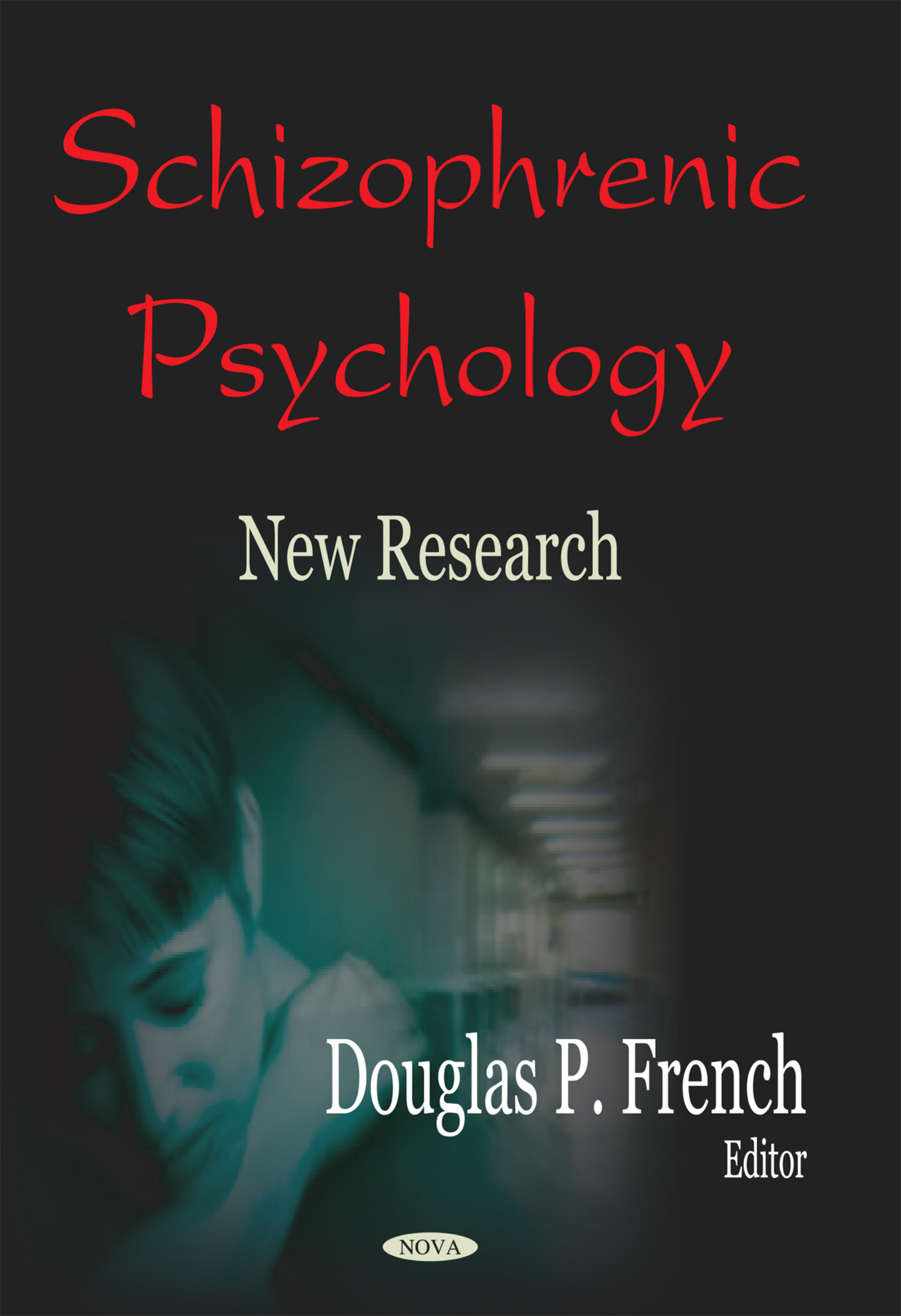
Schizophrenic Psychology

New Research



Douglas P. French
Editor

NOVA

SCHIZOPHRENIC PSYCHOLOGY: NEW RESEARCH

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CONTENTS

PREFACE

Schizophrenic psychology is the study of mental processes and behavior of schizophrenics. This new book presents the latest research in this dynamic field.

Cognitive neuropsychological theories hypothesize that frontal executive deficits play a role in the etiology of schizophrenic symptoms. Recent evidence also suggests that the dysexecutive syndrome may be fractionated. The successful attempts in fractionating the executive system will depend to a considerable extent on the ability to develop more specific models of executive function. The current conventional frontal tests used by clinicians and neuropsychologists tend to be crude and underspecified in terms of the cognitive processes which they engage. These may not be sensitive enough to detect executive dysfunction in clinical groups like schizophrenia. The authors of chapter 1 would like to adopt a systematic approach of examining executive function according to the theoretical models identified from the literature (some of them were based on animal studies). They then discuss how fractionation of executive function in schizophrenia could be studied with the extended design of single-case study to multiple-case study. Evidence will be provided on the differential breakdown of executive function components in this chronic and medication naïve cases. They also attempt to build up a link between specific executive function components to subtypes of clinical symptoms and neurological deficits. Imaging data will also be provided to explore such a relationship.

Thought disorder, a core feature of schizophrenia may stem from a dysfunction of the brain language network. Language and thought are interrelated brain functions that may share the same brain structures. Language function involves several brain regions that are implicated in schizophrenia; some of the brain abnormalities and subtle language, cognitive thought abnormalities appear well before the onset of psychosis supporting developmental origins of the etiology of schizophrenia in this network. Chapter 2 reviews the extant literature in this field and propose a model of abnormal developmental maturation of a widespread network centered on the temporal lobe language association cortex as possible underlying mechanism of adolescent onset schizophrenia. Early developmental abnormalities of this network may underlie the susceptibility to schizophrenia and late maturational deviances may result in the emergence of thought disorder and psychosis during adolescence. Genes involved in language, the developmental maturation of language cortex, environmental factors such as obstetric complications, and other environmental stress such as substance use during developmental years may increase the odds of developing schizophrenia by altering

the trajectory of development or interfering with the late maturation the brain. The proposed model combines the developmental theory, language abnormalities and in vivo neurobiology.

The concept of schizoaffective disorder was first introduced in 1933 by Kasanin, who described a group of patients with good premorbid functioning, sudden onset of illness, following a defined stressor and in some cases with family histories of mood disorders. Chapter 3 outlines the prevalence, clinical features, course and outcome of schizoaffective disorder. Treatment, including special considerations for late- onset illness and medical comorbidities, will be discussed. Finally, efficacy data and tolerability concerns will be presented for specific potential therapeutic agents.

Schizophrenic pathological experiences in which the patient offends people around him/her occupy a characteristic position in schizophrenic psychopathology. S. Kato proposed the concept of *prejudicing autochthonous speech act (thought)*, a schizophrenic pathological experience in which the patient has had prejudicial thoughts, and often believes that he/she has voiced them or has sometimes even actually voiced them, against people in his/her presence. He suggested that *prejudicing autochthonous speech act (thought)* often appears during the remission process of schizophrenia and represents re-establishment of the ego function of the patient during the recovery process from schizophrenia. Chapter 4 focuses on a similar symptom, namely, *prejudicial autochthonous visual representation*, in which the patient has prejudicial visual images of people in their presence, and discuss the significance of this symptom in the clinical course of schizophrenia. *Prejudicial autochthonous visual representation* is deemed to be a variant of *prejudicing autochthonous speech act (thought)*, however, whether they have similar clinical significance remains doubtful. The authors would like to emphasize the visual character of *prejudicing autochthonous visual representation.* In reference to the concept of *illocutionary force* by Austin, they suppose that the pathological illocutionary force which are often observed in schizophrenic pathological experiences, is safely ensconced within the capsule of the visual image in the case of *prejudicial autochthonous visual representation*.

Chapter 5 examines differences in inter- and intra-generational social class trajectory among patients with schizophrenia, bipolar disorder, major depressive disorder and community non-cases. Data were collected between 1983 and 1989 by interviewing all psychotic admissions to fifteen hospitals providing inpatient psychiatric services in the Baltimore Metropolitan Area. Social class of the patient's family of origin and the patient's own social class at the time of admission were obtained through standard survey questions on occupation. Inter-generational differences in social class suggest a lower origin social class for psychotic patients with major depressive disorder than for patients with bipolar disorder, schizophrenia or community non-cases. A multi-group structural equation analysis showed that the magnitude of the effect of educational achievement on social class at the time of hospital admission is strongly patterned after by type of psychotic disorder. Patients with schizophrenia showed a more pronounced "downward drift" (lower returns to education) than patients with bipolar disorder, major depressive disorder and community controls.

Suicide is a major cause of death among patients with schizophrenia. Literature reports that at least 4.9-13% of schizophrenic patients die by suicide, but it is likely that the higher end of range is the most accurate estimate. There is almost total agreement that the schizophrenic patient who is more likely to commit suicide is young, male, white, has never married, has good premorbid function, has post-psychotic depression, and has a history of substance abuse and suicide attempts. Hopelessness, social isolation, awareness of illness, and

hospitalization are also important risk factors in schizophrenic individuals who commit suicide. Deteriorating health with a high level of premorbid functioning, recent loss or rejection, limited external support, and family stress or instability are other risk factors traceable in patients with schizophrenia who commit suicide. These patients usually fear further mental deterioration and experience excessive treatment dependence or loss of faith in treatment. Awareness of illness has been reported as a major issue among schizophrenic patients who at risk of suicide. Yet, some scholars highlighted that insight into illness does not increase suicide risk. Reviewing the literature the authors found that only insight into certain elements of the illness can increase the risk of suicide. Implications for strategy to adopt in dealing with the increased insight both during pharmacotherapy and psychotherapy are discussed. Chapter 6 also discusses awareness of illness, suicide risk and stigmatization among schizophrenic patients.

Need is “something necessary for living. Everything that someone can not do without”. The definition of need in mental health was initially controversial chapter 7. One approach defined need as disabilities in the daily life of the subject. Thus, disabilities were assessed as well as the type of needs relating to them. Another approach took the treatments and interventions available as a starting point. Needs were assessed on the basis of the services for particular deficiencies from which patients could benefit. Nowadays, needs are considered multiaxial and dynamic, and it is as important to assess the subject perception of need as the family’s.

Studies from around the world on first-episode psychosis have consistently shown that there is an average of 1-2 years between the onset of psychotic symptoms and the start of the treatment. Duration of untreated psychosis (DUP) has been suggested as predictor of clinical outcome in patients with first-episode psychosis. It has been reported that patients with a longer DUP had a poorer clinical outcome in a follow-up period of 12 months, characterized by more severe positive and negative symptoms and global psychosocial impairment. Also, it has been described that patients with schizophrenia exhibit a longer DUP when compared to patients with affective psychosis and that this longer DUP is related to their clinical outcome. Chapter 8 determines the effect of DUP on clinical outcome in a 12 month follow-up study in a Mexican population. A total of 104 first-episode psychotic patients were recruited and grouped in affective (n=25, 24%)and non-affective psychoses (n=79, 76%). Diagnoses was obtained with the SCID-I and the DUP was register in each patient. A clinical evaluation for psychotic and affective symptoms was performed using standardized instruments. The sample was divided according the median of DUP in short DUP (<28 weeks) and long DUP (≥ 28weeks). Ten patients were lost during the follow-up. The mean DUP of the 94 patients was 67.1/- 69.5 weeks, no differences were found between lost and remaining patients in clinical variables. Two patients from the long-DUP group committed suicide in the first year. The long-DUP group showed persistent positive and negative symptoms, as well as poor social functioning during the follow-up. Although some studies have considered that first-episode patients in non-developed countries may have a better prognosis not related to DUP, our results suggest that long DUP has an influence on outcome and may increase the suicide risk in Mexican first-episode patients, supporting the importance of early detection and intervention. Early detection programs are required to shorten the interval from onset of illness to first specialized diagnosis and treatment in first-episode psychotic patients.

Source memory impairments have been found repeatedly in schizophrenia as described in chapter 9. Many studies referring to source-memory deficits in patients with schizophrenia

associate them with positive symptomatology. However, the etiological mechanism of this handicap remains unknown. On the other hand, although the existence of cognitive deficits in schizophrenia has been confirmed, the way in which these specific deficits are associated with impaired monitoring of the source of information has not been investigated thoroughly.

Prepulse inhibition (PPI) is thought to reflect a relatively automatic, preattentive sensorimotor gating mechanism that reflects an individual's ability to gate incoming information, so that attention can be focused effectively on specific environmental stimuli. PPI is reduced in patients with schizophrenia. Such impairments in the ability to appropriately inhibit the processing of information have been hypothesized to contribute to the core symptoms of schizophrenia. Chapter 10 covers four areas of interest in PPI studies. The theory that lies behind the mechanism of PPI and delineate the neural substrates and neurotransmitters involved in PPI is summarised. Animal studies have contributed considerably to these domains of interest. Second, the existing literature on PPI deficits in chronic and first-episode schizophrenia patients is critically reviewed. Many studies - but not all - report that PPI is impaired in individuals with schizophrenia. Some of the inconsistencies might be due to different parameters influencing PPI performance in schizophrenia patients and healthy subjects. The type of antipsychotic treatments and the degree of psychotic symptoms appear to influence PPI in schizophrenia patients. Moreover, smoking habits, genetic predisposition, and sex differences as well as varying experimental conditions influence PPI measures in both healthy subjects and patients. The multiplicity of these factors complicates the interpretation of PPI data and might contribute to discrepancies across studies. Third, the relationship between cognition and PPI is reviewed. Specifically, abnormalities in the early stages of information processing could lead to a cascade of downstream effects on higher cortical functions, such as sustained attention, working memory, concept formation, or social functioning. Fourth, the authors review the PPI literature on model psychoses in healthy volunteers. Thus, various drugs that are suggested to reproduce schizophrenia-like states, such as psilocybin and ketamine, have also been used in animal and human studies of PPI.

Considerable evidence suggests that violent behavior observed in schizophrenic patients is motivated by psychotic symptomatology, specially in terms of positive syndrome. A positive relationship between violence and various psychotic symptoms, such as delusions, hallucinations and thought disorder, has been established in patients with schizophrenia. The understanding of violence in schizophrenic patients requires consideration of psychiatric symptomatology. Chapter 11 determines the influence of psychotic symptomatology in the appearance of violent behavior in schizophrenic patients. A total of one hundred and twenty were recruited. Eighteen patients were excluded due to concomitant substance abuse 6 months prior to the assessment. Diagnoses were based on the SCID-I. Psychotic symptom severity was assessed with the SANS and SAPS. Violent behaviors were assessed with the OAS. Violent behaviors were associated with more severe psychotic symptomatology including hallucinations, delusions, excitement, and thinking disturbances. Patients with exacerbation of psychotic symptomatology will have an increased risk to behave violently. Violent behavior in schizophrenic patients is a heterogeneous phenomenon best explained in the context of specific symptoms associated to violence and course of illness, which may in turn may suggest that violence observed in patients is not unpredictable. The content of patient's delusions or hallucinations often imply a specific course of violent action which could be thought of as a psychotic form of "self-defense". The retrospective assessment of the

variables raises methodological questions concerning the reliability of such measurement of the impact of psychotic symptoms on violence.

A number of studies report patients with schizophrenia exhibit disturbances in a wide range of cognitive function. However, little is known about impairment in higher cognitive functions, such as organization of semantic memory. Chapter 12 discusses the relevant issues based on the findings from our recent studies. First, a method to investigate the semantic organization using data from verbal fluency assessments is addressed. Next, factors which affect the severity of impairment of semantic memory organization is discussed. This chapter also provides an overview of the effect of newer generation antipsychotic drugs on organization of semantic memory. Finally, the authors discuss the idiosyncratic degradation of semantic memory in patients from the viewpoint of the neurodevelopmental hypotesis of schizophrenia.

Experimental psychopathology struggles with the fact that patients' behavioral impairments are difficult to interpret as specific cognitive deficits. This difficulty, known as the psychometric confound, occurs because mental disorders such as schizophrenia usually result in impairments across many tasks, and some of these impairments may appear larger simply because a task has greater discriminating power. This frustrates the use of behavioral paradigms to investigate the cognitive, neural and genetic basis of schizophrenia. Chapter 13 illustrates and indexes the psychometric confound in four simulation studies. These studies use the relationship between an imputed effect size and an observed effect size as a gold standard for measuring task discriminating power. The first simulation provides a primer on the sources of the psychometric confound, as well as an investigation of the validity of several metrics of discriminating power. The subsequent simulations evaluated the extent to which the use of standardized scores, demographic norming, and standardized residual scores mitigate the distortions caused by the psychometric confound. These simulations cast light onto how these approaches to the psychometric confound influence the interpretability of behavioral deficits, the range over which they are applicable, and domains where misconceptions about the psychometric confound exist. This approach may be useful for unlocking the potential of behavioral paradigms to reveal or appreciate how they may obscure the cognitive, neural and genetic basis of schizophrenia.

The prevalence of cigarette smoking is significantly higher among patients with schizophrenia (60-90%) than in the general population (23-30%) as reporte in chapter 14. While tobacco smoking decreases in general population (from 45% in the 1960's to 23-30% in the 2000's), smoking in patients with schizophrenia remains high. Patients with schizophrenia smoke more deeply, thereby increasing their exposure to harmful elements in tobacco smoke. Impact of smoking on patients with schizophrenia: As in the general population, smoking contributes to the reduced life expectancy in patients with schizophrenia. Patients with schizophrenia are at elevated risk for cardiovascular disease due to high rates of cigarette smoking. In the Department of Mental Health of the commonwealth of Massachussetts, cardiovascular disease was the factor that most strongly associated with excess mortality. Improvement of cognitive deficits: Patients with schizophrenia may use nicotine to reduce cognitive deficits and negative symptoms or neuroleptic side effects. Smoking may transiently alleviate negative symptoms in patients with schizophrenia in increasing dopaminergic and glutamatergic neurotransmission in the prefrontal cortex. In patients with schizophrenia, nicotine improves some cognitive deficits : 1) Sensory gating deficits and abnormalities in smooth pursuit eye movements associated with schizophrenia

are transiently normalized with the administration of nicotine 2) High-dose nicotine transiently normalizes the abnormality in P50 inhibition in schizophrenic patients and in their relatives 3) In tasks that tax working memory and selective attention, nicotine may improve performance in patients with schizophrenia by enhancing activation of and functional connectivity between brain regions that mediate task performance 4) Cigarette smoking may selectively enhance visuospatial working memory and attentional deficits in smokers with schizophrenia. However, nicotine affects only the attention without effects of nicotine on learning, memory or visuospatial/constructional abilities. In addition, smoking could facilitate disinhibition in patients with schizophrenia. Some authors stressed that nicotine does not appear to have a long-lasting therapeutic effect on schizophrenia's symptoms. Impact of smoking on patients with schizophrenia who are on antipsychotic medications : Smoking increases the metabolism of the antipsychotic medications by inducing the cytochrome P450 1A2 isoform. Smoking lowers the blood levels of typical or atypical antipsychotic medications. Treatment: Although patients with schizophrenia have low motivations to quit smoking, smoking cessation treatment can be effective for these patients. Atypical antipsychotic medications, in combination with the nicotine transdermal patch, or bupropion significantly enhanced the rate of smoking cessation.

Schizophrenia is a severe, chronic mental disorder that appears in 1% of the population. The abnormal neurotransmission of serotonin (5-hydroxytryptamine, 5-HT), dopamine, noradrenalin, and altered neuroendocrine function are implicated in the pathophysiology of schizophrenia. Peripheral biochemical markers might be used to improve the understanding of the underlying neurobiology of schizophrenia, for the preclinical screening, diagnosis, disease staging, and monitoring of treatment. Since there are striking similarities how both central nervous system and platelets store and metabolize 5-HT, blood platelets have been widely used as a peripheral model for the central serotonergic synaptosomes. The dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity and altered secretion of prolactin (PRL) and plasma lipids levels are frequently found in schizophrenia. Clinical diagnosis of schizophrenia was made according to the DSM-IV criteria. Main outcome measures were scores in Positive and Negative Syndrome Scale, Clinical Global Impression of Severity (CGIS) or Change (CGIC), Hamilton Rating Scale for Depression (HAMD), and HAMD subscale for suicidal behavior. Control group consisted of drug free healthy persons with no personal or family history of psychopathology. Biomarkers studied were: platelet 5-HT concentration, platelet monoamine oxidase (MAO) activity, serum lipids levels: cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoproteins cholesterol (LDL-C), plasma PRL levels and cortisol levels at baseline and after dexamethasone suppression test (DST). Biomarkers were determined using spectrofluorimetric, radioimmunoassay, immunoradiometric methods, enzymatic color test and enzymatic clearance assay. Schizophrenic patients had higher values of platelet 5-HT, cortisol and PRL, abnormal cortisol response to DST, and lower values of cholesterol, HDL-C and LDL-C than healthy controls. Platelet 5-HT concentration was correlated to plasma levels of cortisol and PRL in healthy, but not in schizophrenic subjects. There was no significant relationship between plasma PRL and cortisol levels in all groups. Age had no influence on biochemical parameters. Our results suggest an altered relationship between 5-HT system, HPA axis activity and PRL secretion, and abnormal DST response in schizophrenia. The effects of different neuroleptics (fluphenazine, haloperidol) or atypical antipsychotic (olanzapine) on peripheral biochemical markers, clinical response and safety

were studied in naturalistic, comparative or double-blind studies in schizophrenic patients. The data in chapter 15 suggests that the evaluation of the peripheral biological markers might improve the characterization of the baseline group characteristics, might be used to predict a suicidal risk, to help to differentiate particular symptoms, or syndromes, and to predict the treatment response in schizophrenia.

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Chapter 1

FRACTIONATION OF EXECUTIVE FUNCTION IN SCHIZOPHRENIA: RELATIONSHIPS TO CLINICAL AND NEUROLOGICAL MANIFESTATIONS

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ABSTRACT

Cognitive neuropsychological theories hypothesize that frontal executive deficits play a role in the etiology of schizophrenic symptoms. Recent evidence also suggests that the dysexecutive syndrome may be fractionated. The successful attempts in fractionating the executive system will depend to a considerable extent on the ability to develop more specific models of executive function. The current conventional frontal tests used by clinicians and neuropsychologists tend to be crude and underspecified in terms of the cognitive processes which they engage. These may not be sensitive enough to detect executive dysfunction in clinical groups like schizophrenia. Here we would like to adopt a systematic approach of examining executive function according to the theoretical models identified from the literature (some of them were based on animal studies). We then discuss how fractionation of executive function in schizophrenia could be studied with the extended design of single-case study to multiple-case study. Evidence will be provided on the differential breakdown of executive function components in this chronic and medication naïve cases. We also attempt to build up a link between specific executive function components to subtypes of clinical symptoms and neurological deficits. Imaging data will also be provided to explore such a relationship.

Keywords: executive function, supervisory attention system, schizophrenia

INTRODUCTION

Schizophrenia is characterized by a generalized cognitive impairment, with varying degrees of deficit in all domains (Heinrichs and Zakzanis, 1998). Deficits are especially pronounced in the domains of verbal memory, executive functioning and attention (e.g., Albus et al., 1997; Aleman et al., 1999; Bilder, 1996; Censits et al., 1997; Heinrichs and Zakzanis, 1998; Saykin et al., 1994; Sitskoorn et al., 2002,) and less attenuated in the domains of perceptual- and basic language processes (Goldberg and Gold, 1995; Heinrichs and Zakzanis, 1998). Family studies also demonstrate that there is a substantial genetic contribution to the etiology of schizophrenia (Cardno et al., 1999; MuGuffin et al., 1995) and that some cognitive deficits in schizophrenia are heritable (Cannon et al., 2000; Goldberg et al, 2003). Several research groups have now showed that that similar cognitive deficits can also be found in non-affected relatives of patients with schizophrenia (Sitskoorn et al. (2004); Toulopoulou et al., 2003a; 2003b; 2005).

Although evidence for a dysexecutive syndrome in schizophrenia has been sought in a number of neuropsychological studies, there is still a controversy regarding the existence, nature and pattern of selective differential deficits relative to a more general cognitive impairment. Some studies demonstrate that executive impairment is a consequence of a general neuropsychological impairment (Bilder et al., 1991, 1992; 2000; Hoff et al., 1992; Saykin et al., 1994; Heinrichs and Konstantine, 1998; Mohamed et al., 1999; Hill et al., 2002; Addington et al., 2003; Kremen et al., 2004). Others (Saykin et al., 1991; Shallice et al., 1991; Gold et al., 1992; Tamlyn et al., 1992 ; Elliott et al., 1995; Hutton et al., 1998; Towsend et al., 2001; Chan et al., 2004a) show selective executive abnormalities which cannot be explained by a non-specific neuropsychological insult.

For example, Crawford et al. (1993) found clear evidence for a disproportionate deficit in verbal fluency performance. On the other hand two studies (Braff et al., 1991; Morrison-Stewart et al., 1992) found that patients with schizophrenia were impaired on some, but not all of a number of executive tasks. Saykin et al. (1991) concluded that there was no evidence for selective executive function impairment in schizophrenia. Saykin et al. (1994) further commented that there has been too narrow an assessment which may result in attributing a positive finding to a differential deficit when it may be that the difference is accounted for by general cognitive deterioration. In contrast, a study applying the neuropsychological case study approach to five chronic cases of schizophrenia provided a strong argument for the pre-eminence of executive dysfunction, which could be seen against a background of no, some or marked general intellectual impairment (Shallice et al., 1991). (Binks and Gold, 1998; Blanchard and Neale, 1994; Saykin et al., 1994).

The discrepancies in the literature may be partly due to a lack of theoretical guidance for most of the studies resulting in different studies using different classifications and definitions of executive function. Methodological variability between studies and subjects recruited at different phases of the illness also contribute to inconsistent findings. This paper attempts to address the issue of fractionation of executive function in schizophrenia. In particular, we would like to address several weaknesses that have been present in much of this "differential breakdown" of executive function research. The first has to do with a theoretical framework that may be useful for studying executive function in schizophrenia. Second, the recent development of theoretical-based tests of executive function has led to tests capturing specific

components of executive function. Third, we comment on the different methodologies of studying executive function in schizophrenia. Comparison of these methods to address differential strengths and weaknesses is questionable and may partly explain why a comprehensive understanding of the neuropsychology of schizophrenia has yet to be established. Fourth, we illustrate two studies adopting the use of both the quantitative and qualitative methods of studying fractionation of executive function at different phases of schizophrenia. Finally, we attempt to bridge the gap between these specific components of executive function to clinical, neuroanatomical and neurological manifestations.

THEORETICAL FRAMEWORK OF EXECUTIVE FUNCTION

The successful attempts in fractionating the executive system will depend to a considerable extent on the ability to develop more specific models of executive function (Fan et al., 2002; Posner and Petersen, 1990; Posner and Raichle, 1994; Shallice, 1988; Shallice and Burgess, 1991). The current conventional frontal tests used by clinicians and neuropsychologists tend to be crude and underspecified in terms of the cognitive processes which they engage (Burgess, 1997). These may not be sensitive enough to detect executive dysfunction in different clinical groups. The most recent and significant advancement in the past decade has been the attempt to isolate the specific component processes of frontal functions. Research on the influence of the frontal lobes on attention has given us some promising data to back up such proposition.

For example, Goldman-Rakic (1992) has argued that the prefrontal cortex is divided into multiple memory domains where each domain is responsible for a different aspect of working memory. This model leans heavily on Baddeley's (1986) model of working memory that captures a central executive unit and 2 modality specific slave systems. The prefrontal cortex, like other parts of the cortex, operates by inhibiting or exciting other parts of the cortex. These inhibitory or excitatory commands might be issued via neurotransmitters such as the catecholamines, especially dopamine (the prefrontal cortex is rich in these neurotransmitters). When levels of these chemicals are reduced, the types of working memory impairment seen on the delayed-response task in brain-damaged monkeys is apparent. Restoring the level of these chemicals normalizes performance. While not one of the more widely adopted models of frontal lobe function – because of its functional specificity and limitation to animal model – this working memory model does provide a testable explanation of the role of the frontal cortex in working memory and executive functioning in schizophrenia (Perry et al., 2001; Pukrop et al., 2003).

The Supervisory Attention System (SAS) Model proposed by Norman and Shallice's (1986) has provided a stronger theoretical link to both neurocognitive function and clinical symptoms in schizophrenia. This model assumes that the processes involved in the cognitive control of action and thought can be divided into contention scheduling and supervisory attention control. It is the latter system that is considered to be a key to effective control of action in daily life, particularly in novel and complex situations. It is involved in the control of information flow on tasks involving initiation, planning, mental set shifting, strategy allocation, monitoring and inhibition. In this conceptualisation, the enactment of well-learned and routine responses (in form of schema) is governed by their level of activation relative to

possible competitors for control of perceptual and output systems. The level of activation is determined by the strength of external or internal cues and the strength of their association with particular patterns of behaviour. Within such framework, everyday life complex activities such as those involving in car driving can be executed appropriately but in a rather automatic and "stimulus-driven" fashion (Norman and Shallice, 1986; Shallice, 1988). The role of such supervisory attentional system is to construct novel response and to modify or suppress schema expression when the most activated schema is inappropriate to an overall goal. Impairment in this system would be expected to result in the inability to formulate a goal, to plan, and to choose between alternative sequences of behaviour in order to reach a particular goal.

The SAS model outweighs other theories by having a detailed sub-classification or fractionation of specific components (Stuss et al., 1995; Burgess and Shallice, 1 996a, 1 996b). Frith (1992) further incorporated this construct in his cognitive neuropsychological theory of schizophrenia. He proposed that three principal cognitive abnormalities found in schizophrenia can be plausibly understood as a failure at the level of the SAS model. Disorders of willed action results from a dysfunction of the ability to represent goal directed action. Negative and disorganized symptoms, such as poverty of action, perseveration, and inappropriate action, are associated with impaired awareness of goals. On the other hand, disorders of self-monitoring will lead to positive symptoms such as delusions of alien control, thought insertion, and some auditory hallucinations. Finally, disorders in monitoring the intentions of others results in delusions of reference, paranoid delusions, illogical discourse, and third person hallucinations.

On the other hand, other models borrowed from cognitive psychology on healthy population and clinical groups may serve as other important guidelines for studying fractionation of executive function in this non-focal lesion clinical group. For example, Miyake et al. (2000) demonstrated that there are at least 3 often-postulated executive functions among healthy volunteers, i.e., shifting between tasks or mental sets; updating and monitoring of working memory representations, and; inhibition of dominant or prepotent responses. In the following section, we define and review the specific components of executive functions, mainly based on Shallice and colleagues' model and experimental evidence, and briefly discuss the tests we chose as example measures of each component. The components listed in the present chapter may not be exhaustive and mutually exclusive to each other.

THE NEW GENERATION OF EXECUTIVE FUNCTION TESTS

Initiation

The first executive function component involves one's ability to generate or initiate action or verbal responses. It involves either the lower level of ability to randomly generate simple action or the higher cortical level of attentional control in regulating the output of performance. The tests we chose to capture this component are the Hayling Sentence Completion Test Part A (Burgess and Shallice, 1 996a), Tower of Hanoi (Humes et al., 1997) or London (Shallice, 1982), Trails Making Test Part A (Reitan, 1955) or its derivatives (e.g., Colour Trails Test, D'Elia and Satz, 1989). All of these tests require to some extent generation

of action and verbal initiation commonly used in clinical groups such as with frontal lobe lesions or patients with schizophrenia (Burgess and Shallice, 1996; Marcezewski et al., 2001; Chan et al.., 2004a).

The Hayling Sentence Completion test consists of two sections (A and B) of 15 sentences each, in which the last word is missing. Sentences are read aloud by the experimenter. Part A (initiation section) demands the participant to complete the sentences with the expected word. The total number of correct response generated may be considered to be the "initiation" ability. The Tower of Hanoi test is a commonly known problem-solving test. However, the planning time for the participant to initiate the first move of the disk has been regarded as requiring some form of initiation ability (Chan et al., 2004a). Here, other similar tests involving ability to initiate an action like in the verbal fluency test, and those captured by the psychomotor speed processing found in tests like the Trails Making Test Part A may also be classified into this component.

Sustained Attention

The second component, sustained attention, is closely linked to the notion of working memory which intern is often associated with the prefrontal cortex. It is required when relevant events occur at a relatively low rate over prolonged periods of time. Several lines of evidence suggest that the prefrontal cortex is involved in sustained attention (e.g., Wilkins et al., 1987; Posner and Petersen, 1990). Posner and Petersen (1990) suggest a sustained attention (vigilance) system is located in the right lateral midfrontal region.

The tests that appear to capture this component include continuous performance test 3-7 version (Halperin et al., 1991), Monotone Counting Test (Wilkins et al., 1987), and Sustained Attention to Response Task (SART, Robertson et al., 1997). The Monotone Counting Test (Wilkins et al., 1987) and its derivatives (e.g., subtests embedded in the Test of Everyday Attention, Robertson et al., 1994) assess the ability to sustain attention over a short period of time. Participants in this task are asked to silently count regularly paced monotones presented by an audiotape. The number of tones in each trial varied from one to twelve in a randomized order. Each participant completed 12 trials. An instruction was given at the beginning of each trial. Participants were asked to report the number of tones presented after finishing each trial. The number of correct count was then recorded.

The Continuous Performance Test (CPT) 3-7 version (Halperin et al., 1991) has also been used to assess sustained attention. Stimulus, digit ranging from 0–9, displayed on a PC monitor personal computer (Pentium 150) using the Experimental Run Time System software (ERTS, version 3.28, Berisoft Cooperation, 1987-1999) in a quasi-random sequence. In this test participants are normally asked to press a response key whenever they believe that a 3-7 sequence has occurred. There were at least 10 practice trials to ensure that participants were familiarized with the task and the response pad. The number of correct responses and commission error are two of the measures more frequently recorded. Several variations of this task exist.

The Sustained Attention to Response Task (SART) (Robertson et al., 1997) is a similar computer test to assess sustained attention. In this task 225 single stimuli (25 instances of each of the nine Arabic numeric digits) are presented visually over a 4.3-min period. Each digit is presented for 250 msec., followed by a 900-msec mask of a symbol. Participants were

to respond with a key press to each digit, except on the 25 occasions when the digit "3" appeared, when they were to withhold a response. Participants used their preferred hand. The target stimuli were distributed amongst the 225 trials in a pre-fixed quasi-random fashion. Participants were asked to give equal importance to accuracy and speed in performing the task. Sensitivity of the SART has been shown to be impressive in patients with schizophrenia (Chan, et al., 2004 b). The total number of correct response was recorded.

Online Updating

This component requires monitoring and coding incoming information for relevance to the task at hand and then appropriately revising the items held in working memory by replacing old, no longer relevant information with newer, more relevant information (Morris and Jones, 1990). This is different from the passive storage of information. More recently neuroimaing data also support this view by demonstrating dissociations in the areas required for relatively passive storage and active updating of information. The former function has been associated with premotor areas of the frontal and parietal regions whereas the latter function involves the dorsolateral prefrontal cortex (Stuss et al., 1994; Jonides and Smith, 1997).

Tests that are thought to tap into this system include the Letter-Number Span test (Gold et al., 1997), the Visual Pattern Test (Della Sala et al., 1999), and N-Back Test (Callicott et al., 1998). The Letter-Number Span test involves the auditory presentation by an examiner of a mixed series of alternating numbers and letters. The subject is requested to respond by first saying the numbers in order from smallest to the largest, followed by saying the letters in alphabetical order. For Visual Pattern Test, the stimuli consist of a number of boxes, which each can be filled or unfilled. Subjects are asked to attend to the location of the filled boxes and to indicate this after the stimulus has been removed form sight. Stimulus of increasing number of boxes is presented to subjects in successive order. Number of boxes correctly processed is recorded for performance. Similarly, N-back is the computer based test involving temporary holding of visual position of a particular number and then track react to the stimuli in different reverse span. Although the nature of the information that needs to be updated as well as the goals of the tests are rather different, all of them involve constantly monitoring and updating information in working memory.

Switching and Flexibility

This component involves one's ability to switch between tests, operations, or mental sets. Similar terminologies like attention switching, task switching, shifting, or selective attention. The most well-known test of switching and flexibility is the Wisconsin Card Sorting Test (WCST) (Heaton, 1981) and its modified version (Nelson, 1976). However, it should be noted that the WCST has many processing subcomponents. The area of frontal lobe most likely lead to impaired performance on the WCST is the dorsolateral frontal region of either hemisphere (Milner, 1963). The perseverative error is used to assess the selective attention and flexibility.

A test, specifically designed in the theoretical framework of SAS, is called the Brixton Test (Burgess and Shallice, 1996b). This test is similar to the WCST and requires the subject

to switch between sets. A series of plates is presented to the subject, of each plate, one of the 10 positions is filled, but the position of the filled circle changes with each trial. The changes in position are governed by a series of simple rules that changed without warning, and the subject is charged with the test of predicting the filled position on each subsequent trial. Thus if the filled position has previously followed the sequence of 1, 2, 3, the subject is required to say that the filled circle on the next plate would be at position 4.

Another test of switching and flexibility is the Trail Making Test Part B (TMTb) (Reitan, 1955). In this test, subjects are first asked to trace a line joining in alphabetical order a series of letters distributed randomly across a sheet of paper (Trail A), and then to trace a line joining alternatively (or switching between) the letters of the alphabet and the numbers 1 to 20 in alphabetical or ascending order (Trail B).

Disinhibition

Disinhibition or inhibition involves one's ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary. As noted by Miyake et al. (2000), inhibition does not mean inhibition that takes place in typical spreading activation models or connectionist networks. Here, we rather narrow the term "inhibition" or "disinhibition" to the deliberate, controlled suppression of prepotent responses.

Tests that assess disinhibition include the second part of the Hayling Sentence Completion Test (Burgess and Shallice, 1996), Stroop Test (Stroop, 1935), and set of rule-breaking behaviours or commission errors observed in CPT, SART, modified Six Elements Test (SET, Wilson et al., 1996) and Multiple Errands Test (Shallice and Burgess, 1991). Hayling Sentence Completion Test Part B, the commission error of SART and rule-breaking behaviour counted in SET have all been shown to load on the disinhibition factor in a group of chronic patients (Chan et al, 2004a). On the other hand, the use of Stroop and related tests has also demonstrated to involve cognitive conflicting processes (Botvnick et al., 1999; Bush et al., 2000; Casey et al., 2000; Fan et al., 2002; Posner and Raichle, 1994). The Hayling Sentence Completion Test Part B (Burgess and Shallice, 1996) assesses the capacity to inhibit a habitual response. In Part B (inhibition section) participants are required to complete the sentence with a word that does not make any sense in the context of the sentence. In this case, participants have to inhibit a strongly cued automatic response and, in addition, to find an unrelated response. There are two types of errors that are usually scored in Part B of the hayling sentence completion test: not finding a completely relevant word and finding a word that is semantically related to the strongly cued word. The present study adopted the number of errors in part B as the dependent measure.

The Stroop Test (Perret, 1974) is another test often used to assess selective attention and flexibility. In this test each participant is requested to perform two tasks. The first "color task" requires the participant to read the words of color names, which was printed in colors different from the meaning of the words. The second "color-word task" requires the participant to read the printed color of the words. Two minutes were allowed for each task. The numbers of correct and incorrect responses are recorded. The color score and color-word score are calculated from the number of correct responses minus incorrect responses in the color task and the color-word task, respectively.

The number of commission error on the Sustained Attention to Response Task, the CPT, the rule-breaking behaviour of the Six Elements Test, the Multiple Errands Test as well as the Tower of Hanoi test are all also considered to measure disinhibition.

Attention Allocation and Planning

The attention allocation and planning component comprises of the total number of sub-task complete, total profile score of the SET, together with the profile score of the Tower of Hanoi (Humes et al., 1997). These tests and their derivatives are typical examples of assessing attention allocation and planning in schizophrenia (Shallice, 1982, 1988; Hutton et al., 1998; Chan 2001a, 2002; Chan et al., 2003; Chan et al., 2004a, 2004b). SET assesses strategy allocation on performing three sets of tasks (simple arithmetic, written picture naming, and dictation), each of which has two parts. Participants are required to attempt at least part of each of the six sub-tasks within 10 minutes, following the rule that they were unable to switch directly from a sub-task of one type to the counterpart of that type. The total number of sub-task completion was used as the strategy allocation score.

The Tower of Hanoi test (Humes et al., 1997) or London test (Shallice, 1982; Humes et al., 1997) are normally given to assess problem-solving and planning behaviour. This is a disk transfer task that includes a board with three equal-length pegs spaced equidistantly, and four wooden disks that are graduated in size. Participants are requested to solve a series of 12 problems. Each consists of six trials, with a maximum of 20 moves per trial, to solve each problem correctly. A problem had to be solved correctly in two consecutive trials for the participants to receive points and move onto the next problem. Scoring for this task is calculated by assigning points based on the number of trials required for two consecutive solutions: six points for trials 1 and 2; five points for trials 2 and 3 and so forth. This task has been applied successfully to discriminate patients with schizophrenia from those with head injuries and normal controls (Chan et al., 2004c). The category score of the WCST also assesses strategy allocation and planning components.

Clinical Rating, Everyday Life Simulated Tests and Subjective Complaints

In clinical practice, it is more feasible for clinicians to use neurological soft signs items (e.g., Cambridge Neurological Inventory, Chen et al., 1995) to screen out potential executive function deficits. Items like motor coordination, complex motor sequencing and disinhibition of mirror movement have been shown to have small to modest relationships to executive function components in schizophrenia (e.g., Chan and Chen, 2004a, 2004b). The data obtained from neuropsychological tasks may not represent the real life situation and may not be able to detect the true picture of any executive dysfunction in clinical groups. More complex multi-step tasks in unstructured environment or everyday life scenario may require more complicated series of responses to achieve, including goal and sub-goals setting, prioritization of sub-goals, triggering prospective memory to initiate sub-tasks when the conditions for them become ripe, and inhibition of irrelevant and inappropriate actions to different sub-tasks. Therefore, most of the conventional experimental tasks only tackle issues at the impairment level, but cannot reflect a true picture beyond the levels of disability and handicap. As

psychiatrists and psychologists, we need to pay equal attention to these purposes. This can be achieved through the assessment of everyday life simulated scenarios (e.g., Schwartz et al., 2002) and the use of supplementary information from questionnaires or checklists (e.g., Dysexecutive Questionnaires, Wilson et al., 1996; the Frontal Systems Behaviour Scale, Grace et al., 1999; Chiaravalloti and DeLuca, 2003).

Table 1. Classification of Executive Functioning Components and Related Neuropsychological Tests

Components	Tests	Level of assessment
Initiation To initiate action and verbal responses	**Tower of Hanoi or Tower of London** The planning time to initiate the first move of the disc **Trails Making Test and its derivatives** The number of correct items completed in Part A	Impairment and/or disability
	Verbal fluency test Semantic test:The number of exemplars generated Phonological test: The number of words generated starting with F, A, S	
Sustained attention To sustain and monitor ongoing response, whereas inhibit irrelevant responses	**Continuous Performance Tests:** The number of correct responses **Sustained Attention to Response Task:** The number of correct responses withhold to target stimuli **Monotone Counting Test and its derivatives:** The number of correct responses for a serial target auditory presented stimuli	Impairment and/or disability
Online updating To withhold online storage of information and to update incoming information for temporary manipulation in mind	**Letter-Number Span Test and related tests for online manipulation:** The total number of correct responses to manipulate the alternate sequencing of letter and number for semantic working memory span **Visual Pattern Test:** The total number of correct responses to complete the visual span of the filled grids **N-back:** The total number of correct responses to withhold one's action for the delayed visual stimuli	Impairment and/or disability
Switching and flexibility To inhibit and energize one's action and to shift between subtests	**Trails Making Test and its derivatives** The correct responses or reaction time to complete the alternating switching action between numbers and letters **Wisconsin Card Sorting Test (both full version and modified version):** The number of perseverative errors committed **The Brixton Test:** The number of perseverative errors committed	Impairment and/or disability

Table 1. Continued

Components	Tests	Level of assessment
Disinhibition To inhibit irrelevant responses in a behavioural term	**Hayling Sentence Completion Test:** The total number of errors in completing sentences of Part B (with irrelevant words) **Stroop Test and its derivatives:** The interference results from the inability to inhibit the semantically driven response **Continuous Performance Test and Sustained Attention to Response Task:** The number of commission error on target stimuli **Tower of Hanoi or London:** The illegal move of the disc violating the set criteria **The Six Elements Test:** The total number of rule breaks observed during the course of the task **Multiple Errands Test (Shallice & Burgess, 1991):** The total number of rule breaks observed during the course of the task	Impairment and/or disability
Attention allocation and planning To energize and monitor one's one intention to fulfill the optimal performance	**The Six Elements Test:** The raw score and the total profile score of the test **Tower of Hanoi or London:** The profile score to complete the test **Wisconsin Card Sorting Test (both full version and modified version):** The category score for completing the requested categorization ability **Brixton Test:** The total number of correct response for completing the task Multiple Errands Test (Shallice & Burgess, 1991): The total score for the whole task	Impairment and/or disability
Clinical Rating Planning, sequencing and disinhibition	**Cambridge Neurological Inventory (Chen et al., 1995):** Clinical rating for the assessment of the neurological soft sign such as motor coordination and disihibition	Impairment

Table 1. Continued

Components	Tests	Level of assessment
Simulated Everyday Life Tests	**Naturalistic Action Test (Schwartz et al., 2002):** The total profile score of the test **Dysexecutive Questionnaires (Wilson et al., 1996; Chinese version Chan et al., 2001a)** **Frontal Systems Behaviour Scale (Grace et al., 1999; Chiaravalloti & DeLuca, 2003)**	Disability and/or Handicap Disability and/or Handicap Disability and/or Handicap

METHODOLOGIES OF STUDYING FRACTIONATION OF EXECUTIVE FUNCTION IN SCHIZOPHRENIA

Test Oriented Approach

Test oriented approaches take a number of forms: comprehensive neuropsychological batteries referencing norms for comparison (e.g., Heaton et al., 1978; Bilder et al., 2000); specific executive function computerized batteries such as CANTAB (e.g., Elliott et al., 1998; Hutton et al., 1998); small studies of selected executive functions (e.g., Shallice et al., 1991; Nathaniel-James et al., 1996; Nathaniel-James and Frith, 1996; Evans et al., 1997; Marczewski et al., 2001; Chan et al., 2004a). The batteries may not fully cover all aspects of executive function and are expensive, while more selective studies are usually in small samples so the results may not generalise.

Design Methodology Oriented Approach

For those studies relying on design methodological approaches include those with traditional group-means analysis (Bilder et al., 1991, 1992, 2000; Hoff et al., 1992; Towsend et al., 2001; Addington et al., 2003) and others based on cluster-analysis (Gambini et al., 2003; Goldstein, 1990; Goldstein et al., 1998; Heinrichs and Awad, 1993; Hill et al., 2002; Seaton et al., 1999). The group-mean analysis provides quantitative data on the whole group of schizophrenic patients and accommodates the heterogeneous nature of clinical features and cognitive impairments in schizophrenia.

Cluster Analysis

Cluster analysis is classification of cases according to similarity of characteristics or features. Actually, it is used to unfold the natural grouping of neuropsychological deficits in schizophrenia (e.g., Gambini et al., 2003; Goldstein, 1990; Goldstein et al., 1998; Heinrichs and

Awad, 1993; Hill et al., 2002; Seaton et al., 1999). Cambini et al. (2003) implemented several tests of executive function to 81 schizophrenic patients and found three profiles of executive function, 1) a profile of good global frontal scores, 2) a profile of poor scores on Weigl Sorting Test and Word Fluency Test that reflected left frontal malfunctioning without dorsolateral prefrontal cortex, and 3) a pattern of poor score on perseverative error of Wisconsin Card Sorting Test reflecting dorsal lateral prefrontal cortex malfunctioning.

Studies also consistently revealed extensive heterogeneity among patients with schizophrenia but generally produce four- to five-cluster solution with satisfactory internal validity (Goldstein, 1990; Goldstein et al., 1998; Heinrichs and Awad, 1993; Hill et al., 2002; Seaton et al., 1999). These studies showed that cluster membership was only minimally accounted for by demographic considerations, notably age and education, or by a number of clinical variables including years of illness and hospitalization, number of hospitalizations, age of illness onset, and medication status. However, the limitation of cluster analysis is that cases will be classified even with random data and the resulting clusters do not guarantee the cognitively based membership will have differential executive attentional component deficits as *a priori* hypothesis. It also remains unclear as to whether cognitively based membership is related in any systematic way to the distinct pattern of clinical symptomatology of schizophrenia. These studies also do not adopt comprehensive tests based on the theoretical construct of supervisory attentional control. Therefore, the impact of supervisory attentional control or the fractionation of this cognitive process in schizophrenia and its relationship to clinical symptomatology of schizophrenia are not fully understood.

However, the limitation of cluster analysis is that, cases will be classified groups even cases with random data, and hence, it is unclear whether such classification relates in any systematic way to the distinct pattern of clinical symptomatology of schizophrenia.

Single-Case Study Design

The conventional single case study design provides a valuable opportunity for clinicians and researchers to examine the detailed profile of neuropsychological performances in a particular case. It allows us to study the strict phenomenon of double dissociation of neuropsychological performance, i.e., the identification of a pair of cases where one has lost function X but has a normal function Y while the other has the opposite pattern of disabilities. Shallice et al. (1991) adopted this notion to study the neuropsychological performances by examining both executive and non-executive functions in five chronically hospitalized schizophrenic patients. They found that all these patients demonstrated poor performance on a number of executive function tests differentially. There were at least three types of neuropsychological patterns among these cases, i.e., weakness in frontal functioning, weakness in overall cognitive functioning, and a perceptual deficit.

However, it should be noted that the direct replication of the findings from single-case study is declared impossible in neuropsychology and therefore the problem is nonexistent. Another main critique of this design is the small power of analysis when the hypothesis is not confirmed, i.e., negative finding out from a single case that is not representative enough to convince it is the “true” finding. Most recently, Crawford et al. (Crawford and Garthwaite, 2002, 2004; Crawford et al., 2003) developed several methods to improve the statistical inferential power of a single-case study design and to facilitate computation transformation of

data basing on single-case sample for neuropsychological test performance comparison with normative data. These methods therefore will serve as a potential useful tool in determining the actual performance of a particular subject being assessed by neuropsychologists in their clinical setting for research purposes.

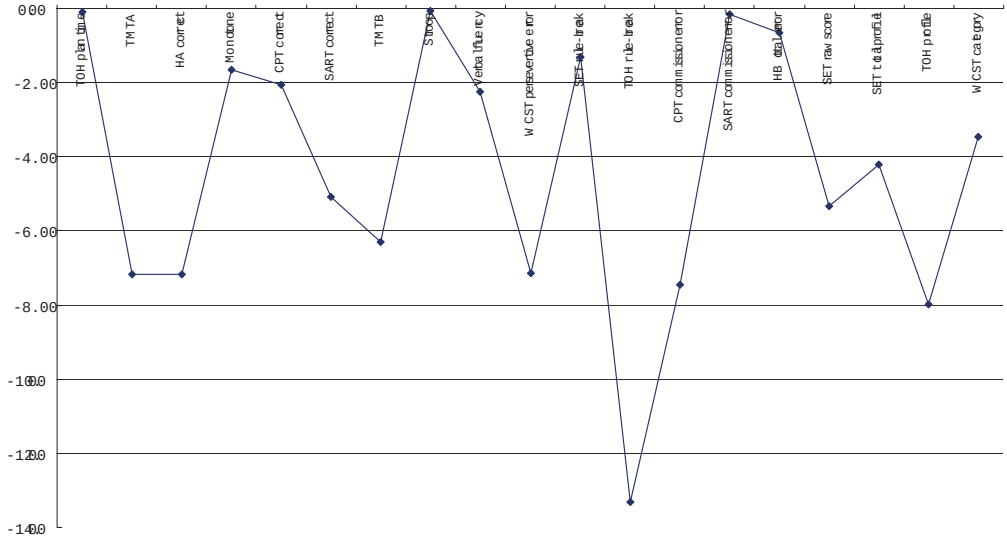
Multiple-Case Study Design

Given the advantages of theoretical relevancy and limitations of both the single-case study and conventional group-means analysis, a combination use of these methods may serve as another alternative to study the phenomenon of fractionation of executive function in schizophrenia (Kremen et al., 2004; Chan et al., 2006 a, b). In doing so, we may capitalize on the respective strengths of each method. On the one hand, we may appreciate the heterogeneity of within schizophrenia, which results in large differences between individuals with the illness in terms of both degree and kind of cognitive symptom manifestations, without losing the averaging artifacts inherent in using the group-means analysis to explore an illness with heterogeneous cognitive symptomatology. On the other hand, it reserves the sufficient statistical power of comparing the illness, as a group, to that of healthy controls.

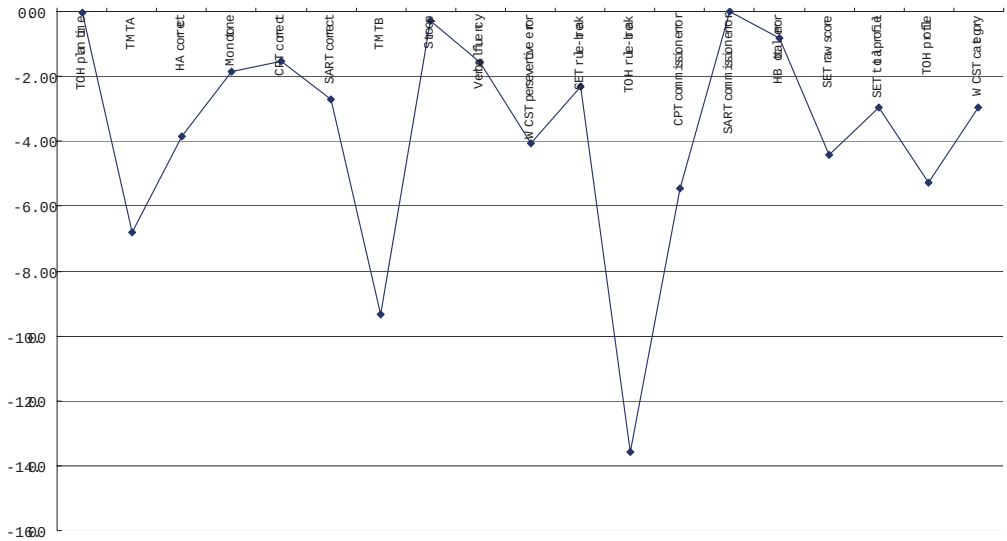
Convergent Evidence from a Trial of Cohort of Chronic Sample to Medication-Naïve Cases

Using the multiple case-study design, we (2006 a) explored whether the phenomenon of fractionation of executive functions existed among a group of patients with chronic schizophrenia. The SAS discussed above served as the theoretical framework of executive functioning components, namely initiation, sustained attention, switching/flexibility, disinhibition, attention allocation and planning. A total sample of 90 patients with chronic schizophrenia were recruited. Unlike the Shallice et al. 's original single-case study of using the lowest 10^{th} or highest 90^{th} percentile to classify patients into intact or impaired in the corresponding tests, we adopted a more lenient method by classifying those patients as having impaired performance with more than half of the tests assessed showing 1.5 standard deviations below that of the norms of the corresponding tests. For instance, if a patient showed impaired performance in three out of four parameters of a specific component he or she would be classified as having impaired performance in that particular component. The findings showed that there was a differential breakdown of executive functioning components in this clinical group (Table 2). 27.8% (n=25) demonstrated poor performance in all of the components whereas 5.6 % (n=5) exhibited intact/fair performance in all of the components. 18.9% (n=17), 16.7% (n=15), 21.1% (n=19), and 10% (n = 9) showed intact/fair performance in one component, two components, three components, and four components, respectively. Figure 1 shows the detailed profiling of these subgroups. The groups did not differ in education, gender, and duration of illness. However, the group showing impaired performance in all components demonstrated the most severe psychotic symptoms, after controlling for background intelligence, age and medication.

Group 1: Intact performance in one component



Group 2: Intact performance in two components



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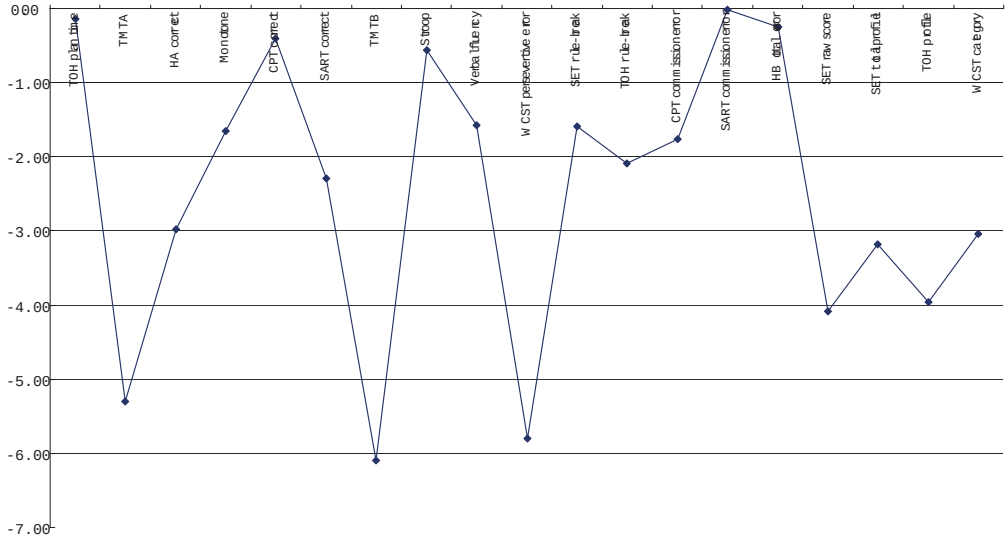
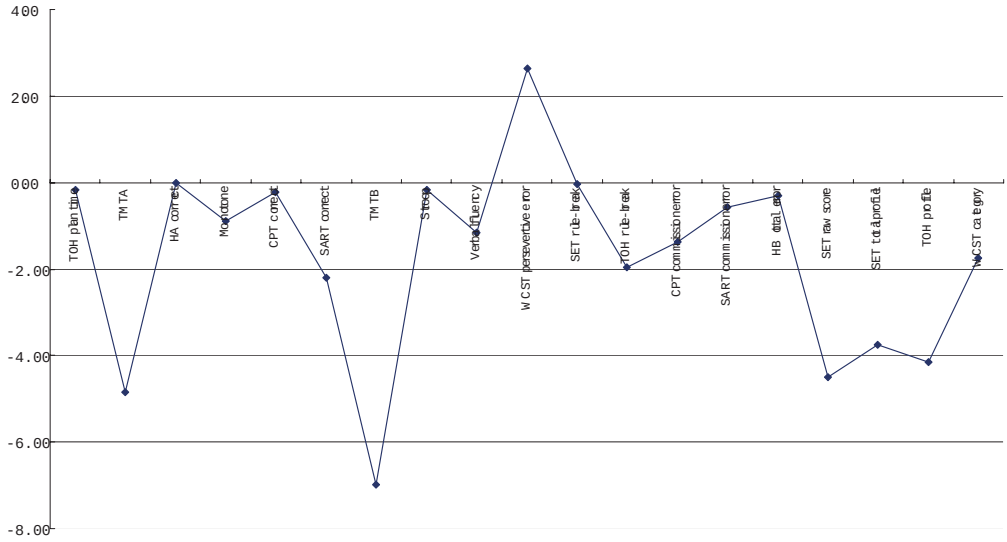
Group 3: Intact performance in three components



Group 4: Intact performance in four components



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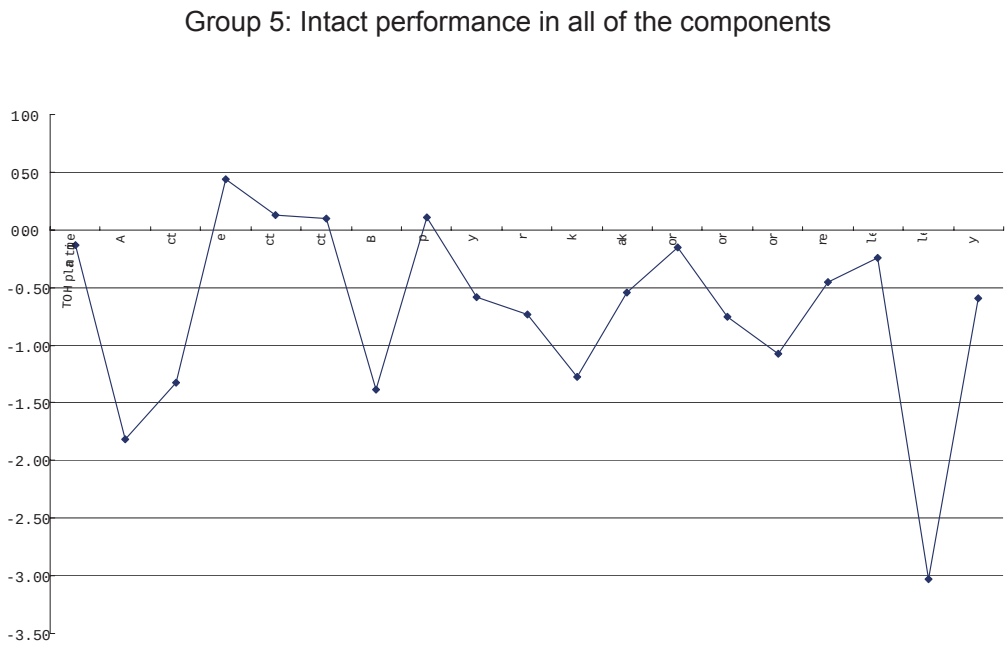

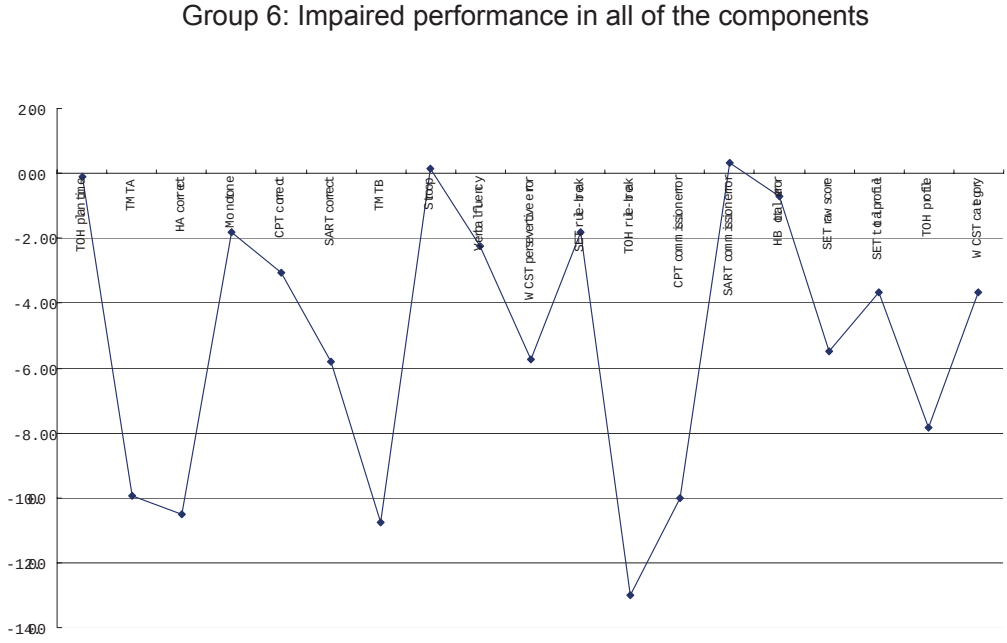

Figure 1. Differential breakdown of executive functioning performance in patients with chronic schizophrenia

Table 2. Fractionation of executive functioning components in patients with chronic schizophrenia

Groups	Executive attentional components		Number	Percentage
Intact in all of the components		subtotal	5	5.6%
Intact in one component	initiation		9	
	sustained attention		3	
	switching		1	
	impulsivity		3	
	attention allocation			
		subtotal	17	18.9%
Intact in two components	sustained attention and impulsivity switching and attention allocation initiation and switching initiation and sustained attention initiation and impulsivity	subtotal	1 5 6 2 15	16.7%
Intact in three components	initiation, sustained attention and impulsivity initiation, impulsivity and attention allocation initiation, switching and impulsivity initiation, switching and attention allocation sustained attention, switching and impulsivity initiation, sustained attention and allocation initiation, sustained attention and switching	subtotal	9 1 3 2 1 1 2 19	21.1%
Intact in four components	initiation, sustained attention, impulsivity and allocation initiation, sustained attention, switching and impulsivity	Subtotal	1 8 9	10.0%
Bad in all of the components		Subtotal total	25 90	100.00%

The differential breakdown of the executive functioning performance tends to be valid in first-onset medication-naïve sample. We (Chan et al., 2006 b) replicated and extended the same multiple case-study design in another first-onset sample and found very similar results. At the group-means analysis level, there was a general decline of executive functioning as well as other neurocognitive functioning in this first-onset group as compared to the healthy controls. However, when examined the detailed executive functioning profiles at the case-by-case level with the 1.5 standard deviation cut-off criteria as described above, we found that none but sustained attention component showed a deficit as compared to healthy controls. Figure 2 shows the comparison of differential breakdown of executive functioning in both the chronic and medication-naïve samples. There is a trend for patients to be compromised in higher proportion of executive functioning components as their duration of illness increases. Moreover, the majority of executive function components did not correlate with intellectual

functioning and memory impairment in a subgroup of medication-naïve patients without intellectual impairment. These findings suggest that first-onset medication-naïve patients show a specific pattern of executive dysfunction compared to healthy controls and patients with an established illness. This differential breakdown in executive functioning components, in both the chronic and medication-naïve samples, is unlikely to be an artifact of general intellectual decline or memory impairment in schizophrenia.

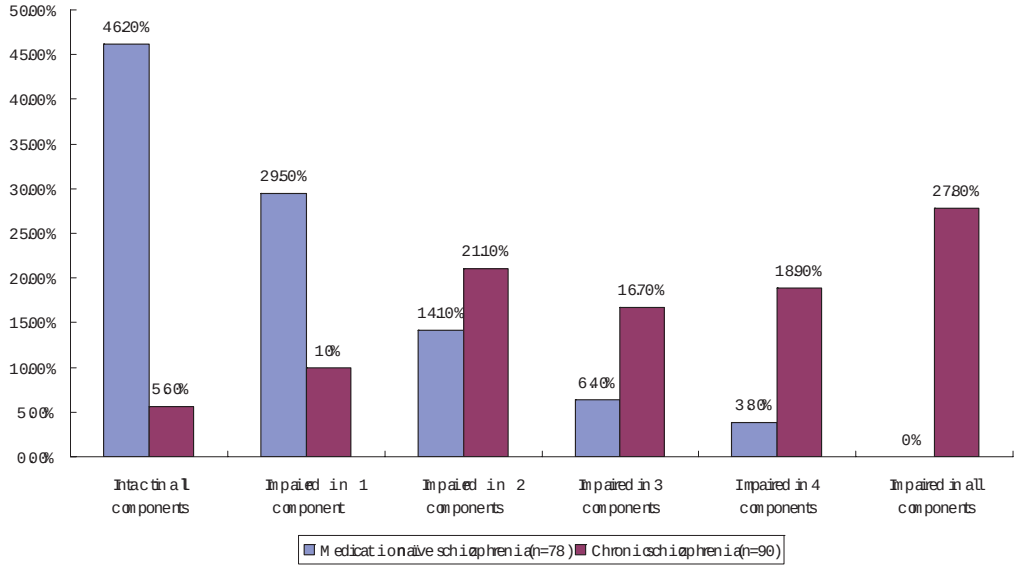

Figure 2. Comparison of differential breakdown of executive functioning components in patients with chronic and medication-naïve schizophrenia

RELATIONSHIPS TO CLINICAL, NEUROANATOMICAL AND NEUROLOGICAL MANIFESTATIONS

Executive Function and its Relationship to Clinical Symptoms

The diversity of clinical expression that hallmarks schizophrenia has prompted intense efforts to better define the disorder. Thus, Liddle (1987) conducted a series of studies that examined the segregation of schizophrenic symptoms in a homogeneous, in terms of chronicity, group of patients. Factor analysis revealed three clearly distinguishable syndromes: *psychomotor poverty* that includes symptoms such as poverty of speech, blunted affect and decreased spontaneous movement; *disorganisation* comprising formal thought disorder, poverty of content of speech and inappropriate affect; and *reality distortion* consisting of hallucinations and delusions. The psychomotor poverty syndrome comprises what is otherwise known as negative symptoms while reality distortion reflects positive symptoms. The third

syndrome, disorganisation, is the defining dimension of Liddle's model, and comprises symptoms that represent "fragmentation of mental activity" (Liddle, 1996). Liddle's three-syndrome model appears to be a robust one, since several studies using independent samples have produced similar patterns of segregation (Frith, 1992; Pantelis et al., 1991; Liddle and Barnes, 1990; Bilder et al., 1985). Though 4 or 5 dimensional models have also been suggested.

Liddle (1987) initially hypothesized that if the three syndromes of schizophrenic symptoms represent a manifestation of separate neuropathological processes, then the emergence of a dissimilar neuropsychological profile reflecting the derangement of the neural tissue sub-serving these functions is expected. In agreement with this proposition, some studies have shown that the neuropsychological profile of the psychomotor poverty syndrome is dis sociable from that of the disorganization syndrome in that the former is associated with deficits involving initiation and planning of mental activity as well as processing speed, while the latter is associated with an inability to inhibit inappropriate responses (Frith et al., 1992; Liddle and Morris, 1991). On the other hand most studies examining at the neuropsychological correlates of positive symptoms do not report often associations.

Neuropsychological studies examining verbal fluency performance, which is thought to require initiation and often generation of a strategy, of psychomotor poverty patients found a reduction in the number of words produced (Frith et al., 1992; Liddle and Morris, 1991) that persisted even after the potentially confounding effects of articulation speed were taken into account (Liddle and Morris, 1991). By adopting a more refined approach to assessing verbal fluency, Allen et al. (1993) demonstrated that the decreased generation of words is not because of a reduction in the number of words stored but rather due to a difficulty in accessing these words. More recently, Simon et al., (2003) found that verbal fluency (letters) was associated with negative, general and total score in PANSS while Brazo et al. (2005), who distinguished between primary and secondary negative symptoms, reported that patients with primary negative symptoms (presumed to be inherent to the pathologic process) were significantly more impaired than those with secondary negative symptoms (hypothesized to reflect a derivative transitory state) on categorical and formal fluency independently of the severity of positive symptoms and IQ levels.

Further support for an association between verbal output and negative symptomatology came from a study examining the amount of verbal production in a large sample of college students to assess if it was differentially associated with negative and positive symptoms of psychometric schizotypy (Tsakanikos and Claridge, 2005). Their results suggested that negative schizotypy among participants who scored one standard deviation above the mean on introvertive anhedonia was associated with decreased verbal fluency, while enhanced verbal production was correlated with increased levels of positive schizotypy.

The disorganization syndrome has also been found in some studies to be associated with a reduced production of words (Barrera et al., 2005; Kravariti et al 2005; Frith et al., 1992; Liddle and Morris, 1991). In a recent study that distinguished between intellectually preserved schizophrenic patients with and without formal thought disorder (FTD), Barrera et al., 2005 reported that even though the non-FTD patients were significantly impaired compared to controls on only the phonological fluency test, the FTD patients (characterised by disturbances in the structure, organization, and coherence of speech) performed worse on both the phonological fluency and the semantic fluency tests. Similarly, Kravariti et al 2005 found

that schizophrenia patients with disorganization were less accurate in semantic verbal fluency, fluency for categories such as "cities/towns", than those with negative symptoms.

It is possible that the verbal fluency deficits observed in both the psychomotor poverty and the disorganization syndrome to reflect distinct underlying abnormalities; it has been suggested, for example, that the association between word production and the disorganization dimension may reflect attentional deficits (Liddle, 1996). In support of this, performance on tasks assessing response inhibition – (Stroop, Trails B, and a modified version of the WCST) showed a differential performance between psychomotor poverty and disorganization syndromes in that only the patients with symptoms that loaded highly on the disorganization factor were found to be impaired (Liddle and Morris, 1991). Frith et al. (1992), using the Continuous Performance Test, also found an association between reduced ability to suppress inappropriate responses and the disorganization syndrome. In a study using un-medicated patients with recent onset schizophrenia, Daban et al., (2002) reported poor performance on the WCST among those experiencing disorganized symptoms supporting, once again, the idea that patients within the disorganized dimension have difficulties in inhibiting a learned response, despite negative feedback. This deficit was not found among people experiencing negative symptoms supporting a dissociable cognitive profile among these two symptom groups.

Differences between the psychomotor poverty and the disorganization syndromes were also found in a study by Brazo et al., (2002), which reported that whereas the deficit subtype, compared to the control group, performed predominantly worse on the Modified Card Sorting Test and on fluency, the group characterised by disorganized symptoms had the lowest scores on the Trail Making Test and on the Stroop test. Similarly, Pantelis et al., (2004) found that while patients with prominent negative symptoms characterised by apathy, lack of motivation, and impoverished affect and speech showed difficulties in representing information internally (as assessed in a spatial working memory task), the patients with disorganized symptoms showed progressive deterioration of attentional set shifting ability reflecting deficits in generalizing a learned rule and in shifting their attention in a flexible manner as required. Further indications supporting a differential performance between the two syndrome groups came from a study mentioned above by Barrera et al., 2005, which found that, compared to non-FTD patients and controls, patients with formal though disorder show deficits in aspects of executive processing assessed including planning, ability to remember to carry out an intention, inhibition of inappropriate responses, changing cognitive set and monitoring including correcting for errors.

Evidence that executive dysfunction is more related to symptom type than the underlying disorder also came from a study using both schizophrenia and bipolar patients (Kravariti et al, 2005). In this study, Kravariti and colleagues examined executive function in two populations of patients with schizophrenia, one with predominate symptoms of disorganization and the second with psychomotor poverty. In addition the authors evaluated two samples of patients with bipolar I disorder, the first experiencing mainly mania while the second depression. As had been predicted by the authors, symptoms, which were characterised by either an excess (disorganization/mania) or deficiency of function (negative symptoms/depression), were more related to executive ability than the diagnostic category itself. Accordingly, patient groups with excess exhibited increased error intrusion, while those with deficiency symptoms showed decreased verbal output compared to healthy controls and patients with the same diagnosis.

Nonetheless, the relationship between symptom dimensions and the cognitive processes comprising the executive system is not clear-cut. In a comprehensive review of executive function and clinical symptomatology, Donohoe and Robertson (2003) reported that impairments on tasks, such as the Wisconsin Card Sorting Test, the Stroop, and the Tower of Hanoi, are often associated with both negative and disorganized symptoms, and that these may reflect underlying deficits in the inhibition or the response monitoring aspects of executive function. However, the authors warned that as most studies do not use an approach that fractionates executive function into its component processes any firm conclusions remain difficult. Furthermore, a number of studies have not found associations between aspects of executive function and the negative or disorganized symptom dimensions (Simon et al., 2003; Joyce et al., 2002; Donohoe and Robertson, 2003 for a review). In addition, associations between poor performance on the WCST (Pantelis et al., 2004; C. Daban et al., 2002) or between Working Memory and selective attention (Daban et al., 2002; Simon et al., 2003) and the positive psychotic syndrome have also been found. Figure 3 shows the relationships between specific executive function components and clinical symptoms in a group of patients with chronic schizophrenia (Chan et al., 2006 a).

