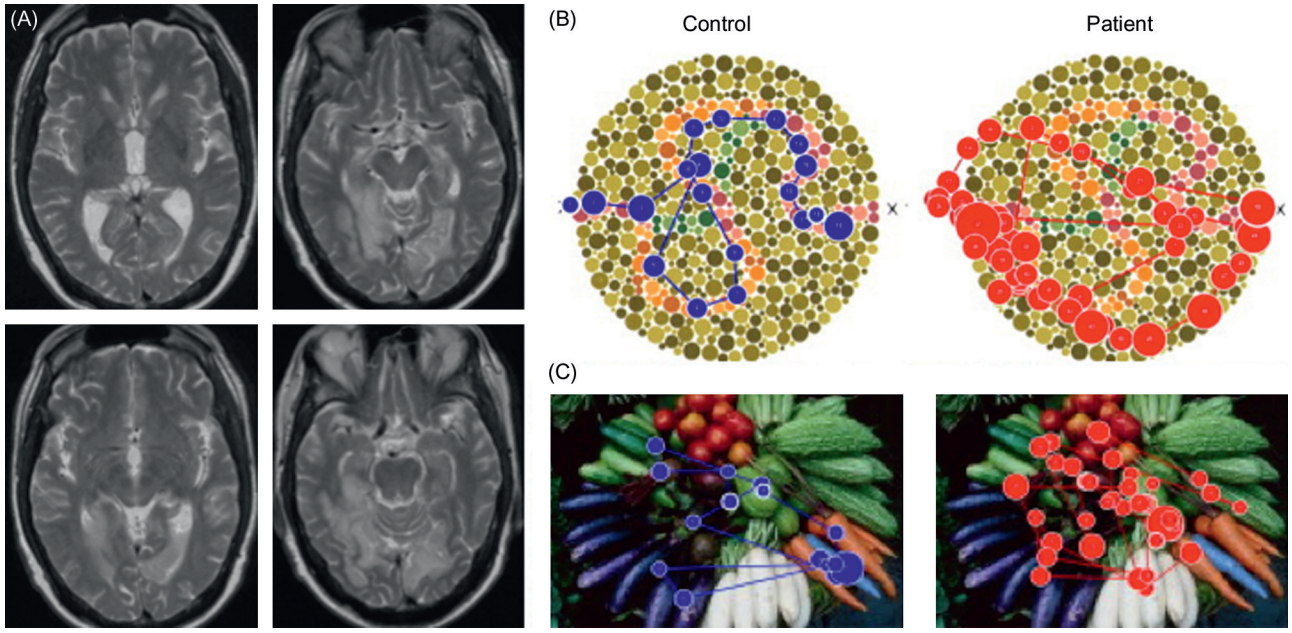

FIGURE 25.2 Cerebral achromatopsia with anosognosia. The patient could only see shades of grey but did not report impaired color perception (the deficit lasted less than 2 months). (A) Axial T2-weighted MRI scan slices of the patient showing bilateral hyperintense lesions in the occipito-temporal cortex 2 days after the stroke. (B) During an Ishihara task, the patient showed visual fixations that were unsystematically distributed while the control subject clearly followed the path. (C) Fixation density plots for an object-color matching task where subjects were instructed to search for any oddity in the image (here a blue carrot). The patient did not notice anything in particular. *Source: Adapted from von Arx et al. (2010).*

deficits in other visual submodalities, such as anosognosia for face perception (Young et al., 1990), and in other modalities, such as anosognosia for hemi-anesthesia, for unilateral neglect, for language comprehension and production, and so on. A dramatic example of anosognosia is unawareness of motor deficit, whereby patients deny that their left arm or leg is paralyzed, and usually ignore requests to move it (often in the absence of sensory loss and intellectual impairment). Recent studies have indicated that unawareness of (left) paralysis may result from lesions of (right) premotor cortex, especially areas 6 and 44, sensorimotor cortex, and right insula (Berti et al., 2005). These lesions would compromise the comparison between signals representing the intended actions and those monitoring the actual action (Spinazzola et al., 2008). In this way, the area responsible for motor awareness ("area C") would receive the motor intention signals (presumably from supplementary motor area) but no mismatch signal, and would thus not be able to tell that the movement was not executed. Alternatively, the input layer to "area C" from the sensory stream may be dysfunctional, so the patient cannot tell anymore whether activity patterns in "area C" are triggered by extrinsic or intrinsic sources.

These examples not only highlight the importance of neuropsychological investigations—above and beyond what can be established with neuroimaging alone—but they also indicate how difficult it is to determine, in each patient, what exactly is amiss within a given modality of consciousness: does he lack the relevant aspects of conscious perception as well as imagination, memory, dreaming and, crucially, first-hand understanding of what he is missing? Does he have a selective anosognosia because of an absolute agnosia, or conversely because he can still concoct conscious images in the absence of sensory input? And can he still make covert (unconscious) use of relevant information? All of these questions must be addressed before cortical "nodes" for individual modalities and submodalities of consciousness can be identified with some confidence.

GLOBAL ALTERATIONS OF CONSCIOUSNESS

In neurology, a distinction is traditionally drawn between the level of consciousness and the content of consciousness. When you fall asleep, for example, the level of consciousness decreases to the point that you become virtually unconscious—the degree to which you are conscious (of anything) becomes progressively less and less. The content of consciousness, instead, refers to the particular experience you are having at any given time, for a similar level of consciousness. This distinction is useful when considering alterations

of consciousness. On one side there are localized brain lesions that lead to the loss of specific dimensions of consciousness—defined above as absolute agnosia—without any major change in the level of consciousness. On the other side there are global alterations in the level of consciousness, such as occur, besides certain stages of sleep, in anesthesia, coma, vegetative states, and generalized seizures. It is to these that we now turn.

Sleep

The most commonplace, daily demonstration that the level of consciousness can change dramatically is provided by sleep (see Chapter 7). In the laboratory, a subject is awakened during different stages of sleep and asked to report "anything that was going through your mind just before waking up." What is most noteworthy for the present purposes is that a number of awakenings from non-rapid eye movement (NREM) sleep, especially early in the night when EEG slow waves are prevalent, can yield no report whatsoever. Thus, early slow wave sleep is the only phase of adult life during which healthy human subjects may deny that they were experiencing anything at all. When present, reports from NREM sleep early in the night are often short and thought-like. However, especially later in the night, reports from NREM sleep can be longer, more hallucinatory and, generally speaking, more dream-like. On the other hand, awakenings during REM sleep almost always yield dreams—vivid conscious experiences, sometimes organized within a complex narrative structure (Hobson et al., 2000; Hobson and Pace-Schott, 2002; Siclari et al., 2013).

What are the neural correlates of the fading of consciousness during early slow wave sleep? Metabolic rates do decrease in many cortical areas, especially frontal and parietal areas, and related thalamic nuclei, as is seen in other conditions characterized by reduced consciousness, such as coma, vegetative states, and anesthesia. By contrast, primary sensory cortices are not deactivated compared to resting wakefulness (Braun et al., 1997; Maquet et al., 1997; Nir et al., 2015). Functional connectivity studies using fMRI and EEG reveal that, during NREM sleep, the hierarchical organization of large-scale networks is changed into smaller independent modules (Boly et al., 2012b; Tagliazucchi et al., 2013b). A decrease in long-range functional connectivity has been observed in frontoparietal default mode and dorsal attention networks (Spoormaker et al., 2012; Tagliazucchi et al., 2013a,b). Decreased corticothalamic functional connectivity has also been found in heteromodal regions such as medial frontal gyrus and precuneus (Picchioni et al., 2014). Altogether, these studies point to a breakdown of functional integration.

EEG studies show that, overall, power in the delta range and slow wave density is lower when subjects report, upon awakening, that they had been conscious (Chellappa et al., 2011). Moreover, a recent study using high-density EEG shows that, when subjects report having been conscious during a NREM sleep episode, the EEG is locally activated over a parieto-occipital hotspot, even though other cortical areas exhibit slow wave activity (Siclari et al., 2014b). This finding is consistent with the observation that NREM slow waves most often occur locally, in just a subset of brain areas (Nir et al., 2011). In REM sleep, this parieto-occipital hotspot of low delta is associated with perceptual experiences whereas a frontal hotspot of high-frequency activity is associated with thought-like experiences. Moreover, content-specific activations such as faces, places, movement and speech closely resemble those observed during wakefulness (Siclari et al., 2014b). In another recent study, machine-learning technique could decode the contents of visual imagery during the sleep-onset period from higher-level visual areas (Horikawa et al., 2013).

What are the mechanisms of loss of consciousness during early NREM sleep? It is well established that, due to a decrease in acetylcholine and other modulators, cortical and thalamic neurons undergo slow oscillations (1 Hz or less) between up- and down-state (Steriade et al., 2001). During the up-state cortical cells remain depolarized at waking levels for around a second and fire at waking rates, often in the gamma range (Destexhe et al., 2007). However, the up-state of NREM sleep is not stable as in wakefulness and REM sleep, but it is inherently bistable. The longer neurons remain depolarized, the more likely they become to precipitate into a hyperpolarized down-state—a complete cessation of synaptic activity that can last for a tenth of a second or more—after which they revert to another up-state. The transition from up- to down-state appears to be due to depolarization-dependent potassium currents and to short-term synaptic depression, both of which increase with the amount of prior activation (Steriade, 2003). The slow oscillation is found in virtually every cortical neuron, and is synchronized across the cortical mantle by cortico-cortical connections, which is why the EEG records high-voltage, low-frequency waves.

An intriguing possibility is that changes in the level of consciousness during sleep may be related to the degree of bistability of corticothalamic networks, leading to a breakdown of cortical integration—loosely defined as the ability of different cortical regions to talk to each other (Tononi, 2004b; Massimini et al., 2012)

(Chapter 7). Alternatively, deep sleep may impair consciousness by leading to bistable, stereotypic cortical responses associated with a loss of information (Tononi, 2004b; Massimini et al., 2007). Consider first the loss of integration. During wakefulness, TMS induces a sustained response made of rapidly changing patterns of EEG responses that persists until 300 ms and involved the sequential activation of specific brain areas. During early NREM sleep, however, the brain response to TMS changes markedly. When applied to any medial cortical regions, the activity evoked by TMS remains localized to the site of stimulation, without activating connected brain regions, and lasts for less than 150 ms (Massimini et al., 2005) (Figure 25.3). This finding indicates that during early NREM sleep, when the level of consciousness is reduced, effective connectivity among cortical regions breaks down, implying a corresponding breakdown of cortical integration. Computer simulations suggest that this breakdown of effective connectivity may be due to the induction of a local down-state (Esser et al., 2009).

Further experiments with TMS/EEG suggest that early NREM sleep may be associated with a loss of information even when the brain can produce global responses. When applied over centromedian parietal regions and using higher intensity of stimulation (i.e., between 65 and 85% of maximal stimulator output), each TMS pulse triggers a stereotypical response implying the induction of a global down-state: a full-fledged, high-amplitude slow wave (Massimini et al., 2007) that closely resembled spontaneous ones and that traveled through much of the cortex (Massimini et al., 2004) (Figure 25.3). Such stereotypical responses can be induced even when, for the preceding seconds, there are no slow waves in the spontaneous EEG, indicating that perturbations can reveal the potential bistability of a system irrespective of its observed state. A recent study using intracerebral local field potential recordings coupled with single-pulse electrical stimulation of the cerebral cortex shows that stimulation during wakefulness induces a chain of deterministic phase-locked activations in its cortical targets lasting up to 600 ms. By contrast, in NREM sleep, the same stimulation triggers a slow wave associated with a cortical down-state (suppression of power >20 Hz), which interrupts the phase-locked chain. Thus, bistability during NREM sleep leads to breakdown of the brain's ability to integrate information (Pigorini et al., 2015). Altogether, these measurements suggest that the sleeping brain, despite being active and reactive, becomes inherently bistable: it either breaks down in causally independent modules or bursts into a global, stereotypical response. By contrast, during REM sleep late in the night, when dreams become long and vivid and the level of consciousness returns to levels close to those of wakefulness, the responses to TMS also recover and come to resemble more closely those

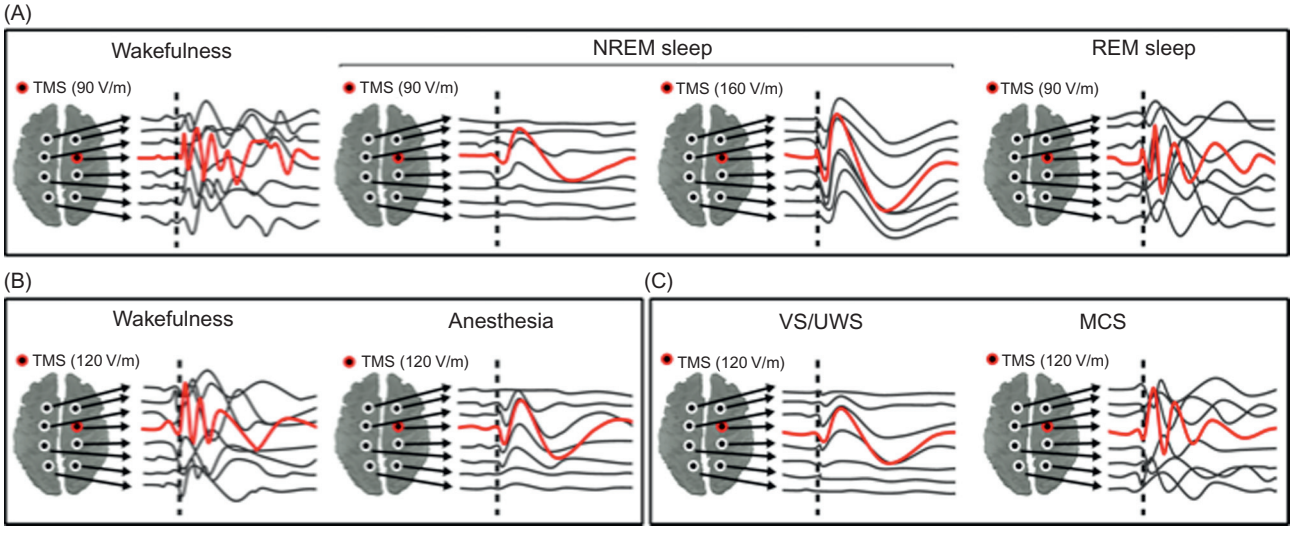

FIGURE 25.3 TMS-EEG responses in sleep, anesthesia, and post-comatose patients. (A) During wakefulness, transcranial magnetic stimulation (TMS) triggers a widespread response with differentiated patterns of activation. During non rapid eye movement (NREM) sleep, the corticothalamic system loses its ability to engage in complex activity patterns and either breaks down in casually independent modules (loss of integration) or it bursts in an explosive response (loss of differentiation/information, with higher intensity of stimulation). During REM sleep, TMS response shows a recovery of spatially and temporally differentiated patterns of activation. (B) As in NREM sleep, similar results have been observed during general anesthesia using propofol, midazolam and xenon. (C) Patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) show similar responses to NREM sleep and anesthesia while patients in a minimally conscious state (MCS) show patterns of activity that resemble those in wakefulness and REM sleep. *Source: Taken from Sarasso et al. (2014).*

observed during wakefulness: evoked patterns of activity become more complex and spatially differentiated, although some late components are still missing (Massimini et al., 2010).

The study of consciousness during sleep provides not only a window into the neural mechanisms that determine the quantity or global level of consciousness, but also its quality. For example, local bistability in some regions (Nir et al., 2011) may produce temporary, reversible alterations in the quality of consciousness similar to persistent, partially irreversible ones caused by lesions resulting in neuropsychological impairments. Thus, localized bistability in Wernicke's area may produce a temporary dream aphasia, posterior parietal bistability may produce the dream equivalent of Balint's syndrome, widespread bistability in visual cortex may produce a dream equivalent of Anton's syndrome, more restricted bistability may produce absolute dream achromatopsia or prosopagnosia, and so on. Parasomnias—dissociated states that mix aspects of both wakefulness and sleep—suggest that such neuropsychological alterations of consciousness can occasionally have a behavioral counterpart. For example, patients with somnambulism often exhibit complex behaviors such as walking and talking, but they are hard to awaken and often deny that they had been conscious of anything (Zadra et al., 2013; Perrault et al., 2014). Indeed, slow-wave activity increases before the onset of sleepwalking (Perrault et al., 2014). Episodes of confusional arousal during NREM sleep are another case in point (Terzaghi et al., 2009; Jaar et al., 2010). Neuroimaging during such states demonstrate mixed signs of local sleep (in associative cortices) and wake (in motor and cingulate cortices) (Bassetti et al., 2000; Terzaghi et al., 2012). At the other end of the spectrum, lucid dreaming, in which subjects become aware that they are dreaming and can partially control and reflect upon their experiences, show that reflective consciousness can also occur when asleep. Neuroimaging correlates of lucid dreaming not only indicate a reactivation of frontal but also parietal and temporo-occipital cortices (Dresler et al., 2012; Stumbrys et al., 2013; Voss et al., 2014; Filevich et al., 2015).

Anesthesia

The most common among exogenous manipulations of the level of consciousness is general anesthesia. Anesthetics come in two main classes: intravenous agents used for induction, such as propofol and ketamine, generally administered together with sedatives such as midazolam and dexmedetomidine; and inhaled agents such as isoflurane, sevoflurane and desflurane, or the gases xenon and nitrous oxide. The doses of inhaled anesthetics are usually referred to their minimum alveolar concentration (MAC): a MAC value of 1 is the dose that prevents movement in 50% of subjects in response to a painful surgical stimulation. At low MAC values (0.1−0.2) anesthetics produce amnesia, first explicit and then implicit. Frequently there are distortions of time perception, such as slowing down and fragmentation, and a feeling of disconnection from the environment. Also, at low MAC values anesthetics produce increasing sleepiness and make arousal progressively more difficult, suggesting that to some extent they can mimic neurophysiological events underlying sleep. At around 0.3 MAC people experience a decrease in the level of consciousness, also described as a "shrinking" in the field of consciousness, as if they were kept on the verge of falling asleep. MAC-awake, usually around 0.3−0.4 MAC, is the point at which response to verbal command is lost in 50% of patients, and is considered the point at which consciousness is lost (LOC). The transition to unconsciousness (LOC) appears to be rather brusque, not unlike the collapse of muscle tone that usually accompanies it, suggesting that neural processes underlying consciousness change in a nonlinear manner. At concentrations above LOC, movements are still possible, especially partially coordinated responses to painful stimuli, suggesting that some degree of "unconscious" processing is still possible. Complete unresponsiveness is usually obtained just above MAC 1.0.