Figure 3a: Relationship of Initiation Components to Clinical Symptoms

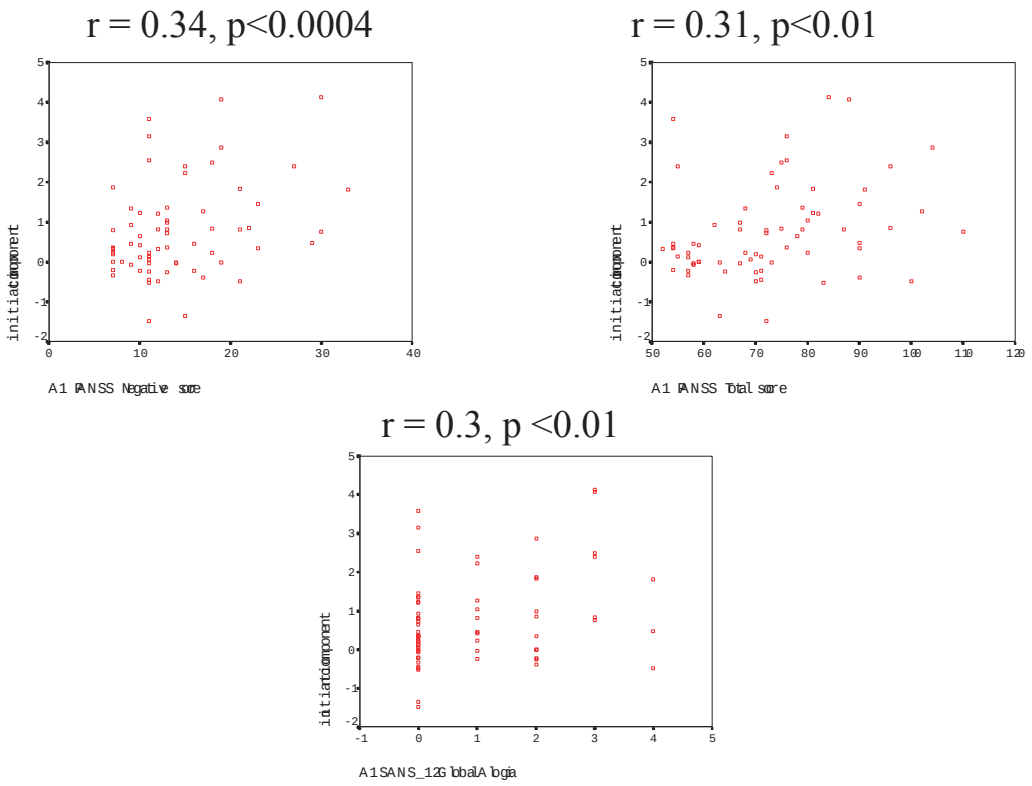

Figure 3. continued on next page.

Figure 3b: Relationship of Online Updating Component to Clinical Symptoms

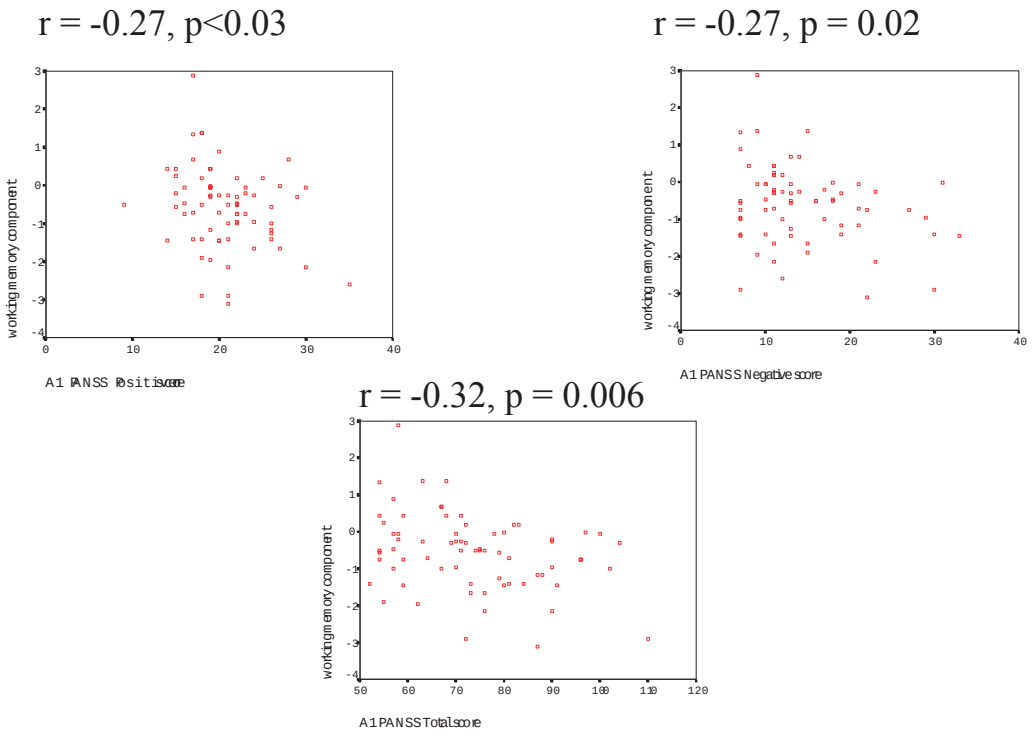

Figure 3c: Relationship of Switching and Flexibility Component to Clinical Symptoms

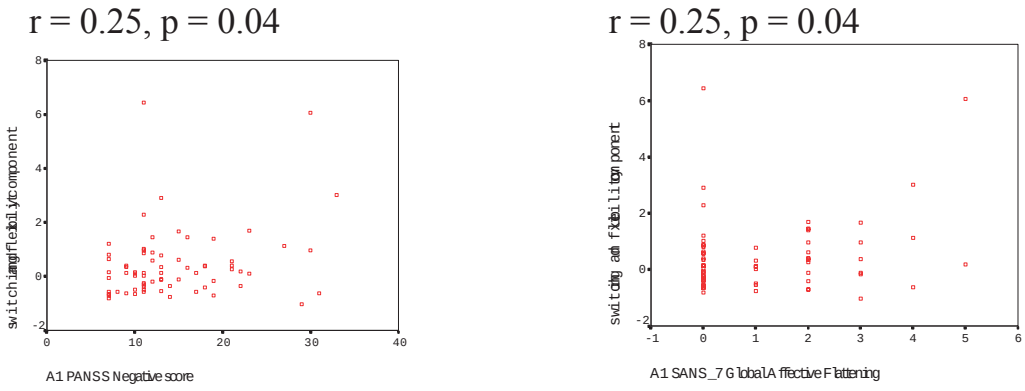

Figure 3. Relationships between specific components of executive function and clinical symptoms

Executive Function and its Relationship to Neuroanatomy

Executive dysfunction has been traditionally attributed to frontal lobe pathology; however the emerging picture suggests that executive processes recruit a network of prefrontal and posterior cortical and subcortical areas (see Elliott 2003 for a review). Within this framework, functional and domain specific fractionation of the prefrontal cortex, supporting a dissociable role of specific prefrontal regions in aspects of executive function, may be possible to some degree. However, evidence for the opposite (i.e. recruitment of the same regions by different aspects of executive function) has also emerged (Elliott, 2003).

The relationship between brain structure and cognitive function, including executive processing, in schizophrenia has been extensively reviewed by Antonova et al., (2004), and the interesting reader is referred to this paper for a detailed account on the issue. Briefly, Antonova et al's review, which focused on a regions of interest approach, suggested that executive dysfunction in schizophrenia might be associated with a distributed network of structures apart from the prefrontal cortex. In particular, after reviewing the evidence these authors suggested that identification and categorization of information might be particularly associated with the volumes of the parahippocampal gyrus and the superior temporal gyrus, while strategy generation and rule acquisition is more related to the integrity of the striatum. Suppression of pre-potent responses, on the other hand, might be more dependent on the integrity of the anterior hippocampus, the anterior cingulate and possibly the thalamus. Whether schizophrenia is characterised by different function/structure relationships compared to controls has been studied extensively. Even though results are inconsistent most studies have found differential function/structure relationships in patients compared to controls. For example, a recent study on patients experiencing their first episode of schizophrenia found that the normal association between cerebellar volume and cognitive function, including in executive function, was absent in patients with schizophrenia (Szeszko et al., 2003). Similarly, in a study examining the cerebral correlates of intelligence, memory and executive processing, Toulopoulou and colleagues (2004) reported associations between spatial working memory and lateral ventricles in patients only, while no such association was found in controls.

Clearly, in some instances lack of an association can be explained on methodological grounds. For example, the more the variability in any two different measure scores (e.g. brain volumes and neuropsychological scores), the greater the possibility of detecting a stronger correlation assuming, of course, that there is one in the first place. Thus often a lack of correlation may be due to a lack of variability in scores within a sample. Variability of scores, in turn, in the case of neuropsychological assessments for example, can be related to the test's psychometric properties. If a test is relatively difficult, for example, we would expect to find more variability of scores in the control group, with most patients possibly showing a floor effect (see also Antonova et al., 2004). In this scenario the controls are likely to show an association between the cognitive scores with the brain region under investigation, while the opposite is expected for the patients.

Differential relationships among male and female patients with schizophrenia have also been found (Antonova et al., for a review). For example Szeszko et al., (2002) found that worse executive and motor functioning correlated significantly with smaller anterior hippocampal volumes in males, but not female patients, suggesting that men may have more pronounced frontolimbic system abnormalities.

In addition to studies taking a region of interest approach, where the associations between specific brain volumes and aspects of executive functioning are examined, studies using functional neuroimaging, which sheds more light on the brain networks involved in executive function, have also been conducted. Most of these studies have found a differential pattern of activation in patients when compared to healthy volunteers. In a study, for example, looking at planning ability using the Tower of London task, Rasser et al., (2005) while reporting predominantly bilateral prefrontal and parietal, high frontal and dorsolatelar prefrontal, and left occipital activation in healthy controls, in patients the hemispheric dominance pattern was either diminished or reversed. In particular Rasser and colleagues found that patients had decreased cortical activation in response to increasing task demands in the right superior temporal gyrus. Furthermore, the authors found that reduced regional gray matter was associated with reduced left-hemispheric prefrontal/frontal and bilateral parietal BOLD activation in the patients, all of which were experiencing their first episode of schizophrenia.

Reduced language lateralization of the frontal cortex with schizophrenia patients showing more bilateral activation compared to healthy controls during a verbal fluency test (Weiss et al., 2004) suggest that the differential activation pattern in the areas recruited by patients compared to controls is found in other areas of executive function in addition to planning ability. In another study also looking at activation in response to a word fluency task, Boksman et al., 2005 showed that, compared to healthy controls, drug naïve patients with schizophrenia exhibit reduced activation in the right anterior cingulated and prefrontal regions. When the authors examined the psychophysiological interactions between the right anterior cingulated and other parts of the brain, a localized interaction was found with the left temporal lobe in healthy controls, while in patients a widespread non-specific interaction emerged. A third recent study also on verbal fluency by Fu et al., (2005) suggested that while schizophrenia is associated with impaired prefrontal function, its manifestation, however, depends, first, on whether patients experience active psychosis as opposed to being in remission, and, second, on the level of task difficulty, with the higher the difficulty level showing the more brain activation.

The issue of whether abnormal activation is the sign of brain pathology or the result of poor performance has been also the subject of a study by Jansma et al (2004) to a different aspect of executive processing to the ones reviewed above, namely working memory. Jansma and colleagues examined activity in the working memory brain network at different levels of task difficulty using a four level spatial N-back task. Compared to healthy controls the patients showed peak activation of the areas implicated in working memory at a lower processing load. Interestingly, increasingly poor performance in patients was associated with normal activity increases in the dorsal lateral prefrontal cortex (DLPFC), bilaterally in the inferior parietal cortex and in the anterior cingulated, with increasing task demands. However, compared to healthy volunteers the patients' activity dropped in the DLPFC at the third level of difficulty showing once again a differential activation compared to controls.

Increases in working memory load increasing brain activity in patients with schizophrenia was also found to some extend in a study by Perlsein et al. (2003). However, schizophrenic patients differed from healthy volunteers in that they showed lesser increases in magnitude in the right dorsolateral prefrontal cortex region during high working memory demands. This study also demonstrated that prefrontal cortex mediates not only deficits in working memory but also is involved to suppression of prepotent responses suggesting that both cognitive processes engage overlapping cortical networks. Overriding prepotent

responses also showed lesser magnitude increases in the right dorsolateral prefrontal cortex compared to controls. Nonetheless, studies showing the same pattern of activation in both patients and controls also exist. Hence Monoach et al., (2005) reported intact hemispheric specialization for spatial and shape working memory on schizophrenia with both patients and controls showing a relative hemispheric specialization in ventrolateral PFC for spatial (right) and shape (left) working memory. This was even though the patients failed to show equal levels of performance to that of controls.

In a study, that preselected patients on the basis of good performance on a selective attention test, as measured by a verbal stroop task, Weiss and colleagues (2003) found that patients who perform relatively well on a task showed increased activity across multiple areas of the brain, including dorsolateral frontal cortex and anterior cingulated. Thus patients appear to recruit more prefrontal areas to achieve similar levels of performance to that of controls making the authors to suggest, as have other investigators before, that task performance may be an important factor that could play a confounding role in the interpretation of the functional neuroimaging findings.

In summary, all aspects of executive processing in schizophrenia appear to be mediated by a network of cortical and subcortical structures in addition to prefrontal cortex. Variations in brain activation in schizophrenia are common when compared to controls but unless we match for level of performance interpretation of the findings are difficult.

Executive Function and its Relationship to Neurological Assessment

Neurological soft signs (NSS) are minor neurological indicators of non-specific cerebral dysfunction and contrast with hard neurological signs, which are indicative of localized brain deficit. As presence of focal neurological brain dysfunction is an exclusion criterion for a psychiatric diagnosis, studies of neurological abnormalities in schizophrenia have focused on neurological soft-signs (Cuesta et al., 2001). These involve complex motor coordination and sequencing, right and left discrimination, developmental reflexes and sensory integration. Patients with schizophrenia, including, even those with first episode psychosis, show an excess of NSS in both sensory and motor neurological domains (Dazzan and Murray 2002).

Recently a small number of studies have started looking at the relationship between neurological soft signs and cognitive dysfunction in an attempt to identify a common neurobiological process that underlies both of these indexes of brain function in schizophrenia. In a study exploring the relationship between executive function and neurological features on chronic schizophrenia, Chan and Chen (2004) found associations between executive function and neurological signs after adjustment for the confounding effects of age, education, and illness duration. In this study the action/attention inhibition factor, comprising items on error commission and rule breaking score, was significantly correlated with motor coordination. A non-significant trend for a correlation between the same factor and sensory integration and disinhibition also emerged as did inverse associations between the output generation factor, comprising items on initiation and generation response, and sensory integration and disinhibition. All suggesting that neurological signs are particularly closely related to impairments in certain aspects of executive functions. In another study, which separated patients into good and poor performers based on their performance on the WCST, those scoring poorly showed a greater incidence and severity of

subtle neurological alterations in general and in the sequencing of complex motor acts in particular (Bersani et al., 2004). This would indicate that a common neurobiological dysfunction could mediate both executive function impairments and subtle neurological abnormalities. Similarly, Das and colleagues (2004) showed that those patients in the high NSS group had greater impaired cognitive function, including in IQ, executive function, memory, attention, psychomotor ability than those in the low NSS group. Furthermore, even though both groups showed significant improvements on cognitive function followed administration of atypical antipsychotics over a 6 month period, the low NSS group exhibited more improvement suggesting to the authors that the presence of high NSS in schizophrenia patients impedes the improvement in cognitive function with atypical antipsychotics treatment.

As the presence of antipsychotic medication may confound the results, studies on medication free patients are particularly valuable. Further support for the association between neurological soft signs and cognitive function came from a study on 86 neuroleptic naïve first episode patients with psychosis (Sanders et al., (2004). Assessments comprised a reliable subset of the neurological evaluation scale (rNES) and tests of attention, executive function, memory and current/premorbid intelligence. Principal components analysis of the rNES suggested that there were two main factors underlying the neurological assessments. Of these, the cognitive-perceptual factor, consisting of more cognitively demanding perceptual tasks, showed stronger correlations, than the second factor, consisting of repetitive manual motor tasks, to neuropsychological measures including the WCST and verbal fluency. Nonetheless, even though the associations were significant the extent of these relationships is moderate indicative of shared variance in the range of 40% to 50%.

CONCLUSIONS

The extensive review of the findings on executive function, clinical, neurological and neuroanatomical manifestations suggests that there are modest to moderate relationships between these variables in schizophrenia. The sophisticated fractionation of executive functions into specific components further provides detailed information illustrating these relationships. We hope that these findings will facilitate us to build up a link between specific executive function components to subtypes of clinical symptoms and neurological deficits in schizophrenia. In sum, recently a number of studies have started looking at the association between neurological soft signs and executive function and most of these studies, including those on medication-naïve patients, show modest correlations between these two indexes of brain function suggesting a common underlying neurobiological factor.

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Chapter 2

DEVELOPMENTAL MATURATION OF LANGUAGE CORTEX, THOUGHT DISORDER AND SCHIZOPHRENIA: A SELECTIVE REVIEW

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ABSTRACT

Thought disorder, a core feature of schizophrenia may stem from a dysfunction of the brain language network. Language and thought are interrelated brain functions that may share the same brain structures. Language function involves several brain regions that are implicated in schizophrenia; some of the brain abnormalities and subtle language, cognitive thought abnormalities appear well before the onset of psychosis supporting developmental origins of the etiology of schizophrenia in this network. In this manuscript, we review the extant literature in this field and propose a model of abnormal developmental maturation of a widespread network centered on the temporal lobe language association cortex as possible underlying mechanism of adolescent onset schizophrenia. Early developmental abnormalities of this network may underlie the susceptibility to schizophrenia and late maturational deviances may result in the emergence of thought disorder and psychosis during adolescence. Genes involved in language, the developmental maturation of language cortex, environmental factors such as obstetric complications, and other environmental stress such as substance use during developmental years may increase the odds of developing schizophrenia by altering the trajectory of development or interfering with the late maturation the brain. The proposed model combines the developmental theory, language abnormalities and in vivo neurobiology.

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INTRODUCTION

According to the neurodevelopmental theory of schizophrenia, the brain abnormalities may result from genetic influence on brain development, pre or perinatal injuries leading to the disruption of long term brain development, a deviation in the developmental maturation of the brain during adolescence, or a combination of these factors. Support for a developmental etiology comes from several lines; a) a lack of evidence for a degenerative pathology, b) common onset of the illness during young adulthood, and c) occurrence of minor physical, neurological, cognitive and behavioral abnormalities long before illness onset. Although this model has gained wide acceptance, direct evidence is limited because such evidence should come from prospective long-term follow-up studies from birth to the age of onset as retrospective studies may not be reliable, non specific and misleading. Considering this, interest in schizophrenia research has seen a recent 'shift to the left' from chronic patients to first episode patients and to individuals at risk. Prospective high risk (HR) studies using genetic, neurobehavioral and clinical high risk strategies can be cost effective and unbiased. Although the high risk studies are not new, older studies have been generally exploratory. These studies have identified a variety of cognitive, behavioral and biological markers that indicate vulnerability to schizophrenia but specific and sensitive biobehavioral markers that can distinguish those at risk and help predict who will develop schizophrenia have been elusive. In addition, these HR studies can also shed more light in to the nature of the neurodevelopmental pathophysiology of schizophrenia.

Investigations of premorbid cognitive markers relevant to schizophrenia and related brain changes during development pose several challenges. Ideally, well established biobehavioral markers of schizophrenia should be employed in high risk studies, but such a marker; a cognitive test, a brain region, or a neurotransmitter that is pathognomonic of schizophrenia has not been well characterized (e.g. Plaques for Alzheimer's disease). First, quantifiable cognitive behavioral traits of the schizophrenia endophenotype need to be characterized (e.g. blood pressure for hypertension). Second, the brain regions and biochemical markers specifically related to both the baseline cognitive measures and psychosis need to be ascertained. Third, maturation of these cognitive and neural markers during the critical period of age of risk should be studied in a cost effective manner. Although this appears daunting, early indicators from high risk research are promising, and in this paper, we have reviewed the current literature and made an attempt to explain the relationship between childhood receptive language abilities, adolescent maturation of critical thinking, developmental maturation of language related cortex in the temporal lobe and their relevance to schizophrenia. We propose that a developmental dysmaturation of the superior temporal gyrus along with a widespread network involved in language perception may play a role in the neurodevelopmental etiopathology of schizophrenia.

IMPAIRMENT OF THOUGHT AND LANGUAGE IS A CORE FEATURE OF SCHIZOPHRENIA

Historically, thought and language disturbances have been central to the conceptualization of schizophrenia. Bleuler considered thought disorder to be the

pathognomonic symptom of schizophrenia (Bleuler '11). Thought disorder is believed to occur early and persist over the course of the illness independent of psychotic episodes (Marengo and Harrow '97; Schultz et al. '97; Asarnow '99). Modern factor analytical studies of symptoms have consistently found thought disorders to be a separate factor from positive and negative symptoms of schizophrenia (Schultz et al. '97). Recent neo-Bleulerian models of schizophrenia propose a misconnection of neural circuits (networks) involved in thought processes resulting from a faulty development. Andreasen et al proposed that a disruption in the coordinated or synchronous functioning of the cognitive brain functions results in schizophrenia symptoms (Cognitive Dysmetria) (Andreasen et al. '98). Another neo-Bleulerian approach attempts to explain disorganization of thought and language disorders occurring due to a deficit in the integration of contextual information (noted as 'dissociation' by Bleuler), supported by semantic priming (semantic associational memory) studies (Hardy-Bayle et al. '03).

Human beings are believed to be born with an innate ability to form thoughts, at least simple ones but use the language skills for complex thinking (Soja et al. '91; Spelke '00). T.J. Crow hypothesized that 'schizophrenia is the price humans pay for language' and proposed that a failure in the hemispheric lateralization of the language may result in schizophrenia (Crow '97). In a recent review of language abnormalities of schizophrenia, Covington et al concluded that thought disorder represents a major linguistic disturbance in schizophrenia, along with 'dysphasia like' impairments such as clanging and neologisms known as schizophasia (Covington et al. '05). They also believe that the genetic susceptibility for schizophrenia may lie within the genetic endowment that makes human language possible. In a detailed review of speech disorder in schizophrenia, DeLisi demonstrated that deficits in human aspects of language are common in schizophrenia, specifically the amount of complexity in sentences. She demonstrated that this deficit runs in the families of patients and concluded that such a language deficit may be related to the genetics of schizophrenia (DeLisi '01). Language abnormalities and thought disorders are found to occur in first degree relatives of patients with schizophrenia spectrum disorders and discordant twins supporting the possibility of a common genetic cause (Shenton et al. '89; Hetherington et al. '94; Docherty '95; Gambini et al. '97; Kinney et al. '97; Prost et al. '97; Docherty et al. '98; Docherty and Gordinier '99; Bartha et al. '00; Barker et al. '01; Tkac et al. '01). Considering these, we believe that studying development of thought, language and related brain regions may help understand the developmental origins of schizophrenia.

LANGUAGE ABNORMALITIES MAY PREDICT FUTURE ONSET OF SCHIZOPHRENIA

Evidence supporting developmental language abnormalities to precede or predict future onset of schizophrenia is accumulating from genetic at risk, clinical at risk and population based studies. The New York high risk study, a large prospective birth cohort study of offspring of mothers with schizophrenia (genetically at risk) support a developmental abnormality of language function as a trait-related vulnerability marker for schizophrenia among others such as attentional abnormalities (Erlenmeyer-Kimling et al. '00; Cannon et al. '02). The same group reported that thought disorder when present in childhood is predictive of

future occurrence of schizophrenia; from an interesting study of childhood home movies of adult schizophrenia patients rated blindly with the scale of Thought Language and Communication (Ott et al. '02). Hallett et al, reported that high-risk children showed deficits in binaural relative to monaural comprehension, impaired overall speech comprehension, and deficient speech sound perception compared to controls (Hallett et al. '86). They proposed that this might reflect an abnormal interhemispheric integration in the high-risk children, in whom the development of hemispheric specialization for language may be affected. Similarly, in a prospective study of young individuals evaluated in a referral clinic (clinically at risk), thought interference, disturbances of receptive language, and visual distortions were found to predict future schizophrenia, even with a probability of up to 91% (specificity: 0.85-0.91; false-positive predictions: 1.9%-7.5%). This study used the Bonn Scale for the Assessment of Basic Symptoms, which was found to have excellent negative predictive ability with a false negative rate of only 1.3 %, meaning schizophrenia almost always is preceded by a receptive language deficiency (Klosterkotter et al. '01).

In a population based study, Cannon et al reported that deficiencies in receptive language and cognitive development in children predicted future schizophreniform disorder in a large lifelong follow up study of children born in one calendar year (one year birth cohort n=1037) in Dunedin, New Zealand (Cannon et al. '02). This study showed that receptive language deficiency at the ages of 3 5 and 7 was able to distinguish individuals who develop schizophrenia from those who developed other mental illness or no mental illness, suggesting that developmental deficiency of receptive language is both sensitive and specific to predict future onset of schizophrenia. On the other hand, individuals with developmental language disorders have been found to have increased risk of developing schizophrenia related psychopathology. Recently Clegg et al reported from a follow up study of men with receptive developmental language disorder that they exhibit significant deficits in theory of mind, social adaptation difficulties and increased risk of psychiatric disorder in adult life including schizophrenia (2 out of 17) and score high on schizotypal personality questionnaire compared to comparison subjects (Clegg et al. '05). Thus, there is considerable evidence for the language system and related genetic and developmental mechanisms to be involved in the pathophysiology of schizophrenia well before the illness onset.

TEMPORAL CORTEX PLAYS A CRITICAL ROLE IN THOUGHT AND LANGUAGE DYSFUNCTION

The brain regions involved in thought process are not well understood but thought and language are considered to be functions of the same brain network (Glucksberg '88) and there is abundant evidence for the involvement of language association cortex in the thought disorder of schizophrenia. The Superior Temporal Gyrus (STG), typically larger on the left in majority of the people, includes the Heschl's Gyrus, planum temporale and most of receptive language cortex (Wernicke's area) and is believed to be a major anatomical substrate for speech, language and communication (Pandya '95). Neurological injuries to STG resulting from epilepsy, stroke or tumors cause disturbances of thought, hallucinations and delusions similar to schizophrenia (Taylor '75; Filley and Kleinschmidt-DeMasters '95). It is believed that the primary auditory cortex plays a role in the discrimination, interpretation, or self-

monitoring of auditory input, both internal and external, and the auditory association areas are involved in integrating the auditory or language input with stored memory, and other somatosensory input (Pandya '95). In the fifties, during experiments done in preparation for epilepsy surgery, Penfield observed psychotic symptoms with electrical stimulation of STG (Penfield and Perot '63). Interestingly, they demonstrated auditory hallucinatory experiences upon stimulation of the anterior STG and detailed, at times unclear and disorganized thoughts arising by stimulation of the posterior STG which contains auditory association and receptive language areas. STG has wide connections to medial temporo-limbic areas, including the hippocampus, amygdala, entorhinal cortex, neocortical association areas in prefrontal and parietal cortices, and the thalamus. Though not well understood, the wide and complex connections seem to integrate these brain regions and coordinate information processing and thought.

Not surprisingly, STG remains as one of the widely studied structures in the brain in schizophrenia, especially with the advent of modern neuroimaging techniques. Volume reduction of the STG in schizophrenia has been widely replicated and such a reduction appears to be mostly from gray matter, specific to schizophrenia, present at illness onset in drug naïve patients and such a reduction in volume has been found to be negatively co-related to thought disorder (table 1) (Barta et al. '90; Shenton et al. '92; McCarley et al. '99; Rajarethinam et al. '00; Shenton et al. '01). Similarly, reduction in the activation of STG during language related tasks and semantic memory tasks in thought disordered patients have been noted by functional imaging studies (Kircher et al. '01; Kircher et al. '02; Kubicki et al. '03). In addition, language functions such as semantic comprehension (Rodriguez-Ferrera et al. '01) and semantic association (Barrera et al. '05) have been found to be impaired in patients with thought disorder. Thus, it is evident that brain language areas are involved in the pathophysiology of schizophrenia and recent reports suggest that these areas may be involved before the onset of the illness during developmental years.

TEMPORAL LOBE ABNORMALITIES MAY PRECEDE THE ONSET OF SCHIZOPHRENIA

From an ongoing high risk study, we examined the volumes of STG in a group of HR subjects (non psychotic offspring of schizophrenia patients) and found that the STG is significantly smaller bilaterally than comparison subjects. We also found that both groups show age related changes in the volume of the STG which reaches a maximum size (compared to the whole brain) at the age of 24-15 followed by a significant reduction (figure 1). Such a reduction in the left STG of the HR subjects was significantly more pronounced than comparison subjects (Rajarethinam et al. '04). Our understanding of normal brain development as well as development in pathological conditions is limited. Brain maturation and gray matter changes continue into late teen years and are reported to be nonlinear with temporal lobe gray matter volume peaking about the age of 16 followed by steady reduction to reach adult size (Chugani '98; Chugani '98; Giedd '04). Such a reduction following the peak in the volume is thought to be due to programmed elimination of synapses. From the Edinburgh high-risk study, Johnstone et al earlier reported that temporal cortical volume loss among HR relatives (Johnstone et al. '02) and also found an exaggerated gray matter loss in

the superior temporal gyrus preceding in individuals who later developed schizophrenia (Job et al. '05). These studies indicate that a reduction in the volume of STG is associated with the susceptibility for schizophrenia and such an abnormality may be mediated by genetic influence. Further, they suggest that worsening of this abnormality or an abnormal maturation among those at risk may lead to full blown psychosis and schizophrenia. These abnormalities may correspond to the receptive language abnormalities seen in these at-risk individuals. It is possible that such a predisposition may undergo an abnormal maturation during adolescence that result in thought disorder, psychosis and schizophrenia.

Table 1 List of Studies involving Superior Temporal Gyrus in schizophrenia. Functional MRI, PET and SPECT studies are not included

Authors and year	n patients/ controls	Findings	Comments
Anderson et al, 2002(Anderson et al. '02)	16/15	Bilateral STG volume reductions correlating to negative symptoms	
Barta *et al.,* 1990(Barta et al. '90)	15/15	Small anterior/middle STG negatively correlated to hallucinations	All male subjects.
Barta *et al.,* 1997(Barta et al. '97)	11/18/12 Late life schizophrenia/ normal older adults/Alzheimer's	Schizophrenics had smaller anterior STG Alzheimer's disease patients did not.	
Bryant et al, 1999(Bryant et al. '99)	36-23/19-18 (M-F)	Left STG volume reduction only in male subjects	Data analyzed for sex differences
Buchanan et al, 2004(Buchanan et al. '04)	44/34	NO difference in STG	
Casanova *et al.,* 1990(Casanova et al. '90)	17/17	Gray matter abnormalities in the middle and posterior STG	
DeLisi *et al.,* 1994(DeLisi et al. '94)	85 drug naïve/ 40 normal controls.	No difference in STG	5 mm slices with 2 mm gap
Flaum *et al.,* 1995(Flaum et al. '95)	102/87	left STG volume inversely correlated with severity of hallucinations.	3 mm slices with 1.5 mm gap
Frangou *et al.,* 1996(Frangou et al. '97)	32 schizophrenics, 55 relatives and 39 unrelated normal controls	No difference in STG volumes	Relatives were older. Data was analyzed combining both sexes.
Hajek *et al.,* 1997(Hajek et al. '97)	10/10	less left STG gray matter in patients.	
Honea et al 2005(Honea et al. '05)	Meta analysis of voxel based morphometry studies (390 subjects)	The most consistent findings were of relative deficits in the left STG and the left medial temporal lobe.	

Table 2 Continued

Authors and year	n patients/ controls	Findings	Comments
Hirayasu *et al.,* 1998(Hirayasu et al. '98)	17 Schizophrenia 16 mood disorder with psychosis 18 normal controls	Smaller posterior STG in Schizophrenia and a negative correlation of posterior STG to thought disorder.	First episode drug free patients
Hirayasu *et al.,* 2000(Hirayasu et al. '00) (Hirayasu et al. '00)	20/22	Left Planum temporale volume reduction STG volume reduction	Drug naïve patients
Hollinger et(Holinger et al. '99)al 1999	8/10	Right STG volume reduction and bilateral posterior STG volume reduction	Left handed patients and controls
Jacobsen *et al.,* 1996(Jacobsen et al. '96)	21 patients (mean age 14.6 SD=2.1) who had schizophrenia by age 12 and 41 control children.	Larger STG. Right bigger than left in patients.	Right and left volumes were combined in the analysis.
Kasai et al, 2003(Kasai et al. '03)	15/14	Decrease in left STG over a year	
Kawasaki *et al.,* 1997(Kawasaki et al. '97)	25 male	No association between P300 amplitude or symptom severity and STG volume.	5 mm no gap
Kim et al, 2003(Kim et al. '03)	25/25	Smaller STG	Drug naïve patients
Keshavan et al., 1998(Keshavan et al. '98)	17/17	Smaller STG in treatment naïve patients	1 year follow up showed a reversal of findings.
Kulynych *et al.,* 1996(Kulynych et al. '96)	12/12	no difference	gray and white matter measured together
Kwon et al, 1999(Kwon et al. '99)	16/16	Left planum Temporale volume reduction	
Marsh *et al.,* 1997(Marsh et al. '97)	56/52	Bilateral less gray matter. Left Posterior STG volume inversely correlated to psychotic symptoms.	Unrelated to age of illness onset.
Matsumoto et al, 2001(Matsumoto et al. '01)	40/40	Right STG volume reduction in early onset schizophrenia	
McCarley *et al.,* 1993(McCarley et al. '93)	15/14	significant volume reduction of left STG in patients	Posterior STG volume reduction specifically associated with P 300 abnormalities.

Table 3 Continued

Authors and year	n patients/ controls	Findings	Comments
Menon *et al.,* 1995(Menon et al. '95)	20/20	Less STG gray-bilateral. Inverse correlation with delusions	
Pearlson *et al.,* 1997(Pearlson '97)	46/60 and 27 bipolar	Smaller left anterior STG in Schizophrenia. Larger right anterior STG in bipolar.	
Rajarethinam et al 2000(Rajarethinam et al. '00)	20/20	Smaller left STG correlating with thought disorder	
Rajarethinam et al 2004(Rajarethinam et al. '04)	29/27	*Smaller STG in non psychotic offspring of patients with schizophrenia*	
Reite *et al.,* 1997(Reite et al. '97)	20(11 males and 9 females/20(10 each)	Smaller STG in patients than controls	Female patients did not show this.
Shenton *et al.,* 1992(Shenton et al. '92)	15/15	Small posterior STG correlated with thought disorder	
Suddath *et al.,* 1990(Suddath et al. '89)	15 MZ twin pairs	no white matter difference	small hippocampus and large ventricles
Sullivan *et al.,* 1998(Sullivan et al. '98)	71 patients, 65 normal controls and 62 subjects with alcohol dependence	Less anterior STG gray matter in schizophrenia but not in alcohol dependence.	Sparing posterior STG gray matter loss from rest of the brain in alcohol dependence but not in schizophrenia.
Taylor et al 2005(Taylor et al. '05)	18 childhood-onset schizophrenia and 16 age- and sex-matched controls	*Larger right posterior superior temporal gyrus*	
Tune *et al.,* 1996(Tune et al. '96)	14/15	Smaller left STG and a negative correlation to striatal D2 receptor B max values	3 mm no gap
Vita *et al.,* 1995(Vita et al. '95)	19/15	No difference	5 mm slice with 2 mm gap
Woodruff *et al.,* 1997(Woodruff et al. '97)	42/43	No difference in STG volumes.	Patients had smaller temporal lobe. There was less association between STG and frontal lobe.
Zipursky *et al.,* 1994(Zipursky et al. '94)	22/20	Bilateral volume reduction of STG gray matter.	No correlation to symptom measures.

ADOLESCENCE IS A CRITICAL PERIOD OF HIGHER COGNITIVE DEVELOPMENT AND ACTIVE MATURATION OF TEMPORAL CORTEX

Piaget described adolescent cognitive development as 'formal operational stage' lasting from 11 to 15+ years (Piaget '55). During this time individuals develop thought and language skills necessary to solve abstract problems in a logical fashion and their process of thinking becomes more scientific. This also is the stage of cognitive development where identity formation occurs and thought processes become more formalized to operate in a logical and meaningful way and the belief system gets established. These cognitive skills correspond to some of the core psychological disturbances that occur in schizophrenia such as insight, delusions and thought disorder. A widespread brain network including temporal lobe language association cortex may play a role in the maturation of these cognitive functions which may in turn be involved in the pathogenesis of schizophrenia.

TOWARD AN INTEGRATIVE MODEL

From the above discussion it is clear that abnormalities of thought constitute the core of psychopathology in schizophrenia and are possibly mediated through the temporal lobe association cortex. There is accumulating evidence for developmental abnormalities of the temporal lobe cortex and related temporal lobe cognitive functions such as receptive language, language association and social behavior to occur long before the onset of psychosis in schizophrenia.

Considering these, we propose that the core pathology of schizophrenia includes thought disorder, which may result from a dysmaturation of language related brain structures in the temporal cortex. Genes associated with language development may be involved in this developmental and maturational process and may contribute to the susceptibility of schizophrenia. Environmental factors such as obstetric complications, psychological stress and substance use during developmental years increase the chance of developing schizophrenia by setting the trajectory of development or interfering with late maturation of the brain respectively. Heteromodal association cortex in the temporal lobe and its subcortical and cortical connections form the framework for normal development of thought. We believe that an abnormality in this area characterized by inadequate and improper synaptic connections resulting from a deviant development and maturation could lead to schizophrenia.

Reduction of volume in this area (STG) denotes susceptibility (genetic marker) (Rajarethinam et al. '04) and an abnormal maturation of STG during late teen years results in schizophrenia (Job et al. '05). Similarly premorbid receptive language deficiency may lead to difficulties in comprehension that involves semantic and linguistic processing (i.e. language association). A developmental failure of this may lead to thought disorder.

While stress factors play an additive role with genetic susceptibility, unknown biological and psychosocial compensatory mechanisms may play a protective role. For example, women have more distributed language association areas (right and left brains as well as non temporal cortices) which along with other sex differences may explain the late onset and better prognosis. It is also possible that the same 'network' or system when affected by a variety of homeostatic disturbances ranging from tumors, strokes, dementia to delirium may

produce psychotic symptoms. Although the role of temporal lobe is emphasized as a major language related area in the brain in this review, there is accumulating body of evidence and proposed hypotheses for the involvement of other brain areas such as frontal lobes, basal ganglia and medial temporal structures (Ullman '01; Lieberman '02; Ullman '04). These areas are also implicated in schizophrenia.

FUTURE DIRECTIONS

We believe that there are compelling reasons for further research in this area. While this model is supported by some preliminary data, there are many unanswered questions. Investigations using biological and behavioral markers of language pathology in genetic and clinical at risk population through the developmental and at risk age will be able to shed more light on this model. Study of high risk (both genetic and clinical at risk) individuals with a specific focus on language and thought and their neurological underpinnings may help identify specific developmental brain changes. Studies during the crucial age of maturation would lead to better understanding of normal maturation and maturational deviances that may undergo in this region that are relevant to schizophrenia. Improved cognitive tests that are more specific and cognitively well connected to the schizophrenia psychopathology are needed to study specific language deficiencies or other cognitive deficiencies that can help understand, identify and predict schizophrenia. Such advancement in knowledge will help primary and early secondary interventions. MR technology is a safe in vivo imaging method and should be exploited to study brain morphology, biochemistry, activation and connectivity. Although it involved radiation, Positron Emission Tomography (PET) may help study the dopamine D2 receptors in the temporal lobe and its role in the development and maturation during this age group. It is also important to study other interconnected language related brain regions such as hippocampus prefrontal cortex including DLPFC; techniques such as Diffusion Tensor Imaging (DTI) can help evaluate key language tracts such as the arcuate fasciculus.

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Chapter 3

SCHIZOAFFECTIVE DISORDER IN THE ELDERLY

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ABSTRACT

The concept of schizoaffective disorder was first introduced in 1933 by Kasanin, who described a group of patients with good premorbid functioning, sudden onset of illness, following a defined stressor and in some cases with family histories of mood disorders[1]. This review outlines the prevalence, clinical features, course and outcome of schizoaffective disorder. Treatment, including special considerations for late- onset illness and medical comorbidities, will be discussed. Finally, efficacy data and tolerability concerns will be presented for specific potential therapeutic agents.

Keywords: Schizoaffective, Elderly

PREVALENCE

Lifetime prevalence of schizoaffective disorder is believed to be less than 1%; its prevalence in the elderly has not been studied. A 1999 report on health resource utilization in a US state psychiatric hospital found that 68% of women aged 50 and above had a diagnosis

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of schizophrenia or schizoaffective disorder[2]. Ritchie et al, in a longitudinal population study of psychiatric disorders in France, noted a prevalence of 1.7% for psychotic disorders in non-institutionalized persons aged 65 years and above[3]. Gavrilov and Kirzhanova found an increased incidence of psychotic disorders with aging in comparison to non-psychotic disorders, where the incidence decreased with age[4]. Psychotic disorders were found to be 2.8 times more common that non-psychotic psychiatric disorders.

Increasing age appears to be a risk factor for psychosis in the elderly. Van Os et al found an 11% increase in incidence with each 5-year increase in age[5]. Henderson et al found a 6% increase in incidence over a 3.6- year period[6]. Risk factors for psychotic disorders in the elderly include the presence of cognitive impairment, living alone, being male, limited former education, social isolation, poor health and depressive symptoms[6]. Specific risk factors for schizoaffective disorder include a family history of psychiatric illness.

Laursen et al conducted a cohort study on all persons born in Denmark after 1952, their parents and siblings, who were followed up for a period of more than 30 years[7]. The study found that there was a high individual relative risk (RR) associated with developing schizoaffective disorder if the mother, father and sibling had a psychiatric illness. The highest RR was associated with parents and siblings having a diagnosis of bipolar disorder and/or a schizophrenia diagnosis. The study found that schizoaffective disorder was equally strongly associated with bipolar disorder and schizophrenia among first-degree relatives, with no significant difference between the RRs. These findings suggested that schizoaffective disorder is equally related to both disorders, because bipolar disorder and schizophrenia coexist in the families of patients with schizoaffective disorder with the same increased risk for schizoaffective disorder. It was concluded that schizoaffective disorder may be genetically linked to both bipolar disorder and schizophrenia, with schizoaffective disorder being a subtype of each or a genetic intermediate form. Gender may also be a risk factor for schizoaffective disorder, as females develop schizoaffective disorder more commonly than males[8].

CLINICAL FEATURES, COURSE AND OUTCOME

Clinical features of late-life schizoaffective disorder resemble those of the early- onset form of illness. Symptoms include psychosis, such as paranoia or bizarre delusions, as well as prominent mood symptoms. Depressive symptoms appear to be more common in older adults. Older patients tend to have more cognitive impairment, especially if negative symptoms are more prominent[9]. As is the case in unipolar depression, older adults with schizoaffective disorder may appear to have cognitive impairment – “pseudo- dementia”.

The course of illness, as in younger adults, is less deteriorating than in schizophrenia, but worse than in mood disorders[10]. Patients with schizoaffective disorder require hospitalization more frequently, have a more recurrent course and are less likely to achieve full remission than patients with mood disorders[11-13]. Mood- incongruent psychotic symptoms have poorer prognostic implications than mood-congruent psychosis[14-16]. Patients with predominant mood symptoms after one year of illness have a better outcome than patients with psychotic symptoms[17]. Post-hospital adjustment in patients with

schizoaffective disorder is poorer compared to those with major affective disorders, but similar to patients with schizophrenia[17].

No significant differences between the bipolar and depressive subtypes have been reported[18]. There are gender differences, with males having a poorer outcome than females[19].

TREATMENT

Special Considerations in the Treatment of Late-Onset Schizoaffective Disorder

1. Age-Related Physiological Changes

Several age-related physiological changes may influence treatment approaches in the elderly. These changes include reduced cardiac output (resulting in reduced renal and hepatic blood flow in comparison to younger age groups) , reduced glomerular filtration rate, possible reduction in hepatic metabolism, and increased fat content. These changes alter the absorption, distribution, metabolism and excretion of medications; which in turn may lead to prolonged drug effects and increased sensitivity to medications[20,21].(Table 1) Response to drugs in the elderly is also influenced by age- associated cognitive decline and changes in receptor- site activity[22].

In view of all these vulnerabilities, the recommendation for the starting dose of antipsychotic medications in the elderly is between one-quarter and one-half of the normal adult doses[23].

2. Medical Comorbidities

Most elderly patients have concomitant medical illnesses. Physical morbidity and mortality in psychiatric patients are reported to be greater than in the general population[23,24]. Medical conditions encountered more commonly in psychotic patients are respiratory, cardiac, digestive and neoplastic disorders .

Polypharmacy in view of medical comorbidities, age-related sensory changes and cognitive deficits that interfere with medication compliance, can all complicate the treatment of elderly patients[25].

3. Adverse Reactions to Antipsychotics

Elderly are especially sensitive to certain side effects of antipsychotic medication- the most significant ones are sedation, anticholinergic, cardiovascular, motor (extrapyramidal symptoms, akathisia and tardive dyskinesia) and metabolic changes[26,27,28].

Sedating effects may predispose elderly to falls and worsening of cognitive deficits. High-potency typical antipsychotics are less sedating than the atypicals[29]. Anticholinergic effects can lead to urinary retention, glaucoma, confusion, constipation or fecal impaction[23].

Cardiovascular effects are more common in the elderly, who have higher rates of cardiovascular morbidity[23]. The adverse effects include orthostatic hypotension, which is

more common with low-potency typicals and atypical antipsychotics, requiring low starting doses and slow titration, and QTc prolongation, among others.

Table I. Pharmacokinetic properties of atypical antipsychotics and implications for use in elderly patients[50-52]

Drug	Metabolite	$t_{1/2}$ (hrs)	CL_R and $t_{1/2}$ changes	CYP enzyme involved in metabolism (potential drug interactions)	Remarks
Clozapine	Norclozapine and clozapine N-oxide (very limited activity)	4-12	CL_R decreased	CYP1A2, CYP2D6, CYP3A4 (theophylline, digoxin, warfarin)	Reduce total daily dose in elderly
Risperidone	9-hyrody-risperidone (active)	20[a]	CL_Rdecreased; $t_{1/2}$ prolonged	CYP2D6 (inhibitor drugs such as quinidine)	Reduce total daily dose
Olanzapine	10-N-glucuronide,N-demethyl-olanzapine (inactive)	30[a]	CL_R decreased; $t_{1/2}$ prolonged	CYP1A2, CYP2D6[b] (theophylline, tacrine, fluvoxamine, carbamazepine)	Lower starting dose
Quetiapine	Multiple(main metabolite is a sulphoxide; generally inactive)	6[a]	CL_Rdecreased; $t_{1/2}$ prolonged	CYP3A4 (phenytoin, thioridazine)	Reduce total daily dose
Ziprasidone	Multiple(limited activity),benzisothiazole sulphoxide, BITP sulphone ziprasidone, sulphoxide s-methyl-dihydroziprasidone	7	unchanged	CYP3A4,CYP1A2 (carbamazepine, ketoconazole)	Lower starting dose
Aripiprazole	Dehydro aripiprazole-major metabolite- limited activity	75-94	CL_R decreased	CYP2D6,CYP3A4 (quinidine, fluoxetine, paroxetine, carbamazepine, ketoconazole)	Lower starting dose

a Mean values
b Minor route
CL_R = renal clearance; CYP = cytochrome P450; $t_{1/2}$ = elimination half- life.
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Motor side effects are more common in the elderly[30]. Extrapyramidal side effects (EPS) occur with lower doses than in younger patients. Antipsychotic- induced parkinsonism has been reported in up to 60% of elderly patients treated with typical antipsychotics[31]. Tardive dyskinesia (TD) is of concern as well in the elderly. Jeste et al found a cumulative annual incidence of 26% in patients aged 45 years and above-this is five to six times higher than that reported in younger patients[31]. Woerner et al found cumulative rates of TD in patients aged 55 years and above, of 25%, 34% and 53% after 1,2 and 3 years of antipsychotic treatment- these rates are three to five times those found in young patients[32]. Risk factors for TD include post-menopausal status, female gender, older age, previous exposure to antipsychotics, a history of alcohol abuse, adult-onset diabetes mellitus, a history

of ECT, higher daily antipsychotic doses and the presence of extrapyramidal symptoms early in treatment[33,34] . Waddington and Yousef postulate that higher rates of tardive dyskinesia may be explained by the neurodegenerative changes that occur with advanced age[33].

Motor side effects occur more commonly with first-generation antipsychotics. There is sufficient evidence that second- generation antipsychotics have a lower incidence of such adverse effects[23]. Clozapine may reduce tardive dyskinesia and dystonia in the elderly[23].

Metabolic side effects, including increase in serum glucose and lipids, weight gain, diabetes and ketoacidosis have been increasingly reported in recent publications, mostly with atypical antipsychotics[35]. A recent consensus panel of the American Psychiatric Association, American Diabetic Association, American Association of Endocrinologists and North American Association for Study of Obesity, have concluded that the available atypical agents have differential risk for metabolic disturbances, with clozapine and olanzapine at the highest and ziprasidone and aripiprazole at the lowest[35]. The panel also provided recommendations for systematic screening, surveillance and management of glucose metabolism and lipid abnormalities in persons receiving atypical antipsychotics. These metabolic side effects are of concern especially in elderly patients, who already have medical comorbidities. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[36] found olanzapine to be associated with greater weight gain, and increase in serum glucose and lipid levels compared to risperidone, quetiapine, ziprasidone and perphenazine. Ziprasidone was the only atypical antipsychotic associated with improvement in all metabolic variables. Atypical antipsychotics have a propensity for weight gain that can lead to worsening of arthritis and mobility problems.

Hyperprolactinemia induced by antipsychotics may worsen osteoporosis and may lead to severe fractures[22]. Elevated prolactin has been reported with risperidone.

4. Adverse Reactions of Antidepressants

Elderly patients are particularly predisposed to orthostatic hypotension and anticholinergic side effects from antidepressants. They are more common with tricyclics, which should generally be avoided in the elderly[22]. Newer antidepressants- selective serotonin reuptake inhibitors (SSRI's) , venlafaxine, bupropion, mirtazapine, and duloxetine appear to be better tolerated than monoamineoxidase inhibitors (MAOI's) and tricyclics. Among tricyclics, desipramine and nortriptyline are often prescribed in the elderly due to better tolerability.

5. Adverse Effects of Mood Stabilizers

General principles for treating bipolar disorder in the elderly are similar to those in younger patients. However, lower doses are recommended in view of the physiological changes with aging, the use of concomitant medications and the presence of concurrent medical problems that can affect the metabolism and clearance of psychotropic medications[22].

Elderly patients usually require lower lithium doses and in many cases low serum levels can be therapeutic. They are also more likely to develop cognitive side effects from lithium than younger patients[22]. Anticonvulsants also generally require lower dosing in older adult populations. As with lithium, anticonvulsants may be associated with cognitive side effects in geriatric patients.

6. Drug- Drug Interactions

The concomitant medical problems and resultant higher rates of polypharmacy, the physiological changes associated with aging and co-prescribing mood stabilizers or antidepressants with antipsychotics in schizoaffective disorder, may predispose elderly to potentially fatal drug- drug interactions. Interactions between psychotropic drugs and other medications commonly prescribed in the elderly are summarized in table II .

Drug Treatment

Schizoaffective disorder should be considered a heterogeneous diagnostic category, and treatment should be tailored to the individual presentation of each patient. Guidelines for treatment of this disorder refer to atypical antipsychotics as first- line agents[37].

McElroy et al reviewed available data regarding acute and maintenance treatment, and developed treatment guidelines for this disorder in adults[38]. Both affective and psychotic symptoms appear to be equally important in evaluation and treatment. It is therefore useful to classify patients into the bipolar and depressive subtypes[39,40]. Most patients will need to be treated with agents that have antipsychotic and thymoleptic properties- usually a combination of antipsychotics and mood stabilizers or antidepressants, antipsychotics alone or in combination with thymoleptic agents[39, 40-3]. Due to their thymoleptic properties, better side effect and safety profile, second-generation antipsychotics are considered the first- line treatment for schizoaffective disorder[37,39]. ECT has been found to be very effective in schizoaffective depression[41]. Some studies suggested comparable responses to treatment with lithium and typical antipsychotics in patients with acute episodes of schizoaffective disorder, bipolar type, except for highly agitated cases where antipsychotic monotherapy was superior. Combined antidepressant and antipsychotic treatment was not found to be superior to antipsychotic treatment as monotherapy.

No controlled studies have been conducted combining antipsychotic and thymoleptic treatment as a prophylactic strategy. Atypical antipsychotics, including clozapine, have mood stabilizing properties [44,45].

The elderly are more sensitive to drugs. Hence, lower starting doses and slow titration are recommended. 25-50% of usual adult doses of psychotropic medications are recommended for the elderly[23]. A clearly positive clinical response is less likely to occur in elderly patients, particularly with underlying cognitive deficits[45].

A. Conventional Antipsychotics

First-generation antipsychotics are effective in treating psychosis, but are not as effective for mood symptoms or cognition. It appears that all conventional agents are equally effective in treating positive psychotic symptoms. Individual agents are selected based on side effect profile, patient preference, prior history of response and comorbid conditions.

Studies have found that modest doses of first- generation antipsychotic agents are as or more efficacious than higher doses; moderate doses have been reported to improve comorbid depression[22]. Higher doses are associated with a greater incidence of extrapyramidal side effects. Long-acting injectable formulations can be used in the maintenance treatment of patients for whom adherence is a problem[46].

Table II. Drug- drug interactions[16]

Psychotropic drugs	Potential drug interactions	Potential manifestations
Atypical antipsychotics	A. CNS depressants, alcohol, TCA's	-increased risk of seizures, sedation and cardiac effects
	B. Benzodiazepines	-increased risk of orthostatic hypotension, syncope, respiratory depression
		-risperidone, olanzapine, quetiapine, ziprasidone antagonize their effect
	C. Levodopa, dopamine agonists	-increase atypical antipsychotic clearance
		-not to be used concomitantly due to combined risk of bone marrow suppression
	D. P450 inducers, glucocorticoids	
I.Clozapine	CBZ, propylthiouracil, phenytoin, sulphonamides, captopril	-can precipitate clozapine- induced neutropenia
		-increased risk of seizures, confusion, movement disorders; should never be co-administered if past history of NMS
	Paroxetine	
	Lithium	-can increase clozapine serum levels
		-severe cardio-vascular or respiratory depression
	Risperidone, fluoxetine,fluvoxamine, paroxetine	-can decrease clozapine serum levels
	Diazepam, flurazepam, lorazepam	-can increase olanzapine serum levels
	(clonazepam OK)	-priapism
	Oral hypoglycemiants	-EPS in combination with risperidone
II.Olanzapine	Fluoxetine, fluvoxamine, imipramine	-can increase risperidone serum levels
	Clozapine	-can increase clearance for quetiapine
III.Risperidone	Phenytoin, SSRI's	-can decrease clearance
	Fluoxetine, paroxetine	-quetiapine can increase it's blood levels
IV.Quetiapine	Pheytoin, thioridazine	-avoid co-administration due to QTc prolongation potential
	Cimetidine	
	Lorazepam	
V.Ziprasidone	Drugs that can prolong QTc intervals	
VI.Aripiprazole	No additional interactions known	

Table II. Drug- drug interactions[16] (Continued)

Psychotropic drugs	Potential drug interactions	Potential manifestations
Lithium	A. Antipsychotics	-encephalopathy, worsening of EPS and NMS, altered plasma concentrations of antipsychotic, lithium or both
	B. Antidepressants	-serotonin-like syndrome
	C. Mood stabilizers	-neurotoxicity with CBZ
	D. NSAID's	-reduce renal lithium clearance, increase serum levels
	E. Diuretics - Thiazides	-reduce renal clearance, increase serum levels, toxicity
	-Loop	-no change
	-Potassium sparing	-may increase serum levels
	-Osmotic	-increase renal clearance and decrease serum level
	-Xanthine	-increase renal clearance
	-Carbonic	-increase renal clearance
	F. ACE inhibitors	-reduced clearance, increased concentration, toxicity
	G. Calcium channel blockers	-reports of neurotoxicity; unspecified mechanism
	H. Miscellaneous	
	Succinylcholine	-prolonged neuromuscular blockade
	Metronidazole	-increased lithium levels
	Methyldopa	-neurotoxicity
	Sodium bicarbonate	-increased renal clearance
	Iodides	-additive antithyroid effects
	ECT	-increased risk of delirium (stop lithium 2 days before ECT)
CBZ	**A**.Alprazolam, clonazepam; amitriptyline, bupropion, clomipramine, imipramine; clozapine, fluphenazine, haloperidol; lamotrigine, desipramine, doxepin; nimodipine; valproate, phenytoin, primidone, ethosuximide; methadone; doxycycline, fentanyl, OCP's, warfarin	CBZ may decrease these drugs' plasma levels
	B.Clomipramine, phenytoin, primidone	
	C.Fluoxetine, fluvoxamine, nefazodone, valproic acid, lamotrigine, allopurinol, cimetidine, clarithromycin, danazol,diltiazem, erythromycin, verapamil, gemfibrozil,itraconazole, ketoconazole, isoniazid, loratadine, terfenadine	-CBZ may increase these drugs' plasma levels -These agents can increase CBZ plasma levels
	D.CBZ (autoinduction), valproate, phenytoin, phenobarbital, primidone, rifampin	-These agents can decrease CBZ plasma levels

Table II. Drug- drug interactions[16] (Continued)

Psychotropic drugs	Potential drug interactions	Potential manifestations
Valproate	Lithium	-increased tremor
	CNS depressants	-increased sedation
	Antipsychotics	-increased sedation, EPS, delirium and stupor; confusional syndrome with clozapine
	Fluoxetine, amitriptyline	-may increase valproate serum concentrations
	CBZ	-may decrease valproate concentrations
	Diazepam, Phenobarbital	-serum concentrations increased by valproate
	Phenytoin	-serum concentrations decreased by valproate
	Clonazepam	-absence status- in pre-existing seizure disorder
Gabapentin	Antacids with aluminium and magnesium hydroxide	-decrease gabapentin absorbtion if taken concurrently
Lamotrigine	**A.**Valproate	-valproate concentration is reduced by lamotrigine
	B.CBZ	-concentration of epoxide metabolite increases
		-increased incidence of CBZ side effects
	C.CBZ, phenytoin, phenobarbital	-decrease lamotrigine concentrations
	D.Valproate, sertraline	-increase lamotrigine concentrations
SSRI's	Lithium and serotonergic drugs	-may precipitate seizures
	Clozapine	-SSRI's raise clozapine levels and may precipitate seizures (more pronounced with fluvoxamine)
I.Fluoxetine	CBZ, diazepam, phenytoin, antineoplastic drugs	-fluoxetine may slow their metabolism
II.Fluvoxamine	Alprazolam, triazolam, diazepam	-fluvoxamine may increase their half-life
	Clozapine, CBZ, methadone, propranolol, diltiazem, theophylline, warfarin	-fluvoxamine may increase their blood levels
	Tramadol	
III.Paroxetine		-coadministration in elderly may precipitate serotonin syndrome
	Cimetidine	-may increase blood levels of paroxetine
	Phenobarbital, phenytoin	-may reduce blood levels of paroxetine
	Warfarin	-paroxetine may increase it's anticoagulant effect
IV. Sertraline	Warfarin	-may be displaced from plasma proteins
	Cimetidine	-increases concentrations of citalopram
V.Citalopram	Metoprolol	-it's concentrations can increase

Table II. Drug- drug interactions[16] (Continued)

Psychotropic drugs	Potential drug interactions	Potential manifestations
TCA's	**A**.Diazepam, alprazolam, fluoxetine, fluvoxamine, paroxetine,aspirin, paracetamol, OCP's, cimetidine, erythromycin, thyroxine **B.**Clonazepam,CBZ, lithium, pheytoin, primidone, barbiturates, chronic alcohol use, OCP's, smoking **C**.Insulin, oral antidiabetics, warfarin **D**.Digoxin, heparin **E.**Antipsychotics **F.**Simpatomimetics **G.**CNS depressants **H**.Antihypertensives	-can increase TCA levels or effects -can reduce TCA levels -TCA's can increase their serum levels or effects -TCA's can decrease their serum levels or effects -increase each other's plasma concentrations -serious cardiovascular effects -additive effects -their effects may be blocked by TCA's
MAOI's	**A.**Sympatomimetcs **B**.Dextrometorphan **C**.Buspirone **D**.Meperidine, pethidine **E**.Tranylcypromine **F**.Paroxetine	-serotonin syndrome, hypertensive crisis -severe serotonin syndrome -hypertensive reactions -hyperpyrexia, respiratory failure ,impaired consciousness, death -cerebral hemorrhage -increases MAOI levels

Legend: CNS=central nervous system; CBZ= carbamazepine; NMS= neuroleptic malignant syndrome; NSAID's= nonsteroidal antiinflammatory drugs; OCP's= oral contraceptives; ACE= angiotensin- converting enzyme; SSRI= selective serotonin reuptake inhibitors; TCA's= tricyclic antidepressants; MAOI= monoamine- oxidase inhibitors

Few studies have compared the efficacy of conventional agents to atypical antipsychotics in patients with schizoaffective disorder. One such study found haloperidol decanoate to be as effective as oral quetiapine in preventing symptom exacerbation; however, quetiapine was more efficacious in treating negative symptoms. The study did not compare responses to treatment between patients with schizophrenia and schizoaffective disorder[46].

A multi-center, double-blind study comparing olanzapine to haloperidol in schizoaffective disorder, bipolar subtype, found olanzapine to be superior in treating mood symptoms[47].

Neurological side effects, particularly tardive dyskinesia, are more common in elderly patients with affective symptoms, including schizoaffective disorder. Anticholinergic agents should be avoided in the elderly, due to their propensity to cause or worsen cognitive impairment.

B. Atypical Antipsychotics

Second- generation or atypical antipsychotics are recommended as first-line medications in late- onset psychotic illness[37]. Current literature supports the view that atypicals are as effective against positive symptoms as first- generation agents, more effective against negative symptoms, and have an improved side-effect profile in the elderly[48,49].

Table III illustrates the receptor binding profiles of currently used atypical agents. Table I summarizes their pharmacokinetic properties. Data on atypical antipsychotic efficacy in schizoaffective disorder in the elderly have generally been extrapolated from combined studies on patients with schizophrenia or schizoaffective disorder. No randomized, placebo-controlled studies have been done specifically on elderly schizoaffective patients as a homogenous group; rather, patients with this disorder have been included in studies of psychotic or affective illness[60].

Recent warnings regarding an increase in the incidence of cerebrovascular accidents and mortality risk in elderly patients with dementia treated with atypical antipsychotics, pose additional concerns regarding the use of atypicals in demented elderly. However, risk has not been demonstrated to be elevated in individuals with primary psychotic disorders or bipolar disorder.

Table III. Receptor binding profiles of atypical antipsychotic agents [50,52-59]

Agent	Dopamine D2	Serotonin $5HT_{1A}$	Serotonin $5HT_{2A}$	Serotonin $5HT_{2C}$	Adrenergic α_1	Histamine H_1	Muscarinic M_1
Clozapine	126	875	16	16	7	6	1.9
Risperidone	4	210	0.5	25	0.7	20	>10,000
Olanzapine	11	>10,000	4	23	19	7	1.9
Quetiapine	160	2,800	295	1,500	7	11	120
Ziprasidone	4.8	3.4	0.4	1.3	10	47	>10,000
Aripiprazole	0.34*	1.7*	3.4*	22*	57	61*	>6,780

*Data with cloned human receptors

Note: Data represented as K_I(nM) and IC_{50}(nM)

1. Clozapine

To date, clozapine is the only antipsychotic with proven efficacy in treatment- resistant psychosis. It is effective against both positive and negative symptoms and does not produce motor side effects. It also has proven efficacy in reducing suicidality, hostility and aggression in patients with schizophrenia or schizoaffective disorder[23]. No placebo-controlled, randomized studies have been done, however, in elderly patients with schizoaffective disorder.

Frankenburg et al studied clozapine use in eight patients over age 65 with treatment-resistant psychoses, out of which six improved[61].

Howanitz et al compared the efficacy and tolerability of clozapine to chlorpromazine, in a 12- week, double- blind study in 42 elderly patients with schizophrenia[62]. Both groups of patients improved their PANSS scores as compared to baseline. The difference in response between the two groups was not statistically significant. Both groups showed improvement in mean Clinical Global Improvement (CGI) scores compared to baseline. Adverse effects occurred in similar proportions. The conclusion was that both agents are effective and well tolerated in the treatment of psychosis in the elderly. The clozapine group had statistically significant retention rates, which may suggest higher efficacy or tolerability of clozapine. The statistical significance of this study, however, is limited by the small sample size.

Sajatovic et al conducted an open-label trial of clozapine in older adult inpatients and outpatients with treatment- resistant psychosis in a US Veterans Administration Medical Center [63]. Clozapine was found to be effective, more significantly on positive symptoms and aggression, as evidenced by Brief Psychiatric Rating Scale (BPRS) changes of 20% or greater. Suicidality also appeared to have been reduced.

Barak et al also found clozapine to be effective in 133 elderly patients on a mean dose of 134 mg daily. However, the incidence of leucopenia/agranulocytosis was higher than in younger patients[64]. The risk of agranulocytosis is higher in elderly women.

The recommended starting dose of clozapine in elderly patients is 6.25-12.5 mg/day. Advantages of clozapine therapy in the elderly include a very low incidence of EPS and TD, and efficacy against positive and negative symptoms and use in treatment resistant or intolerant patients. Areas of concern in the elderly include sedation, anticholinergic side effects, postural hypotension, lowering of seizure threshold, agranulocytosis, metabolic syndrome and FDA warnings regarding myocarditis, increased incidence of cerebrovascular accidents and mortality risk in patients with dementia.

2. Risperidone

Numerous reports (case series, retrospective, open-label and placebo-controlled studies) have been published comparing the efficacy of risperidone to other atypicals and to first-generation antipsychotics, in adult patients with schizophrenia, schizoaffective and schizophreniform disorders.

A prospective, open-label trial in 103 elderly patients with schizophrenia/ schizoaffective disorder conducted at 14 psychiatric centers in the US found risperidone to be effective and well tolerated[65]. Another open-label study – this one conducted over a 12 month period - in 180 elderly patients with chronic psychosis found significant reductions in Positive and Negative Symptom Scale (PANSS) scores, a decrease in the severity of EPS and reduced incidence of TD[66].

In an international double blind study, Jeste et al randomly assigned 175 patients aged 60 years and above to risperidone or olanzapine[67]. Both treatment groups improved significantly over time (as evidenced by improvements in PANSS total scores) with no differences between the two. Four of the five PANSS factor scores (positive and negative symptoms, disorganized thoughts, anxiety/ depression) also improved significantly in both groups. The incidence of side effects did not differ significantly.

Total scores in the Extrapyramidal Symptom Rating Scale (ESRS) were reduced in both groups. Weight gain occurred with both antipsychotics but was significantly less with risperidone than with olanzapine.

Barak et al conducted a naturalistic, retrospective study of typical antipsychotic treatment in comparison to risperidone in 51 elderly patients with schizophrenia or schizoaffective disorder[68]. Both treatment groups showed improvement, with the group on risperidone showing more significant changes in Clinical Global Improvement (CGI) and (PANSS) scores. Use of anticholinergic agents was less in the risperidone group. Minimal increases in body- mass index (BMI) and fewer side effects were noted in the risperidone group.

DeVane and Mintzer reviewed published reports on risperidone in elderly patients with schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder, dementia and neurologic conditions such as Parkinson's and Huntington's disease[69]. Results supported the efficacy of this agent, which was well tolerated and had a low incidence of movement disorders and anticholinergic effects.

Sajatovic et al found similar results in a US Veterans Administration Clinic[70]. Lasser et al assessed the efficacy and tolerability of long-acting risperidone in 57 elderly patients with schizophrenia and schizoaffective disorder. The patients received 25, 50 and 75 mg every two weeks, up to 50 weeks. The study found good tolerability and significant symptom improvement, as proven by significant improvement in PANSS total scores as well as PANSS factor scores (positive and negative symptoms, disorganized thoughts, uncontrolled hostility/ excitement, anxiety/ depression)[71].

The recommended starting dose in elderly patients is 0.5 mg either once or twice daily, which can be titrated to the usual maintenance dose of 2-3 mg/day. The advantages of risperidone in the elderly include minimal anticholinergic effects and efficacy against positive and negative symptoms. Areas of concern include the potential for dose-related EPS, postural hypotension, hyperprolactinemia, metabolic side effects and FDA warnings regarding increased incidence of cerebrovascular accidents and mortality risk in dementia patients.

3. Olanzapine

Compared to risperidone, there are fewer published studies on olanzapine use in elderly patients with schizoaffective disorder.

A study of 11 hospitalized elderly patients with schizophrenia and schizoaffective disorder showed significant improvement in both positive and negative symptoms, with greater improvement in positive symptoms[72]. PANSS and CGI scores improved significantly in 9 patients, the Extrapyramidal Symptom Rating Scale (ESRS) showed significant reductions and 9 patients showed improved scores on the Mini Mental State Examination (MMSE). The Calgary Depression Scale for Schizophrenia (CDSS) showed significant reduction from baseline in all patients. No motor side effects were observed and there were no significant changes in prolactin levels and EKG's. Co-administration with other agents (including lithium and sodium valproate) caused no drug interactions.

Harvey et al found that olanzapine in doses between 5 and 20 mg daily and risperidone 1-3 mg daily improved cognitive function in 176 elderly patients with schizophrenia or schizoaffective disorder[73]. This was evidenced by improvement in Continuous Performance Test (CPT), Serial Verbal Learning Test (SVLT), Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST) and Verbal Fluency Examination (VPE) scores.

Solomons and Geiger conducted a retrospective chart analysis on 58 hospitalized elderly patients with psychotic symptoms, who had previously failed to respond, or had intolerable side effects to other antipsychotics[74]. Olanzapine was found effective, with 60.3% of patients improving, and well tolerated, with 38% of patients developing side effects.

Barak et al conducted an open- label naturalistic follow-up study of olanzapine compared to haloperidol treatment in 20 elderly patients with chronic schizophrenia[75]. PANSS total scores decreased more significantly with olanzapine than with haloperidol and PANSS negative subscores improved with olanzapine and deteriorated with haloperidol. CGI scores improved with both agents, more significantly with olanzapine. Olanzapine was associated with less EPS than haloperidol.

Deberdt et al conducted a 10- week, double- blind, flexible- dose study comparing olanzapine (mean dose 5.2 mg daily) and risperidone (mean dose 1.0 mg daily) to placebo in a group of 494 elderly patients with dementia- related psychosis[76]. Most measures of neuropsychiatric functioning improved in all three groups, with no significant treatment differences between them. The overall discontinuation rate due to side effects was lowest in the placebo group, followed by risperidone and olanzapine.

Risperidone was associated with more treatment- emergent extrapyramidal symptoms and prolactin elevation. No other statistically significant clinically relevant side effects occurred. It was concluded that patients improved similarly with all three treatments, with no significant differences between the three groups, including placebo.

Kennedy et al conducted a post- hoc analysis of a group of 39 patients with psychosis ages 50-65, from a 28- week international multi- center double- blind study of olanzapine and risperidone[77]. After 28 weeks, both treatment groups improved with no significant difference between the two. The olanzapine group had lower PANSS negative and BPRS negative scores.

There have been recent reports of metabolic syndrome associated with atypical antipsychotics, more frequently with olanzapine and clozapine[35]. While Barak et al did not find a higher incidence of metabolic abnormalities in the elderly, this was based upon a relatively small sample analysis (21 patients)[78].

Olanzapine use in the elderly has been associated with a good effect on both positive and negative symptoms, and a low incidence of motor side effects.

The recommended dose of olanzapine for elderly patients is 5-10 mg/day. The advantages of olanzapine in the elderly include availability of a short acting parenteral form, low incidence of EPS and a good effect on positive and negative symptoms. Areas of concern include the potential for sedation, metabolic syndrome and FDA warnings regarding increased incidence of cerebrovascular accidents and mortality risk in dementia patients.

4. Quetiapine

A one year multicenter, open-label trial of quetiapine in elderly patients was conducted, with analysis of findings at 12 weeks and at 52 weeks. The 12 week analysis showed significant improvement with a low occurrence of EPS (6%)[79]. The authors used the BPRS,

CGI, Simpson- Angus Neurologic Rating Scale and Abnormal Involuntary Movement Scales to study the efficacy and tolerability.

The 52 week analysis reported similar findings of efficacy and tolerability. Quetiapine use was associated with somnolence, dizziness and orthostatic hypotension[80]. The same scales were used as in the 12 week analysis. EPS-related events occurred in 13% of cases. No cardiovascular abnormalities were noted.

Madhusoodanan et al reviewed quetiapine use in 7 elderly inpatients with schizophrenia, schizoaffective and bipolar disorder, who had been treated with conventional or other atypical antipsychotics[81]. Response was assessed by observing the patients' behavior. Four patients responded while three did not. Positive symptoms improved in all four responders, and negative symptoms improved in three. Preexisting EPS diminished in three patients. Quetiapine was well tolerated- two patients experienced transient hypotension, dizziness and sedation. No interactions occurred when it was co-administered with agents such as lithium, carbamazepine, sodium valproate or venlafaxine .

Quetiapine should be started at lower doses and titrated at a slower rate in elderly populations in comparison to younger patients, due to the potential for reduced clearance and side effects of dizziness and orthostatic hypotension[82].

The recommended starting dose of quetiapine in the elderly is 25-50 mg twice daily. The usual maintenance dose is about 100-200 mg twice daily. Higher doses may be used if needed depending on tolerability. The advantages of quetiapine include negligible EPS, minimal anticholinergic effects and good effect on positive and negative symptoms. Areas of concern include sedation, postural hypotension, metabolic side effects and FDA warnings regarding increased incidence of cerebrovascular accidents and mortality risk in dementia patients.

5. Ziprasidone

Ziprasidone's efficacy on positive symptoms in younger patients with schizophrenia and schizoaffective disorder has been demonstrated through placebo- controlled studies. No placebo-controlled studies have been conducted in elderly patients with schizophrenia or schizoaffective disorder.

Keck et al conducted a 4- week placebo- controlled, multicenter study in 139 adult (ages 18-65) patients with acute exacerbation of schizophrenia or schizoaffective disorder[83]. Ziprasidone was significantly more effective than placebo in improving scores on the BPRS, CGI- S, BPRS depression cluster and BPRS anergia cluster scales. Patients treated with ziprasidone were not significantly different from placebo on the Simpson- Angus, Barnes, Akathisia and AIMS scales.

Arato et al conducted a 1-year, double- blind, placebo- controlled trial of ziprasidone in adult patients below age 65 with stable, chronic schizophrenia[84]. Patients on ziprasidone showed significant improvements in PANSS total and PANSS negative scores.

Ziprasidone was not associated with movement or cardiovascular abnormalities. It was effective in reducing the frequency of relapse and produced long-term improvement in negative symptoms.

Etemad conducted a retrospective study of 9 elderly patients admitted to an inpatient unit with acute psychotic symptoms and diagnosis of schizophrenia or schizoaffective disorder, with most of them having medical comorbidities[85]. The patients were treated with oral ziprasidone and received intramuscular ziprasidone during episodes of acute agitation. These patients showed improvement of psychotic symptoms on ziprasidone, with no ECG changes

(QTc remained below 500 msec) and no evidence of drug- drug interactions. Ziprasidone proved to be effective and well tolerated in this group of patients.

Loebel et al analyzed patients aged 55 years and above with schizophrenia/ schizoaffective disorder from the phase 2/3 ziprasidone clinical development programs[86]. Ziprasidone was effective, with efficacy increasing at higher doses and well tolerated. Efficacy and tolerability of ziprasidone in this age group was comparable to the adult patient population.

Hirsch et al found comparable efficacy to haloperidol in adult patients, on both positive and negative symptoms, as shown by statistically significant improvements in PANSS, CGI-severity of illness scale and the Montgomery- Asberg Depression Rating Scale[87]. Significantly more patients in the ziprasidone group were negative symptoms responders (20% or more reduction in PANSS negative subscale score) than in the haloperidol group (48% compared to 33%). Ziprasidone had a lower incidence of movement disorders, as evidenced by scores on the Barnes Akathisia and Abnormal Involuntary Movement Scales.

Addington et al found ziprasidone to be equally effective as risperidone in patients with acute exacerbation of schizophrenia and schizoaffective disorder, with a lower risk of movement disorders, weight gain and prolactin elevation[88]. The efficacy was measured using the PANSS total and PANSS negative scores, CGI- improvement and PANSS-derived Brief Psychiatric Rating Scale (BPRS d).

The recommended starting dose of ziprasidone in the elderly is 20 mg twice daily. The usual maintenance dose is 40-60 mg twice daily. The advantages of ziprasidone in the elderly include availability of a short acting parenteral form which may be beneficial in acute psychotic episodes and negligible EPS, anticholinergic, sedative or metabolic side effects. Areas of concern include the FDA warnings of QT_c prolongation, and increased incidence of cerebrovascular accidents and mortality risk in dementia patients.

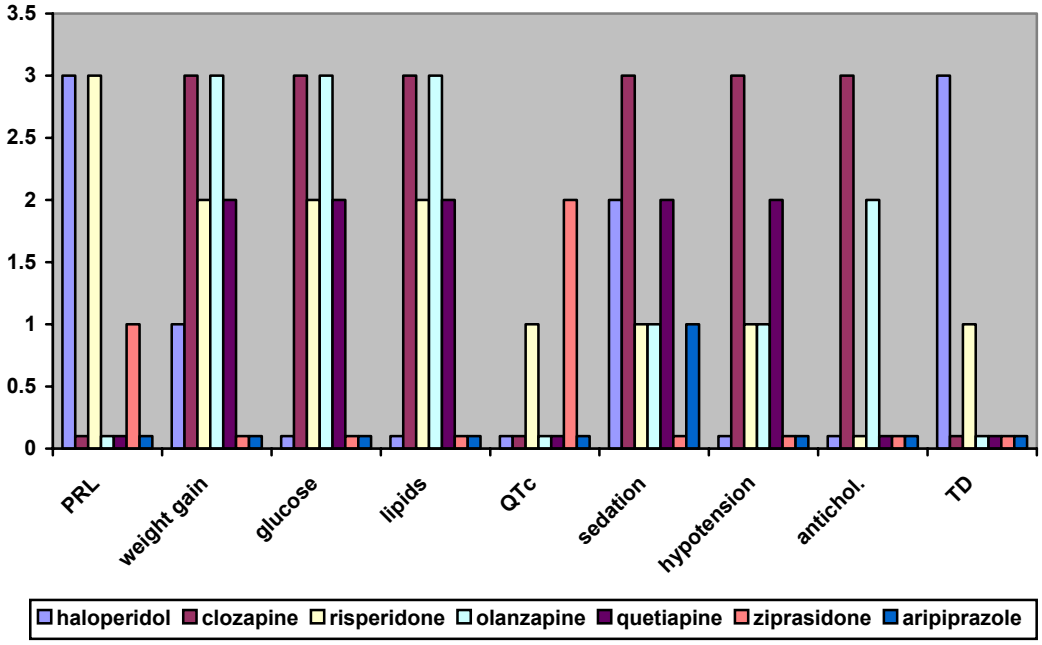
6. Aripiprazole

Madhusoodanan et al found aripiprazole to be safe and effective in elderly patients with schizoaffective disorder or schizophrenia, with significant improvement in CGI scores[89]. Pre-existing EPS improved and two patients were able to discontinue antiparkinsonian medications, while one patient showed improvement in severe pre-existing TD. No adverse consequences occurred with co-administration of valproic acid, clonazepam, carbamazepine or citalopram.

The recommended starting dose of aripiprazole in the elderly is 10-15 mg/day. The usual maintenance dose is 15-30 mg/day. The advantages of aripiprazole include minimal EPS, negligible anticholinergic, sedative, metabolic, hematological or QT_c related side effects. The areas of concern in the elderly include the FDA warnings regarding increased incidence of cerebrovascular and mortality risk in dementia patients.

Combinations of atypical agents have been tried in the treatment of treatment- resistant schizoaffective disorder and found to be well tolerated and effective; however, further double-blind placebo- controlled studies are needed in this area[90].

A comparison of selected side effects of atypical antipsychotics and haloperidol is outlined in Figure I.



PRL- prolactin elevation; glucose- glucose abnormalities; lipids- lipid abnormalities; QTc- QTc prolongation; TD- tardive dyskinesia

Figure I. [22] Comparison of selected side effects of atypical antipsychotics and haloperidol

C. Mood Stabilizers

Relatively few studies have been conducted regarding the use of mood stabilizers in schizoaffective disorder; even fewer have been conducted in elderly patients. Data regarding the use of mood stabilizers in the elderly are usually extrapolated from studies in adult populations or in patients with bipolar disorder[91]. However, there is evidence to suggest their efficacy, primarily in the bipolar subtype of schizoaffective disorder.

Lithium

Several studies have found lithium to be comparable in efficacy to typical antipsychotics, in the treatment of adults with schizoaffective disorder, except in agitated patients, in which antipsychotics were superior[41].

Sproule et al reviewed the differential pharmacokinetics of lithium in elderly patients[92]. Elderly individuals required lower doses to achieve equivalent serum levels to younger adults, due to reduced volume distribution and renal clearance. Age-related reduction in glomerular filtration rates led to a decrease in lithium clearance. Comorbid medical conditions such as hypertension, congestive heart failure or renal dysfunction also contribute to reduced lithium clearance. Drugs commonly used in the elderly such as thiazide diuretics, ACE inhibitors and non- steroidal antiinflamatory medication can increase serum lithium level. Therefore, lithium levels need to be monitored more frequently in the elderly to avoid toxicity.

In a 3-year randomized, double- blind study, Placidi et al found lithium and carbamazepine to be effective in the treatment of adult patients with bipolar and

schizoaffective disorders[93]. Both drugs were effective in two-thirds of patients and appeared more effective in preventing excited rather than depressive symptoms.

Baethge et al found lithium and carbamazepine to be effective in the treatment of schizoaffective disorder to minimize recurrences[94].

Sodium Valproate/ Divalproex

Most of the information regarding valproate use in the elderly is extrapolated from adult studies or from reports on valproate use in patients with dementia and agitation. Tariot et al reviewed case reports or series in patients with mixed neuropsychiatric disorders and placebo-controlled studies in patients with dementia[95]. These studies found valproate to be effective in reducing agitation.

McElroy et al suggest that valproate may be effective in reducing symptoms of schizoaffective disorder in adults, both in the acute and maintenance treatment, in combination with antipsychotic agents[96].

In a retrospective study, Bogan found valproate to be effective and well tolerated in the treatment of adults with schizoaffective disorder[97]. Dosages used varied between 500 and 2000 mg, with peak serum levels between 20-92 μg/ ml. Efficacy was assessed using CGI scoring. No patients discontinued the study because of side effects.

Raja et al showed that valproate is effective on both mood and positive symptoms in adult inpatients with mood or schizoaffective disorders; its efficacy was similar to oxcarbazepine[98]. Patients were evaluated based on length of hospitalization, changes in BPRS, Scale for the Assessment of Positive Symptoms (SAPS) , Scale for the Assessment of Negative Symptoms (SANS), MMSE, CGI, global assessment of functioning (GAF) and Morrisons's scales.

Valproate is also effective as an adjunct to clozapine in the treatment of schizoaffective disorder[99].

Carbamazepine and Oxcarbazepine

Kutluay et al assessed the safety and tolerability of oxcarbazepine in patients with seizure disorder above the age of 65, as compared to younger patients ages 18- 6[100].

There were no significant differences between the two groups with regard to premature discontinuation of the agents. The most common side effects experienced by the elderly group of patients were vomiting, dizziness, nausea and somnolence. Three patients developed asymptomatic hyponatremia and it was more frequent in elderly patients concomitantly taking natriuretic drugs. The conclusion of the study was that oxcarbazepine is safe to use in elderly patients and its tolerability in this age group is similar to younger adult patients.

Gabapentin

Sethi et al followed up 7 elderly manic patients treated with gabapentin[101]. The patients received gabapentin in combination with antipsychotics or valproate. All 7 patients improved, without experiencing significant side effects. It was concluded that gabapentin was safe and effective in geriatric mania in combination with antipsychotic medication or valproate.

Lamotrigine

There are no studies on lamotrigine use in elderly with schizoaffective disorder. Results can be extrapolated from studies on it's use in bipolar disorder and seizure disorders.

Bowden et al reviewed the use of mood stabilizers in adults with bipolar disorder[102]. Maintenance studies support the efficacy of lithium, valproate and lamotrigine.

Lamotrigine appears to be effective in delaying relapse, with most benefits limited to delaying time to depression. It has not shown anti- manic activity in placebo- controlled studies, but has not been associated with induction of mania or rapid- cycling illness symptomatology, unlike antidepressants.

Giorgi et al compared lamotrigine use in elderly patients with epilepsy, to carbamazepine and phenytoin[103]. Out of the 146 lamotrigine patients, 46% had side effects compared to 72% of the 53 patients on carbamazepine and 89% of the 9 patients on pheytoin. They concluded that lamotrigine was effective and well tolerated.

Rowan et al conducted an 18- center, double- blind, parallel study of lamotrigine, gabapentin and carbamazepine use in 593 elderly patients with the mean age of 72[104]. Patients taking lamotrigine and gabapentin had fewer side effects than those taking carbamazepine. They concluded that lamotrigine and gabapentin were better tolerated than carbamazepine.

D. Antidepressants

Antidepressants are the least studied psychotropics in the treatment of schizoaffective disorder. They are generally used as adjuncts to antipsychotics in the treatment of the depressive subtype[38]. McElroy et al found only 2 studies with amitriptyline. In one study, Brockington et al found that combined amitriptyline/ chlorpromazine treatment was not superior to treatment with either agent alone[105]. In a study conducted by Prusoff et al, amitriptyline was found superior to placebo for depression, but not for thought disorder, when added to ongoing antipsychotic treatment[106].

E. ECT

ECT is used relatively infrequently in elderly or younger patients with schizoaffective disorder, but is indicated in severe, treatment- resistant cases, more commonly in the depressive subtype. There are few reports of ECT use in elderly patients with schizoaffective disorder. Kramer describes five elderly patients with schizophrenia or schizoaffective disorder who underwent ECT- four patients were deemed medication- resistant[107]. All five patients showed improvement in symptoms. Swoboda et al found maintenance ECT effective in selected patients with affective or schizoaffective disorder, either alone or in combination with medication[108]. In this study of younger patients-, the schizoaffective group had a poorer outcome than the depressed group.

DISCUSSION

The treatment of schizoaffective disorder in the elderly generally follows the guidelines for treatment of chronic schizophrenia and of bipolar disorder. Atypical antipsychotics, alone or in combination with thymoleptic medications, are considered first-line agents, as they are

better tolerated, if not more effective, compared to the typical agents. They also are reported to improve cognition. Among atypical agents, however, no single agent has been found to be superior in the elderly. More studies have been conducted on risperidone and olanzapine than other atypicals in the elderly. The only published comparative study between atypical antipsychotics in elderly patients with schizophrenia or schizoaffective disorder is that by Jeste et al, which compared risperidone to olanzapine[67]. Both agents were found to be effective in reducing positive and negative symptoms, as well as extrapyramidal symptoms, and had a low incidence of side effects.

CONCLUSION

With the aging of population, the absolute numbers of elderly patients with schizoaffective disorder are expected to increase. The elderly represent a challenging treatment group in view of age-related biological changes which make them more susceptible to medication side effects, and medical comorbidities that can complicate the clinical picture and lead to drug-drug interactions. Newer psychotropic agents – particularly atypical antipsychotics - show promising results in terms of good clinical effect, as well as reduced incidence of adverse effects. Recent warnings regarding metabolic and cardiovascular adverse effects and cerebrovascular and mortality risks in dementia patients emphasize the need to customize treatment decisions based upon patient unique clinical profiles.

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Chapter 4

PREJUDICIAL AUTOCHTHONOUS VISUAL REPRESENTATION AND ILLOCUTIONARY FORCE

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ABSTRACT

Schizophrenic pathological experiences in which the patient offends people around him/her occupy a characteristic position in schizophrenic psychopathology. S. Kato proposed the concept of *prejudicing autochthonous speech act (thought)*, a schizophrenic pathological experience in which the patient has had prejudicial thoughts, and often believes that he/she has voiced them or has sometimes even actually voiced them, against people in his/her presence. He suggested that *prejudicing autochthonous speech act (thought)* often appears during the remission process of schizophrenia and represents re-establishment of the ego function of the patient during the recovery process from schizophrenia. In this paper, we focus on a similar symptom, namely, *prejudicial autochthonous visual representation*, in which the patient has prejudicial visual images of people in their presence, and discuss the significance of this symptom in the clinical course of schizophrenia. *Prejudicial autochthonous visual representation* is deemed to be a variant of *prejudicing autochthonous speech act (thought)*, however, whether they have similar clinical significance remains doubtful. We would like to emphasize the visual character of *prejudicing autochthonous visual representation.* In reference to the concept of *illocutionary force* by Austin, we suppose that the pathological illocutionary force which are often observed in schizophrenic pathological experiences, is safely ensconced within the capsule of the visual image in the case of *prejudicial autochthonous visual representation*.

INTRODUCTION

Although most schizophrenic patients manifest persecutory delusions, pathological experiences in which the patient has been offending other people or surroundings occupy a

unique position in the psychopathology of schizophrenia. In the case of delusions of persecution, the pathological experience has an egocentric direction: the injurious force is directed towards the patient from the world around. In contrast, in the case of prejudicial experiences, the pathological experience has an exocentric direction: the injurious force is directed from the patient to the outside world. S. Kato [1] proposed the concept of *prejudicing autochthonous speech act (thought)* (PASA(T)), a schizophrenic pathological experience in which the patient has prejudicial thoughts, and often believes that he/she has voiced these prejudicial thoughts, against people in his/her presence. He found that PASA(T) often appears following auditory hallucinations and switches with thought broadcasting during the remission process of schizophrenia. Even during the pathological experience in which the patient has prejudicial thoughts against other people, the patient must confront others one-to-one, gathering incompletely recovered activities that are damaged by the schizophrenic condition. Therefore, he concluded that PASA(T) represents re-establishment of the ego function of the patient during the recovery process from schizophrenia. On the other hand, he found that some patients with PASA(T) who continuously present with thought broadcasting or who develop *Schädigungswahn* (delusion of persecuting others) [2] in which the patient believes that he/she brought on a plague among wide-ranging people, including of the entire nation, the world, and so on, are likely to have a poor prognosis.

In this paper, the author reports three schizophrenic patients presenting with a similar type of symptom, namely, *prejudicial autochthonous visual representation* (PAVR), in which the patient has prejudicial visual images of people in his/her presence. In a way, this symptom is unique, because it is an exocentric pathological experience, as mentioned above. In addition, PAVR is also considered to be unique because it is a pathological *visual* experience. It is said that schizophrenic patients more commonly have auditory hallucinations, and that visual hallucinations are less common.

The author also discusses the clinical significance of the symptom, referring to J. L. Austin's pragmatics [3].

CASE PRESENTATIONS

Case 1: Lisa A., 20- Year-Old Female

Lisa A., the daughter of a self-employed worker who had learnt to play the piano from when she was a small child was admitted to a music academy with a college dormitory. Seven months after enrollment into the academy, she had trouble concentrating on her studies and lost a grip on herself; she developed symptoms of depersonalization. Although she telephoned her parents and complained, "I am crazy and had better consult a psychiatrist," her parents dismissed her complaint with a laugh. In 10th month of her first grade, she developed insomnia and began to have bizarre thoughts when she was alone (She could not clarify what the bizarre thoughts were afterward). She then returned home to consult a psychiatrist at a clinic near her house.

Her complaints were near-psychotic: "I will end up losing my mind"; "There are about three alter egos, and my thoughts are circling inside my head"; "I can do everything, but I feel I am not me and that the other me seems to do things." However, she did not have typical

psychotic symptoms, including delusions or hallucinations. The psychiatrist diagnosed her as suffering from exhaustion and not psychosis, and prescribed an antidepressant drug and an anxiolytic agent. This medication temporarily relieved her symptoms.

When the new term began, and Lisa started to go to school again, her condition deteriorated with the development of new symptoms. She complained that brutal images crossed her mind: "When I saw the legs of people sitting on the opposite seat in a railcar, I pictured their legs being severed and blood gushing out"; "I imagined stabbing my parents with a kitchen knife"; "I had an image of tearing apart every part of my sister's body and boiling her head." In this manner, she frequently had prejudicial visual images of people, mainly in their presence. This phenomenon of brutal images crossing her mind is also called "association of ideas." This phenomenon reported by the patient was not always confined to visual images, but also sometimes took the form of obsessive thoughts: "I almost want to tear up the neck of the student sitting in front of me when attending a lecture"; "When I see a child, I have an impulse to murder or abduct the child"; "I cannot go to walk the dog, because I nearly want to tear up the dog's ears." Chiding herself for having such images or ideas, she said she was so embarrassed that she wanted to die. She sometimes wanted to throw herself in front of a train, and imagined her mangled body. Subsequently, she reported auditory hallucinations corresponding to the first-rank symptoms of Schneider [4]. She reported hearing a TV announcer asking her why she did not watch a particular TV program about a serial killer, or conversations between a male and a female.

Lisa was then diagnosed as having schizophrenia and begun on treatment with neuroleptic drugs. The psychiatrist in-charge advised her to withdraw from school and to become hospitalized, however, her parents dismissed this advice and said, "If you try not to think about it, you will be cured." They occasionally took her to lectures by members of a cult religion. On other occasions, they flared up, saying, "Take it or leave it, you can leave school or you can take a year off, we don't care about it!" Meanwhile, while the neuroleptics relieved her of her auditory hallucinations, the inappropriate images crossing her mind or "association of ideas" intensified. She longed for hospital treatment as per the psychiatrist's advice, however, seemed to have been driven into the corner by her parents' opposition to it.

In the sixth month of her second grade, her parents finally consented for hospital treatment, and she was introduced to a medical school hospital. However, she had to wait for three more months until a vacancy was available. During this period, she continued to have inappropriate images crossing her mind, with occasional auditory hallucinations. When she complained of such images crossing her mind, she asked how she could forget such brutal ideas, on each occasion.

In the ninth month of her second grade, she was admitted to the psychiatric ward of the medical school hospital. As for the symptom which she called "inappropriate images" or "association of ideas," when she was asked whether she could see the images, she replied "I can rather see." The images occupied her right upper field of vision and had a somewhat sensory nature, however, they did not have the supernatural reality comparable to visual hallucinations. Even when she did not have brutal images crossing her mind, she suffered from recollections of such images that she had previously had. She said, "I want to get rid of the images in my head as early as possible," or "I want to wipe out my memories."

While several neuroleptics were tried, none were sufficiently efficacious. Nevertheless, the frequency of brutal images crossing her mind decreased within three months of hospitalization. During the course of her hospital stay, she exhibited marked negative

symptoms, including loss of energy and loss of spontaneity. However, after 7 months of hospitalization, while she still complained of loss of energy, she was discharged from the hospital.

One year later, Lisa was readmitted to the academy. She appeared to enjoy her school life and smoothly graduated from the academy. Intermittent administration of low-dose neuroleptics appeared to keep her illness from recurring.

Summary

This patient developed mental illness with loss of energy and thought disturbance, after she was enrolled at a music academy. Initial treatment with an antidepressant temporarily relieved her from the symptoms, however, she later presented mainly with PAVR and auditory hallucinations, whence she was diagnosed as having schizophrenia. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria [5], she was diagnosed as having a psychotic disorder, not otherwise specified, because among the symptoms in the DSM-IV criteria for schizophrenia, she only had hallucinations. However, the overall picture of the illness, with the history of visual pseudohallucinations, namely PAVR, auditory hallucinations including Schneiderian first-rank symptoms, and negative symptoms, suggested the diagnosis of schizophrenia. Finally, she had a good prognosis outcome, despite the marked negative symptoms during her hospitalization.

Case 2: Mari B., 26- Year-Old Female

Mari B. is the daughter of an executive officer. Her father often went on a drunken rampage and punched her in her face. She did not understand the meaning of life and often wanted to die, even since she was an early-teenager. In her high school days, when she saw someone getting yelled at, she felt as if it was she who was getting yelled at and recalled her father's drunken rampage. Ever since she fell out with her college friend at one point, she became afraid to deal with people. Mari started living on her own, avoiding her drunken father. After graduation from the college, she changed jobs frequently, because she could not relate well with her colleagues. She said, "I feared belonging to companies or societies."

At the age of 24, Mari began to have a recurring grotesque nightmare of injuring other people. She consulted a nearby psychiatric clinic. Initially, she was treated with antidepressnts. She then developed auditory hallucinations, in which a voice called her "Stupid!", a feeling of having her thoughts known by others, and a feeling of being watched by others. She also complained of other strange experiences: "I can't separate TV visuals from reality"; "When I was reading a book, I felt my brain was connected with the book. The book began to get distorted and I felt my brain also beginning to melt, as the two were connected to each other."

After 2 months of being in a psychotic state, she frequently began to have thoughts of committing suicide. At the age of 26, she consulted a medical school hospital. She continuously complained of insomnia, depressive mood, memory loss, and grotesque nightmares. She reluctantly got admitted to the hospital, because her father wanted it so.

She showed marked absence of volitional activity and mostly lay in bed. The essential problems that were the focus of her hospital treatment were improvement of her volition and training to manage interpersonal relationships. The latter was done to some extent during the

course of the hospitalization, however, her volition did not improve despite trial of drugs. She was always guiltily saying, “Is a useless person like me worth living?” When she went out, she felt that the patterns on other passengers’ clothes came close to her, or that objects around her were assaulting her. Her hospitalization was prolonged because of the lack of effect of neuroleptics on her abulia and her expression of anxiety about home life after leaving the hospital.

When her discharge from the hospital was close at hand, she first complained of having images of hurting people in their presence, which she said she had even before her admission: during her interview with the doctor, she imagined blowing the doctor’s brains out with a weapon; when she was talking with another patient, she imagined that she tore the patient’s stomach with a knife.

After discharge from the hospital, she lived a solitary life in an apartment, mostly lying in bed. Her psychological condition remained unstable for about five years after her discharge from the hospital: sometimes, she was cheerful and at other times, she complained of having grotesque dreams and prejudicial images.

Summary

Mari had a depressive mood, abulia, social withdrawal, and suicidal ideation, but no obvious schizophrenic symptoms. Although she did not meet the DSM-IV criteria [5] for the diagnosis of schizophrenia, this diagnosis was strongly suggested by her marked vulnerability in interpersonal relationships, feeling of memory loss and confused thoughts suggestive of thought disturbances, germination of delusions of injury, including the feeling of her thoughts being known to others and the awful feeling of being assaulted, long-lasting avolition, grotesque nightmares, PAVR, continuous pessimism, suicidal ideation, and a transient cenesthopathic symptom, in which she felt her brain began to melt and that it was connected to a book. She first complained of PAVR just before she was discharged from the hospital, but the symptom existed even before she was admitted the hospital. Mari’s PAVR was similar to Lisa’s. However, Lisa had images like video clips recorded by a third person in which both she herself and persons injured by her showed up, while images Mari had were as if she herself had recorded the video clips. After discharge, she suffered from long-lasting avolition.

Case 3: Norio K., 35- Year-Old Male

Norio K. is the son of a divorced woman. His mother got divorced even before he entered elementary school. Thereafter, he had lived with his mother and sister. He was an awkward child who could not describe his feelings well. He was unable to go to a good high school because of poor academic performance. He then began to have an inferiority complex about his poor academic background. He went along with a neighborhood friend to high school, and was admitted to a professional school with the friend after graduation. However, the friend soon became disgusted with the school and left it. Norio felt somewhat disconsolate and followed him a month later, and got the same job as his friend. From then on, he repeatedly got and left jobs with the friend. Initially staying in step with the friend, he gradually began to feel that he was always at the friend's beck and call. Finally, he got a different job from his friend, but was unable to remain at any job for long.

At the age of 27, he began to isolate himself from the society. At the age of 29, when he was riding a streetcar, he heard an announcement that the streetcar had collided with a car, causing injury to people. After he returned home, he had an image of the accident resulting in injury, which he felt he was responsible for, even though he did not even witness the accident. Thereafter, he felt that his mother's friends talked about him. He kept thinking about it and lost his power of concentration. In addition, he began to have terrible images: when he drove past a crossing, he would imagine that his car hit a passenger, and he was afraid thereafter to get into any car. He often imagined punching and kicking the friend who had always been dragging him along earlier. He remained in this condition for about five years.

When Norio became 33 years old, his mother invited a man of the same age, the son of a friend of her's, to provide him with companionship. However, Norio's "academic inferiority complex" was aggravated by the visitor's thoughtless words. After the man returned home, he imagined punching and kicking the man, and every time he remembered this unpleasant visit, he had the very same imagery. These images were from a third person's objective point of view, like video clips recorded by a third person. When he had these images, while he thought that it served the man right, he also felt somehow guilty. He had such images against his will, and autochthonous emergence of the images obstructed his mental activity. When he was agitated, he sometimes imagined that he was destroying his precious property. These images emerged frequently for several months, but subsequently, decreased gradually.

Recently, he had images of punching his mother when he was upset by her. He almost completely withdrew from society and lived a lackadaisical life, although he had got a 30-minute part-time job of newspaper delivery, half a year before he consulted us.

At the age of 35, he visited our psychiatric clinic, complaining of having a dull sensation in his right leg, and went on talking about the above-mentioned symptoms. However, his thoughts seemed to be very confused, and he could not give a cogent explanation about his symptoms and often responded irrelevantly to the doctor's inquiry or was confused by the question. His condition seemed to be near sub-stuporose. Electroencephalography and brain computed tomography were performed, which showed no abnormality.

Treatment with neuroleptics relieved him of his confused thoughts and allowed him to speak coherently. He said that before the treatment, when he tried to think, he could not concentrate and became confused as if many things were flying around him, and just could not understand what the person talking to him was saying, because his thoughts became obstructed by unpleasant memories or images of injuring other people or things against his will. He also complained, "Anyway, my body is divided. I feel the existence of another myself somewhere else: when I remember my past, I feel I am there in the past. For example, when I returned home from a newspaper delivery and remembered about being confused during the job, I felt as if I were still in the same place at which I had been confused."

In addition, he had to endlessly recheck and make sure that he had actually delivered the newspapers, and took almost double the time to do the job. Therefore, he gradually became unable to carry though with the job. Now, he was in social withdrawal again.

Summary

Norio mainly exhibited mild delusions of reference, ego disturbance, including complaints of a divided body and another self, and PAVR, along with abulia, lack of concentration, and social withdrawal. At the first contact, he showed marked thought disturbance, which disabled smooth conversation. His illness met the DSM-IV criteria for the

diagnosis of schizophrenia [5]. He had PAVR when he was 29 years old and continued to have it for 4 or 5 years. Objects that he had prejudicial thoughts against were usually co-passengers or people he held a grudge against: it was rather unusual for him to have such thoughts against people close to him. The prejudicial images were not so grotesque. Also, he did not have auditory hallucinations or thought broadcasting.

DISCUSSION

Prejudicial Autochthonous Visual Representation

All the three reported patients presented with the characteristic symptom of visual representation, in which they had prejudicial visual images against people in their presence. Although, such a symptom rarely seems to have been reported in the psychiatric literature, we have found a few reports of similar symptoms: in regard to schizophrenic symptoms in which the patients believe they injure others, *Schädigungswahn* (delusion of persecuting others) has been listed in the German literature [2] and PASA(T) was reported by S. Kato[1]; as for schizophrenic visual symptoms, we have come across reports of visual hallucinations and *Gedankensichtbarwerden* (visible thoughts) [6].

Kato [1] discovered that some schizophrenic patients, during their recovery process, have prejudicial thoughts, and often believe that they have voiced them or have sometimes actually voiced them, against people in their presence. He called this symptom *prejudicing autochthonous speech act (thought)*. Needless to say, the symptom of the patient believing that he/she speaks out such thoughts is referred to as *prejudicing autochthonous speech act*, while merely such thought is referred to as *prejudicing autochthonous thought*. Both symptoms are theoretically distinguishable, however, if the patients insist that they have spoken the hurtful words, they possibly suffer from hallucinations in which they are speaking and hearing their own voices, like the *hallucination of soliloquy* reported by T. Kobayashi and S. Kato [7]. From the viewpoint of Kato [1], both of these symptoms can be categorized together as PASA(T), because the important issue is that the patients believe that they have virtually attacked people in their presence, and whether they are actually voicing it or not is not quite relevant. Therefore, the patients often have a guilty conscience about such thoughts.

T. Seki discussed *Schädigungswahn* (delusion of persecuting others), “a sort of delusion of guilt in which the patients insist that they did what they cannot be actually involved and that they caused incidents or accidents caused injury and were the reason for incidents and accidents that they were actually not involved in at all”[8]. Seki presented patients with chronic schizophrenia who insisted that they were the cause of war, or that they were the cause of some serious incidents shown on TV. Unlike the pattern of aggression in PASA(T), aggression in the delusion of persecuting others tends to be directed widely at the society or the world rather than at people in their presence. However, the important issue is that in this symptom, a certain power of the patient works from the self toward others, taking on a life of its own, and that therefore the patient has a feeling of guilt because of such power not within his/her control. In this type of delusions, instead of being persecuted by others, the patients persecute the world around them. The patients want to and try to erase their supernatural influence on the world, so as to resume order in the world. Therefore, delusion of persecuting

others reflects a tendency towards re-establishment of their ego function and order in the world. This is a common feature in patients with PASA(T).

Most patients with PASA(T) present with this symptom during their recovery process, which is followed by nearly complete remission [1]. PASA(T) often appears after the patients have obtained relief from auditory hallucinations, sometimes with thought broadcasting [1]. In general, schizophrenic patients are located in a passive position in their pathological experiences: the patients are passively and one-sidedly spoken to by hallucinatory voices. In the case of PASA(T), however, the patients regain their activity to some extent: the patients' utterances or thoughts belong to the patients themselves, even though these are prejudicial and against their will. In other words, the orientation of the patients' pathological experiences is shifted from the others-to-self direction (or, egocentric direction) to the self-to-others direction (or, exocentric direction). Unlike in the delusions of persecuting others, in which the activity is directed diffusely to an unspecified number of people, the activity in PASA(T) focuses on the dual relationship (simultaneously, the duel-like relationship, in reference to the French word "duel") between people in their presence. We can find some semblance of self-healing and ego re-establishment in PASA(T); a schizophrenic patient who has been at the mercy of inexplicable forces puts together some mental activity of his/her own, albeit disturbed after all, and the recovery of this activity marks the beginning of recovery in actual relationship with others.

The theme of this paper is the visual equivalent of PASA(T) described by Kato; we call it *prejudicial autochthonous visual representation* (PAVR). Although PAVR can be roughly classified as a hallucination or a pseudohallucination, the patients are not at the receiving end of persecution, as is common in schizophrenia, but at the giving end. Furthermore, it is said that schizophrenic patients commonly have auditory hallucinations, and visual hallucinations are rather rare. PAVR is a pathological experience in the visual modality. It, therefore, has a psychopathologically unique nature and evinces interest in relation to its significance in the course of schizophrenia as compared to PASA(T).

Prejudicial Autochthonous Visual Representation and Recovery from Schizophrenia

Case 1, Lisa A., was a 20-year-old college student who mainly complained of PAVR in which she was injuring people in whose presence she was, or immediate family. Severe abulia and PAVR lasted for about a year and then gradually disappeared. Lisa exhibited infrequent auditory hallucinations and no thought broadcasting, unlike typical cases with PASA(T). The PAVR in Lisa seemed to be a visual equivalent of PASA(T), however, throughout the entire course of Lisa's illness, her abnormal experiences had a self-to-others orientation (exocentric direction). At present, she is in complete remission, possibly because her schizophrenic illness remained at a budding level; she exhibited few symptoms showing others-towards-self orientation (egocentric direction), which may be the core characteristic of schizophrenia. While most patients with PASA(T) reported by Kato [1] presented the symptom during their recovery phase from schizophrenia, Lisa showed PAVR during a prolonged exacerbation of her illness. If PASA(T) in Kato's patients was represented recovery of disturbed activity, in Lisa, PAVR was probably noted because she was never completely deprived of her mental activity by the schizophrenic illness.

Then, the question arises of why she had PAVR rather than PASA(T). It seemed that PAVR, a disturbance experienced in the visual modality, was a prominent feature of her illness. According to generally accepted knowledge, in schizophrenia, auditory hallucinations are by far the most common, followed in frequency by visual hallucinations, and then by tactile and olfactory or gustatory hallucinations [9]. If the patient prominently exhibits visual hallucinations, the clinician may consider a clinical diagnosis characterized by disturbance of consciousness, including substance-induced psychosis. However, visual hallucinations may be more common in schizophrenia than is generally acknowledged, the clinicians carefully inquired about them in addition to the major symptoms.

T. Sato and S. Iida [10] reported 9 chronic schizophrenic patients with persistent and almost fixed visual hallucinations. The patients often saw figures of certain persons, but not scenic hallucinations like our patients. They concluded that these patients have an affinity for thought via visual images, and that they are possibly related to eidetics. Interestingly, Lisa was a music academy student who was not an eidetic and did not even have any particular tendency towards visual thinking. Thus, it is difficult to explain based on her disposition why Lisa exhibited PAVR.

In PASA(T), the patients believe that they have voiced aggressive words against people present around which actually hurt them, even though the words were not actually spoken. In PAVR, the patients have similar aggressive thoughts, but in the form of visual images, however, these patients possibly know that such thoughts do not directly affect the relevant person, because they are merely visual imagery and not spoken out, although it is difficult to assert that they never feel that they hurt the people concerned. In other words, PASA(T) may be a more aggressive and more hurtful symptom than PAVR in the patients' reality from the patients' perspective.

As mentioned previously, PASA(T) probably represents recovery of mental activity and probably actually represents re-establishment of relationships with others. However, in Lisa's case, recovery of mental activity was incorporated merely in visual imagery, and did not represent re-establishment of relationships with others. It is likely that the healing momentum associated with the aggressive thoughts in PAVR was relatively weak, because of its visual nature. That is to say, Lisa's PAVR had aggressive content which did not directly hurt others, as if it were a mere picture. While this may be a sort of reflection of Lisa's defensive capability which possibly suppresses aggressiveness or destructiveness of the symptoms, this defensive capability possibly stabilized the schizophrenic symptoms and prolonged the duration of her symptoms.

When we take the latter two cases into consideration, we may suppose that PAVR does not have the power to promote the healing process of schizophrenia. Case 2, Mari, exhibited non-specific symptoms and occasional budding schizophrenic symptoms, but no typical schizophrenic symptoms. The budding schizophrenic symptoms, that is, the experience of being influenced but not quite reaching the level of delusion of persecution, including experience in which the objects around her appear to be assaulting her, had an others-to-self orientation (egocentric direction). At the same time, the PAVR had a self-to-others orientation (exocentric direction). These bidirectional abnormal experiences suggest still-unsettled rippling conflicts between damage and re-establishment of the patient's mental activities.

H. Nakai and K. Iwai [11] argued that a chronic state of schizophrenia represents antagonism between two forces; a *pathogenetic force* and a *resistance force*. The antagonistic

facet between the two forces generates various interfacial phenomena, including minor psychotic symptoms. The PAVR in Mari seems to be one of such interfacial phenomena. Mari had been standing at the gateway to a full-fledged psychotic breakdown, rather than in the chronic state of schizophrenia as described by Nakai and Iwai, however, Mari's condition represented the conflicting state in which the *pathogenetic force* and the *resistance force* were opposing each other and was therefore, still unsettled. In other words, disturbed activity and recovery of activity were in an equilibrium in which the two opposing forces never change significantly, and the patient proceeded neither towards healing nor towards deterioration.

Furthermore, the reason why Mari, who "feared belonging to companies or societies," remained at the gateway to schizophrenia may be that social withdrawal caused by significant loss of energy resulted in protection against the society and from deterioration of schizophrenia. Under such a condition, the *pathogenetic force* and the *resistance force* maintaining a fragile equilibrium generate an interfacial phenomenon or PAVR. If this were so, it is difficult to find sufficient momentum for self-healing or re-establishment of the ego in PAVR, unlike PASA(T).

Before the onset of the illness, Case 3, Norio, might have had an *as if* personality [12]; he identified with a friend and went along with him. But the friend changed jobs frequently. Norio unwillingly changed jobs frequently too with the friend. Later, he felt that he was always at the friend's beck and call. At the age of 27, he went into social withdrawal and gradually developed delusions of reference. Due to his fragile identity, PAVR was, in a way, a manifestation of his independence in the form of anger or aggression; on the other hand, it could also have been aggression leaking from Norio, which might have been suppressed. Kato [1] also noted the very same bilateral character about PASA(T). As for Norio, when he had PAVR, he felt only a little guilty and rather gloated, and his PAVR seemed to function wish-fulfillment images which he passively watched like a video clip, rather than representing consolidation of disturbed activity.

So, in Norio's case also, as in Mari's, we cannot find sufficient momentum for self-healing or re-establishment of the ego.

Prejudicial Autochthonous Visual Representation and Illocutionary Forces

PAVR is a pathological experience in the visual modality. Clinicians' attention is usually focused on auditory hallucinations in schizophrenia, and in fact, most of the patients complain of auditory hallucinations. However, visual hallucinations are also not very rare [13-15] and are frequent and vivid, especially in the acute phase [16].

Can PAVR be deemed as visual hallucinations? The visual nature of PAVR is somehow vague. The visual images come to the patients' head unwillingly, and they *see* the images in their heads. That is the reason we describe the symptom as *visual representation*. However, its intensity is far stronger than the banal visual representations in everyday life: PAVR appears to be a sort of pseudohallucinations in the Jaspersian meaning [17]. Sato and Iida [10] argued that visual hallucinations in schizophrenia are often located vaguely or clinicians cannot understand from the patient's words whether the hallucinations are located in the internal subjective space, namely, in the patient's head, etc., or in external objective space; even, in the case of visual hallucinations located in the external objective space, the hallucinations can hardly meet the definition of true hallucinations proposed by Jaspers [17],

because in schizophrenic patients' experiences, the external objective space itself has often become fragile and disordered [10]. Arieti [18] suggested that the reason why visual hallucinations are infrequent in schizophrenia is that, on awaking, the visual nerve center is occupied by perception from the external world, and there is no room for hallucinatory activities. Schizophrenic patients, who see hallucinations on awaking, therefore, tend to have visual hallucinations in the internal subjective space, for example, in their heads: from Arieti's viewpoint, when an awaking brain is exposed to visual hallucinations, they must be located outside the visual field.

Then, we discuss the clinical meaning of visual (pseudo)hallucinations. In contrast to schizophrenic auditory hallucinations, visual (pseudo)hallucinations like PAVR are *not* linguistic. Therefore, we introduce pragmatics into the discussion. We suppose that the function of PASA(T) described by Kato [1], briefly, consolidation and recovery of the patients' disturbed activities, is reflected by the fact that PASA(T) functions as an *act*. It makes no difference whether the patient with PASA(T) actually utters the words or remains silent, like hallucination of soliloquy [7], during the time that he/she believes that he/she is speaking. The important issue is that the patient believes that he/she is uttering prejudicial words in his/her subjective reality [1]. Whether or not the patient really speaks the words, PASA(T) is significant as an illocutionary act [2], and the patient becomes confused and feels guilty because the words might hurt others [2]. Kato [1] illustrated concrete examples of PASA(T) as follows: "I (inwardly) blurted out to a passenger, *Drop dead!*, or *That serves you right*"; "I (inwardly) blurted out to an old man, *half dead*." The curses here, "Drop dead!", "That serves you right", and "half dead", are not constative utterance, but performative utterance.

Even in prejudicing autochthonous *thought*, for example, "I can't help but think bad things about surrounding people. When I see a woman, I think, *she is a vamp*", the utterance of "she is a vamp" is not constative, but performative. In this sense, prejudicing autochthonous *thought* could also be called prejudicing autochthonous *speech act.*

Expanding on Lacan's concept [19], Kato [1] supposed that schizophrenic abnormal experiences are attributable to repudiation (forclusion) of the patient's activity itself, and that this repudiated activity simultaneously returns from outside and becomes PASA(T). Pragmatics may tell us that the returning activity is incorporated as an illocutionary force [2] of words in PASA(T), rather than in the meaning of words in PASA(T). When we translate *activity* in Kato's concept to *illocutionary force*, we can represent it as follows: in PASA(T), *illocutionary force* is repudiated from the subject, returns to the subject from outside, and is imposed on the subject; the imposed illocutionary force first appears as an autochthonous force belonging to nothing, then relocates to the subject; after relocation to the subject, the imposed illocutionary force reveals its genuine character and is directed at others, mostly people present around. This is our interpretation of the causal mechanism of PASA(T).

In first place, Kato [20] assumed that the *force of nonsense*, which is unidentifiable, essentially takes on an absolute alterity, and cannot be reduced to any particular meaning, and exists on the basis of schizophrenic hallucinations and delusions. He claimed that auditory hallucinations are not merely abnormal experiences in which the patient hears voices, but also experiences accompanied by certain forces which cannot be reduced to any particular meaning, as can be attested to by some patients' statements, as follows: "someone's voice or many people's voices…I can't recognize what they are speaking, but their voices ring ding-

dong in my head"; "I hear nonsensical words, or rather pressure." [1] The patients described the auditory hallucinations as if they were actually a physical force.

Illocutionary force in pragmatics exerts its effects when the utterance is incorporated in an appropriate situation, or in an appropriate interpersonal relationship [2]. It cannot exert its effect directly in the absence of an appropriate situation or someone to talk to. On the other hand, when *I*, the agent of utterance, does not separate out in a schizophrenic abnormal experience, the illocutionary force may not be able to exert its effect. In schizophrenic hallucinations, if the patient gives the speaker a certain name, the speaker is not a real person: in other words, there is nobody who speaks out hallucinations. However, we must point out pathological illocutionary forces in schizophrenic hallucinations, when we see schizophrenic patients who obey the hallucinatory voices, or patients influenced by hallucinations with significant but nonsensical contents. More specifically, extremely intensive force equivalent to illocutionary force is activated in schizophrenic hallucinations in the absence of an appropriate situation and occupies a part of the *force of nonsense*. If the pathological illocutionary force is located in an appropriate situation and helps in re-establishing *I*, the agent of utterance, it may have a healing momentum, as described by Kato [1].

Kato [1] reported that the following complaints fall under the category of *prejudicing autochthonous thought*: "When I see a person, I imagine myself slashing the person's body"; "When I see a person, I imagine myself slapping the person's face"; "I can't stop imagining scragging the person with a chain, or cutting the person's head with a sickle." If this *imagination* were a visual image, these complaints would represent PAVR. However, it is uncertain whether these thoughts in the patients are linguistic, visual, or body-movement related. By the same token, our patients possibly had a linguistic element and a body-movement element with visual PAVR, because our mental activities are linked to various perceptional modalities. Then, we can surmise that both PASA(T) and PAVR are located within the same spectrum. PAVR is a visually intensive type of *prejudicial autochthonous phenomenon*. However, a visual image by itself cannot have an illocutionary force. When we imagine injuring a person who we have a grudge against, the aggressive emotion in the visual image is not very strong. We have an irresistible urge to take revenge against the person and utter oaths: for instance, "Fuck you." However, the moment we utter such a curse, we surely recoil at the rampancy and violence of the utterance. We can see the advent of the illocutionary force in such a situation. In this case, aggression in the illocutionary force is directed at others from us, while in the case of PASA(T), the aggression appears automatically and is imposed on the subject.

As long as the prejudicial experience remains visual imagery, the pathological illocutionary force cannot exert its effect. Thus, patients with PAVR may have relatively less strong feelings of injuring other people than PASA(T). The image is probably equivalent to the consequence of an act unwillingly done, as if the patient were merely looking at the consequence of the act. From the viewpoint of pragmatics, what is imposed on the subject in PAVR is not *force,* but the *meaning* of *scragging a person* or *ripping a person*. This discussion surely obviously applies only to theoretically pure visual images. Actual PAVRs may contain additional linguistic elements and some pathological illocutionary forces.

Meanwhile, it appears that the visual images in PAVR can be classified into two types: a type with third-person images, as observed in Case 1 and Case 3, in which the patients' prejudicial visual imagery is like a video clip recorded by a third person, and the type with first-person images, as observed in Case 2, in which the person's visual imagery is like a

video clip recorded by the person himself/herself. The performative element in the latter seems to be more powerful than that in the former; the first-person images probably have a stronger pathological illocutionary force. But then, the patients' complaints are floating and ambiguous; the patients themselves are often unable to define whether their images were the first-person or the third-person type.

As mentioned above, PASA(T) and PAVR can be incorporated in a spectrum of *prejudicial autochthonous phenomena*. In this spectrum, *prejudicing autochthonous speech act*, e.g., "I involuntarily blurted out to an old man, *half dead*," most strongly represents a illocutionary force, while *prejudicial autochthonous thought*, e,g., "I involuntarily think, *half dead*, when I see an old man," shows the illocutionary force in a more weakened form. We cannot demonstrate the visual equivalent of the speech act, "half dead": the illocutionary force, or the aggression incorporated in the words "half dead" may be transformed to an image of the old man nearly killed by the patient. This transformation may take away the illocutionary force from the speech act.

Because *prejudicing autochthonous speech act* is not normal speech, and *I*, the subject of the speech act, and an appropriate situation are not sufficiently well established, the illocutionary force cannot be located at an appropriate situation and tends to exhibit an inappropriate character, that is, the *force of nonsense*. In such a risky balance, the *force of nonsense* in PASA(T) can change to the normal illocutionary force involved in the re-establishment of the disturbed ego. Kato [1] assumed that an elevation of the mental dynamis, which may be equated to *acceleration of the activity in the remission activity process of schizophrenia,* underlies the emergence of PASA(T). The above-mentioned pathological illocutionary force emerges on the basis of this *acceleration of the activity*. The pathological illocutionary force is ambiguous in character: while it helps to relocate the subject in the society through dual/duel relationship between people around the patients, there is the risk of its recklessly expanding the dymanis to reactivate pathological symptoms. Thus, the pathological illocutionary force is coexistence of the *pathogenetic force* and the *resistance force*. When it emerges as the *resistance force*, it has the healing momentum, however, it can also be related to deeper layers of the schizophrenic pathology.

Our three cases were neither in the remission phase of schizophrenia, nor showing any acceleration of disease activity. The pathological illocutionary force is obscure, too. Thus, the PAVR in our patients may be a reflection of an interfacial phenomenon between the *pathogenetic force* and the *resistance force*, however, neither force might be as strong as that seen in PASA(T). Our patients were at the gateway to a full-fledged psychotic breakdown. They suffered from vulnerability of the ego functions and exposed to the menacing forces operative in schizophrenia. They resisted budding schizophrenia with extreme difficulty. The still weak *pathogenetic force* and the disordered *resistance force* generated an interfacial phenomenon, namely, *prejudicial autochthonous visual representation*, in which the pathological illocutionary force was safely ensconced within the capsule of the visual imagery.

CONCLUSION

Prejudicing autochthonous speech act (thought) described by Kato [1] is often observed during the recovery phase from schizophrenia and appears to represent self-healing and ego re-establishment. On the contrary, *prejudicial autochthonous visual representation*, its visual equivalent, is not necessarily observed during recovery from schizophrenia and is not always followed by remission. It more likely represents a stalemate between deterioration and remission.

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Chapter 5

SOCIAL CLASS TRAJECTORY AND PSYCHOTIC DISORDERS: A COMPARISON BETWEEN SCHIZOPHRENIA, BIPOLAR DISORDER, MAJOR DEPRESSIVE DISORDER, AND COMMUNITY NON-CASES

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ABSTRACT

The present study examines differences in inter- and intra-generational social class trajectory among patients with schizophrenia, bipolar disorder, major depressive disorder and community non-cases. Data were collected between 1983 and 1989 by interviewing all psychotic admissions to fifteen hospitals providing inpatient psychiatric services in the Baltimore Metropolitan Area. Social class of the patient's family of origin and the patient's own social class at the time of admission were obtained through standard survey questions on occupation. Inter-generational differences in social class suggest a lower origin social class for psychotic patients with major depressive disorder than for patients

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with bipolar disorder, schizophrenia or community non-cases. A multi-group structural equation analysis showed that the magnitude of the effect of educational achievement on social class at the time of hospital admission is strongly patterned after by type of psychotic disorder. Patients with schizophrenia showed a more pronounced "downward drift" (lower returns to education) than patients with bipolar disorder, major depressive disorder and community controls.

INTRODUCTION

The inverse association between social class and schizophrenia has been a repeated finding in mental health research (Eaton, Day, and Kramer, 1988; Kohn, 1973). This association has found renewed empirical support during the eighties, due to the availability of prospective designs and DSM-III definitions of case (Bruce, Takeuchi, and Leaf, 1991; Dohrenwend et al., 1992; Murphy et al., 1991). Both social causation and social selection/drift hypotheses have been proposed to explain the association between class and major psychosis (Dohrenwend et al., 1992; Eaton, 2001; Fox, 1990; Cooper 2005a,b; Muntaner et al., 2004; Cantor-Grae and Selten 2005; Byrne et al., 2004). The social causation hypothesis states that factors associated with lower social class life chances contribute to schizophrenic breakdown. The selection/drift hypothesis, on the other hand, emphasizes the detrimental effect of psychosis on a person's social class position. "Selection" refers to the inter-generational downward mobility experienced by psychotic patients with respect to their parents' social class (i.e., origins), and "drift" alludes to the person's downward mobility after the onset of psychosis with respect to the patient's own educational achievement or premorbid occupation (i.e., destination) (Lewine, 2005). With few exceptions (Fox, 1993), studies of inter-generational mobility, in which father's class is compared to son's class, have established additional support for the "selection" hypothesis for schizophrenia (Aro, Aro, and Keskimaki, 1995; Cohen, 1993; Dauncey, Giggs, Baker, and Harrison, 1993; Dohrenwend et al., 1992; Jones et al., 1993; Rodgers and Mann, 1993).

In this study, our preliminary step in modeling the process of social class trajectory is the testing of the selection/causation hypothesis through a comparison of the social origins of schizophrenic patients with other psychiatric patients and a comparable community sample (Dohrenwend et al., 1992; Eaton, 2001). Less attention has been devoted to the process of "drift" in social class trajectory. This process is crucial to investigations of the course and quality of life among patients with schizophrenia (Eaton, 2001). The identification of the mechanisms leading to a drop in social class position may lead to the design of appropriate and timely interventions (Jones et al., 1993; Kessler, Foster, Saunders, and Stang, 1995). Kessler et al. (1995) have shown that early-onset psychiatric disorders are associated with truncated educational achievement in a national representative sample drawn from the forty-eight contiguous states. Jones et al. (1993) studied a hospital sample of 195 psychotic patients that included 100 patients with schizophrenia in the UK. By comparing the best premorbid occupation with current occupation, they found a "drift" following the onset of psychosis among patients with schizophrenia and affective disorders. Nevertheless, due to the low number of cases, the authors combined schizophrenia with schizophreniform disorders, and bipolar disorder with depression and other psychoses. As a consequence, there is no evidence regarding the generality of the "drift" process for specific psychotic disorders.

Thus, the second aim of the present study is to investigate the specificity of the "drift" hypothesis for schizophrenia, as compared to other psychotic disorders (bipolar, major depression and community non-cases), first admission patients and comparable community residents from a delimited geographical region from where the patients were drawn. To test the hypothesis of equal drift among psychotic disorder patients we use a social class trajectory model (Blau, Duncan, and Tyree, 1978; Nakao and Treas, 1994). The social class trajectory model conceptualizes mobility in terms of the influences that individuals' socioeconomic origins, and other attributes, have on their life chances, specifically on their occupational status (Blau, 1992). In addition to examining the effect of socio-economic background, different versions of the social class trajectory model have explained the effects that variables such as migration and fertility have on careers (Blau, 1992).

We examine the association between patients' educational achievement and occupational status at first hospital admission. Although the "drift" process continues after first admission, an investigation of its differences during the early stages of the illness can suggest early interventions among specific groups of patients. Thus, our study determines "drift" differences in the intragenerational stability of socioeconomic stratification between patients affected with schizophrenia, affective disorders and community controls.

METHODS

Schizophrenia, Bipolar Disorder and Major Depressive Disorder Patients

Participants were drawn from a large sample of psychotic patients in the greater Baltimore area (Pulver et al., 1992). This sample was developed by systematic screening of all admissions presenting psychotic symptoms to 15 facilities providing inpatient psychiatric services in the greater Baltimore Area over a six-year period (June 1983-April 1989). These hospitals included all psychiatric hospitals in the Baltimore Metropolitan Statistical Area (five state psychiatric hospitals and two private psychiatric hospitals), and eight community hospitals with psychiatric services --60 per cent of their type. Patients were considered eligible for inclusion in the sample if they met the following criteria at hospital admission: 1) white; 2) at least 18 years of age; 3) had a psychotic diagnosis or psychotic symptoms.

Procedures

Patient Participation

Patients who gave their informed consent were administered a semi-structured diagnostic interview (a modified version of the DIS: Robins, Helzer, Croughan, and Ratcliff, 1981), which elicited information about current psychiatric state and lifetime history of symptoms. The major modifications to the DIS included: 1) administration of the interview by a master's degree level psychologist, or social worker who had prior experience with psychotic patients; 2) the addition of questions about a wider range of psychotic experiences; 3) changes in the probe flow in the section which inquires about psychotic symptoms, so that "below critical" symptoms would be treated in the same way as unexplained, severe symptoms.

Response Rates

Over the data collection period (1983-1989), 3,073 patients met the inclusion criteria; 1,670 (54%) of the patients entered the sample. The most frequent reasons for non-participation were that patients refused to participate (18%) or were discharged from the hospital before they could be approached by a member of the research team (21%). To assess selection bias, respondents and non-respondents were compared with respect to the following set of variables abstracted from their admission forms: gender, age, marital status, place of birth (Maryland versus other), usual occupation, education and diagnosis. Respondents were significantly more likely than non-respondents to be male (58% versus 53%), younger (29% versus 23% under age 25), and single (62% versus 55%).

Best Estimate Research Diagnosis

Patients were diagnosed through a "best estimate" procedure utilizing multiple sources of information to formulate DSM-III diagnoses. Six months after the patient's index admission, one of the study's psychiatrists reviewed the results of the patient's diagnostic interview, reviewed admission and discharge summaries from all of the patient's hospitalizations and telephoned the patient or an informant to clarify the clinical picture and to acquire information about six-month outcome functioning. A series of inter-rater reliability evaluations were conducted over the course of the data collection period. In these evaluations, up to six psychiatrists independently formulated diagnoses for a group of 19-30 patients. Kappas reflecting agreement for the diagnosis of schizophrenia, bipolar disorder, major depression or "other disorder" were within acceptable limits (range = .61 to .84). The average Kappa for schizophrenia was .83. The analyses in this report utilize data from first inpatient admission patients in the sample who received the following best estimate research diagnoses: 1) schizophrenia; b) bipolar disorder; and c) major depressive disorder.

Measures of Sociodemographic Characteristics

During the diagnostic interview, patients were administered standard survey questions to assess sociodemographic characteristics such as age, years of education, and occupation. The patient's last occupation during the 12 months prior to admission, and that of the patient's head of household at age 16, were assessed with open-ended questions from the U.S. Labor Force Surveys. The questions were: "What kind of work (did/are) you do(ing)? e.g. electrical engineer, sales clerk, typist", and "What (are/were) your most important activities or duties?, e.g. type, keep account books, sell cars". Trained coders used verbatim responses from the patients to categorize jobs into one of 502 detailed occupational categories of the 1980 U.S. Census. We used the Duncan Socio-economic Index (SEI) as a measure of occupational status. The original (Duncan, 1961) and revised (Stevens and Featherman, 1981) versions of the Duncan SEI were used to assign scores to the patient's head of household and patient census occupational categories, respectively. We used the original SEI to assess the patient's head of household occupational status and the updated SEI to assess the occupational status of the patients at admission.

Community Controls

The community sample of non-cases was based on a telephone survey of the population of white residents between the ages of 21 and 89, living in the Baltimore Metropolitan Statistical Area at least one year between 1983 and 1989 (MSA; Baltimore and surrounding counties). The Waksberg telephone sampling method (Olson, Kelsey, Pearson, and Levin, 1992; Waksberg, 1978) was used and thought to be appropriate for the following reasons: 1) the Baltimore MSA has high availability of telephones [95.3 per cent of households have telephones (Survey Sampling, Inc., 1991)]; and 2) it ensured the inclusion of unlisted numbers [27.5 per cent of households in the Baltimore MSA (Survey Sampling, Inc., 1991)]. Four hundred respondents were obtained using this method, with a response rate of 69 per cent and a refusal rate of 1 per cent. An effort rate of up to eight calls at different times on different days per prospective respondent was employed. A telephone interview was administered that included the questions on sociodemographic characteristics administered to the sample of psychotic patients (see "measurement of sociodemographic characteristics above). Two-hundred and sixty respondents had an occupation while living in the Baltimore area and thus were selected as the community non-cases in our study. SEI scores were assigned to occupation codes as in the patient samples.

RESULTS

Preliminary Analyses

Because of age differences in onset of psychotic symptoms across disorders, length of illness was included and thus controlled in early models but later removed due to its high correlation with age. We obtained essentially similar results when we repeated the analyses using length of illness instead of age. Males and females were analyzed separately for comparison. We did not find substantive differences across gender subsamples. Therefore we report findings from the total sample.

Social Selection: Origins

Differences in social origins (father's SEI) between the four groups were assessed with one-way analysis of variance (ANOVA) followed by post-hoc comparisons. In order to determine how the four groups differ we used the Tukey's test. This test is used to determine which of the differences between disorder group means are significant and which are not.

Differences in Social Origins

The ANOVA revealed a significant effect of disorder group ($F(3)=4.35$, $p<.05$). Tukey's test revealed that the means for patients with major depressive disorder (41.3, $SD=24.8$) were lower ($p<.05$) than the means for patients with schizophrenia (48.2, $SD=25.7$), bipolar disorder (49.5, $SD=25.1$) and community non-cases (50.4, $SD=22.5$).

Thus, although the social origins of the schizophrenic cases were lower than those of community non-cases, they were far from significantly so. This lack of significance is striking given the number of individuals in the analysis. It is the major depressive cases, rather than the schizophrenic cases, who had significantly and notably lower social origins (approximately one third of a standard deviation) than both other psychotic and community control groups.

Social Class Trajectory

To simultaneously assess the social class trajectory model on different subsamples of psychotic patients and community non-cases, we used structural equation modeling (e.g., Ganzeboom, Treiman, and Ultee, 1991; Jöreskog, 1978; Schooler, 1983).

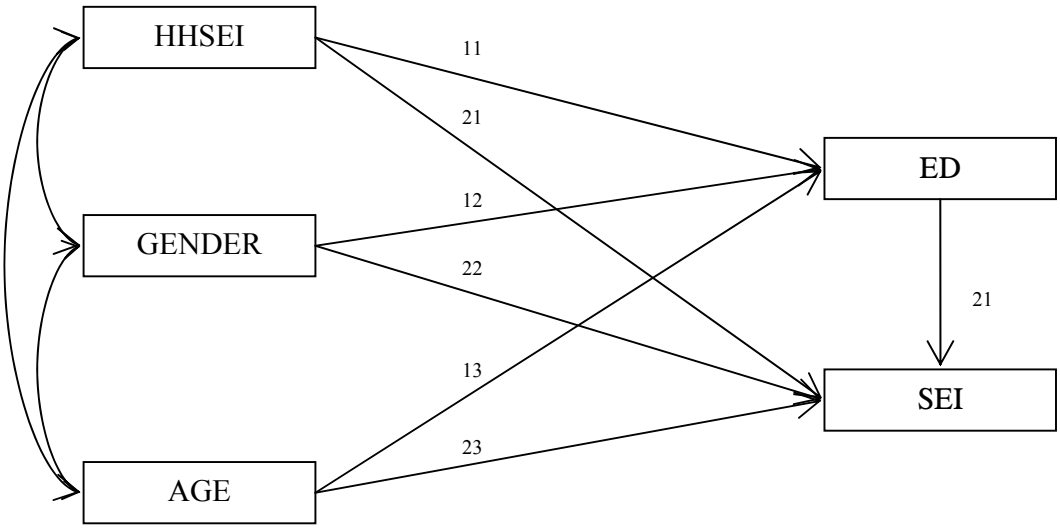

Figure 1. Structural relations among explanatory and outcome variables for the class trajectory model

Figure 1 presents variables and implied structural relations among them. The following variables were included in the model: age (AGE), gender (GENDER), head of household's years of education and occupational status (HHSEI), and patient's years of education (ED) and occupational status (SEI). These variables are represented in rectangles because they were all measured (i.e., there are no latent variables in our model). LISREL 8 allowed us to produce simultaneous estimates of the structural relations from four input polychoric matrices of covariances among variables (Jöreskog and Sörbom, 1993). Each disorder subsample (i.e., schizophrenia, bipolar, major depressive disorder, community non-cases) contributed with one input matrix to this multisample model (available upon request).

Model Specification, Identification and Parameter Estimation

Figure 1 presents the path coefficients representing the structural relations among variables (i.e., the social class trajectory model). Paths γ_{11} and γ_{21} represent the effects of father's occupational status on respondent's education and occupational status respectively. Similarly, paths γ_{12} and γ_{22} correspond to the estimates of respondent's gender on

respondent's education and occupational status, and paths γ_{13} and γ_{23} represent the effects of respondent's gender on respondent's education and occupational status. Lastly, β_{21} provides an estimate of the returns to education, the association between respondent's education and occupational status that allows us to test the hypothesis of equal "drift" between psychotic disorders.

Testing Fit

The overall fit of the stacked models was evaluated with a chi-square goodness of fit statistic. This chi-square statistic is based on the similarity between the predicted and the observed covariance matrices.

We began by estimating the "constrained" between-group model which constrained each of the seven hypothesized paths to be invariant across psychotic disorders. Next we estimated seven "unconstrained" between-group models by relaxing, one by one, the equality constraints for each of the seven path coefficients across the four groups. Unconstrained models did not contain specific cross-group invariance constraints (e.g., the path between education and occupational status was allowed to vary across the four groups). Thus, structural parameters were "freely" estimated within psychotic disorder and community non-case samples. If the chi-square for the constrained models was significantly greater than the chi-square for the unconstrained model, the assumption of invariance of a given structural parameter across samples was rejected. We choose a criterion probability value of .05 for the chi-square goodness of fit tests.

Parameter Estimates

Table 1 presents the estimated coefficients in the social class trajectory model for schizophrenia, bipolar, major depression and community non-case samples. Head of household occupational status had statistically significant positive effects on respondent's education for all groups. The effect of head of household occupational status on educational status was smaller for the community non-cases (.15) than for the groups of psychotic patients. Only community non-cases show a positive and significant effect of head of household socioeconomic status on occupational status. These results suggest that psychotic patients can take advantage of an beneficial economic background when it comes to years of education. In fact they did so more than the community controls. However, psychotic patients are unable to translate an advantageous socioeconomic background into high occupational status.

The path between education and occupational status argues against the hypothesis of equal "drift" between schizophrenia, bipolar, and major depression when this path is permitted to vary across the four groups. The relationship is weak and non-significant for schizophrenia, weak but significant for bipolar disorder, and moderate and significant for major depression. Returns to education follow a gradient from schizophrenia to community non-cases.

Multiple Group Comparisons

Our unconstrained models provided the best estimated coefficients for each group separately. Our baseline – constrained model – allow us to test the possibility that the parameter estimates were the same across diagnostic groups. Next, we looked at which paths

the modification indices (MI) suggested should be opened (i.e., the fit would improve significantly) for a given population, while the remaining groups were being kept equal (Bollen, 1989). Thus, we opened those paths that would improve the overall model fit while keeping the remaining paths constrained to be equal. This method provides a rationale for arguing that a given path was significantly different across populations.

Table 1. Maximum likelihood estimates for multigroup structural model of schizophrenia, bipolar, major depression and community non-cases[a]

Path[b]	Unconstrained models[d]				Constrained model			
	SCHI[c]	BIP	DEP	CONT	SCHI	BIP	DEP	CONT
HHSEI->ED	.70*	.69*	.53*	.15*	.61*	.61*	.61*	.61*
HHSEI->SEI	-0.05	0.04	0.02	.12*	0.05	0.05	0.05	0.05
GENDER->ED	-.17*	-.11*	-.08*	0	-0.12	-0.12	-0.12	-0.12
GENDER->SEI	0.08	0.02	-0.05	-0.08	0.01	0.01	0.01	0.01
AGE->ED	-.16*	-.19*	-.19*	0.1	-0.14	-0.14	-0.14	-0.14
AGE->SEI	.23*	.36*	.24*	.29*	.28*	.28*	.28*	.28*
ED->SEI	0.1	.15*	.27*	.55*	.33*	.33*	.33*	.33*

* significance of Wald test: $p < .05$.

[a] Our model was tested using the LISREL 8 program for structural equations (Joreskog and Sorbom, 1993). The program input were four 5x5 covariance matrices. The simultaneous between-group model allowed us to test whether the size and sign of the hypothesized paths was invariant across groups of psychotic disorders and community controls.

[B] See figure 1 for the status attainment model. HHSEI= head of household occupational status; ED = Education; SEI = occupational status.

ED=education.

[C] SCHI=schizophrenia (n=369); BIP=bipolar disorder (n=251); DEP=major depressive disorder (n=130; CONT= community non-cases (n=260).

[D] The "unconstrained" between-group models do not contain the cross-group invariance constraint for a specific path. For each model we present only the estimates corresponding to "unconstrained" path. On the right side of the Table, we present a baseline "constrained" between-group model that constrains each of the hypothesized paths to be invariant across psychotic disorders.

Table 2 provides a summary of goodness-of-fit indices for unconstrained and constrained multi-sample structural models. Parameter estimates for the relationships between head of household occupational status and education, between age and education, and between education and occupational status were different across groups, confirming differences in the social class trajectory process of patients with schizophrenia, affective psychosis and community non-cases. Our final model can best be seen in Figure 2 which presents unstandardized parameter estimates.

Table 2. Goodness-of-fit indices[a] for between-group comparisons

Model	X^2	df	p	X/df AIC[b]
Baseline				
Unconstrained between-group model[c]	133.6	21		6.3
Path HHSEI->ED				
Constrained between-group model	74.4	18		4.1
X^2 difference				
(constrained-unconstrained)[d]	59.2	3		
Path HHSEI->SEI				
Constrained between-group model	128.3	18		7.1
X^2 difference				
(constrained-unconstrained) [d]	5.3	3	ns	
Path GENDER->ED				
Constrained between-group model	128.5	18		7.1
X^2 difference				
(constrained-unconstrained) [d]	5.1	3	ns	
Path GENDER->SEI				
Constrained between-group model	128.6	18		7.1
X^2 difference				
(constrained-unconstrained) [d]	5.0	3	ns	
Path AGE->ED				
Constrained between-group model	119.4	18		6.6
X^2 difference				
(constrained-unconstrained) [d]	14.2	3		
Path AGE->SEI				
Constrained between-group model	130.4	18		7.2
X^2 difference				
(constrained-unconstrained) [d]	3.2	3	ns	
Path ED->SEI				
Constrained between-group model	90.9	18		5.0
X^2 difference				
(constrained-unconstrained) [d]	42.7	3		

[a] The overall fit of the stacked models was evaluated with a chi-square goodness of fit statistic. This chi-square statistic is based on the prediction of the predicted and the observed covariance matrices.

[B] AIC indicates the information criterion of Akaike (1987). This goodness-of-fit index is based on the chi-square. The smaller the value of the AIC the better the model fits.

[C] The "unconstrained" between-group model does not contain any cross-group invariance constraint. Structural parameters are "freely" estimated within psychotic disorder groups. On the other hand, the "constrained" between-group model constrains each of the 9 hypothesized paths to be invariant across psychotic disorders.

[D] If the chi-square for the constrained model is significantly greater than the chi-square for the unconstrained model, the assumption of invariance of structural parameters across psychotic disorder groups is not defensible.

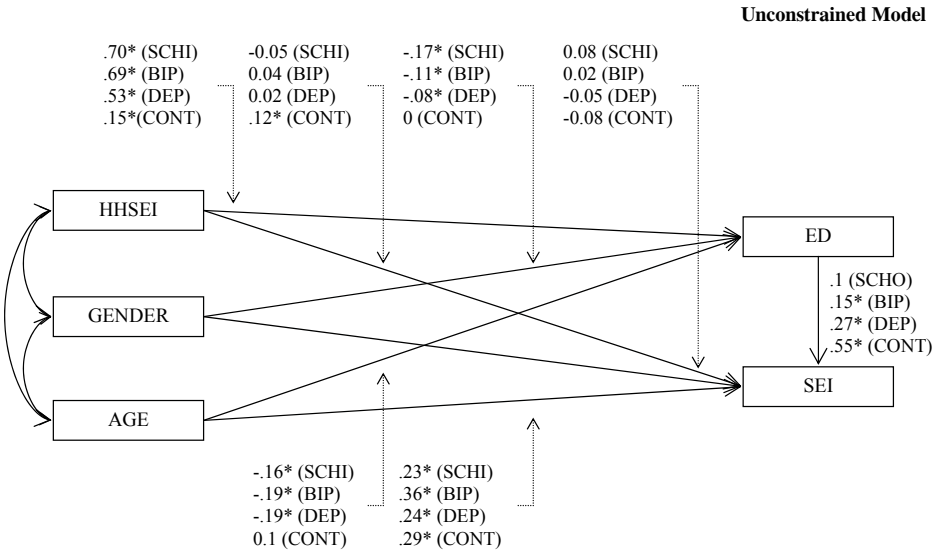

Figure 2. Parameter estimates for unconstrained and constrained multi-sample structural models of class trajectory among psychotic patients and community controls

DISCUSSION

Differences in social origins (i.e., father's SEI) are consistent with previous results in psychiatric epidemiology. For example, in the ECA study of five US metropolitan areas, lower social stratification emerged as a strong risk factor for major depressive disorder (Anthony and Petronis, 1991; Bruce et al., 1991). Longitudinal evidence comparable to the ECA study on social stratification as a risk factor for Bipolar Disorder does not exist. Nevertheless, our finding that Bipolar disorder patient's social origins are close to community non-cases is in line with previous findings of a middle class background among bipolar patients (e.g., Andreasen, 1987). However, results showing that the social origin of patients with Schizophrenia do not differ significantly from community non-cases are also in concordance with recent studies in the United States (Fox, 1990) and abroad (Dohrenwend et al., 1992).

The social class trajectory model obtained an acceptable overall fit across all groups indicating that it is a reasonable model for psychotic patients and community controls from the greater Baltimore Metropolitan Area. This is not surprising because similar models have been tested many times in the US population during the last two decades (Blau, 1992). There were several potential influences in the process of social class trajectory that were not included in this simple structure. Potentially relevant individual (e.g., migration, ethnic origin; Eaton et al., 1988) and social (e.g., institutional arrangements governing the transition between education and occupation; (Kerckhoff, 1995) variables were absent from the present social class trajectory model. However, our main goal was not to provide an expanded model

of social class trajectory but to compare the social class trajectory process of patients with schizophrenia with that of affective psychosis and community non-cases.

Social origins showed an expected positive effect on social class trajectory, even among psychotic patients. Thus, we found a positive association between the occupational status of head of household when the patient was 16 and the patient's own educational and occupational achievement. In fact, the effect of head of household occupational status on education is stronger for psychotic patients than for community non-cases. This indicates that, in spite of the negative effect of mental illness on educational achievement (Kessler et al., 1995), psychotic patients can translate an advantageous socioeconomic background into relatively more years of education. A likely health policy implication is that patients with schizophrenia and bipolar disorder living in disadvantaged households might benefit from social services to enhance their educational achievement.

CONCLUSION

Our findings give some support to the hypothesis that returns to education (i.e., "drift") vary between patients with schizophrenia and patients with affective psychosis. Educational attainment still results in some occupational payoff (i.e., there is a positive relationship between patient's educational level and occupational attainment) for patients with affective psychosis and schizophrenia. However, as Figure 2 indicates, the positive effect of years of education on occupational status is not the same across groups. The size of the association between years of education and occupational status is lower for schizophrenia and bipolar disorder than for major depression patients and community non-cases. Thus, a clear "drift" is observed for patients with schizophrenia and bipolar disorders in comparison to patients with major depression, as well as in comparison to community non-cases. These results are compatible with the claims of Jones et al. (1993) that the "drift" process is a general phenomenon across psychotic disorders. However our finding with larger and specific groups of psychotic disorders also evidence heterogeneity in the "drift" process across psychotic disorders. We observed an important difference in returns to education between patients with schizophrenia and patients with affective psychosis.

The comparison of returns from education between patients with schizophrenia and bipolar disorder suggests potential explanations for the observed differences in the "drift" process across the most severe forms of psychotic breakdown. Psychotic patients still face a severe burden of stigma which should partially account for differences in returns to education between diagnostic groups and community controls (i.e., the modified labeling perspective; Link, Struening, Rahav, Phelan, and Nuttbrock, 1997; Rosenfield, 1997). However, as opposed to patients with schizophrenia, patients with bipolar illness might have benefited from increasingly less stigmatizing attitudes towards their illness (e.g., Goodwin and Jamison, 1990; Jamison, 1993). The frequent observation of a seemingly uncommon number of intellectual achievers among bipolar patients (Andreasen, 1987; Goodwin and Jamison, 1990; Keynes, 1995) suggests that bipolar patients might be less vulnerable to the stigma associated with psychotic disorders than schizophrenic patients. Although this might be the case for a small number of truly exceptional artists (Jamison, 1993), our data strongly suggests that on average, the effect of a putative lower stigmatization on the occupational achievement of

bipolar patients is still modest, albeit larger than among patients with schizophrenia. An alternative explanation for the observed lower returns from education among schizophrenic patients is that the effects of schizophrenia on workplace social cognition are more severe than those of bipolar illness (Penn, Corrigan, Bentall, Racenstein, and Newman, 1997; Schooler and Spohn, 1982) thus greatly thwarting the transformation of human capital into occupational status.

Occupational attainment at the time of first hospitalization seems to be a matter of selection for major depression patients and of drift for schizophrenia and bipolar patients. According to the association between parent's status and their children's education, schizophrenia and bipolar disorder patients take advantage of their parent's social capital and are particularly disadvantaged by its absence. Future studies should determine the role of economic (e.g., access to health care) or cultural resources (e.g., early disease awareness) play in this process.