At the cellular level, many anesthetics have mixed effects, but the overall result is a decrease in neuronal excitability by either increasing inhibition or decreasing excitation. Most anesthetics act by enhancing gamma-amino-butyric-acid (GABA) inhibition or by hyperpolarizing cells through an increase of potassium leak currents. They can also interfere with glutamatergic transmission and antagonize acetylcholine at nicotinic receptors (Campagna et al., 2003; Franks, 2006, 2008). But what are critical circuits mediating the LOC induced by anesthetics (Alkire et al., 2008)?

A considerable number of neuroimaging studies in humans have recently shed some light on this issue (Alkire and Miller, 2005; Mashour, 2014) (see Chapter 9). A common site of action of several anesthetics is posterior cingulate cortex and medial parietal cortical areas, as well as lateral parietal areas. During propofol- or sevoflurane-induced LOC, high-level cortical networks become functionally disconnected but primary sensory networks seem relatively preserved (Boveroux et al., 2010; Martuzzi et al., 2010; Liu et al., 2012) (Figure 25.4). However, it is difficult to say if anesthetics produce unconsciousness when they affect a particular set of areas, as opposed to by producing a widespread deactivation of corticothalamic circuits. The most consistent effects produced by most anesthetics at LOC

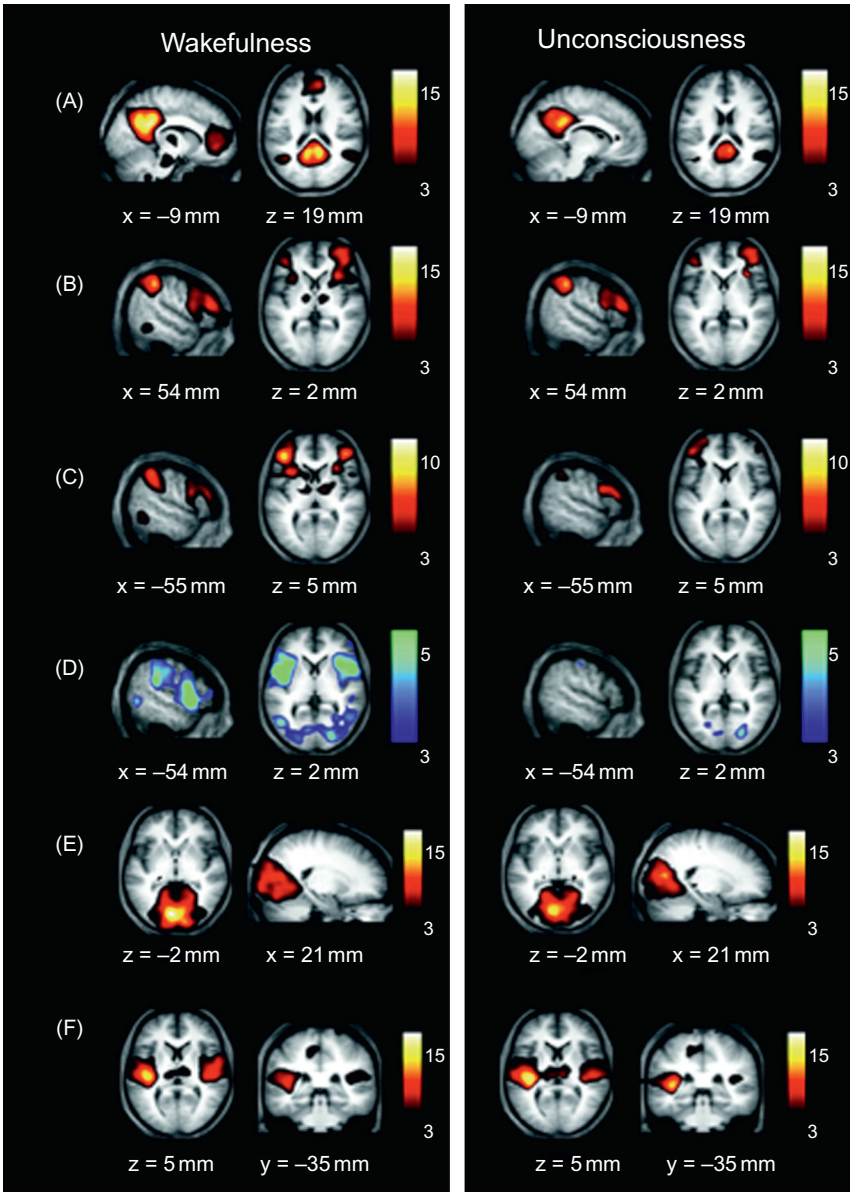

FIGURE 25.4 Functional connectivity in primary and in higher order cortices. (A) Normal wakefulness and propofol-induced unconsciousness resting-state networks connectivity in the default network, (B) in the right executive control network, (C) in the left executive control network, (D) anticorrelations between default network and lateral frontoparietal cortices. (E) Connectivity patterns in the visual resting-state networks, and (F) in the auditory resting-state networks during wakefulness and during unconsciousness. Large-scale network connectivity such as in the default network and executive control networks is reduced during unconsciousness. In contrast, visual and auditory networks connectivity remains globally stable across state. *Source: Adapted from Boveroux et al. (2010).*

is a reduction of thalamic metabolism and blood flow, suggesting the possibility that the thalamus may serve as a consciousness switch (Alkire et al., 2000). However, both positron emission tomography (PET) and fMRI signals mostly reflect synaptic activity rather than cellular firing, and the thalamus receives a massive innervation from cortex. Moreover, the relative reduction in thalamic activity occurs on a background of a marked decrease in global metabolism (30–60%) that involves many cortical regions. Thus, thalamic activity as recorded by neuroimaging may represent an especially sensitive, localized readout of the extent of widespread cortical deactivation, rather than the final common pathway of unconsciousness (Ori et al., 1986). In fact, spontaneous thalamic firing in animal models of anesthesia is mostly driven by corticothalamic feedback (Vahle-Hinz et al., 2007), and the metabolic effects of enflurane on the thalamus can be abolished by an ipsilateral cortical ablation (Nakakimura et al., 1988), suggesting that the switch in thalamic unit activity is driven primarily through a reduction in afferent corticothalamic feedback more than by a direct effect of anesthesia on thalamic neurons. Recently, thalamic activity was recorded using depth electrodes in a patient undergoing anesthesia for the implant of a deep brain stimulator (Velly et al., 2007). With either propofol or sevoflurane, when the patient lost consciousness, the cortical EEG changed dramatically. However, there was little change in the thalamic EEG until almost 10 min later. This result implies that the deactivation of

cortex alone is sufficient for loss of consciousness, and conversely that thalamic activity alone is insufficient to maintain it (see below). More recent fMRI and EEG studies confirmed that LOC induced by propofol is mostly tied to cortico-cortical and not to thalamo-cortical processes (Boly et al., 2012a; Monti et al., 2013). However, anesthetic-induced LOC in rodents was associated with changes in the centromedial thalamus prior to changes in the cerebral cortex (Baker et al., 2014), and in another study propofol led to a simultaneous depression of cortical and thalamic (ventroposterolateral nucleus) activity (Verdonck et al., 2014).

Whatever the ultimate target of anesthetics, loss of consciousness may not necessarily require that neurons in these structures be inactivated. In fact, it may be sufficient that subtler, dynamic aspects of neural activity be affected. As with sleep, some evidence indicates that anesthetic agents may impair consciousness by disrupting cortical integration (Schrouff et al., 2011; Boly et al., 2012b). Alternatively, anesthetics may impair consciousness by leading to bistable, stereotypic cortical responses associated with a loss of information.

Consider first large-scale integration. Anesthetics are known to slow down neural responses (Munglani et al., 1993; Andrade et al., 1996; Plourde et al., 1998). As this effect may not occur uniformly across the cortex, it is likely to disrupt synchronization among distant areas. Indeed, when consciousness fades there is a drop in coherence in the gamma range (usually 20−80 Hz) between right and left frontal cortices as well as between frontal and occipital regions (John et al., 2001). Animal experiments also show that anesthetics suppress fronto-occipital gamma coherence, both under visual stimulation and at rest. The effect is gradual and much stronger for long-range than local coherence (Imas et al., 2006). The loss of front-to-back interactions between anterior and posterior regions of the cortex may be especially critical: at anesthetic concentrations leading to unresponsiveness in rats, transfer entropy, which provides a directional measure of information flow, decreases in the front-to-back direction—from frontal to parietal and from frontal or parietal to occipital cortex—when feed-forward transfer entropy is still high (Imas et al., 2005). Several human studies have also identified a selective suppression of feedback connectivity in fronto-parietal networks after the administration of various anesthetic agents (Lee et al., 2009, 2013; Ku et al., 2011; Boly et al., 2012a). In line with these observations, at hypnotic concentrations the anesthetic desflurane suppresses selectively the late component of neuronal firing (>100 ms), presumably due to reentrant connections, but not the early (~ 40 ms), feed-forward component, in rat visual cortex (Hudetz et al., 2009). Unit recording studies in animals also show that feed-forward responses persist during anesthesia (in fact, that is how they were traditionally investigated), but contextual modulation of firing, associated for instance with attention and presumably mediated by back-connections, are abolished (Lamme et al., 1998a,b; Lamme and Roelfsema, 2000). Anesthetic agents may be especially effective at disrupting integration because the corticothalamic system seems to be organized like a small-world network—mostly local connectivity augmented by comparatively few long-range connections (Buzsaki et al., 2004). Thus, anesthetics need only disrupt a few long-range connections to produce a set of disconnected components (Rozenfeld and Ben-Avraham, 2007). Indeed, computer simulations demonstrate a rapid state transition at a critical anesthetic dose (Steyn-Ross et al., 2001a,b). On the other hand, recent human and rodents studies suggest that small-world networks may be maintained during anesthetic-induced LOC (Liang et al., 2012; Schroter et al., 2012). An overall explanation of how various anesthetics, despite different mechanisms of action, may lead to loss of consciousness, is that they invariably cause a breakdown of information integration, as shown using TMS-EEG for midazolam, propofol, sevoflurane and xenon (Ferrarelli et al., 2010; Casali et al., 2013). (Figure 23.3 and Figure 25.5). As with sleep, it is likely that the breakdown of integration may be especially sensitive to the occurrence of bistability in cortical and thalamic cells.

Consider now the information aspect. When the number of differentiated activity patterns that can be produced by the corticothalamic system shrinks, neural activity becomes less informative, even though it may be globally integrated (Tononi, 2004b, 2012). Several general anesthetics produce a characteristic burst-suppression pattern in which a near-flat EEG is interrupted every few seconds by brief, quasi-periodic bursts of global activation that are remarkably stereotypic. It has now been shown that such stereotypic bursts can also be elicited by visual, auditory, and even micromechanical stimuli (Hartikainen et al., 1995; Makela et al., 1996; Hudetz and Imas, 2007; Kroeger and Amzica, 2007). Whether evoked or spontaneous, this stereotypic burst-suppression pattern indicates that during deep anesthetic unconsciousness the corticothalamic system can still be active—in fact hyperexcitable—and can produce global, integrated responses. However, the repertoire of responses has shrunk to a stereotypic burst-suppression pattern, with a corresponding loss of information.

An intriguing phenomenon that occurs occasionally during anesthesia is "intraoperative awareness" (Mashour and Avidan, 2015). Intraoperative awareness with explicit recall has been found in approximately 1−2/1000 patients (Mashour et al., 2012). The isolated

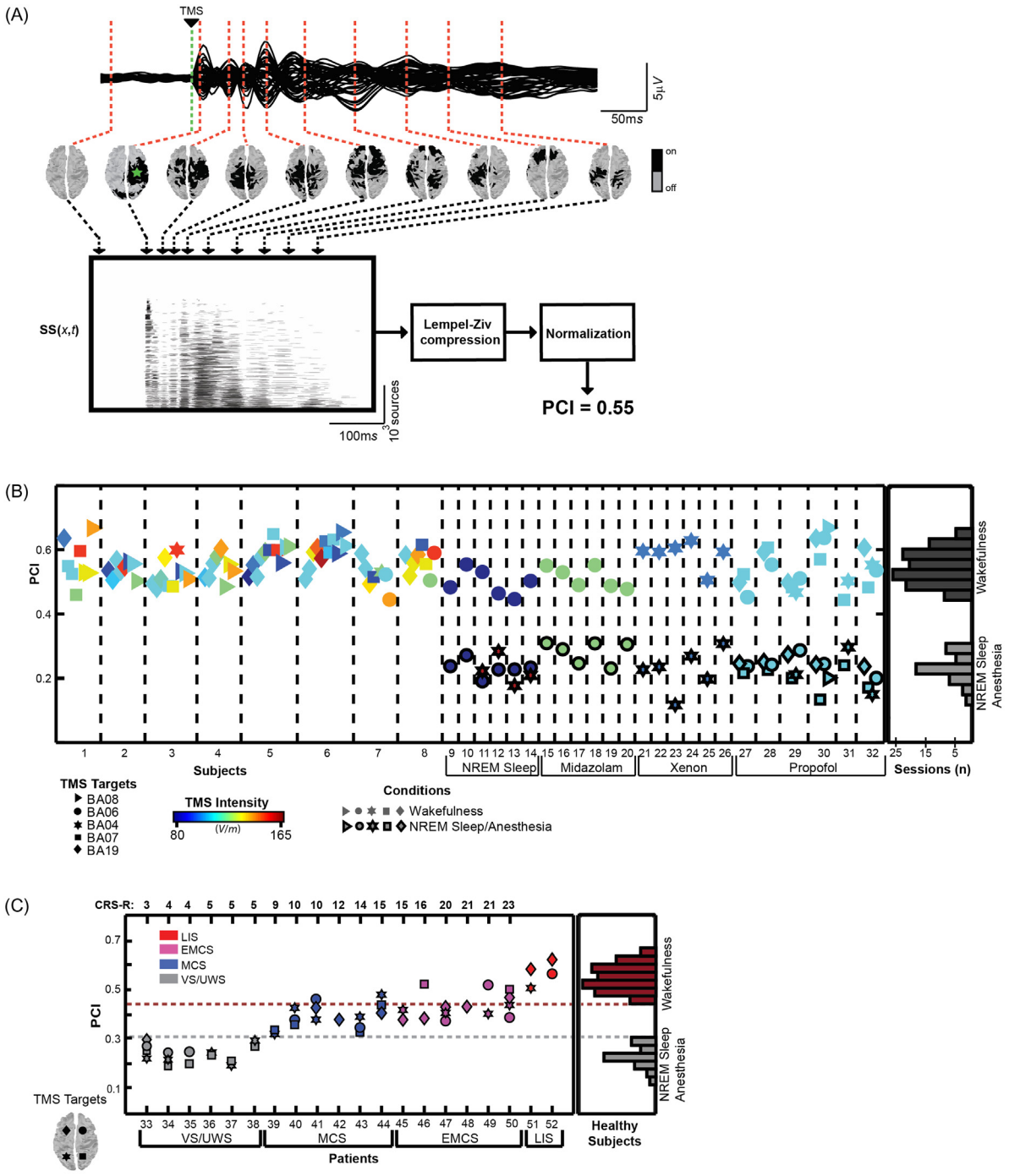

FIGURE 25.5 The Perturbational Complexity Index (PCI). (A) To calculate PCI, a binary spatiotemporal matrix of significant cortical activation triggered by TMS is compressed ("zipped") by Lempel-Ziv algorithmic complexity. (B) In healthy subjects, PCI measured during consciousness ranged between 0.44 and 0.67, whereas the PCI measured during unconsciousness ranged between 0.12 and 0.31. (C) In severely brain-injured patients, PCI progressively increases from vegetative state/unresponsive wakefulness syndrome (VS/USWS) to a minimally conscious state (MCS) and to recovery of functional communication (EMCS). PCI attains levels of healthy awake subjects in locked-in patients (LIS). CRS-R: Coma-Recovery Scale-Revised. *Source: Adapted from Casali et al. (2013).*

forearm technique can be used to assess awareness during anesthesia: a cuff prevents paralysis of the hand, which allows the patient to move the arm in response to a verbal command. Using this technique, the incidence of awareness during anesthesia, without explicit recall afterwards, seems to be much higher than the incidence of awareness with recall (Sanders et al., 2012). However, the use of the isolated forearm

technique in clinical practice is still controversial (Russell, 2013; Sleigh, 2013; Mashour and Avidan, 2015), partly because it is difficult to be sure that forearm responses always reflect full consciousness.

Coma and Related States

While consciousness may nearly fade during certain phases of sleep, and be kept at very low levels for a prescribed period during general anesthesia, coma and the vegetative state, are characterized by a loss of consciousness that is hard or impossible to reverse (Posner and Plum, 2007). Coma—an enduring sleep-like state of immobility with eyes closed from which the patient cannot be aroused—represents the paradigmatic form of pathological loss of consciousness. Typically, coma is caused by a suppression of corticothalamic function by drugs, toxins, or internal metabolic derangements. Other causes of coma are head trauma, strokes, or hypoxia due to heart failure, which again cause a widespread destruction of corticothalamic circuits. Smaller lesions of the reticular activating system can also cause unconsciousness, presumably by deactivating the corticothalamic system indirectly.

Patients who survive a coma may recover while others enter the so-called vegetative state, now called "unresponsive wakefulness syndrome" (Laureys et al., 2010), in which eyes reopen, giving the appearance of wakefulness, but unresponsiveness persists (Chapter 10). Soon, sleep/waking cycles follow, though in many cases they remain highly irregular (Cruse et al., 2013). Respiration, other autonomic functions and brainstem functions are relatively preserved, and stereotypic, reflex-like responses can occur, including yawning and grunting, but no purposeful behavior. Patients may remain unresponsive for a long time, or may emerge to a "minimally conscious state." This is distinguished from the unresponsive wakefulness syndrome because of the occasional occurrence of some behaviors that do not appear to be purely reflexive, suggesting that some degree of consciousness may be present (Giacino et al., 2002). The minimally conscious state has recently been subcategorized into minimally conscious *plus* (presence of language processing) and minimally conscious *minus* (presence of purposeful behaviors that do not necessitate comprehension, such as visual pursuit) (Bruno et al., 2011, 2012).

Post-mortem analysis in unresponsive patients reveals that the brainstem and hypothalamus, and specifically the reticular activating system, are largely spared, which explains why patients look awake. Usually the unresponsive wakefulness syndrome is due to widespread lesions of grey matter in neocortex and thalamus, to widespread white matter damage and diffuse axonal injury, or to bilateral thalamic lesions, especially of the paramedian thalamic nuclei (Posner and Plum, 2007). Thalamic damage can be secondary to diffuse cortical damage due to retrograde degeneration (just like in metabolic studies of anesthesia, changes in the thalamus are much more concentrated and therefore easier to document that in cortex). However, isolated paramedian thalamic damage can cause persistent unconsciousness. Indeed, recovery from an unresponsive wakefulness syndrome was associated with the restoration of functional connectivity between intralaminar thalamic nuclei and prefrontal and anterior cingulate cortices (Laureys et al., 2000b). A seminal study by Schiff et al. shows the role of the thalamus even more dramatically: bilateral deep brain electrical stimulation of the central thalamus restored a degree of behavioral responsiveness in a patient who had remained in a minimally conscious state for 6 years following brain trauma (Schiff et al., 2007). In an older study, a state of akinetic mutism was associated with hypersynchronous spike and wave activity in paramedian thalamus. After an induced Phenobarbital coma, seizures activity resolved and the patients began to speak (Williams and Parsons-Smith, 1951).

In patients with unresponsive wakefulness syndrome, brain metabolism is globally reduced by 50−60%, most notably in regions such as the posterior cingulate cortex and the precuneus (Laureys et al., 2004; Schiff, 2006b). These are also the areas that reactivate most reliably if a patient regains consciousness. A case study reported an extraordinary recovery of verbal communication and motor function in a patient who had remained in a minimally conscious state for 19 years (Voss et al., 2006). Diffusion tensor MRI showed increased fractional anisotropy (assumed to reflect myelinated fiber density) in posteromedial cortices, encompassing cuneus and precuneus. These same areas showed increased glucose metabolism as studied by PET scanning, likely reflecting the neuronal regrowth paralleling the patient's clinical recovery.

The differential diagnosis between unresponsive and minimally conscious patients is often challenging and can lead to up to 40% of misdiagnoses if it is based exclusively on clinical consensus without the adoption of standardized behavioral scales, such as the Coma-Recovery Scale Revised (Giacino et al., 2004; Schnakers et al., 2009; Stender et al., 2014). But even the most accurate behavioral assessment cannot rule out some degree of awareness. Neuroimaging studies have now shown that, even in completely unresponsive patients, as long as significant portions of the corticothalamic system are preserved, cognitive stimuli can induce patterns of activation similar to those seen in healthy subjects (Laureys et al., 2004; Schiff, 2006a). Since stimuli that are not perceived consciously can

still activate appropriate brain areas (see below and Chapters 4 and 18), inferring the presence of consciousness may be unwarranted. However, in a seminal study, a clinically unresponsive patient was put in the scanner and asked to imagine playing tennis or navigating through her room. Remarkably, the patient showed fMRI activation patterns of the appropriate cortical regions, exactly like healthy subjects. Obviously, these activations could not be due to unconscious processing of stimuli (Owen et al., 2006). Of note, this patient had widespread frontal lesions, while posterior cortex was largely preserved. Using the same fMRI paradigm, one patient in minimally conscious state has been able to accurately answer yes−no biographical questions (Monti et al., 2010). Since then, several studies have reported similar results using other paradigms (e.g., other imagery tasks, attentional task, passive viewing of a movie) and techniques (e.g., EEG, event-related potentials, electromyography) (Schnakers et al., 2008; Bardin et al., 2011; Cruse et al., 2011; Naci and Owen, 2013; Habbal et al., 2014). Recent PET, fMRI and EEG studies have had some success in distinguishing between minimally conscious and unconscious patients at the group level, for example, by considering the functioning of feedback connections (Boly et al., 2011), or by employing a combination of many different indices (Sitt et al., 2014, see also Boly et al., 2008, 2011; Vanhaudenhuyse et al., 2010; Gosseries et al., 2011; Wu et al., 2011; Lehembre et al., 2012; Fingelkurts et al., 2013; King et al., 2013; Forgacs et al., 2014; Sitt et al., 2014; Stender et al., 2014). TMS-EEG has also been applied in these patients and showed clear-cut differences at the individual level (Rosanova et al., 2012; Casali et al., 2013; Gosseries et al., 2015). As seen in NREM sleep and general anesthesia, in unconscious subjects TMS typically triggers a stereotypical slow wave that remains local, which indicates a breakdown of effective connectivity. In minimally conscious patients, brain activation patterns to TMS are widespread and differentiated, as observed in healthy awake subjects and locked-in patients (Figure 25.3). In order to quantify these TMS-EEG responses, the perturbational complexity index (PCI) has recently been developed (Casali et al., 2013). This measure estimates brain complexity, that is, information content and the integration of brain activations, via algorithmic compressibility ("zipping") (Figure 25.5A). PCI successfully differentiates between conscious and unconscious states: it is invariably high in healthy awake subjects, in patients in a minimally conscious state and in locked-in syndrome as well as in REM sleep, whereas PCI is always low in both patients in an unresponsive wakefulness syndrome and under general anesthesia as well as during NREM sleep (Figure 25.5B and C).

Seizures

The abnormal, hypersynchronous discharge of neurons is a frequent cause of short-lasting impairments of consciousness. Consciousness is lost or severely affected in the so-called generalized seizures, such as absence and tonic-clonic seizures, and to a lesser extent in complex partial seizures (Chapter 16). Absence seizures, which are more frequent in children, are momentary lapses of consciousness during which a child stops what she was doing and stares straight ahead blankly. Absence seizures are accompanied by spike-and-wave complexes at around 3 Hz in the EEG, reflecting cycles of synchronous firing and silence of large number of neurons. There is great variability in the degree of unresponsiveness both across subjects and, within the same subject, between seizures. Sometimes, simple behaviors such as repetitive tapping or counting, can proceed unimpaired during the seizures, but more complex tasks come to a halt.

Generalized convulsive seizures usually comprise a tonic phase of muscle stiffening, followed by a clonic phase with jerking of the arms and legs. After the convulsion the person may be lethargic or in a state of confusion for minutes up to hours. During the tonic phase of a convulsive seizure neural activity is greatly increased, as indicated by high-frequency activity in the EEG. The clonic phase is accompanied by synchronous spikes and waves in the EEG, corresponding to millions of neurons alternately firing in strong bursts and turning silent. Loss of consciousness during the tonic phase of generalized seizures is noteworthy because it occurs at times when neuronal activity is extremely high and synchronous.

Partial complex seizures often begin with strange abdominal sensations, fears, premonitions, or automatic gestures. The person progressively loses contact with the environment, exhibits a fixed stare and is unable to respond adequately to questions or commands. Stereotyped, automatic movements are common. Complex partial seizures usually last from 15 s to 3 min. Seizure activity is usually localized to the medial temporal lobe.

The diagnosis of seizures is made through clinical observation and EEG recordings. Recent studies have attempted to better characterize the degree of loss of consciousness during seizures using behavioral scales (Lambert et al., 2012; Yang et al., 2012). These studies have demonstrated a range of different alterations of consciousness during seizures, the largest impairment of conscious level being observed during generalized seizures (Yang et al., 2012) while partial seizures showed a more moderate impairment (closest to minimally conscious state) and followed a bimodal pattern (Cunningham et al., 2014). In absence and

tonic-clonic seizures the scalp EEG shows diffuse abnormalities, suggesting a generalized involvement of brain networks, whereas in partial complex seizures the abnormalities are confined to a medial temporal focus on one side. However, neuroimaging studies using single photon emission computed tomography (SPECT), PET, and fMRI, and depth EEG recordings in humans and animals have revealed that generalized seizures do not affect all brain areas indiscriminately, whereas complex partial seizures alter brain activity less focally than initially thought (Blumenfeld and Taylor, 2003; Blumenfeld et al., 2003, 2004; Blumenfeld, 2005). In fact, it now appears that all seizures causing an impairment of consciousness are associated with changes in activity in three sets of brain areas (Chapter 16), namely: (i) increased activity in the upper brainstem and medial thalamus; (ii) decreased activity in the anterior and posterior cingulate, medial frontal cortex, and precuneus; (iii) altered activity in the lateral and orbital frontal cortex and in the lateral parietal cortex. In tonic-clonic seizures, fronto-parietal association areas show increased activity, while the pattern is more complex and variable in absence seizures, though parietal areas are usually deactivated. Another recent study showed a variable activation of different areas of the cortex during the generalized phase of secondary generalized tonico-clonic seizures, while postictally frontoparietal cortices were deactivated (Blumenfeld et al., 2009). Complex partial seizures show decreased activity in frontal and parietal association cortex, which is associated with the onset of slow waves similar to those of sleep or anesthesia (rather than to epileptiform discharges) (see also Englot et al., 2010). Loss of consciousness during complex partial seizures (parietal or temporal in origin) has also been linked to an increase in long range-cortical synchronization in fronto-temporo-parietal cortices (Arthuis et al., 2009; Lambert et al., 2012).

At this stage, it is not clear which of these three sets of areas, alone or in combination, are crucial for the loss of consciousness. However, two things are clear: first, the areas involved in the loss of consciousness associated with seizures correspond to those affected in sleep, anesthesia, and the unresponsive wakefulness syndrome, pointing to a common substrate for the most common forms of loss of consciousness; second, especially during the tonic phase of convulsive seizures, it would seem that consciousness is lost when neurons are excessively and synchronously active, rather than inactive. Perhaps, as with the bistable, hypersynchronous transitions between down- and up-states during sleep, and with the hypersynchronous burst-suppression patterns during deep anesthesia, consciousness fades when the repertoire of available neural states shrinks, and with it the information capacity of the system (see below, and Tononi, 2004b, 2008, 2012).

THE NEUROANATOMY OF CONSCIOUSNESS

Despite the wealth of evidence reviewed in this book, it is still difficult to converge on a circumscribed set of brain structures that are "minimally sufficient and jointly necessary" for consciousness (Crick and Koch, 2003) (Chapter 1). It is also important to keep in mind that, at this stage, we have no idea whether the elementary neural units that contribute to consciousness are local groups of neurons, such as cortical minicolumns, or individual neurons, and perhaps only neurons located in certain layers or belonging to a particular class. What is undisputed, and certainly not new, is that broad lesions or inactivations of the corticothalamic system abolish consciousness, whereas lesions of other parts of the brain do not. Beyond this, it is still difficult to be more precise with a sufficient degree of confidence. Recent developments, however, make it at least possible to ask some pertinent questions and suggest comparisons that may help to sharpen scientific inquiry.

Below, we briefly review, without any pretence at completeness: (i) the evidence that establishes the central role of the corticothalamic system and rules out other areas of the brain; (ii) the role of the thalamus versus that of the cortex; (iii) that of primary areas versus higher-level areas; (iv) the ventral versus the dorsal stream; (v) fronto-parietal networks versus the default system; (vi) posterior versus anterior (prefrontal) cortices; (vii) reentrant versus feed-forward connections; and finally, (viii) superficial versus deep layers of cortex.

The Corticothalamic System vs. the Rest of the Brain

As we just mentioned, the only conclusion that can be drawn for sure about the neural substrate of consciousness is that it includes parts of the corticothalamic system. The evidence comes from many different sources, and it constitutes the true bedrock of the neurology of consciousness. Unambiguous examples of unresponsive wakefulness syndrome demonstrate that the loss of consciousness is usually associated with widespread lesions of the grey or white matter of the cortex, and most of the time with a significant thalamic involvement (Posner and Plum, 2007).

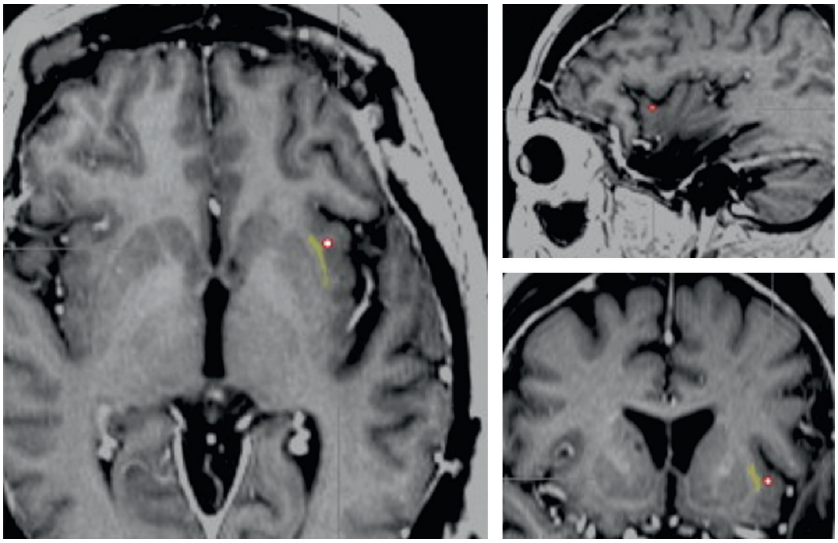

FIGURE 25.6 Loss of consciousness induced by electrical stimulation. In a patient with intractable epilepsy, electrical stimulation of the anterior-dorsal insula area elicited loss of consciousness (red circle). The claustrum is highlighted in yellow to show its proximity to the stimulated target. So far, no similar response to electrical stimulation of any other brain area has ever been reported. *Source: Taken from Koubeissi et al. (2014).*

The evidence is just as persuasive that patients remain conscious after lesions of brain structures outside the corticothalamic system, first among them the spinal cord, which can be severed without affecting consciousness in any direct manner. The cerebellum offers another interesting case study. Even widespread cerebellar lesions or complete ablations hardly affect consciousness (Boyd, 2010; Lemon and Edgley, 2010; Yu et al., 2014), yet the cerebellum has even more neurons that the cerebral cortex (Herculano-Houzel, 2012), is richly endowed with connections, neurotransmitters and neuromodulators, receives inputs from the sensory periphery, controls motor outputs, contains maps of the body and the outside space, is strongly connected in both directions with thalamus and cortex, and often shows selective activation during cognitive tasks and in relation to emotion (Glickstein, 2007; Schmahmann et al., 2007; Buckner, 2013). Altogether, rather than playing a direct role in consciousness, the cerebellum appears to function to control the acquisition of sensory inputs (Baumann et al., 2015) and as a learning device for motor, perceptual and cognitive functions (Deluca et al., 2014). As we shall briefly discuss in a later section, the cerebellum can be usefully contrasted to the corticothalamic complex to evince which aspects of neural organization are important for generating consciousness.

Concerning other brain structures the evidence is more complex. A case has been made for the claustrum as a key structure for consciousness. The claustrum is a thin sheet of nerve cells located just underneath the insular cortex and connected to most cortical regions (Crick and Koch, 2005). To this day selective lesions have not been reported, but claustral lesions associated with widespread striatal lesions do not necessarily cause unconsciousness (Straussberg et al., 2002). On the other hand, in a recent single case report, electrical stimulation of the forebrain induced an abrupt loss of consciousness in which the patient stared blankly ahead and became unresponsive (Figure 25.6). After the stimulation was stopped, the patient became conscious again but without recalling the intervening events (Koubeissi et al., 2014).

Selective, bilateral lesions of the basal ganglia are rare (Jain et al., 2013), although there are cases of selective bilateral necrosis of the striatum and related structures, including the claustrum (Leuzzi et al., 1988, 1992; Craver et al., 1996; Caparros-Lefebvre et al., 1997; Straussberg et al., 2002), as well as several instances of bilateral pallidotomy for the control of movement disorders (Scott et al., 1998; Ghika et al., 1999; York et al., 2007). Also, a case can be made for a virtual blockade of basal ganglia function in extreme Parkinson's disease and perhaps in catatonic states (Northoff, 2002; Northoff et al., 2004). Such cases show some degree of cognitive impairment, but most problems have to do with movement initiation and control, dysphonia progressing to aphonia, dysarthria and finally mutism, and/or with the execution of abnormal (athetoid) or automatic movements (Tremblay et al., 2015). Consciousness, however, appears to be preserved—children affected before 3 years of age may not speak but respond to sensory stimuli and communicate with their parents (Straussberg et al., 2002); adults may develop cognitive problems, including a frontal syndrome, but are clearly conscious (Caparros-Lefebvre et al., 1997). However, lesions involving portions of the basal ganglia as well as the anterior cingulate can result in akinetic mutism (see below) or in the "slow syndrome" (Posner and Plum, 2007), and have been implicated in the recovery of consciousness in brain-damaged patients (Schiff, 2010, "the meso-circuit hypothesis"). In

the latter case, patients are slow and somnolent, but communication is possible. Circuits involving the basal ganglia originate mostly from anterior cortex, the portion of the corticothalamic complex whose necessity for consciousness is more questionable, as discussed below. Thus, despite being an integral component of at least five parallel cortico−subcortico−cortical circuits, the basal ganglia may not contribute directly to consciousness. Rather, basal ganglia (and cerebellar circuits) are thought to play an important role in transforming hard, slow, error-prone sequences of movements that are performed under conscious control, into smooth, fast, and error-free routines that are executed automatically (Debaere et al., 2004; Floyer-Lea and Matthews, 2004).

Finally, we have seen above, on the section on memory, that bilateral hippocampal lesions that abolish episodic, autobiographical memory do not abolish consciousness. However, what consciousness remains is less rich—there is a deficit in imagination—and it may be especially constricted in its temporal dimension—the duration of the conscious present (see Chapter 21).