It is possible that the effects of social structural factors are different in this population than would be the case in a non-hospitalized population of psychotic individuals or in a non-metropolitan area (e.g., Marshall, Rose, Newby, and Vogler, 1988). However, by sampling all the inpatient psychiatric hospitals of the Baltimore Metropolitan Statistical Area during the period 1983-89 we can assume that virtually all individuals with major psychotic disorders would be in contact with a hospital of this network (Eaton, Romanoski, Anthony, and Nestadt, 1991), i.e., there is a very small non-hospitalized population of psychotic individuals (Kessler, Olfson, and Berglund, 1998). In addition to the role of stigma mentioned above, the present analyses generate substantive questions which future research should address. For example, what accounts for the process of diminished returns to education among patients with schizophrenia and bipolar disorder? Namely, can early diagnosis, treatment and rehabilitation prevent such diminished returns? Does the drift occur in the transition between school and first occupation, or is it related to exposure to workplace stressors once in the labor force (Lennon, 1995; Link, Lennon, and Dohrenwend, 1993; Link et al., 1997). Furthermore, how do transitions in and out of the labor force affect the "drift" process?

We need to know more about the sociological and psychological processes of social class trajectory among patients with schizophrenia and other psychotic disorders. Our study provides initial evidence of the generality of the "drift" phenomenon for psychotic disorders and highlights important differences in returns from education among patients with schizophrenia, bipolar disorder, major depression, and community non-cases.

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END NOTES

[1] Weighting the sample from community hospitals to reflect gender and age composition of its reference population of community hospitals in the are does not produce a notable change in estimates (e.g, Pulver, 1992).

[2] We do not use the term "social class" as "social class" is considered distinct from socioeconomic stratification or occupational stratification. Its usage is limited to groups differentiated by their social relations (manager vs non-manager; employer vs employee).

[3] A structural equation model needs to be identified before it can be estimated. Identification allows us to ascertain whether the is enough information in our model to obtain unique parameter estimates (Bollen, 1989). Our structural equation model is a just-identified recursive model (see Bollen, 1989) that can be expressed in the following matrix form:

$$B_{(2\times2)}y_{i\ (2\times1)}+\Gamma_{(2\times3)}x_{i\ (3\times1)}=Y_{i\ (2\times1)}$$

The maximum likelihood method of parameter estimation was used to analyze this simultaneous linear structural equation system.

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Chapter 6

SUICIDE RISK IN SCHIZOPHRENIA WITH PARTICULAR ATTENTION TO AWARENESS OF ILLNESS AND STIGMATIZATION

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ABSTRACT

Suicide is a major cause of death among patients with schizophrenia. Literature reports that at least 4.9-13% of schizophrenic patients die by suicide, but it is likely that the higher end of range is the most accurate estimate. There is almost total agreement that the schizophrenic patient who is more likely to commit suicide is young, male, white, has never married, has good premorbid function, has post-psychotic depression, and has a history of substance abuse and suicide attempts. Hopelessness, social isolation, awareness of illness, and hospitalization are also important risk factors in schizophrenic individuals who commit suicide. Deteriorating health with a high level of premorbid functioning, recent loss or rejection, limited external support, and family stress or instability are other risk factors traceable in patients with schizophrenia who commit suicide. These patients usually fear further mental deterioration and experience excessive treatment dependence or loss of faith in treatment. Awareness of illness has been reported as a major issue among schizophrenic patients who at risk of suicide. Yet, some scholars highlighted that insight into illness does not increase suicide risk. Reviewing the literature the authors found that only insight into certain elements of the illness can increase the risk of suicide. Implications for strategy to adopt in dealing with the increased insight both during pharmacotherapy and psychotherapy are discussed. The authors also discuss awareness of illness, suicide risk and stigmatization among schizophrenic patients.

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Suicide is the single major cause of death among patients with schizophrenia. Literature abounds with reports on risk factors and prevention of suicide among these patients but death by suicide are still alarming and do not show any reduction. Tatarelli, Pompili and Girardi (2006) have edited an entire volume dedicated to the issue and managed to collect papers written by opinion leaders. The main aim of this book, which the first dedicated to the topic, is to provide comprehensive knowledge for all those people who take care of schizophrenic patients. In fact, suicide is the first cause of death among these patients and a great burden for all those left behind.

In 1977 Miles (1977) reviewed 34 studies of suicide among schizophrenics and estimated that 10% of schizophrenic patients kill themselves. Follow-up studies have estimated that 10-13% of individuals with schizophrenia die by suicide, which is the main cause of death among these patients (Caldwell and Gottseman, 1990). The lifetime incidence of suicide in the general population is about 1% (Fremouv et al., 1980). It has been estimated that the life expectancy among schizophrenic persons, as a group, is shortened by 9 to 10 years, and that the excess in mortality is chiefly accounted for by suicide and accident deaths (Tsuang and Woolson 1978; Tsuang et al. 1980). Methods used for the identification of risk factors for suicide among schizophrenic patients were detailed previously (Pompili et al, 2004a, Pompili et al, 2004b, Pompili et al, 2004c, Pompili et al, 2005; see also Pompili, 2006, Pompili et al, 2006). Risks factors for suicide in schizophrenia are listed in table 1.

Montross et al. (2006) stressed that even if no statistically significant relationship can be found between command hallucinations and violence toward self or others, many researchers continue to abide by the clinical wisdom that they are important to monitor. For example, Zisook et al. (1995) illustrated how during the course of their study, two patients completed suicide – both of which experienced command hallucinations. Rogers et al. (2002) also noted that two of the 37 patients experiencing self-harm command hallucinations committed suicide within three months of leaving the medium-security hospital. None of the patients in that study's comparison group had committed suicide during post-discharge follow-up. Harkavy-Friedman et al. (2003) found a corresponding trend. Although the authors stated patients with command hallucinations were not statistically more likely to make suicide attempts, 24% of all the patients who had attempted suicide did so in response to an auditory command hallucination. Thus, each study suggests that clinicians should still be cognizant of the danger command hallucinations may pose for patients vulnerable to suicide, even if no statistical significance is established. Kaplan and Harrow (2006) suggested that the surviving schizophrenia patients may be the types of people who are able to adjust to life as chronic or moderately and episodically impaired schizophrenia patients, and they may be less likely to commit suicide. Despite major difficulties, these patients may not experience despair and/or an active and militant dissatisfaction with the quality of their lives. However, even among these remaining schizophrenia patients, the unhappy circumstances connected with their disorder and possible vulnerability to depression still leave some risk for suicide, although less than during early phases of their disorder. Lester (2006) recently provided comprehensive analysis of hopelessness and suicide risk in schizophrenics. He reported that it has been consistently shown that hopelessness and depression predict which schizophrenics will subsequently complete suicide (Cohen, et al., 1990), and Caldwell and Gottesman (1990) list depression and a depressed mood and hopelessness as well-documented risk factors for suicide in schizophrenics (see also, Pompili, et al, 2004a). Cohen et al. (1994) found that both depression and hopelessness (as measured by Beck's hopelessness scale) predicted past

attempted suicide in first-admission psychotic inpatients of whom 34 percent were schizophrenics. Interestingly, those making very recent attempts and attempts in the more distant past did not differ in hopelessness, but the recent attempters were more depressed. Suicidal patients were characterized by a syndrome of depression, hopelessness, negative symptoms and hallucinations and less thought disorder, as well as a history of unipolar affective disorder.

Table 1. Risk factors for suicide in schizophrenic outpatients and inpatients (Pompili, 2006)

White, young, male
Unmarried
High premorbid expectations
Gradual onset of illness
Social isolation
Fear of further mental deterioration
Excessive treatment dependency
Loss of faith in treatment
Family stress or instability
Limited external support
Recent loss or rejection
Hopelessness
Deteriorating health
Paranoid schizophrenia
Substance abuse
Deliberate self-harm
Unemployment
Chronicity of illness with numerous exacerbation
Family history of suicide
Pre-admission and intra-admission suicidal attempts
Agitation and impulsivity
Fluctuating suicidal ideation
Extrapiramidal symptoms caused by medications
Prescription of a greater number of neuroleptic and antidepressants
Increased length of stay and increased number of ward changes
Period of approved leave
Apparent improvement
Past and present history of depression
Frequent relapses and rehospitalization
Longer hospitalization periods than other psychiatric inpatients
Negative attitudes towards medication
Reduced compliance with therapy
Undertreatment or non compliance with therapy and negative attitude towards medication
Living alone before the past admission
Discharge planning
Charged feelings about their illness and hospital admission
Early signs of a disturbed psychosocial adjustment
Dependence and incapability of working
Age under 30 years
High number of hospital admissions
Period following discharge
Difficult relationship with staff and difficult acclimation in ward environment
Hospitalization close to crucial sites [big roads, railway stations, rivers, etc]

It is crucial to assess suicidality in the clinical interview by assessing trait-dependent risk factors and state-depending risk factors (Lindenmayer, 2003).

The former are factors that can be potentially be modified, the latter on the other hand are factors that are unchangeable (Tab. 2)

Table 2. State-dependent risk factors vs. trait-dependent risk factors (Pompili, 2006)

State-dependent risk factors	*Trait-dependent risk factors*
- Clinical depression, - Substance abuse, - Hopelessness - Social isolation, - Lack of truth toward therapy, - Psychotic symptoms, - Loss of faith in treatment - Undertreatment or non compliance with therapy and negative attitude towards medication, - Agitation and impulsivity	-Younger age, -Male sex, -High socioeconomic family status. -High intelligence, -High premorbid level of education, -Unmarried status, -Reduced self-esteem -Enhanced awareness of illness, -Long duration of illness

The assessment of suicide risk should also take into account protective risk factors (Tab. 3).

Table 3. Protective factors for suicide in schizophrenia (Pompili et al, 2004a)

- Compliance to therapy
- Therapy with atypical antipsychotics
- Family support for the illness and for the stigma that arises from it
- Regular sessions of family therapy that is able contribute to reduce the
- number and the duration of hospitalizations, the number of the relapses
- and increases compliance to therapy
- Suitable antidepressant therapy
- Possibility to speak of the intention to commit suicide
- Family history negative for suicide
- Support and programmers of aftercare at discharge
- Programmers of prevention about substance abuse
- Possibility of working and carrying out pleasant tasks
- Subtypes of schizophrenia as simplex and hebephrenic
- Training in the development of social and cognitive skills
- Limitations to the more common methods of suicide
- Not being stigmatized
- Live in an environment adjusted to patient's needs
- Psychological well-being: given by the mastery of choices and by the relationships with others

The literature abounds with descriptions of various psychosocial interventions for schizophrenic patients whose treatment often requires integration of pharmacological and

rehabilitative strategies. Nevertheless, the impact of these strategies on suicide has only rarely been investigated. Drake et al. (1989) pointed to the need for empathic support for reducing suicide risk. These authors suggested that clinicians should acknowledge the patient's despair, discuss losses and daily difficulties and help to establish new and accessible goals. Social isolation and work impairment are frequently reported as risk factors for suicide in individuals with schizophrenia.

SUICIDE AMONG INPATIENTS WITH SCHIZOPHRENIA

Pompili et al. (2005) reviewed the literature on suicide among inpatients with schizophrenia and found that the suicide rate in cohorts of schizophrenic patients who were followed-up after the first hospitalization for variable period, ranging from 1-26 years was 6.8%.

Prevention of suicide of inpatients with schizophrenia is a daily-based challenge, which has to be performed with various modalities. Nordentoft and Mortensen (2005) recently highlighted a recent Danish register-based study by Qin and Nordentoft (Qin and Nordentoft 2005). They found that 37% men and 57% women who committed suicide had a history of admission to psychiatric hospitals. This study confirms previous reports that suicide risk is highly associated with a history of admission to psychiatric hospital. It further demonstrates that the risk peaked not only shortly after discharge, as reported in the literature (Appleby et al. 1999;Goldacre, Seagroatt, and Hawton 1993;Lawrence et al. 1999;Mortensen and Juel 1993;Rossau and Mortensen 1997), but also shortly after admission. For patients with schizophrenia and related disorders, there was, as in other conditions, two sharp peaks in suicide risk, the first immediately after admission (adjusted risk ratio around 80 compared with persons with no history of admission) and the second peak shortly after discharge (adjusted risk ratio around 110 compared with persons with no history of admission). The risk ratios were clearly higher among women. Suicide among patients currently admitted with schizophrenia, accounts for approximately 2 percent of all suicides in Denmark.

Crammer (1984) highlighted the importance of taking environmental factors into account when thinking proactively about suicide among inpatients. He pointed to the potentially disruptive effects of transitions – for example, initial acclimation to ward life or plans for discharge or rehabilitation. He also emphasized the environmental impact of staff variables, such as low morale or the absence of key personnel, as well as the need for effective communication among relevant staff about patients judged at increase risk of suicide. Yarden (1974) drew attention to the importance of suitable discharge plans and aftercare programs. Supportive, supervised living arrangements are ideal. With chronic, incapacitated patients, surveillance should be increased in times of personal crisis and impeding environmental change, including staff, therapist, or contact person changes, hospitalization, discharge, or rehospitalization.

PHARMACOLOGICAL TREATMENT

Despite great efforts, both on the side of drug treatment and psychosocial strategies, the number of suicides among schizophrenic patients has remained unchanged (Meltzer et al., 2003). Although Nordentoft et al. (2004) have shown that in Denmark suicide among patients with schizophrenia has fallen, paralleling the reduction of suicide in the general population.

The impact of atypical antypsychotics on suicidality in patients with schizophrenia has been reviewed (Keck et al., 2000). Clozapine, olanzapine, risperidone and quetiapine have shown some power in reducing suicidality among schizophrenic patients (Meltzer, 2001; Meltzer, 1995). Clozapine was shown to reduce suicide in schizophrenia (Meltzer, 1998; Meltzer and Okayli, 1995). According to these authors, the potential decrease in suicide mortality with clozapine treatment is estimated to be as high as 85%. In terms of benefit versus risk, while 1.5 of every 10,000 patients with schizophrenia who were treated with clozapine would be expected to die from agranulocytosis (evidence suggests an even lower percentage), 1000 to 1300 would be expected to complete suicide with standard treatment (Meltzer and Fatemi, 1995). In fact, the U.S. Food and Drug Administration recently approved clozapine for the treatment of suicidal behavior in patients with schizophrenia or schizoaffective disorder (Meltzer et al., 2003). Yet, according to Sernyak et al. (2001), clozapine treatment was not associated with significantly fewer deaths due to suicide. These authors used for the first time a matched control group to examine the effect of clozapine on the rate of suicide in patients with schizophrenia. In their sample, they did not observe a significant reduction of suicides due to clozapine. However, one third of the sample received clozapine for less than six months, even though the follow-up period was five to six years.

AWARENESS OF ILLNESS

Wilson and Amador (2005) reviewed the literature on insight and suicide risk in schizophrenia. They reported that overall, the early studies identified hopeless awareness of one's illness as an important predictor of completed suicide in patients with schizophrenia, when compared to both non-attempters as well as attempters who did not commit suicide. In addition, although often rich in clinical description, these early studies were typically not well controlled, and very likely unduly influenced by significant biases. As a result, none were able to ascertain whether it was insight or the profound hopelessness that was distinctive about these individuals. In contrast, the more recent studies, which have generally been much more rigorous and methodologically sound, have produced decidedly mixed results with their efforts. With few exceptions, these studies have generally compared attempters/ideators and non-attempters/non-ideators, and found different classifications of suicidality related to different dimensions of insight. Recent studies examining multiple predictors of suicidality have concluded that hopelessness is the main driver of suicidal behavior. Taken together, research findings thus far seem to suggest that awareness of illness is associated with increased suicide risk, but only if that awareness leads to hopelessness. The severity of the hopelessness that a person with schizophrenia experiences seems contingent, at least in part, on the level of premorbid functioning, and the magnitude of the decline in functionality relative to that premorbid capacity. The atypical antipsychotic drugs can improve cognitive

function and reduce hopelessness. Pallanti, Quercioli, and Pazzagli (1999) reported that in their sample of twenty-two patients with schizophrenia, clozapine enhanced neurocognitive function and increased awareness of illness in schizophrenic patients. Treatment combining transcranial magnetic stimulation and clozapine was reported to reduce hallucinations and improve neurocognition (d'Alfonso et al., 2002). Clozapine was shown to reduce suicide in schizophrenia dramatically (Meltzer, 1998; Meltzer and Okayli, 1995). Nevertheless, it should be seriously considered that increased awareness might be responsible for the demoralization syndrome; leading to suicide despite the fact that clozapine may treat hopelessness. We understand that the assessment of awareness of illness in schizophrenia is a very important issue. Amador et al. (1993) suggested that the Scale to Assess Unawareness of Mental Disorder (SUMD) had a good reliability and validity, allowing a multidimensional view of a complex concept. As mentioned earlier, this scale was used to assess the relationship between insight and suicidality in schizophrenia, pointing to the fact that certain aspects of awareness may be strongly associated with suicide in schizophrenia. Pallanti et al. (1999) reported that patients who received clozapine improved SUMD–measured awareness. Tamam and Özpoyraz (2001) have provided anecdotal evidence that increased insight associated with clozapine treatment may lead to suicide According to these authors, their patient committed suicide when awareness of illness increased dramatically. They commented that increased awareness of illness could leave patients vulnerable to intrusive thoughts concerning the chronicity of illness, the devastating global impact of disease on patients' lives, and the impossibility that previous expectations for the future could come true. As a result, a hopeless state could occur for which suicide is a perceived response. This matches Farberow et al.'s (1965) description of suicide of schizophrenic patients due to improved insight after drug treatment.

Although general awareness seems not to predict suicide, there seems to exist an awareness spectrum, whose elements may or may not lead to suicide (Pompili et al., 2004c). According to Drake et al. (1984), a patient may be aware of current disability and remain confident of improvement in the future. Nevertheless, when patients fear further mental deterioration, suicide becomes more likely (Spießl et al., 2002). Schwartz and Petersen (1999) and Schwartz (2000) underlined the role of hopelessness in patients with awareness of illness. They observed that if treatment does not diminish emotional symptoms and does not improve psychosocial skills, hopelessness may result. This is the pathway which eventually leads to depression and suicide. Drake and Cotton (1986) described a demoralization syndrome in which schizophrenic patients become aware of their illness and its consequences. Patients then may compare their fair premorbid adjustment with the current one and become hopeless and depressed and eventually become suicidal. At the moment we still do not know if improved awareness of illness, which can predict a more favorable outcome, may also expose patients to suicidal tendencies. Summarizing, drug treatment of schizophrenia is generally associated with lower suicidality. However, since the administration of newer, atypical antipsychotics may be accompanied by increased insight and illness awareness, and since sudden increases in insight by more than 25% may lead to increased suicidality in schizophrenic patients (Turkington et al., 2002), caution is needed and the patient should be followed-up closely to contain such abrupt insight increases within an appropriate therapeutic relationship.

SUICIDE ATTEMPTS

Compared with suicide attempts among persons without schizophrenia, attempts among those with schizophrenia are serious and typically require medical attention. Intent is generally strong, and the majority of those who attempt suicide have made multiple attempts. In addition, the methods used to attempt suicide are considered more lethal than those used by suicidal persons in the general population. Gupta and colleagues (1998) reported that in their sample of patients with schizophrenia, suicide attempts were associated with the number of lifetime depressive episodes. Depression has been recognized as a major risk factor among persons with schizophrenia who have attempted suicide. Also, Roy and associates (1984) found that significantly more of their sample of patients with schizophrenia who had attempted suicide had suffered from a major depressive episode at some time during their illness. Great caution is required in the period after hospital discharge, because patients with schizophrenia usually experience hopelessness and demoralization. For these patients, discharge often means losing the hospital environment and the people who in some way have become central in their life. The number of psychiatric admissions, which are usually higher among patients who have attempted suicide, may be indicative of a severe relapsing illness.

Drake (2006) recently reviewed his previous investigation on suicide in schizophrenia and stressed that in terms of suicide history, the completed suicide group had more previous attempts, but the differences were not statistically significant. Only a history of explicit suicide threats differentiated the two groups statistically. Remarkably, most of the explicit threats were based on awareness of illness and fears regarding course of illness. For example, several patients stated quite explicitly that they planned to kill themselves if they continued to have relapses of illness and inability to function. These statements were coded as fears of further mental disintegration. Patients who subsequently completed suicide also expressed higher performance expectations, consistent with their awareness of illness and accurate perceptions of functional status.

The completed suicides were also clearly more depressed. During hospitalization, they reported feeling depressed, inadequate, hopeless, worthless, and suicidal. Thus, psychological symptoms of depression, rather than biological symptoms of depression, differentiated the suicide completers from the suicide attempters. Behaviors during hospitalization, such as being impulsive, demanding, and agitated, failed to discriminate between completed suicides and attempters. The only hospital-based behavior that did discriminate between the two groups was that the completed suicides were more likely to be rated as "improved" at discharge (Tab. 4).

Table 4. A comparison of schizophrenic patients who completed suicide with schizophrenic patients who attempted suicide (Drake, 2006)

Characteristics	Suicides (n=15)	Attempters (n=19)	Sig. level[1]
Age (years)	31.7	24.l8	NS
Sex (male)	60%	47%	NS
Previous suicide attempt	73%	47%	NS
Three or more attempts	40%	21%	NS
Explicit suicide threat	67%	16%	<0.01
Lives with family of origin	27%	63%	<0.05
Lives alone	60%	11%	<0.01
Depressed mood	80%	52%	<0.05
Feels inadequate	80%	42%	<0.05
Hopelessness	67%	26%	<0.05
Worthlessness	53%	21%	<0.05
Suicidal ideation	87%	37%	<0.01
Fears of mental disintegration	33%	5%	0.05
High self-expectations	47%	16%	0.06
Improved at discharge	67%	32%	<0.05

1. Significance levels refer to *t* tests or $_x^2$ tests

STIGMATIZATION

Corrigan (2004) provided comprehensive analysis on how stigma interferes with mental health care. He stressed that despite the plethora of evidence-based interventions, many people with mental illness never pursue treatment and others begin treatment but fail to fully adhere to services as prescribed. Stigma is one of the several reasons why people make such choices. Mentally-ill people may be subjected to public stigma derived from stereotypes, prejudice and discrimination; also these people face self-stigma derived from self-prejudice and internalization of stigmatizing ideas that are widely endorsed within society; therefore they believe that they are less valued because of their psychiatric disorder. Self-stigma can yield label avoidance and decrease treatment participation.

Drake and Cotton (1986) described a demoralization syndrome in which schizophrenic patients become aware of their illness and its consequences. Patients then may compare their fair premorbid adjustment with the current one and become hopeless and depressed and eventually become suicidal. In this process stigmatization and reduced social interactions play an important role.

The impact of stigma toward the patient's family in facilitating a patient's insight into illness should be also taken into account. Empirical evidence suggests that stigmatization may constrain the family to unconsciously communicate to the sick member that suicide is a valid option to cope with illness disability. According to Whitaker (1989) in all suicides there is a person that wants to die and another individual that wants that person dead. According to this author, it is amazing how we can both improve or ruin our life. It would appear that the people that we engage with may produce positive or negative changes in an individual's

physiology. Hidden hates is likewise a powerful weapon to destroy someone and this has common roots with stigmatization.

The possibility that stigma may lead to suicide has been reported (Pompili et al., 2003a) and efforts should focus at reducing it in suicide prevention interventions (Eagles, et al., 2003). Stigmatization towards these patients is often unrecognized, as schizophrenic individuals are only rarely clearly rejected. In most instances, people behave ambiguously and not overtly. Another field that should be investigated is the impact of stigma towards the patient's family in facilitating a patient's insight into illness. Recently, Pompili, et al. (2003b) proposed a pattern of family behavior which might induce suicide in the schizophrenic member. These authors stressed that patients and family members are stigmatized for being involved with schizophrenia (Phelan et al., 1998; Dickerson, et al., 2002). Stress, reduced social contacts, and the difficulties posed by the illness may facilitate the development of an unconscious network of subtle messages that may suggest to the patient that suicide is the best solution for a chronic illness. Langs' (1986) theory of everyday unconscious communication was used to support this speculation. This process may be carried out by facilitating a patient's insight into illness. This behavior is even recognizable among psychiatrists and mental health professionals. Saarinen and colleagues (1999) have recognized various elements that impair the staff's ability to identify markers of suicide in patients with schizophrenia. They indicated difficulties in dealing with suicide and personal problems as major elements of the disturbance; this might be linked to stigma (Tab. 5).

Table 5. Elements that impair recognition of suicide risk by treatment professional and that are associated with stigmatization (Adapted from Saarinen, 2006)

-	lack of knowledge and skills in relation to treatment of self-destructiveness
-	professional's loss or absence of concern
-	acceptance of patient's suicide as a solution to problems
-	wishes that patient would commit suicide as a solution to his or problems
-	degree of familiarity with patients
-	unfounded optimism in relation to treatment
-	fear of patient
-	defects or problems associated with treatment system
-	sadism toward the patient
-	denial's of the patient's psychiatric problems
-	denial's of the patient's suicide risk
-	repression of knowledge of suicide risk

Saarinen (2006) reported that staff knowledge of suicidology and psychological readiness to deal with suicidal patients' anxiety and despair are important in the treatment process, and uncertainties may be fatal (Ramberg and Wasserman, 2003). It was already noted quite long ago that increased attention to interpersonal behavior may provide a basis for more accurate recognition and more successful long-term treatment of high risk suicidal patients (Jensen and Petty, 1958; Fawcett et al., 1969). It is understandable that research into the interactional process in the treatment relationship is very complicated. We investigated interactional factors and the recognition of suicide risk in schizophrenia by treatment professionals in a psychological autopsy study during the Finnish suicide-prevention project (which lasted from

1 April 1987 to 31 March 1988). The study method of the prevention project has been described in detail elsewhere (Marttunen et al., 1991; Isometsä et al., 1994; Saarinen, 1995; Heilä et al., 1997; Saarinen et al., 1998, 1999). A consensus case report was written on each suicide, including information on the findings of the inquest, forensic medical investigations, interviews with close relatives and health-care or social workers, and the documents used. Each consensus case report was discussed in detail in a multiprofessional project group.

Taboos in staff impair professional judgment and communications about patients identified as suicidal. Because of these blocks, professional staff are often hampered in applying what they already know, and they may even avoid eliciting or reporting information about the suicidal behavior of their patients, whether is attempted or committed. Patients who attempt suicide or are at risk for suicide are the ones that most benefit from empathic relationships with nurses and doctors (Pompili et al., 2002a). Pompili et al. (2003c; 2004d) recently reviewed the international literature that dealt with the nursing of schizophrenic patients who are at risk of suicide These authors outlined key elements in the nursing of these individuals, such as the unpredictability of suicide due to fluctuating suicide ideation, staff's "countertransference" reactions to these patients and the apparent improvement that precedes suicides. Nursing a schizophrenic patient who is at risk of suicide involves the establishment of very uncommon relationship. An interesting topic is the concept of "terminal malignant alienation" (Morgan and Priest, 1984; 1991). Some patients, particularly those with recurrent relapses and resistance to treatment, may be perceived by staff as manipulative, provocative, unreasonable, over-dependent and feigning disability. Patients with fluctuating suicidal ideation are particularly likely to fall into these categories and may lead to under-reporting of suicidal ideation by nursing staff. This may result in criticism and a lower level of support leading to alienation. The combination of such alienation and fluctuating suicidal ideation can lead to failure in the recognition of seriousness of suicidal risk (Morgan and Priest, 1984, 1991; Schwartz et al., 1975).

Unfortunately, family members are also stigmatized for dealing with schizophrenia. This psychiatric disorder often results in impairment of daily activities, relapses and chronicity. Family members are seen with suspicion for dealing with their sick relative and may be subjected to lack of socialization and reduced job opportunities.

Also, very often schizophrenic patients meet GPs for drug prescription or for request of psychiatric consultation. Physicians often do not take into consideration their role in the prevention of suicidality (Pompili et al., 2002b; 2004e). In fact, not only do people who are considering suicide often contact their doctors for general consultation prior to the suicidal action, but those who are at risk should be promptly recognized.

CONCLUSIONS

Pompili et al. (2004a) investigated non medical resources for suicidal schizophrenic patients finding that most treatments available still lack scientific validation. However, psychosocial interventions and psychotherapy should be among available options. Over the past few years, evidence suggested that cognitive-behavioral therapy is effective in reducing suicidality in patients with schizophrenia (Turkington et al., 2002; Power et al., 2003; Bechdolf et al., 2004). Other types of psychotherapy should be adequately tested to better

understand the global value of psychotherapeutic interventions in decreasing suicidality in schizophrenic patients.

Despite a considerable number of studies and the many indications how to reduce suicide in schizophrenia, this event remains a major health problem. In Italy, suicidal behavior among schizophrenic is underestimated and official data are still lacking.

A new prevention of suicide in schizophrenia should include proper information. Information should be addressed to family and hopefully hostility toward the patient should be investigated. But information should constitute a key element for promoting changes in people's attitude toward these patients.

Pompili et al. (2004a) have recently stressed the need to implement prevention of suicide among schizophrenic patients. These authors focused on primary, secondary and tertiary prevention. Primary prevention represents the search for the prevention and elimination of risk factors. These factors include developing social isolation, substance abuse, depression, hopelessness and disappointment for lost expectations toward the future. Also, insight into the illness should be monitored very carefully, as it has become apparent that the awareness of one's illness leads to discouragement and suicide risk. Appropriate pharmacotherapy and psychotherapy should prevent the emergence of risk factors for suicide and the reduction of those factors already detected in the patient. Patients should always be asked about their intention to commit suicide. There are no contraindications to the investigation of suicidality in schizophrenic patients. They are instead relieved by an explicit investigation, as they have the opportunity to share their inner feelings (Harkavy-Friedman and Nelson 1997). Secondary prevention is identifiable as an operation that aims to check the phenomena in those subjects who have already developed risk factors for suicide. State-dependent risk factors are those that can potentially be modified (such as depression, substance abuse, hopelessness, etc.); on the contrary, trait-dependent risk factors are unchangeable (gender, age, premorbid functioning, etc.). No doubt, a prompt recognition of individuals who are at risk is a key element in the prevention of suicide. Screening procedures taking into account suicidal indicators should be implemented. Patients who are depressed, substance abusers and hopeless should be monitored carefully. Also, those who have experienced multiple hospitalizations and threatened or attempted suicide should be treated according to adequate procedures, such as programs of aftercare and psychosocial intervention. Tertiary prevention is addressed to those individuals who have attempted suicide or are suicidal. Not only risk factors for suicide are identifiable in these patients, but also suicide spectrum activities are easily detected. Destigmatisation should be addressed to mental illness as well as suicide. Increasing the stigma associated with having suicidal feelings will increase the suicide rate. Interventions among families, mental health ventions professionals, and church activists aimed at decreasing the stigma associated with mental illness and suicide may contribute to the reduction of deaths by suicide. Pharmacological interventions are no doubt of paramount importance, but psychosocial interventions also play a central role. Psychotherapy with suicidal schizophrenic patients should also be considered.

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Chapter 7

NEEDS OF OUTPATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

The definition of need in mental health was initially controversial. One approach defined need as disabilities in the daily life of the subject. Thus, disabilities were assessed as well as the type of needs relating to them. Another approach took the treatments and interventions available as a starting point. Needs were assessed on the basis of the services for particular deficiencies from which patients could benefit. In this review, we can appreciate that the needs of people with schizophrenia vary from country to country, which could be due to cultural differences and the provision of mental health services. It is necessary, therefore, for both users and staff to assess needs before planning new services or mental health programs.

1. DEFINING NEED

Need is "something necessary for living. Everything that someone can not do without" (Gili ,1983).

The definition of need in mental health was initially controversial. One approach defined need as disabilities in the daily life of the subject. Thus, disabilities were assessed as well as the type of needs relating to them. Another approach took the treatments and interventions available as a starting point. Needs were assessed on the basis of the services for particular deficiencies from which patients could benefit.

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Nowadays, needs are considered multiaxial and dynamic, and it is as important to assess the subject perception of need as the family's (Brewin, 1992).

2. MODELS OF NEEDS

From a psychological perspective, in the twenties, Abraham Maslow proposed a classification of human needs called "Maslow's Pyramid of needs". This author saw human needs as being hierarchized and scaled in a way that once the needs of one order are covered, the needs of the higher order begin to be felt. The basic order refers to physiological needs, the following to safety needs and belonging needs and the last to the self-actualization need (Hewstone et al, 1990).

From a sociological perspective, Bradshaw (1972) proposed a classification of needs as normative, felt, expressed and comparative. Normative needs are related to norms defined by political rules and by scientific knowledge. Felt needs refer to those perceived and expressed by the services' target group; these needs will depend on their background/personal history, their expectations, the information they have of their own problems and the resources required to solve them. Expressed needs are those that the services' target group or users express as data on service use, waiting lists, etc. Comparative needs are those established by comparing different services, programs, or care levels.

The health services approach to needs can be taken from three different areas: epidemiology, needs expressed by people suffering from a specific illness and the quality of care (Steinchwachs, 2003).

The epidemiological approach assesses the incidence and prevalence of the illness, risk factors and the interventions that prove to be effective for the treatment. What we are assessing from this perspective, among other things, is the existence of effective interventions that reduce the presence of concrete needs.

On a more micro level, needs can be studied from the perspective of the consumers of mental health services, and so, needs that people suffering from particular illnesses consider to be unmet are assessed.

On the other hand, we can assess needs from the quality of care perspective, from the professional point of view, by appraising scientific data or professional consensus care services which are designed to meet the needs present in society.

In his Quality in Medical Care Model, Avedis Donabedian (1966) contributed the definition of needs related to the quality of services. Donabedian subdivided this model for needs analysis into Health Needs (first order), Service Needs (second order) and Resource Needs (third order).

3. WHY ASSESS THE NEEDS OF PEOPLE SUFFERING FROM SCHIZOPHRENIA?

In the time when patients lived in institutions, most of their needs, basic as well as health related, were met by the hospital services. The needs of patients attending these centers were mainly related to basic aspects such as accomodation, food, self-care and psychopathological

restraint. On admission, patients were given a place to sleep and eat and a medical check-up, after which they were treated with the necessary or available medication.

The 1950's saw the beginning of a psychiatric de-institutionalization process, caused by three phenomena: the anti-psychiatry movement (Basaglia et al, 1975), the discovery of anti-psychotic medication (Álamo et al, 2000) and the importance of communitary treatment (Guimón, 2001).

With the beginning of the community psychiatry, the assessment of aspects related to the social integration of schizophrenia sufferers to their social environment became necessary. In this context, assessing patients' needs during the process of adequate integration gains in importance.

This concern for the needs of schizophrenia sufferers appears mainly in the United Kingdom, where the closure of psychiatric hospitals has led to communitary psychiatry. When all the questions related to planning and assessing communitary programs take on importance, it is necessary to determine what kind of needs these people have in order to provide adequate health and social services. The needs shown by people living in the community are different from those of patients living in a hospital. Wing (1994) pointed to the necessity of assessing whether needs are being met or not; not only physical, accomodation, food or safety needs, but also quality of life-related needs such as self-respect, autonomy, contribution to society and gaining knowledge. Below follows an outline of the needs described by different studies of people with schizophrenia receiving communitary care.

4. NEEDS ASSESSMENT IN SCHIZOPHRENIA

There are different methods for assessing the needs of people with schizophrenia.

Qualitative studies assess needs in schizophrenia sufferers with focus group or semi-structured interviews techniques. These methods could be useful in the assessment of needs in people who are being attended in day care services, as they should adequate activities to the meeting of patients' needs (Madoz et al, 1999; Olivella et al, 2001).

In most needs studies, the assessment is done through specially designed questionnaires. Individual needs have been assessed with different instruments, such as the Needs for Care Assessment Schedule (NFCAS) (Brewin et al,1987), the Cardinal Needs Schedule (Marshall,1994) and the Camberwell Assessment of Need (CAN) (Phelan et al,1995)

The NFCAS is based on the definition of presence of need when the level of functioning of a patient is under a specified minimum and there is a way of coping with this disability. This questionnaire is designed to allow individualized assessment of the type of needs that a subject shows, by an interview with two independent interviewers. It is divided into two parts. The first part assesses clinical variables as well as positive psychotic symptoms, negative psychotic symptoms, adverse effects, no psychotic symptoms, organic brain syndrome, physical disorders, risky or embarrassing behaviors, substance abuse and anxiety. The second part assesses eleven variables regarded as basic abilities of autonomous daily living in the community, which are looking after the home, self-care, occupation, money handling, communication abilities, inactivity, food, handling personal tasks, shopping, transport use and education (Comtois et al, 1998).

The Cardinal Needs Schedule is a modification of the previous one. It is based on the identification of cardinal problems that satisfy three conditions: the patient accepts that s/he has a problem, the problem causes anxiety or stress and the problem can damage the patient's or others' health or safety. A computerized version has been developed.

Nowadays, the instrument most used is the CAN. This questionnaire was developed in the Communitary Psychiatry Section (PRISM) of the Institute of Psychiatry Health Services in London, and has been translated and validated into different languages, besides English, such as Swedish (Hansson et al, 1995) and Italian (Ruggeri et al, 1999). Also, the EPSILON Group did a European validation of this questionnaire (Knudsen et al, 2000; Mc Crone et al, 2000), while members of the Research Group Granada Sur were in charge of validating the scale in Spain (Rosales et al, 2002). The results obtained revealed high concordance between assessors and scores were optimum in test-retest assessment. The instrument was shown to be more sensitive if there was knowledge of the patient being assessed, meaning that it was more useful in the clinical version.

The novelty of the CAN lies in the dual assessment by the user and the staff responsible for each of the needs, so the instrument in fact consists of two independent scales that can be used with regard to the objectives of the study proposed.

The CAN covers 22 need areas: accommodation, food, looking after the home, self-care, daytime activities, physical health, psychotic symptoms, information, psychological distress, personal safety, the safety of others, alcohol, drugs, company, intimate relationships, sexuality, child care, basic educaton, telephone, transport, money and benefits. For every one of these areas, the presence or absence of need is assessed. The presence of need is further classified as being severe or capable of being coped with the help of others. This help is assessed as coming from an informal or a formal source, and the adequacy of the formal source of help is also determined. The formal source of help is conceptualized as being the health services or social services providing help in meeting needs. The informal source of help is the family members or friends coping with the meeting of needs.

There are two, relatively similar versions of the CAN for clinical and research purposes. This is why this questionnaire is so useful for daily clinical practice as well as for the assessment of needs for research studies. There is also a short version (CANSAS), which only assesses the first item of the questionnaire (presence or absence of need, met or unmet) for every need assessed by both professional and user (Slade et al, 1999; Andresen et al, 2000).

The authors of the questionnaire propose a factor grouping of needs in five subscales: health (physical health, psychotic symptoms, drugs, alcohol, personal safety, the safety of others and psychological distress), basic needs (accommodation, food, and daytime activities), social (sexuality, company, intimate relationship), services (information, telephone, transport, benefits) and functioning (education, money, child care, self care and looking after the home) (Slade, 1998).

Different studies have been conducted to confirm the factor structure of the CAN. Wennstrom et al (2004) found three factors, named functional disability, social loneliness and emotional loneliness. Korkeila et al (2005) found five factors when the assessment of needs was made by the user (skills, illness, coping, substance abuse and miscellaneous) and four factors when the assessment was made by the professional (skills, impairment, symptoms and substance abuse).

Different versions of the CAN have been specifically designed in order to assess the needs of people with mental retardation or mental health problems (CANDID) (Xenitidis et

al, 2000); the needs of old people with mental health problems (CANE) (Reynolds et al, 2000) and forensic needs patients (CANFOR) (Thomas et al,2003). These versions keep the structure of the CAN but modify, add and remove some of the needs that this questionnaire originally assessed.

Recently the 2-COM has been designed, another questionnaire of assessment of needs based on the CAN (Van Os et al, 2002). A total of 707 subjects with mental health problems were assessed three times over two years and the needs most frequently reported were selected. These needs are: accommodation, home-care, self-care, daytime activities, physical health (including problems with medication and adverse effects), psychotic symptoms, information, psychological distress (including sleep problems, forgetfulness, tiredness, capacity of enjoyment, being tense and feeling concerned), company, intimate relationships, sexuality, transport, money and benefits. For each one of the areas, users are asked if it is a problem for them and if they feel like talking about it.

5. STUDIES OF NEEDS ASSESSMENT IN SCHIZOPHRENIA

5.1. Number of Needs

The mean number of needs is different across studies and countries, which makes it difficult to know when it is appropriate to intervene. In Sweden, a cut-off score of ten needs was set, considering that people above this level should be attended and helped with the needs they showed (Foldemo et al, 2002). Different studies have been conducted, mainly in the United Kingdom, Northern Countries, Italy, Holland and Spain.

Table 1 shows the results of the studies mentioned previously where the instrument CAN was used. The mean number of met and unmet needs is shown as assessed by staff and users. Some of the studies did not provide all the information, so the table shows available data.

The studies detect a similar number of needs, although they are from different countries with different services of mental health and socioeconomic conditions.

The mean number of needs as assessed by professionals ranges from 4.5 to 7.5. In Sweden, Hansson et al (1995) studied a sample of psychiatric patients and found a mean number of needs of 5.29. It is important to consider that less than half of the patients assessed had a diagnosis of schizophrenia, the rest being being diagnosed as having affective psychosis, personality disorders and other non-psychotic disorders. The sample was divided into inpatients (n=59) and outpatients (n=60). Lasalvia et al (2000) found a mean number of needs in the subgroup of psychotic outpatients lower than in previous studies (3.64 as assessed by users and 4.50 as assessed by staff). This difference in the amount of needs could be due to the variability of diagnosis, as it comprises patients with schizophrenia but also with affective psychosis.

The total number of needs gives us important information about the level of needs present in a sample of people suffering from a mental disorder. However, not only should we consider the total number of needs or the total number of unmet needs, but we should also study each one of them in detail, due to the hetrogeneity of the areas they describe.

Table 1. Mean of total number of needs and unmet needs from different European studies, rated by user and staff

Author reference	City/ Country	N	Total needs by staff	Total needs by user	Total unmet needs by staff	Total unmet needs by user
Hansson(1995)	Sweden	119	5.29			
Slade (1996)	London (UK)	49	7.5	7.9	-	-
Slade (1998)	London (UK)	137	6.1	6.7	1.2	1.8
Leese (1998)	London (UK) Norwood Nunhead		 6.08 5.28	-	 1.57 1.23	-
Slade (1999)	London (UK)	212	5.9	6.6	-	-
Lasalvia (2000)	Verona (Italy)	88	4.5	3.6	1.46	1.56
Mc Crone(2001) Estudio Epsilon	 Amsterdam (Holland) Copenhague London (UK) Verona (Italy) Santander (Spain)	404 61 52 84 107 100	-	 6.3 5.2 6.0 4,9 4.8	-	 2.5 1.3 2. 2 1,5 1.6
Hansson (2001)	Sweden	300	6.17	5.76	2.27	2.02
Middelboe(2001)	Northern countries	418	-	6.2	-	2.6
Rosales (2002)	Granada (Spain)	246	6.4	6.4	-	-
Ochoa (2003)	Barcelona (Spain)	196	6.6	5.3	1.82	1.32

5.2. Types of Needs

The assessment of the areas where there is presence of need is important, as it will determine the services needed to meet these needs.

London

Phelan (1995) found that the most present needs as assessed by staff in a sample of 60 subjects with some psychotic disorder are: daytime activities (83%), psychological distress (73%), food (65%), psychotic symptoms (63%), company (55%), transport (55%) and money (53%).

Later, Slade (1996) described the needs most frequently described by the user: daily activites (84%), food (82%), transport (59%), company (55%) and psychological distress (53%).

Northern Countries

Hansson et al (1995) described a greater presence of needs in the areas of psychological distress, psychotic symptoms, physical health, company and daily activites.

In a later study (2001) with only people diagnosed with schizophrenia, they found similar results. In the assessement made by the user, the most frequently described needs were psychotic symptoms, company and daily activities, whereas staff considered psychological distress to be more important than company and the others. With regard to unmet needs, those most frequently reported by the user were company, intimate relationships and psychological distress, and by staff, company, psychotic symptoms and daytime activities.

Middelboe et al (2001) found that more than 50% of the sample described needs in the areas of psychotic symptoms, company, psychological distress and daily activites. In the case of unmet needs, they report the same ones as the previously mentioned, with the addition of information.

Mediterranean Countries

In a study by Lasalvia et al (2000), the results showed that the most frequently reported needs in a sample of people suffering from a psychotic disorder were psychotic symptoms and psychological distress.

In the doctoral thesis by Rosales (1999) carried out with people diagnosed with schizophrenia attending a mental health area in Granada (Spain), it was found that more than 30% of the sample showed, as assessed by staff, any of the following needs: psychotic symptoms (95%), daily life activities (62%), company (53%), psychological distress (36%) and money (30%). In the assessment made by users, the needs present in more than 30% of the sample were: psychotic symptoms (89%), daytime activities (56%) and information (38%). A later study by the same authors replicated the initial results (Rosales et al , 2002)

The results of a study carried out by the NEDES group (Ochoa, 2003) showed that the most present need is psychotic symptoms, which were present in 96% of the sample when assessed by staff and in 68% of the sample when assessed by users. This finding is predictable, as the sample was made up of outpatients with schizophrenia attending a Mental Health Center. The following needs when assessed by staff were, in descending order: company (58%), looking after the home (57%), daytime activities (55%), food (52%) and information (46%); when the assessment was made by the user, the needs were: looking after the home (50%), food (46%), information (42%), company (39%) and daytime activities (36%).

Other Countries

Wiersma et al (1998), in a Danish population of people with schizophrenia, found the needs most frequently reported to be daytime activities, company and information.

The results of the EPSILON study (Mc Crone et al, 2001) indicate the existence of differences between northern countries and southern Europe. The needs most present in all five countries were company and psychotic symptoms. Specifically, the most common needs were: in London, psychotic symptoms (100%), psychological distress (57%) and company (40%); in Copenhague, psychotic symptoms (80%), psychological distress (45%), company (41%) and transport (40%); in Amsterdam, psychotic symptoms (95%), daytime activities (64%), physical health (49%), psychological distress (58%), company (47%) and intimate relationships (47%); in Verona, psychotic symptoms (73%), psychological distress (57%) and company (49%); and in Santander, psychotic symptoms (97%), daytime activities (57%), information (67%) and company (42%). Regarding unmet needs, in Santander daytime activities (32%), information (29%), psychotic symptoms (25%) and company stand out against the other areas.

Table 2 shows the most frequently reported needs in the previously mentioned studies. We have summarized staff descriptions, as most studies focus on this assessment.

With the aim of reducing the presence of the most outstanding needs of the different studies, different therapeutic interventions have been successfully made. Social Skills programs have been demonstrated to be efficient to improve the interpersonal relationships of

schizophrenia sufferers. This is why this kind of intervention could be used to cope or help to cope with the problematic high percentage of need in the company area (Saltó et al, 1990; Heinssen et al, 2000). Also, psycho-educational interventions should reduce the problems in the information area, as patients would be more informed of their treatment and abilities (Pekkala et al, 2003).

Table 2. Type of needs most frequently described by staff in European studies

Autor	Food	Daytime activities	Physical Health	Psychotic Symptoms	Infor-mation	Psychological distress	Company	Transport	Money
Phelan (1995)	X	X		X		X	X	X	X
Hansson (1995)		X	X	X		X	X		
Wiersma (1998)		X			X		X		
Lasalvia (2000)				X		X			
Middelboe (2001)		X		X		X	X		
McCrone (2001) Londres				X		X	X		
Copenhague				X		X	X	X	
Amsterdam		X	X	X		X	X		
Verona				X		X	X		
Santander		X		X	X		X		
Rosales (2002)		X		X		X	X		X
Ochoa (2003)	X	X		X			X		

5.3. Agreement between Staff and User

The CAN questionnaire allows us to assess the needs rated by user and staff, and also to know their level of agreement.

In the aforementioned studies, we find that the number of needs reported by users is higher than the number of needs reported by staff (Slade et al, 1996; Slade et al, 1998; Slade et al, 1999), although there are some studies where staff exaggerate or identify more needs than those expressed by users (Lasalvia et al, 2000; Hansson et al, 2001; Ochoa, 2003).

Wiersma et al (1998) computed a level of agreement between users and staff of 21%.

In the study presented by Slade et al (1996), the needs where there was most agreement between staff and users were accommodation and daily life activities, while those where there was less agreement were safety of others and information. The authors explained that there was more agreement in those areas where specific intervention services were available.

With regard to agreement between staff and users over the kind of help they received, higher agreement regarding informal help was found in the areas of looking after the home and money, and regarding formal care, in the areas of education, food, psychotic symptoms, daytime activities, money, looking after the home and accommodation.

In a later study by the same authors (Slade et al, 1998), higher agreement was found regarding the presence and meeting of need in the areas of child care, accommodation and psychotic symptoms, coinciding with the previous study. When studying unmet needs, they found a higher level of agreement in child care, education and accommodation and a lower level of agreement in food, information and personal safety.

In the study by Rosales (1999) in Granada (Spain), the needs showing a higher level of agreement were child care, transport and personal safety, whereas those with a lower level of agreement were information, sexuality and psychotic symptoms.

In the NEDES study (Ochoa et al, 2003), there was total agreement between users and staff in the areas of accommodation, food, education and transport. The lowest agreement was found in the areas of drugs and psychotic symptoms. In the assessment of unmet needs, the lowest agreement found between users and staff was in the areas of self-care, information, personal safety and that of others, drugs and child care. The explanation of these results could be related to lack of insight, one of the main characteristics of the illness.

When assessing the level of agreement between users and staff in the subclassification of the areas of the CAN as proposed by Slade et al (1998), the most remarkable differences are found in service needs, namely information, telephone, transport and benefits.

Hansson (1989) and Svensson et al (1994) studied levels of satisfaction and found that the participants in the study showed less satisfaction in the area of information about the state of the patient and his/her treatment. It seems that users expects the professionals involved to consider how they view their own illness and to improve the communication between patient and professional. Nowadays, different communitary services, even some hospital services, run psychoeducational programs that allow the patient to know more about the illness they suffer and to detect the symptoms preceding a relapse (Feldmann et al, 2002). This greater knowledge of their illness will not only reduce the presence of this need but also increase compliance and satisfaction with services and reduce the number of relapses (Merinder, 2000).

5.4. Formal and Informal Help Received to Meet Needs

Middelboe et al (2001) found that most of the needs reported by users were being met with formal rather than informal help. The only needs where informal help (friends and familiy) was of greater help were child care, self care, telephone and sexuality.

Rosales et al (2001) found that most needs were being covered by both informal and formal help. The needs that were met mainly by friends and family were accommodation, food, looking after the home, selfcare, daytime activities, physical health, company, personal safety, basic education, telephone, transport, money and benefits. The needs with greater involvement of social and health services were daytime activities, physical health, psychotic symptoms, information, psychological distress, personal safety, the safety of others, alcohol, drugs, company, intimate relationships, sexuality and child care. However, in the assessment by users of the help they were receiving, they considered informal help more often than formal help.

Ochoa et al (2003) described a high percentage of informal help, accomodation (45%) being the area where less informal help was being given. Some needs did not receive any kind

of formal help (telephone) or received a little (looking after the home, money, food). People with schizophrenia had their needs met mainly by family members.

Such questionnaires do not reveal why the needs of participants are not met, even though they receive some kind of help. One possible answer is that the given help (formal or informal) is insufficient. Another is that people with a specific need do not make use of the help provided or that the help is inappropriate.

Despite the development of communitary mental health services in Spain, patients are receiving more informal than formal help. In areas where the intervention of services is clearly defined, such as psychotic symptoms, physical health, information about the illness, personal safety and psychological distress, formal help is similar to or greater than the informal help provided. However, these results differ from those found by Middelboe et al (2001) in northern countries, maybe because these countries offer more specialized services and family help is not so readily available.

Generally, with the psychiatric de-institutionalization process, basic assistance falls on families and social networks of the person with schizophrenia (Denker et al, 1994). The family is in charge of meeting needs related to everyday and social life and mental health or social services do not have a direct impact on such needs. This is why it is important to assess the burden placed on the family of having to be meet these needs. Magliano et al (2000) commented that there is a heavy burden on the family when more basic needs related to everyday life have to be coped with. Families, especially in western society and culture, assume as their own the responsibility of taking care of domestic activities related to the person suffering an illness, leading them to make a special effort to deal with care correctly (Martínez et al, 1999).

In this sense, mental health or social services should pay attention to some of the needs met by informal carers, in order to avoid a greater burden on the family and to provide quality of life to relatives living with a schizophrenia sufferer.

5.5. Relation between Needs and Sociodemographical Variables

5.5.1. Gender

Most studies describe a better premorbid adjustment (Cannon-Spoor et al,1982; Childers et al, 1990; Larsen et al,1996), a better course of illness (Test et al,1990; Goldstein, 1988; Angermeyer et al,1989) and a better social adaptation (Mc Glashan et al, 1990; Usall et al, 2001; Usall et al, 2002) in women than in men diagnosed with schizophrenia. Although the existence of a better social functioning in women is a confirmed finding, few studies have assessed the relationship between gender and the needs of people with schizophrenia.

Rosales (1999) found significant differences between men's and women's needs in the following areas: selfcare, daytime activities, intimate relationships, information, child care and transport, with women showing greater presence of need in the last three areas and men in the rest of them.

In a recent study (Thornicroft et al, 2002), the results revealed differences between the needs of male and female schizophrenia sufferers. Women showed more needs in the areas of child care and self safety, whereas men showed more needs in the areas of safety of others and drugs, although these last differences were also related to the younger age range in the male sample.

Ochoa et al (2001) found that men had more needs than women as assessed by staff, but no differences were found in the users' assessment. Several previous studies suggest that the social role of women and men and the attitudes of professionals could influence their clinical judgments (Pekarik et al, 1987; Hintikka et al, 1999). Men have more basic and functioning needs and women have more service needs.

Basic needs comprise accommodation, food and daytime activities. In the case of food and daytime activities, there was a higher percentatge of men showing needs in these areas. This finding could be related to the role of men: rather than being required to attend to domestic tasks, they are more concerned with others, such as work and family safety. Women, however, have social functions related to domestic tasks conferred upon them.

With regard to functioning needs (education, money, child care, self care and looking after the home), and considering the assessment by professionals, men showed more needs. The only item where this was not the case is child care, where women assessed more needs than men, with professionals finding no difference. This finding is related to the role of woman as mother, to the frequency in which women have children in their charge and to a proper awareness of the difficulties of bringing them up. There are two studies that specifically assess the needs of women with psychotic disorders. In both studies, 60% of the women had children. In the study by de Howard et al (2001), the percentage of women with child care needs was 10%. Joseph et al (1999) found that 50% of women showed some need in child care, but the fact that this study was based on women admitted to hospital could explain the higher percentage of women with this need.

With regard to both personal hygiene and cleanliness in the home, women showed fewer needs than men. A higher percentage of women were married and living with their own famiy or independently, which could be related to an older age at onset. Also, women are expected to be able to run a household, whereas men are not. In this sense, women with a need in this area should be retrained in order to cope with this task, while most men should be trained as they might never have acquired enough knowledge in this task, possibly due to gender differences assigned by society (Seeman,1995).

Considering the classification of needs made by Slade et al (1998), in the subgroup of service needs (information, transport, telephone and social assistance) women showed more needs than men: significant differences were found in the items of benefits and transport.

In the subgroup of social needs (sexuality, company and intimate relationships), women showed less need than men only in the subgroup of patients with few years since onset. (Ochoa et al,2001)

5.5.2. Marital Status

Assessing need with the instrument NFCAS, Lefebre et al (2000) found that single people and people who are not working showed more unmet needs.

Married people show fewer needs when the assessment is made by staff (Rosales et al 2002; Ochoa et al, 2003). Moreover, married people showed a smaller amount of need in the area of daytime activities, possibly because living with their own family makes them pay attention to some daily duties.

5.5.3. Socioeconomical Level

People with a higher purchasing power have been found to show fewer needs than those with smaller incomes (Ochoa, 2004). Rosales (1999) found that people being paid a pension

showed more needs in the area of daytime activities, information, company, education, transport and money, whereas there were more people not receiving a pension and showing needs in the area of physical health.

5.5.4. Cultural Level

People who could not finish their primary education showed more needs (Rosales et al, 2002; Ochoa, 2004). This could be related to the severity or course of illness; they might have fallen ill before ending their studies, which could have caused more problems for them.

5.5.5. Age

As age increases, patients show more needs, and in the case of people with schizophrenia, this situation gets worse.

Hansson et al (1995) found that older people showed more needs than younger people.

Ochoa et al (2003) found that older people have more problems in accommodation, looking after the home and daytime activities. Considering that half of the subjects in the sample were living with their relatives, it is to be expected that patients find themselves with more problems in their household as their relatives die (lodging and looking after the home needs). This fact suggests that there should be services like sheltered homes or residences catering especially for older people.

In a study by Mc Nulty et al (2003), the needs shown by senior patients with a diagnosis of schizophrenia were studied. The instrument of assessment was the Cardinal Needs Schedule, which assesses social and clinical needs. Comparing the results obtained with those of a previous similar study with patients between 18 and 65 years old (Murray et al, 1996), they found social needs to be similar in both groups, though clinical needs were assessed three times more by the senior population.

5.6. Relation between Needs and Psychopathology

Few studies assess the relationship between needs and psychopathology.

In the EPSILON study (Mc Crone et al, 2001) and in the study by the NEDES group (Ochoa, 2005), people with a greater number of needs and unmet needs were found to have more symptoms.

Ochoa et al (2005) found that disorganised and excitative dimensions of psychopathology are the ones which have more predictive value in order to determine the presence and meeting of needs.

The disorganized dimension assesses symptoms related to cognitive decline (Honey et al, 2003). Results obtained seem to suggest that an intervention by a cognitive rehabilitation program could not only improve cognitive functioning, as has been widely reported (Twamley et al, 2003), but also the psychopathological symptoms of the disorganized dimension as well as reducing the presence of some needs (Bark et al, 2003).

The excitative dimension is composed of symptoms related to disruptive behaviour (excitation, poor impulse control, hostility, uncooperativeness and tension). This variable seems to differentiate people showing social problems of integration, especially if it is related to needs of psychological distress, alcohol, self safety and safety for others (Kay,1990).

The presence of need in the areas of self safety and psychological distress is related to the affective dimension of Positive and Negative Syndrome Scale (PANSS). This indicates that an exhaustive assessment of affective symptoms is needed in order to prevent suicide risk that the patient could show (Busch et al, 2003).

The presence of needs in daily activities (looking after the home, self care, food) are related to negative, disorganized and excitative symptoms. Also, negative symptoms are related to needs in company, money and education. Day centers and rehabilitation centers undertake activities aimed at coping with some of these needs: daily activities (looking after the home, food, money, self care) and activities of socialization and promoting relations with others (Croose, 2003). Van et al (2002) argued that people who can benefit from a rehabilitation service show a reduction in the number of needs and an improvement in their quality of life.

Although needs and psycopathology are related, Middelboe et al (2001), Mc Crone et al (2001), Hanson et al (2001) and Ochoa et al (2005) found that symptoms only explain around 15-20% of the variability of total needs.

5.7. Relation between Needs and Quality of Life

Needs are related to quality of life, and may be considered to be two sides of the same coin. In chronic diseases such as schizophrenia, it is essential to assess aspects related to the improvement of quality of life and which take into account the subjectivity of the person suffering from it. Despite this, few studies have related quality of life to needs.

A recent study by Slade et al (1999), belonging to the PRISM (Psychiatric Research in Service Measurement Psychosis Study), related needs to the quality of life of outpatients with schizophrenia. The assessment of needs was made with the CAN and quality of life with the LQoLP (Lancashire Quality of Life Profile). The results indicate that those patients with higher amount of needs also get worse scores in the LQoLP. Also, this relation becomes more evident in those people showing more unmet needs, as they have lower quality of life levels.

Heinze et al (1997) compared a sample of people with schizophrenia in London and in Berlin, describing that the Berlin sample showed a smaller number of needs, better quality of life and fewer economic and social problems.

Hansson et al (2001) did a multiple regression analysis by which he found that one of the variables that explained the presence of unmet needs, as assessed by user, was a worse quality of life (together with a poor social network), while when the assessment was made by professionals, quality of life did not result significant.

Ochoa et al (2003) found that people with more unmet needs have lower levels of quality of life when the assessment is made by users. In particular, quality of life relates to accommodation, daytime activities, company, intimate relationships and sexuality. This is why we should pay attention to the presence of this kind of expressed needs, as it seem to be the most influential in the lessening of their quality of life. Interventions to help cope with these needs will not only improve their quality of life, but will also ease therapeutic compliance.

5.8. Longitudinal Studies in the Assessment of Needs

There are few studies that assess the evolution of needs along time.

In a two-year period, Wiersma et al (1998) found that a total of 50% of the sample showed more needs. A total of 28% of the people had unmet needs. Only 20% of the sample had any need in both assessments. These results suggest that needs are dynamic and change over time and in function of the services available, so longitudinal assessment of need is important.

Foldemo et al (2002) did a study with inpatients diagnosed with schizophrenia in which they assessed the course of needs once they returned to life in the community. The mean number of needs a few days after de-institutionalization was higher than the number of needs described after five years of living in a sheltered home (with a mean variation from 7.1 to 6.3 needs). The results were obtained from 17 pateints, so further longitudinal studies are needed to explore this finding in detail.

6. CONCLUSION

The assessment of needs should be designed to explore the problems of people with schizophrenia in greater depth. It is clear that the presence of needs is related to sociodemographical characteristics, psychopathological variables and quality of life.

In this review, we can appreciate that the needs of people with schizophrenia vary from country to country, which could be due to cultural differences and the provision of mental health services. It is necessary, therefore, for both users and staff to assess needs before planning new services or mental health programs.

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Chapter 8

THE IMPACT OF DURATION OF UNTREATED PSYCHOSIS (DUP) ON CLINICAL OUTCOME IN A 12-MONTH FOLLOW UP STUDY WITH MEXICAN PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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ABSTRACT

Background

Studies from around the world on first-episode psychosis have consistently shown that there is an average of 1-2 years between the onset of psychotic symptoms and the start of the treatment. Duration of untreated psychosis (DUP) has been suggested as predictor of clinical outcome in patients with first-episode psychosis. It has been reported that patients with a longer DUP had a poorer clinical outcome in a follow-up period of 12 months, characterized by more severe positive and negative symptoms and global psychosocial impairment. Also, it has been described that patients with schizophrenia exhibit a longer

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DUP when compared to patients with affective psychosis and that this longer DUP is related to their clinical outcome.

Objective

To determine the effect of DUP on clinical outcome in a 12 month follow-up study in a Mexican population.

Method

A total of 104 first-episode psychotic patients were recruited and grouped in affective (n=25, 24%)and non-affective psychoses (n=79, 76%). Diagnoses was obtained with the SCID-I and the DUP was register in each patient. A clinical evaluation for psychotic and affective symptoms was performed using standardized instruments. The sample was divided according the median of DUP in short DUP (<28 weeks) and long DUP (≥ 28weeks).

Results

Ten patients were lost during the follow-up. The mean DUP of the 94 patients was 67.1/-69.5 weeks, no differences were found between lost and remaining patients in clinical variables. Two patients from the long-DUP group committed suicide in the first year. The long-DUP group showed persistent positive and negative symptoms, as well as poor social functioning during the follow-up.

Conclusions

Although some studies have considered that first-episode patients in non-developed countries may have a better prognosis not related to DUP, our results suggest that long DUP has an influence on outcome and may increase the suicide risk in Mexican first-episode patients, supporting the importance of early detection and intervention. Early detection programs are required to shorten the interval from onset of illness to first specialized diagnosis and treatment in first-episode psychotic patients.

Key words: First-episode psychosis, duration of untreated psychosis, outcome.

INTRODUCTION

Schizophrenia has been recognized as one of the conditions that cause major disabilities in several spheres of a person's functioning. According to the Global Burden of Disease Study[1], schizophrenia causes a high degree of disability that accounts for 1.1% of the total DALYs and 2.8% of years living with disability (YLDs). DALY combines information on the impact of mortality (years of life lost because of premature death=YLL) and disability (years lived with disability=YLD). One DALY can be thought as one lost year of healthy life. The

World Health Organization placed schizophrenia as the 8th leading cause of disability (according the adjusted life years) worldwide in the age group of 15 to 44 years old[2].

The incidence of schizophrenia seems to be very similar worldwide[3, 4],its lifetime prevalence rate has been reported in the range of 1.4 to 4.6 per 1000 and its incidence rates in the range 0.16-0.42 per 1000 [5]. It has a chronic course with an early onset, generally during adolescence and young adulthood[6, 7]. Most first episode cases represent schizophrenia or other schizophrenia spectrum disorders [8, 9]. It has been estimated that approximately 25% of people with schizophrenia will recover during the first five to six years after the onset of their first psychotic episode, but another 15% become chronically disabled [10, 11]. The most frequent course of the illness includes a chronically poor functioning, with little evidence of long-term improvement[11]. In addition, the mortality risk of schizophrenic patients is increased compared to the general population[12, 13]. A recent meta-analysis estimated that 4.9% of schizophrenics will commit suicide, usually near the onset of their illness[14]. There are also many reports of excess mortality related to the diagnosis of schizophrenia in association with tobacco and alcohol abuse, a poorly balanced diet, metabolic syndrome, cardiovascular disease and other factors, such as sedentary life [15-17].

In the last three decades, the efforts to diminish the burden of the disease were directed to establish better treatment programs; so long-term, prospectively designed studies which included mainly patients on their first psychotic episode were conducted around the world. The earliest findings confirmed the remission of psychotic symptoms in 70-83% of the patients in their first episode treated with antipsychotics[18, 19]. However, most recent reports observed that 80% of the patients diagnosed with a first-episode of schizophrenia or schizoaffective disorder had at least two relapses during the first 5 years of the disorder [20]. A recent epidemiological study established that 74% of first episode schizophrenia patients and 47% of other psychotic disorders were symptomatic after 5 years of illness [21]. The advances in the definition of recovery in schizophrenia, including the longitudinal evaluation of the different psychopathology dimensions (Positive, Negative and disorganization) as well as the psychosocial functioning[22, 23], showed that after 5 years only 47% of the subjects achieved symptom remission, and 25% had adequate social functioning for 2 years or more. Meanwhile, only 13% of subjects met full recovery criteria for 2 years or longer[24]. Although the patients on their first psychotic episode achieved a higher response rate to the treatment at the end of one year follow-up, the overall rate of recovery during the early years of the illness was low.

Predictors of poorer outcome which have been consistently reported include family history of schizophrenia, insidious onset, poor premorbid functioning, severe initial negative symptoms, low cognitive functioning and long duration of untreated psychosis (DUP)[24-30].The mean DUP in psychotic patients has been shown a great variability, since some subjects receive attention in the first weeks or months after the onset of psychotic symptoms, while others remain without attention for years[31]. In general, the mean DUP has been reported to be between 1 and 2 years [32-34]. Since this variable depends on other variables, such as the knowledge about psychosis in general population and health professionals, and the availability of mental health services, it becomes the most suitable factor to be modified by medical interventions, such as the early detection programs [35, 36].

Previous studies had examined whether DUP predicts time to remission of psychotic symptoms, or their severity after a 6 to 12 months follow-up [10, 27, 35, 37-46] Although some of these reports did not find associations, many of them establishes a relationship

between longer DUP and longer time to remission or lower level of positive symptoms at follow-up.

Some of the inconsistencies between those studies are for instance; the distribution of DUP tends to have a marked positive skew, suggesting the appropriateness of transformations or non-parametric analyses. These procedure was not followed by some of the negative reports [10, 39, 42]. Non-significant reports could also be a result of a restricted range of DUP[10]; combining data for patients who may vary widely in the treatment received [42] or possible marked difficulties in estimating DUP[39].

Regarding the impact of DUP on the negative symptoms outcome, few studies reported a significant relationship[39, 40, 44, 47]. The examination of the possible relationships between DUP and psychosocial functioning during follow-up have been done in few reports[35, 43, 48]and no direct relationships have been consistently found.

The above mentioned findings about the impact of DUP on the outcome in schizophrenia were confirmed on a recent meta-analysis [49] suggesting a bivariate relationship between DUP and time to or level of remission of positive symptoms, although there may be less consistency with respect to DUP predicting level of negative symptoms after treatment. Indeed, these findings support the hypothesis that the predominance of negative symptoms and cognitive dysfunctions in patients with long DUP [39, 50] could be related the toxic effect of the presence of psychotic symptoms for a long period of time [51]. Both conditions have also been related to a poor response to the currently available pharmacological treatment [52-55]. Also, attention and treatment delay may increase the risk for suicide behaviors and legal problems as a result of violent behavior, which is a common feature in psychotic patients [56]. Familial dysfunction and psychosocial impairment of the patients are also some of the main social implications of a late diagnosis [57].

Another factor which has been suggested to impact the outcome in schizophrenia is the degree of development of the Country which patients live. For example, in the WHO-DOS Study, a higher proportion of patients in developing countries were reported to achieve full remission at 2 years compared to patients from developed countries [4, 58]. It is important to examine if the DUP in psychotic patients in a developing Country differs from the reported in Europe and other industrialized Countries, and also if it impacts on the outcome of illness The aim of the present study was to determine the impact of duration of untreated psychosis on the recovery in a group of Mexican patients with first-episode psychosis during one year of follow-up.

METHOD

Study Setting

The study protocol was approved by the Institutional Review Board of the National Institute of Psychiatry. Written informed consent was obtained after the procedures had been fully and detailed explained to patients and to their families.

Subjects

Patients were recruited from the inpatient and outpatient services of the National Institute of Psychiatry in Mexico City. The patients were male and female, between 15 and 45 years old, with current psychotic symptoms of sufficient severity to achieve in the PANSS positive syndrome a score at least 16, with two items scoring at least four. All the patients were in their first-episode of psychosis, defined as the first contact in life with a specialized service of psychiatry due to the present psychotic episode and without antipsychotic treatment one month before admission[59]. Patients with more than 5 years of illness duration, diagnosis of mental retardation, dementia, delirium or psychosis secondary to medical conditions or substance abuse were excluded.

Assessment Procedures

Patients were diagnosed according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-I) [60]. Diagnoses were performed at the initial assessment and confirmed in the last evaluation of the patient. Demographic data and DUP were registered in a previously design instrument[61]. All information was collected by a direct interview with the patient and his /her relatives. DUP was defined as the time between the manifestation of the first positive psychotic symptoms and the onset of an adequate antipsychotic drug treatment. The duration was measured in weeks.

The patients were grouped according to their diagnosis. The first group comprised patients with non-affective psychoses (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief reactive psychosis and psychosis NOS) and the second group comprised patients with affective psychosis (bipolar disorder and major depression with psychotic symptoms).

The severity of symptoms was assessed with rating scales previously translated and validated for Mexican psychiatric patients[62]. All patients were assessed with the Positive and Negative Syndrome Scale (PANSS) (30 items, 1–7 severity scale)[63, 64]. The Calgary Depression Scale for Schizophrenia (CDS) [65] was administered to patients with non-affective psychosis. The Affective psychosis group was evaluated with the Hamilton Depression Scale (HDS) [66] and with the Mania Rating Scale (MRS)[67]. To define the presence of severe depressive symptoms, cutoff points of 7 and 18 were selected for the CDS and HDS respectively [68].

Clinical assessment was performed at baseline and every three months until patients completed a 12 months of follow-up. At the end of the follow-up, all patients were assessed with the Strauss-Carpenter Prognostic Scale [69] to determine their recovery among several dimensions (number of hospitalizations, social relationships, occupational functioning and active psychotic symptoms in the previous month). This scale is scored from 0 to 4, where 4 represent a complete recovery and 0 represents the presence of continuous symptoms, multiple hospitalizations and inadequate occupational or social functioning. A patient can be considered as “recovered” if he/she exhibits scores between 3 and 4 in the subscales of the Strauss-Carpenter Scale, and as “non-recovered” if scored from 0 to 2 points. The rate of recovery was obtained according the criteria described by Tohen [70] and Frank [71].

Statistical Analysis

Demographic and clinical characteristics description was done with frequencies and percentages for categorical variables and with means and standard deviations (+/-) for continuous variables. For the comparison between diagnostic groups, the Chi square test (x^2) was used for categorical contrasts while the Student t test for independent samples was used for continuous variables. For the analysis of the PANSS domains an analysis of variance (ANOVA) with Bonferroni correction, using the diagnostic group as independent variable, was performed. Non-parametric tests were used for the comparison of the DUP between groups. For the evaluation of recovery rate a Kaplan-Meier survival analysis was performed and to determine the variables associated to recovery, a Cox regression analysis was used. The confidence intervals were established at 95% and significance level with a $p<0.05$.

RESULTS

a) Demographic and Clinical Characteristics of the Sample

A total of 104 first-episode patients were included. Most of the patients had the diagnosis of non-affective psychosis (n=79, 74%). The diagnostic distribution was as follows: Schizophrenia N=52, schizophreniform disorder N= 12, schizoaffective disorder N=10, delusional disorder N= 3, psychosis NOS N=2, bipolar disorder N=12 and major depression with psychotic symptoms N=13.

The mean DUP of the sample was of 57.1 +/- 69.5 weeks, with a median of 28 weeks, without differences between affective and non-affective psychosis. Nevertheless, the patients with schizophrenia were considered as an independent group, their mean DUP was of 79.0+/- 78.3 weeks, while for the non-affective group was of 32.9+/- 40.4 weeks and for the affective group of 38.8+/- 62.4 (Kruskal-Wallis $x^2= 12.9$, df 2, $p=0.002$)The baseline demographic and clinical characteristics of the diagnostic groups are shown in Table 1. Twenty-five patients (32.9%) of the non-affective group had a score greater or equal to 7 points in the CDS and 64% of the patients in the affective psychosis group had a score $\geq$ 18 in the HDS.

During the follow-up: two patients refused to continue in the study and another changed his address at the third month, two more during the sixth month refused to continue in the study and five more patients were lost during the ninth month (two patients changed their addresses and 3 refused to continue in the study). The final follow-up index was of 90.4%.

b) Improvement of Symptoms During the Follow-Up

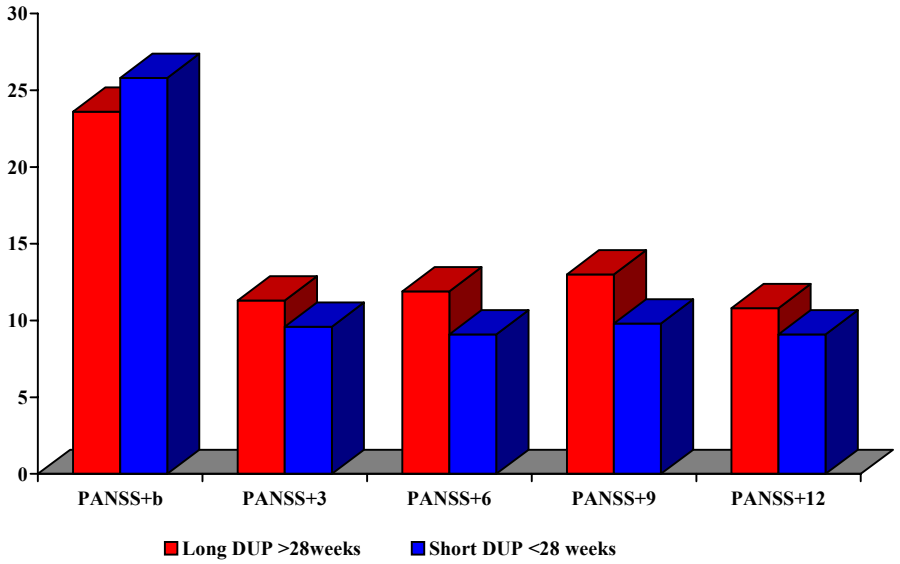
Both diagnostic groups showed reduction in the scores on the different domains of the PANSS scale without significant differences between them (Table 2). When patients were divided in Long DUP and Short DUP according to the median score of the total sample, a significant difference was observed in terms of the positive PANSS subscale (Figure 1). There were no differences in the negative subscale or in the total PANSS scores between DUP groups.