Cortex vs. Activating Systems

Brainstem structures, as well as their hypothalamic and basal forebrain extensions, offer an instructive example concerning the difference between the neural substrate of consciousness and factors that merely enable it. Every neurologist knows that if the brainstem is damaged or compressed, coma is likely to ensue—even minor lesions affecting the "ascending reticular activating system" (Moruzzi and Magoun, 1949) can produce unconsciousness. The reticular activating system in the upper brainstem reticular formation ultimately acts by "activating" the EEG, that is, by promoting low-voltage fast activity, presumably by increasing excitability and facilitating effective interactions within cortex. In the classic account, the activating system acts on the cortex through two branches: the thalamic branch, which innervates intralaminar, relay, and reticular thalamic nuclei; and the extrathalamic branch, which reaches hypothalamic nuclei and the basal forebrain, and also contains some projections to cortex. Subsequent work revealed neurochemically specific components of the upper brainstem activating system, primarily noradrenergic neurons in the locus coeruleus and various groups of cholinergic neurons, and identified additional hypothalamic arousal systems including the histaminergic and orexinergic systems. However, selective lesions of brainstem noradrenergic and cholinergic cell groups did not reproduce the deep coma seen after acute paramedian midbrain lesions that transect ascending axons at the caudal midbrain level. Recent work in rats has demonstrated that cell specific lesions of glutamatergic neurons in a parabrachial-precoeruleus complex cause behavioral unresponsiveness and a monotonous sub-1 Hz cortical EEG. These reticular activating neurons act indirectly by projecting to the basal forebrain, whose lesion also produces coma and slow EEG. Indeed, brainstem stimulation that produces an arousal reaction and the activation of the EEG (Moruzzi and Magoun, 1949) also becomes ineffective when the local anesthetic lidocaine is injected into the basal forebrain, but not so much when it is injected into the thalamus (Dringenberg and Olmstead, 2003).

Animal experiments indicate that as long as some activating systems remain, for example both cholinergic and non-cholinergic cells in the basal forebrain (Buzsaki et al., 1988; Dringenberg and Olmstead, 2003), consciousness may be possible. However, as demonstrated by patients who awaken from coma and evolve into an unresponsive wakefulness syndrome, a functioning brainstem is insufficient for consciousness in the absence of a functioning corticothalamic system—there is wakefulness (eyes open), but no experience. Whether the corticothalamic system can resume its function and sustain consciousness if the brainstem reticular activating system and its basal forebrain relay are permanently damaged is unclear but, as suggested by the dramatic effects on consciousness of deep cortical stimulation in the median thalamus, the reticular activating system appears to have the role of an enabler or controller of the level of consciousness, an on-off "switch," rather than of a generator of consciousness. Another effective consciousness switch may be located in the basal forebrain, as long as both cholinergic and noncholinergic cells are targeted (Buzsaki et al., 1988).

Cortex vs. Thalamus

The thalamus is sometimes considered as a seventh layer of cortex, so contrasting its role with that of the cortex proper may be a useless enterprise. Nevertheless, it has been suggested that the thalamus, and especially the intralaminar nuclei, may constitute a "centrencephalic system" where consciousness resides (Bogen, 1997). Very few patients in a unresponsive state or minimally conscious state have circumscribed brain lesions. As we have seen, however, those who do often have bilateral damage in a region including paramedian thalamic nuclei (Posner and Plum, 2007). Moreover, the restoration of functional connectivity between paramedian thalamus and cingulate cortices is an early sign of recovery from the unresponsive wakefulness syndrome (Laureys et al., 2000b), and bilateral deep brain electrical stimulation of the central thalamus restored behavioral

responsiveness in a patient who had remained in a minimally conscious state for 6 years (Schiff et al., 2007). In animals, acute thalamic manipulations can have major effects. For example, an infusion of GABA agonists (mimicking anesthetic action) into central medial intralaminar nuclei causes animals to fall "asleep" and the EEG to slow down (Miller and Ferrendelli, 1990; Miller et al., 1993). Conversely, rats kept under an anesthetic concentration of sevoflurane can be awakened by a minute injection of nicotine in the same area (Alkire et al., 2007). However, other experiments indicate that the thalamus may not be necessary for consciousness. Thus, paramedian thalamic lesions inducing coma usually include neighboring fiber tracts, including the newly discovered projection from glutamatergic neurons in the parabrachial-precoeruleus complex of the brainstem that activate the cortex through a basal forebrain relay (Fuller et al., 2011). The same rodent study showed that extensive thalamic lesions have little effect on EEG or behavioral measures of wakefulness (Fuller et al., 2011). It was also reported long ago that, following a complete ablation of the thalamus, the cortex can still produce an activated EEG (Villablanca and Salinas-Zeballos, 1972; Vanderwolf and Stewart, 1988). Moreover, as was mentioned above, when a patient with depth electrodes in the thalamus was anesthetized, the cortical EEG changed dramatically the instant the patient lost consciousness, but the thalamic EEG remained unchanged until almost 10 min later (Velly et al., 2007). A complementary result is provided by another study in epileptic patient: during REM sleep—a state usually associated with dreaming—the cortical EEG was duly activated, but the thalamic EEG in the medial pulvinar nucleus showed slow wave activity (Magnin et al., 2004). Also, unlike sedation, loss of consciousness *per se* is accompanied by a decrease in cortico-cortical rather than by changes in thalamo-cortical connectivity (Boly et al., 2012a; Monti et al., 2013).

On the other hand, the thalamus is important in ensuring connectedness to the external environment (Steriade et al., 2001; Sanders et al., 2012) and in facilitating cortico-cortical interactions (Theyel et al., 2010). Thus, when the thalamus is acutely deactivated, interfering with environmental connectedness, the cortex may become more bistable and consciousness may be lost. Indeed, some studies show that thalamic activity can change before or simultaneously with changes in cortical activity during the transition to unconsciousness (Magnin et al., 2010; Baker et al., 2014; Verdonck et al., 2014). Thus, it may be that thalamic deactivation may promote loss of consciousness, acting as an acute "consciousness switch" (Alkire et al., 2000), probably through an indirect action on cortical excitability. However, only cortical deactivation is sufficient for inducing and maintaining unconsciousness. Moreover, consistent with the role of the thalamus as a seventh layer of cortex, efficient communication between cortical areas might requires a thalamic relay (Guillery et al., 2001; Guillery and Sherman, 2002; Sherman and Guillery, 2002, but see Shipp, 2003; Jones, 2007), in that case thalamic lesions would lead to a functional disconnection within cortex, despite an activated EEG. The anatomy is also consistent with such a role: calbindin-positive matrix cells, which are especially concentrated within some of the intralaminar thalamic nuclei (Jones, 1998, 2007), project diffusely to many areas of the cortex, where they provide a more superficial innervations (layers I, II, and upper III). Also, matrix cells receive collaterals mostly from cortical cells in layer V, which in turn have much wider intracortical collaterals than layer VI cells, (and are especially sensitive to anesthetics). Cells within intralaminar thalamic nuclei are capable of firing in the gamma range and can provide NMDA receptor activation, subthreshold depolarization and coherent oscillatory bias to distant cortical areas (Llinas et al., 2002), thereby potentially facilitating long range interactions. Also, intralaminar nuclei are ideally poised to work as an anatomical hub connecting many cortical regions (Scannell et al., 1999), and are a prominent target of inputs from the reticular activating system of the brainstem. For these reasons, matrix cells can be conceptualized as a veritable thalamic activating system capable of facilitating effective interactions among many cortical areas and thereby of sustaining consciousness.

Primary Areas vs. Higher Level Areas

Since the suggestion by Crick and Koch that primary visual cortex may not be part of the "neural correlate of consciousness" (Crick and Koch, 1995), a remarkable amount of refined neuroscience has attempted to settle the question whether this brain area is "in" or "out." That is, does primary visual cortex contribute directly to visual consciousness, or only indirectly—a sort of larger, higher-up retina (Silvanto, 2014)? Consider retinal neurons. Though they certainly rely information to all parts of the visual system, and their activity usually determines what we see when we open our eyes, they do not seem to contribute directly to conscious experience. For example, their rapidly shifting firing patterns do not correspond well with what we perceive, which is much more stable. Moreover, during blinks and eye movements retinal activity changes dramatically, but visual perception does not. Also, the retina has a blind spot at the exit of the optic nerve where there are no photoreceptors, and it has low spatial

resolution and no color sensitivity at the periphery of the visual field, but we are not aware of any of this. More importantly, lesioning the retina does not prevent conscious visual experiences. As we have seen, a person who becomes retinally blind as an adult continues to have vivid visual images and dreams. Conversely, stimulating the retina during sleep by keeping the eyes open and presenting various visual inputs does not yield any visual experience and does not affect visual dreams (Rechtschaffen and Foulkes, 1965).

What is the situation with primary visual cortex? Psychophysical experiments indicate that several stimuli known to affect the activity of V1 neurons have no perceptual counterpart (Andrade et al., 1996; He and MacLeod, 2001; Jiang et al., 2007). Also, single neuron recordings from the monkey, using paradigms such as binocular rivalry, find that activity in V1 tends to follow the physical stimulus, rather than the percept, unlike neurons higher up in the visual hierarchy (Logothetis, 1998; Leopold and Logothetis, 1999; Blake and Logothetis, 2002). On the other hand, a number of fMRI BOLD studies found that activity in human V1, and even in the lateral geniculate nucleus, was correlated with perception (Chapter 4) during binocular rivalry (Polonsky et al., 2000; Lee et al., 2005b) or working memory tasks (Harrison and Tong, 2009), this is not true for motion-induced blindness (Donner et al., 2008). Similarly, V1 fMRI signals associated with unperceived line drawings were modulated by visual attention (Bahrami et al., 2007). Finally, it is possible to decode from V1 BOLD activity the orientation of a masked stimulus, even though subjects could not guess its orientation (Haynes et al., 2005).

Lesions of V1 lead to the striking phenomenon of "blindsight," in which patients claim to have no conscious perception of stimuli, though they perform better than chance on forced-choice tasks where they are asked to detect stimuli, locate them, decide on their orientation and direction of motion (Weiskrantz, 1996) (see also Chapter 18). Compelling evidence supports the idea that blindsight is subserved by subcortical visual pathways that originate from the superior colliculus and bypass primary visual cortex. The subjective blindness of blindsight patients may perhaps be explained purely in terms of insufficient feed-forward activation of higher visual areas, denying any direct role to V1 *per se* in generating experience. Alternatively, their blindness could be due to lack of feedback to V1, in which case V1 would be necessary for conscious vision. Current evidence indicates that patients with damaged extrastriate visual areas and intact V1 can have quadrantanopia (Horton and Hoyt, 1991) (blindness in a quarter of the visual field), suggesting that V1 is insufficient for conscious vision. Conversely, in blindsight patients with intact extrastriate areas and damaged V1, phosphene-like percepts can be induced by stimulating parietal cortex with TMS (Figure 25.7) (Mazzi et al., 2014).

Additional evidence against a direct contribution of not only V1 but other primary sensory cortices comes from studies of sensory stimulation during slow wave sleep (Chapter 9, general anesthesia, and in patients with unresponsive wakefulness syndrome, Chapter 10). Using evoked responses or neuroimaging techniques, these studies show the localized activation of primary areas in the absence of any indication of consciousness (Figure 25.4) (Laureys et al., 2000a, 2002; Coleman et al., 2009; Boveroux et al., 2010). In contrast, when patients are (minimally) conscious, they typically recruit a widespread set of associative sensory cortices (Boly et al., 2004, 2008). However, it should be remembered that areas higher up in the cortical hierarchy, often considered to be contributing to experience, can also be activated, at least at the fMRI level, in the absence of conscious perception, as shown by studies of backward masking (Dehaene et al., 2001), inattention (Marois et al., 2004; Sergent et al., 2005), and neglect (Vuilleumier et al., 2001). Perhaps in some of these instances the activation that reaches higher areas is merely insufficient, for instance in masking. Alternatively, the fMRI signal may be strong, as in inattention and neglect, but it may lack some other features that would only be evident with units recordings, such as fast oscillations or synchronization with other areas, or it may be that higher areas must respond to inputs from lower areas for their activation to contribute to consciousness. Finally, less is known about the possible contribution to consciousness of other primary cortices such as motor cortex. However, some evidence exists to show, for example, that masked visual stimuli can elicit motor cortex activation and increase its excitability as probed with TMS (Theoret et al., 2004), and yet remain unperceived. Of course, demonstrating that activation or changes in excitability in primary cortices do not translate in reportable changes in experience does not prove that no activation pattern would be able to elicit experience—just think of the fact that even high intensity TMS or direct electrical stimulation usually fail to affect consciousness, no matter what brain area is the target, with only a few exceptions (Penfield, 1975; Salminen-Vaparanta et al., 2014).

Current evidence thus seems to support the hypothesis that V1 does not contribute directly to visual experience, and this may be generalized to other primary areas such as the auditory cortex (Meyer, 2011, but see Wiegand and Gutschalk, 2012). However, it is hard to say whether this applies to all

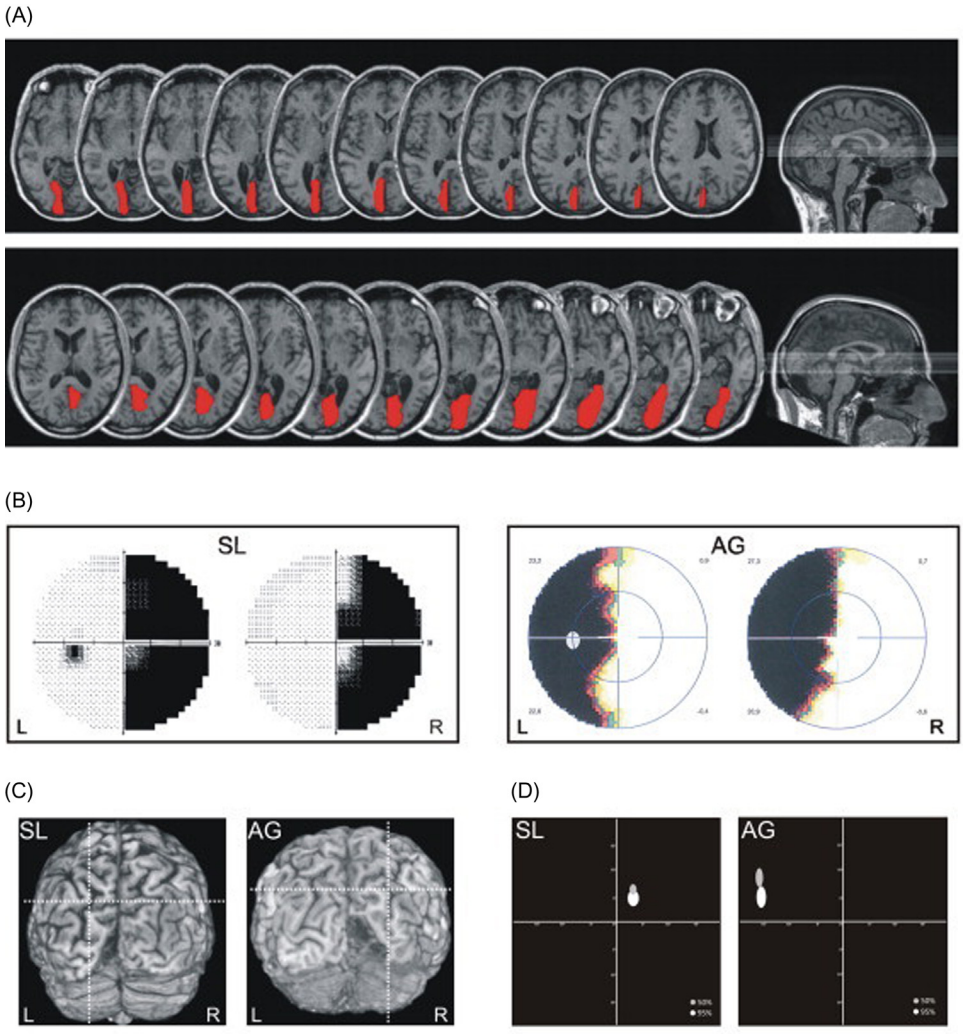

FIGURE 25.7 TMS applied to parietal cortex induces phosphene in blindsights patients. Stimulation of the parietal lobe of the lesioned hemisphere elicited conscious visual percepts in two hemianopic patients, even in absence of any involvements of the occipital cortex, specifically of V1. (A) Brain lesion reconstruction. (B) Visual field defect. (C) Location of stimulation in the two patients. (D) Phosphene drawings for two TMS intensities (50 and 95%). *Source: Adapted from Mazzi et al. (2014).*

visual attributes, such as precise topography, detailed contours, or luminosity, as has been argued by some (Zeki, 1993; Pollen, 2008; Oizumi et al., 2014).

Ventral vs. Dorsal Stream

Based on previous work indicating a subdivision between a ventral and a dorsal visual stream diverging from primary visual cortex, a case has been made for distinguishing between a ventral stream for perception and a dorsal stream for action (Milner and Goodale, 1995; Goodale and Milner, 2005). The ventral stream includes a number of areas in ventral temporal and lateral occipital cortex (the lateral occipital complex); the dorsal stream includes areas V3A, V5, V7 and intraparietal areas in the posterior parietal cortex. According to the initial account (Milner and Goodale, 1995), which was subsequently refined (Goodale and Milner, 2005), activity in the ventral stream gives rise to conscious experience, extracting invariant features that subserve object identification, as well as the relationships among objects within the context of a visual scene. This system would allow us to construct a lasting representation of the world, categorize objects and events, talk about them, form explicit memories, and plan long-term actions (Milner, 2012). By contrast, the dorsal stream deals with the moment-to-moment information about the precise size, shape, location, and disposition of objects for the rapid visual control of skilled actions, such as tracking, reaching, and grasping the object. It has little memory and its activity remains unconscious. There is in fact neurological evidence for a double dissociation between the two systems: some patients with ventral stream lesions have a "visual object agnosia" in which they lack the conscious experience of the shape of objects, but can unconsciously adapt the reaching and grasping to the unperceived object just as well as healthy controls (Goodale et al., 1991). Other patients with dorsal stream lesions have an "optic ataxia" in

which they perceive the objects but cannot execute the appropriate skilled movements (Pisella et al., 2000) (see also Chapter 18). Some visual illusions can also be used to show a dissociation between the two systems. One sees here another aspect of the dichotomy between the slow, consciously controlled actions when first learning a new skill, and the rapid, effortless executed skill after it has been learned: in the first case, the brain calls on a large and diverse amount of information, specifying a wide context, whereas in the latter case it employs only the minimum amount of information that is required to execute the movement at hand.

Recently, however, it was shown that areas in the dorsal stream respond not only to the location of objects but also to their identity, and that hierarchically higher intraparietal areas in the dorsal stream do so in a viewpoint- and size-invariant manner, just as ventral areas do (Konen and Kastner, 2008), and as required by perceptual constancies that are characteristic of conscious experience. These selective, invariant responses to objects could be elicited irrespective of any requirement for action, and were not due to attentional confounds. As we have seen, areas in posterior parietal cortex implement a detailed map of space, so both spatial and object information are available in close proximity. Indeed, given that visual objects can activate ventral areas in neglect syndromes and inattentional blindness without giving rise to conscious experience, one wonders which set of object-selective areas is more important for experience. As mentioned above, phosphenes induced by TMS to intraparietal cortex correlated with an early EEG response in parietal cortex in both healthy subjects (70 ms) and in a patient with a complete lesion of ipsilateral V1 (80 ms) (Bagattini et al., 2015). Finally, projections from the dorsal stream to the prefrontal, premotor and medial temporal cortices may support not just unconconscious visuospatial processes but also conscious ones (e.g., working memory, visually guided action and navigation) (Kravitz et al., 2011).

Posterior vs. Anterior (Prefrontal) Cortex

Lesion studies support the notion that consciousness does not require prefrontal cortex and, by inference, the functions it performs. Early studies showed that large, bilateral prefrontal resections did not abolish consciousness. Brickner's patient A. was the first human to undergo bilateral frontal lobectomy: "... one of the salient traits of A's case was his ability to pass as an ordinary person under casual circumstances, as when he toured the Neurological Institute in a party of five, two of whom were distinguished neurologists, and none of them noticed anything unusual until their attention was especially called to A. after the passage of more than an hour" (Brickner, 1952). In another case, Hebb reported that removal of large portions of the frontal cortex had little effect on intelligence: Penfield had resected one third or more of each frontal lobe of patient K.P. to eliminate epileptic foci, yet K.P. showed "a striking post-operative improvement in personality and intellectual capacity" (Hebb and Penfield, 1940). Psychosurgery led to the widespread adoption of prefrontal lobotomy and leucotomy, in which prefrontal cortex was deafferented from its thalamic inputs, again with no major impairment of consciousness (Fulton, 1949; Mashour et al., 2005) (with the exception of anterior cingulotomy, which could result in akinetic mutism, see below). A number of psychiatric patients also underwent the bilateral resection of prefrontal cortical areas, either in isolation or in combination, according to Brodmann's atlas ("topectomy") (Mettler et al., 1949). Yet even patients receiving a bilateral resection of, say, areas 10, 11, 45, 46, 47, or 8, 9, 10, or 44, 45, 46, 10, or area 24 (ventral anterior cingulate) showed no gross behavioral change and certainly maintained consciousness. Some received both topectomy and lobotomy, again with no gross effects on consciousness.

Patients with widespread, bilateral damage to prefrontal cortex remain rare, but two more recent clinical studies provide additional, intriguing evidence. A young man who had fallen on an iron spike that completely penetrated through both of his frontal lobes, nevertheless went on to live a stable family life—marrying and raising two children—in an appropriate professional and social setting. Although displaying many of the typical frontal lobe behavioral disturbances, he never complained of loss of sensory perception nor did he show visual or other deficits (Mataro et al., 2001). Another case is that of a young woman with massive bilateral prefrontal damage of unclear etiology (Markowitsch and Kessler, 2000). While manifesting grossly deficient scores in frontal lobe tests, she showed no abnormal perceptual abilities, and there was no issue whether she was conscious (that is not to say that such patients do not suffer from subtle visual deficits (Barcelo et al., 2000)).

The evidence is more ambiguous with medial prefrontal lesions, especially those involving anterior cingulate cortex and supplementary motor areas, often due to ruptured aneurysms of the anterior communicating artery. The presentation of such patients has been described as *akinetic mutism* (Cairns et al., 1941), which is usually categorized as a variant of minimally conscious states (Schiff and Plum, 2000). Although the term akinetic mutism has been sometimes used to denote different clinical conditions having different pathology (e.g., the so-called slow syndrome), the classic presentation is that of a patient who lies indeed

immobile and mute, but gives the impression of hypervigilance, following actions and objects with conjugated eye movements. However, it is generally impossible to elicit any responses, establish contact (though in some patients, occasionally, monosyllabic answers are reported), and there is no spontaneous purposive activity. In a few cases, clinicians have the impression that such patients may understand what is going on (which is why they are considered to be mute rather than having an unresponsive wakefulness syndrome), implying that consciousness is present (though possibly impaired), but not evidenced in behavior due to a complete lack of motivation or block of executive function (as opposed to paralysis, as in the locked-in syndrome, Chapter 12). Others instead consider such patients as essentially unconscious. The interpretation is complicated by the fact that, in the rare instance in which such patients recover, there is usually amnesia for the akinetic episode, as in the original case of Cairns, though one patient who eventually recovered reported that she remembered the questions posed by the doctor but did not see a reason to respond (Laureys, personal communication). Cases in which the syndrome resolves through dopaminergic therapy, as well as acute akinesia in Parkinsonism, are also difficult to interpret, and may or may not resemble classic akinetic mutism from a functional point of view. Perhaps the most intriguing results have been obtained in such patients by using event-related potentials. Such studies have shown that, while several aspects of the EEG responses may be altered, there can be a differential response to semantically meaningful stimuli, for example in oddball paradigms (Kotchoubey et al., 2003, 2005; Kotchoubey, 2005). Similar findings have been obtained in a number of patients with unresponsive wakefulness syndrome, usually when the background EEG contained frequencies above 4 Hz. Though these preserved responses are hard to interpret, they support the possibility that at least some degree of consciousness may be preserved after medial anterior lesions and possibly also in other instances of clinical unresponsiveness.

Contrast these examples of widespread anterior damage with patients with bilateral posterior damage resulting in a syndrome of *hyperkinetic mutism* (Fisher, 1983; Inbody and Jankovic, 1986; Mori and Yamadori, 1989; Schiff and Plum, 2000): such patients are engaged in a whirlwind of motor activity, coordinated but without purpose. There is no indication that they have any awareness of self or environment (and of course they do not speak). An extreme case was described by Schiff and colleagues (2002). The patient exhibited continuous, spontaneous, non-directed choreiform movements of head, body, and extremities when awake. He was mute and his movements had no relationship to visual, auditory or tactile stimuli. A PET study showed a profound hypometabolism of posterior forebrain regions, whereas anterior, cortico-striato-pallido-thalamo-cortical circuits showed comparatively high metabolism. Is there any experience left in such patients? Is a self despairing in complete nothingness, experiencing thoughts of action with no object? Or is this condition associated with a complete disappearance of the world and the self, and thus of consciousness? Intriguingly, a late posterior positivity having a parietal peak is the event-related potential component that is most reliably impaired in states of seeming unconsciousness, and which distinguishes best between consciously detected versus undetected stimuli (Kotchoubey, 2005). Additionally, posterior cortex has been correlated with consciousness in experiments contrasting awareness with task relevance (Pitts et al., 2014), in studies matching expectations and performance during target presentation (Melloni et al., 2011), and in an no-task, within state paradigm during both REM and NREM sleep (Siclari et al., 2014b). Another interesting finding is that, during the transition to sleep, slow waves tend to first affect the medial frontal cortex rather than the occipital, temporal, and lateral posterior parietal areas (Siclari et al., 2014a). This anterior-posterior slow-wave gradient at sleep onset may explain certain patterns of mental activity such as the visual experiences typically observed during sleep onset along with the lack of voluntary control (i.e., the primary visual cortex and the lateral parieto-temporal areas are still relatively unaffected by slow waves, while the prefrontal cortex is already "asleep").

Altogether, at present it would seem that consciousness abides mostly in the back of the corticothalamic complex (though maybe not in the very back), rather than in the front, and that the front may not be strictly required for experience to be present, but instead, it may be needed to report the experience itself (Frässle et al., 2014). Also, there is no doubt that the bulk of experience is sensory, and as such resides in posterior cortex. As we have seen, neuroimaging experiments do some justice to this view, showing that prefrontal cortex is deactivated when self-reflection is abolished by task demand, but experience is vividly present (Goldberg et al., 2006). Similarly, prefrontal cortex is relatively deactivated during REM sleep, when subjects dream vividly (Nir and Tononi, 2010). Moreover, multivariate pattern analysis of fMRI data can decode the identity of visual stimuli from medial and lateral occipital regions but not from regions of prefrontal cortex and intraparietal sulcus, despite their task-related activation. Also, decoding strength in visual regions correlates with the precision of visual working memory for the stimuli, whereas decoding of frontal cortex and intraparietal sulcus

activity is related to attentional context, kind of task, and task difficulty (Postle, 2015).

However, that anterior cortex may not be necessary for consciousness does not entail that it does not contribute directly to it in any aspect (Stuss and Alexander, 2001). After all, being self-conscious (reflecting upon what one perceives) is different from being conscious (perceiving it), yet both are experiences. Perhaps feelings of thought, reflection, effort, will, emotion and so on are generated by anterior cortex, though no firm evidence exists. Also, premotor and supplementary motor cortex may contribute to specific aspects of consciousness, such as the awareness of movement (Sarrazin et al., 2008). Alternatively, prefrontal cortex may provide unconscious plans, strategies, skills and memories, as well as attention. If this were the case, we would need to know what is wrong with this large portion of the cortex. Is it wired in radically different way from posterior cortex? Is it broken up into segregated loops encompassing the basal ganglia? At the very least, the study of the contribution of anterior cortical areas to consciousness is one of the ripest areas for future investigations.

Lateral Fronto-Parietal Network vs. (Medial) Default System

An orthogonal way of slicing the cortical cake is to distinguish between the relative contribution to consciousness of lateral versus mesial regions. In fact, there is increasing evidence for the existence of two corticothalamic networks usually characterized by antagonistic activation patterns in fMRI studies (Raichle et al., 2001; Fox and Raichle, 2007; Raichle and Snyder, 2007) (Chapter 6). One is a lateral "attention" network, the other a predominantly mesial "default" system. The lateral attention network is further subdivided into a dorsal and a ventral attentional system (Corbetta et al., 2000). The dorsal system is bilateral and composed of the intraparietal sulcus and frontal eye field at the junction of the precentral and superior frontal sulcus. It is involved in voluntary (top-down) orienting and shows activity increases after presentation of cues indicating where, when, or to what subjects should direct their attention. The ventral system is right-lateralized and composed of the right temporal-parietal junction and the right ventral frontal cortex. This system shows activity increases upon detection of salient targets and after abrupt changes in sensory stimuli. The dorsal and ventral lateral attentional systems also appear in functional connectivity maps during spontaneous activity, and their function can be coordinated by other prefrontal regions (Fox et al., 2006). Not surprisingly, since attention and consciousness often go together, many neuroimaging studies show an activation of this lateral network, usually with the addition of anterior cingulate areas, in paradigms contrasting perceived versus unperceived stimuli (Rees et al., 2002; Dehaene et al., 2006) (Chapter 4). For instance, these regions are more active for unmasked versus masked words and images; detected versus undetected changes during change blindness; reported versus missed stimuli during the attentional blink, seen versus extinguished stimuli in neglect patients.

The "default" network (Raichle et al., 2001; Raichle and Snyder, 2007) includes primarily medial cortical areas such as the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus. However, it also includes a lateral parietal component posterior to the intraparietal sulcus. The default network was identified because it typically shows decreased activity when subjects perform cognitive tasks. In resting functional connectivity studies, regions of the default network show strong positive correlations among themselves, presumably due to the high density of anatomical connections (Fox and Raichle, 2007). Posteromedial cortex appears to be a particularly important area of the brain, since it happens to have higher levels of baseline energy consumption (the precuneus) than the rest of the cortex. Nevertheless, the functional role of posteromedial cortex is only partially understood, as selective, bilateral lesions of these areas are hardly ever reported. Therefore, evidence comes mostly from neuroimaging studies and transient, incomplete disruption through TMS. Regions within posteromedial cortex, especially the precuneus, are activated during visuo-spatial imagery, retrieval of episodic memories, spontaneous thought, and during tasks that refer to the self and require a first-person perspective (Cavanna and Trimble, 2006). While these studies suggest a role in conscious processes focusing on internal signals rather than on external ones, other studies point to a more direct relevance to consciousness *per se*. Activity in posteromedial areas is altered during generalized seizures, and a strong deactivation is observed in hypnosis, sleep, general anesthesia with both propofol and inhalation agents, and in the unresponsive wakefulness syndrome. As we have seen, recovery of function in posteromedial cortex and reestablishment of functional connectivity with thalamus and frontal cortex are among the early signs of recovery of consciousness. However, it should be noted that posteromedial cortex appear to be deactivated to a similar extent in both NREM and REM sleep (Maquet et al., 1996, 1997; Braun et al., 1997). Given that REM sleep is usually associated with vivid dreams, it is questionable whether the activation of posteromedial cortex is necessary for consciousness *per se* or rather for certain aspects of self-consciousness and related

cognitive activities (reviewed in Nir and Tononi, 2010). For instance, at intermediate doses certain anesthetics such as xenon produce a selective deactivation of posterior mesial cortex, yet subjects report depersonalization and out of body experiences, rather than unconsciousness. Moreover, a patient with bilateral hypometabolism in the precuneus and superior temporal lobe, as well as in right posterior cingulate gyrus, was demented and psychotic, with delusions and hallucinations, but evidently conscious (Le Ber et al., 2007, but see Damasio, 1999 for the view that posteromedial lesions may compromise consciousness).

Switching between the "default" network and the "attention" network seem to occur spontaneously every 20 s on average. Activation of the "attention" network has been correlated with subjects' reports of being "strongly externally aware" (i.e., perception of environmental sensory stimuli) whereas activation of the "default" system has been correlated with reports of being "strongly internally aware" (i.e., stimuli-independent thoughts such as inner speech or autobiographical memories) (Vanhaudenhuyse et al., 2011). Other studies also showed that awareness of somatosensory and visual stimuli typically correlates with an increase in activity in lateral fronto-parietal cortices and a deactivation of the default network (Dehaene et al., 2001; Boly et al., 2007). In another study, however, awareness of auditory stimuli triggered the opposite pattern (Sadaghiani et al., 2009). Despite the temptation to assign consciousness to either the lateral or medial component given their task-on versus task-off activation pattern, and their anticorrelated functional connectivity, there are reasons to wonder whether these two subdivisions may actually be jointly involved in generating experience. For example, the anticorrelated functional connectivity emerges only after regressing out a large, correlated component (Fox et al., 2005). It has also recently been demonstrated that over the fast time scale of consciousness, medial and lateral networks are actually often co-activated in various combinations (Allen et al., 2014; Barttfeld et al., 2015), making it unlikely that consciousness is supported exclusively by one or the other. Moreover, there is evidence that both medial and lateral areas may be part of a larger, anatomically defined "structural core." Recently, the application of graph-theoretical methods to diffusion spectrum imaging of fiber tracts in humans has revealed the existence of a structural core of heavily interconnected cortical regions (Hagmann et al., 2008; Bullmore and Sporns, 2009; Sporns, 2013). This core is centered on a prominent medial "backbone" that includes the posterior cingulate cortex, the precuneus, the cuneus, as well as the paracentral lobule, and the isthmus of the cingulate (retrosplenial) cortex. The structural core thus overlaps in part with the "default network," although the medial prefrontal cortex is conspicuously absent. There is, however, an important lateral component of this structural core, which includes the bank of the superior temporal sulcus, the temporo-parieto-occipital junction, and the inferior and superior parietal cortex. Thus, the structural core also includes the posterior portion of the lateral attentional system. The structural core extends symmetrically to both hemispheres, and all its constituent areas have strong bilateral connections to associative (non-primary) nuclei of the thalamus, as well as to diffusely projecting thalamic cells.

Neuroimaging studies also point to a joint involvement of both lateral and medial regions: in unresponsive patients, minimally conscious patients, seizures associated with alterations of consciousness, general anesthesia, and sleeping subjects, there is a remarkably similar set of regions that are deactivated compared to control conditions: these include both the lateral fronto-parietal network and medial regions such as medial prefrontal cortex and precuneus. Another interesting case is that of patients emerging from a minimally conscious state (due to diffuse axonal injury) after the administration of the GABA agonist zolpidem (Clauss et al., 2001; Clauss and Nel, 2006; Brefel-Courbon et al., 2007; Whyte and Myers, 2009; Chatelle et al., 2014). In these patients, blood flow as measured by SPECT and PET increased by almost 40% bilaterally in medial frontal cortex as well as in lateral areas such as middle frontal and supramarginal gyri. So perhaps both the medial and lateral contingents are important. Given the evidence just reviewed that posterior cortex is more important than anterior cortex, and the examples of posterior damage resulting in hyperkinetic mutism, it may be that a *posterior complex of associative areas* comprising the lateral temporo-parieto-occipital junction and perhaps a posteromesial backbone currently represents the safest bet as to the brain regions that are most likely to be necessary for the bulk of conscious experience. As mentioned above, a similar posterior hotspot was found to distinguish between retrospective reports of conscious experience and non conscious experience upon awakening from both NREM and REM sleep—two physiological states that are otherwise extremely different and do not require responsiveness to stimuli or task preparation and performance (Siclari et al., 2014b).

Left vs. Right Hemisphere

One should also consider the most traditional of dichotomies: the one between the left and the right brain. As discussed by Marinsek, Gazzaniga, and Miller (Chapter 17), the evidence from split brain patients, and even more so the results of right

hemispherectomy operations, show beyond any doubt that the isolated left hemisphere, whether alone or disconnected from the right hemisphere, can support a conscious self that is similar to that supported by of an intact, fully equipped brain. Importantly, after a hemispherectomy or split-brain operation, the patient (speaking through the left hemisphere) is anosognosic and feels in no way changed, although for example the left half of the visual field is no longer available (Gazzaniga, 2014).