Table 1. Baseline demographic and clinical characteristics between non-affective and affective psychosis

	Affective Psychosis n=25		Non-Affective Psychosis n=79		**Statistic**
	n	**%**	**n**	**%**	
Gender					
Male	8	32	50	63.3	x^2=7.5, df 1, p=0.006
Female	17	68	29	36.7	
Marital status					
Married	11	44	15	19	x^2=6.3, df 1, p=0.01
Single	14	56	64	81	
Socioeconomic status					
High	2	8	0		
Medium	12	48	35	44.3	x^2=6.8, df 2, p=0.03
Low	11	44	44	55.7	
Occupational status					
With occupation	21	84	36	45.6	x^2=11.3,df 1, p=0.001
Without occupation	4	16	43	54.4	
Attention service					
Inpatients	8	32	53	67.1	x^2=9.6, df 1, p=0.002
Outpatients	17	68	26	32.9	
	Mean	**S.D.**	**Mean**	**S.D.**	
Age	27.8	11.0	26.8	7.7	N.S.
Age at illness onset	27.2	11.1	25.4	7.8	N.S.
School years	9.8	1.7	11.1	3.1	t=2.5,df 102, p=0.01
PANSS					
Positive	24.6	6.5	24.6	4.5	N.S.
Negative	17.8	5.9	23.5	9.1	t=2.9,df 102,p=0.004
Total	88.7	15.7	95.2	18.0	N.S.
Calgary Depression Scale	--		5.6	4.4	--
Mania Rating Scale	38.4	7.2		--	--
Hamilton Depression Scale	30.7	5.5		--	--
DUP (weeks)	38.8	62.4	62.9	71.0	N.S.

*Categorical variables with Yates correction.
*Continuous variables with CI 95%%
*N.S. (no significant)

At the end of the follow-up, the mean scores of affective symptoms according the rating scales were CDS: 2.1 +/- 3.9 points, with 7 patients (10.8%) having a score $\geq$ 7; Mania Rating Scale: 0.47 +/- 1.2 points and the Hamilton Depression Scale : 11.3 +/- 9.6 points, with 4 patients (28.6%) having a score $\geq$ 18. Although no differences were observed between Long and Short DUP groups in the severity of depressive symptoms, two patients from the Long DUP group (both with a final diagnosis of Schizophrenia) committed suicide.



Between groups: F=7.2, df 1, p=0.008

Figure 1. Positive symptoms in first-episode psychotic patients according to DUP during the follow-up.

Table 2. PANSS scores of patients with first episode of psychosis during the follow-up

	Affective Psychosis (n=25)		Non-affective Psychosis (n=79)	
	Mean	D.E.	Mean	D.E.
Positive PANSS[a]				
Baseline	24.9	6.4	24.6	4.5
Month 3	9.2	3.7	10.9	4.6
Month 6	9.7	4.5	10.8	5.4
Month 9	10.7	6.6	11.7	5.9
Month 12	9.8	4.9	10.0	4.2
Negative PANSS[b]				
Baseline	17.8	6.0	23.6	9.2
Month 3	10.5	4.1	14.6	5.4
Month 6	10.1	5.0	13.5	5.6
Month 9	10.0	5.9	13.9	6.3
Month 12	9.5	4.3	12.9	5.1
Total PANSS[c]				
Baseline	89.1	15.9	94.9	18.3
Month 3	44.7	11.4	54.1	14.5
Month 6	44.4	14.5	50.8	17.5
Month 9	46.7	22.5	53.4	19.7
Month 12	45.2	19.8	49.1	16.3

[a] Between groups: F=0.05, df 1,p=0.94, time effect F=196.6, df 1. p<0.001
[b] Between groups: F=1.12, df 1,p=0.29, time effect F=68.7, df 1. p<0.0001
[c] Between groups: F=0.22, df 1,p=0.64, time effect F=163.1, df 1. p<0.001

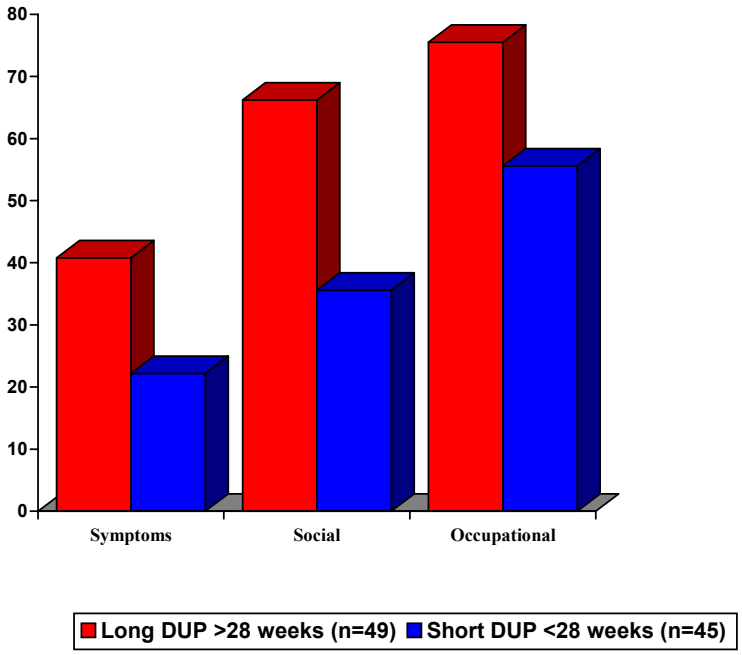
c) Recovery Rates during the Follow-Up

The patients with long DUP showed a reduced recovery according the Strauss Carpenter Scale in symptoms, occupational and social functioning (Figure2). Only one patient belonging to the long DUP group had a readmission to the hospital. No differences were observed between the affective and non-affective psychosis groups.

The recovery rate of the total sample was 82.7%, being similar in patients with non-affective and affective psychosis (81.6% vs 96% respectively).

The cumulative recovery rate of the patients with non-affective psychosis was 81.6%, the time to achieve recovery was 6 months (CI 95% 5-7) and for the affective group the cumulative rate was 96%, the time to achieve recovery was 4 months (CI 95% 3-5) (Log rank X^2= 5.1, df 1, p=0.02).

According to DUP, the Long DUP group showed a recovery rate of 83.1% reached in 6 months (CI 95% 5,7), while the Short DUP group showed a 87.5% achieved in 4 months (CI 95% 4,5) (Log Rank X^2= 3.9, df 1, p=0.04) (Figure 3).



Symptoms x^2=3.7, df 1, p=0.05
Social x^2=6.1, df 1, p=0.01
Occupational x^2=4.1, df 1, p=0.04

Figure 2. Percentage of Non-recovered patients between DUP groups at the end of the follow-up

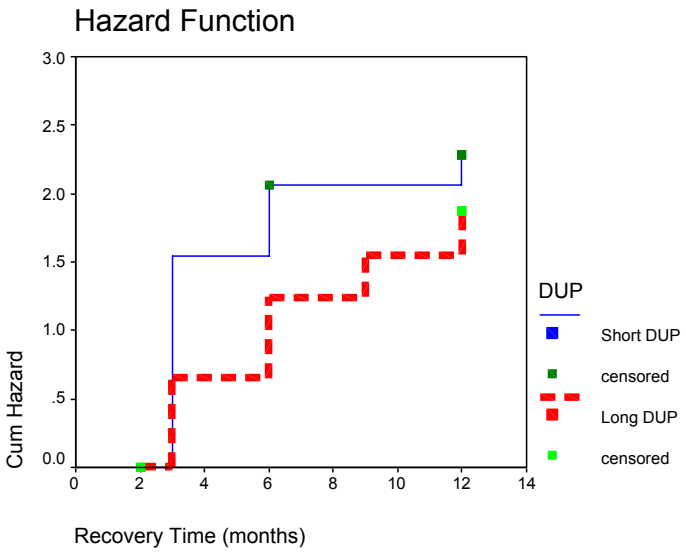


Figure 3. Probability of recovery between DUP groups

d) Predictive Factors for Recovery

The variables included in the Cox regression analysis were gender, economical status, years of education, unemployment, duration of untreated psychosis, , type of attention service received (inpatient/outpatient) and baseline positive PANSS scores. The final model showed that the DUP (Hazard Ratio=3.7, df 1, p=0.05) and female (Hazard Ratio=4.1, df 1, p=0.03) were associated with recovery.

DISCUSSION

The definition of Duration of Untreated Psychosis refers to the time that a given patient spends between the onset of psychotic symptoms and the administration of an adequate antipsychotic medication scheme (equivalent to haloperidol 5 mg/day administered for at least 3 or 4 weeks), which promotes a significant clinical response in non-chronic, non-resistant patients [72]. Although it has been described that patients with affective psychosis had a shorter DUP because affective symptoms are easier to identify, no differences emerged between the affective and the non-affective psychotic patients in this study[37]. However, the DUP of schizophrenic patients was longer than the observed in the other diagnostic categories.

In the present study, patients exhibited severe psychotic symptoms and almost half of the patients required hospitalization. Patients with non-affective psychosis showed higher levels of negative symptoms. This finding may be related to their longer DUP, in particular, for patients with schizophrenia. The fact that both diagnostic groups showed high rates of severe depressive symptoms supports the theory proposed by Crow [73], where schizophrenia and affective disorders are genetically determined in a severity continuum, with a phenotypic

expression that depends on the gene structure and the association with familial history of major depression or schizophrenia with depressive symptoms [74].

During the follow-up, a reduction in the severity of psychotic symptoms was observed, being more robust in patients with short DUP. This finding confirms the association between DUP and outcome previously described above. The severity of affective symptoms was also reduced, but interestingly, a considerable percentage of patients with non-affective psychosis continued showing depressive symptoms and two patients committed suicide. Depressive symptoms have been related to a poor outcome [75] and their presence is a common problem during the acute phase of illness and during the first year of illness evolution [76]. This fact could be related with the longer time to achieve remission observed in patients with non-affective psychosis. Similarly to previous reports, the differences in outcome between patients with long vs short is mainly due to the persistence of positive symptoms and low psychosocial functioning[30, 46, 77-83].

Although both patients with affective and non-affective psychosis improved on their symptoms, they could not achieve the same level social and occupational recovery, which is in accordance with previous descriptions [84, 85]. The short DUP and female gender were associated , this last finding could be related with the later onset of illness that women show, leading to these patients to achieve more social (e.g. to start their own family) and occupational goals (e.g more school years) prior to become ill, which helps them to deal better with their symptoms.

In the present study, recovery was assessed in a dimensional way considering both syndromatic and functional aspects. It was very similar between diagnostic groups; but patients with Short DUP had fewer symptoms and a better functioning at the end of the study. Recovery rate was better in patients with affective psychosis and Short DUP, result that supports its relation with a better outcome [85-91]. This has been reported in samples from industrialized Countries [27, 30, 33, 46, 77, 79, 81, 82, 92-95], and could be related to some aspects of schizophrenia which not depend on the development of the Country where patient lives, such aspects are denial of illness, social isolation, and the negative symptoms; in particular, the abulia and diminished will to ask for professional assistance. However, it has been described that the schizophrenic patients from developing countries, such as Mexico, show a better outcome than patients from developed countries[96-100]. This could be explained by the interactions between allelic variations of a given set of genes and the environment, which is supposed to include a higher frequency of patients living with their families or more interactive with their communities, although these interactions remain poorly studied[5].

The results from present study show that the schizophrenic patients had a poor outcome, being more similar to that of industrialized countries, this could be explained by the fact that the previous reported comparative studies were done twenty years ago, and the socioeconomical conditions of Mexico have changed; for example, there is a higher number of working women, leading to changes in the family interactions with the community[101, 102]. Another factor is the increase of drug abuse and dependence, as well as the prevalence of mental illness [103-106]. This findings point to the importance of performing new studies in several countries, to examine if the setting continues as a protective factor for a poor outcome in schizophrenia.

The DUP observed in our study show that pathways to care and reference to specialized attention centers has not change in our country as stated in other previous works [101, 107-

111]. This suggest that there has not been any progress with respect to the reordering of mental health services and the lack of education for early detection and treatment of these disorders, which are very important for prevent the neurobiological disruptions associated with a poor outcome in these patients.

The main limitations of this study were that it was carried out in a specialized attention center with a short follow-up period and the reduced patient sample included in the follow-up phase, which makes difficult the generalization of the results. Another limitation is the inclusion of patients with affective disorders, who could have a better outcome. Future studies should exclude them and patients with brief psychotic syndromes in order to evaluate the DUP more precisely.

In conclusion, the DUP of Mexican patients is as long as in other Countries, and the social and occupational recoveries were very poor. These findings support the need of early detection programs in our Country to improve the prognosis if psychotic patients.

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Chapter 9

DEFICITS IN SOURCE MEMORY IN SCHIZOPHRENIA: RELATIONSHIP TO BASIC COGNITIVE FUNCTIONING AND PSYCHOPATHOLOGY*

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ABSTRACT

Source memory impairments have been found repeatedly in schizophrenia. Many studies referring to source-memory deficits in patients with schizophrenia associate them with positive symptomatology. However, the etiological mechanism of this handicap remains unknown. With the exception of the research that supports the relationship between positive symptoms and source memory, studies have generally documented a deficit in source memory in patients with schizophrenia, but have not linked it to hallucinations. Our first goal in the present investigation was to study source memory in schizophrenia, which according to the literature is seriously impaired. Our second goal was to investigate the clinical significance of these errors, that is whether they are related to overall symptomatology in schizophrenia. Our third goal was to understand the relationship between source memory and cognitive functions.The implications of our findings are twofold. On one hand, they highlight the complexity of the process of source monitoring. On the other hand, they suggest that impaired source memory in schizophrenia reflects – at least partially – the basic cognitive impairments typical of this disorder. More specifically, verbal memory and executive functions deficits affect the source memory process on three levels: a) organization and storage of the material in the memory system, b) recall strategies, and c) executive functions control and monitoring

* This study is based on the Master's thesis of the first author under the supervision of M.H. Kosmidis and V.P. Bozikas.

1. INTRODUCTION: SOURCE MEMORY AND SCHIZOPHRENIA

Source memory impairments have been found repeatedly in schizophrenia. Many studies referring to source-memory deficits in patients with schizophrenia associate them with positive symptomatology (Frith et al., 1991; Brébion et al., 2000). However, the etiological mechanism of this handicap remains unknown. On the other hand, although the existence of cognitive deficits in schizophrenia has been confirmed, the way in which these specific deficits are associated with impaired monitoring of the source of information has not been investigated thoroughly.

1.1. Source Memory and Psychopathology in Schizophrenia

Much of the research on source memory has focused on the relationship between positive symptoms, particularly hallucinations, and impaired monitoring of the provenance of information. Frith and Done (1989) suggested that some positive symptoms, like hallucinations, delusions and intrusive thinking result from the failure to distinguish internal and external events. One's inability to follow one's thoughts and actions results in appreciating them as if they were coming from an external source, like computers or pictures. Later, the same authors (Frith et al., 1991) suggested that patients with schizophrenia make mistakes attributing what they produce to external sources, because they are not aware of their efforts or their intentions.

Bentall et al. (1991) tested this assumption of "distinguishing reality" (Frith and Done, 1989) experimentally using a source memory task. They found that patients do not differ from controls in recognizing words they produced themselves. Furthermore, the two groups performed better on words they produced with great cognitive effort, compared to those produced with low cognitive effort. On the other hand, patients with hallucinations attributed the words they had produced with great cognitive effort to the experimenter more often than did patients without that symptom. Thus, the investigators suggested that patients with hallucinations favour the attribution of internal events to external sources either because they do not trust their judgment, or because they do not recognize their own way of thinking (metacognitive processes) (Bentall and Slade, 1985).

Οι Morrison and Haddock (1997) agreed on the basic theoretical framework with Bentall and Slade (1985) and argued that the tendency of patients with schizophrenia to attribute internal events to external sources appeared when these events did not agree with their metacognitive beliefs. For example, a "sinful" internal thought may cause cognitive discord, which the patient tries to avoid by attributing it to external sources ("there is no way I would think something like this"). According to Ensum and Morrison (2003), the degree of the bias seems to be affected by the level of attention to the self. In other words, the more attention is driven towards oneself, the greater is the number of internal events incorrectly attributed to external sources. The above suggestion is of clinical interest, as training in techniques that could help a patient focus his or her attention on external events may decrease the severity of his or her symptoms (Morrison and Haddock, 1997).

In a more recent study, Brébion and colleagues (2002) assessed the performance of patients and controls on a source memory task, wherein the participants had to recall words

they had either said themselves or they had been told by the experimenter or they had seen as pictures. Afterwards, they had to recognize them among new interfering words. The investigators found a correlation between positive symptoms and recognition errors of new interfering words as if they were old. There was also a correlation between positive symptoms and errors of attribution of words made by patients to an external source (the experimenter). On the contrary, they noted no correlation between the ability to maintain words in memory (coding and storage of words) and positive symptomatology. They claimed that hallucinations are associated with deficits in the process of comparing internal with external events and with impaired self-monitoring in schizophrenia.

The aforementioned difficulty of patients with schizophrenia is not restricted to the distinction between events of internal and external sources, but extends to situations in which a distinction between two internal sources must to be made. Franck and colleagues (2000) investigated the ability to monitor information on a task in which information came from two internal sources (reading of words silently and aloud). Patients with hallucinations remembered more often words they had read silently than words they had read aloud. The authors suggested that the poor processing of characteristics concerning cognitive functions involved in the production of internal events, either because of lack of awareness or because of some impairment in the internal perception of speech, can explain the failure of patients in source memory tasks.

The failure in discriminating reality in schizophrenia affects not only thoughts, but also acts. Mlakar and colleagues (1994) observed that patients with schizophrenia showed greater difficulty in recognizing pictures they had made when the task required self-monitoring (i.e., monitoring their own conscious acts).

Moritz and colleagues (2003) observed that patients with symptoms of disorganization (conceptual disorganization, rigidity, and mannerisms) were biased towards wrongly recognizing new interfering words as if they were old. According to the authors, disorganization is associated with the rapid and extended propagation of neural activity in semantic memory. Listening to a new interfering word may lead to the activation of additional related mnemonic traces (for example, more semantic characteristics), resulting in patients thinking that this new interfering word had been included in the list they should have memorized (Moritz et al., 2003).

In contrast to Moritz and colleagues (2003), Brébion and colleagues (2000) did not find a relationship between the errors of recognizing new interfering words as if they were old and disorganization of thought or delusions. However, the authors didn't exclude the possibility that delusions of specific content (like external control or thought intrusions) may be related to impaired source memory. Regarding negative symptoms, Brébion and his colleagues (1999) noted that some of them, like social and emotional withdrawal, affective flattening, avolition and anhedonia are associated with errors of recognizing new interfering word as if they were old, and with source memory errors.

With the exception of the research that supports the relationship between positive symptoms and source memory, studies have generally documented a deficit in source memory in patients with schizophrenia, but have not linked it to hallucinations. Vinogradov and colleagues (1997) conducked such a study, noting that patients often attributed words they had produced to an external source (to the experimenter) and often recognized incorrectly new interfering words as if they were old. However, they did not find relationship between these errors and positive and negative symptoms, but found a correlation only

between these errors and hostility, a symptom which, according to the authors, prevents patients from monitoring the source of information. A very interesting finding of the Vinogradov and colleagues study (1997) is that in a two-year re-examination of 11 patients from their sample, the source memory deficit reported initially remained the same, despite changes in pharmacotherapy and variations in symptomatology.

In a similar study, Seal and Crowe (1997) compared two groups of patients – those with and those without hallucinations – on an source memory task. They failed to find any differences between groups in source memory errors, particularly attribution of internal events to external sources, even after controlling for the effect of verbal memory and verbal IQ. In addition, contrary to Bentall and colleagues (1991), Seal and Crowe (1997) noted that the two patient groups did not differ in terms of errors of attribution to external sources of the words they produced following great cognitive effort compared to those produced following lesser effort.

1.2. Source Memory and Cognitive Functions in Schizophrenia

While there is considerable research on the relationship between positive symptomatology and source memory, there are few studies investigating the relationship of cognitive deficits and the ability to monitor the source of information. Source memory does not constitute an independent function. It is speculated that basic cognitive functions are involved in the process of source memory, like attention, working, verbal, and visual memory, and mainly executive functions.

1.3. Attention and Working Memory

The ability to attend to information presented or to answers given is very important for encoding and retaining that information. There are different types of attention that constitute relatively independent processes. One type is selective attention, i.e., the ability to focus on certain characteristics of an event while simultaneously ignoring irrelevant information. Another type is sustained attention, which is the ability to maintain a constant behavioural response while performing a continuous and repeating action. In schizophrenia, both these types of attention are impaired (Bozikas et al., 2005; Bozikas et al., in press; Kurtz et al., 2001).

A source memory task demands of a person a) to sustain his or her attention for as long as the information is being presented or the person is generating some response, b) to focus his or her attention on the features of various bits of information that help to distinguish among them, and c) to process the features of the information's source while retaining its content. Impairment in selective or sustained attention can impede to source memory. The attribution of this event to its source may be incorrect, because of the limited information about its source.

Brébion and colleagues (1996) administered a source memory task to patients with schizophrenia and controls, in order to investigate selective attention using the Stroop Test. In the patient group, selective attention correlated with both the number of false alarms (recognition errors of wrongly recognizing new interfering words as old), and the index of

discrimination between orally and pictorially produced external events. There was no significant correlation between selective attention and errors made by attributing self-produced words to an external source (self/external discrimination).

On the other hand, Stirling and colleagues (1998) examined the ability of self-monitoring and both selective and sustained attention in patients with schizophrenia and controls. Participants were administered a self-monitoring task, in which they had to monitor their movements while drawing, in order to be able to later recognize the drawings they had produced without seeing them. The correlation between selective attention and the patients' poor performance on the task did not reach significance. On the contrary, a significant correlation appeared between the patients' performance on the self-monitoring task and sustained attention. However, when they controlled for the difference in selective attention between patients and controls, the two groups still differentiated on their performance on the self-monitoring task. Thus, the authors argued that self-monitoring is an independent function and different from the other cognitive deficits seen in schizophrenia.

Working memory, i.e., the ability to hold on to and to manipulate information in a temporary storage for several seconds, may play an important role in the process of self-monitoring. A number of studies of patients with schizophrenia have demonstrated a deficit in working memory (Bozikas et al., in press; Carter et al., 1996; Gold et al., 1997). Working memory appears to have an active role and intervenes in the process of source monitoring, by keeping the mnemonic trace of the event active, while various features of the specific source are being encoded (e.g., perceptual features, semantic information). However, to date, the relationship between working memory and source memory impairment in schizophrenia has not been investigated.

1.4. Verbal and Visual Memory

Immediate and delayed recall, learning and recognition of visual and verbal information are considered to contribute to the ability to monitor the source of information. The retention of the information as well as the features of the internal and external sources is very important for the proper functioning of source memory. Impaired verbal and visual memory in schizophrenia has been confirmed by a number of studies and according to Aleman and colleagues (1999), it does not merely constitute a problem secondary to impaired attention.

Danion and colleagues (1999) studied recognition and source memory in schizophrenia. They evaluated recognition ability with the help of standardized measures and found no difficulty among patients. On the contrary, they noted that patients performed worse than controls on a source memory task using pairs of words. Patients relied on the feeling of familiarity triggered by the presentation of the pairs by the experimenter and attributed them more often than the control group to external sources (Danion et al., 1999; Weiss et al., 2002).

According to the authors (Danion et al., 1999), these findings supported the theory that the source memory problem is associated with the deficit of patients with schizophrenia to combine all features (content and information of the source) of an event in a uniform framework (Danion et al., 1999; Keefe, 2002). These deficits may appear due to problems in the processes of encoding or recall, that form part of a greater problem concerning the strategies involved in the processing of information in working memory.

1.5. Executive Functions

The role of the frontal lobes in executive functions and cognitive processes that demand control, organization and planning is essential. Consequently, the frontal lobes are involved in the processes of source monitoring. In fact, patients with schizophrenia present serious deficits in executive functions (Bozikas et al., in press).

In a study of source memory, Vinogradov and colleagues (1997) examined executive functions and IQ in patients with schizophrenia. However, their data showed that the influence of the frontal lobes deficit on source memory is not independent of the IQ. Thus, they suggested that the involvement of executive functions in the processes of source monitoring is limited. In contrast, studies with patients with Korsakoff's syndrome, multiple sclerosis, and Parkinson's disease, who present alterations in frontal cerebral areas, demonstrated difficulties in the chronological sequencing of events (Beatty and Monson, 1991; Shimamura et al., 1990; Kopelman et al., 1989). It has also been observed that patients with organic damage in the prefrontal cortex have difficulties in monitoring reality, and refer often to past unreal events (confabulation) without having the intention to deceive, but in an attempt to fill their memory gaps (Johnson et al., 1993). While some studies with patients with frontal lobe damage have supported the relationship between source memory and executive functions, this is not the case in studies of schizophrenia.

2. GOALS AND HYPOTHESES

Our first goal in the present investigation was to study source memory in schizophrenia, which according to the literature is seriously impaired. Our initial hypothesis was that patients with schizophrenia make 1a) more recognition errors, falsely recognizing new words as if they were old, and 1b) more source memory errors, compared to controls. In this study we sought to explore the type of recognition and source memory errors patients with schizophrenia make and how these two types of errors differ in two source memory tasks that set different demands, containing visual vs. auditory stimuli.

Our second goal was to investigate the clinical significance of these errors, that is whether they are related to overall symptomatology in schizophrenia. We studied thoroughly the relationship between both the erroneous recognition of new words as old and the errors in source memory with clinical symptoms (hallucinations, delusions, semantic disorganization). Thus, our second hypothesis was that patients with those symptoms face greater difficulties in 2a) recognizing new words as if they were old, and 2b) source memory, in comparison to patients without these symptoms.

Our third goal was to understand the relationship between source memory and cognitive functions. We investigated how basic cognitive functions (working memory, sustained attention, verbal and visual memory, executive functions) correlate with recognition errors and misattributions to the source. On a second level, we studied the influence of these cognitive functions on 3a) recognition and 3b) source memory, in order to investigate whether source memory deficits reflect more basic impairments in schizophrenia.

3. METHOD

3.1. Participants

3.1.1. Patients with Schizophrenia

Thirty-five patients (25 men) who had been diagnosed with schizophrenia (DSM-IV, APA, 1994) (18 of them were inpatients and 17 outpatients) participated in our study voluntarily. Their mean age was 35.00 years (S.D.=9.79) and their mean level of education was 10.14 years (S.D.=2.79). All patients underwent pharmacotherapy during the research. We excluded those with neurological damage or traumatic brain injury, those who had used drugs for the past 6 months, those who had a history of developmental disorder and, finally, those who had any disease that may compromise their cognitive functioning.

The clinical examination of patients was based on the Greek version of the Positive and Negative Symptoms Scale (PANSS, Lykouras, 1997). We assessed the five factors of the scale: Positive, Negative and Cognitive Symptoms, Depression and Agitation (Lykouras et al., 2000) (Table 1). We also studied the symptom of hallucinations (Bentall et al, 1991; Keefe et al, 2002; Brébion, 2002), delusions (Cahill et al, 1996; Garety et al., 1991) and semantic disorganization (Moritz et al, 2003; Harvey, 1990) more closely, as they have been associated to source memory deficits in the literature. Patients were divided into subgroups based on their scores on certain symptoms: patients with and without delusions, patients with and without semantic disorganization, and finally patients with and without hallucinations. It is important to note that only 7 patients in our sample presented hallucinations. The small sample of patients with hallucinations is due to the fact that half of the patients of our sample were outpatients under medication, and that the clinical and neuropsychological evaluation of inpatients took place during the last few days of their hospitalization and, thus, their clinical state was good enough to be discharged.

Table 1. Means and Standard Deviations on 5 PANSS factors and on 3 positive symptoms

	Minimum	Maximum	M	S.D.
Positive Symptoms	5	20	12.48	4.96
Agitation	5	17	7.31	3.33
Delusions	1	5	2.71	1.38
Semantic Disorganization	1	4	1.91	1.17
Hallucinations	1	4	1.74	1.09
Negative Symptoms	6	32	17.48	7.74
Cognitive Symptoms	5	20	10.25	3.98
Depression	3	13	5.48	2.80

3.1.2. Control Group

Thirty-four healthy adults (14 men) participated voluntarily in our study. Based on a clinical interview, they had no family or personal history of psychosis, had no history of a neurological disease, traumatic brain injury, alcohol or substance abuse, or any that might compromise their cognitive functioning and were not taking any medication at the time of

their participation. The mean age of group was 35.50 years (S.D.=11.67) and the average years of education was 10.47 years (S.D.=3.03). The two groups did not differ in either age ($t(67)$=-.204, p>.05) or in level of education ($t(67)$=-.467, p>.05).

3.2. Material

Source Memory Tasks

We administered two source memory tasks: one with visually and one with auditorially presented stimuli.

3.2.1. Task 1: Visual Stimuli

The first task comprised eight categories: furniture, known faces, fruits, body parts, clothes, sports, objects, and vegetables. Two examples from each category were chosen. One of them was presented as a colored picture (picture-example) and the other as a written word (written word-example) on a 17cm x 10cm card. The third example of each category was given by the participant (self-generated example).

Initially, the experimenter indicated a category (e.g. furniture) and then the participants saw the colored picture of the category (bed) for 5 seconds without naming it, and then gave an example of the same category (e.g., table) and finally they read silently a written word of the same category that was presented to them for 5 seconds (i.e., wardrobe). This procedure was repeated for each of the 8 categories with the same order for all participants. There was an alternative written word for each category in the event that the example generated by the participant was the same as the written word. The experimenter instructed the participants to remember the examples of the categories they saw as well as those they generated themselves, but did not warn them to remember their mode of presentation.

After a 15-minute delay, in which another test was administered (sustained attention test), recognition was tested. The participant had to recognize the 24 examples ("old" words) of the 8 categories (picture, written word, self-generated word) among 24 new interfering words (3 new words for each category). An alternative interfering word was available in each category, in case the participant had generated as an example one of the interfering words. The experimenter read the list with the 48 words aloud and the participant had to say for each word, whether it was new or one of the words that had been presented during the acquisition phase. If he or she said that it was one of the words presented earlier, the experimenter asked the participant to recall whether it had been presented as a picture, as a written word or whether it was self-generated.

3.2.2. Task 2: Auditory Stimuli

The second source memory task comprised seven categories of auditory stimuli: animals, means of transportation, physical phenomena, tools, musical instruments, home electrical devices, and human sounds. Two examples of each category were chosen. One example was presented as a verbal message by a male voice (verbal message-example) and the second was the representative sound of another example of the category (auditory message-example). The third example of the category was generated by the participant (self-generated example).

As in Task 1, the experimenter indicated initially a category (e.g., human sounds) and then the participant heard the auditory message (a man crying) and then he or she heard the verbal message from a male voice ("cough") and finally gave an example of the category of his or her own (e.g., sneeze). Recognition followed a 15-minute delay, during which another test was administered (verbal competency test). The participant had to recognize the 21 examples ("old" words) of the 7 categories among 21 new interfering words (3 new interfering words for each category and an alternative new word available in case the example of the participant coincided with one of the interfering words). The experimenter read the 42 words of the list aloud and the participant had to say whether it was a new word or whether it was one of the examples presented earlier. If he or she claimed that it was not a new word, then the experimenter asked the participant to recall if it had been presented as a verbal or an auditory message or if he or she had said it.

3.2.3. Variables

A) Recognition

This variable reflect the number of words that the participant correctly recognized, independently of whether he or she remembered the source correctly. The maximum score in the Task 1 with the visual stimuli is 48 and in the Task 2 with the auditory stimuli 42. Recognition errors are divided in two categories: a) Omissions, and b) incorrect recognition of new interfering words as old. We calculated the Total of Omissions [TO1=(OES1+OEP1+OEW1) and TO2= (OES2+OEP2+OEW2)] and the Total of Recognition Errors [TRE1= (RES1+REP1+REW1) and TRE2=(RES2+REP2+REW2)] based on the sum of the 3 omissions and the 3 recognition errors for each task separately as defined below.

B) Types of Recognition Errors

Task 1:

i. Recognition errors of wrongly recognizing new interfering words as source "self" examples (RES1): when the participant incorrectly recognized a new interfering word as the example that he or she generated himself or herself (maximum score 24).
ii. Omissions of source "self" examples (OES1): when the participant did not remember the example he/she generated himself/herself (maximum score 8).
iii. Recognition errors of incorrectly recognizing new interfering words as source "picture" examples (REP1): when the participant incorrectly recognized a new interfering word as the example-picture (maximum score 24).
iv. Omissions of source "picture" examples (OEP1): when the participant did not remember the example-picture (maximum score 8).
v. Recognition errors of incorrectly recognizing new interfering words as source "written word" examples (REW1): when the participant incorrectly recognized a new interfering word as the example-written word (maximum score 24).
vi. Omissions of source "written word" examples (OEW1): when the participant did not remember the example-written word (maximum score 8).

Task 2:

i. Recognition errors of incorrectly recognizing new interfering words as source "self" examples (RES2): when the participant incorrectly recognized a new interfering word as the example that he/she generated himself/herself (maximum score 21).
ii. Omissions of source "self" examples (OES2): when the participant did not remember the example he/she generated himself/herself (maximum score 7).
iii. Recognition errors of incorrectly recognizing new interfering words as source "verbal message" examples (REV2): when the participant incorrectly recognized a new interfering word as the example-verbal message (maximum score 21).
iv. Omissions of "verbal message" examples (OEV2): when the participant did not remember the example-verbal message (maximum score 7).
v. Recognition errors of incorrectly recognizing new interfering words as source "auditory message" examples (REA2): when the participant incorrectly recognized a new interfering word as the example-auditory message (maximum score 21).
vi. Omissions of source "auditory message" examples (OEA2): when the participant did not remember the example-auditory message (maximum score 7).

C) Source memory: we calculated the Percentage of the Total Source Memory Errors in correct recognition (PTSME1 and PTSME2 for Tasks 1 and 2 respectively) so that the results could be comparable.

D) Source memory errors

Task 1:

i. Misattributions to the source "self" (MSS1): when the participant misattributed the example-picture or the example-written word to himself/herself (maximum score 16).
ii. Failure in attributing to the source "self" (FASS1): when the participant recalled the example he or she gave as if it were the example-picture or the example-written word (maximum score 8).
iii. Misattributions to the source "picture" (MSP1): when the participant recalled the example-written word as a picture (maximum score 8).
iv. Misattributions to the source "written word" (MSW1): when the participant recalled the example-picture as if it were a written word (maximum score 8).

Task 2:

i. Misattributions to the source "self" (MSS2): when the participant misattributed the example-verbal message or the example-auditory message word to himself/herself (maximum score 14).
ii. Failure in attributing to the source "self" (FASS2): when the participant recalled the example he or she gave, as if it were the example-verbal message or the example-auditory message (maximum score 7).
iii. Misattributions to the source "verbal message" (MSV2): when the participant recalled the example-auditory message as a verbal message (maximum score 7).

iv. Misattributions to the source "auditory message" (MSA2): when the participant recalled the example-verbal message as an auditory message (maximum score 7).

3.3. Neuropsychological Tests

We administered a short neuropsychological battery in order to evaluate the cognitive functions of patients with schizophrenia (Kosmidis and Bozikas, 2003). The cognitive functions evaluated are listed below:

3.3.1. Working Memory

In order to assess working memory we administered the Digit Span Test (both forward and backward) from the Wechsler Adult Intelligence Scale-III (WAIS-III, Wechsler, 1997). This test assesses auditory attention, short-term storage and mental manipulation of information, based on the string of digits correctly retained by the examinee.

3.3.2. Sustained Attention

We used Penn's Continuous Performance Test (PCPT; Kurtz, 2001), a computerized task to evaluate sustained attention. We assessed sustained attention based on the ratio of correct answers to the mean total reaction time.

3.3.3. Visual Memory

Visual memory was assessed with the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944) and was based on the performance of the individual in Immediate and Delayed Recall of the figure and Recognition of its parts. A principal components analysis showed that these three subtests add to the visual memory factor (Table 2).

3.3.4. Verbal Memory

In order to assess learning ability and verbal memory we administered two tests, the Word List Learning (Kosmidis and Bozikas, 2003) and Story Recall (Kosmidis and Bozikas, 2003). The variables of the first test were the total number of correctly recalled words over the four learning trials, 30-minute Delayed Recall, and Recognition of the words on the list. From the second test we used: Immediate Recall of the story (how much information the participant retained over two trials) and Delayed Recall of the story after a 20-minute delay. A principal components analysis showed that these five variables load on the verbal memory factor (Table 2).

3.3.5. Executive Functions

The second part of the Trail Making Test (Vlahou and Kosmidis, 2002) assessed the ability to coordinate vision and movement, to categorize, and to switch mentally, based on the time needed for task execution. The semantic and phonological parts of the Greek Verbal Fluency Test (Kosmidis et al., 2004) assessed the ability to organize the search of words belonging to a specific semantic category or beginning with a certain letter. The variables were the total number of words generated by the participant for the semantic category "animals" and the phonological category of the Greek letter chi (χ). We also administered the

Wisconsin Card Sorting Test (64-card version) (Axelrod, Henry, and Woodard, 1992), which evaluates the ability to inhibit certain behaviour, to use feedback and abstract thinking. The variables here were the number of categories used and the number of preservations. A principal components analysis showed that the aforementioned variables loaded on the factor executive functions (Table 2).

3.4. Procedure

Before the neuropsychological evaluation a clinical interview by a psychiatrist took place. However, the experimenter was unaware of the results of the clinical interview. The interval between the clinical interview and the neuropsychological evaluation was not longer than one day. The neuropsychological evaluation lasted an average of one and a half hour.

Table 2. Principle components analysis factors

	Visual Memory	Verbal memory	Executive Functions
Rey Immediate Recall	.951		
Rey Delayed Recall	.944		
Rey Recognition	.556		
Word List Learning Test, Total correct		.876	
Delayed Recall		.864	
Recognition		.744	
Immediate Story Recall		.867	
Delayed Story Recall		.896	
WCST, Number of Categories			.655
WCST, Number of Perseverations			-.720
Trail Making Test, Part B			-.801
Verbal Fluency, Semantic Part			.744
Verbal Fluency, Phonological Part			.701

4. STATISTICAL ANALYSIS

In order to analyze the Omissions and the Recognition Errors, we used a 2x3 analysis of variance (two-way ANOVA). The groups (patients with schizophrenia and control group) and the subgroups (i.e., patients with and without delusions) were the between group factor. The type of omissions and the type of recognition errors were the levels of the within group factor. We used this method to control for the main effect of the factor “group” and the factor “subgroup” on the Total number of Omissions and Recognition Errors, as well as for the possible interaction of those factors.

We also used analysis of variance with one factor (one-way ANOVA) to see whether the means of the two groups (patients with schizophrenia and control group) and the subgroups (i.e., patients with and without delusions) differed in the Percentage of the Total Source Memory Errors in correct recognition.

We performed a multiple analysis of variance on the source memory errors, because the four types of source memory errors studied did not have the same measurement unit [MSS1 differs from MSS2 (Misattribution to the source 'self') because their highest score is 16 and 14 respectively, while the highest score of the other errors in source memory is 8 in the first task and 7 in the second].

We used Mann-Whitney U-tests to compare the patient subgroups (patients with and without hallucinations), because of the small sample size of the group with hallucinations. More specifically, we explored the difference of patients with and those without hallucinations on the type of omission and on the type of recognition errors, as well as on the Percentage of the Total Source Memory Errors on every type of source memory error separately.

In order to control for the performance of patients with and without semantic disorganization in recognition errors, we used the method of 2x3 covariance analysis (ANCOVA), with the covariate being the years of education (the subgroup of the patients with semantic disorganization had significantly fewer years of education than the subgroup of patients without that particular symptom), where the two subgroups differed significantly; the 2 subgroups constituted the levels of the between group factor, while the 3 types of recognition errors constituted the levels of the within group factor. This particular method was used, as mentioned previously, to control for the main effect of the factor "subgroup" as well as the existence of a possible interaction between the 2 factors. We used the same 2x3 analysis of covariance (ANCOVA) to control for the main effect of the factor "group" (patients and control group) on the Total of Recognition Errors, as well as the possible interaction between the two factors and covariates being cognitive functions significantly correlating with recognition errors and possibly affecting the performance of the participants.

We used the method of analysis of covariance with one factor (ANCOVA), with the covariate being the years of education (because the subgroup of patients with semantic disorganization had significantly fewer years of education than the subgroup of patients without semantic disorganization) to compare the Percentage of the Total Recognition Errors of the two subgroups. We used the same method to compare the Percentage of the Total Source Memory Errors in the group of patients with schizophrenia and in the control group, with covariates the Cognitive Functions that correlated significantly with all the source memory errors.

We performed a multivariate analysis of covariance (MANCOVA), with the covariate being the years of education, in order to explore statistical differences on the four types of source memory errors of the two subgroups of patients with and without semantic disorganization.

Finally, we used Pearson correlation coefficients to study a) the correlation between the Total number of Recognition Errors and the percentage of the Total Source Memory Errors with psychopathology (5 factors of the Positive and Negative Symptoms Scale, PANSS) and b) the correlation of the total number of Recognition Errors and the Percentage of the Total Source Memory Errors with the 5 Cognitive Functions assessed (i.e., working memory, sustained attention, verbal memory, visual memory, executive functions).

5. RESULTS

5.1. Recognition

5.1.1. Omissions

The two groups committed generally the same number of omissions, as there was no statistically significant main effect of the factor "Group" [$F(1,67)=2.26$, $p>.05$] (Table 3). There was, however, an interaction between the two factors [$F(2,134)=5.43$, $p=.005$]. Figure 1 depicts the interaction between the 2 factors. We calculated the simple main effects of the factor "Group" for each omission type. In comparison to the control group, the patients with schizophrenia omitted more examples of the source "self" (OES1) [$F(1,201)=9.79$, $p=.001$]. In contrast, there was no significant difference in omissions of source "picture" examples (OEP1) [$F(1,201)=0.86$, $p>.05$], nor in omissions of source "written word" examples (OEW1) [$F(1,201)=0.94$, $p>.05$] (Table 3).

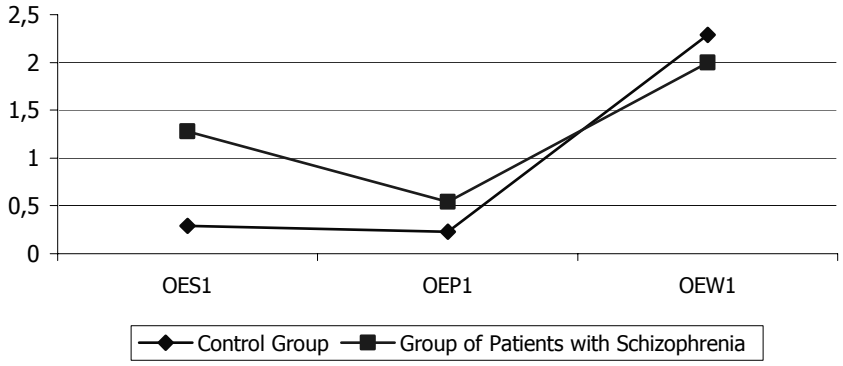

Figure 1. Means of Omissions in the 2 Groups

Table 3. Means and Standard Deviations of Omissions in the 2 Groups

	TO1 M (S.D.)	OES1 M (S.D.)	OEP1 M (S.D.)	OEW1 M (S.D.)
Control Group	2.82 (2.34)	0.29 (0.76)	0.23 (0.50)	2.29 (1.83)
Patient Group	3.83 (3.14)	1.28 (1.65)	0.54 (0.78)	2.00 (1.68)

TO1: Total of the 3 types of omissions (OES1+ OEP1+ OEW1)
OES1: Omissions of examples of the source "self"
OEP1: Omissions of examples of the source "picture"
OEW1: Omissions of examples of the source "written word"

5.1.2. Incorrect Recognition of New Distracting Words as if they were Old

Compared to the control group, the patients with schizophrenia committed more recognition errors [F (1,67)=9.06, $p=.004$] (Table 4). There was no interaction between the two factors [$F(2,134)=.15$, $p>.05$] (Figure 2).

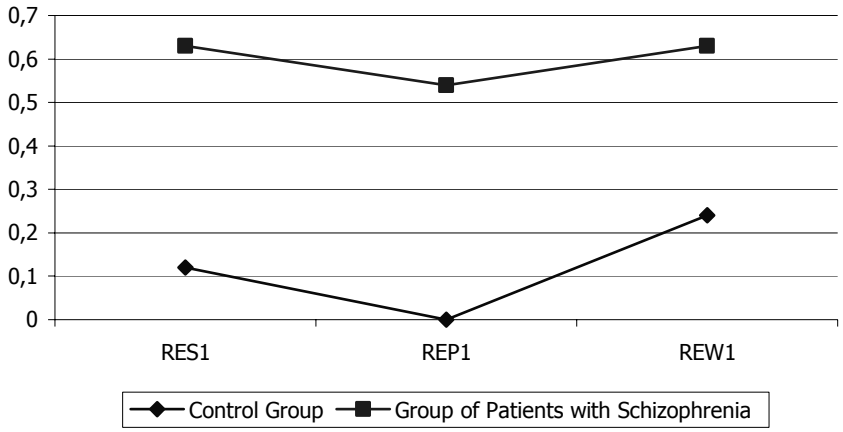

Figure 2. Means of Recognition Errors in the 2 Groups

Table 4. Means and Standard Deviations for the Recognition Errors in the 2 groups

	TRE1 M (S.D.)	RES1 M (S.D.)	REP1 M (S.D.)	REW1 M (S.D.)
Control Group	0.41 (0.70)	0.12 (0.33)	0.00 (0.24)	0.24 (0.61)
Patient Group	1.80 (2.60)	0.63 (1.00)	0.54 (1.04)	0.63 (1.24)

TRE1: Total of the 3 types of recognition errors (RES1+ REP1+ REW1)

RES1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"

REP1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "picture"

REW1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "written word"

5.2. Source Memory

Patients with schizophrenia (M=5.33, S.D.=7.73) attributed more frequently than the control group (M=1.07, S.D.=1.42) [F(1,67)=9.98, p=.002] words they recognized to incorrect sources (PTSME1).

We also noted that the factor "Group" is statistically significant in a multivariate analysis of variance (MANOVA) [Pillais value=.197, $F(4,64)=3.91$, $p=.007$]. Upon inspection of the univariate analyses, we found that patients with schizophrenia committed more misattributions to the source "picture" (MSP1) than the control group [$F(1,67)=11.538$, $p=.001$] (Figure 3 and Table 5). The two groups did not differ on the misattributions to the source "written word" (MSW1) [$F(1,67)=1.05$, $p>.05$], the misattributions to the source "self" (MSS1) [$F(1,67)=2.1$, $p>.05$], and the failure in attributing to the source "self" (FASS1) [$F(1,67)=2.2$, $p>.05$] (Figure 3 and Table 5)

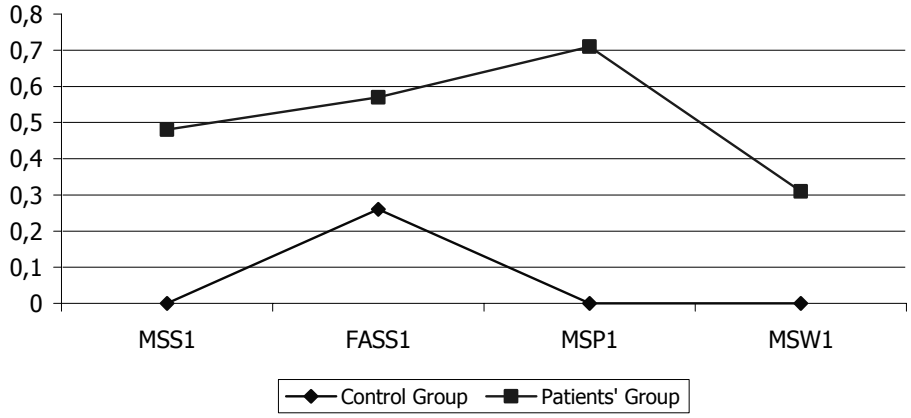

Figure 3. Means of the Source Memory Errors in the 2 Groups

Table 5. Means and Standard Deviations of the Source Memory Errors in the 2 Groups

	MSS1	FASS1	MSP1	MSW1
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Control Group	0.00 (0.24)	0.26 (0.51)	0.00 (0.24)	0.00 (0.39)
Patients' Group	0.48 (1.70)	0.57 (1.10)	0.71 (1.10)	0.31 (1.23)

MSS1: Misattributions to the source "self"
FASS1: Failure in attributing to the source "self"
MSP1: Misattributions to the source "picture"
MSW1: Misattributions to the source "written word"

5.3. Source Memory and Psychopathology in Patients with Schizophrenia

5.3.1. Correlations of the Total Number of Recognition Errors and the Percentage of the Total Source Memory Errors with the 5 Factors of the Scale

Out of the 5 PANSS factors, only the Cognitive symptoms dimension was found to correlate significantly with the total number of the recognition errors (r=.366, p=.039) and the percentage of the total source memory errors (r=.351, p=.030) (Table 6).

Table 6. Correlations of Psychopathology and the Total Number of Recognition Errors and the Percentage of the Total Source Memory Errors

	Positive Symptoms	Negative Symptoms	Cognitive Symptoms	Depression	Agitation
TRE1	.181	.077	.366*	-.322	.278
PTSME1	.203	.086	.351*	-.179	-.110

TRE1: Total of the 3 types of recognition errors (RES+ REP+ REW)
PTSME1: Percentage of Total Source Memory Errors
*Significance level .05

5.4. Subgroups of Patients with Schizophrenia

In order to study more thoroughly the relationship between both recognition and source memory on one hand, and Hallucination Behavior, Semantic Disorganization and Delusions on the other, we split our sample of patients with schizophrenia into subgroups.

5.4.1. Patients with and without Hallucinations

In order to investigate the relationship between hallucination behavior and performance on Task 1, the patient group was split in two subgroups: patients with hallucination behavior (n=7) (PANSS, "Hallucination Behavior">=3) and those without (n=28). Preliminary analyses (with Mann-Whitney tests) showed that the subgroup of patients without hallucinations and the subgroup of patients with hallucinations did not differ in age (M=35.46, S.D.=10.1; M=33.14, S.D.=8.85, respectively; U=86.5, p>.05) nor in level of education (M=9.86, S.D.=2.92; M=11.28, S.D.=1.89, respectively; U=61.5, p>.05).

5.4.2. Patients with and without Hallucinations and Cognitive Functions

The two subgroups did not differ in Cognitive Functions: Working Memory (U=77.5, p>.05), Sustained Attention (U=85, p>.05), Visual Memory (U=97, p>.05), Verbal Memory (U=97, p>.05), and Executive Functions (U=80, p>.05) (Table 7).

Table 7. Means and Standard Deviations of the performance on Cognitive Functions in the 2 subgroups

	Working Memory	Sustained Attention	Visual Memory	Verbal Memory	Executive Functions
	M. (S.D.)	M. (S.D.)	M. (S.D.)	M. (S.D.)	M. (S.D.)
Patients without hallucinations	4.60 (1.80)	0.057 (0.013)	-0.47 (0.97)	-0.44 (0,99)	-0.59 (0.91)
Patients with hallucinations	4.00 (1.60)	0.055 (0.013)	-0.36 (1.13)	-0.51 (1,60)	-0.83 (0.96)

5.4.3. Patients with and without Hallucinations and Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old (TRES1, RES1, REP1, REW1)

We found a difference between the two subgroups in the Total Number of Recognition Errors (U=49.5, p=.044). The analysis of the 3 types of recognition errors showed that patients more often incorrectly recognized new interfering words as if they were examples of the source "written word" (REW1) (U=41, p=.016). They did not differ, however, in a) Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self" (RES1) (U=57, p>.05) and b) Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "picture" (REP1) (U=63.5, p>.05) (Table 8).

5.4.4. Patients with and without Hallucinations and Source Memory Errors (PTSME1, MSS1, FASS1, MSS1, MSW1)

The two subgroups did not differ in the Percentage of Source Memory Errors (U=59.5, p>.05), nor in either of the following four source memory errors: a) Misattribution to the source "self" (MSS1) (U=91, p>.05), b) Failure in attributing to the source "self" (FASS1) (U=80.5, p>.05), c) Misattribution to the source "picture" (MSP1) (U=83, p>.05), and d) Misattribution to the source "written word" (MSW1) (U=77.5, p>.05) (Table 8).

5.4.5. Patients with and without Semantic Disorganization

We split the patient group based on their score on 'Semantic disorganization' (>=3) in two subgroups: patients without semantic disorganization (n=23), and those with that symptom (n=12). An analysis of variance showed that the two subgroups did not differ in age (ANOVA) [M=32.82, S.D.=10,1; M=39.17, S.D.=7.99, respectively F(1,33)=3.55, p>.05], but the group with hallucinations had a lower level of education that that without [M=10.91, S.D.=2.5; M=8.67, S.D.=2.8, respectively; F(1,33)=5.85, p=.021].

5.4.6. Patients with and without Semantic Disorganization and Cognitive Functions

We performed a multivariate analysis of covariance (MANCOVA), using the level of education as a covariate and found that patients with and without semantic disorganization have similar performance on all cognitive functions [Pillais value=.143, F(5,28)=.937, p>.05] (Table 9).

Table 8. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE1	RES1	REP1	REW1	PTSME1	MSS1	FASS1	MSP1	MSW1
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Hallucinations	1.11 (1,49)	0.43 (0.63)	0.39 (0.87)	0.28 (0.65)	3.95 (5.82)	0.25 (0.44)	0.50 (1.07)	0.57 (1.29)	0.28 (1.33)
Patients with Hallucinations	4.57 (4.12)	1.43 (1.71)	1.14 (1.46)	2.00 (2.00)	10.85 (11.88)	1.43 (3.78)	0.86 (1.21)	1.28 (1.70)	0.43 (0.79)

TRE1: Total of the 3 types of Recognition Errors (RES1+ REP1+ REW1)

RES1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"

REP1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "picture"

REW1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "written word"

PTSME1: Percentage of Total Source Memory Errors

MSS1: Misattribution to the source "self"

FASS1: Failure in attributing to the source "self"

MSP1: Misattribution to the source "picture"

MSW1: Misattribution to the source "written word"

Table 9. Means and Standard deviations of performance on cognitive functions of the 2 subgroups

	Working Memory	Sustained Attention	Visual Memory	Verbal Memory	Executive Functions
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Semantic disorganization	4.90 (1.78)	0.059 (0.013)	-0.23 (1.10)	-0.15 (1.20)	-0.39 (0.84)
Patients with Semantic disorganization	3.67 (1.50)	0.052 (0.011)	-0.88 (0.55)	1.02 (0.58)	-1.10 (0.88)

5.4.7. Patients with and without Semantic Disorganization and Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old (TRE1, RES1, REP1, REW1)

Patients with semantic disorganization committed more recognition errors compared to patients without semantic disorganization [$F(1,32)=5.49$, $p=.025$]. However, the interaction between the 2 factors was not significant [$F(2,64)=2.07$, $p>.05$] (Table 10).

Table 10. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE	RES	REP	REW	PTSME	MSS	FASS	MSP	MSW
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Semantic Disorganization	1.17 (1.61)	0.52 (0.66)	0.30 (0.87)	0.35 (0.77)	3.57 (5.67)	0.17 (0,39)	0.61 (1.27)	0.74 (1.29)	0.00 (0.00)
Patients with Semantic Disorganization	3.00 (3.64)	0.83 (1.47)	1.00 (1.20)	1.16 (1.74)	8.70 (10.10)	1.08 (2.84)	0.50 (0.67)	0.67 (0.65)	0.92 (2.02)

TRE1: Total of the 3 types of Recognition Errors (RES1+ REP1+ REW1)

RES1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"

REP1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "picture"

REW1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "written word"

PTSME1: Percentage of Total Source Memory Errors

MSS1: Misattributions to the source "self"

FASS1: Failure in attributing to the source "self"

MSP1: Misattributions to the source "picture"

MSW1: Misattributions to the source "written word"

5.4.8. Patients with and without Semantic Disorganization and Source Memory Errors (PTSME1, MSS1, FASS1, MSS1, MSW1)

The two subgroups committed the same number of source memory errors in relation to the number of correct recognitions (PTSME1) [$F(1,32)=2.62$, $p>.05$] (Table 10). We also found that the groups did not differ on "Semantic disorganization" [Pillais value=.261, $F(5,29)=2.56$, $p>.05$] (Table 10).

5.4.9. Patients with and without Delusions

The patient group was split in two subgroups, patients with (n=22) and without (n=13) delusions (PANSS, "Delusions">=3). These two subgroups did not differ in age [M.=34.85, S.D.=9,73; M.=35.10, S.D.=10.06, respectively; $F(1,33)=0.00$, $p>.05$] nor in years of education [M.=10.69, S.D.=2.49; M.=9.82, S.D.=2.95, respectively; $F(1,33)=.79$, $p>.05$].

5.4.10. Patients with and without Delusions and Cognitive Functions

The subgroup of patients with and the one without delusions had the same performance on cognitive functions [Pillais value=.349, $F(5,29)=1.168$, $p>.05$] (Table 11).

Table 11. Means and Standard deviations of the 2 subgroups' (patients with and without delusions) performance on Cognitive functions

	Working Memory	Sustained Attention	Visual Memory	Verbal Memory	Executive Functions
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Delusions	4.46 (1.61)	0.063 (0.011)	-0.40 (0.97)	-0.23 (0.96)	-0.53 (1.09)
Patients with Delusions	4.50 (1.89)	0.054 (0.013)	-0.48 (1.02)	-0.59 (1.19)	-0.71 (0.81)

5.4.11. Patients with and without Delusions and Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old (TRE1, RES1, REP1, REW1)

The two subgroups made the same number of recognition errors [$F(1,33)=.737$, $p>.05$]. No statistically significant interaction was found between the two factors [$F(2,66)=3.03$, $p>.05$] (Table 12).

5.4.12. Patients with and without Delusions and Source Memory Errors (PTSME1, MSS1, FASS1, MSS1, MSW1)

There was no statistically significant difference in the Percentage of Source Memory Errors [$F(1,32)=2.62$, $p>.05$] (Table 12). Similarly, there was no group difference on "Delusions" [Pillais value=.115, $F(4,30)=.976$, $p>.05$] (Table 12).

5.6.1. Patients Group: Correlation of Both Total Recognition Errors (TRE1) and Percentage of Total Source Memory Errors (PTSME1) with Cognitive Functions

We found a significant negative correlation between the Total Recognition Errors with Working memory ($r=-.419$, $p=.012$), Verbal Memory ($r=-.536$, $p=.001$) and Executive functions ($r=-.463$, $p=.005$). We also found a negative correlation of the Percentage of Total

Source Memory Errors with Working memory (r=-.346, p=.042), Verbal Memory (r=-.456, p=.006) and Executive functions (r=-.421, p=.012) (Table 14).

Table 12. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE	RES	REP	REW	PTSME	MSS	FASS	MSP	MSW
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Delusions	1.31 (1.60)	0.77 (0.72)	0.38 (1.12)	0.15 (0.37)	3.68 (5.89)	0.15 (0,37)	0.38 (0.77)	0.38 (0.65)	0.54 (1.94)
Patients with Delusions	2.10 (3.04)	0.54 (1.14)	0.64 (1.00)	0.91 (1.48)	6.31 (8.61)	0.68 (2,12)	0.68 (1.25)	0.91 (1.27)	0.18 (0.50)

RE1: Total of the 3 types of Recognition Errors (RES1+ REP1+ REW1)
RES1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"
REP1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "picture"
REW1: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "written word"
PTSME1: Percentage of Total Source Memory Errors
MSS1: Misattributions to the source "self"
FASS1: Failure in attributing to the source "self"
MSP1: Misattributions to the source "picture"
MSW1: Misattributions to the source "written word"

5.6. Source Memory and Cognitive Functions

5.6.2. Control Group: Correlation of the Total Recognition Errors (TRE1) and the Percentage of Total Source Memory Errors (PTSME1) with Cognitive Functions

Only a negative correlation of Verbal Memory with the Total Source Memory Errors was found (r=-.369, p=.032) (Table 14).

Table 13. Correlations of Total Recognition Errors and the Percentage of Source Memory Errors with Cognitive functions

		Working memory	Sustained Attention	Verbal Memory	Visual Memory	Executive functions
Control group	TRE1	.094	.249	.015	.159	.002
	PTSME1	.010	-.136	-.369*	.037	-.085
Patient Group	TRE1	-.419*	-.161	-.536*	-.313	-.463*
	PTSME1	-.346*	-.258	-.456*	-.212	-.421*

TRE1: Total of the 3 types of Recognition Errors (RES+ REP+ REW)
PTSME1: Percentage of the Total Source Memory Errors
*significance level .05

5.6.3. Comparison of the Two Groups' Performance on Verbal Memory, Executive Functions and Working Memory

The performance of patients with schizophrenia on Verbal Memory, Executive functions and Working memory (M=-.45, S.D.=1.10; M=-.64, S.D.=.91; M=4.48, S.D.= 1.77, respectively) was poorer than the control group's (M=.48, S.D.=.59; M=.66, S.D.=.56; M=5.64, S.D.=2.28, respectively) [$F(1,67)=18.38$, $p<.001$; $F(1,67)=50.64$, $p<.001$; $F(1,67)=5.59$, $p=.021$, respectively].

5.6.4. Comparisons of the Two Groups in Total Recognition Errors and in the Percentage of Source Memory Errors with Verbal Memory, Executive Functions and Working Memory as Covariates

In paragraphs 5.1.2. and 5.2. it was noted that patients with schizophrenia made more Recognition errors and more Source memory errors than the control group. In the present comparisons of the two groups (patients with schizophrenia and control group) Verbal Memory, Executive functions and Working memory are used as covariates; according to the results described in paragraphs 5.6.1. and 5.6.2., they correlate significantly with the variables studied, and, in addition, according to paragraph 5.6.3., the two groups differ in their performance in these specific cognitive functions.

It was noted that when we used Verbal Memory [$F(1,66)=17.37$, $p<.001$] and Executive functions [$F(1,66)=11.35$, $p=.001$] as covariates with a significant effect, the analyses with each covariate separately rendered the difference in the Total number of Recognition Errors between the groups not significant [$F(1,66)=1.08$, $p>.05$; $F(1,66)=0.05$, $p>.05$, respectively]. Furthermore, we did not find a statistically significant interaction between the two factors (Group, Recognition Errors) in both cases [$F(2,132)=.367$, $p>.05$; $F(2,132)=.417$, $p>.05$, respectively].

Similarly, we noted that when using Verbal Memory [$F(1,66)=14.76$, $p<.001$] and Executive functions [$F(1,66)=9.98$, $p=002$] as covariates with a statistically significant effect, the difference between the two groups concerning the Percentage of Source Memory Errors in both cases was not significant [$F(1,66)=1.66$, $p>.05$; $F(1,66)=.218$, $p>.05$, respectively].

The effect of working memory was not significant when comparing the two groups either on the Total number of Recognition Errors [$F(1,66)=3.75$, $p>.05$], or in the Percentage of Source Memory Errors [$F(1,66)=3.75$, $p>.05$]. As a result, the difference of the two groups in specific variables remained significant [$F(1,66)=5.82$, $p=.019$; $F(1,66)=5.82$, $p=.019$, respectively], while there was no significant interaction between the factor "Group" and recognition errors [$F(2,132)=2.88$, $p>.05$].

TASK 2

5.7. Recognition

5.7.1. Omissions

Patients with schizophrenia omitted in total more words than the control group [F(1,67)=8.91, p=.004] (Table 14). There was no statistically significant interaction between the 2 factors [F(2,134)=1.51, p>.05] (Figure 4).

Table 14. Means and Standard deviations of omissions in the two groups

	TO2 M (S.D.)	OES2 M (S.D.)	OEV2 M (S.D.)	OEA2 M (S.D.)
Control group	2.12 (2.13)	0.23 (0.43)	1.12 (1.43)	0.76 (1.16)
Patient Group	4.23 (3.55)	0.68 (1.02)	1.71 (1.50)	1.83 (1.87)

TO2: Total of the 3 omission types (OES2+ OEV2+ OEA2)
OES2: Omissions of the examples of the source "self"
OEV2: Omissions of the examples of the source "verbal message"
OEA2: Omissions of the examples of the source "auditory message"

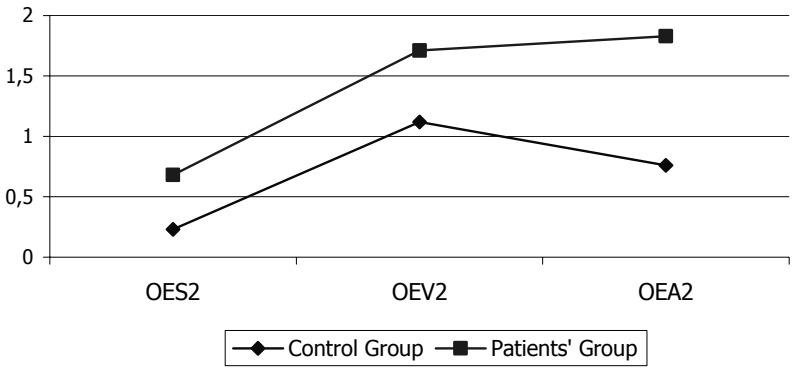

Figure 4. Means of Omissions in the 2 groups

5.7.2. Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old

We noted that patients with schizophrenia made more Recognition errors than the control group [$F(1,67)=13.86$, $p<.001$] and that the interaction between the two factors is not significant [$F(2,134)=1.71$, $p>.05$] (Table 15) (Figure 5).

Table 15. Means and Standard Deviations of Recognition Errors in the 2 groups

	TRE2 M (S.D.)	RES2 M (S.D.)	REV2 M (S.D.)	REA2 M (S.D.)
Control group	0.41 (0.66)	0.15 (0.36)	0.00 (0.24)	0.20 (0.41)
Patient Group	1.17 (1.93)	0.46 (0.85)	0.37 (0.91)	0.88 (1.13)

TRE2: Total of the 3 types of Recognition Errors (RES2+ REV2+ REA2)
RES2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"
REV2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "verbal message"
REA2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "auditory message"
*significance level .05

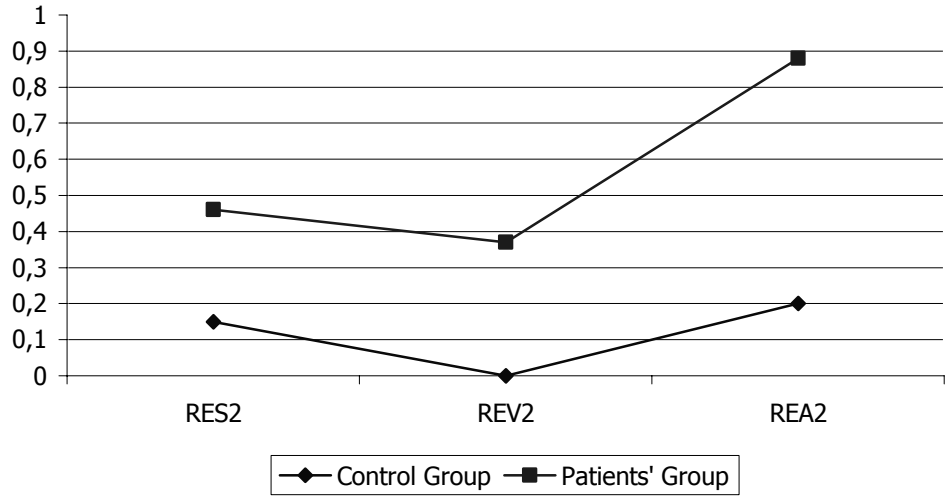

Figure 5. Means of the Recognition Erorrs in the 2 groups

5.8. Source Memory

Patients with schizophrenia (M=5.31, S.D.=5.71) make in total more source memory errors in correct recognitions (Percentage of Source Memory Errors in correct recognitions) than the control group (M=1.68, S.D.=3.10) [F(1,67)=10.69, p=.002].

When studying the 4 source memory error types, we found a significant main effect for group [Pillais value=.206, $F(4,64)=4.16$, $p=.005$]. Further analysis showed that patients made more failures in attributing to the source "self" (FASS2) [$F(1,67)=8.24$, $p=.005$], as well as more misattributions to the source "auditory message" (MSA2) [F(1,67)=2.2, $p=.001$]. There was no statistically significant difference between the two groups in misattributions to the source "self" (MSS2) [$F(1,67)=.33$, $p>.05$] and in misattributions to the source "verbal message" (MSV2) [$F(1,67)=.004$, $p>.05$] (Table 16) (Figure 6).

Table 16. Mean and Standard Deviation of the source memory errors in the two groups

	MSS2	FASS2	MSV2	MSA2
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Control group	0.23 (0.43)	0.00 (0.17)	0.32 (0.68)	0.00 (0.29)
Patient Group	0.31 (0.68)	0.45 (0.85)	0.31 (0.58)	0.71 (0.96)

MSS2: Misattributions to the source "self"
FASS2: Failure in attributing to the source "self"
MSV2: Misattributions to the source "visual message"
MSA2: Misattributions to the source "auditory message"

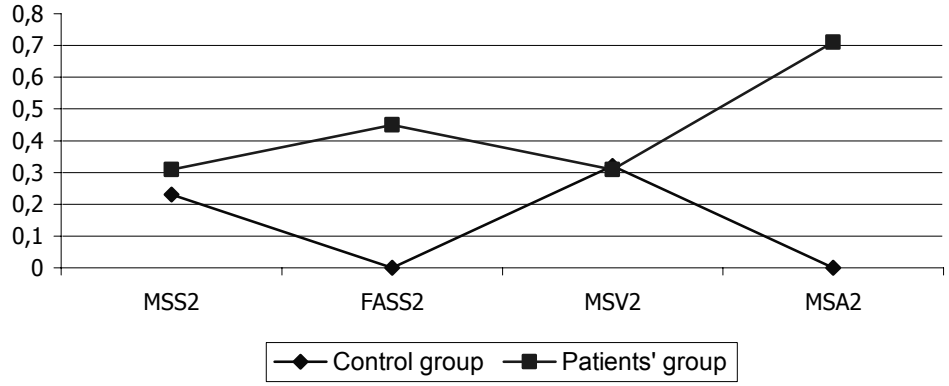

Figure 6. Means of the Source Memory Erorrs in the 2 groups

5.9. Source Memory and Psychopathology in Patients with Schizophrenia

5.9.1. Correlations of the Total Number of Recognition Errors and the Percentage of Source Memory Errors with the 5 Factors of the PANSS

The Cognitive factor correlated significantly with a) the Total number of Recognition Errors (r=.499, p=.007), and b) with the Percentage of Source Memory Errors (r=.437, p=.009). Depression also correlated negatively with the Total number of Recognition Errors (r=-.397 p=.018) (Table 17).

Table 17. Correlations of the Psychopathology with the Total Recognition Errors and the Percentage of the Total Source Memory Errors

	Positive Ssymptoms	Negative Symptoms	Cognitive Symptoms	Depression	Agitation
TRE2	.260	.143	.499**	-.397*	-.278
PTSME2	.177	.041	.437**	-.247	-.161

TRE2: Total nmber of the 3 types of Recognition Errors (RES2+ REV2+ REA2)
PTSME2: Percentage of Source Memory Errors
*significance level .05 ** significance level .01

5.10. Subgroups of Patients with Schizophrenia

5.10.1. Patients with and without Hallucinations

The characteristics of the two subgroups are mentioned in paragraphs 5.4.1. and 5.4.2.

5.10.2. Patients with and without Hallucinations and Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old (TRE2, RES2, REV2, REA2)

Using the Mann-Whitney testl, we found that patients with hallucinations made, in general, more recognition errors (U=45.0, p=.028) than patients without hallucinations. When studying the recognition errors separately, we found that they committed more recognition errors by incorrectly recognizing new interfering words as if they were examples of the source "auditory message" (REA2) (U=43.5, p=.022). No significant difference was found between the two subgroups in a) Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self" (RES2) (U=93.0, p>.05), and b) Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "verbal message" (REV2) (U=82.5, p>.05) (Table 18).

5.10.3. Patients with and without Hallucinations and Source Memory Errors (PTSME2, MSS2, FASS2, MSV2, MSA2)

As it was mentioned before, the two subgroups did not differ in the Percentage of Source Memory Errors (*U*=81.5, *p*>.05), nor in any of the types of source memory errors: a) Misattribution to the source "self" (*U*=88.5, *p*>.05), b) Failure in attributing to the source "self" (*U*=76.5, *p*>.05), c) Misattribution to the source "verbal message" (*U*=96.5, *p*>.05), and d) Misattribution to the source "auditory message" (*U*=86.5, *p*>.05) (Table 18).

Table 18. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE2	RES2	REV2	REA2	PTSME2	MSS2	FASS2	MSV2	MSA2
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Hallucinations	1.21 (1.31)	0.36 (0.56)	0.21 (0.49)	0.64 (0.95)	4.61 (4.63)	0.25 (0.52)	0.36 (0.73)	0.32 (0.61)	0.68 (0.94)
Patients with Hallucinations	3.71 (2.75)	0.86 (1.57)	1.00 (1.73)	1.86 (1.34)	8.10 (8.76)	0.57 (1.13)	0.86 (1.21)	0.28 (0.49)	0.86 (1.07)

TRE2: Total number of the 3 types of Recognition Errors (RES2+ REV2+ REA2)

RES2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"

REV2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "verbal message"

REA2: : Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "auditory message"

PTSME2: Percentage of Source Memory Errors

MSS2: Misattributions to the source "self"

FASS2: Failure in attributting to the source "self"

MSV2: Misattributions to the source "verbal message"

MSA2: Misattributions to the source "auditory message"

5.10.4. Patients with and without Semantic Disorganization

Information concerning the two subgroups is provided in paragraphs 5.4.5. and 5.4.6.

5.10.5. Patients with and without Semantic Disorganization and Recognition Errors of Incorrectly Recognizing New Interfering Words as if They Were Old (TRE2, RES2, REV2, REA2)

Patients with semantic disorganization made overall more Recognition errors than patients without that particular symptom, when for level of education was used as a covariate [$F(1,32)=11.757$, $p=.002$]. There was no significant interaction between the 2 factors [$F(2,64)=.652$, $p>.05$] (Table 19).

5.10.6. Patients with and without Semantic Disorganization and Source Memory Errors (PTSME2, MSS2, FASS2, MSV2, MSA2).

Using the analysis of covariance (ANCOVA), we found that patients with semantic disorganization made more source memory errors in positive recognitions (PTSME2) than did patients without [$F(1,32)=24.03$, $p<.001$] (Table 20). We also found that the factor "Semantic disorganization" was statistically significant [Pillais value=.527, $F(5,28)=6.23$, $p=.001$]. Patients with semantic disorganization showed greater Failure in attributing to the source "self" (FASS2) [$F(1,67)=5.66$, $p=.023$] and made more Misattributions to the source "auditory message" (MSA2) [$F(1,67)=8.42$, $p=.007$]. On the contrary, there was no difference between the two groups in a) Misattribution to the source "self" (MSS2) [$F(1,67)=3.01$, $p>.05$], nor in b) the Failure in attributing to the source "verbal message" (MSV2) [$F(1,67)=3.85$, $p>.05$] (Table 19).