People familiar with split-brain patients have little doubt that the isolated right hemisphere can support a second consciousness (Chapter 17). Long-term observations make it clear that the disconnected right hemisphere not only has its own private sensory and motor channels with which it can communicate with the environment, but it has its specific perceptual skills, can have a word lexicon, has its own memories and may even have its own characteristic preferences and dislikes. After spending some time testing split-brain patients, examiners spontaneously refer to the two hemispheres as if they were distinct people.

Naturally enough, being limited in language and reasoning skills, under usual circumstances the right hemisphere is literally dominated by the left hemisphere—it is usually passive, and does not complain or cause trouble, just as in some highly asymmetric marriages. Also, its cognitive style seems to be very different. As we have seen, it is much more literal in its recognition of images and events, and thereby often more accurate, in contrast with a left hemisphere that is constantly formulating hypotheses and trying to make sense of what happens. Also, in some tests the right hemisphere's cognitive style is strangely "un-human." For example, in a guessing game in which a stimulus is red say 75% of the time, and green 25% of the time, and the occurrence of stimuli is entirely at random, humans respond by trying to match the probability of red and green, thereby making many mistakes. By contrast, animals such as rats and goldfish respond red all the time, and in this way maximize their success rate. In such a game, the left hemisphere behaves just like a human, probably because it is a characteristic human feature to try and find a pattern even in random events. The right hemisphere, by contrast, behaves just like a rat or a goldfish would. Michael Gazzaniga has also shown that the right hemisphere fails in certain simple reasoning and classification tasks that are solved both by 12-month-old children as well as by monkeys. The right hemisphere may however play a role in updating inappropriate beliefs or hypotheses. Indeed, during verbal moral judgments, the split-brain patients' left hemispheres fails to update its initial judgment when new evidence was provided (Miller et al., 2010). In the domain of inferential reasoning, another recent study showed that the right hemisphere tries to resolve inconsistency while the left hemisphere tries to reduce uncertainty (Marinsek et al., 2014).

The extraordinary patient P.S., studied by Joseph Ledoux and Michael Gazzaniga, who had a remarkable ability to comprehend words with the right hemisphere, and went on to develop a limited ability to speak through it, leaves little doubt that the right hemisphere can at times even have an individual sense of self. The rare cases of left hemispherectomy in right-handed adolescents also indicate that the right hemisphere can sustain a consciousness and a self, although when the right hemisphere is left alone after the operation it is certain to undergo a variety of plastic changes that may partly modify its original functioning. It seems inconceivable, however, that consciousness would return in a left hemispherectomized patient only when and to the extent that language is recovering—it is much more plausible that consciousness and self are already there, and it is just language skills that are being added, just as in a recovering aphasic patient (see above).

Despite the remarkable evidence that the disconnected right hemisphere has its own conscious experience and perhaps at times even its own self (Damasio and Meyer, 2009), it is worth considering the alternative possibility that the isolated right hemisphere may actually be just an unconscious "zombie." Could it be that its responses are not dissimilar from those provided by a patient with blindsight? Or by the "unconscious action system" of Miller and Goodale? Several considerations cast doubt on this possibility. Unlike blindsight patients, the isolated right hemisphere does not respond just in forced-choice tests, but can exhibit spontaneous choices. It is capable not just of adjusting behavior for action, but can master perceptual tasks that are impossible for patients with temporal lesions that lack explicit object recognition. It can do much more than just "automatic routines," and can initiate purposeful behaviors if properly asked. It is far more lucid than a sleepwalker or a patient with a partial complex seizure. Finally, the isolated right hemisphere can even express individual preference and goals, and recognize a picture of itself (although less easily than the left hemisphere). Thus, the kind of consciousness associated with the isolated right hemisphere could be comparable, and in some cases more sophisticated, with that of other primates lacking language.

Reentrant vs. Feed-Forward Connections

Another possibility that has been investigated for explaining the presence of awareness is the occurrence of a "reentrant" wave of activity (also described as

recurrent, recursive, or reverberant) from higher to lower level cortical areas. This view is based on several considerations. An important one, though rarely confessed, is that a mere sequence of feed-forward processing steps seems far too "straightforward" and mechanical to offer a substrate for subjective experience. Reentrant processes, by "closing the loop" between past- and present activity, or between predicted and actual versions of the input, would seem to provide a more fertile substrate for giving rise to reverberations (Lorente de Nó, 1938), generating emergent properties through cell assemblies (Hebb, 1949), implementing hypothesis testing through resonances (Grossberg, 1999), linking present with past (Edelman and Mountcastle, 1978; Edelman, 1989), and subject with object (Damasio, 1999).

A more concrete reason why reentrant activity is an attractive candidate for the neural substrate of consciousness is that it travels through back-connections, of which the cerebral cortex is extraordinarily rich (Felleman and Van Essen, 1991). In primates, feed-forward connections originate mainly in supragranular layers and terminate in layer 4. Feedback connections instead originate in both superficial and deep layers, and usually terminate outside of layer 4. The sheer abundance of back-connections in sensory regions suggests that they ought to serve some important purpose, and giving rise to a conscious percept might just fit the bill. However, back-connections, and associated reentrant volleys, are just as numerous between V1 and visual thalamus, which is usually denied any direct contribution to awareness. Also, there does not seem to be any lack of back-connections within the dorsal stream. It should be emphasized that the strength and termination pattern of back-connections seems more suited to a modulatory/synchronizing role than to driving their target neurons. For example, the focal inactivation of area 18 can slightly increase or decrease discharge rates of units in area 17, but does not change their feature selectivity for location and orientation (Martinez-Conde et al., 1999). Also, the numerosity of backward connections is a natural consequence of the hierarchical organization of feed-forward ones. For instance, cells in the lateral geniculate nucleus (LGN) are not oriented, while cells in area 17 are. To be unbiased, feedback to any one LGN cell should come from area 17 cells of all orientations, which requires many connections; on the other hand, since at any given time only area 17 cells corresponding to a given orientation would be active, feedback effects would not be strong. If they were, properties of area 17 cells, such as orientation selectivity, would be transferred upon LGN cells, which they are not (to a first approximation). Backward signals certainly play a role in sensory function: for instance, they can mediate some extra-classical receptive field effects, provide a natural substrate for both attentional modulation and imagery, and can perhaps dynamically route feed-forward signaling processing according to prior expectations. But are backward connections really critical for consciousness?

The most intriguing data in support of a role for reentrant connections in conscious perception have come from neurophysiological experiments. Experiments requiring ultra-rapid categorizations, such as deciding whether a natural image contains an animal or not (Thorpe et al., 1996; Bacon-Mace et al., 2005; Kirchner and Thorpe, 2006) can also be used to partially dissociate feed-forward from reentrant signaling. In such experiments, a sweep of activity travels from the retina through several stages of feed-forward connections along the hierarchy of ventral visual areas, until it elicits an appropriate categorization response. This process takes as little as 150 ms, which leaves only about 10 ms of processing per stage. Thus, only a few spikes can be fired before the next stage produces its output, yet they are sufficient to specify selective responses for orientation, motion, depth, color, shape, and even animals, faces, or places, conveying most of the relevant information about the stimulus (Hung et al., 2005). While this fast feed-forward sweep within the ventral system is sufficient for the near-automatic categorization of stimuli and a behavioral response, it seems insufficient to generate a conscious percept (VanRullen and Koch, 2003). For example, if another image (the mask) is flashed soon after the target image, subjects are still able to categorize the target, though they may deny having seen it consciously.

A set of elegant experiments in animals and humans, supported by computational models, have provided evidence that visual stimuli become conscious only when the feed-forward sweep is joined by a reentrant sweep (Lamme and Roelfsema, 2000, see also Self et al., 2012). In awake monkeys trained to signal whether or not they saw a salient figure on a background, the early, feed-forward response of V1 neurons was the same, no matter whether or not the monkey saw the figure (Super et al., 2001). However, a later response component was suppressed when the monkey did not see the figure. Light anesthesia also eliminated this later component without affecting the initial response. Late components are thought to reflect reentrant volleys from higher areas (Rossi et al., 2001). The late response component crucial for the visibility of stimuli under backward masking might also be due to a reentrant volley (Lamme and Roelfsema, 2000), which is mediated primarily by NMDA receptors (Self et al., 2012). However, others have suggested that the timing of maximal masking depends on the timing of target offset, suggesting that the component that is

obliterated is a feed-forward offset discharge, not a reentrant one (Macknik, 2006). Moreover, the late component can be dissociated from a behavioral response simply by raising the decision criterion (Super et al., 2001), and it can occur in the absence of report during change- and inattentional blindness (Scholte et al., 2006). Perhaps in such cases subjective experience is present but, due to an insufficient involvement of frontal areas, it cannot be reported (Block, 2005; Tsuchiya and Koch, 2005; Lamme, 2006).

Another main source of evidence for a role of reentrant volleys in consciousness comes from early experiments using TMS. In an early experiment, Pascual-Leone and Walsh applied TMS to V5 to elicit large, moving phosphenes (Pascual-Leone and Walsh, 2001). They then applied another, subthreshold TMS pulse to a corresponding location in V1. When TMS to V1 was delivered after TMS to V5 (+5 to +45 ms), subjects often did not see the V5 phosphene, and when they saw one, it was not moving. Their interpretation was that disruption of activity in V1 at the time of arrival of a reentrant volley from V5 interferes with the experience of attributes encoded by V5. In a subsequent study (Silvanto et al., 2005), it was shown that, when a subthreshold pulse was applied over V5, followed 10–40 ms later by a suprathreshold pulse over V1, subjects reported a V5-like phosphene (large and moving), rather than a V1 phosphene (small and stationary). Their interpretation was that activity in V5 that, on its own, is insufficient to induce a moving percept, can produce such a percept if the level of induced activity in V1 is high enough.

In another study (Boyer et al., 2005), subjects were shown either an oriented bar or a colored patch—stimuli that are processed in visual cortex. If, around 100 ms later, a TMS pulse was applied to V1, the stimulus became perceptually invisible, although on forced-choice subjects could still discriminate orientation or color. This result indicates that, without any overt participation of V1, stimuli can reach extrastriate areas without eliciting a conscious percept, just as in blindsight patients. It also suggests that, since the forward sweep reaches V1 after just 30 or 40 ms, the TMS pulse may abolish the awareness of the stimulus not so much by blocking feed-forward transmission, but by interfering with the backward volley (see also Ro et al., 2003). On the other hand, it cannot be ruled out that the TMS pulse may act instead by triggering a cortical–thalamo–cortical volley that interferes with the offset discharge triggered by the stimulus, as may indeed be the case in backward masking.

Yet another study, this time using fMRI, examined the neural correlates of brightness (perceptual lightness) using backward masking. The psychometric visibility function was not correlated with the stimulated portion of V1, but with downstream visual regions, including fusiform cortex, parietal–functional areas, and with the sectors of V1 responding to the unstimulated surround (Haynes et al., 2005). Remarkably, visibility was also correlated with the amount of coupling (effective connectivity) between fusiform cortex and the portion of V1 that responded to the surround. Once again, this result could be explained by the activation of reentrant connections, though fMRI cannot distinguish between forward and backward influences.

While the above studies provide evidence for a role of back-connections to V1 in visual experience, a recent TMS experiment in a blindsight patient with intact extrastriate areas and damaged V1 has shown that the patient could experience phosphenes after stimulation of parietal cortex (Figure 25.7) (Mazzi et al., 2014). This finding suggests that back-connections to V1 are not necessary for visual consciousness, though it does not rule out the involvement of back-connections to other brain areas.

Finally, recent human directional connectivity studies show that top-down connectivity is stronger when somatosensory stimuli are perceived than when they are not (Auksztulewicz et al., 2012, see also Sachidhanandam et al., 2013 in rodents). Neuroimaging studies using directed transfer entropy and dynamic causal modeling in anesthetized human subjects (Ku et al., 2011; Boly et al., 2012a) and in brain-damaged patients (Boly et al., 2011) also support the hypothesis that preserved feedback connectivity is necessary for consciousness (Tononi and Edelman, 1998; Lamme and Roelfsema, 2000; Dehaene and Naccache, 2001; Lamme, 2006; Dehaene and Changeux, 2011; Oizumi et al., 2014).

Superficial vs. Deep Layers of Cortex

An important open question is whether distinct cortical cell types have a privileged association with consciousness. During slow wave sleep in cats, autoradiography shows a reduction in the activity of infragranular layers of visual cortex (Livingstone and Hubel, 1981). Large, thick-tufted pyramidal neurons of layer 5B are ideally suited to integrate local and long-distance inputs (Larkum, 2013), and their distal apical tufts are the recipients of massive feedback from higher-level cortical regions. On the other hand, these cells project primarily to subcortical structures and their limited connectivity within cortex may be more appropriate for implementing cortico-subcortico-cortical loops that mediate unconscious behaviors (Harris and Shepherd, 2015). By contrast, thin-tufted pyramidal cells in L5A, as well as some cells in L6, have exclusively cortico-cortical connections and are more heavily interconnected. Supragranular pyramidal cells in L2/3 are even more densely interconnected and more specific in their discharge properties (Douglas and Martin, 2004;

Binzegger et al., 2009; Sakata and Harris, 2009; Harris and Shepherd, 2015). Accordingly, both feed-forward and feedback projections originating in superficial layers exhibit greater topographic precision than those from infragranular layers (Markov et al., 2014). The apical dendrites of supragranular pyramidal cells and that of different types of inhibitory interneurons in superficial layers (Zhang et al., 2014) are also the preferential target of back-connections and of diffusely projecting thalamic matrix cells (Shipp, 2007). An intriguing finding is that supragranular layers, while interconnected, can become uncoupled through attentional modulation (Maier et al., 2010; Buffalo et al., 2011) and during sleep (Funk et al., 2014). Neuronal avalanches are spatiotemporal patterns of spontaneous activity that reflect a critical state of network excitability favorable to information integration, and they occur only in supragranular layers (Shew and Plenz, 2013). Furthermore, neural activity in supragranular layers often correlates with conscious sensation across species. Between stimulus onset and response, a negative slow potential of likely supragranular origin (He and Raichle, 2009) occurs only when a near-threshold stimulus is perceived (Libet et al., 1967; Pins and Ffytche, 2003). The late negative shift in slow cortical potentials disappears with propofol anesthesia, whereas the early positive component is preserved (Fitzgerald et al., 2001). In somatosensory cortex of awake monkeys conscious detection is correlated with magnitude and latency of the N1 potential, presumably generated by excitatory input onto supragranular layers through back-connections from higher cortical areas (Cauller and Kulics, 1991). Notably, the N1 is abolished during general anesthesia (Arezzo et al., 1981) and slow wave sleep (Cauller and Kulics, 1988). Finally, a late membrane potential depolarization occurs in supragranular neurons in somatosensory cortex of head-fixed mice on trials in which the mouse detects vibrissal stimulation (Sachidhanandam et al., 2013). In the near future, laminar recordings coupled with selective optogenetic stimulation should help clarify the involvement of specific cell types in consciousness.

THE NEUROPHYSIOLOGY OF CONSCIOUSNESS

The studies discussed above indicate that, even within the cerebral cortex, changes in neural activity do not necessarily correlate with changes in conscious experience. Also, we saw earlier that most of the cortex is active during early NREM sleep and anesthesia, not to mention during generalized seizures, but subjects have little conscious content to report. Thus, it is natural to suggest that some additional dynamic feature of neural activity must be present to generate conscious content. Here we consider the role of: (i) synchronous or oscillatory activity; (ii) the P3b wave and other evoked potentials; (iii) cortical "activation"; and (iv) sustained versus phasic activity.

Synchronization and Oscillations

An idea that has prompted much experimental and theoretical work is that consciousness may require the synchronization, at a fine temporal scale, of large populations of neurons distributed over many cortical areas, in particular via rhythmic discharges in the gamma range (30–70 Hz and beyond) (Crick and Koch, 1990; Fries et al., 2007; Brunet et al., 2014) (Chapter 3). The emphasis on synchrony ties well with the common assumption that consciousness requires the "binding" together of a multitude of attributes within a single experience, as when we see a rich visual scene containing multiple objects and attributes that is nevertheless perceived as a unified whole (Singer, 1999). According to this view, the neural substrate of such an experience would include two aspects: first, the underlying activation pattern (groups of neurons that have increased their firing rates) would be widely distributed across different areas of the cerebral cortex, each specialized in signaling a different object or attribute within the scene; second, the firing of these activated neurons would be synchronized on a fast time scale to signal their binding into a single percept. In this respect, synchrony seems ideally suited to signal relatedness: for example, in the presence of a red square, some neurons would respond to the presence of a square, while others would respond to the presence of the color red. If they synchronize at a fast time scale, they would indicate to other groups of neurons that there is a red square, "binding" the two features together (Tononi et al., 1992). By contrast, signaling relatedness by increased firing rates alone would be more cumbersome and probably slower (Singer, 1999). Also, fine temporal scale synchrony has the welcome property of disambiguating among multiple objects—if a green cross was present simultaneously with the red square, cross and green neurons would also be active, but false conjunctions would be avoided by precise phase locking (Tononi et al., 1992). Moreover, computational models predict that, for the same level of firing, synchronous input is more effective on target neurons than asynchronous input (Abeles, 1991; Tononi et al., 1992), and indeed synchrony makes a difference to the outputs to the rest of the brain (Brecht et al., 1999; Schoffelen et al., 2005). Finally, large-scale models predict that synchrony in the gamma range occurs due to the reciprocal connectivity and loops within the corticothalamic system