Table 19. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE2	RES2	REV2	REA2	PTSME2	MSS2	FASS2	MSV2	MSA2
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without Semantic disorganization	1.04 (1.10)	0.17 (0.39)	0.26 (0.69)	0.61 (0.78)	2.89 (3.46)	0.17 (0.39)	0.30 (0.70)	0.17 (0.49)	0.39 (0.72)
Patients with Semantic disorganization.	3.00 (2.56)	1.00 (1.20)	0.58 (1.24)	1.42 (1.50)	9.92 (6.41)	0.58 (0.99)	0.75 (1.05)	0.58 (0.67)	1.33 (1.07)

TRE2: Total number of the 3 types of Recognition Errors (RES2+ REV2+ REA2)

RES2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"

REV2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "verbal message"

REA2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "auditory message"

PTSME2: Percentage of Source Memory Errors

MSS2: Misattributions to the source "self

FASS2: Failure in attributting to the source "self"

MSV2: Misattributions to the source "verbal message"

MSA2: Misattributions to the source "auditory message"

5.10.7. Patients with and without Delusions

In paragraphs 5.4.9. and 5.4.10. we provide information about the two subgroups.

5.10.8. Patients with and without Delusions and Recognition Errors of Wrongly Recognizing New Interfering Words as if They Were Old (TRE2, RES2, REV2, REA2)

Patients with delusions and those without did not differ in the total number of recognition errors [F(1,33)=1.777, p>.05]. There was also no significant interaction between the 2 factors [F(2,66)=.094, p>.05] (Table 20).

Table 20. Means and Standard deviations of recognition errors and source memory errors in the two subgroups

	TRE2	RES2	REV2	REA2	PTSME2	MSS2	FASS2	MSV2	MSA2
	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)
Patients without delusions	1.15 (1.14)	0.23 (0.44)	0.15 (0.37)	0.77 (1.10)	3.83 (5.30)	0.00 (0.28)	0.54 (0.97)	0.23 (0.60)	0.46 (0.66)
Patients with delusions	2.04 (2.23)	0.59 (1.00)	0.50 (1.10)	0.9 (1.17)	6.18 (5.87)	0.45 (0.80)	0.41 (0.79)	0.36 (0.58)	0.86 (1.08)

TRE2: Total number of the 3 types of Recognition Errors (RES2+ REV2+ REA2)
RES2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "self"
REV2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "verbal message"
REA2: Recognition errors of incorrectly recognizing new interfering words as if they were examples of the source "auditory message"
PTSME2: Percentage of Source Memory Errors
MSS2: Misattributions to the source "self
FASS2: Failure in attributting to the source "self"
MSV2: Misattributions to the source "verbal message"
MSA2: Misattributions to the source "auditory message"

5.10.9. Patients with and without Delusions and Source Memory Errors (PTSME2, MSS2, FASS2, MSV2, MSA2)

The two groups made the same number of source memory errors once they had positively recognized the item (PTSME2) [F(1,32)=1.39, p>.05]. Concerning Source Memory Errors, the factor "Delusions" was not found to be significant [Pillais value=.176, F(4,30)=1.60, p>.05] (Table 20).

5.11. Source Memory and Cognitive Functions

5.11.1. Patient Group: Correlation of the Total Number of Recognition Errors (TRE2) and the Percentage of Source Memory Errors (PTSME2) with Cognitive Functions

Total number of Recognition Errors was correlated negatively with Working memory (r=-.370, p=.029), Verbal Memory (r=-.462, p=.005), and the Executive Functions (r=-.488, p=.003). Concerning the patient group, there was a negative correlation between the Percentage of Source Memory Errors and Working memory (r=-.367, p=.030), Verbal Memory (r=-.476, p=.004), Visual Memory (r=-.354, p=.037) and the Executive functions (r=-.447, p=.007) (Table 21).

5.11.2. Control Group: Correlation of Total Number of the Recognition Errors (TRE2) and the Percentage of Source Memory Errors (PTSME2) with Cognitive Functions

There was a correlation of the Total Recognition Errors with Verbal Memory (r=-.487, p=.003) and Executive functions (r=-.563, p=.001). In the control group, no correlation of the cognitive functions with the Percent Proportion of the Total Source Memory Errors was found (Table 21).

Table 21. Correlations of Cognitive Functions with Total number of Recognition Errors and the Source Memory Errors

		Working Memory	Sustained Attention	Verbal Memory	Visual Memory	Executive functions
Control group	TRE2	-.143	.140	-.487**	-.135	-.563**
	PTSME2	-.038	-.263	-.048	.177	-.290
Patient Group	TRE2	-.370*	-.194	-.462*	-.313	-.488*
	PTSME2	-.367*	-.091	-.476*	-.354*	-.447*

TRE: Total number of the 3 types of Recognition Errors (RES2+ REV2+ REA2)
PTSME: Percentage of Source Memory Errors
* significance level .05 ** significance level .01

5.11.3. Comparisons of the Two Groups in the Total Recognition Errors (TRE2) and the Percentage of Source Memory Errors (PTSME2) with Cognitive Functions that were Correlated Significantly with Variables Studied as Covariates

According to paragraph 5.6.3., the two groups differed in their performance in Verbal Memory, Working Memory and Executive functions. Furthermore, the control group (M=.46, S.D.=.78) had a better performance than the patient group (M=-.45, S.D.=.99) in Visual Memory [F(1,67)=18.13, p=<.001]. According to paragraphs 5.11.1. and 5.11.2., the aforementioned cognitive functions were correlated significantly with Recognition errors and source memory errors; so, they were used as covariates, in order to control for their effect.

Indeed, the effect of Verbal Memory [F(1,66)=17.68, p<.001] and the Executive functions [F(1,66)=20.7, p<.001] was significant when comparing the two groups in the Total Recognition Errors and the analyses with each covariate separately made the difference between the two groups not significant [F(1,66)=3.01, p>.05; F(1,66)=0.45, p>.05, respectively]. There was no significant interaction between the 2 factors [F(2,132)=.724, p>.05; F(2,132)=.448, p>.05, respectively in the two analyses].

When Verbal Memory [F(1,66)=11.26, p=.001] and Executive functions [F(1,66)=13.17, p=001] were covariates, having a statistically significant effect, the difference of the two groups in the Percent Proportion of the Total Source Memory Errors was not significant [F(1,66)=2.41, p>.05; F(1,66)=0.91, p>.05, respectively].

On the other hand, the effect of working memory was significant when comparing the groups in the Total of Recognition Errors [F(1,66)=4.51, p=0.37], but wasn't when comparing the two groups in the Percentage of Total Source Memory Errors [F(1,66)=3.19, p>.05]. In both cases the difference between the patients with schizophrenia and the control group remained statistically significant [F(1,66)=9.48, p=.003; F(1,66)=7.26, p=.009, respectively]. No significant interaction was found between the factor "Group" and the recognition errors [F(1,132)=1.27, p>.05].

About Visual Memory, we noted that its effect as covariate was not statistically significant [$F(1,66)=2.62$, $p>.05$] and that the difference between the patients with schizophrenia and the control group in the Percentage of Source Memory Errors remained significant [$F(1,66)=11.26$, $p=.001$].

6. DISCUSSION

6.1. Source Memory

In the present study we investigated recognition and source monitoring with two source memory tasks, one with visual and one with auditory stimuli. We noted that recognition in schizophrenia is seriously impaired independently of the stimuli's modality (Appendix, Table 22). These deficits are associated with psychopathology and certain cognitive functions. We found a deficit in source memory, and, more specifically, in the discrimination between events coming from external and internal sources (Appendix, Table 22). The source monitoring deficit is associated only with semantic disorganization and specific cognitive functions, whose role has been shown to be decisive in the source memory processes.

6.1.1. Recognition Errors

Hypothesis 1a predicted that patients with schizophrenia tend to think that words they hear for the first time have been previously presented to them. The analyses we performed supported this view. The recognition deficit is independent of the stimuli's presentation modality (visual, auditory, self-generated) as mentioned in various studies, with different theoretical approaches. More specifically, Brébion and colleagues (2002) confirmed that patients with schizophrenia face difficulties in recognition. Furthermore, they found a correlation between this impairment and hallucination behavior, and explained it by the difficulty patients with hallucinations have to monitor reality. Vinogradov and colleagues (1997) had similar initial findings, but they did not find a correlation of these difficulties in recognition to positive symptoms. They noted that patients with schizophrenia tend to attribute the examples they generate themselves as well as the new interfering words to external sources.

Moritz and his colleagues (2003) mentioned this deficit in recognition and related it to the general problem of verbal memory in schizophrenia. Likewise, Weiss and colleagues (2002) observed that recognition errors are associated with deficits in the recall process. In the recognition task, the participants had to discriminate the target words from interference. Thus, it was necessary to use more complex mnemonic strategies as well as the pragmatics of the target word, as the interference was caused by words relevant to the target. The patients with schizophrenia failed to do so and the authors attributed that failure to the strategy they used, that is the feeling of familiarity provoked by the words, and the failure to make an effortful recall of the source. Recognition based on the strategy of familiarity takes place when the person does not remember any information at all about the source (Johnson et al., 1993).

The deficit in recognition, which is independent from the stimulus type, reflects, as we will explain further, the deficit in verbal memory and executive functions in patients with schizophrenia.

6.1.2. Source Memory Errors

We noted that generally patients with schizophrenia made more errors in source memory than the control group. More specifically, the source memory deficit in the first task with the visual stimuli reflects difficulties in the discrimination between the external sources. Patients with schizophrenia recall as a picture the example presented as a written word. Similar were the findings of Brébion and colleagues (1998), who found that patients recalled as pictures the words that had been orally presented to them. They explained this finding by the specific interaction of mental imagery and perceptual process, which plays a significant role in the mechanism of hallucinations in schizophrenia (Grossberg, 2000). Similarly, Belli and colleagues (1992) in an attempt to study how important the features of the sources are and how they affect the discrimination between the sources, found that healthy adults recall as a picture an event that they had read, whereas the opposite did not occur often.

However, the same pattern of error appeared in the group of patients also in the Task 2, confirming that the problem of patients with schizophrenia relies in the discrimination between the external sources. Patients had difficulties in monitoring the stimulus that came from two external sources and attributed to the source "auditory message" examples that had been presented as verbal messages. Therefore, the patients' difficulty may rely on the defective/inadequate coding of information that characterize uniquely each external source (i.e., word of a male voice, auditory message- example) or be associated with the defective strategies patients use in order to judge (Johnson et al., 1993). If patients rely only on available perceptual features in making a decision (heuristic strategy) and don't compare them or do not evaluate the importance of the features stored (systematic strategy), than the risk of misattributing is high.

Besides the difficulty in discriminating between the external sources, there was another difficulty in discriminating between the internal and the external source (monitoring of reality), only in the Task 2. Patients attributed examples they had generated themselves to an external source ("verbal message" or "auditory message"). This finding that has been reported also in other studies and associated with the deficit of self monitoring in schizophrenia, i.e., the difficulty to monitor the generation of their own thoughts (Keefe, 1999; Frith, 1991).

The internal events differ from the external events in that the former contain information about cognitive functions that have been involved in their generation. Confusing them shows that the phenomenological characteristics of the two types of events do not seem to differentiate clearly enough, that is that the internal events in one hand do not offer much information about the cognitive functions, and the external events on the other hand don't dispose many perceptual information. According to Bentall and colleagues (1991), patients with schizophrenia fail to use their cognitive effort as a characteristic of the internal source, which would help them to attribute the examples to the correct sources. The problem may not be in the maintenance and storing, but in the executive functions of monitoring and of controlling the cognitive system and the internal processes.

The difficulty in discriminating between the events originating from internal and external sources was observed only in Task 2, which means that it probably has to do with the type of the stimulus. According to the assumption of the competitive relationship (Jurica and Shimamura, 1999) between memory for objects and source memory, we expect that the auditory stimuli, because of their short presentation time, require greater cognitive effort, in order to be coded and retained, so that the cognitive reserve that remains for the processing of the source's context, the storing of information about the cognitive functions and the

gathering of all that in a unified set is limited. Consequently, the deficit of monitoring reality, which was observed only with auditory stimuli, is related to the type of the task and its difficulty. The aforementioned finding agrees with the fact that basic cognitive functions, like working and verbal memory and executive functions, which are seriously impaired in schizophrenia, underlie the processes of the source monitoring.

6.2. Source Memory and Psychopathology

From all the symptoms assessed with the Positive and Negative Symptoms Scale (PANSS), only the factor representing cognitive symptoms correlated with recognition and source memory in both tasks. Depression was found to correlate with recognition errors, but only in Task 2. On the other hand, there was no correlation between positive and negative symptoms and agitation with recognition errors and failure to attribute the examples to their sources.

Brébion and colleagues (2002) suggested a reverse relationship between negative symptoms (social withdrawal, emotional withdrawal, flat affect and loss of spontaneity and anhedonia) and source memory errors, as compared with the relationship of positive symptoms to these variables. They found that negative symptomatology was related to a lesser degree to misattribution to the picture of orally presented words, and to a greater degree to attributions to the self of words presented by an external source. However, this is the only study of negative symptoms and needs further investigation.

6.2.1. Semantic Disorganization

In the present study, the subgroup of patients with semantic disorganization made more recognition errors of wrongly recognizing new interfering words as if they were examples that had been presented in the acquisition phase in both source memory tasks (Appendix, Table 23). In patients with that particular symptom, a number of mnemonic traces relevant to the interfering word was activated the moment the experimenter named the word. Patients with semantic disorganization tended to think that this new interfering word was included in the list of words they had to retain, because of the amount of activated relevant mnemonic traces (for example perceptual or semantic information). Similar was the finding of Moritz and colleagues (2003), where the severity of semantic disorganization was significantly correlated with the tendency patients had to think that words they heard for the first time during the examination phase, they had also heard before during the acquisition phase.

Furthermore, semantic disorganization is the only symptom, out of the three studied, that differentiated the two patient subgroups with respect to source memory (Appendix, Table 23). Semantic priming experiments have shown that this symptom causes widespread and rapid activation of the semantic network. The priming caused by relevant, but also by non-relevant words in patients with thought disorder is characterized by rapid and distant associations (Spitzer, 1993; Moritz, 2002). Studies have found a correlation between semantic disorganization and impairment in tasks of executive functions (for example semantic and phonological verbal fluency), which require organization of mental vocabulary, control of semantic processes and of inhibition, whereas there was no respective correlation with hallucinations (Bow-Thomas et al., 2000).

In our sample, patients with semantic disorganization misattributed examples they generated themselves to an external source in Task 2 and recalled erroneously as auditory messages, those examples that had been presented verbally. Harvey and colleagues (1990 and 1985) noted a respective deficit in patients with thought disorder. They observed that patients with schizophrenia and thought disorder had difficulties in discriminating between information they had said themselves and information they had thought, while bipolar patients with thought disorder had difficulties only in discriminating events from external sources. The same authors associated this deficit with impaired control of information processing, which, according to former studies, is associated with thought disorder in schizophrenia.

What is worth noting is that semantic disorganization is the only symptom out of the three studied, that correlated significantly with those cognitive functions (i.e., working memory, verbal memory and executive functions) that underlie the source memory deficit.

6.2.2. Delusions

According to the current literature, patients with delusions face difficulties in reasoning, and draw conclusions based on very limited information (Garety et al., 1991). The aforementioned deficits of patients with delusions have been found to relate to impaired recognition and source memory (Cahill et al., 1996). In our sample, as in similar studies (Brébion et al., 2002), patients with delusions did not differ from patients without delusions in recognition (Appendix, Table 24). Similarly, the two patient subgroups did not differ in source monitoring of information (Appendix, Table 25). Still, because specific types of delusions affect verbal memory in different ways and self monitoring in schizophrenia, it would be useful to study the deficit in source memory with those delusions, that have to do the limits of the "self", and the delusions of control of thoughts and acts (Mlakar et al., 1998; Stirling et al., 1998).

6.2.3. Hallucinations

In the present study, we noted that patients with hallucinations differ from patients without hallucinations, only in recognition, but not in source memory (Appendix, Table 25). However, there are some methodological limitations we must consider. The sample of patients with hallucinations was small. Only 7 of the patients had hallucinations of mild or moderate severity. The small number of this subgroup increases the risk of type II error, that is, the acceptance of the null hypothesis, which suggests a group difference with respect to recognition and source memory. Moreover, because of the small sample size of patients with hallucinations we conducted Mann-Whitney non-parametric analyses an approach with smaller power than parametric analyses. Given these limitations, we maintain some reservations concerning the relationship between hallucinations on the one hand and recognition and source memory on the other.

There is evidence that patients with hallucinations tend to mistake examples they hear for the first time as information that had been presented to them as written words (Task 1) and as auditory messages (Task2). This tendency is linked to deficits in processing the pragmatic information that patients with positive symptomatology present (Servant-Schreider et al., 1996). Patients with hallucinations confuse target words presented to them in the specific experimental context, with words familiar to them for other reasons. There is evidence that

patients with schizophrenia have difficulties in processing context information related to time and space, or to inhibit irrelevant information from influencing their decisions.

Concerning hallucinations and source memory errors, in the present study there is evidence that the two subgroups of patients do not differ in the discrimination of events originating from external sources, nor in the discrimination between internal and external sources. On the contrary, many authors (Frith et al., 1991; Bentall et al., 1991; Brébion, 2002) believe that many of the symptoms in schizophrenia and hallucinations in particular, derive from the weakness to monitor the generation of internal events. They have proposed a direct connection between hallucinations and misattributions of internal events to external sources.

Keefe and colleagues (2002) studied the source memory deficit, referred to as autonoetic agnosia, i.e., impaired recognition of self-generated mental events, and noted that patients with schizophrenia who presented at least one of the Schnederian symptoms (voices commenting or having a conversation, alien control of thoughts, emotions, actions and impulses) had serious difficulties in the recognition of self-generated events and in the discrimination of events that came from external sources. Similarly, Cahill and colleagues (1996) investigated how patients with schizophrenia perceive their voice and found that during exacerbations, patients thought they heard some else's voice. The authors concluded that this difficulty might be linked to positive symptomatology and impaired perception of inner speech in schizophrenia.

On the other hand, there are studies in the literature (Moritz et al., 2003 and 2002; Stirling et al., 1997; Vinogradov et al., 1997), which do not support the relationship between illusions and source memory impairment. These studies do not confirm the mechanism linking hallucinations with misattributions of internal events to external sources. Their findings, like ours, support the view that the source monitoring deficit does not underlie positive symptomatology, but characterizes patients with schizophrenia regardless of type of symptomatology.

Another limitation of this finding is that in the present study we did not control for the emotional value of the examples used as stimuli in the two source memory tasks. There is some evidence (Morrison and Haddock, 1997) showing a tendency of patients with hallucinations to attribute internal events to external sources when the material is emotionally charged.

6.3. Source Memory and Cognitive Functions

6.3.1. Recognition Errors

Hypothesis 3a predicted that the performance in the ability to discriminate between new and old stimuli is affected by basic cognitive functions. Indeed, in the patient group, recognition errors correlated highly with working memory, verbal memory and executive functions in both tasks. On the other hand, in the control group, we observed a correlation of recognition errors with verbal memory and executive functions, but only Task2.

In a second level of analyses, we noted that working memory has an effect on and plays a supporting role in recognition. More precisely, it contributes to the retention of the content of an example simultaneously to other mental processes, like searching for and generating examples. The effect of working memory is not sufficiently crucial as to eliminate the

difference between the two groups. This happens when we control for the effect of verbal memory and executive functions.

Recognition errors of incorectly recognizing new words as if they were stimuli that had been presented again in a previous acquisition phase, have been associated with frontal lobe functioning (Melo et al., 1999; Parkin et al., 1999). The aforementioned researchers have associated these kinds of recognition errors with impaired strategies of recalling an event. They suggested that these errors occur because the individuals do not use strategies of effortful recall, but rely on the feeling of familiarity created by the events. In other words they state that a stimulus has been presented only because it reminds them of something.

The significant contribution of verbal memory to recognition was expected and predicted, as the verbal memory tasks contained interference from irrelevant material, which clearly affected the patients' performance negatively. Moritz and his colleagues (2003) found a correlation between recognition and verbal memory, which they evaluated with the Rey Auditory Verbal Learning Test.

It appears that recognition errors arise because of failure in retaining information, in using recall strategies effectively, but also in inhibiting the automatic processes that rely on the familiarity effect.

6.3.2. Source Memory Errors

While investigating hypothesis 3(b) of our study, we found that some cognitive functions were associated with the ability to monitor the source of information and we noted that certain functions are crucial for this process. Verbal and working memory, as well as executive functions, correlates very highly with source memory in both tasks for the patient group. Similarly, in the same group, visual memory correlated with source memory in Task 2. However, impaired mental imagery and retention of auditory stimuli does not appear to source monitoring in a decisive way. On the other hand, in the control group, verbal memory was found to be associated with source memory only in Task 1. There was no correlation between sustained attention and the variables studied in either of the two tasks or groups.

Although there are no studies in the schizophrenia literature linking source memory with working memory, we considered that this basic function plays an important role in the mental manipulation of information about the context and the content and that is why we included a task of working memory in the neuropsychological evaluation battery. We noted that working memory and source memory are correlated, meaning that the intact functioning of the monitoring processes is enforced by the intact functioning of working memory. However, when controlling for source memory, the difference between the two groups on working memory remained. It would appear that working memory contributes to the adequate management of the cognitive reserve in such a complex process as the monitoring of the source of information, but it does not impaired source memory in patients with schizophrenia.

Verbal memory has an important contribution to the process of source monitoring. When we controlled for verbal memory in the comparisons of the two groups in source memory errors, the statistically significant difference between the groups disappeared. The maintenance and storage of information and its characteristics, as well as the ability to recall this information, are an important part of the of source monitoring process. Intact verbal memory is associated with correct organization of the material and successful recall of information in short-term memory. The auxiliary role of verbal memory has been indicated in studies by Seal and Crowe (1997) and Johnson and colleagues (1993).

The present study confirmed the important role of the frontal lobes and executive functions in the correct recall of the source of information. When the effect of executive functions was controlled for, we found no statistically significant difference between the two groups in source memory errors. The control strategies of the activated mnemonic traces, the inhibition of irrelevant connections and the comparison of content information were found to constitute a substantial part of the complex processes involved in monitoring the source of information.

However, the majority of the studies focusing on source memory in schizophrenia failed to find any relationship with executive functions. Moritz and colleagues (2003) did not find a relationship between the recognition of new interfering words and the ability to make correct attributions of the source of information, using two variables of the Wisconsin Card Sorting Test (number of categories completed and number of perseveration). Similarly, Striling and colleagues (1998), who investigated the ability of self-monitoring in an executive task, did not find correlation between the ability of patients with schizophrenia to self-monitor and the Trail Making Test (Parts A and B) (Stirling et al., 1998), which evaluates mental shifting and inhibition, as well as speed of execution.

On the other hand, many researchers (Wheeler et al., 1997; Jurica and Shimamura, 1999; Shimamura et al., 1990) supported the view that source monitoring demands more than merely recalling information; instead executive control on the processing of information, evaluation of the information recalled and mainly a combination of these processes in a unified framework is needed. According to the model of Johnson and her colleagues (Johnson et al., 1993), intact source memory depends on the strategy one chooses to apply. It has been found that the application of a heuristic strategy, which is more automatic as a process, is associated with misattributions to the sources. In case executive functions are impaired, we expect an overall source memory deficit, independently of the sources of the events. In fact, as demonstrated by current research, patients with schizophrenia have difficulty in discriminating between internal and external sources, as well as between two external sources.

The connection between source monitoring ability and executive functions has been demonstrated by studies with 4 to 6 year old children (Ruffman et al., 2001; Lindsay and Johnson, 1991). Children of this age present difficulties in discriminating if their father was the one who spoke about big cars in the streets or if it was the teacher at school, and if they actually touched their nose or they had only imagined it. The researchers suggested that the ability to monitor information develops gradually and in parallel to the development of the frontal lobes.

Ruffman and colleagues (2001) studied source memory and recognition in children aged 6, 8 and 10 and investigated the relationship of these functions with working memory and inhibition. They noted that the ability to inhibit the use of recall strategies based on the feeling of familiarity correlated with source monitoring of the events, as well as with recognition. On the other hand, they found that working memory is associated only with source memory. They interpreted the above finding as an indication that both functions rely on intermediate processing strategies and metacognitive monitoring, i.e., on awareness of the former experience with the context.

Studies with healthy elderly people found a relative correlation between source memory and executive functions (Glisky et al., 1995). More precisely, Glisky and colleagues (1995) divided their sample in elderly people with good performance on executive functions tests

and those with poor performance. These two subgroups of elderly people differed in their performance on a source memory task, but not on an object memory task. Similarly, Craik and colleagues (1990) found a correlation between source memory and the performance of elderly people in tasks evaluating inhibition of organization of mental vocabulary, like Wisconsin Card Sorting Test and Verbal Fluency.

Thus, the implications of our findings are twofold. On one hand, they highlight the complexity of the process of source monitoring. On the other hand, they suggest that impaired source memory in schizophrenia reflects – at least partially – the basic cognitive impairments typical of this disorder. More specifically, verbal memory and executive functions deficits affect the source memory process on three levels: a) organization and storage of the material in the memory system, b) recall strategies, and c) executive functions control and monitoring (Johnson et al., 1993).

7. APPENDIX

Table 22. Source memory tasks: collective data from comparisons between the group of patients with schizophrenia (n=35) and the control group (n=34)

1st task with visual stimuli					
Omissions			**Recognition errors**		
Self	Picture	Written word	*Self*	*Picture*	*Written word*
Source Memory Errors					
Discrimination between internal source and external sources			Discrimination between the two external sources		
Attribution to self	Failure in attributing to self		Attribution to word	*Attribution to Picture*	
2nd task with auditory stimuli					
Omissions			**Recognition errors**		
Self	*Auditory message*	*Verbal message*	***Self***	*Auditory message*	*Verbal message*
Source Memory Errors					
Discrimination between internal source and external sources			Discrimination between the two external sources		
Attribution to self	*Failure in attributing to self*		Attribution to verbal message	*Attribution to auditory message*	

Note: In italics are the error types in which patients with schizophrenia do worst than the control group.

Table 23. Source memory tasks: collective data from comparisons between patients with semantic disorganization (n=12) and patients without semantic disorganization (n=23)

1st task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	*Picture*	*Written word*	Attribution to self	Failure in attributing to self	Attribution to word	Attribution to picture
2nd task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	*Verbal message*	*Auditory message*	Attribution to self	*Failure in attributing to self*	Attribution to verbal message	*Attribution to auditory message*

Note: In italics are the error types in which patients with semantic disorganization do worst than patients without that symptom.

Table 24. Source memory tasks: collective data from comparisons between patients with delusions (n=22) and patients without delusions (n=13)

1st task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	Picture	Written word	Attribution to self	Failure in attributing to self	Attribution to word	Attribution to picture
2nd task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	Verbal message	Auditory message	Attribution to self	Failure in attributing to self	Attribution to verbal message	Attribution to auditory message

Note:. Patients with delusions don't differ from patients without delusions in recognition errors nor in source memory errors.

Table 25. Source memory tasks: collective data from comparisons between patients with hallucinations (n=7) and patients without hallucinations (n=28)

1st task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	Picture	***Written word***	Attribution to self	Failure in attributing to self	Attribution to word	Attribution to picture
2nd task with visual stimuli						
Recognition errors			**Source Memory Errors**			
			Discrimination between internal source and external sources		Discrimination between the two external sources	
Self	Verbal message	*Auditory message*	Attribution to self	Failure in attributing to self	Attribution to verbal message	Attribution to auditory message

Note: In italics are the error types in which patients with hallucinations do worst than patients without that symptom.

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Chapter 10

PREPULSE INHIBITION - A PARADIGM TO ASSESS GATING FUNCTIONS IN SCHIZOPHRENIA PATIENTS

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ABSTRACT

Prepulse inhibition (PPI) is thought to reflect a relatively automatic, preattentive sensorimotor gating mechanism that reflects an individual's ability to gate incoming information, so that attention can be focussed effectively on specific environmental stimuli. PPI is reduced in patients with schizophrenia. Such impairments in the ability to appropriately inhibit the processing of information have been hypothesized to contribute to the core symptoms of schizophrenia.

This review covers four areas of interest in PPI studies.

First, we summarize the theory that lies behind the mechanism of PPI and delineate the neural substrates and neurotransmitters involved in PPI. Animal studies have contributed considerably to these domains of interest.

Second, we critically review the existing literature on PPI deficits in chronic and first-episode schizophrenia patients. Many studies - but not all - report that PPI is impaired in individuals with schizophrenia. Some of the inconsistencies might be due to different parameters influencing PPI performance in schizophrenia patients and healthy subjects. The type of antipsychotic treatments and the degree of psychotic symptoms appear to influence PPI in schizophrenia patients. Moreover, smoking habits, genetic predisposition, and sex differences as well as varying experimental conditions influence PPI measures in both healthy subjects and patients. The multiplicity of these factors complicates the interpretation of PPI data and might contribute to discrepancies across studies.

Third, the relationship between cognition and PPI is reviewed. Specifically, abnormalities in the early stages of information processing could lead to a cascade of downstream effects on higher cortical functions, such as sustained attention, working memory, concept formation, or social functioning.

Fourth, we review the PPI literature on model psychoses in healthy volunteers. Thus, various drugs that are suggested to reproduce schizophrenia-like states, such as psilocybin and ketamine, have also been used in animal and human studies of PPI.

1. THEORY, NEUROANATOMY, AND NEUROTRANSMITTERS INVOLVED IN PPI

1.1. Theory of Prepulse Inhibition (PPI)

Human beings can normally gate incoming information; i.e. gating mechanisms protect a normal individual from meaningless stimuli so that they never reach consciousness *(Braff et al. 1995)*. According to *McGhie and Chapman 1961,* such a reduction of information is an important cognitive function that prevents sensory overstimulation. Gating functions are believed to be impaired in schizophrenia. Schizophrenia patients are supposed to have difficulties in screening out irrelevant information, that might lead to increased distractibility, cognitive fragmentation, and thought disorder *(Braff et al. 1995)*. These impairments have been hypothesized to represent the unifying component of schizophrenia since the original descriptions by Kraepelin 1912 and Bleuler 1950. Prepulse inhibition (PPI) of the acoustic startle reflex is a psychophysiological measure thought to assess gating functions - particularly, sensorimotor gating (both sensory inputs and motor outputs are involved) -, and information processing *(Braff et al. 1995)*. As early as 1978 *(Braff et al. 1978)* and multiple times thereafter, PPI has been found to be impaired or blunted in schizophrenia patients.

1.1.1. Prepulse Inhibition of the Acoustic Startle Reflex (ASR)

Gating functions can be tested with the PPI paradigm of the startle response. The acoustic startle response is a series of flexions and extensions in response to strong, sudden acoustic stimuli (i.e. startle-eliciting pulse) that can be studied in all mammals including human beings.

During a startle reflex measurement, the acoustic stimuli are typically delivered through earphones and elicit an eyeblink. This aspect of the startle response can be assessed by recording the electromyographic activity of the right and/or left orbicularis oculi muscles.

Most studies use brief (20 to 40 ms) startle-eliciting acoustic stimuli, with intensities varying from 105 to 115 dB and presented for 20 to 50 ms. On some trials in a test session, the startle stimulus is preceded by a prepulse, which is not thought to elicit a startle response by itself. The prepulse (PP) is relatively weak, i.e. around 86 dB and is presented for about 20 to 40 ms, either 30 ms (abbreviated as pp30), 60 ms (abbreviated as pp60), 120 ms (abbreviated as pp120), 240 ms or 2000 ms in advance. The amplitude of the startle response is attenuated by this weak prepulse. Thus, PPI is usually expressed as the percentage of inhibition of the startle amplitude on prepulse trials as compared with the amplitude during pulse-alone trials.

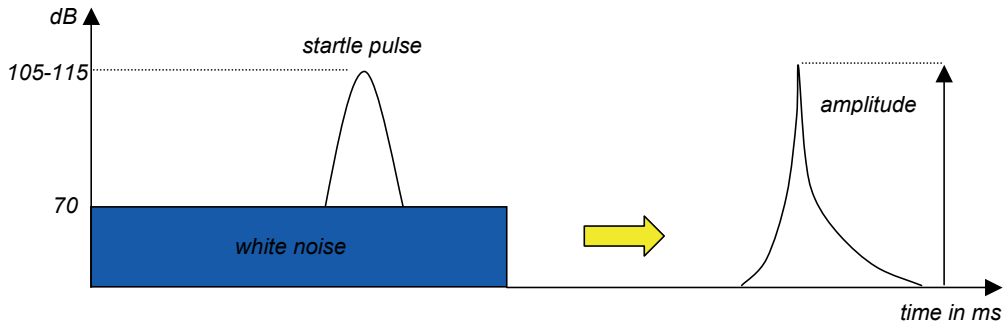

Figure 1. The startle pulse elicits a startle response

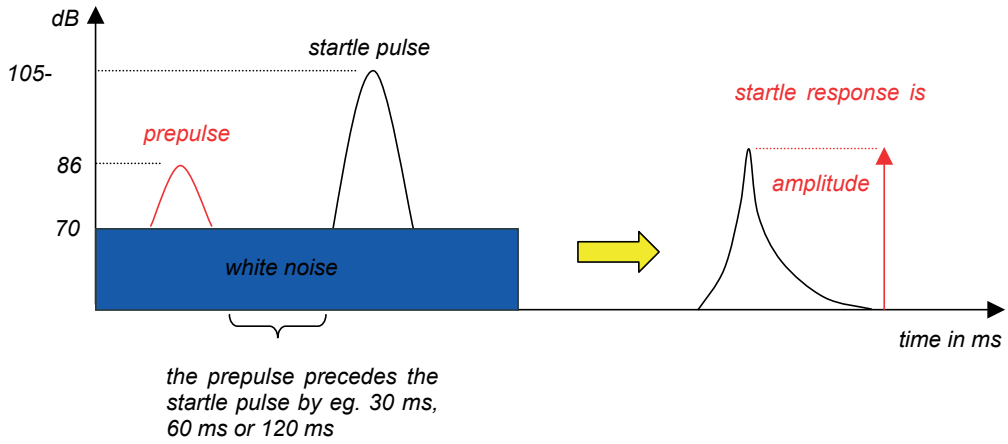

Figure 2. The startle pulse is preceded by a weak prepulse. Thus, the response (amplitude) is reduced (PPI).

This inhibition is thought to reflect the action of a largely automatic (i.e. pre-attentional) and unlearned sensorimotor gating mechanism. Indeed, deficient PPI in schizophrenia has been observed with intervals between the prepulse and startle stimuli being too short (e.g. 30 or 60 ms) to be accessible to the conscious allocation of attentional resources *(Braff et al. 2001).*

Different studies use different experimental conditions: i.e. varying stimulus intensities and durations; controlled background noise vs. non-controlled background noise; or pure tone stimuli in contrast to white noise stimuli. Moreover, three PPI paradigms differing in the instructions given to the participants, are used at present. In the passive PPI paradigm, as used by several research groups *(Braff et al. 1978, 1992; Cadenhead et al. 1993; Ludewig et al. 2003; Duncan et al. 2003),* subjects are not specifically instructed to attend or to ignore the prepulse or startle pulse. In the active PPI paradigm, however, subjects are asked to attend to the prepulses *(Hazlett et al. 1998, 2001; Dawson et al. 2000).* A third, more recent PPI paradigm differs from the latter in that the participants are directed to attend to both the

prepulse and startle stimuli. This PPI paradigm was evaluated by *Heekeren et al. 2004.* The startle reflex measurement lasts for approximately 15 min.

1.2. The Neuroanatomy of the Acoustic Startle Reflex (ASR) and Prepulse Inhibition

1.2.1. Cerebral Structures Involved in the ASR

Uninstructed PPI can be studied in humans and rats using almost identical experimental paradigms. The similarity of the phenomena across species supports the suggestion that the neurobiological mechanisms underlying the PPI response may be very similar across species *(Swerdlow et al. 1998, 2001).* The acoustic startle reflex circuitry is thought to consist of a brain network encompassing very few structures located in the lower brainstem: the auditory nerve; ventral cochlear nucleus; nuclei of the lateral lemniscus; nucleus reticularis pontis caudalis (PnC); and the spinal motoneurons *(Davis et al. 1982).* The PnC is the most important sensorimotor structure. First, it receives auditory input from various brainstem nuclei *(Koch 1999).* Second, the PnC neurons project onto different motor neurons including the facial, cranial and spinal motor neurons and are therefore responsible for the facial and somatic components of the ASR *(Koch 1999)*. And third, descending information, mediating the inhibitory function of the prepulse, also converges on the PnC *(Swerdlow et al. 2001a).*

1.2.2. Cerebral Structures Involved in Prepulse Inhibition

ASR and PPI are mediated by different pathways. Whereas the startle response is controlled by brain structures at the level of the brain stem, it is the limbic cortico-striato-pallido-pontine (CSSP) forebrain circuit modulating the inhibitory functions of the prepulse *(Swerdlow et al. 1998, 2001)*. It involves the limbic cortex (medial prefrontal cortex, amygdala and ventral hippocampus), the ventral striatum (i.e. nucleus accumbens - NAC), the ventral pallidum and the pontine tegmentum (PnC) *(Koch and Schnitzler 1997; Swerdlow et al. 2001a)*. Moreover, the mesolimbic-cortico-pallido-thalamic circuitry is also supposed to influence PPI in rats *(Swerdlow et al. 1992; Lee et al. 1996).*

The nucleus accumbens is thought to be a core structure in the regulation of PPI because it connects forebrain and limbic structures that control cognition and behaviour *(Swerdlow et al. 2001a).* It integrates glutamatergic inputs from the hippocampus, amygdala, and medial prefrontal cortex as well as dopaminergic inputs from the ventral tegmental area (VTA) *(Swerdlow et al. 2001a).* This convergence within the NAC creates a mechanism by which forebrain DA activity can regulate the passage of information *(Swerdlow and Koob 1987).* The processed signal is then transmitted to the ventral pallidum *(Meincke et al. 2001).* Pallidal outputs project to the pedunculopontine nucleus, where they provide access to the primary startle circuit via the PnC and to the thalamus, which is believed to exert an inhibitory effect *(Zahm et al. 1987).* At the level of the PnC, PPI is thought to inhibit the ASR pathway *(Koch 1999).* The CSPP circuit thus subserves the fundamental cognitive operations of stimulus selection and inhibition *(Swerdlow et al. 2001a).*

In healthy human subjects, neuroimaging studies also confirmed the activation in the striatum *(Kumari et al. 2003a),* the thalamus *(Hazlett et al. 2001* using the active PPI paradigm and *Kumari et al. 2003a* using the passive PPI paradigm), and parietal regions

(Hazlett et al. 1998; Kumari et al. 2003a) in relationship with PPI. However the PFC was only activated during the active PPI task *(Hazlett et al. 1998),* but not with passive PPI *(Kumari et al. 2003a).*

It is interesting that all of the CSPP structures and the thalamus have also been implicated in the pathophysiology of schizophrenia *(Swerdlow et al. 2001a).* Particularly, these regions were hypoactivated in fMRI studies performed by *Hazlett et al. 1998* and *Kumari et al. 2003a.*

1.3. Models of PPI Disruption and the Reversal of PPI Deficits by Antipsychotic Treatments in Animals

Evidence for the involvement of various neurotransmitter systems comes from animal studies. Specifically, dopamine agonists, $5HT_{2A}$ agonists, and NMDA antagonists disrupt PPI in rats. In addition, isolation rearing has the same effect. These four main models of schizophrenia-like disruptions in PPI can be affected by antipsychotic treatments.

In the following paragraphs, it appears that atypical antipsychotics are more capable to remove these deficits than typical antipsychotics; this might be due to their broader pharmacological profile (in addition to D_2 receptors, they bind to 5HT receptors, NMDA receptors and cholinergic receptors) than typical antipsychotics. Furthermore, different antipsychotics might operate on different systems mediating PPI and are therefore differentially effective in restoring PPI performance.

1.3.1. The Dopamine Model of PPI Deficit

Swerdlow et al. 1986 and *Mansbach et al. 1988* reported the first examples of disruptions in PPI produced by administrations of either the direct DA agonist apomorphine or the DA releaser amphetamine in rats. The typical antipsychotic haloperidol, a DA D_2-family antagonist, reduces the effects of apomorphine *(Mansbach et al. 1988)* and amphetamine on PPI *(Ellenbroek et al. 2001; Swerdlow et al. 2005b).* Atypical compounds clozapine, olanzapine, quetiapine, and risperidone also reduce the PPI-disruptive effects of apomorphine *(Geyer et al. 2001; Swerdlow et al. 1991).* Moreover, quinpirole, a D_2/D_3 agonist *(Peng et al. 1990),* bromocriptine, a D_2 agonist *(Swerdlow et al. 1998)* and pergolide, a D_1/D_2 receptor agonist *(Swerdlow et al. 2001b)* were demonstrated to disrupt PPI in rats. In mice, however, the direct D_2/D_3 agonist quinpirole failed to disrupt PPI, whereas the D_1/D_2 agonist pergolide and other more specific D_1 agonists were effective in disrupting PPI *(Ralph-Williams et al. 2003)*. Thus, in contrast to rats, it appears possible that the direct activation of the D_1 receptor, but not of D_2 receptor, produces PPI deficits in mice.

Similar to the inconsistencies in rodents, the effect of DA agonists in healthy human beings is also unclear. Amphetamine and the D_2 agonist bromocriptine were, on one hand, found to reduce PPI *(Abduljawad et al. 1998, 1999; Hutchison and Swift 1999)* but on the other hand, found to have no effects (bromocriptine, amphetamine or pergolide; *Swerdlow et al. 2002). Bitsios et al. 2005a* proposes that baseline PPI is an important determinant of the effects of DA agonists on PPI in healthy subjects. PPI-disruptive effects of amphetamine and bromocriptine can prevented by pretreatment with DA antagonists, such as haloperidol *(Abduljawad et al. 1998)*.

It is suggested that apomorphine, amphetamine as well as bromocriptine, primarily disrupt PPI by activation at D_2 receptors *(Geyer et al. 2001).* This conclusion is also in line with *Ralph et al. 1999* reporting that the D_2 knockout mouse was resistant to the PPI-disruptive effects of d-amphetamine, whereas mice lacking D_1, D_3 or D_4 receptors were, in contrast, susceptible to the PPI-disruptive effects of amphetamine *(Ralph et al. 1999; Ralph-Williams et al. 2002)*. Hence, it seems that only the D_2 receptors contribute to sensorimotor gating deficits induced by presynaptic dopaminergic activation.

Koch and Schnitzler 1997 and *Koch 1999* presented models of animal studies, in which a hypofunction of prefronto-cortical DA (i.e. by administering DA antagonists or DA-depleting agents) leads to excessive DA release in the nucleus accumbens which, in turn, reduces PPI in rats. This model is in accordance with suggestions that elevating mesolimbic dopaminergic activity reduces PPI in rats *(Swerdlow et al. 2001a).*

The effect of DA antagonists on PPI, however, is inconsistent in rodents. DA antagonists were demonstrated to reduce PPI (*Swerdlow et al. 2005b*; *Ellenbroek et al. 1996; Zavitsanou et al. 1999; Stevenson and Gratton 2004*), to potentiate PPI (*Schwarzkopf et al. 1996*; *Stevenson and Gratton 2004)* and to have no effect on PPI (*Bast et al. 2002)*. These discrepancies might be due to strain differences, differences in experimental conditions, in doses and in the neural target. Likewise, the effect of DA antagonists on PPI in healthy human beings are unclear. *Abduljawad et al. 1998* reported that haloperidol, a D_2–family antagonist, elicited a small, but nevertheless significant, reduction in PPI. This finding is consistent with *Oranje et al. 2004* and *Kumari et al. 1998* but could not be replicated by *Abduljawad et al. 1999.*

1.3.2. The Serotonin PPI Model

Dysfunction of the serotonin system has been suggested to be important in the neurobiology of schizophrenia. Hence, a second PPI model derives from the fact that PPI in rats is disrupted by either direct serotonin agonists such as the hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), a $5HT_{2A}$ receptor agonist *(Sipes and Geyer 1994, 1997; Padich et al. 1996)* or serotonin-releasing agents, such as the substituted amphetamine methylene-dioxymethamphetamine (MDMA) *(Vollenweider et al. 1999)* and N-ethyl-3,4-methylenedioxyamphetamine (MDEA) *(Mansbach et al. 1989).* The PPI-disruptive effect of DOI was reversed by the selective $5HT_{2A}$ receptor antagonist M100907, confirming that DOI exerts its PPI-disruptive effect by acting on $5HT_{2A}$ receptors (*Geyer et al. 2001).* The typical antipsychotic haloperidol does not appear to be reliably effective in reducing DOI-induced PPI deficits *(Geyer et al. 2001).* Inconsistent effects were observed with $5HT_{1A}$ receptor agonists in rats. They disrupt PPI in Wistar rats and in Sprague-Dawley rats, but not in Fischer F344 rats *(Geyer et al. 2001.* In contrast, in mice, $5HT_{1A}$ receptor agonist robustly *increase* PPI *(Dulawa et al. 2000).*

Many studies have also failed to identify consistent effects of psilocybin, a mixed $5HT_{1/2}$ receptor agonist, on PPI in rats or have not been reported to influence PPI in rodents *(Braff et al. 2001)*. In human beings, however, psilocybin *(Gouzoulis-Mayfrank et al. 1998)* and MDMA *(Vollenweider et al. 1999)* increase PPI slightly.

1.3.3. The NMDA Antagonist PPI Model

The PPI model that shows the greatest potential to provide insight into the unique effects of atypical rather than typical antipsychotics is the NMDA antagonist model (Geyer and

Ellenbroek 2003). Noncompetitive NMDA antagonists - phencyclidine (PCP), dizocilpine (Mansbach and Geyer 1989; Bakshi and Geyer 1998), and ketamine (Mansbach and Geyer, 1991) produce robust deficits in PPI in rats, mice (Dulawa and Geyer 1996) or infrahuman primates (Linn and Javitt, 2001). Atypical antipsychotics such as clozapine (Bakshi et al. 1994), olanzapine (Bakshi and Geyer 1995) and quetiapine (Swerdlow et al. 1996) attenuate them. These medications bind to $5HT_{2A}$ receptors. Varty et al. 1999 suggested that serotonin and glutamate interact, by means of this $5HT_{2A}$ receptor, in modulating PPI. Furthermore, the reduction in NMDA antagonist induced PPI deficits following atypical antipsychotics, likely reflect interaction within the complex forebrain circuitry that modulates PPI (Swerdlow et al. 2001a). It is not clear whether risperidone can antagonise the PPI-disruptive effect of NMDA-antagonists. In rats it seems that its positive effect is strain-dependent (reviewed by Geyer et al. 2001). In contrast to the second generations antipsychotics discussed above, first generation antipsychotics, such as haloperidol, fail to reduce the effects of PCP and other NMDA antagonists on PPI in rats (Geyer et al. 2001). Thus, it was suggested that the NMDA antagonist induced disruption of PPI would be an interesting model for detecting atypical antipsychotics rather than typical antipsychotics (Geyer and Ellenbroek 2003).

As already observed with DA agonist in human beings, NMDA antagonists also produce inconsistent results in healthy volunteers. Van Berckel et al. 1998 failed to detect an effect of a low dose of ketamine in healthy volunteers. However, follow-up studies showed that a higher dose of ketamine increases PPI, rather than disrupting it in rodents (Abel et al. 2003). This finding is also in line with the report of Duncan et al. 2001 administering the same dose. It may be that these discrepancies between animal and human literature are due to the use of inappropriate stimulus parameters, doses, and/or time courses.

1.3.4. The Isolation Induced PPI Model

A promising alternative to these pharmacological models can be seen in the study of non-invasive developmental models for deficient PPI in animals, an approach that has received considerable attention. Although pharmacological approaches that alter PPI, help to identify relevant neural substrates, they do not assess environmental or developmental contributions to PPI deficits. These non-pharmacological models are typically based on the neurodevelopmental hypothesis of schizophrenia, which suggests that an abnormal development of the brain connectivity could be one of the mechanisms implicated in the genesis of schizophrenia *(Weinberger 1986; Ellenbroek et al. 1998)*. Investigators have incorporated this developmental perspective into animal models of sensorimotor gating deficits in schizophrenia. One such approach is isolation rearing of rats.

Rats that are reared in single housing from weaning through adulthood exhibit deficient PPI compared with socially reared controls in adulthood *(Cilia et al. 2001, 2005; Powell and Geyer 2002; Geyer et al. 1993)*. The deficits reach significance during or after puberty, but not earlier *(Bakshi and Geyer 1999)* as commonly seen in patients with schizophrenia. Isolation-rearing-induced deficits in PPI are reversed by treatment with either typical (e.g. haloperidol - *Varty and Higgins 1995)* or atypical antipsychotics, including olanzapine, clozapine, and the putative antipsychotic M100907 *(Geyer et al. 2001)*. Thus, the isolation-rearing paradigm may provide a non-pharmacological, neurodevelopmental approach inducing PPI deficits, that are sensitive to both typical and atypical antipsychotic medications *(Geyer et al. 2001)*.

2. PPI IN HEALTHY VOLUNTEERS AND SCHIZOPHRENIC PATIENTS

2.1. Parameters that Could Contribute to PPI Variability

PPI is influenced by several parameters in healthy volunteers and schizophrenia patients. Nicotine is one of various pharmacological agents that modify PPI. In healthy human smokers, PPI was shown to be increased after smoking compared to a smoking deprived condition *(Kumari et al. 1996; della Casa et al. 1998; Duncan et al. 2001)*. However, other researchers observed that PPI was decreased shortly after smoking *(Hutchison et al. 2000)*. Moreover, personality influences PPI performance in healthy volunteers *(Simons and Giardina 1992; Hutchison et al. 1999b)*. Other sources of variance that could contribute to alterations in the amount of PPI are genetic predispositions, sex differences, and experimental conditions.

2.1.1. Different Genetic Predispositions

Anokhin et al. 2003 first reported that genes influence PPI in human subjects. Examining healthy female twins, they found that PPI showed significant heritability, and suggested that over 50% of PPI variance in their sample can be attributed to genetic factors. Further evidence for a genetic contribution to PPI, comes from a recent study investigating startle response measures in Caucasian and Asian subjects. *Swerdlow et al. 2005a* observed that PPI was significantly greater in Asian versus Caucasian subjects at 60 ms and 120 ms prepulse intervals.

In the animal literature, it is long been known, that there are strain-related differences in the dopaminergic modulation of PPI *(Rigdon 1990)*. These strain differences of apomorphine effects on PPI might reflect genetically based differences in sensitivity to D_1 versus D_2 receptor stimulation *(Swerdlow et al. 2000)*. Moreover, the first direct evidence for a genetic contribution to PPI in the absence of drug treatments was the report that rats selectively bred on the basis of behavioral responses to apomorphine differed at baseline in their levels of PPI *(Ellenbroek et al. 1995)*. It is therefore important to carefully choose individuals with similar genetic background.

2.1.2. Sex Differences

Women typically have lower PPI than men *(Swerdlow et al. 1993a, 1999; della Casa et al. 1998; Kumari et al. 2004)*. These findings are also in line with animal literature indicating that PPI is greater in male rats than in female rats *(Koch 1999; Lehmann et al. 1999; Weiss et al. 2001). Swerdlow et al. 1997* proposed that progesterone and estrogen interacted with brain substrates underlying the processes of sensorimotor gating to modulate PPI. Women have reduced PPI in the mid-luteal phase of the menstrual cycle; i.e. during peaks of oestrogen and progesterone. Thus PPI undergoes changes across the menstrual cycle. In addition, a recent study performed by *Kumari et al. 2004* showed that women with schizophrenia did not differ in PPI from healthy women, whereas men with schizophrenia showed less PPI compared to healthy men. However, this finding is not in accordance with a follow-up study by *Braff et al. 2005,* who compared female medicated schizophrenia patients with normal comparison subjects. They found that female schizophrenia patients exhibited lower levels of PPI. This disparity in results might be due to the fact that normal subjects in Kumari's study

demonstrated less PPI than female controls in Braff's study. All in all, it is important to control for sex and phase of the menstrual cycle in PPI studies.

2.1.3. Experimental Conditions

PPI is extremely sensitive to experimental conditions and stimulus parameters. It is particularly important to identify experimental conditions that allow replicable effects of neurobiological interventions.

2.1.3.1. Attentional Manipulations

Although PPI is thought to be automatic, several studies have shown that by directing attention toward the prepulse, PPI can be enhanced *(Dawson et al. 1993; Filion et al. 1993; Hazlett et al. 1998)*. This is particularly the case with longer prepulse intervals (i.e. 120 ms). Further evidence for attention to influence PPI is given by the study of *Heekeren et al. 2004.* These researchers asked the participants to direct attention to the prepulse *and* the startle pulse and observed that attention enhanced PPI at the lead interval of 240 ms, but not at the lead interval of 100 ms. Hence, attentional mechanisms can only influence PPI, when there is enough time. However, prepulse intervals less than 120 ms, thought to represent automatic processing, cannot be influenced *(Dawson et al. 1993; Filion et al. 1993)*. These findings underscore one strength of the PPI paradigm; it appears to bridge automatic and voluntary processing. It is very likely that different neuroanatomical substrates regulate attentional versus automatic forms of PPI.

2.1.3.2. Is PPI Attenuated in Healthy Subjects in Longitudinal Studies?

There are conflicting reports regarding changes in PPI across test sessions. One group recently reported that PPI may be significantly reduced across three monthly test sessions in healthy volunteers *(Quednow et al. 2005a)*. In two studies *(Quednow et al. 2005ab),* they observed a significant decrease of PPI across sessions within their control group and suggested that PPI exhibits long-term attenuation. This result is in contrast to other studies in control subjects. For example, *Abel et al. 1998* found PPI to be stable when tested three times in one day as did two other groups who tested PPI three times at monthly intervals *(Cadenhead et al. 1999; Ludewig et al. 2002)* and one group who retested normal subjects at an interval of 2-3 weeks *(Meincke et al. 2004)*. In addition, Ludewig found PPI to be stable in clinically stable schizophrenia patients, as well as in control subjects, tested at monthly intervals *(Ludewig et al. 2002)*. Thus, the majority of the evidence indicates that PPI does not change over repeated testing in the absence of changes in clinical state. This disparity in results may be due to the startle paradigm used by *Quednow et al. 2005ab* - they used considerably more PP trials within a single condition compared with the previous studies. However, a test-retesting of healthy volunteers in longitudinal studies is recommended, as the potentiation of PPI regarding the antipsychotic might only be revealed by a comparison with a control group *(Quednow et al. 2005b)*. It should be noted, however, that *Meincke et al. 2004* showed that clinical improvement in schizophrenia patients was associated with concomitant improvement in PPI in a paradigm that yielded stable levels of PPI across testing in control subjects.

2.1.3.3. Background Noise, Prepulse Type, EMG Measured from the Left or Right Eye

Often in the literature, results of studies using different background noise, different prepulse types and EMG measured from the left or right eye are compared without considering that these different experimental conditions might have an impact on PPI results. One of the earliest demonstrations of this difference was conducted in rats. *Davis et al. 1990* demonstrated that the PPI-disruptive effects of the dopamine agonist apomorphine were only evident when the same intensity prepulse was used in the presence of controlled background noise than in the presence of only a very low ambient noise. That is, the sensitivity of the PPI paradigm for demonstrating drug effects in rats can be increased by providing an appropriate level of controlled background noise. Of course, no studies can be conducted in the absence of background noise, as some ambient noise is always present. The only source of variance between studies is whether or not a constant level of background masking noise is supplied by the experimenter or whether the background is left uncontrolled and external noises are left un-masked. In humans as in animals, different background noise levels might generate different levels of PPI *(Hsieh et al. 2005)*. Prepulses arising from a lower level (54 dB) ambient background *(Wynn et al. 2000)* induced more powerful PPI than prepulses arising from continuous 70 dB white noise background (*Braff et al. 1978, 1992; Grillon et al. 1992; Cadenhead et al. 1993, 2000; Kumari et al. 2000; Ludewig et al. 2003*. Thus, *Wynn et al. 2004* might have found comparable PPI in schizophrenia patients and in healthy comparison subjects primarily due to the fact that they used no controlled level of background noise. Moreover, they might have found PPI differences when recording EMG from the right eye, as schizophrenia has been theorized as a disorder of left hemisphere dysfunction (*Gruzelier 1999)*.

Furthermore, prepulses can be either pure tones *(Duncan et al. 2003)* or consist of white noise *(Kumari et al. 1999)*. Discrete white noise prepulses elicited more PPI than either continuous white noise prepulses, discrete tone prepulses or continuous tone prepulses in both normal comparison subjects *(Wynn et al. 2000)* and schizophrenia patients *(Braff et al. 2001)*. Most studies measure PPI with white noise prepulses and white noise startle stimuli whereas only few studies use pure tone prepulses and pure tone startle stimuli *(Parwani et al. 2000; Weike et al. 2000; Oranje et al. 2002; Duncan et al. 2003)*.

Taken together, these fundamental paradigmatic influences account for part of the variance in divergent reports of PPI deficits in normal and schizophrenia subjects.

2.2. Deficient Prepulse Inhibition - A Potential Marker for Schizophrenia

Deficits in PPI have been proposed as a biological marker of information processing abnormalities in schizophrenia *(Geyer and Braff 1987; Nuechterlein et al. 1994)* and are assumed to reflect a core deficit in schizophrenia. PPI deficits are best observable at short lead intervals between approximately 50 ms and 100 ms *(Leumann et al. 2002)*. However, PPI deficits are not specific to schizophrenia as they also occur in other disorders such as Huntington's Chorea, Tourette Syndrome, non-epileptic seizures, enuresis *(Braff et al. 2001),* bipolar mania *(Perry et al. 2001),* and panic disorder *(Ludewig et al. 2002)*. PPI as a marker for schizophrenia could encompass both trait and state components.

The trait component is supported by findings of PPI deficits in relatives of schizophrenia patients and unmedicated individuals with schizotypal personality disorder, which is psychopathologically and genetically related to schizophrenia *(Cadenhead et al. 1993; 2000; Kumari et al. 2005a)*. PPI deficits were also reported in chronic, unmedicated (*Weike et al. 2000; Perry et al. 2002; Duncan et al. 2003)* as well as in drug-naive patients (*Mackeprang et al. 2002; Ludewig et al. 2003)*. Furthermore, PPI deficits in (medicated) patients were shown by *Braff et al. 1978.* Several other follow-up studies *(Braff et al. 1992; Bolino et al. 1992; Grillon et al. 1992)* replicated these findings. Based on these studies, the reduction in PPI has often been regarded as a fundamental trait or vulnerability marker of schizophrenia spectrum disorders related to genetic and/or neurodevelopmental factors that predispose individuals to develop this disorder.

The state component of this disorder can be seen in the fact that medication and positive symptoms seem to influence PPI in schizophrenia patients *(Braff et al. 2001)*. For example, clinical improvement in antipsychotic-treated patients with schizophrenia has been reported in longitudinal studies *(Weike et al. 2000; Meincke et al. 2004)*. These findings of relatively normal PPI associated with atypical antipsychotic treatments and relationships between PPI and psychometric measures suggest that PPI may involve both trait and state linked information-processing disturbances in schizophrenia *(Meincke et al. 2001, 2004; Ludewig et al. 2003)*

2.2.1. Parameters that Influence PPI Deficits in Schizophrenic Patients

2.2.1.1. PPI Deficits in Schizophrenia Patients may be Reversed by Antipsychotics

According to animal data, neuroleptic medication should have an effect on PPI deficits in humans. *Weike et al. 2000* found PPI impairment only in five unmedicated subjects with schizophrenia, compared to healthy controls, whereas the medicated patients (atypical and typical) did not differ from the controls. These findings suggest that medication status might be important in modulating the amount of PPI in schizophrenia patients in a passive PPI paradigm. Moreover, it is suggested that typical antipsychotics, as they were used in *Kumari et al. 1999, 2000, 2002b; Oranje et al. 2002; Mackeprang et al. 2002* do not improve PPI, whereas atypical antipsychotics are believed to have PPI-restoring effects in schizophrenia patients. Atypical antipsychotics share common features, such as broader receptor profiles and/or low affinity at the D_2 receptor *(Kapur et al. 2001)* that might influence their PPI enhancing effects. Patients treated with atypical antipsychotics (*Kumari et al. 1999; Oranje et al. 2002; Leumann et al. 2002; Quednow et al. 2005b)* had comparable PPI as controls. *Kumari et al. 1999* tested two groups of stable schizophrenia patients with similar symptom scores. The authors found that patients treated with clozapine had higher levels of PPI (30 and 60 ms) than patients treated with typical antipsychotic and comparable PPI as healthy comparison subjects in all lead-intervals. These findings were confirmed by a later study by the same group (*Kumari et al. 2002b)*. Schizophrenic patients treated with typical antipsychotics displayed deficient PPI with 30 ms and 60 ms prepulse trials, whereas patients stable on risperidone did not differ from healthy subjects for PPI in any prepulse intervals. These findings are also in line with the study performed by *Oranje et al. 2002*. The PPI ability in schizophrenic patients treated with typical antipsychotics differed significantly from that in healthy control subjects, while patients treated with atypical antipsychotics, particularly clozapine, exhibited similar sensorimotor gating as healthy volunteers. Clozapine

may thus normalize preattentive information processing functions. Neuropsychological studies have frequently found that clozapine is unique in its ability to improve cognitive function in patients with schizophrenia *(Lee et al. 1994).*

Moreover, *Kumari et al. 2005b* examined patients medicated with either atypical or typical antipsychotics in a passive PPI paradigm. As expected, patients overall had less PPI than healthy controls particularly in the 60 ms prepulse condition but not in 120 ms, where all three groups were comparable. The patients receiving typical antipsychotics had reduced PPI in pp30 compared to patients on atypical medication and healthy controls.

As most of the studies mentioned above applied between-subject designs comparing two groups of patients, they did not control for the neurobiological differences between the groups. It is necessary to examine the same patient group before and after antipsychotic treatment and to compare their performance to healthy controls with a within-between subject design. This approach would allow one to observe a possible beneficial effect of atypical vs. typical medication related to a baseline value (drug-free, drug-naive). There are three studies using such a longitudinal design: *Mackeprang et al. 2002, Duncan et al. 2003a* and *Quednow et al. 2005b*. Neither Mackeprang nor Duncan found any effect of typical or atypical antipsychotic medication on PPI. Mackeprang's group reported, on one hand, that drug-naive schizophrenic patients had severe PPI deficits and, on the other hand, failed to demonstrate any effect of the typical antipsychotic zuclopenthixol and the atypical drug risperidone on the deficit after three months treatment. However, the effect of risperidone on PPI is a matter of debate. Since risperidone has inconsistent and strain-dependent effects on the PPI-disruptive effects of NMDA antagonists, it is not like other atypical antipsychotics in animal models *(Geyer et al. 2001; Varty and Higgins 1995). Duncan et al. 2003* used both a between-group and a within-subjects test-retest design and reported comparable PPI between subjects on atypical (olanzapine), typical (haloperidol) or on acutely decompensated off medication in either design. Impaired gating can thus persist despite symptomatic improvements associated with antipsychotic medication. In contrast to the above-mentioned studies, *Quednow et al. 2005b* found, that both amisulpride and olanzapine reverse PPI deficits. They examined two patient groups acutely ill, and a control group at baseline (one week after the beginning of treatment with olanzapine or amisulpride), one month and two months after amisulpride and olanzapine treatment. At baseline, they found significant lower PPI (only pp120 was tested) in medicated patients, that was improved after two months. Schizophrenic patients overall did not differ from healthy controls anymore. Both olanzapine and amisulpride were effective in abolishing the initial sensorimotor gating deficit as well as in alleviating negative and positive symptoms. Quednow suggested that D_2/D_3 blockade might be responsible for the PPI-restoring effect of the tested substances, because both medications share high affinity to D_2/D_3 receptors. This conclusion is inconsistent, however, with the frequent demonstrations of deficient PPI in schizophrenia patients treated with a variety of typical antipsychotics having substantial antagonist activity at D_2/D_3-dopamine receptors *(Braff et al. 1978, 1992, 2001).* Another explanation for the observed PPI-restoring effect of amisulpride could be its fast dissociation from the D_2 receptor, which it shares with all other atypical antipsychotics *(Kapur and Seeman 2001)*. Other studies, nevertheless (*Duncan et al. 2003ab; Mackeprang et al. 2002; Parwani et al. 2000; Perry et al. 2002),* do not report an effect of antipsychotic medication - whether typical or atypical - on PPI in schizophrenia patients. *Parwani et al. 2000* did not detect differences in PPI between unmedicated schizophrenic subjects and those on antipsychotics. In line with this report, *Perry et al. 2002* found equivalent PPI deficits in

acutely hospitalised subjects with schizophrenia whether they were on medication (including both atypicals and typicals) or unmedicated for one week prior to testing.

Taken together, the clinical literature leaves the issue of treatment status effect on PPI unresolved. It seems that PPI increases from unmedicated patients through those medicated with typical antipsychotics to patients medicated with atypical antipsychotics *(Kumari et al. 2005ab).* Moreover, discrepancies across studies and in schizophrenic patients could partly be explained that "compensatory changes at downstream levels of the PPI circuitry might at least partially restore normal levels of PPI" (*Swerdlow et al. 2001a).*

2.2.1.2. Anticholinergic Drugs Impair PPI

Kumari et al. 2003b reported that in patients with schizophrenia given risperidone or quetiapine, the anticholinergic drug procyclidine, significantly impaired PPI compared to placebo. It is thus suggested, that the use of anticholinergics needs to be carefully considered in studies of PPI.

2.2.1.3. Symptom Scores Appear to be Related to PPI

The PPI literature to date is inconclusive regarding whether impaired PPI is a stable abnormality across clinical conditions or is linked to the subjects being acutely ill or unmedicated. Thus, many studies have searched for correlations between symptom severity and the degree of PPI impairment.

Meincke et al. 2004b found that medicated schizophrenia patients in the acute psychotic state displayed PPI deficits (particularly visible in the 100 ms lead interval, but not in the 30 ms interval), whereas they had normal PPI assessed after improvement of symptoms (2-3 weeks after baseline testing). This group therefore suggested that impairments of PPI in schizophrenic patients were state dependent. Moreover, this group reported significant correlations between PPI deficits and formal thought disorder and bizarre behaviour in acutely psychotic patients but not in remitted patients. These data are in line with other reports of impairments that preattentive information processing and psychotic symptoms are related. *Weike et al. 2000* and *Braff et al. 1999* demonstrated moderate associations between PPI deficits and positive symptoms, *Karper et al. 1996* found an association with distractibility and *Perry and Braff 1994* and *Perry et al. 1999* reported a linkage with formal thought disorder. Furthermore, *Perry et al. 1999* suggested that PPI impairments were correlated with "perceptual inaccuracy and disordered cognitive reasoning" and demonstrated that the schizophrenia patients with the lowest levels of PPI exhibited the poorest performance on thought disturbance indices. This finding is in accordance with *Dawson et al. 2000,* who reported that impaired PPI to attended prepulses was significantly correlated with higher levels of unusual thought content, conceptual disorganization and suspiciousness. Additionally, *Perry et al. 2002* proposed that antipsychotic medication does not have an effect on PPI during severe psychotic states. They assessed two groups of schizophrenia patients - both acutely psychotic at the time of PPI testing, one of them receiving medication and the other one unmedicated - as well as a group of healthy subjects in order to compare the contribution of symptom level versus medication status to PPI. Perry did not note PPI differences between those who were unmedicated at the time of measurement and those who had been receiving medication.

However, it remains unclear whether improved PPI findings are due to the direct pharmacological impact of antipsychotics or secondary to antipsychotic-related symptom reduction.

2.2.1.4. Nicotine Consume in Schizophrenia Patients

The incidence of smoking in the mentally ill, particularly in schizophrenia is much higher than in the general population. *Dalack et al. 1998* documented that 70-90% of schizophrenic patients smoke. Based on the idea that nicotine facilitates information processing and attention, several recent studies have investigated the effect of nicotine on PPI.

Kumari et al. 2001 showed that chronic patients, who smoked 10 min before startle reflex measurement, had significantly higher PPI than patients who were smokers, but did not smoke 10 min before testing. Moreover, chronic nicotine consumption might influence pp30 and pp60 (*Kumari et al. 2001)*. Chronic intake of nicotine is also thought to be a self-attempt to correct for sensorimotor deficits *(Kumari et al. 2001)*. Moreover, *Cadenhead et al. 2000* found that smokers within the groups of schizophrenia patients, schizophrenia relatives and schizotypal persons had greater PPI than non-smokers.

It may be important to allow patients to smoke normally. A preliminary report by *Termine et al. 2003* found a trend for impaired PPI after smoking abstinence in chronic, medicated patients, which was not as obvious in healthy smokers. Thus, PPI in medicated patients might be reduced due to deprivation. In *Mackeprang et al. 2002* study, patients and controls also had to stop smoking four hours before startle examination, which could have led to a differential withdrawal condition for the patients normally smoking 20 cigarettes per day versus the controls who likely smoked less on average. It therefore appears as if smoking and smoking-deprivation would exert differential effects in schizophrenic smokers and healthy smokers. Indeed, *Olincy et al. 1997* observed that schizophrenic smokers extract more nicotine from each cigarette, a behaviour that is thought to more effectively activate low-affinity α-7-nicotinic receptors in addition to the high affinity receptors in the brain, relative to healthy smokers. However, it remains questionable whether and how far these low-affinity α-7-nicotinic receptors are also involved in the regulation of PPI *(Schreiber et al. 2002)*.

Taken together, nicotine is thought to modulate PPI. Hence, it is important to match patients and controls regarding the amount of cigarettes smoked per day.

2.2.1.5. Age at Onset of Schizophrenia

One study suggested that the patients' age at schizophrenia onset was related to their PPI performance *(Kumari et al. 2000)*. In this study, early onset of schizophrenia co-varied with less pronounced PPI. Furthermore, Kumari and colleagues found that early onset of illness was associated with PPI deficits, which did not improve with atypical antipsychotic treatment as it did in those patients with later onset. They suggested that "age of illness onset may be a moderation variable in the disruption of prepulse inhibition".

2.3. Unpredictable PPI Variance among Healthy Subjects Complicates the Interpretation of Findings of Deficient PPI in Schizophrenic Patients

Generally, a between-group analysis examines whether the amount of PPI varies between schizophrenia patients and healthy control subjects. That is, the PPI values of the control group also determine whether or not the amount of PPI in the schizophrenia patients is relatively deficient *(Hamm et al. 2001)*. *Hamm et al*. evaluated the existing literature on PPI findings in schizophrenic patients and healthy controls and observed that studies reporting deficient PPI in schizophrenic patients had "better" controls than studies not reporting significant PPI differences between these groups. Thus, there was an unexpected source of unwanted variability among the control subjects. However, *Hamm et al.* found remarkably consistent PPI in schizophrenia patients across all studies. Medicated schizophrenia patients overall showed around 20% less PPI than healthy control subjects. Moreover, the data clearly revealed that both medicated schizophrenia patients and healthy controls consistently showed the typical pattern of increased PPI with increasing lead intervals from 30 to 60 to 120 ms in the within group comparisons.

Interestingly, two studies performed by *Braff et al. 2005* and *Kumari et al. 2004* investigated the PPI ability in female schizophrenic patients and control subjects. Kumari did not find PPI deficits in control subjects in contrast to Braff's group. The most striking difference between the studies, as noted by Braff, was that normal control subjects tested by *Kumari et al. 2004* showed less PPI (only 32% PPI vs. 67% PPI in Braff's cohort at the 120 ms interstimulus interval), which may have induced a floor effect, from which it was difficult to detect schizophrenia patients deficits.

3. RELATIONSHIPS BETWEEN COGNITION AND PPI

Patients with schizophrenia spectrum disorders have deficits in inhibitory functioning that lead to difficulties in inhibiting responses to internal and external stimuli. This might account for observed attention and cognitive abnormalities in schizophrenics *(Venables 1963)*. These abnormalities may be related to impairments in sensorimotor gating. Such a correlation links the fundamental neurophysiological phenomenon of PPI to higher level cognitive operation. Several studies have investigated the relationship between PPI and cognitive deficits in schizophrenia.

For example, *Butler et al. 1991* found that schizophrenic subjects with poorer Wisconsin Card Sort Test (WCST) performance had reduced PPI compared to those subjects with better WCST performance. The WCST putatively taps impaired frontal lobe functioning associated with increased mesolimbic dopamine tone. Such an increased subcortical dopamine tone is also thought to lead to decreased levels of PPI. Thus the relationship between the WCST and PPI deficits in schizophrenia may be based on common neurobiological substrates *(Braff et al. 1995)*. Furthermore, *Karper et al. 1996* showed a relationship between neuropsychologically assessed disturbances in attention (i.e. modified Continuous Performance Task) and a reduction of PPI in schizophrenics. This group reported that lower PPI is associated with greater distractibility in schizophrenia patients. Another study performed by *Bitsios et al. 2005b* found a negative association between overall %PPI and the

interference scores on the Stroop task and suggested cautiously, that subjects with the best cognitive inhibition and selective attention tend to have more PPI. Moreover, the same study found a relationship between PPI and some measures of the SOC (Stockings of Cambridge), a planning task, but did not report an association between PPI and the RVP (Rapid Visual Information Processing Task) measuring selective and sustained attention. Additionally, *Wynn et al. 2005* demonstrated an association between PPI and social cognition in schizophrenia. Patients who had reduced PPI tended to perform poorer on a videotape-based measure of social perception; i.e. patients who were better able to gate out competing stimuli were also better at detecting relevant social cues. These findings suggest that deficits in early information processing can negatively impact high-level processes necessary for normal social perception and social functioning. However, these results have to be taken cautiously, because this group measured EMG from the left eye and did not use a controlled background noise.

Further evidence for a relationship of PPI and cognition comes from the medication side. Atypical antipsychotics seem to influence positively cognitive deficits in schizophrenia patients *(Keefe et al. 1999),* which supports the relationship between alterations in PPI and cognitive performance.

According to Mr. Hagan at the MATRICS-meeting (Measurement and Treatment Research to Improve Cognition in Schizophrenia) in September 2004, we still need to understand more extensively as to how PPI relates to cognitive deficits, given the rich pharmacological and methodological data set of PPI studies as well as its good face validity, construct validity and predictability *(Swerdlow et al. 1994).* For this purpose, relationships to deficits in the seven cognitive domains (Working memory, attention/vigilance and pre-attentive processing, verbal learning and memory, visual learning and memory, speed of processing, reasoning and problem solving and social cognition), as identified by the MATRICS Program (see www.matrics.ucla.edu), are of particular relevance.

4. MODEL PSYCHOSES REFLECT AN ATTEMPT TO MODEL A SCHIZOPHRENIA-LIKE STATE IN HEALTHY VOLUNTEERS

After the introduction of antipsychotic medications, it seemed that schizophrenia was due to abnormal neurotransmission, because the new drugs were effective in reducing symptoms. More evidence for these neurotransmitter hypotheses comes from model psychosis in humans. Drugs, that alter glutamatergic (i.e. ketamine), dopaminergic (i.e. amphetamine) and serotonergic (i.e. psilocybin) transmission in healthy volunteers can induce psychotic symptoms and alter PPI.