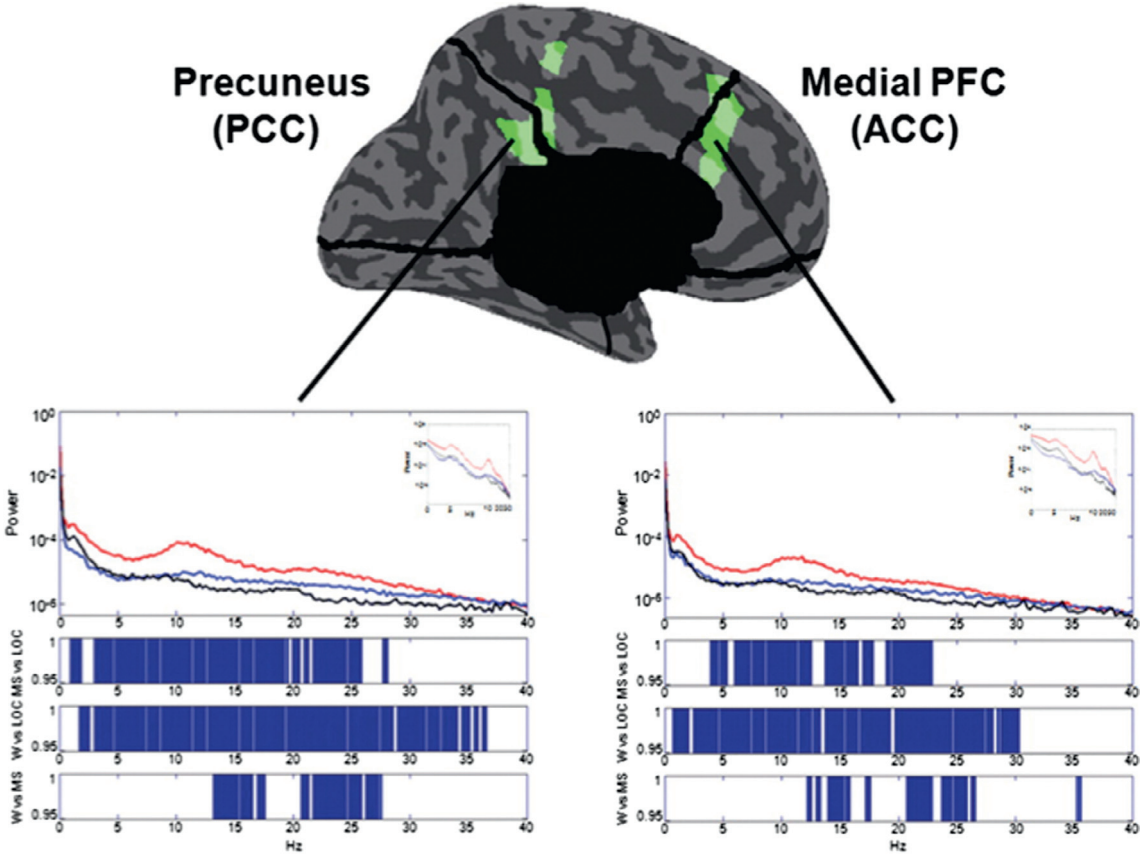

FIGURE 25.8 Gamma synchrony without consciousness. Power spectrum changes across vigilance states in frontal (anterior cingulate) and parietal (posterior cingulate) regions showing increased gamma power during propofol-induced loss of consciousness (LOC) compared with wakefulness. Semi-logarithmic plots of power spectra for each region are displayed in waking (W, black), mild sedation (MS, blue), and LOC (red). The blue bars in the lower panel show frequency band-specific changes in power during the transition from waking (W) to sedation (S) and then to LOC. *Source: Taken from Boly et al. (2012a).*

(Lumer et al., 1997a,b), and indeed phase alignment between distant groups of neurons in the gamma range anticipates by a few milliseconds an increase in gamma-band power (Womelsdorf et al., 2007). In this respect, oscillatory activity, even when subthreshold, could further facilitate synchronous interactions by biasing neurons to discharge within the same time frame (Engel et al., 2001).

Experimental evidence concerning the role of synchrony/synchronous oscillations in perceptual operations was initially obtained in primary visual areas of anesthetized animals (Chapter 3). For example, in primary visual cortex, neurons have been found that respond to a coherent object by synchronizing their firing in the gamma range. Stimulus-specific, gamma range synchronization is greatly facilitated when the EEG is activated by stimulating the mesencephalic reticular formation (Munk et al., 1996; Herculano-Houzel et al., 1999), by attention (Roelfsema et al., 1997), and increases for a dominant stimulus under binocular rivalry even though firing rates may not change (Fries et al., 1997, 2001). However, it has since become clear that synchrony in one or another frequency band is not necessarily a marker of consciousness. For example, while some EEG and MEG studies in humans also suggest that long-distance gamma synchrony may correlate with visual consciousness (Rodriguez et al., 1999; Melloni et al., 2007; Wyart and Tallon-Baudry, 2009), often they did not fully distinguish the effects of conscious visibility from those of selective attention. Moreover, one may see a stimulus with or without accompanying gamma activity, depending on the context. Thus, a recent study using intracranial recordings in humans showed gamma activation in visual cortex when a degraded stimulus is made visible by increasing sensory evidence. However, when visibility was increased to the same extent by showing the pictures beforehand, there was no "gamma ignition" (Aru et al., 2012a). Also, gamma synchrony is high and may even be enhanced during early NREM sleep, anesthesia (Figure 25.8) (Imas et al., 2005; Murphy et al., 2011), or seizures (Pockett and Holmes, 2009), and can be observed with emotional stimuli that remain

unconscious (Luo et al., 2009), suggesting that there may be gamma synchrony without consciousness. Furthermore, there may be consciousness without synchrony. In human visual cortex narrowband gamma oscillations is induced reliably only by certain luminance gratings, and not by many natural images that were easily seen and recognized (Hermes et al., 2014), suggesting that gamma band oscillations are not necessary for seeing (Ray and Maunsell, 2011).

Finally, there are some difficult conceptual problems in characterizing synchrony as an essential ingredient that unifies perceptual states and thereby makes them conscious. While many experiences do indeed involve several different elements and attributes that are "bound" together into a unified percept, there are many other experiences, equally conscious, that do not seem to require much binding at all: for instance, an experience of pure darkness or of pure blue, or a loud sound that briefly occupies consciousness and has no obvious internal structure—would merely seem to require the strong activation of the relevant neurons, with no need for signaling relatedness to other elements, and thus no need for synchrony. Also, the idea that the neural correlate of a given conscious experience are given by active neurons bound by synchrony discounts the importance of inactive ones: information specifying that particular unified experience must be conveyed both by which neurons are active and which are not, yet for inactive neurons there does not seem to be anything to bind. On the other hand, if most neurons in the cortex were to become active hypersynchronously, as is the case in generalized seizures, they should result in maximal "binding," but consciousness vanishes rather than become more vivid.

P3b and other Evoked Potentials

In addition to gamma synchrony, another influential idea has been that the P300 wave, or more specifically the P3b component, may constitute a reliable indicator of consciousness (Dehaene and Changeux, 2011). The P300—a late positive event-related potential (ERP) appearing after 300 ms or more, discovered 50 years ago (Sutton et al., 1965), is often observed when a subject reports that he is aware of a sensory stimulus. Many studies have employed masking, attentional blink, and manipulations of stimulus strength and shown that the P3b component of the ERP correlates with reports of stimulus visibility (Dehaene and Naccache, 2001; Sergent et al., 2005; Del Cul et al., 2007). Accordingly, the P3b has been proposed as a "signature" of consciousness. Specifically, the occurrence of the P3b wave would reflect a non-linear amplification or "ignition" of cortical activity through a distributed network involving frontoparietal areas (Dehaene and Changeux, 2011). However, there is increasing evidence that the P3b signals instead the occurrence of post-perceptual processes, including memory updating, decision-making and motor preparation. For example, when subjects already have a working memory representation of the target stimulus, there is no P3b when they see the stimulus (Melloni et al., 2011). Moreover, stimuli that are task-irrelevant do not trigger a P3b (Pitts et al., 2012), yet subjects are clearly conscious of them (Pitts et al., 2014). Also, the P3b component cannot be used to distinguish the state of consciousness from that of unconsciousness. For example, one cannot rely on the P3b triggered by global violations of auditory regularities to discriminate between unresponsive and minimally conscious patients (Sitt et al., 2014). Moreover, the P3b is absent in the majority of brain-damaged patients who are clearly conscious (Kotchoubey et al., 2005; Fischer et al., 2010; Holler et al., 2011) and virtually useless for the identificartion of patients who are minimally conscious (Faugeras et al., 2011). By contrast, up to 40% of patients who are comatose, as well as pharmacologically sedated and hypothermic can be shown to have a P3b-like component (Tzovara et al., 2015).

While it is now clear that the P3b cannot serve as an indicator of consciousness, recent work supports the notion that an earlier ERP, the visual awareness negativity (VAN), may constitute a promising correlate of the visibility of stimuli, though an attentional component is hard to rule out. The VAN starts as early as 100 ms from the onset of a visual stimulus, peaks at around 200−250 ms, and is localized to posterior cortex (occipital, temporal, and posterior parietal lobes) (Railo et al., 2011). Correlates of visibility of phosphenes elicited by TMS can be obtained earlier (~70 ms) in parietal cortex after parietal stimulation and in temporal cortex after occipital TMS (Pitts et al., 2014; Bagattini et al., 2015).

Cortical "Activation"

Since the early days of the EEG, and the early work of Moruzzi and Magoun (1949), neurologists and neuroscientists have routinely relied on the occurrence of EEG low-voltage fast-activity, also known as "activated" EEG, to assess the likely presence of consciousness. When REM sleep was discovered (Aserinsky and Kleitman, 1953), it became apparent that, despite behavioral immobility and unresponsiveness, the occurrence of an activated EEG was a reliable marker for the occurrence of dreams. By contrast, EEG high-voltage, low-frequency activity, typically in the delta range, often correlates with the loss of consciousness. Over the last decades, intracellular recordings from

cortical and thalamic neurons have revealed the mechanisms that underlie the transition from the low-voltage fast-activity typical of wakefulness, to the high-voltage, slow-activity of deep NREM sleep and general anesthesia (Steriade, 2000). Hyperpolarization of thalamocortical neurons makes them switch from a tonic into a bursting mode, leading to a synchronization of the EEG in the spindle (12–14 Hz) and theta (5–8 Hz) range. When cortical neurons are further disfacilitated and start alternating synchronously between depolarized up-states and hyperpolarized down-states every second or so, larger slow waves in the delta range (<4 Hz) appear in the EEG (Steriade et al., 2001). This schematic sequence of events accompanies the loss of consciousness in physiological, pharmacological, and pathological conditions (Brown et al., 2010). Slow waves can be initiated by different factors, such as a decrease in the firing rate of subcortical activating systems (Moruzzi and Magoun, 1949; McCormick et al., 1993), excessive thalamic inhibition due to the globus pallidus (Schiff, 2009), or a critical level of cortical deafferentation (Timofeev et al., 2000).

Repeated high-amplitude (>75 μV) slow waves in the EEG remains the simplest and most effective way to assess the loss of consciousness (Boly et al., 2009), superior to most alternatives (Murphy et al., 2011; Kertai et al., 2012). Prominent slow waves during deep NREM early in the night herald the time when subjects, if awakened, are most likely to deny that they were experiencing anything at all (Stickgold et al., 2001). Similarly, upon induction of general anesthesia with propofol, a sudden increase of slow wave power coincides with behavioral loss of consciousness (Purdon et al., 2013). Indeed, the visual detection of slow waves and their relative contribution to total EEG power outperforms by far most other proposed markers of consciousness, including gamma power and the P3b, when the goal is to discriminate between conscious and unconscious brain-injured patients at the group level (Forgacs et al., 2014; Sitt et al., 2014). Overall, the progression from a predominance of delta, through theta, to alpha-range frequencies corresponds to the progression from coma or the unresponsive wakefulness syndrome, through the minimally conscious state, to behavioral consciousness (Schiff et al., 2014). However, slow waves are not as reliable when discriminating between unresponsive and minimally conscious patients based on single-subject EEG (Forgacs et al., 2014; Sitt et al., 2014). Also, some unconscious patients who are in a severe post-anoxic coma show steady, widespread alpha rhythm rather than slow waves (Westmoreland et al., 1975). Conversely, in some cases consciousness is present but there are large slow waves, as with atropine administration (Wikler, 1952; Bradley, 1968) or with some rare forms of status epilepticus (Gokyigit and Caliskan, 1995). Importantly, however, in such cases high-voltage, slow-activity may involve only some cortical areas and not others, in a way that cannot be resolved by conventional EEG. Indeed, as already mentioned, subjects awakened from NREM sleep report visual dreams if the EEG is locally activated over a parieto-occipital hotspot, even though other cortical areas display low-frequency activity. Conversely, if the same hot spot shows delta activity, subjects do not report any dream (Siclari et al., 2014b).

Sustained vs. Phasic Activity

A plausible idea is that neural activity may contribute to consciousness only if it is sustained for a minimum period of time, perhaps around a few hundred milliseconds. At the phenomenological level, there is no doubt that the "now" of experience unfolds at a time scale comprised between tens and several hundred milliseconds (Bachmann, 2000), and in some aspects may even stretch to 1 or 2 s (Poppel and Artin, 1988). Other experiments have made use of the attentional blink phenomenon: when an observer detects a target in a rapid stream of visual stimuli, there is a brief period of time during which the detection of subsequent targets is impaired. Remarkably, targets that directly follow the first target are less impaired than those that follow after 200–400 ms (Raymond et al., 1992). By manipulating attention, identical visual stimuli can be made conscious or unconscious. In such studies, event-related potentials reflecting early sensory processing (the P1 and N1 components) were identical for seen and unseen stimuli, but quickly diverged around 270 ms, suggesting that stimuli only become visible when a sustained pattern of activation/deactivation is elicited in a distributed network of cortical association areas (Vogel et al., 1998; Sergent et al., 2005). By the same token, there must be ways for such sustained patterns of activation to dissolve quickly and leave room for new patterns, for example, when new stimuli occur (*metastability*).

It has been recognized for a long time that the massive interconnectivity within and among cortical areas (and with thalamus) provides an ideal substrate for cooperative dynamics among distributed neurons, which Hebb called cell assemblies, others called coalitions (Crick and Koch, 2003). Simply put, neurons in the corticothalamic system seem coupled in such a way as to ensure the rapid emergence of firing patterns that are distributed over wide regions of the cortex, where some neurons are strongly activated, and many more are deactivated. These patterns of activity can be thought of as *transient attractors* (Friston, 1997, 2000; Rabinovich et al., 2006; Deco et al., 2009): they

remain stable (hence attractors) over a time scale of tens/hundreds of milliseconds, but then dissolve rapidly (hence transient), to make room for another transient attractor. Indeed, some EEG and MEG studies suggest that cortical activity patterns show brief periods of stability linked by even shorter periods of instability (Lehmann, 2010; Musso et al., 2010; Van de Ville et al., 2010). An example of this attractor dynamics from an early model of large-scale cortical networks is shown in (Tononi, 2012). The rapid formation of transient attractors is facilitated by the connectional architecture of the corticothalamic system, which includes strong local links as well as a network of long-range connections among nearby and distant areas, often reciprocal, supporting reentrant loops that favor integration (Stratton and Wiles, 2010; Sporns, 2011). Connectional hubs along the medial surface of the cortex may facilitate the interaction of distant cortical regions; more diffuse projections from thalamic matrix cells may provide a shared background of excitability that also facilitates long-range interactions; and the reticular thalamic nucleus may provide strong inhibitory coupling among distributed cortical areas. The rapid formation of attractors may be enhanced by short-term strengthening of activated synapses, while their dissolution after a period of stability may be facilitated by the short-term depression of synapses or destabilizing signals from neuromodulatory systems (Sporns et al., 1991; Tononi et al., 1992). The time constants of neuronal integration, of various intrinsic currents, of AMPA and GABA receptors, and especially of NMDA receptors, ranging from tens to hundreds of milliseconds, also seem well suited to boosting, sustaining, and terminating interactions in a way that is both effective and flexible. It is also important that neurons are extremely reactive to perturbations, being poised at the edge of firing, in line with work on avalanches, criticality, and neural "noise" (Chen et al., 2010; Sporns, 2010; Deco et al., 2011). On theoretical grounds, it is expected that the time scale of attractor formation and dissolution would correspond to the macro time scale at which integrated information reaches a maximum (Tononi, 2012; Hoel et al., 2013). In that case, consciousness would flow at the longer time scale of metastable transient attractors, while the micro-level interactions among neurons at the time scale of a few milliseconds would not contribute to phenomenology, despite constitute the underlying microstructure.

On the other hand, other data would seem to suggest that it may actually be the phasic, onset- or offset discharge of neurons that correlates with experience. The most stringent data come again from studies of visual masking (for a review see Macknik, 2006). To be effective, masking stimuli must either precede (forward masking) or follow (backward masking) target stimuli at appropriate time intervals, and usually need to be spatially contiguous. Macknik and collaborators showed, using a combination of psychophysics, unit recordings in animals, and neuroimaging in humans, that for simple, unattended target stimuli, masking stimuli suppress visibility if their "spatiotemporal edges" overlap with the spatiotemporal edges of the targets, that is, if they begin or end when target stimuli begin or end, in space and time. They confirmed that such spatiotemporal edges correspond to transient bursts of spikes in primary visual cortex. If these bursts are inhibited, for example if the offset discharge elicited by the target stimulus is obliterated by the onset of the mask, the target becomes invisible. Most likely, these spatiotemporal edges of increased firing are both generated (target stimuli) and suppressed (masking stimuli) by mechanisms of lateral inhibition, which are ubiquitous in sensory systems (Macknik, 2006).

Additional evidence for the importance of phasic, transient activation of neurons in determining the visibility of stimuli comes from studies of microsaccades—the small, involuntary movements that our eyes make continually (Martinez-Conde et al., 2004). If microsaccades are counteracted by image stabilization on the retina, stationary objects fade and become completely invisible. In a recent study (Martinez-Conde et al., 2006), subjects were asked to fixate a central dot (which tends to reduce microsaccades) while attending to a surrounding circle. Soon, the circle fades and merges into the background (the Troxler illusion). It was found that before a fading period, the probability, rate, and magnitude of microsaccades decreased. Before transitions toward visibility, the probability, rate, and magnitude of microsaccades increased, compatible with the hypothesis that microsaccades are indeed necessary for visibility. Importantly, in macaque monkeys, when an optimally oriented line was centered over the receptive field of cells in V1, the cell's activity increased after microsaccades, and tended to emit bursts (Martinez-Conde et al., 2002), suggesting again that phasic activity may be crucial for visibility.

One should remember, however, that the importance of phasic discharges for stimulus awareness has only been demonstrated for early visual cortex but, as we saw above, the neural substrate of consciousness is more likely to lie elsewhere. Psychophysically, masking is similarly effective when masking stimuli are presented monoptically (through the same eye as the target) and dichoptically (through the other eye). The analysis of fMRI data in humans show that a correlate of monoptic visual masking can be found in all retinotopic visual areas, whereas dichoptic masking is only seen in retinotopic areas downstream of V2 within the occipital lobe (Tse et al., 2005), suggesting an anatomical

lower bound for the neural substrate of consciousness. Thus, it could be that phasic onset- and offset discharges are important not in and of themselves, but because they are particularly effective in activating downstream areas that directly support consciousness. In these downstream areas, perhaps, consciousness may actually require sustained firing. Indeed, the duration of the activation of face-selective neurons in IT is strongly correlated with the visibility of masked faces (Rolls et al., 1999).

A THEORETICAL PERSPECTIVE

Progress in neuroscience will hopefully lead to a better understanding of what distinguishes neural structures or processes that are associated with consciousness from those that are not. But even if we come closer to this goal, we still need to understand *why* certain structures and processes have a privileged relationship with subjective experience. For example, why is it that neurons in corticothalamic circuits are essential for conscious experience, whereas cerebellar neurons, despite their huge numbers, are not? And what is wrong with many cortical circuits that may make them unsuitable to yield subjective experience? Or why is it that consciousness wanes during slow wave sleep early in the night, despite levels of neural firing in the corticothalamic system that are comparable to those in quiet wakefulness? Other questions are even more difficult to address in the absence of a theory. For example, is consciousness present in animals that have a nervous system considerably different from ours? And what about computerized robots or other artifacts that behave intelligently but are organized in a radically different way from human brains?

Consciousness as Integrated Information

It would seem that, to address these questions, we need a theoretical approach that tries to establish, at the fundamental level, what consciousness is, how it can be measured, and what requisites a physical system must satisfy in order to generate it. *Integrated information theory* of consciousness (IIT) represents such an approach (Figure 25.9) (Tononi, 2004b, 2008, 2012; Oizumi et al., 2014).

According to the theory, an essential property of consciousness is that it *exists intrinsically*—an experience exists for the experiencing subject, rather than for an external observer. Another essential property of consciousness is that it is extraordinarily *informative*. This is because, whenever you experience a particular conscious scene, it rules out a huge number of alternative experiences. For example, you lie in bed with eyes open and experience pure darkness and silence. This is one of the simplest experiences you might have, one that may not be thought as conveying much information. One should realize, however, that the informativeness of what you just experienced lies not in how complicated it is to describe, but in what makes it what it is and thereby different from myriads of other experiences that you could have had but actually did not have: you could have experienced any one frame from any of innumerable movies, or the smoke and flames of your room burning, or any other possible scene, but you did not—instead, you experienced darkness and silence. This means that when you experienced darkness and silence, whether you think or not of what was ruled out (and you typically do not), you actually gained access to a large amount of information. This point is so simple that its importance has been overlooked. It is just as essential to realize that the information associated with the occurrence of a conscious state is *integrated* information. When you have a particular experience, that experience is an integrated whole—it cannot be subdivided into components that are experienced independently. For example, the conscious experience of the particular phrase you are reading now cannot be experienced as subdivided into, say, the conscious experience of how the words look independently of the conscious experience of how they sound in your mind. Similarly, you cannot experience visual shapes independently of their color, or perceive the left half of the visual field of view independently of the right half.

Based on these and other considerations, the theory claims that the neural substrate of consciousness is a set of elements, called "complex," that specifies an "intrinsic, maximally irreducible cause-effect structure of a specific form," called "conceptual structure" (Tononi, 2012, 2015; Oizumi et al., 2014). That is, substrate of consciousness must be a set of elements whose present state (say, some neurons firing, some not) makes the most difference to itself, rather than to an external observer (intrinsic cause-effect power). The form of the conceptual structure in cause-effect space—the possible past states (causes) and future states (effects) of the complex as specified by its subsets in their present state—specifies the quality or content of an experience (informativeness)—what the experience is like. The irreducibility of the conceptual structure (integration), measured by integrated information (Φ) specifies the quantity or level of consciousness. The set of elements constituting the complex (the neural substrate of consciousness), their spatial grain (neurons or groups) and the relevant temporal intervals are the ones at which Φ reaches a maximum (Φ^{Max}).

Some properties of complexes are worth pointing out. A given physical system, such as a brain, is likely

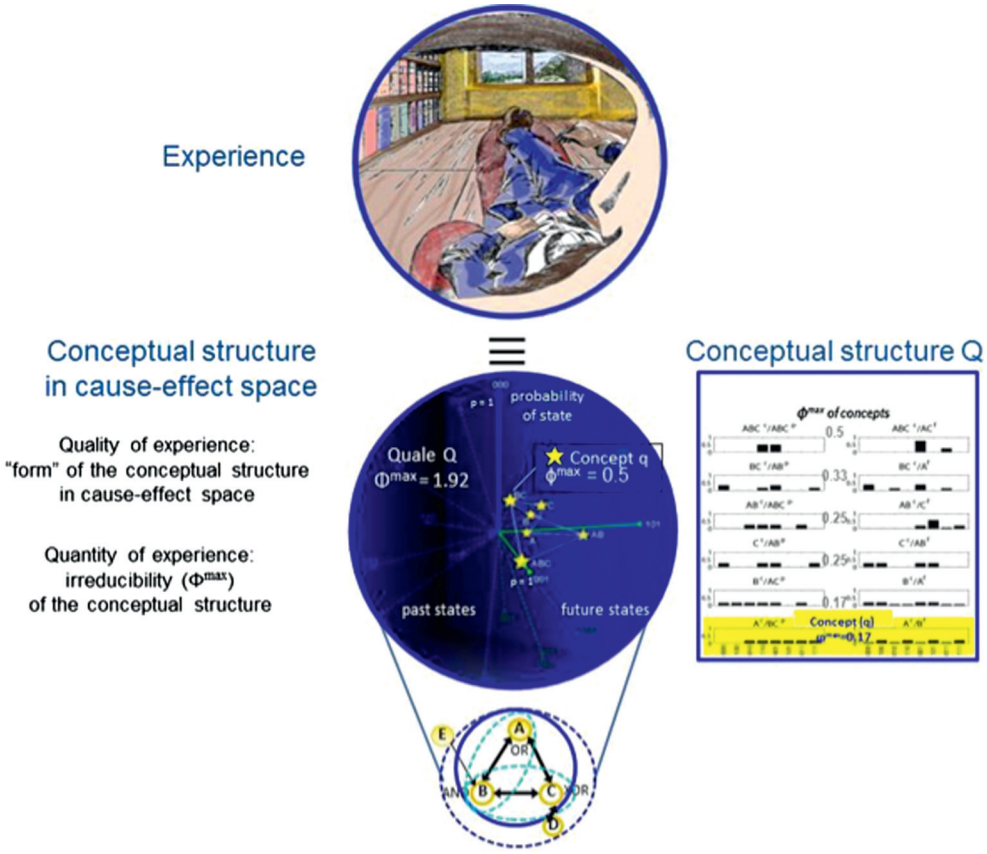

FIGURE 25.9 Integrated information theory. An experience is a maximally irreducible conceptual structure composed of concepts specified over itself by a complex constituted of elements in a state—a "form" in cause-effect space. In this example, the system constituted of logic gates A,B,C,D,E, and contains a complex ABC. This complex specifies a conceptual structure (a maximally irreducible cause-effect structure made of concepts). The conceptual structure is presented as the set of concepts specified by a mechanism of the system in its present state over all past and future states of the system (right). It is presented as a 2-D projection in which the cause-effect repertoire of each concept is a "star" in cause-effect where each axis is a possible past (in blue) and future (in green) state of the complex, and the position along the axis is the probability of that state (middle). The position of each star in cause-effect space specifies how the corresponding concept changes the "form" of the quale and thus *how* it contributes to experience as a phenomenal distinction (quale—q). The size of the star measures how irreducible the concept is and thus *how much* it contributes to experience. The overall "form" of the conceptual structure or quale sensu lato (Q) (constellation of stars) is identical to the quality of the experience, *how* the experience feels. The intrinsic irreducibility of the entire conceptual structure measures *how much* consciousness there is—the quantity of experience. Different shapes of qualia correspond to different experiences. *Source: Taken from Tononi (2015).*

to contain more than one complex, many small ones with low Φ values, and perhaps a few larger ones. Some of the "*minor*" complexes may mediate behaviors that are usually considered to be unconscious (e.g., Mudrik and Koch, 2013), although behavior mediated by purely feedforward circuits would be strictly unconscious. On the other hand, it is likely that the neural substrate of our everyday consciousness is a "*major*" complex of very high Φ. As discussed earlier, it is still unclear where in the brain this major complex may be located, although areas of posterior cortex, extending around the temporo-parieto-occipital junction, are most likely involved. It is also unclear whether the borders of this major complex may change much during wakefulness. Whatever the final answer, according to IIT the major complex must correspond to a maximum of intrinsic cause-effect power. Moreover, neural elements that are part of the major complex must contribute to its conscious experience, while elements that are not part of it do not, even though they may be connected to it and exchange signals with it through ports-in and ports-out (Tononi, 2015). Also, this major should support consciousness whether or not we are functionally connected to the environment or dreaming. Finally, the major complex may shrink (say with absolute achromatopsia), move (say when having experiences of pure thought during certain stages of sleep), split anatomically (as in split brain patients) and perhaps functionally (perhaps in certain dual-task conditions and in some psychiatric disorders).

Accounting for Neurobiological Observations

Measuring Φ and finding complexes is not easy for realistic systems, but it can be done for simple networks that bear some structural resemblance to different parts of the brain (Tononi, 2004b, 2005). For example, by using computer simulations, it is possible to show that high Φ requires networks that conjoin functional specialization (due to its specialized connectivity, each element has a unique functional role within the network) with functional integration (there are many pathways for interactions among the elements). In very rough terms, this kind of architecture is characteristic of the mammalian corticothalamic system: different parts of the cerebral cortex are specialized for different functions, yet a vast network of connections allows these parts to interact profusely. And indeed, as we have seen, the corticothalamic system is precisely the part of the brain that cannot be severely impaired without loss of consciousness.

Conversely, Φ is low for systems that are made up of small, quasi-independent modules. This may be why the cerebellum, despite its large number of neurons, does not contribute much to consciousness: its synaptic organization is such that individual patches of cerebellar cortex tend to be activated independently of one another, with little interaction between distant patches (Cohen and Yarom, 1998; Bower, 2002).

Computer simulations also show that units along multiple, segregated incoming or outgoing pathways are not incorporated within the repertoire of the main complex. This may be why neural activity in afferent pathways (perhaps as far as V1), though crucial for triggering this or that conscious experience, does not contribute directly to conscious experience; nor does activity in efferent pathways (perhaps starting with primary motor cortex), though it is crucial for reporting each different experience.

The addition of many parallel cycles also generally does not change the composition of the main complex, although Φ values can be altered. Instead, cortical and subcortical cycles or loops implement specialized subroutines that are capable of influencing the states of the main corticothalamic complex without joining it. Such informationally insulated cortico-subcortical loops could constitute the neural substrates for many unconscious processes that can affect and be affected by conscious experience (Baars, 1988; Tononi, 2004a,b), such as those that enable object recognition, language parsing, or translating our vague intentions into the right words. At this stage, however, it is hard to say precisely which cortical circuits may be informationally insulated. Are primary sensory cortices organized like massive afferent pathways to a main complex "higher up" in the cortical hierarchy? Is much of prefrontal cortex, and the parallel loops originating there and going through basal ganglia and thalamic nuclei, organized like a massive efferent pathway? Do certain cortical areas, such as those belonging to the dorsal visual stream, remain partly segregated from the main complex? Do interactions *within* a corticothalamic minicolumn qualify as intrinsic mini-loops that support the main complex without being part of it? Unfortunately, answering these questions and properly testing the predictions of the theory requires a much better understanding of cortical neuroanatomy than is presently available.

Other simulations show that the effects of cortical disconnections are readily captured in terms of integrated information (Tononi, 2004b): a "callosal" cut produces, out of large complex corresponding to the connected thalamocortical system, two separate complexes, in line with many studies of split-brain patients (Gazzaniga, 1995). However, because there is great redundancy between the two hemispheres, their Φ value is not greatly reduced compared to when they formed a single complex. Functional disconnections may also lead to a restriction of the neural substrate of consciousness, as is seen in neurological neglect phenomena, in psychiatric conversion and dissociative disorders, and possibly during dreaming and hypnosis. It is also likely that certain attentional phenomena may correspond to changes in the composition of the main complex underlying consciousness. Phenomena such as the attentional blink, where a fixed sensory input may at times make it to consciousness and at times not, may also be due to changes in functional connectivity: access to the main corticothalamic complex may be enabled or not based on dynamics intrinsic to the complex (Dehaene et al., 2003). Phenomena such as binocular rivalry may also be related, at least in part, to dynamic changes in the composition of the main corticothalamic complex caused by transient changes in functional connectivity (Lumer, 1998). Computer simulations confirm that functional disconnection can reduce the size of a complex and reduce its capacity to integrate information (Tononi, 2004b). While it is not easy to determine, at present, whether a particular group of neurons is excluded from the main complex because of hard-wired anatomical constraints, or is transiently disconnected due to functional changes, the set of elements underlying consciousness is not static, but form a "*dynamic complex*" or "*dynamic core*" (Tononi and Edelman, 1998).

From the perspective of integrated information, a reduction of consciousness during early sleep would be consistent with the ensuing bistability of cortical circuits. As we have seen, studies using TMS in conjunction with high-density EEG show that early NREM sleep is associated either with a breakdown of the effective connectivity among cortical areas, and thereby

with a loss of integration, or with a stereotypical global response suggestive of a loss of repertoire and thus of information (Massimini et al., 2007). As we have also seen, similar changes are seen in animal studies of anesthesia (Imas et al., 2005; Hudetz and Imas, 2007; Kroeger and Amzica, 2007). Computer simulations also indicate that the capacity to integrate information is also reduced if neural activity is extremely high and near-synchronous, due to a dramatic decrease in the available degrees of freedom (Balduzzi and Tononi, 2008). This reduction in degrees of freedom could be the reason why consciousness is reduced or eliminated in absence seizure and other conditions characterized by hypersynchronous neural activity.

Finally, we have seen that consciousness not only requires a neural substrate with appropriate anatomical structure and appropriate physiological parameters: it also needs time (Bachmann, 2000). The theory predicts that the time requirement for the generation of conscious experience in the brain emerge directly from the time requirements for the build-up of an integrated repertoire among the elements of the corticothalamic major complex (Tononi, 2004b; Balduzzi and Tononi, 2008). To give an obvious example, if one has to perturb half of the elements of the main complex for less than a millisecond, no perturbations would produce any effect on the other half within this time window, and the repertoire measured by Φ would be equal to zero. After say 100 ms, however, there is enough time for differential effects to be manifested, and Φ should grow.

Some Implications

Naturally, IIT converges with other neurobiological frameworks (e.g., Edelman, 1989; Crick and Koch, 2003; Dehaene et al., 2006) and cognitive theories (Baars, 1988) on certain key facts: that our own consciousness is generated by distributed corticothalamic networks, that reentrant interactions among multiple cortical regions are important, that the mechanisms of consciousness and attention overlap but are not the same, and that there are many "unconscious" neural systems. Importantly, however, the examples discussed above show that IIT can begin to account, in a coherent manner, for several puzzling facts about consciousness and the brain. This goes beyond proposing a provisional list of candidate brain areas for the neural substrate of consciousness, and of seemingly important neural ingredients, such as synchronization, sustained or phasic firing, reentrant activity, or widespread "broadcasting," without a principled explanation of why they would be important or whether they would be always necessary. Starting from first principles—consciousness is a maximum of irreducible intrinsic cause-effect power, IIT can actually explain why: because no purely feedforward system has intrinsic cause-effect power. Synchronization may signify that elements of the physical substrate of consciousness are interacting efficiently, but it is neither necessary nor sufficient for consciousness, as there can be strong synchronization with little consciousness and consciousness with little synchronization.

IIT also avoids the pitfalls associated with assigning conscious qualities to individual brain elements. For example, it is sometimes assumed loosely that the firing of specific corticothalamic elements (e.g., those for red) conveys some specific information (e.g., that there is something red), and that such information becomes conscious either as such, or perhaps if it is disseminated widely. However, a given corticothalamic element has no information about whether what made it fire was a particular color rather than a shape, a visual stimulus rather than a sound, a sensory stimulus rather than a thought. All it knows is whether it fired or not, just as each receiving element only knows whether it received an input or not. Thus, the information specifying "red" cannot possibly be in the message conveyed by the firing of any neural element, whether it is located in a high-order cortical area, or whether it is broadcasting widely. According to the theory, that information resides instead in form of the conceptual structure specified by the major complex in the brain—the complex, and not its elements, is the locus of consciousness. Indeed, within a complex, both active and inactive neurons count, just as the sound of an orchestra is specified both by the instruments that are playing and by those that are silent.

IIT also predicts that consciousness depends exclusively on the ability of a system to integrate information, whether or not it has a strong sense of self, language, emotion, or is immersed in an environment, contrary to some common intuitions, but consistent, as reviewed in this overview, with the overall neurological evidence. Of course, the theory recognizes that these same factors are important historically because they favor the development of neural circuits forming a main complex of high Φ. For example, integrated information grows as that system incorporates statistical regularities from its environment and learns (Tononi et al., 1996). In this sense, the emergence of consciousness in biological systems is predicated on a long evolutionary history, on individual development, and on experience-dependent change in neural connectivity.

Finally, IIT says that the presence and extent of consciousness can be determined, in principle, also in cases in which we have no verbal report, such as infants or animals, or in neurological conditions such as minimally conscious states, akinetic mutism,

psychomotor seizures, and sleepwalking. In practice, of course, measuring Φ accurately in such systems will not be easy, but approximations and informed guesses are certainly conceivable. The theory also implies that consciousness is not an all-or-none property, but is graded: specifically, it increases in proportion to a system's repertoire of available states. In fact, any physical system with some capacity for integrated information would have some degree of experience, irrespective of the constituents of which it is made, and independent of its ability to report.

Whether these and other predictions turn out to be compatible with future clinical and experimental evidence, a coherent theoretical framework should at least help to systematize a number of neuropsychological and neurobiological results that might otherwise seem disparate.

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