4.1. Dopaminergic Compounds

Amphetamine administration leads to *(Kapur 2003)* positive schizophrenia-like symptoms with obsessive and compulsive behavioural and cognitive activities, hallucinations, and paranoid delusions *(Ellinwood et al. 1973).* This is in line with the dopamine synthesis, suggesting that dopaminergic overactivity in the mesolimbic area could be linked to positive

symptoms *(Davis et al. 1991)*. Moreover, there is some evidence that "patients with psychostimulant-induced psychosis display *both positive and negative symptoms* as well as *cognitive abnormalities*" *(Srisurapanont et al. 2003)*. Moreover, *Hutchison and Swift 1999* reported that a 20 mg oral dose of amphetamine disrupted PPI in normal, non-smoking human subjects, as predicted from animal studies. Amphetamine administration in drug-free schizophrenia patients was also associated with transient emergence or worsening of positive symptoms *(Abi-Dargham et al. 1998)*.

4.2. Serotoninergic Compounds

Hallucinogenic agents such as mescaline, psilocybin, LSD and DOI are known to generate schizophrenia-like positive symptoms and ego-disturbances in healthy volunteers. All of them are chemically similar to serotonin and are supposed to mediate their psychological effect in humans through action at $5HT_{2A}$-receptors (*Nichols 2004)*. *Gouzoulis-Mayfrank et al. 1998* observed that psilocybin, a $5HT_{2A}$-agonist triggers symptoms of a "pre-psychotic state" such as perceptual alterations, cognitive disturbances and mood shifts while it tended to increase PPI. The authors proposed that this enhanced sensorimotor gating would mirror the "patient's effort to compensate the flooding with sensory overload" and suggested that healthy volunteers under psilocybin appeared to be more able to effectively inhibit or gate irrelevant information. This finding is in conflict to animal literature suggesting that hallucinogens, such as DOI, disrupt PPI in rats *(Sipes and Geyer 1994)*. Gouzoulis-Mayfrank further explained that these discrepant findings might depend on the dosage; high dosages in animals may mimic severe psychosis (e.g. hallucinations and delusions) as experienced by decompensated patients, whereas low dosages - as used by the authors - rather trigger "prepsychotic" symptoms.

Similarly, while serotonin releasers such as MDMA disrupt PPI in rats *(Mansbach et al. 1989; Kehne et al. 1992)* preliminary studies suggest that opposite effects occur in humans. *Vollenweider et al. 1999* directly compared the effects of MDMA in rats and healthy human volunteers on PPI. MDMA reduced PPI in rats, and increased PPI in humans. This result points towards a species-specific difference in the mechanism of action of MDMA or in the behavioural expression of a similar pharmacological effect.

4.3. Glutamatergic Compounds

Ketamine induces transient states characterised by both positive *and* negative symptoms *(Malhotra et al. 1996; Adler et al. 1999)* as well as cognitive impairment *(Krystal et al. 1998; Umbricht et al. 2000)* in healthy volunteers. It also triggers a resurgence of symptoms in remitted schizophrenic patients *(Lahti et al. 1995; Malhotra et al.1997)*. The effect of ketamine on PPI in human beings, however, is inconsistent. *Karper et al. 1994* reported that ketamine disrupted PPI in humans. *Van Berckel et al. 1998* suggested that it has no effect on PPI in humans and *Duncan et al. 2001* and *Abel et al. 2003* observed that ketamine increased PPI in healthy humans. Duncan found that 0.5 mg/kg ketamine generated profound negative symptoms (increases in dissociative and negative symptoms) and less evident positive symptoms as well as significantly enhanced PPI in pp30 and elevated PPI in pp60 and pp120

in healthy volunteers. Abel observed the same phenomenon (increased PPI in pp30) in healthy male non-smoking volunteers and a relative lack of positive symptoms. Both studies traced this back to the low dose. In contrast to human studies, ketamine disrupts PPI in rats *(Mansbach and Geyer 1991)*.

5. CONCLUSION

The PPI paradigm is a useful translational model for measuring preattentive information processing, as the neuroanatomical structures and neurotransmitters are similar across species. Lesions, pharmacological interventions, and genetic or early environmental manipulations can cause alterations in PPI. PPI deficits induced by these multiple manipulations are thought to serve as models for detecting new antipsychotics.

First, future research on PPI performance in schizophrenia and healthy subjects should focus on the delineation of those factors that influence PPI performance within each subject population. Studies should carefully investigate the effects of various antipsychotic medications (atypical vs. typical) and psychopathology in schizophrenia patients. This should preferably be done using longitudinal designs. In addition, more studies are needed that explore the variability in PPI performance in healthy controls and address the question, whether this variability contributes to discrepant findings across studies comparing schizophrenia patients and healthy controls.

Second, all participants must be matched regarding sex, stage of the menstrual cycle, and smoking habits (e.g. smoking deprivation in schizophrenic patients might confound PPI performance).

Third, experimental conditions are of great importance, as they are known to influence PPI performance. Most studies comparing schizophrenia patients and healthy volunteers use white noise prepulses preceding the startle stimulus for 30, 60, or 120 ms and included a controlled white noise background. Moreover, they measure the EMG binaurally or from the right eye.

Fourth, as PPI is supposed to measure unattended preattentive stimuli processing, relationships between higher cognitive functions, such as tasks involving attention, and PPI merit further investigations.

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Chapter 11

PSYCHOTIC SYMPTOMS AND THE PREDICTION OF VIOLENCE IN SCHIZOPHRENIC PATIENTS

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ABSTRACT

Considerable evidence suggests that violent behavior observed in schizophrenic patients is motivated by psychotic symptomatology, specially in terms of positive syndrome. A positive relationship between violence and various psychotic symptoms, such as delusions, hallucinations and thought disorder, has been established in patients with schizophrenia. The understanding of violence in schizophrenic patients requires consideration of psychiatric symptomatology.

Objective

To determine the influence of psychotic symptomatology in the appearance of violent behavior in schizophrenic patients.

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Method

A total of one hundred and twenty were recruited. Eighteen patients were excluded due to concomitant substance abuse 6 months prior to the assessment. Diagnoses were based on the SCID-I. Psychotic symptom severity was assessed with the SANS and SAPS. Violent behaviors were assessed with the OAS.

Results

Violent behaviors were associated with more severe psychotic symptomatology including hallucinations, delusions, excitement, and thinking disturbances.

Conclusions

Patients with exacerbation of psychotic symptomatology will have an increased risk to behave violently. Violent behavior in schizophrenic patients is a heterogeneous phenomenon best explained in the context of specific symptoms associated to violence and course of illness, which may in turn may suggest that violence observed in patients is not unpredictable. The content of patient's delusions or hallucinations often imply a specific course of violent action which could be thought of as a psychotic form of "self-defense". The retrospective assessment of the variables raises methodological questions concerning the reliability of such measurement of the impact of psychotic symptoms on violence.

Key Words: Violence, schizophrenia, psychotic symptomatology.

INTRODUCTION

Violent behavior causes great public concern and is recognized as a significant problem of our society. It has been considered that almost 3.7% of the population is involved in several violent behaviors each year and that this prevalence can be up to 24% when non-recurrent acts of violence are included [1].

Various well-designed studies conducted after a period of deinstitutionalization show a consistently elevated risk for people suffering from severe mental illnesses to commit violent acts as compared with the general population [1-5]. Although it has been considered that certain diagnostic categories are more likely to commit violent acts than patients in other diagnostic categories, psychosis, specially schizophrenia, has been the diagnosis most often associated with violence [6] as it has always played a specific role in forensic psychiatry, serving as a paradigm of insanity, incompetence and dangerousness [7].

Considerable evidence suggest that violent behavior in schizophrenic patients is not a phenomenon exclusively derived by the diagnosis, considering that these behaviors are motivated and directed by various psychotic symptoms [8-11], specially in terms of delusions, hallucinations and thought disorder [8, 12-14]. Several studies have shown that violent schizophrenic patients have more positive psychotic symptoms prior to their admission to a psychiatric unit than those patients who were not violent [12-19]. Although

most of these studies were conducted around the time of hospital admission, it has been observed that even when violence and psychotic symptoms decreased during hospitalization, violent behaviors persisted after patients were discharged [20-22]. In these way, the association between violent behavior and psychotic symptoms is not limited to the period prior to hospital admission and violence may be present at any time during illness course [23,24].

The association between psychotic symptoms and violent behavior suggest that violence in schizophrenic patients is not unpredictable. What frequently seems obvious is that violence is consistent with the content and themes of delusions and hallucinations [22]. The content of patient's delusions or hallucinations often imply a specific course of violent action which could be thought of as a psychotic form of "self-defense" [25].

Little has been written on phenomenological correlates of delusions associated with violent behavior, so that the precise nature of the relationship between delusions and violence appears to be unclear. Certain delusions, including delusions of misidentification [26], threat/control override delusions [27,28] and delusions of infidelity [29] have been reported to be associated with an increase risk of violence. Nevertheless, the strong relationship between delusions and violence is mainly explained by the effect of persecutory delusions [30] which generate attitudes that may be held with stronger conviction and exert a greater influence over behavior [15]. Some research has shown that patients who experience delusions act on them fairly frequently [9, 19,20] and that persecutory delusions are specially likely to be acted upon [31]. Invoking the principle of "rationality within-irrationality", it has been reasoned that when an individual with mental illness feels threatened, and when his or her internal controls are compromised, then violence becomes more likely as an understandable response, i.e. when seen as a defense or retaliation against harmful and manipulative actions that the person believes to be directed against himself or herself [32].

With respect to hallucinations, systematic literature reviews on the relationship between hallucinations and violence are mainly concentrated on the role of command hallucinations [19, 33-44]. Several authors have concluded that findings from studies on the link between command hallucinations and violence are scarce and fragmented [33], and suggest that although not everyone who experiences command hallucinations will behave violently, a specific inquiry about command hallucinations may be recommended as an integrated part in violent risk assessment [45-47]. Clinical experience suggests that some patients who have hallucinations commanding them to engage in violent behavior do engage in such behavior [37]. In addition, some studies have reported that there is a violence-escalating interaction between delusions and hallucinations [48], and some indicate that in the absence of delusions, hallucinations appear to have minimal violence-triggering effect [9]. It has been argued that a logically consistent relationship between hallucination and delusion seems to increase compliance, because the patient interprets these perceptual experiences as congruent with his or her understanding of the world [49, 50].

Neuropsychological studies examining cognitive functioning in violent groups have frequently cited the relationship between neural dysfunction and violence [51, 52] and have generally reflected cognitive deficits in violent schizophrenic patients that can be representative of certain types of neuropathology such as executive function deficits reflecting prefrontal cortex impairments [53]. In the same way, multiple neuropsychopathological factors have been proposed as contributors for violent behavior including reduced inhibition, as well as impairment in memory, attention and concentration

[54]. For many years, these proposed factors, mainly disturbances of signal perception and signal processing, have been conceived as the core problems in schizophrenia and that are conceptualized as impairments in attention, cognition and information processing [55-58]. Nevertheless, within the schizophrenia populations, those with violent behaviors are found to demonstrate a greater degree of impairment compared to nonviolent patients [59-60].

There is a need for additional research to elucidate the specific factors and cognitive impairments that facilitate violence in schizophrenic patients. Therefore, this study investigates which symptoms can be considered as risk factors for violent behavior in schizophrenic patients. We hypothesized that persecutory delusions and cognitive deficits will be the main risk factors for violence in schizophrenia.

METHOD

Subjects

Patients were consecutively recruited from the inpatient and outpatient admission wards at the National Institute of Psychiatry (Mexico City). Patients were included if they met the following criteria: i) male or female, 18–50 years old; ii) diagnosis of schizophrenia as per DSM-IV criteria [61] and no other major psychiatric Disorder.

Assessment Procedures

Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [62] and confirmed by consensus of two clinical psychiatrists (AR, NH). The Scale for the Assessment of Negative Symptoms (SANS) [63] and the Scale for the Assessment of Positive Symptoms (SAPS) [64] were used to evaluate general psychopathology and symptom severity. The SANS scale comprises 25 items designed to assess five categories: 1) affective flattening, 2) alogia, 3) avolition/apathy, 4) anhedonia, and 5) attention. The SAPS scale has 30 items grouped in four categories: 1) hallucinations, 2) delusions, 3) bizarre behavior, and 4) positive formal thought disorder. Both scales have a scoring range from 0 to 5, where “0” denotes the absence of the symptom, and “5” the most severe form of the symptom [65].

Violent behaviors were assessed with the Overt Aggression Scale (OAS) [66,67]. All violent behaviors presented in the week prior to the clinical assessment were included. The OAS checklist of aggression is widely used because of its documented reliability and validity [66,67]. The scale scores four categories of aggressive behavior: 1) verbal aggression, 2) physical aggression against self, 3) physical aggression against objects, and 4) physical aggression against others. Scores range from 0 to 4 where 0 indicates nonaggressive and 4 indicates extreme aggression. Aggressive episodes were also rated according to the intervention used in response to the violent behavior. Severity of intervention was also ranked. The total aggression score was the sum of weighted scores for the most severe of each type of behavior and the most restrictive intervention.

The sample was divided in violent and non-violent patients, according to a score of seven as a cutoff point in the total aggression score of the OAS (TAS). In a study of 137 schizophrenic patients, sensitivity and specificity data of the TAS were obtained from a cutoff of 5 to a cutoff of 10 points. ROC curves were performed to establish the effects of sensitivity and specificity on the predictive and negative power of the instrument. It was observed that the cutoff point of seven presents the most adequate data of sensitivity (0.80) and specifcity (0.97), as well as an adequate clinimetric behavior with the remaining indicators (positive predictive power = 0.93 and negative predictive power = 0.91) [68].

Demographic data and the information concerning the SANS and SAPS scales and the OAS were obtained by a personal interview with the patient and his/her relatives.

The study was conducted according to the Good Clinical Practices. Before enrolling patients into the study, raters were trained to administer all the rating scales and achieved an inter-rater reliability greater than 0.80. After the patients had given their informed consent, the SANS and the SAPS scales were rated by an experienced psychiatrists (AR or NH). On the same day, the OAS was performed by an experienced clinician (FA), who was blind to the scores of the SANS and the SAPS scales.

Statistical Analyses

Demographic and clinical characteristics were described using frequencies and percentages for categorical variables as well as means and standard deviations for continuous variables. The Chi square test (x2) was used for categorical contrasts, and the Student's "t" test for independent samples for the comparison between violent and non-violent schizophrenic patients in terms of continuous variables. Logistic regression was used with the forward stepwise selection method for the calculation of the likelihood that violence would occur. Symptoms were included in the logistic regression analysis if any statistical significant difference emerged between violent and non-violent schizophrenic patients. The symptoms included were classified (dummy coding) in auxiliary variables to perform this analysis. The variables were represented by two values, "0" or "1" based in a 3 point scoring of the symptom item. For example, the symptom "persecutory delusions" was represented as "present" if the patient scored with 3-5 points, and as "absent" if the patient scored with less than 3 points.

The significance level for the inclusion of symptoms in the regression analysis was established at p=0.01 (2-tailed), while for the risk estimation, the significance level was established at p=0.05 (2-tailed).

RESULTS

a) Demographic and Clinical Data

One hundred and twenty schizophrenic patients were recruited. Eighteen patients with concomitant alcohol or substance abuse in the six months prior to the assessment, were excluded. Diagnoses of the sample were paranoid schizophrenia (79.4%, n=81),

undifferentiated schizophrenia (14.7%, n=15), and disorganized schizophrenia (5.9%, n=6). A total of 56.9% (n=58) of the sample were men and 43.1% (n=44) were women. The mean age of the patients was 31.7 years (S.D. = 7.3, range 18-57 years). The educational level was 9.8 years (S.D. = 3.5, range 1-19 years), 91.2% (n=93) were single and 65.7% (n=67) were unemployed at their recruitment. Most of the patients had been hospitalized at any time during their illness evolution (75.5%, n=77), with a mean of 4.1 (S.D. = 3.8) hospitalizations (range 1 – 20 hospitalizations). According to the cutoff point of 7 in the OAS, 59.8% (n=61) of the total sample of patients were classified as violent and 40.2% (n=41) as non-violent.

There were no significant differences between violent and non-violent schizophrenic patients on demographic characteristics. Both groups were also comparable in terms of some illness features at baseline (Table 1).

Table 1. Demographic and clinical data of violent and non-violent patients

	Violent Patients (n=61)		**Non-violent Patients (n=41)**		**Statistics**
	n	**%**	**n**	**%**	
Gender					
Male	32	52.5	26	63.4	x^2= 1.2, df 1, p=0.27
Female	29	47.5	15	36.6	
Laboral Status					
Employed	17	27.9	18	43.9	
Unemployed	44	72.1	23	56.1	x^2= 2.7, df 1, p=0.09
Marital Status					
Single	58	95.1	35	85.4	
Married	3	4.9	6	14.6	x^2= 2.8, df 1, p=0.09
Previous Hospitalization	53	86.9	24	58.5	
Yes	8	13.1	17	41.5	x^2= 10.6, df 1, p=0.001
No					
	Mean	**SD**	**Mean**	**SD**	
Age	31.4	8.1	32.0	6.8	t=0.4, df 100, p=0.68
Educational level	9.4	3.8	10.3	2.9	t=1.2, df 100, p=0.20
No. Hospitalizations	4.9	4.1	2.3	1.8	t=-2.9, df 75, p=0.004

b) Symptom severity differences between violent and non-violent patients

Significant differences emerged between violent and non-violent patients in terms of specific negative symptoms assessed by the SANS scale, where violent patients showed higher scores than the non-violent patients (Table 2). Also, violent schizophrenic patients exhibited more prominent positive symptoms when compared to the non-violent patients (Table 3).

c) Symptoms as predictors of violent behavior in schizophrenia

According to the differences found between violent and non-violent patients, the negative symptoms included in the logistic regression analysis were: 1) blocking, 2) increased latency

or response, 3) inpersistence at work or school and, 4) social inattentiveness. The positive symptoms included in the analysis were: 1) auditory hallucinations, 2) voices commenting, 3) voices conversing, 4) persecutory delusions, 5) delusions of reference, 6) delusions of being controlled, 7) agitated behavior and, 8) derailment thought. Each of these symptoms was proved in an independent logistic regression analysis before their inclusion in regression model as a whole. The results of the risk conferred by these symptoms as independent variables are shown in Table 4.

Table 2. Negative symptom severity differences between violent and non-violent patients

	Violent Patients n=61		**Non-violent Patients n=41**		**Statistic**
	Mean	**SD**	**Mean**	SD	
Affective flattening	2.5	1.2	2.2	1.4	t=-1.3, df 100, p=0.18
Unchanging facial expression	2.2	1.2	2.1	1.5	t=0.6, df 100, p=0.51
Decreased spontaneous movements	2.1	1.3	1.8	1.5	t=1.0, df 100, p=0.27
Paucity of expressive gestures	2.3	1.3	2.1	1.6	t=0.5, df 100, p=0.61
Poor eye contact	1.5	1.5	1.1	1.3	t=1.4, df 100, p=0.16
Affective nonresponsivity	1.8	1.5	1.6	1.7	t=0.5, df 100, p=0.60
Inappropriate affect	1.2	1.6	0.7	1.3	t=1.5, df 100, p=0.12
Lack of vocal inflections	1.9	1.3	1.8	1.4	t=0.3, df 100, p=0.73
Alogia	2.2	1.3	1.4	**1.3**	**t=3.0, df 100, p=0.003**
Poverty of speech	1.9	1.4	1.5	1.3	t=2.0, df 100, p=0.06
Poverty of content of speech	2.4	1.5	1.9	1.4	t=2.0, df 100, p=0.06
Blocking	1.0	1.4	0.3	**0.8**	**t=2.5, df 100, p=0.01**
Increased latency or response	2.4	1.6	1.6	**1.4**	**t=2.9, df 100, p=0.008**
Avolition/apathy	2.3	1.2	2.0	1.6	t=2.0, df 100, p=0.06
Grooming and hygiene	2.2	1.8	2.2	1.5	t=2.0, df 100, p=0.06
Inpersistence at work or school	3.3	1.5	2.2	**1.8**	**t=3.3, df 100, p=0.001**
Physical anergia	2.5	1.3	1.8	1.6	t=2.3, df 100, p=0.02
Anhedonia	3.1	1.3	2.5	1.5	t=1.9, df 100, p=0.07
Recreational interests and activities	2.8	1.4	2.3	1.5	t=1.5, df 100, p=0.13
Sexual activity	2.8	1.6	2.5	1.7	t=1.0, df 100, p=0.30
Ability to feel intimacy	2.9	1.6	2.4	1.6	t=1.4, df 100, p=0.16
Relationships with friends and peers	3.2	1.3	2.7	1.6	t=1.4, df 100, p=0.15
Attention	2.1	1.4	1.3	**1.2**	**t=2.7, df 100, p=0.008**
Social inattentiveness	2.5	1.5	1.7	**1.5**	**t=2.6, df 100, p=0.009**
Inattentiveness during mental testing	2.3	1.5	1.5	1.5	t=2.3, df 100, p=0.02
Total SANS	12.9	5.5	9.6	**6.3**	**t=2.7, df 100, p=0.006**

Positive and negative symptoms that were independent predictors for violent behavior in schizophrenia were included in a logistic regression model with the forward stepwise selection method. The logistic regression was capable of correctly classifying 70.6% of the

cases. The equation was generally more exact on predicting non-violent patients (80.8%) than violent patients (66.0%). The stepwise procedure only included two predictor symptoms for violent behavior in schizophrenia. These symptoms are: a) persecutory delusions, in which patients with these symptom have a risk 10.3 times greater of being violent in comparison with those without the symptoms (β=2.3, S.D.β=0.7, CI95%=2.1-48.9, p=0.003), and b) patients that are inpersistence at work or school have a risk 10.8 times greater risk to behave violently (β=2.3, S.D.β=1.0, CI95%=1.2-90.5, p=0.02).

Table 3. Positive symptom severity differences between violent and non-violent patients

	Violent Patients n=61		**Non-violent Patients n=41**		**Statistic**
	Mean	**SD**	**Mean**	**SD**	
Hallucinations	2.0	1.5	0.7	**1.2**	**t=4.4, df 100, p<0.001**
Auditory	2.1	1.7	0.8	**1.2**	**t=3.9, df 100, p<0.001**
Voices commenting	1.8	1.7	0.4	**1.0**	**t=4.6, df 100, p<0.001**
Voices conversing	1.3	1.6	0.5	**1.1**	**t=2.7, df 100, p=0.007**
Somatic	0.2	0.8	0.09	0.3	t=1.0, df 100, p=0.30
Olfactory	0.08	0.5	0.09	0.3	t=0.1, df 100, p=0.88
Visual	0.5	1.1	0.07	0.3	t=2.2, df 100, p=0.02
Delusions	2.2	1.4	1.2	**1.2**	**t=3.6, df 100, p<0.001**
Persecutory	2.0	1.5	0.6	0.9	**t=5.0, df 100, p<0.001**
Jealousy	0.2	0.8	0.07	0.4	t=0.9, df 100, p=0.32
Guilt	0.2	0.7	0.04	0.3	t=1.5, df 100, p=0.13
Grandiose	0.4	0.9	0.09	0.3	t=2.3, df 100, p=0.02
Religious	0.4	1.0	0.09	0.4	t=1.8, df 100, p=0.06
Somatic	0.3	0.8	0.1	0.6	t=0.9, df 100, p=0.33
Reference	2.0	1.5	1.2	1.4	**t=2.5, df 100, p=0.01**
Being controlled	1.3	1.3	0.4	0.9	**t=3.8, df 100, p<0.001**
Mind reading	0.8	1.3	0.4	0.9	t=1.8, df 100, p=0.06
Thought broadcasting	0.8	1.3	0.2	0.7	t=2.2, df 100, p=0.02
Thought insertion	0.7	1.2	0.2	0.6	t=2.2, df 100, p=0.02
Thought withdrawal	0.5	1.0	0.1	0.5	t=2.0, df 100, p=0.04
Bizarre behavior	0.9	1.2	0.4	0.9	**t=2.5, df 100, p=0.009**
Clothing and appearance	0.2	0.6	0.1	0.6	t=0.8, df 100, p=0.37
Social and sexual behavior	0.6	1.2	0.3	1.0	t=1.2, df 100, p=0.20
Agitated behavior	1.1	1.3	0.3	0.6	**t=3.4, df 100, p=0.001**
Repetitive behavior	.4	1.0	0.07	0.3	t=2.2, df 100, p=0.02
Formal thought disorder	1.8	1.1	1.1	1.2	**t=2.7, df 100, p=0.007**
Derailment	1.5	1.6	0.2	0.7	**t=4.8, df 100, p<0.001**
Tangentiality	1.5	1.4	0.7	1.2	t=2.7, df 100, p=0.008
Incoherence	0.3	0.8	0.09	0.6	t=1.3, df 100, p=0.18
Illogicality	0.5	1.0	0.1	0.6	t=2.2, df 100, p=0.02
Circumstantiality	1.5	1.3	1.0	1.4	t=2.1, df 100, p=0.02
Pressure of speech	0.1	0.6	0.1	0.6	t=0.3, df 100, p=0.97
Distractible speech	0.7	1.0	0.5	0.9	t=1.3, df 100, p=0.17
Clanging	0.01	0.1	0		t=0.8, df 100, p=0.41
Total SAPS	7.0	4.4	3.5	3.6	**t=4.2, df 100, p<0.001**

Table 4. Independent symptoms that conferred a risk for violent behavior in schizophrenia

Symptoms	β	S.D. β	Odds Ratio	CI 95%	p
Negative Symptoms					
Blocking	1.1	0.6	3.1	0.8 – 11.7	0.08
Increased latency of response	0.6	0.4	2.0	0.8 – 4.9	0.13
Inpersistence at work or school	1.2	0.4	3.5	1.5 – 8.2	0.003
Social inattentiveness	0.6	0.4	1.9	0.8 – 4.5	0.09
Positive Symptoms					
Auditory hallucinations	1.6	0.4	5.3	2.0 – 13.9	0.001
Voices commenting	2.3	0.6	10.0	2.7 – 36.1	<0.001
Voices conversing	1.1	0.5	3.2	1.1 – 9.3	0.03
Persecutory delusions	2.8	0.7	16.5	3.6 – 74.6	<0.001
Delusions of reference	1.0	0.4	2.8	1.1 – 6.9	0.02
Delusion of being controlled	1.4	0.6	4.1	1.1 – 15.3	0.03
Agitated behavior	8.0	17.4	80.0	0.96 – 92.1	0.64
Derailment thought	3.0	1.0	20.9	2.6 – 62.8	0.004

CONCLUSION

The aim of the present study was to determine which symptoms can be considered as risk factors for violent behavior in schizophrenic patients with the hypotheses that persecutory delusions and cognitive deficits will be the main risk factors for violence in schizophrenia. Positive psychotic symptoms, including hallucinations, delusions and thinking disturbances were markedly more severe in violent patients, result that has been previously reported [8, 15, 17, 69].

The results of the present study support that the association between violence and delusions is mainly explained by the presence of persecutory delusions [30, 69], which by themselves conferred a risk 16.5 times greater for violence in schizophrenia. Some authors have concluded that persecutory delusions increase anxiety and preoccupation levels in patients with schizophrenia [70], which suggest that the discomfort secondary to delusions increases the patients' risk to act toward their delusions [31].

Frequently, the theme of delusions related to violence persist throughout the illness course, so that violence can be justified as the result of the belief that other persons try to harm the patient [19, 22]. In this way, violence appears as a forced option for patients that have persecutory delusions that are held with the strong convictions of being threatened and need to defend himself/herself [30].

Some studies have reported an association between hallucinations, delusions and violence, and depending on the degree of association the patient will behave violently [71]. This means that the patient will respond to auditory hallucinations that are consistent with their delusions [72]. In this way, when the patient exhibits delusions of minor intensity, hallucinations will have a minimal triggering effect on violent behavior, while if delusions are of mild or severe intensity, hallucinations will have a direct influence on violent manifestations [9]. The results of the present study support this assumption. When considering auditory hallucinations, including voices commenting or conversing, they confer

a risk from 3.2 to 10 times greater for the appearance of violence. Nevertheless, when other symptoms were added to the risk estimation model, in particular persecutory delusions, auditory hallucinations lose their predictive value.

It´s important to notice that although significant differences emerged between violent and non-violent patients in terms of negative symptoms (attention and alogia, specifically), these symptoms were not risk factors for violence in schizophrenia. Patients included in the present study exhibited a mixed syndrome characterized by positive and negative symptoms. It has been reported that patients with a mixed syndrome are less cooperative and show poor response to the structure given by hospital wards [73] and that they tend to behave more violently throughout illness course [74]. However, the presence of negative symptoms has been related to several neurologic dysfunctions in schizophrenia [75, 76], so that the differences found in terms of severity of some negative symptoms in the violent schizophrenic patients may be just the manifestation of a major neurologic dysfunction in these patients more than a feature related to violent behavior.

The negative symptom "inpersistence at work or school", which conferred a risk 10.8 times greater for violence. In general, it has been described that patients with schizophrenia tend to be unemployed and do not reach a high educational level, which suggest that social disadvantages may be present even before illness onset [77]. It is not surprising that these social difficulties exacerbate due to the associated incapacities of schizophrenia, such as cognitive disturbances, which restrict educational, laboral and social functioning of the patients [78, 79].

We may infer that the continuous incapacity to maintain an occupational activity leads to frustration, inadequate social relationships or personal difficulties with friends and relatives, which may in turn promotes the appearance of violent behaviors as a way to cope and relieve frustration or to engage in reciprocal interactions with others, although this adaptative mechanism may produce the opposite of the desire effect.

Some limitations of the current study should be considered. Even though there were significant differences between violent and non-violent patients in terms of symptom severity, and that some of these symptoms may predict violent behavior in schizophrenia, the specific hallmarks of these symptoms were not assessed. For example, subjective factors of persecutory delusions are usually omitted from studies of violence. Some authors have proposed violence may be manifested differently between patients who are convinced of the reality of their delusions and those who retain doubt of the reality of their delusions [22, 80]. Also, with respect to affectiveness, there are quite a number of studies on the impact of delusional distress and violent acting on delusions [30]. Findings indicate that presence of "distress factors" as low self-esteem [70], high levels of anxiety [9, 81] and anger [15, 28] have an aggravating effect upon delusions. Negative affective responses to delusions, generated by external situations or internal stimuli preceding violent behavior, play a determinant role in the occurrence of such behavior and had an effect much greater than the total level of psychopathology [38].

On the other hand, the negative symptom "inpersistence at work or school" may be mediated by the social environment of the patient [12, 82]. It has been reported that the emotional and economical stability of family environment is directly affected by the illness itself [83]. As a result, violence may emerge as a response to the pressure and demands of family members secondary to socioeconomical difficulties [84] and the difficulties of the

patient to seek or maintain employment, school work, etc. These social and familial factors were not accounted in this study and should be included in future studies.

The retrospective assessment of the symptoms raises methodological questions concerning the reliability of their impact on violence in schizophrenia. More prospective studies should be performed before firm conclusions can be made on the role of psychotic symptoms on violent behavior in schizophrenia. The present study used a sample from a clinical setting and the population is not representative. Future studies related to the development of violence will more surely advance knowledge if they focus on more homogeneous groups.

However, the results of the present study have practical implications for the assessment and treatment of violent behaviors in schizophrenia. Violent behavior in schizophrenic patients is a heterogeneous phenomenon best explained in the context of specific symptoms associated to violence and course of illness. Hence, while patients are in clinically remission, the variables considered as predictors of violence, such as psychotic symptoms, become those of the general population [85]. In behalf of this, it is important to promote the assessment and follow-up of these symptoms to decrease the risk of occurrence of violent behaviors secondary to psychotic symptoms.

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Chapter 12

SEMANTIC MEMORY DEFICITS IN SCHIZOPHRENIA

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ABSTRACT

A number of studies report patients with schizophrenia exhibit disturbances in a wide range of cognitive function. However, little is known about impairment in higher cognitive functions, such as organization of semantic memory. In this chapter, we discuss the relevant issues based on the findings from our recent studies. First, we address a method to investigate the semantic organization using data from verbal fluency assessments. Next, factors which affect the severity of impairment of semantic memory organization is discussed. This chapter also provides an overview of the effect of newer generation antipsychotic drugs on organization of semantic memory. Finally, we discuss the idiosyncratic degradation of semantic memory in patients from the viewpoint of the neurodevelopmental hypotesis of schizophrenia.

INTRODUCTION

Cognitive deficit is defined as "dysfunction" of attention, learning, memory, or language and not just as typical psychiatric symptoms of distortion of reality, such as delusion or auditory hallucination. Although cognitive deficit has been thought of as a core feature of schizophrenia, it is not included in standard manuals for diagnosis such as the Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 1994) or the International classification of diseases and related health problems (ICD; World Health Organization, 1992). This is in contrast to other mental disorders like dementia, in which memory dysfunction is a basis of diagnosis. Despite an indirect connection with diagnosis, cognitive deficit in schizophrenia has been rigorously investigated using various neurocognitive tests. A previous study (Harvey and Keefe, 1997) summarized cognitive

degradation according to the severity of disturbance (Table 1). The table shows that a wide range of cognitive function including verbal learning, executive function, vigilance, motor speed, and verbal fluency are severely impaired.

Table 1. Cognitive impairments in schizophrenia and their severity

Severe Impairments (2-3 SD below the mean)
Serial learning Executive functioning Vigilance Motor speed Verbal fluency
Moderate Impairments (1-2 SD below the mean)
Distractibility Delayed recall Visuo-motor skills Immediate memory span Working memory
Mild Impairments (0.5-1 SD below the mean)
Perceptual skills Delayed recognition memory Confrontation naming Verbal and full-scale IQ
No Impairment
Word recognition reading Long-term factual memory

SD = standard deviation

Note: The "mean" refers to the average level of normal individuals who are similar in age and educational attainment. From Harvey & Keefe (1997) with permission from publishers.

Most functions listed in Table 1 can be estimated by various types of neurocognitive tasks. The Stroop test or the Wisconsin Card Sorting Test (WCST; Heaton, et al., 1993), for example, are supposed to be a measure of executive function (Spreen and Strauss, 1998). Verbal fluency is exclusively linked with one particular task, i.e. the verbal fluency task (VFT). VFT is a free recall task which consists of the category fluency task (CFT) and the letter fluency task (LFT). In CFT, subjects are asked to retrieve as many category members (e.g. dog, cat…for ANIMAL) as possible within a designated time (typically, 1 minute). In LFT, on the other hand, an initial letter (e.g. F, A, and S) is given as the cue for the retrieval of words beginning with that specified letter (e.g. *flower, furniture,...*for "F").

Although Table 1 covers a wide range of cognitive impairments in patients with schizophrenia, higher cognitive function such as organization of semantic memory is not included. This is partly because effective measures of the function have not been sufficiently studied in the clinical domain.

In the domain of cognitive psychology, the organization of semantic memory has been visualized in various forms such as hierarchical tree structures (Collins and Quillian, 1969) or semantic networks (Collins and Loftus, 1975). They were derived under experimental

paradigm, such as sentence verification or the semantic priming task. An experiment-based derivation of the organization of semantic memory, however, might be difficult for clinical samples as often the tasks are too demanding.

Recently, an advantageous method was devised to estimate semantic memory organization for clinical samples. The analysis uses the verbal outputs in CFT, transforming the order of outputs into dissimilarity values. Statistical techniques, such as multidimensional scaling (MDS; Kruskal and Wish, 1978) or cluster analysis, is applied to represent subjective dissimilarities in the form of a "map" or coherent groups. Hereafter, we will call these representations as "semantic structure". The details are explained in the next section.

Originally, the method was devised to estimate the semantic memory organization of patients with Alzheimer's Disease (Chan, et al., 1993a, b). Soon, the method was applied to patients with schizophrenia (Aloia, et al., 1996; Paulsen, et al., 1996; Rossell, et al., 1999; Sumiyoshi, C. et al., 2001; Sumiyoshi, C. et al., 2005; Tallent, et al., 2001). Major findings concerning disorganization of semantic memory in patients with schizophrenia will be introduced in the later sections.

ANALYSIS OF SEMANTIC STRUCTURE

As noted in the previous section, a basic element of semantic structure is the order of verbal outputs in CFT. This can be transformed into dissimilarity values by an algorithm devised by Chan et al. (Chan, et al., 1993a). The details are explained by the following examples.

First the most frequently generated items across all subjects are chosen. If fifteen examples are chosen, 15 x 15 half-matrices are collected for each subject. Each cell contains the order value between two examples. For example, the verbal outputs of "DOG, CAT, LION, RABBIT" produces the order value between DOG-CAT=1, DOG-LION=2, and DOG-RABBIT=3. Because the number of generated words varies across subjects, the values in cells need to be normalized by the number of generated examples. Then, the dissimilarity matrix of the whole group is constructed from the accumulated matrices of each subject. In the whole matrix, the values of cells are weighted by the number of subjects who produce certain pairs (e.g. DOG-CAT). Chan et al. (Chan, et al., 1993a) devised an equation for the above algorithm.

$$D_{ij} = (N / T_{ij}^{2}) \sum (d_{ijk} / n_{k})$$

$D_{ij,}$ the distance between animals i and j in the matrix
d_{ijk}, the distance between animals i and j of the subject k
n_k, the total number of responses of subject k
N, the total number of possible responses for animal i and j
T_{ij} , the total number of actual responses for animals i and j

According to this equation, the dissimilarity value of CAT-DOG in the dissimilarity matrix with the following three subjects should be:

Subject 1: CAT, DOG, MONKEY, GIRAFFE
Subject 2: CAT, TIGER, LION, DOG, SNAKE, MOUSE, GOAT
Subject 3: CAT, MOUSE, GIRAFFE, ZEBRA

d_{i1k}/n_1=1/4, d_{i12}/n_2=3/7, d_{i13}/n_3=N/A,
N=3, T_{ij}=2
D_{ij}=3/2^2 (1/4+3/7)=0.51

A schematic representation of the process is summarized in Figure 1.

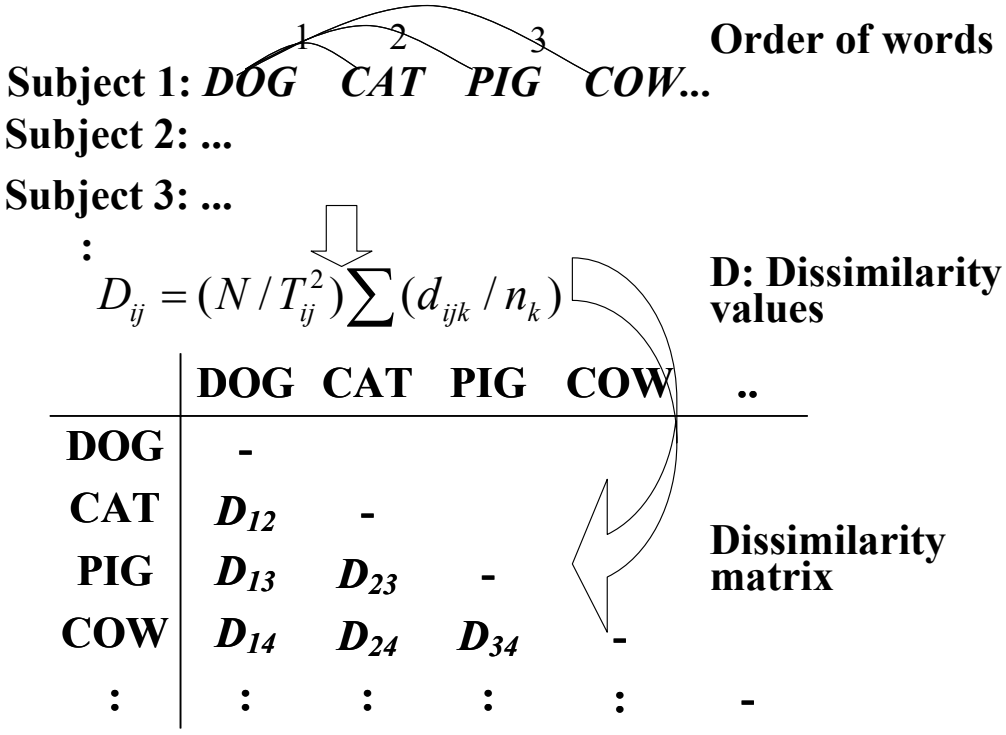

Figure 1. Schematic representation for derivation of dissimilarity values and matrix

There are several ways to visualize the dissimilarity values so that they can be easily grasped. Multidimensional scaling analysis (MDS; Kruskal and Wish, 1978) and hierarchical cluster analysis are the most widely used. In the former analysis, "distance" among items is calculated based on dissimilarity values to be represented as a "map" (Figure 2, right). According to the configuration of items, dimension is extracted. In cluster analysis, on the other hand, dissimilarity is changed to "coherence", locating similar items in the same clusters (Figure 2, left).

In the subsequent sections, we will report several studies using these techniques to evaluate the semantic structure in patients with schizophrenia.

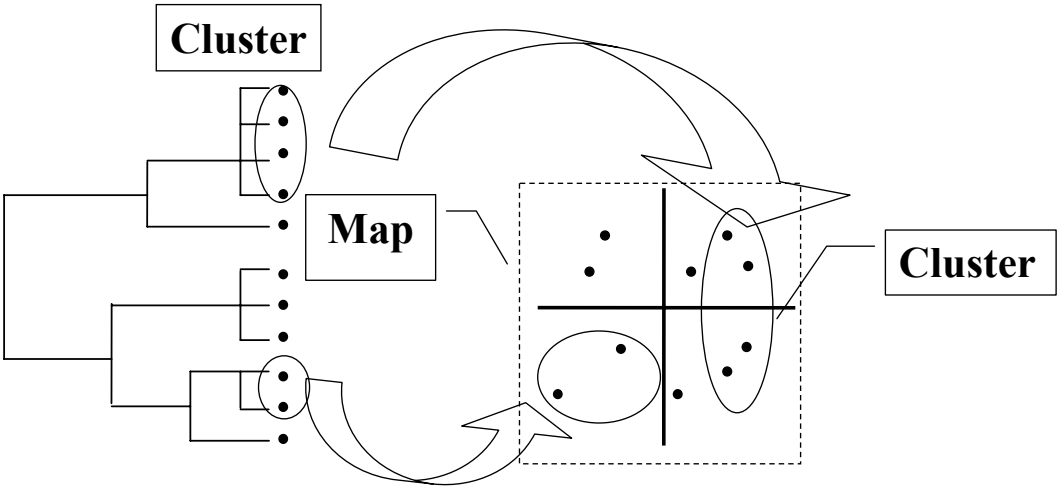

Figure 2. Schematic representation of two types of semantic structure

FACTORS AFFECTING ORGANIZATION OF SEMANTIC MEMORY IN PATIENTS WITH SCHIZOPHRENIA

Originally, MDS or cluster analysis was developed to externalize internal representation for semantic association. An ANIMAL category is commonly used to study semantic structure as it is the most familiar "natural kinds" for us. Several studies using normal individuals (Henley, 1969; Rips, et al., 1973; Sumiyoshi, 1998) revealed that the basic construction of semantic structures includes two types of dimensions, i.e. knowledge-based (e.g. predatory or domesticity) and perceptual (e.g. size) dimensions.

Clinical studies which used CFT to derive semantic structure replicated the basic finding obtained in the psychological studies for normal controls. In patients with schizophrenia, however, it was found that either perceptual-based (Paulsen, et al., 1996) (Figure 3) or both dimensions (Aloia, et al., 1996) were deteriorated. In the following sections, we discuss relevant factors for the degradation of semantic structure with reference to our recent studies.

Study 1: Language and Culture

The previous studies noted above well characterized the degradation of semantic structure in English patients with schizophrenia. However, the order of recall for the ANIMAL exemplars might vary depending on the nationality of subjects as typicality of the category items differs across culture (Roth and Frisby, 1986). It is possible that this cultural diversity might reflect on the degradation of semantic structure in patients with schizophrenia. We investigated this issue by analyzing the semantic structure of Japanese patients with schizophrenia (Sumiyoshi, C. et al., 2001).

Fifty-seven patients (male/female=28/30) meeting DSM-III-R or DSM-IV criteria for schizophrenia (N=51) and schizotypal personality disorder (N=6) entered the study. Normal volunteers (male/female=18/15) participated in the study for comparison. Demographic and

cognitive profiles are summarized in Table 2. The ANIMAL category fluency task was conducted following the usual method (Spreen and Strauss, 1998). Subjects were instructed to name as many animals as they could in 1 minute. Verbal outputs in CFT for ANIMAL category were analyzed using the method mentioned above. Fifteen exemplars, BEAR, CAT, COW, DOG, ELEPHANT, GIRRAFE, HIPPO, SHEEP, LEOPARD, LION, MONKEY, PIG, RABBIT, RACOON-DOG, and TIGER were chosen for MDS analysis.

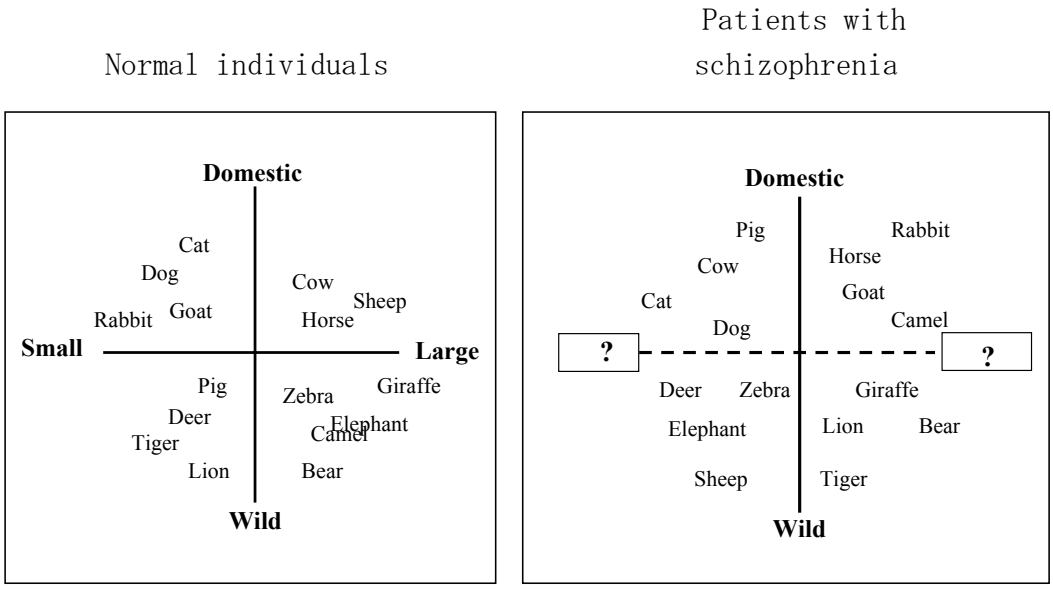

Figure 3. Semantic structure for normal individual and patients with schizophrenia derived from category fluency task of ANIMAL. From Paulsen et al. (1996) with permission of publishers.

Table 2. Demographic and cognitive variables for Nomal controls and Patients with schizophrenia

	Schizophrenia (*N*=57)	Normal Controls (*N*=33)
Age (yr)	27.21 (10.04)	25.78(10.59)
Education (yr)	13.21 (2.45)	13.55 (1.21)
Neuroleptics dose (mg)[a]	8.82 (12.12)	-
Onset (yr)	22.15 (8.80)	-
Duration (yr)	8.21 (8.22)	-
Block Design (WAIS-R)[b]	8.27(3.58)	12.21 (2.45)
Vocabulary (WAIS-R)	7.60 (3.97)	10.33 (2.69)
CFT ANIMAL[c]	13.02 (4.49)	18.45(4.70)

a. Haloperidol equivalent.

b.WAIS-R: Wechsler Adult Intelligence Scale-Revised

c. CFT: Category Fluency Task

Note. Values represent mean (standard deviation). From Sumiyoshi, C. et al. (2001) with permission of the publishers.

Figure 4 shows the semantic structure of patients with schizophrenia (right) and that of normal controls (left). In the normal controls, the first dimension was labeled as "domesticity" or "size", with domestic or small animals on the left side and wild or large animals on the right[1]. On the other hand, no meaningful dimension was detected in the patient group.

The result suggests that the degradation of semantic structure is independent of language or cultural background and one of the generalized deficits of patients with schizophrenia.

It is known that the severity of cognitive degradation in patients with schizophrenia is associated with various clinical factors (Harvey and Sharma, 2002). We investigated this issue focusing on the factors of age of onset, verbal intelligence and psychiatric symptoms.

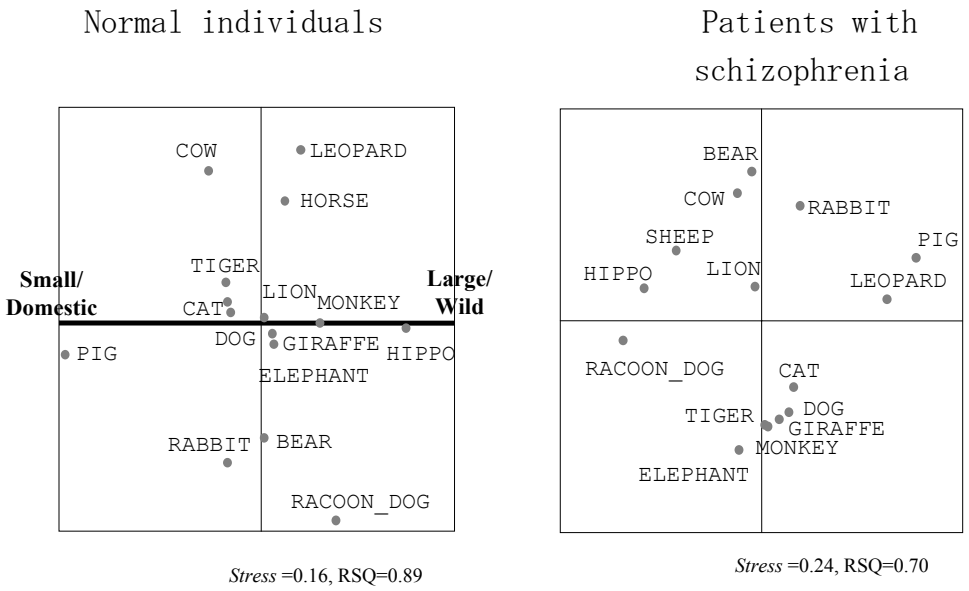

Figure 4. Two-dimensional semantic structure of the normal control group and the group of patients with schizophrenia. From Sumiyoshi, C. et al. (2001) with permission of publishers.

Study 2: Age of Onset

Previous neurological or neurocognitive studies of patients with schizophrenia reported that age of onset was associated with the severity of illness. Neurological studies (Frazier, et al., 1996; Rapoport, et al., 1997) have demonstrated that structural abnormalities in the brain, commonly found in patients with schizophrenia at the adult stage, had been already evident in an earlier phase (around 12 years old). Parallel findings were reported in a neruocongnitive study (Paulsen, et al., 1995), showing that relatively early onset groups (mean ages=21.9-23.3 yr) showed worse performances in learning tasks such as the California Verbal Learning Test (CVLT; Delis, et al., 1987). These previous studies indicate that relatively earlier (adolescent)

1 One exception, TIGER in the left side might have been brought about by the Japanese notion of zodiac signs originated from Chinese astrology. In this sexagenary cycle, the year of the TIGER is between those of the DOG, COW, and RABBIT, all of which appear in the left quadrant. This cultural background, specific to some Asian countries, may have promoted the sequential verbal outputs leading to TIGER being located on the left side.

onset is related to a more pronounced disruption of cognitive development and possibly to the organization of semantic structure.

In order to clarify whether semantic structure qualitatively differs between the earlier (adolescent) - and later onset patients, subgroup analysis was conducted. Twenty-three earlier onset patients and 20 later onset patients were chosen from patients who entered Study 1. The two groups were characterized by the mean age of onset (Table 2). In order to examine the net effect of age of onset, cognitive variables related to verbal abilities (i.e., the level of verbal intelligence and the number of verbal outputs in CFT) were adjusted between the two groups. Based on the most frequently produced exemplars across the two groups, BEAR, CAT, COW, DOG, ELEPHANT, GIRAFFE, HORSE, LION, MONKEY, PIG, and RABBIT were chosen to construct the semantic structure.

Figure 5 shows the result from MDS analysis. In the later onset group (Figure 5, left), the first dimension was interpreted as domesticity, with wild animals in the left and domestic animals in the right quadrants. In contrast, the distinction was less clear in the earlier onset group (Figure 5, right) due to some exceptions such as RABBIT on the left and CAT on the right. In addition, higher *stress* and lower RSQ values were obtained in this group, indicating a less properly constructed semantic structure.

The results clearly demonstrated that age of onset was associated with the severity of degradation in patients with schizophrenia. The semantic structure of the earlier onset group was more severely damaged, at least in younger (mean age<40) patients. The theoretical explanation for the age-related degradation is considered in the final section.

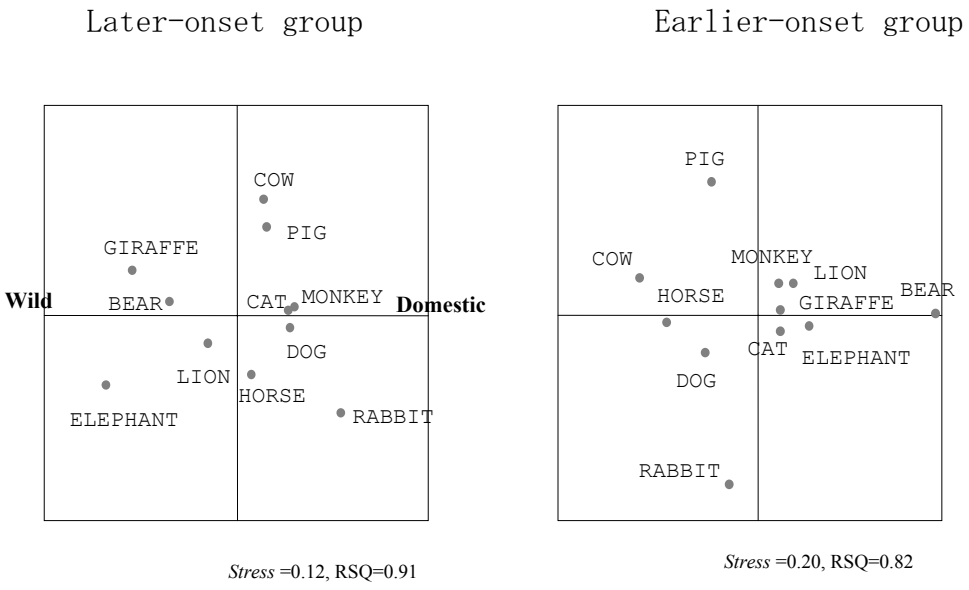

Figure 5. Two-dimensional semantic structure of the later onset group and the earlier onset group of patient with schizophrenia. From Sumiyoshi, C. et al. (2001) with permission of publishers.

Study 3: Verbal Intelligence

Preliminary multiple linear regression analysis revealed that the score of the Vocabulary subtest of WAIS-R was significant predictive variable for the amount of verbal outputs of CFT in patients with schizophrenia. Therefore, it was hypothesized that verbal intelligence, as measured by this subtest of WAIS-R, was also associated with the severity of disorganization of semantic structure. To examine this issue, we chose 45 patients from Study 1, who had completed the Vocabulary subtest of WAIS-R. They were divided into the higher- (*N*=25) and lower Vocabulary (*N*=20) score groups. The criteria for the classification was based on whether their scores were higher or lower than the score of seven, which means 1 SD below the standard score (i.e. 10). The clinical and demographic variables were equated across the two groups (Table 3).

Table 3. Demographic and cognitive variables for Earlier- or Later-onset group

	Earlier-onset group (*N*=23)	Later-onset group (*N*=20)
Age (yr)	25.70 (7.40)	37.0(10.57)
Education (yr)	11.80 (1.52)	15.05 (2.31)
Onset (yr)	15.85 (1.57)	30.62(8.60)
Duration (yr)	9.96 (8.48)	6.38 (6.65)
Vocabulary (WAIS-R)[a]	6.96 (2.96)	9.05 (4.48)
CFT ANIMAL[b]	12.20 (5.44)	13.43(3.73)

a.WAIS-R: Wechsler Adult Intelligence Scale-Revised

b. CFT: Category Fluency Task

Note. Values represent mean (standard deviation). From Sumiyoshi, C. et al. (2001) with permission of the publishers.

Among the most frequently generated items across the groups, LION, CAT, MONKEY, DOG, BEAR, ELEPHANT, GIRAFFE, HORSE, RABBIT, SHEEP, and PIG were chosen for MDS analysis. Semantic structures for both groups are shown in Figure 6. As for the higher Vocabulary score group, the first dimension was interpreted as domesticity, with domestic animals (SHEEP, CAT, DOG, HORSE) in the left and wild ones (BEAR, LION, ELEPHANT, GIRAFFE) in the right quadrants (Figure 6 left). On the other hand, logical interpretation was difficult for the lower Vocabulary score group (Figure 6, right), although the two goodness-of-fit measures of this score group (*stress*=0.13, RSQ=0.89) were as good as those of the higher Vocabulary score group (*stress*=0.18, RSQ=0.83).

The qualitative difference in the semantic structure between the higher- and lower Vocabulary groups seemed to be analogues to those observed between normal control subjects vs. schizophrenia patients as a whole (Study 1) and between earlier onset vs. later onset patients (Study 2), which indicates that verbal intelligence is also associated with severity of degradation of semantic structure in patients with schizophrenia.

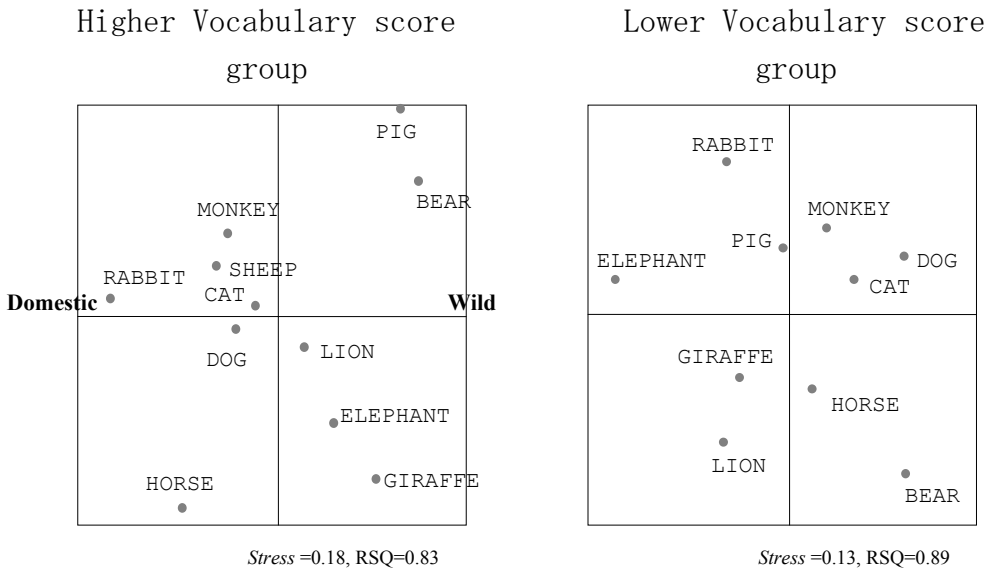

Figure 6. Two-dimensional semantic structure of the high vocabulary score group and the low vocabulary score group of patient with schizophrenia. From Sumiyoshi, C. et al. (2001) with permission of publishers.

Study 4:A Factor of Psychiatric Symptoms

Psychiatric symptoms of schizophrenia are roughly classified into two major types, the positive and negative symptoms: Negative symptoms include psychomotor retardation, affective flattening, social withdrawal, while positive ones are characterized as delusions, hallucination and thought disorder. The phenomenology of the two symptoms became clearer by the advent of comprehensive scales, such as the Scale for Assessment of Positive Symptoms (Andreasen, 1984),the Scale for Assessment of Negative Symptom (Andreasen, 1984), Positive and Negative Syndrome Scales (Kay, et al., 1987), and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). As with the development of these scales, a number of studies have revealed connections between both types of symptoms and cognitive functioning. Regarding verbal fluency performance, several studies (Allen, et al., 1993; Howanitz, et al., 2000) have reported that negative symptoms as a whole inhibit rigorous word production in patients with schizophrenia (Joyce, et al., 1996; Stolar, et al., 1994; Sumiyoshi, C. et al., 2004). In addition, certain domains of negative symptoms such as alogia have been reported to be related with CFT. Alogia symptoms are characterized by Poverty of Speech, Poverty of Content of Speech, and Thought Blocking. Joyce et al. (1996), for example, showed that patients with severe alogia symptoms tend to receive less benefit from cueing for item retrieval in CFT. Other studies (Stolar, et al., 1994; Sumiyoshi, C. et al., 2004) also reported that verbal outputs in CFT were exclusively correlated with alogia rather than other negative symptoms. Then, the question arises as to whether alogia is also associated with the disorganization of semantic memory, as measured by the CFT. We investigated this by subgroup comparison, as was done in the previous sections. Thirty-eight subjects (male/female=20/18) who met DSM-IV criteria for schizophrenia entered the study. They were divided into two groups according to the alogia score from the SANS (the sum of

Poverty of Speech, Poverty of Content of Speech, Blocking, and Increased latency of Speech; MAX=20). The alogia group consisted of patients who showed an alogia score of more than 1. The non-alogia group included patients with an alogia score of 0 or 1. The mean alogia score, as well as the demographic and cognitive variables, for these two subgroups are summarized in Table 4. The most frequently produced 11 animals (CAT, DOG, BEAR, ELEPHANT, GIRAFFE, LION, HORSE, MONKEY, TIGER, RABBIT, and SHEEP) across the two groups were chosen for the analysis.

Table 4. Demographic and cognitive variables for Higher or Lower Vocaburaly score group

	Higher Vocabulary score group(*N*=25)	Lower Vocabulary score group (*N*=25)
Age (yr)	31.36 (11.28)	32.25 (10.87)
Education (yr)	13.70 (2.88)	12.55 (1.88)
Onset (yr)	24.00 (10.06)	21.75 (8.33)
Duration (yr)	7.50 (6.18)	10.34 (10.21)
Vocabulary (WAIS-R)[a]	10. 48(2.95)	4.05 (1.77)
CFT ANIMAL[b]	14.16 (4.29)	11.0 (4.27)

a.WAIS-R: Wechsler Adult Intelligence Scale-Revised

b. CFT: Category Fluency Task

Note. Values represent mean (standard deviation). From Sumiyoshi, C. et al. (2001) with permission of the publishers.

The organization of semantic structure, as revealed by MDS and cluster analyses, is shown in Figure 7. In the semantic structure of the non-alogia group, carnivorous animals were located on the left and herbivorous ones on the right, creating a predation dimension (Figure 7, left). On the other hand, no meaningful dimension was observed in the alogia group (Figure 7, right). The qualitative difference in the organization of semantic structure between the two groups became more apparent by cluster analysis. Highly coherent clusters are shown as circles in Figure 7. In the non-alogia group, the coherence of items did not represent specific meanings. On the other hand, coherent clusters seemed odd in the alogia group. For example, DOG and ELEPHANT made one cluster while CAT and MONKEY formed another one, and so on.

The results from MDS and cluster analysis are summarized as “mildly disorganized” for the non-alogia group while “severely disorganized” for alogia group. The semantic structure of the alogia group exhibited dimensionless construction and oddly coherent clusters appeared.

A previous study investigating deluded patients with schizophrenia revealed that the semantic structure was more disorganized in that sample (Rossell, et al., 1999). The present result suggests that certain types of negative symptoms, such as alogia, are also associated with the severity of degradation of semantic structure in patients with schizophrenia.

So far, we have demonstrated that the disorganization of semantic memory in patients with schizophrenia varies depending on clinical factors such as age of onset, verbal intelligence, and psychiatric symptoms. In the next section, the recovery of semantic structure by the antipsychotic treatment is discussed.

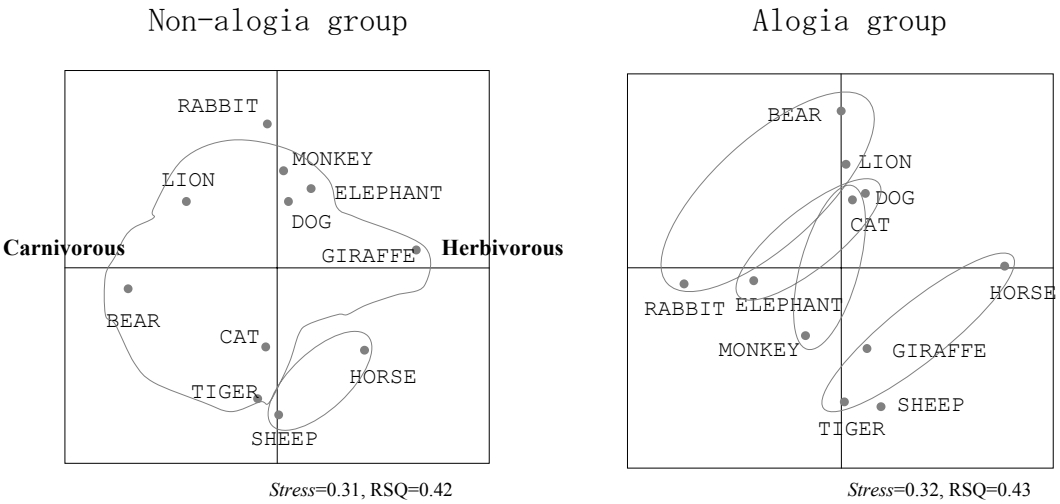

Figure 7. Two-dimensional semantic structure for non-alogia and alogia patients with schizophrenia. The circles represent highly cohesive assemblies as revealed by cluster analysis. From Sumiyoshi, C. et al. (2005) with permission of publishers.

TREATING DISORGANIZATION OF SEMANTIC STRUCTURE: EFFECT OF ANTIPSYCHOTIC DRUGS ON SEMNATIC MEMORY ORGANIZATION IN SCHIZOPHRENIA

Atypical Antipsychotic Drugs (AAPDs) in the Treatment of Schizophrenia

Effective treatment of psychosis and cognitive disturbances in schizophrenia largely depends on the use of antipsychotic (anti-schizophrenia) drugs. Other treatment measures, e.g. cognitive or behavioral therapy, may also work as an adjunct to appropriate medications.

While conventional, or "typical," antipsychotic drugs, such as haloperidol, are effective to treat positive symptoms (e.g. hallucinations, delusions), they tend to induce undesirable side effects (e.g. extrapyramidal signs, akashisia, and tardive dyskinesia). Moreover, typical antipsychotic drugs have a limited ability to ameliorate negative symptoms (e.g. blunt affect, social withdrawal, avolition) and cognitive impairment associated with schizophrenia. On the other hand, a class of antipsychotic drurgs termed as "atypical antipsychotic drugs (AAPDs)", or "second generation antipyschotics", such as clozapine, melperone, olanzapine, risperidone, quetiapine, ziprasidone, and perospirone, have been shown to be more efficatious than typical antipsychoitcs in treating negative symptoms and cognitive deficits (Araki, et al., in press; Meltzer and McGurk, 1999; Meltzer and Sumiyoshi, 2003; Sumiyoshi, et al., 2003; Woodward, et al., 2005).

Mechanism of Actiong of AAPDs

The traditional definition of AAPDs consists of: 1) limited ability to produce catalepsy in rats; 2) low propensity to cause extrapyramidal symptoms in man; and 3) limited ability to produce serum prolactin elevations in man (Meltzer, et al., 1989). Only clozapine, fluperapine, melperone, and RMI-81582 have been recognized to meet these criteria before the advent of the aforementioned newer drugs (Meltzer, et al., 1989; Meltzer, et al., 2001; Sumiyoshi, et al., 1997; Sumiyoshi, et al., 2003a; Sumiyoshi, et al., 2003b; Sumiyoshi, T. et al., 2005). While typical antipsychotic drugs mainly block dopamime (DA)-D2 eceptors, AAPDs act as a relatively strong antagonist at serotonin 5-HT_{2A} receptors than at D2 receptors (Meltzer, et al., 1989; Stockmeier, et al., 1993; Sumiyoshi, et al., 1995). This property of AAPDs is thought to contribute to the ability of these agents to release DA and acetylcholine in brain regions reulating cognitive functions, such as prefrontal cortex (Ichikawa, et al., 2002; Ichikawa, et al., 2001; Kuroki, et al., 1999).

AAPDs and Cognition

There is now abundant evidence for the advantage of using AAPDs for ameliorating cognitive disturbances in patients with schizophrenia (Keefe, et al., 2006; Woodward, et al., 2005). Specifically, AAPDs have been shown to improve key domains of cognition relevant to the improvement of social function and quality of life, e.g. verbal learning and memory, executive function, word recall, verbal and working memory, and attention and vigilance (Keefe, et al., 2006; Meltzer and McGurk, 1999; Woodward, et al., 2005).

We have conducted a series of studies of the effect of AAPDs or serotonergic agents on higher cognitive functions, such as memory organization (Araki, et al., *in press*; Sumiyoshi, T. et al., 2005; Sumiyoshi, T. et al., 2001b). So far, little attention has been paid to organization of verbal (semantic) memory as a target for pharmacotherapy, in spite of the fact that this aspect of cognition has a significant impact on quality of life for patients. Sumiyoshi et al (Sumiyoshi, T. et al., 2001b) revealed that organization of episodic memory, as measured by the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R), was significantly improved by augmentation therapy with tandospirone, a partial 5-HT_{1A} agonist. Araki et al. (*in press*) reported that treatment with perospirone, an AAPD with potent partial 5-HT_{1A} agonist property, was associated with improvement in verbal memory organization, as assessed by the Auditory Verbal Learning Test (AVLT). These findings indicate that treatment with some AAPDs improves encode *new* information in patients with schizophrenia, via stimulating 5-HT_{1A} receptors. However, whether AAPDs are also effective to restore the organization of *acquired* information has not been fully addressed.

We recently conducted a study to investigate this issue by analyzing the semantic structures in patients with schizophrenia treated with olanzapine or ziprasidone for 6 weeks (Sumiyoshi, et al., *in press*). Thirty-three patients meeting DSM-IV criteria for schizophrenia entered the study. Fourteen patients received treatment with olanzapine while 19 patients were treated with ziprasidone. Demographic and cognitive data for both groups are summarized in Table 6. MDS and cluster analyses were conducted to construct semantic structures using the same methods described in the previous sections. The words most frequently produced across baseline and 6 weeks were used for both analyses.

Table 5. Demographic and cognitive variables for Alogia and Non-arogia

	Alogia group (*N*=21)	Non-alogia group (*N*=17)
Age (yr)	27.17 (9.10)	34.18 (10.02)
Education (yr)	13.40 (2.60)	13.50 (2.16)
Neuroleptics dose (mg/day)[a]	9.71 (8.12)	8.58 (8.52)
Onset of illnes (yr)	20.48 (7.01)	22.33 (10.35)
Duration of illnes (yr)	6.09 (7.03)	12.00 (9.42)
Alogia Score	4.90 (3.01)	0.18 (0.38)
Block Design (WAIS-R)[b]	8.95 (2.97)	9.87 (3.58)
Vocabulary (WAIS-R)	8.33 (2.87)	9.27 (2.82)
CFT ANIMAL[c]	14.57 (5.16)	16.59 (3.65)

a. Haloperidol equivalent.
b.WAIS-R: Wechsler Adult Intelligence Scale-Revised
c. CFT: Category Fluency Task.
Note. Values represent mean (standard deviation).
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Table 6. Demographic and cognitive variables for paients treated with Olanzapine and Ziprasidone

	Patients treated with Olanzapine (*N*=14)	Patients treated with Ziprasidone (*N*=19)
Age (yr)	41.71 (10.18)	39.16 (11.73)
Education (yr)	12.29(1.73)	11.95 (1.99)
Neuroleptics dose(mg/day)[a]		
base	8.86 (12.22)	5.33 (7.29)
6 Weeks	6.41 (1.98)	3.13 (1.80)
Onset of illnes (yr)	25.71 (10.96)	20.94 (7.62)
Duration of illnes (yr)	16.00 (9.32)	18.18 (12.56)
CFT ANIMAL[b] base	13.27 (2.72)	16.73 (4.34)
6 Weeks	14.69 (3.02)	17. 95 (5.25)

a. Haloperidol equivalent.
b. CFT: Category Fluency Task
Note. Values represent mean (standard deviation). From Sumiyoshi, C. et al. (*in press*) with permission of the publishers.

The MDS results for olanzapine and ziprasidone groups were shown in Figures 8. In both groups, semantic structures were disorganized at baseline; no meaningful dimensions were deteced (Figure 8, left panels). In contrast, a wild-domestic dimension appeared after treatment with either drug. In the semantic configuration of patients treated with olanzapine, wild animals (e.g. GIRRAFE, TIGER, ELEPHANT, LION) gathered in the right upper quadrant, while domestic ones (e.g. PIG, HORSE, COW) were placed in the left lower

quadrant (Figure 8, upper right panel)[2]. Similar division was also found after treatment with ziprasidone for 6 weeks, in a manner that wild animals were placed in the right lower quadrant while domestic ones were in the left upper quadrant (Figure 8, lower right panel).

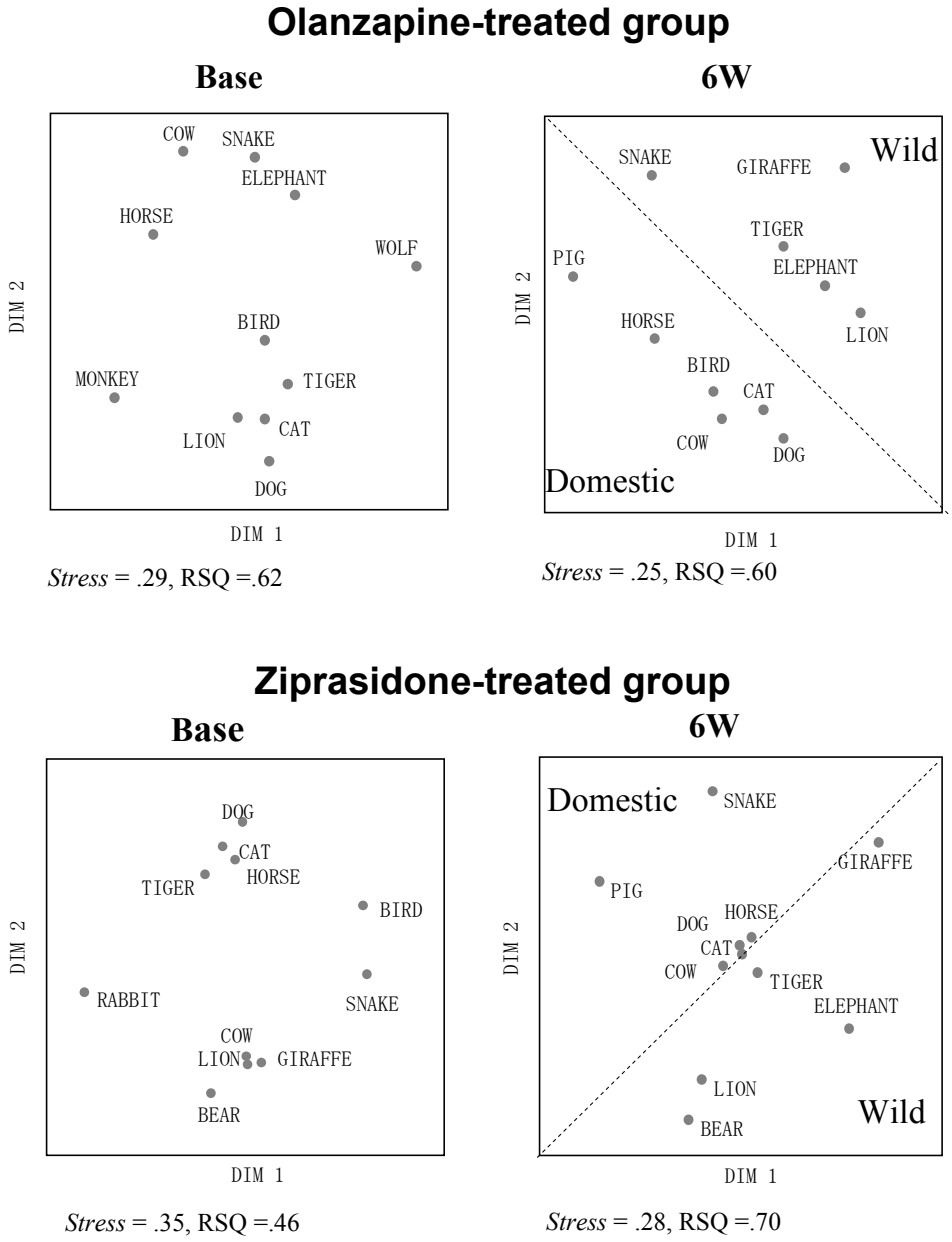

Figure 8. Two-dimensional semantic structure in patients treated with olanzapine or ziprasidone. From Sumiyoshi et al. (in press) with permission of publishers.

2 Technically, it is permissible to rotate axes as far as configuration itself, i.e. distance between each item, are reserved (Kruskal and Wish, 1978). Thus, the second dimension (typically shown as a vertical axis) in the 6 week configuration was rotated either anticlockwise (olnazaipine group) or clockwise (ziprasidone group).

The cluster structures for the two groups were shown in Figures 9. As for the olanzapine group, the clusters became organized at 6 week compared to baseline (Figures 9, upper panels); items were gathered in clusters roughly according to size (i.e. TIGER, ELEPHANT, LION, HORSE, subsequently include GIRAFFE; COW; CAT, DOG, PIG subsequently include BIRD) at 6 week (Figures 9, upper right panel). Although such apparent clusters did not appear in the ziprasidone group (Figures 9, lower right panel), a vague cluster structure (i.e. HORSE, COW, CAT, BEAR, TIGER, LION, GIRRAFE DOG), which was not evident at baseline, emerged at 6 week.

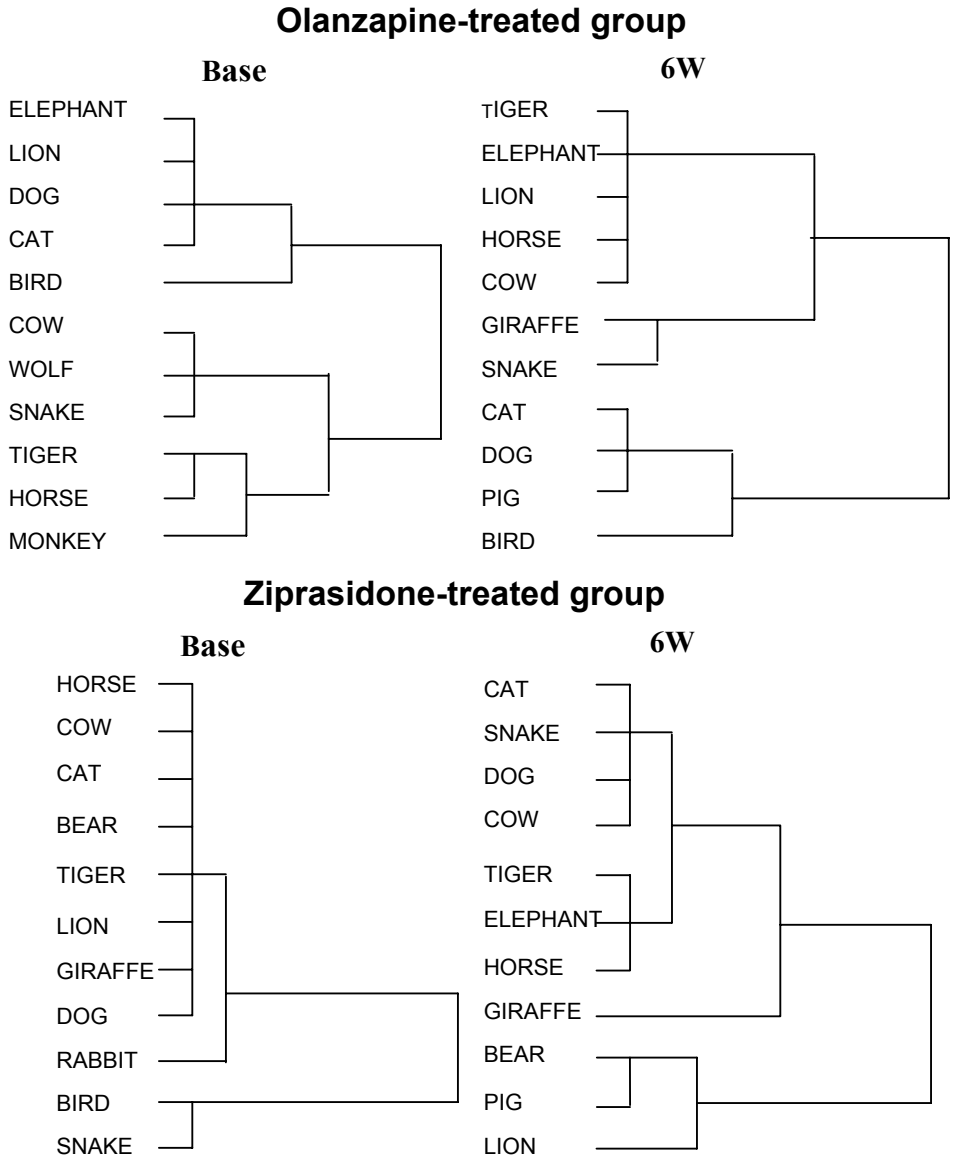

Figure 9. Cluster structure in patients treated with olanzapine or ziprasidone. From Sumiyoshi et al. (in press) with permission of publishers.

MDS analysis revealed that treatment with olanzapine or ziprasidone was associated with the emergence of a wild-domestic dimension in the semantic structure. Similarly, cluster structures became more consistent during treatment with either drug, indicating that organization of semantic memory in patients approached the pattern of control subjects. Interestingly, the quality of life scale scores across the whole patients have concurrently improved during 6 week treatment (Figure 10), producing a moderate effect size (0.33). These results suggest that AAPDs have the ability to improve higher-level cognitive functions in patients with schizophrenia, and that well-organized semantic structures are associated with better functional outcomes.

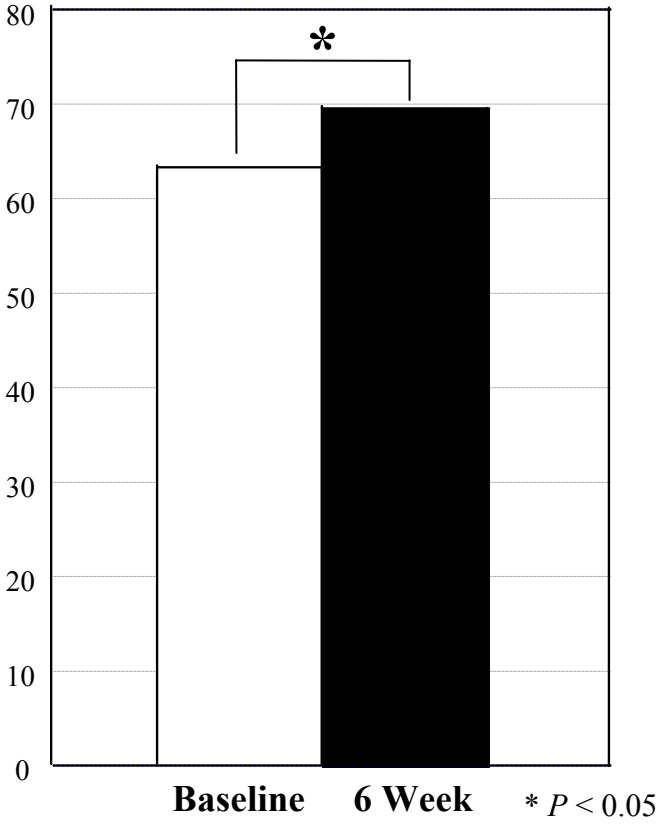

Figure 10. Improvement of Quality of Life Scores (QLS) by atypical antipsychotics treatment.

5-HT_{1a} Receptor as a Target for Cognitive Enhancement

Postmortem studies have indicated an increased number of 5-HT_{1A} receptors in the prefrontal cortex of subjects with schizophrenia (e.g. (Hashimoto, et al., 1991; Sumiyoshi, et al., 1996). Although some researchers (Yasuno, et al., 2004) failed to replicate the 5-HT_{1A} receptor up-regulation with PET, due probably to limited sensitivity, we (Sumiyoshi, et al., 1996) found that the high-affinity 5-HT_{1A} receptor biding sites, but not low-affinity sites, were increased by 80% in subjects with schizophrenia compared to normal control subjects. Since these high-affinity 5-HT_{1A} receptors are shown to be coupled to the second messenger

systems (Nenonene, et al., 1994), it is reasonable to hypothesize that stimulation of 5-HT_{1A} receptors leads to enhancement of cognitive performance in patients with schizophrenia (Sumiyoshi, T. et al., 2001a; Sumiyoshi, T. et al., 2001b; Sumiyoshi, et al., 2000; Sumiyoshi and Meltzer, 2004).

In fact, augmentation therapy with the partial 5-HT_{1A} agonist tandospirone resulted in improved performance on verbal learning and memory (Sumiyoshi, et al., T. 2001a; Sumiyoshi, T. et al., 2001b; Sumiyoshi, et al., 2000), memory organization (Sumiyoshi, T. et al., 2001b), and executive function (Sumiyoshi, T. et al., 2001a) in patients with schizophrenia already treated with typical antipsychotic drugs. A subsequent study (Araki, et al., in press) report that switching from previous medications to perospirone, an AAPD and agonist a t5-HT_{1A} receptors, selectively improved memory organization, as measured by the AVLT, in patients with schizophrenia. Our discovery with regard to 5-HT_{1A} agonism in the action AAPDs and cognitive enhancement has drawn interest of researchers conducting basic studies (Diaz-Mataix, et al., 2005; Marona-Lewicka and Nichols, 2004; Newman-Tancredi, et al., 2005), and has stimulated the development of novel antipsychotic drugs in lieu of the "5-HT_{1A}/D2 hypothesis" (Claustre, et al., 2003; Depoortere, et al., 2003).

IDIOSYNCRATIC DEGRADATION IN PATIENTS WITH SCHIZOPHRENIA?

Alzheimer's disease (AD) is a degenerative brain disorder characterized by neural loss over a wide brain area. Although the temporal progression of the neuropathological changes associated with AD are not fully known, recent studies suggest that the hippocampal area (i.e., hippocampus and entorhinal cortex) is involved in the earliest stage of the disease and that cerebral cortices (mainly frontal, temporal, and parietal areas) become gradually deteriorated as the disease progresses. It is possible that neural degeneration across a wide brain areas is a direct or indirect cause of the disorganization of semantic memory in AD patients. In fact, several studies have investigated this issue, and the major findings are summarized as follows: 1) The semantic structure of AD patients was disorganized compared with elderly normal controls or patients with Huntington's disease (Chan, et al., 1995; Chan, et al., 1993a); 2) Deterioration became more severe as the disease progressed (Chan, et al., 1997); 3) Perceptual dimension (i.e. size) was relatively robust compared with knowledge-based dimension (i.e. domesticity or predation; Figure 11) (Chan, et al., 1997; Chan, et al., 1995; Chan, et al., 1993b; Chan, et al., 1995). The second finding is interesting in that degradation in AD patients progressed in a reverse order compared with patients with schizophrenia. In the latter case, knowledge-based dimensions are relatively intact than perceptual ones, as was shown in the Study 2 or Study 3. Developmental studies on semantic structure might provide us with useful information about the priority of the two dimension types.

Developmental studies on the organization of semantic structure equivocally reported that perceptual-based formation firstly became salient. Sumiyoshi (Sumiyoshi, 1998) demonstrated that only the size dimension was recognized in the semantic structure of younger children (5-6 yeara old; Figure 12). A similar result was obtained by hierarchical cluster analysis; size-ordered clusters were recognized even in younger children (Storm, 1980). In addition, Howard and Howard (Howard and Howard, 1977) revealed that the weight

of dimensions of the semantic structure shifted from perceptual (i.e. size) to knowledge-based ones (i.e. ferocity or domesticity) from children (6 years old) to adults. All these developmental studies indicate that semantic structure for the ANIMAL category starts to be organized based on firstly perceptual, subsequently on knowledge-based features.

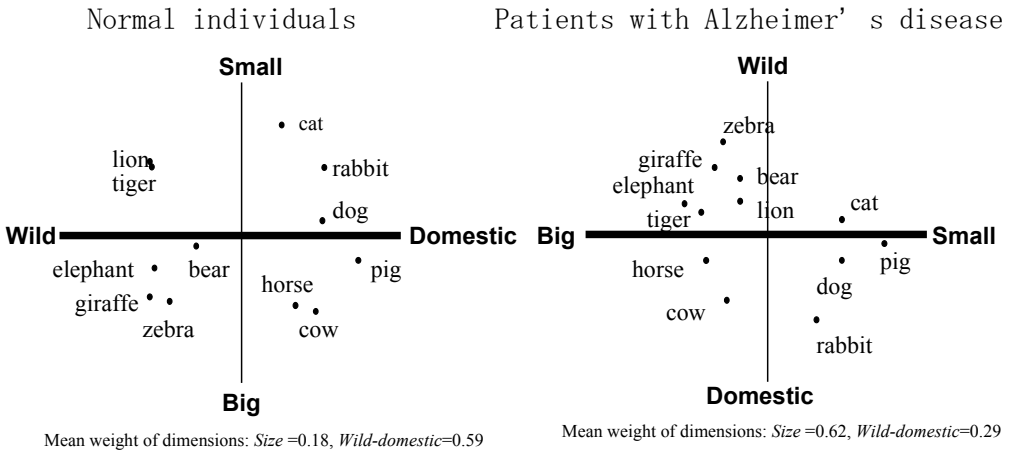

Figure 11. Semantic structure for patients with Alzheimer's disease and normal controls. From Chan et al. (1993b) with permission of publishers.

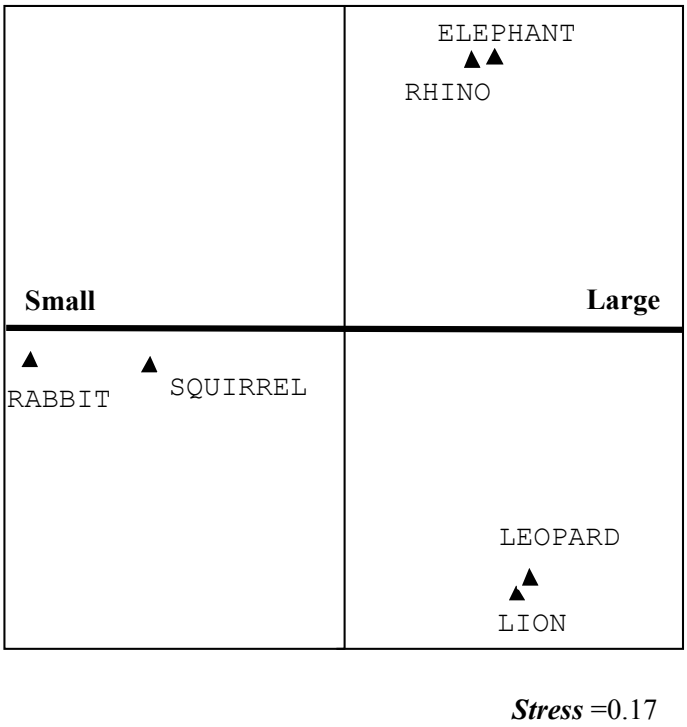

Figure 12. Semantic structure for ANIMAL in normal children. From Sumiyoshi (1998) with permission of publishers.

If perceptual-based formation is more basic as developmental studies suggest, the degradation pattern of patients with schizophrenia seems to be rather peculiar, in which the perceptual dimension is firstly diminished. One possibility is that their cognitive development does not trace a normal way as far as the formation of semantic structure is concerned. This assumption is supported by the result in Study 2, which revealed a more sever degradation of semantic structure in earlier-onset patients. In addition, cohort studies, investigating the cognitive function of family members of patients with schizophrenia, found selective deficits in the execution of the CFT, but not other cognitive tasks, in non-psychotic siblings of schizophrenia subjects (Chen, et al., 2000). This indicates that the well-organized semantic association, which is reflected in CFT performance, has not been fully developed in subjects who are vulnerable to developing schizophrenia.

In order to examine the hypothesis that deficits of semantic strucrue is derived from subnormal development in patients with schizophrenia, it might be useful to investigate the developmental process of children with developmental disorders, such as high functioning autism. Certain similarities in cognitive impairment, including executive function, language ability and interpersonal communication are found between the two clinical samples. Specifically, impairment in verbal fluency is serious in both autistic subjects and patients with schizophrenia (Boucher, 1980). Some researchers even afgued that the two disorders might be regarded as the same type of syndrome as far as cognitive impairment is concerned, although their deficits might be originated from different neural abnormalities (Goldstein, et al., 2002). The comparison between the two clinical samples as to degradation pattern may shed light on the basis for the semantic structure impairment in patients with schizophrenia.

CONCLUSION

This chapter discussed the semantic memory deficits in patients with schizophrenia, focusing on the disorganization of semantic structure. First, we introduced the methods for analyzing semantic structure using verbal fluency data. Although there is a dispute about validity of this method (Elvevag and Storms, 2003), we think it as an excellent way to estimate disorganization of the semantic memory, as the method is easily adapted to clinical samples. Future studies, which refine the algorithm to obtain dissimilarity values, might resolve the doubt for the use of the method.

Second, factors associated with disorganization of semantic structure were considered. Age of onset, verbal intelligence, and specific psychiatric symptoms, are all related to severity of degradation. On the other hand, the mode of disorganization does not depend on language or cultural backgrounds, suggesting that the deficits are ones of general cognitive dysfunction in patients with schizophrenia.

Finally, peculiarity of patients with schizophrenia as to disorganization of semantic structure was discussed by comparing to patients with geriatric disease or to development process. Numerous studies have reported that patients had traced abnormal or subnormal cognitive development in their premorbid stage (for a review, Weickert and Goldberg, 2000). It is possible that semantic memory is improperly organized preceding to onset of illness and disorganization is accelerated on emerging psychotic symptoms.

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Chapter 13

CASSANDRA'S CALCULATIONS: SIMULATION STUDIES OF THE PSYCHOMETRIC CONFOUND

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ABSTRACT

Experimental psychopathology struggles with the fact that patients' behavioral impairments are difficult to interpret as specific cognitive deficits. This difficulty, known as the psychometric confound, occurs because mental disorders such as schizophrenia usually result in impairments across many tasks, and some of these impairments may appear larger simply because a task has greater discriminating power (Chapman and Chapman, 1973). This frustrates the use of behavioral paradigms to investigate the cognitive, neural and genetic basis of schizophrenia. This chapter illustrates and indexes the psychometric confound in four simulation studies. These studies use the relationship between an imputed effect size and an observed effect size as a gold standard for measuring task discriminating power. The first simulation provides a primer on the sources of the psychometric confound, as well as an investigation of the validity of several metrics of discriminating power. The subsequent simulations evaluated the extent to which the use of standardized scores, demographic norming, and standardized residual scores mitigate the distortions caused by the psychometric confound. These simulations cast light onto how these approaches to the psychometric confound influence the interpretability of behavioral deficits, the range over which they are applicable, and domains where misconceptions about the psychometric confound exist. This approach may be useful for unlocking the potential of behavioral paradigms to reveal or appreciate how they may obscure the cognitive, neural and genetic basis of schizophrenia.

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INTRODUCTION

As responsible, well-meaning authors who hold the welfare of our readers foremost in our thoughts, we are obliged to begin this chapter with the following warning. The computer simulation studies that form the core of this inquiry and the accompanying musings reflect poorly on much of experimental psychopathology as currently practiced. They suggest that many studies from which we have derived our understanding of a variety of mental illnesses are flawed and uninterpretable. As a result the field may know less about the cognitive basis of mental illness than we think we do. At the same time the authors are reluctant to crack the rose-colored spectacles of those readers who cling to an optimistic assessment of cherished studies in the field. Such readers are admonished to skip-over the rest of this chapter. No, do not even glance at the figures.

We make no claim to be unique in our concern that many published studies in psychopathology fail to overcome a fundamental challenge underlying the study of group differences. Early Cassandras such as Loren and Jean Chapman and Raymond Knight pointed out long ago that studying the relationship between behavioral abnormalities and the causes of mental illness is perilous (Chapman and Chapman, 1973; Chapman and Chapman, 1978; Knight, 1984; see also Strauss, 2001). The simplified model in Figure 1 illustrates the rationale behind studying these relationships and some of the difficulties it entails. Assume an illness is associated with some indeterminate number of genetic and environmental factors, and that these factors cause cellular, pharmacological and regional neuroanatomical abnormalities. These abnormalities underlie (and are influenced by) pathological cognitive and affective mechanisms. These specific cognitive and affective deficits are in turn manifest as diagnosable problem behaviors and symptoms. An intuitively appealing approach to understanding the cause of these symptoms is to work backward, determining the underlying cognitive deficits, their neural basis and their genetic and environmental precursors. But the model also illustrates a number of ways in which one may seize on the wrong path across these levels of analysis: genetic and environmental factors have multiple effects including secondary neural changes that are irrelevant to developing the disorder; the relevant neural abnormalities themselves have secondary effects which are not relevant to developing the disorder. What's more, neural and cognitive processes change as a result of feedback from the environment. For example, institutionalization may lead to an affection for the 6 o'clock news, or an uncooperative attitude toward test-taking, either of which will influence performance on certain tests. Furthermore, different strengths or strategies may emerge to compensate for a deficit (with idiot-savants being an extreme example).

The revelation of Figure 1 is not that psychopathology is a difficult endeavor. Psychopathology is, in this sense, a hard science, but we shall not bemoan that here. The point is to make explicit the logic on which we rely when studying group differences. First, it is clear that identifying patients' abnormalities on a task in isolation does not allow one to interpret this as a cognitive deficit relevant to a disorder, that is a specific cognitive deficit. Patients' abnormalities could as well be the result of secondary cognitive impairments, reactive cognitive impairments or, in some cases, compensatory cognitive processes. Therefore, patients must demonstrate a deficit on one cognitive process *relative* to another. This demonstration itself rests on two assumptions. The first is that, other things being equal, specific cognitive deficits will be more closely correlated with the illness than other kinds of

impairments; a group selected for a certain outcome should be most homogeneous as regards the causes of that outcome, and more heterogeneous as regards non-causal factors. This assumption is so fundamental to the quasi-experimental or "ex post facto" design used in psychopathology that we will not speak further of it here. The second assumption is that the different cognitive processes are measured equally well. The psychometric confound is the interpretive problem that arises when the two (or more) tests are not equally good measures of their respective cognitive processes. Therefore, *addressing the psychometric confound is crucial to establishing whether any behavioral deficit is relevant to the link between illness manifestation and its cognitive, neural and genetic causes.*

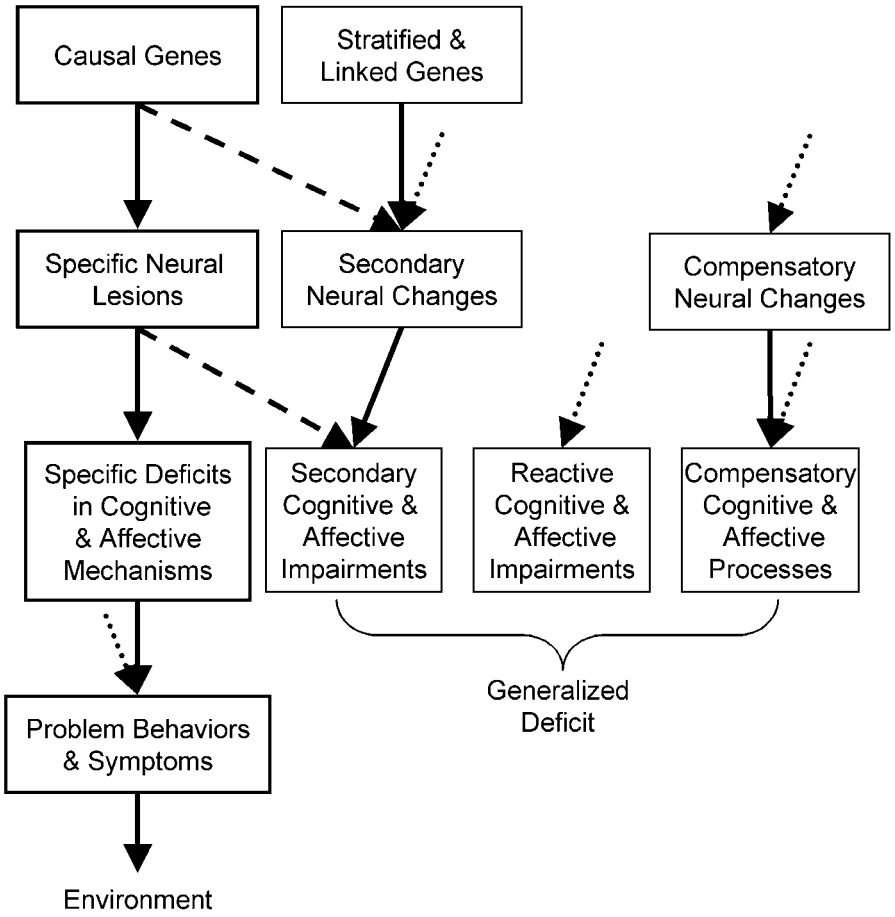

Figure 1. Levels of Analysis and Confounds in Etiological Research. The goal of etiological research is to identify causal environmental factors and genetic polymorphisms that lead to specific neural lesions which underlie specific deficits in cognitive and affective mechanisms that in turn lead to diagnosable problem behaviors and symptoms (white boxes). Isolating this core etiological path is complicated by secondary impacts at all levels of analysis (grey boxes) whose relationship to the disorder is largely spurious. Other factors being equal, quasi-experimental research designs assume the strongest effect sizes will be observed between direct causes (solid lines) whereas smaller effect will be associated with indirect causes (dashed lines), or effects associated with feedback from the environment (dotted lines).

ADDRESSING THE PSYCHOMETRIC CONFOUND

What does it mean to say that two measures of cognitive processes are equally good? The relevant concept in classical psychometrics is discriminating power, which reflects how sensitivity a task is to a patient groups' impairments.[1] To be sensitive, a test must measure a construct, or an impairment, consistently. Reliability is typically how we think of the ability to measure something consistently. But discriminating power incorporates more than reliability. Sensitive tasks are reliable, but not all reliable tasks are sensitive. For instance, a task may reliably measure working memory performance, but if it is not sensitive to differences between those with moderate memories and poor memories, it is unlikely to have good discriminating power. That is because, ultimately, tasks that are most able to discriminate among groups are those capable of accurately measuring individual differences within groups across the full spectrum of ability. The metric that captures this aspect of discriminating power is variance, or more precisely observed variance. (For some readers it will be counter-intuitive to think a patient groups' impairment, which is commonly measured as an effect size, will be maximal where the observed variance is maximal. Variance, after all, is the denominator in effect size equations. We will address this complaint in our results and for the nonce follow the above reasoning -- which turns out to be correct.) Thus, it is thought that two or many cognitive processes are equally well measured and sensitive to group differences if they have equal reliabilities and equal observed score variances, for then the true score variances are equal. It is easy to imagine instances, however, in which measures' reliabilities and variances are not equal. That is, they suffer from the psychometric confound. In fact, this is far more common than the rare instance in which they are matched. When the psychometric confound occurs, larger group differences might well appear on measures of secondary or reactive impairments or compensatory cognitive processes. That is, these generalized deficits may appear to be more closely linked to the illness than a measure of a specific cognitive deficit with lower discriminating power. Unaware of the psychometric confound, we may blithely trot off after neural and genetic willow-wisps.

Matching for reliability and observed variance is quite onerous (for procedures to do this, see Chapman and Chapman, 1973; Chapman and Chapman, 1978). In 30-odd years of schizophrenia research, such efforts have been undertaken only a handful of times (examples include Oltmanns and Neale, 1975; Spring et al., 1989). It is also occasionally hazarded in the Alzheimer's Disease and developmental literature. Rather than match for reliability and observed variance, it is far more common to attempt other methods of controlling for the

[1] Classical testing theory has been supplanted by item-response theory (IRT) in many domains of ability testing. IRT involves a number of methods which allow for the simultaneous estimation of individuals' latent ability and the accuracy with which that is measured. In many respects this addresses the psychometric confound, which may explain why so little work formal work has addressed this issue since the advent of IRT in the 1970's. However, much of the practice of experimental psychopathology is incompatible with the requirements of IRT. For example, IRT is sensitive when a range of items are presented, whereas experimental tasks often have a fixed level of difficulty in each condition. IRT generally involves sample sizes in the 100's, if not thousands (Embertson SE, Reise SP. Item Response Theory for Psychologists. Mahwah, NJ: Lawrence Erlbaum Associates, 2000, Lord FM. Applications of Item Response Theory to Practical Testing Problems. Hillsdale, NJ: Lawrence Erlbaum, 1980.), whereas most experimental studies have far fewer than this. Experimental psychopathology studies that have used IRT methods with small samples have been criticized for unstable parameter estimates. Whether for these reasons or out of habit, experimental psychopathology remains dominated by classical psychometrics of the kind simulated herein.

psychometric confound. As part of a larger project designed to quantify simpler and valid approaches to the psychometric confound, the studies described herein focus on three common procedures for addressing it.

The first technique is perhaps the most common, which is simply to standardize the data. This approach is no more difficult that either z-scoring all the data on the tests to be compared, or, more commonly, z-scoring the data of the control group and applying that transformation to the patient data. In this case, the standardization is generally sample-normed. A slightly more involved technique is demographic reference norming. This is standard practice in neuropsychological testing and involves correcting for nuisance variables such as age, generally through the use of a published formula or table, which at the same time standardizes the scores and variances of the residual scores. The third procedure we will examine is mathematically related to previous two, but was proposed by the Chapmans themselves (Chapman and Chapman, 1989). This approach involves covariation for performance on a second test. Covariation of performance is similar to demographic reference norming in that it involves examining a residual score on the test of interest after partialling-out a correlated nuisance variable. In this case the nuisance variable is conceptualized as a measure of the generalized deficit and may therefore be more closely related to performance on the task of interest than demographic variables.

This chapter examines these three techniques using computer simulations. In our view simulation studies are not a substitute for formal analysis, which we hope will be brought to bear on these questions in the future. For our purposes, simulation studies are useful for examining the cumulative effects of numerous variables on non-linear outcomes. Computer simulations allowed us to impute the underlying effect size, and compare these techniques as regards their ability to faithfully recover, or distort, that effect size. These simulations also allowed us to investigate the relationship between discriminating power and other psychometric properties, such as item difficulty, reliability, observed variance and true score variance.

METHOD

General Procedures

All simulations were conducted using MATLAB. The simulations shared the following fundamental features unless otherwise noted. Latent ability in 10,000 subjects in each of two groups was randomly assigned from a standard normal distribution. A mean group difference of 1.0 was imputed by adding 0.5 to the mean of the control group and subtracting 0.5 from the mean of the patient group. This imputed deficit of 1.0 SD's has the combined virtue of being both a simple, round number and of being close to the overall mean performance difference of 0.92 between schizophrenia patients and controls calculated in meta-analyses (Heinrichs, 2005). Performance on each item of a 20-item test was then calculated for each subject as follows. Each item was assigned an error value, which was randomly assigned from a normal distribution with a mean of 0 and a standard deviation of 1, 2, 3 or 4 standard deviations. Thus item error was simulated separately for each subject and was measured in standard deviations, with a higher standard deviation simulating the underlying instability of

an unreliable test. A combined item score was calculated by simply adding each individual's 20 item error scores with each individual's latent ability score.

To convert these 20 combined item scores per subject to dichotomous accuracy scores, we applied a threshold to the each item. For example, one accuracy threshold score separated the lowest 10% of the distribution from the other 90% of combined scores. This dichotomization was calculated separately for each item in the test for each of 21 levels of test difficulty from 0.1 to 99.9% correct. Subjects scoring below the threshold were determined to have made errors, whereas subjects above the cut point were considered to have responded correctly. Because the combined score included both latent ability and random item error, the lowest scores on any item were not necessarily those with the lowest latent ability, although low scorers were more likely to have low latent ability. Notice that this approach to dichotomization was similar to having guesses count as misses, in that there was no alternative likelihood of a correct response due to chance. This occurs in "free response" tests.

The sum of accuracy scores across all items was each subject's observed score for that difficulty level. Effect sizes (Cohen's *d*) for each difficulty level were calculated as the difference between the group means of observed scores divided by pooled standard deviation of observed scores for both groups[2]. Reliabilities of the tests at each difficulty level were estimated as the mean of the item intercorrelations using Kuder and Richardson's formula 21 (or KR-21, Kuder and Richardson, 1937)[3]. KR-21 formula is formally equivalent to alpha (Cronbach, 1951) for dichotomously scored data. While the simulation environment allows direct calculation of reliability, we have opted to use KR-21 as this is a standard practice with empirical data.

This method for evaluating the influence of task parameters allowed us to calculate how closely the observed effect size reflected the effect size imputed into the latent ability scores. In other words, if you have a number of tests measuring *exactly* the same trait with *exactly* the same latent group difference, how might the intervening test characteristics distort or obscure the latent effect size, opening the possibility of concluding that patients were more impaired on one of the tests relative another? Subsequent simulations then focused on three procedures for recovering an unbiased measure of the imputed effect size.

The first method for recovering the imputed effect size was simply to use a standard normal (z-score) transformation. In this case we standardized scores for both patients and controls based on the control group's mean and standard deviation. We then simulated the impact of removing from the observed score variance attributable to a demographic variable. Demographic variables frequently have low to moderate correlations with task performance, and it is standard practice to account for such factors when scoring neuropsychological or cognitive tests. The influence of a demographic variable was evaluated by introducing a correlation between latent ability and a random, uniformly-distributed demographic variable, similar to age. The common variance attributable to the demographic variable was varied

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[2] $d = \frac{Mean_{controls} - Mean_{patients}}{SD_{pooled}}$ where $SD_{pooled} = \sqrt{\frac{SD^2_{controls} + SD^2_{patients}}{2n-2}}$

[3] KR-21 = $\frac{K}{K-1} \times \left(1 - \frac{M(K-M)}{K \times s^2}\right)$, where K is the number of items in the test, M is the mean score on the test, and the s is the overall standard deviation of the scores on the test

across four levels, including 0%, 10%, 20% and 30%. Other aspects of the simulation were the same as described above, with the exception that scores were generated only with item error of 2 SD's. This level of item error corresponded to a KR-21 of about .75 on average.. Variance attributable to the demographic variable was then regressed out of the observed accuracy scores before calculating an observed effect size.

The simulation of the standardized residual scores procedure required calculating performance on two tasks, one that measured a latent generalized deficit and a second that measured both a generalized deficit and specific deficit. Following the convention established by the Chapmans (1989), we will call this second test measuring the generalized deficit Task A and the first one measuring the candidate specific deficit as well as the generalized deficit Task B. In this case, Task A had a latent effect size of 1.0. Task B shared exactly the same latent ability scores as Task A for the generalized deficit, which contributed to a close correlation between the two tasks. Additionally, Task B had a further latent effect size of 1.0 for a specific deficit. After creating these latent ability scores, the same procedures described above were applied to generate observed scores for both Task A and B, with the exception that scores were generated only with item error of 2 SD's.

The purpose of performance covariation is to "correct," or partial-out, the variance in Task B that is accounted for by the generalized deficit measured by Task A. To do this, we computed the standardized residual scores using the formula proposed by Chapmans (1989)[4] for observed scores from every difficulty level of Task B correcting for observed scores from every difficulty level of Task A using the equation for the regression of B on A computed for the observed scores of control subjects[5]. The scores of only control subjects were used to compute the regression so that deviations from performance predicted from controls, that is the residuals, could be considered specific deficits.

RESULTS

Study 1. Simulations of the Psychometric Confound

To illustrate the impact of the psychometric confound, we first examined how difficulty, observed variance and reliability interacted to change the relationship between a fixed, imputed effect size and various observed effect sizes. Figure 2A illustrates the influence of

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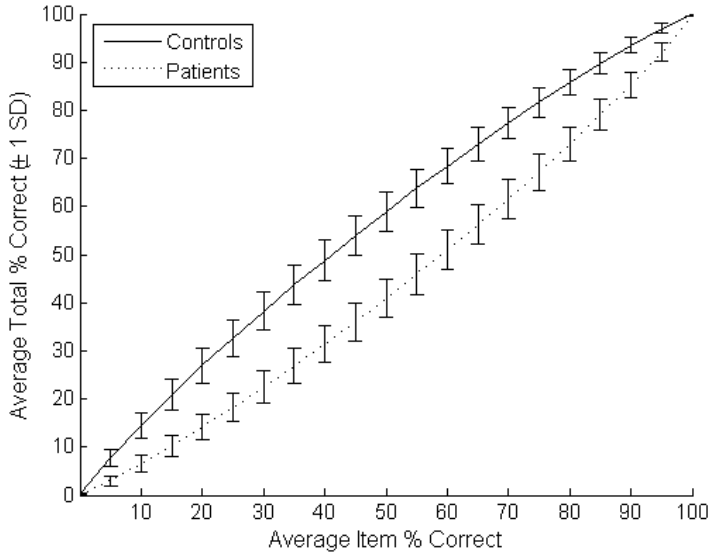
[4] $z_B = \frac{B - B'}{SE_{B.A}}$ where zB is the standardized residual score, B is the observed score on task B, B' is the predicted score from the regression of B on task A, and SEB.A is the standard error of the observed B scores on the regression line of A, which can be calculated by following equation. $SE_{B.A} = \frac{SD_B}{SD_A}\sqrt{\frac{1-r^2}{n-2}}$ where r is a correlation between the control subjects' observed scores on the task A and B, and SDB and SDA are the standard deviation of the control subjects' observed score on the task A and B respectively.

[5] $B_i' = r\frac{SD_B}{SD_A}(A_i - \overline{A}) + \overline{B}$ where $\overline{A}$ and $\overline{B}$ are the means of the observed scores of control subjects on the task A and B respectively.

ceiling and floor effects on the constant, latent group difference of 1.0 standard deviations across a range of test difficulty from very difficult to very easy. The gap between the means of the groups was narrowest at the extremes and was widest in the middle, at around a combined difficulty of 50%. The standard deviations also appeared to be narrowest at the top and bottom of the range, and were maximal in the middle.



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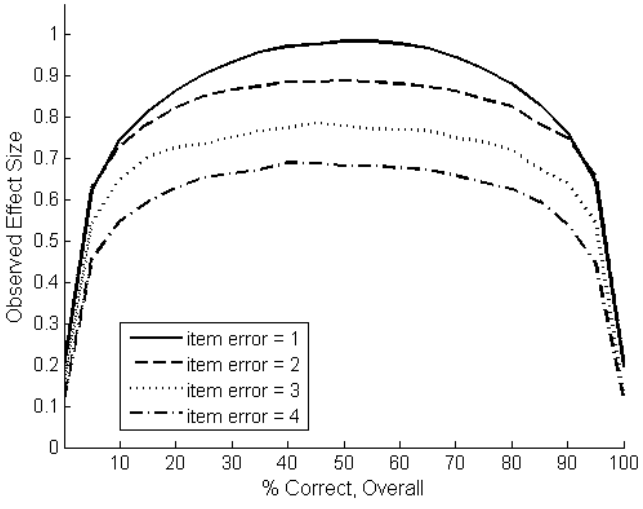

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Figure 2. Impact of Difficulty on Group Differences. Simulation of 10,000 controls and 10,000 patients with a 1 SD difference in their latent ability scores on a 20 item test. **A.** Accuracy scores across 21 levels of test difficulty (when item error = 2 SD's). **B.** Observed effect size by test difficulty for 4 different levels of item error. Note, tasks of the same difficulty level but different levels of item error can have different degrees of discriminating power (as measured by the observed effect size). Tasks with the same item error level but different degrees of difficulty can also have different degrees of discriminating power.

Given that an effect size is the mean difference between groups divided by the standard deviation, it may be unclear whether the effect size in the middle will be smallest (if the standard deviation grows faster than the mean difference), unchanged (if the mean difference and standard deviation grow proportionally), or largest (if the mean difference grows faster than the standard deviation). Figure 2B shows that, without a doubt, the mean difference grew faster than the standard deviation. That is, the effect size was maximal halfway between very difficult (chance performance) to very easy (perfect performance), no matter how much error there was in measuring each item. Measurement error did influence the effect size, however. The influence of item error, which was measured in standard deviations of the normal distribution added to each item before dichotomization, reduced the effect sizes across the range of difficulty by about one third. Thus, matching on difficulty alone is insufficient control over the psychometric confound. At the same time, task difficulty played an important role in discriminating power.

Why is the observed effect size greatest at a combined difficulty of 50%? One possibility is that halfway between chance and perfect performance is where the observed variance is maximized. Figure 3 illustrates that there was indeed a direct, loglinear relationship between observed variance and effect size, such that the effect size was maximal when the observed variance was maximal. Only half of the distribution of difficulty was shown in the figure because the pattern was symmetrical on both sides of 50%. As difficulty approached 70%, the observed effect sizes became more bunched together. That is, the effect size was influenced less and less by changes in difficulty. This is presumably because difficulty had a decreased effect on observed variance below this point and, by implication, above 30% accuracy – which is to say furthest away from ceiling and floor effects. As predicted, the relationship between variance and effect size was again moderated by item error. The effect size linearly increased for a given level of variance (and at a given difficulty level) for item error of 2, 3 and 4 standard deviations. Surprisingly, when the item error was 1, that is when the reliability was greatest, the line did not follow this pattern as closely. Even here the relationship between observed variance and observed effect size pertained. In almost every case the advantage in reliability led to a slightly higher observed effect size than when item error was 2. These findings suggest that simply knowing the level of variance of a measure is not enough to predict its discriminating power.

We stated above that another aspect of discriminating power is reliability. In the current simulations, reliability changed with different amounts of item error and different degrees of difficulty. Figure 4 illustrates the effect of these variables on reliability, and in turn their effect on the observed effect size. In this case, each line represents a given level of difficulty, and each of the four dots from left to right indicate the effect of 4, 3, 2 or 1 standard deviations of item error. This figure provides a degree of real-world grounding for the item error manipulation. Regardless of difficulty, tests with an item error of 1 had a KR-21 of .9. As item error increased, different levels of difficulty resulted in a small range of reliabilities. For example, when item error was 2 there was a KR-21 between about .7-.8, and so forth. These findings suggest that the current simulation of 20 items were similar in this regard to many of the tasks currently used in experimental psychopathology. The figure also illustrates that reliability was most linearly related to the observed effect size near the point of peak effects. As the task approached the ceiling of performance, the relationship became increasingly flat. That is, incremental gains in reliability did not have a further influence on the effect size.

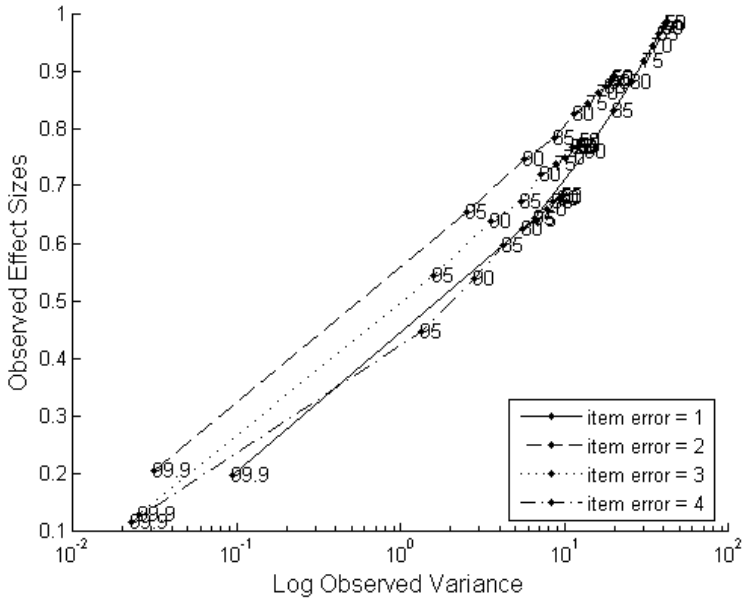


Figure 3. Observed Variance (log scale) and Observed Effect Size. This relationship is illustrated for 4 different levels of item error (lines) and 11 different levels of difficulty (notations).

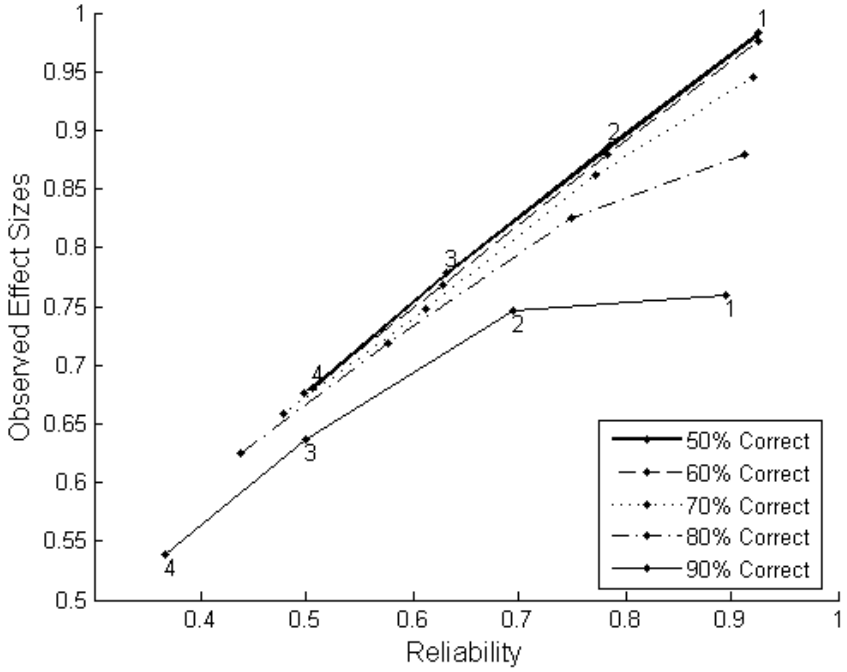


Figure 4. Reliability and Observed Effect Size. This relationship is illustrated for 5 different levels of difficulty (lines) and 4 different levels of item error (notations). Note that the relationship between item error (which is imputed) and reliability (which is measured) is mediated, to some extent, by difficulty.

Is there some relationship between difficulty, observed variance and reliability that can predict a task's discriminating power? True score variance is the product of reliability and observed variance. Thus, it draws toward the mean each individual's score to the extent that a measure is unreliable. In the extreme, the best predictor of anyone's true score on a completely unreliable measure would be the mean score. Figure 5 shows our calculations for the relationship between true score variance, on a log scale, and observed effect sizes. If true score variance were a good predictor of discriminating power, higher true score variance should lead to higher observed effects. This was true in general. However, if true score variance were enough to predict discriminating power, the lines that correspond to different amounts of item error should have been superimposed, which they clearly were not. Several points along the axis illustrate the problem. For example, when item error was 1 and difficulty was 95%, the true score variance was nearly exactly what it was when item error was 2 and difficulty was 85. However in the former case the observed effect size was about .60, whereas in the latter it was about .75, a 25% increase in discriminating power. Thus, true score variance appears to be related to discriminating power – as we have previously demonstrated that its components are related – but the nature of this relationship may be less straightforward that previously advertised.

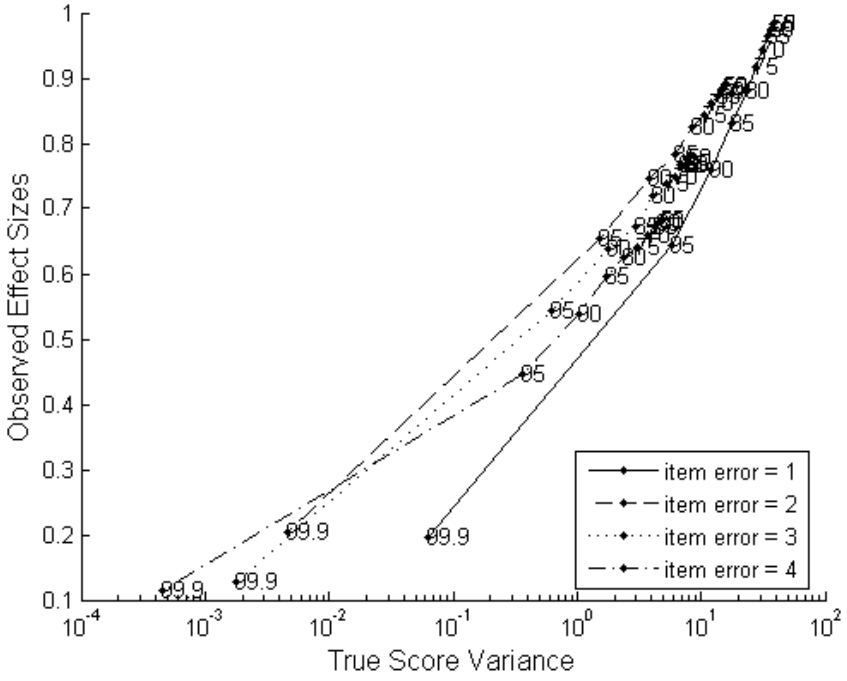


Figure 5. True Score Variance (log scale) and Observed Effect Size. This relationship is illustrated for 4 different levels of item error (lines) and 11 different levels of difficulty (notations).

Many of the above results have been argued previously (cf. Chapman and Chapman, 1978). Our purpose in reiterating them here is to remind the cognoscenti, persuade any remaining skeptics, and demonstrate that simulations like the current one are able to capture these basic, psychometric properties. Not everything we thought we knew about the

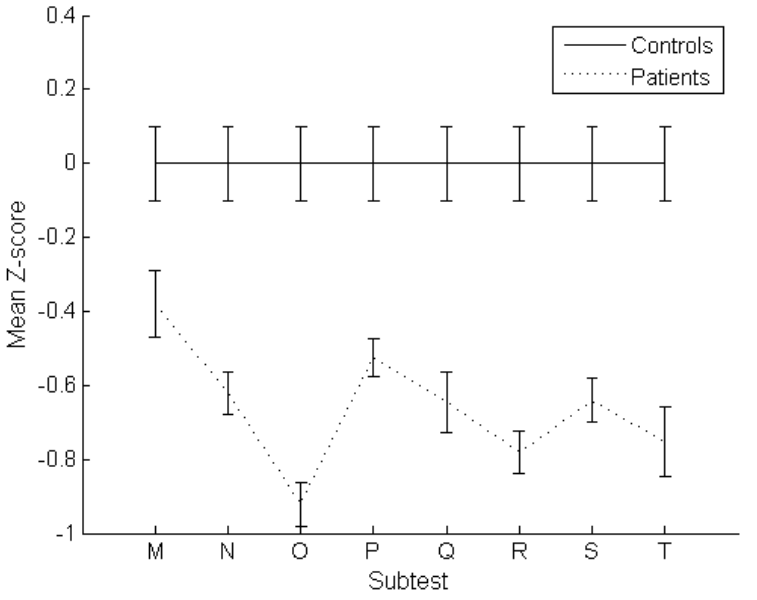
psychometric confound turned out to be gospel truth – the thumbnail equivalence of true score variance and discriminating power, for example. Despite this, the main gist of the psychometric confound and its relationship to ceiling and floor effects deep into the distribution of difficulty (down to about 70% accuracy) was supported. The rest of this chapter will examine whether several common data-processing procedures can reduce or eliminate the distortion of the psychometric confound to our imputed effect size.

Study 2. Simulations of the Standard Scores Procedure

Standard scores have long been used to allow comparisons across different traits or abilities. Standard scores are generally produced using a linear transformation in which a group mean is first subtracted from each individual's score, and then this difference is divided by the standard deviation. This results in a scale that has a mean of 0 and a standard deviation of 1. Of course this is arbitrary. In disciplines where negative numbers are thought scary, equivalent standardizations can result in means of 100 and standard deviations of 15, and so on. Standardization can be done on any scale any time one can calculate a mean and standard deviation. If this procedure can be used to eliminate mean differences between tasks in difficulty and variance, then surely it must be useful in addressing the psychometric confound.

Figure 6A illustrates a common use of standardization in the service of removing task differences. That is, the group of control subjects were normed to a mean of 0 and a standard deviation of 1 across 8 tasks, labeled M through T. The same transformation (using the control group's mean and SD) was then applied to a small patient group. The result was something formally equivalent to a neuropsychological profile, that is a graph of group differences across tasks. The fact that patients performed worse than controls on all tasks demonstrates a large generalized deficit. However, the fact that there were greater deficits observed on some tasks (O, R and T) compared to others (M and P) was suggestive of specific deficits.

Figure 6A is in fact a trompe l'oeil. These 8 tasks measured exactly the same latent ability across individuals and across groups used in Study 1, and exactly the same imputed effect size of 1.0. That is, they were the equivalent of the unstandardized data illustrated in Figure 2B, which your nefarious authors mixed around to make look like a familiar profile of the kind frequently published in the field. Figure 6B is a more honest representation of these data. A comparison of Figures 2B and 6B shows that, far from addressing the psychometric confound, the standardization procedure did not influenced the effect size at all**.** In fact, we're in a worse position than we were before, because we have obscured the variance of the raw scales.



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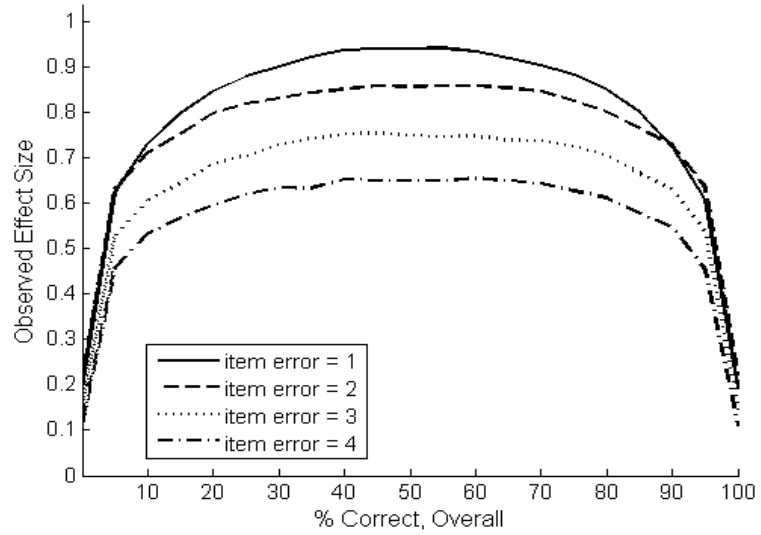

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Figure 6. Impact of Standard Score Procedure. **A.** A "neuropsychological profile" drawn from a test measuring the same latent deficit at eight different levels of difficulty (M through T, *n*=10 per group). **B.** The effect on observed effect size of standardizing scores using the control group's mean and SD (*n*=10,000 per group).

Why didn't standardization address the psychometric confound? Well, obviously it did not affect the reliability of a scale, which is a key aspect of discriminating power. Some might assert that if one's tasks have approximately the same reliability to begin with, then standardization will bring their observed variances in line, resulting in psychometrically matched tasks. But this is careless optimism. Standardization fails not simply because the

reliability of the scales might be unequal, but because it does not address the causes of differences in variance. The simplicity of the transformation merely requires the ability to calculate a mean and a standard deviation. It does not account for the fact that a raw scale may be closer to or further from the point of peak effects. In an extreme case, a scale in which subjects in the top half of the distribution all have the same score (say, 100%) can be perfectly equated with a scale that has maximal discriminating power in terms of their mean and standard deviation. That is, both scales can be standardized. But this will not change the underlying advantage of the second scale. This reasoning extends to more realistic scales as well. Other things being equal, the scale with a mean accuracy of 80% will have greater discriminating power than a scale with a mean accuracy of 90%, even after they have both been standardized.

Study 3. Simulation of Demographic Norming Procedure

Generally, published tests as well as tests described in the neuropsychology literature are not only standardized, as described above, but nuisance variance is also removed using some kind of norming procedure. Nuisance variance is not attributable to the cognitive process of interest, but is instead traced to some other feature of the participants, such as their age, sex, education level or shoe size. It is feared, and perhaps rightly so, that variability from such sources will decrease the clinician's ability to identify a patient's impairment, or a researcher's ability to observe a group difference. If this procedure can be used to eliminate nuisance variability attributable to inessential factors, then surely it must be useful in addressing the psychometric confound.

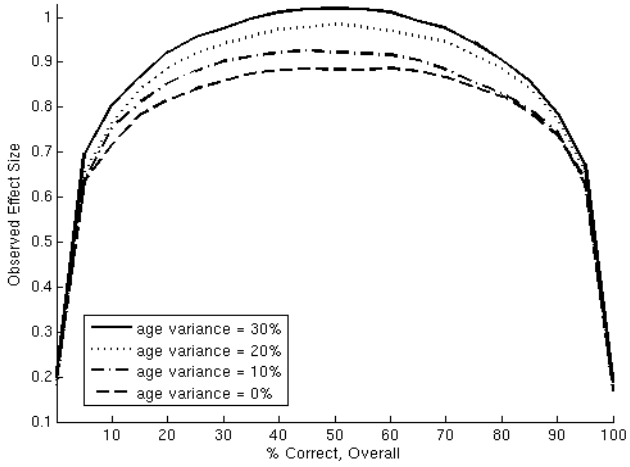


Figure 7. Impact of Demographic Norming Procedure. The effect on observed effect size of partialling-out a variable with an influence on task performance independent of group status. In this case the variable was continuous and uniformly distributed, and fixed for each individual as age might be in an experimental sample. This relationship is illustrated for 4 different levels variance in the latent ability score accounted for by age variance. The Pearson correlations between age variance and observed raw scores were approximately .45, .35, .25 and 0 (with some changes across the range of difficulty) corresponding to the addition of age variance of .3, .2, .1 and 0, respectively. There was no relationship between age and group status.

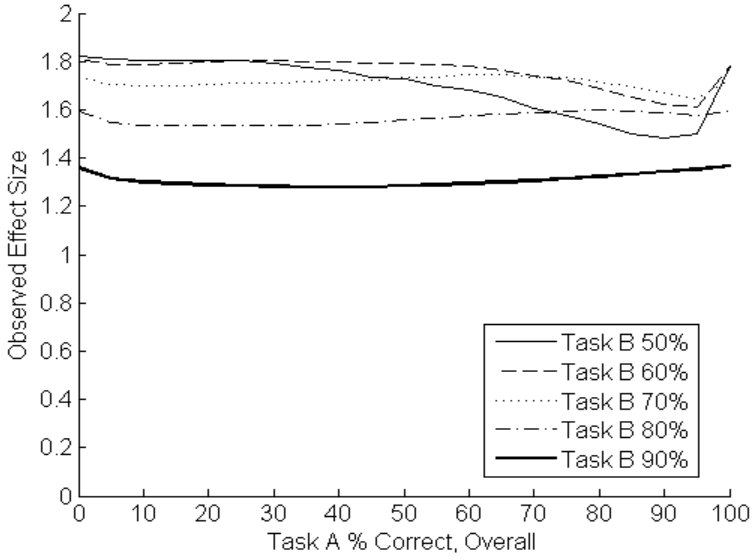
Figure 7 illustrates the simulated effect of removing variance associated with nuisance variance attributable to a demographic factor. Of course, when age accounted for no variance in performance, the line was identical that calculated in Figure 2B (or 6B for that matter) when the item error was 2 SD's. The other three lines describe the change to the observed effect size as age becomes more closely related to performance. Under these circumstances, the higher the covariance, the greater the observed effect size at the point of peak effects after the nuisance variance was removed. Most importantly for our purposes, the influence of difficulty and observed variance was unaffected by this procedure at best, and at worst will increase the challenge of matching tasks for discriminating power. That is, tasks with otherwise similar levels of difficulty and variance will become unmatched if they are related to such nuisance variables to differing degrees. Whatever its other merits, this procedure cannot in good conscience be prescribed as a technique for addressing the psychometric confound.

Study 4. Simulation of Standardized Residual Scores Procedure

Thus far, our efforts to address the generalized deficit using popular, established, and above all easy transformations have come to naught. This is the uncomfortable state of affairs that the Chapmans found they had contributed to, when, in 1989, they published another potential solution to the psychometric confound based on using a residual score. This method was based on Lord's techniques for measuring change over-and-above regression to the mean (Lord, 1963). Instead of z-scoring patients' scores and instead of correcting for a demographic variable assumed to influence scores equally across individuals, this technique proposed that the generalized deficit be estimated for each individual using a second task. Performance on this test could then be used to predict how well one should perform on the task of interest, that is the measure of the candidate specific deficit. Any difference between groups on the difference score calculated between observed performance on the task of interest and the predicted performance for this task based on the measure of the generalized deficit could then be interpreted as a deficit in patients over-and-above the generalized impairment. This simulation required two tasks, Task A, which measured a generalized deficit with an imputed effect size of 1.0, and Task B, which measured the same generalized deficit plus an additional specific deficit with an imputed effect size of 1.0. That is, Task B had a total imputed effect of 2.0, half of which was a generalized deficit (that is measured in common with Task A) and half of which was a specific deficit (over-and-above and uncorrelated with the impairment measured in Task A).

In our first analysis of the standardized residual score procedure, we calculated a Task B residual score across 5 levels of difficulty of Task B and across all levels of difficulty for Task A using the Chapman's formula. These residual scores were then rescaled as the observed effect sizes graphed on Figure 8A. As can be seen, this procedure has a very desirable feature not seen in the previous simulations. For a given difficulty level of Task B, the difficulty (and by implication the observed variance) of Task A does little to change the observed effect size. The minor caveat to this general principle occurs when Task B approaches the point of maximal effects (50% difficulty) and Task A is near the ceiling, which is the result of the differential impact of the ceiling on controls and patients. (This wobble can be eliminated if patients are given a mean of 0 and the entire group difference is

added to the controls' mean.) Overall, and for most of the range of difficulties for Task A, the observed effect size for the residualized B score remained much more constant and robust than in the previous simulations.



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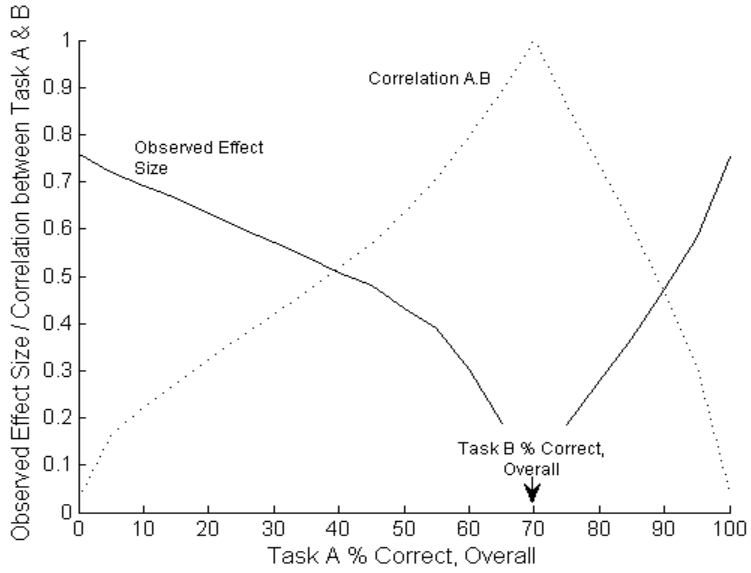

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Figure 8. Impact of Standardized Residual Scores Procedure. **A.** The effect on observed effect size of covarying 21 different difficulty levels of Task A from 5 different difficulty levels on Task B. The generalized deficit measured by both Tasks A and B was 1 SD. The specific deficit measured by Task B was an additional 1 SD. **B.** Test of correctly rejecting a false null hypothesis. Neither Task A nor Task B measured a specific deficit over-and-above the generalized deficit and item error was removed. This graph illustrates the phantasmal effect of the procedure when the difficulty of the two tasks is increasingly different (solid line), and how this is related to the correlation between Task A and B among controls (dotted line).

Too robust, in fact. Our elation at how conveniently the curves of the previous simulations illustrated in Figure 2B and 6B had flattened out when using a residualized score was dampened by the realization that these observed effect sizes were in fact *greater* than the imputed effect size. While the overall imputed effect size (including both the generalized and specific deficit) was 2.0 after partialling-out the generalized deficit, our intuition was that the specific deficit should have had a maximal observed effect of 1.0.

What good is intuition, right? An effect is an effect, why get prickly about whether it is distorted a little bit. In practice, an adequately powered study will still show a group by task interaction, and the impairment can then be interpreted as a specific deficit. One way to test this logic is to observe what happens when there is in fact no effect of a specific deficit to observe. To do this, we modified our simulation so that Task A and Task B both measured a generalized deficit with an imputed effect size of 1.0 and Task B measured a specific deficit with an imputed effect size of 0.0. Thus, the latent abilities that Task A and Task B measured were perfectly correlated, and a procedure that accurately reflected a residual specific deficit should have an observed effect size not meaningfully different from 0. However, when we conducted the residualization procedure, Task B again showed a large observed effect size which would have been interpreted as a specific deficit if we didn't know that it should be 0. We thought this might have been the result of item error variance introduced before combining the item scores. So we reduced the item error to 0, which eliminated the introduction of uncorrelated variance into the combined item scores. Thus Tasks A and B were perfectly correlated up until the items were dichotomized based on the difficulty cut-offs. The rest of the simulation followed the procedures used in creating Figure 8A.

The fundamental result from this supplemental simulation is illustrated in Figure 8B. This figure shows what happened at a single difficulty level of Task B across multiple levels of difficulty in Task A. The observed effect size of the Task B residual scores was greatest where there was the greatest difference in difficulty between Tasks A and B. In fact, near the ceiling and floor a phantasmal effect of almost .80 SD's was observed. This qualifies as a large effect according to Cohen's (1988) conventions. Conversely, as Tasks A and B approached the same difficulty level, the phantasmal effect shrank, and where the two tasks had exactly the same difficulty level, the residual score could not be calculated at all. To investigate this phenomenon further, we calculated what happened to the correlation in the observed accuracy scores as the difficulty of the two tasks changed. Although the tasks' underlying combined item scores were identical, the process of dichotomizing (i.e. adjudicating whether each item was correct or incorrect at a given difficulty threshold) increasingly decorrelated the observed accuracy scores. For the example presented in Figure 8B, the correlation between the observed accuracy scores is also illustrated. This correlation is perfect when A and B have the same level of difficulty, and then it drops to 0 at the extremes of the floor and ceiling of difficulty. The less correlated the accuracy scores, the greater the phantasmal effect size.

This result flies in the face of our hope that an effect is an effect, whether or not it is slightly distorted. Instead it presents the sobering possibility that using a residualized score can result in false positive effect sizes even under optimal circumstances – that is where Tasks A and B have an equal number of items, an equal level of item error and measure exactly the same latent generalized deficit in an arbitrarily large sample – conditions never actually realized in practice. Thus, the procedure shares with the previous simulations the risk

of observing a specific deficit in the absence of an impairment in any underlying, interpretable process.

DISCUSSION

Where does this leave us? What are the implications of these simulations for the study of psychopathology? This chapter has illustrated several aspects of the psychometric confound: its relationship to difficulty, observed variance, reliability, and true score variance, and its resistance to various linear transformations commonly used in the field. These findings push our knowledge about the psychometric confound further in two ways. We have gained some direct insight into the relationship between the components of true-score variance and the observed effect size, and determined that while there is indeed a relationship, that this relationship may be logarithmic, and that it may be approximate rather than absolute. We have illustrated where and how much these various psychometric characteristics influence the observed effect size, and by implication, how they could lead to deceptive results in an group by task interaction for psychometrically dissimilar tasks. It was not our intention, in the course of conveying these complications, to drained all hope from anxious readers. Our intention was to focus, or refocus, creative minds on the necessity of grappling with the psychometric confound using appropriate, and perhaps novel, tools.

Are these demonstrations relevant beyond the domain of experimental psychopathology, or is this field uniquely benighted by the psychometric confound? As pointed out above, the confound was originally investigated in the domain of schizophrenia largely because the generalized impairments in schizophrenia are so apparent. However, the confound is not restricted by diagnosis, nor even is a diagnosis necessary. Controlling for the psychometric confound is important whenever group differences may influence performance in more than one domain. Since this is a very likely circumstance, the need to control for the psychometric confound should be the default assumption for most studies of the relationship between individual differences (or experimentally manipulated differences) and ability. Development and ageing, personality factors, brain damage and brain lesions all have the potential to influence ability across a number of domains, some of which will be more directly involved in causing the individual difference in behaviors.

Given the broad relevance of understanding the psychometric confound, why do experimental psychopathologists and others still run afoul the confound three decades after its discovery? There are a number of potential reasons. One has to do with the nature of the task development pipeline. Modern experimental psychopathologists generally obtain their tasks from two sources: cognitive experimental psychology and clinical neuropsychology. Cognitive experimental tasks contain internal, within-subject control conditions that provide interpretive leverage for isolating the mental mechanism tapped by the condition of interest. Within-subject control conditions are tempting to use as control conditions when demonstrating a group difference. Unsurprisingly, they are often not up to snuff, because they have not been developed to have equal discriminating power. Thus, an elegant paradigm may provide misleading results when used to look at group differences (for a slightly different perspective, see Knight and Silverstein, 2001). On the other hand, clinical neuropsychologists have a battery of off-the-shelf tasks of numerous cognitive domains. The most impressive

method for validating such tasks is the evaluation of focal brain damage patients. In these circumstances, the focal damage might impair performance so markedly on a single task while sparing all others that the likelihood this might be caused by a psychometric confound is very low indeed. However, from this strong ground of validation, lesser impairments are given increasing likelihoods based on the kinds of population norms critiqued in Studies 2 and 3. As one begins to generalize from the focal brain damage case to less obvious cases, the psychometric confound subtly settles over the whole endeavor. To our knowledge, no test battery has yet been developed with the specific aim of controlling for discriminating power across all the component tests.

The pipeline of task development is not itself a limitation, however; it is a convenience. The pipeline of task development could include a phase during which control tests are developed that have demonstrably equal discriminating power. However this is rarely done in practice because it takes a lot of time. Thus, in our estimation the primary reason that the psychometric confound is generally not surmounted in modern experimental psychopathology boils down to one factor: haste.

It is important to appreciate that the psychometric confound is not ubiquitous. Much experimental psychopathology research can be accomplished perfectly well without concern for the psychometric confound. If someone cannot drive safely, it doesn't matter whether that is because she has a specific driving deficit or she is blind – she is still a danger to herself and others. If a patient has difficulty making change for a ten dollar bill, it doesn't matter whether that is a specific change-making deficit, or a secondary or reactive impairment; the cash drawer still will not balance at the end of the day. Such impairments are important to study because they have important implications for vocational and quality-of-life related outcomes, and the specificity of these impairments is not crucial to determine.

Besides limits to the domain of the psychometric confound, there are limitations to the current investigation of it. The simulation studies used herein to demonstrate the domain of the psychometric confound depended on a number of simplifying assumptions that should be made explicit. First, patients will commonly have more variance than controls on cognitive variables. This empirical observation was captured in those simulations where controls were differentially affected by ceiling effects (generally from 70% accuracy and higher). However it may well be that this phenomenon is fundamental to patients' latent ability, or is a function of reduced consistency (great item error) when answering an individual item. While group differences in variance over-and-above what we have already modeled may change some of the specifics of the simulation, they are unlikely to affect the general shape of the psychometric confound or alter its relationship to its components: difficulty, observed variance and reliability. Another simplifying assumption rarely realized was that each item in any simulated task was modeled as having exactly the same difficulty. Perhaps a more important limitation of the current study is that we simulated free-response style questions. This is equivalent to a task in which chance guessing has a close to zero likelihood of being correct. Thus, someone without a clue as to the correct response will find the floor at zero rather than at 50%, as one might find for a forced-choice response task. Although forced-choice response tasks are more common in experimental psychopathology, they present several complicating factors that we have opted to avoid at this time. There are a number of ways to model the influence of chance on performance which seemed an important enough source of confusion to leave for a later time. Additionally, the influence of chance on forced-choice response tasks has been shown to skew the point of peak effects (Lord, 1952). Instead

of being precisely halfway between chance and perfect performance, the point of peak effects is shifted a little closer to perfect performance. This was considered a complication that did detract from the general principle illustrated by the simulations. It may, however, limit their applicability in some specific regards – for example in determining the range within which difficulty has a reduced effect on the observed effect size. Finally, these simulations should not be considered the final word on the relationship between true score variance and sensitivity to group differences. That is, we have measured effect sizes, but have not thoroughly examined other measures of group difference, for example mean differences, which are relevant to interaction effects on ANOVA's. This is another important future direction for this work.

Bearers of bad news, like scholars of the psychometric confound, have had mixed results throughout history. Two stories that have echoed through the ages illustrate two different kinds of bad news bearers: Chicken Little and Cassandra. Chicken Little is renown for making a pessimistic forecast about the future of the sky based on a whooping over-generalization. Chicken Little was believed, but his claim has (so far) turned out to be invalid. Cassandra had the opposite problem. She was fated not to be believed when she foretold with all too much accuracy the fall of Troy. Neither bearer of bad news fared well for publicizing their ill-tidings. We hope this bad news about common practices in experimental psychopathology is both valid and believable. The purpose of the current simulations is to assist in both these regards. There is a way forward for our science, but it requires acknowledging the psychometric challenges inherent to experimental psychopathology. Not ignoring them.

ACKNOWLEDGEMENTS

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Chapter 14

SMOKING AND SCHIZOPHRENIA

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ABSTRACT

Frequency: The prevalence of cigarette smoking is significantly higher among patients with schizophrenia (60-90%) than in the general population (23-30%). While tobacco smoking decreases in general population (from 45% in the 1960's to 23-30% in the 2000's), smoking in patients with schizophrenia remains high. Patients with schizophrenia smoke more deeply, thereby increasing their exposure to harmful elements in tobacco smoke.

Impact of smoking on patients with schizophrenia: As in the general population, smoking contributes to the reduced life expectancy in patients with schizophrenia. Patients with schizophrenia are at elevated risk for cardiovascular disease due to high rates of cigarette smoking. In the Department of Mental Health of the commonwealth of Massachussetts, cardiovascular disease was the factor that most strongly associated with excess mortality.

Improvement of cognitive deficits: Patients with schizophrenia may use nicotine to reduce cognitive deficits and negative symptoms or neuroleptic side effects. Smoking may transiently alleviate negative symptoms in patients with schizophrenia in increasing dopaminergic and glutamatergic neurotransmission in the prefrontal cortex. In patients with schizophrenia, nicotine improves some cognitive deficits : 1) Sensory gating deficits and abnormalities in smooth pursuit eye movements associated with schizophrenia are transiently normalized with the administration of nicotine 2) High-dose nicotine transiently normalizes the abnormality in P50 inhibition in schizophrenic patients and in their relatives 3) In tasks that tax working memory and selective attention, nicotine may improve performance in patients with schizophrenia by enhancing activation of and functional connectivity between brain regions that mediate task performance 4) Cigarette smoking may selectively enhance visuospatial working memory and attentional deficits

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in smokers with schizophrenia. However, Harris et al. found that nicotine affects only the attention without effects of nicotine on learning, memory or visuospatial/constructional abilities. In addition, smoking could facilitate disinhibition in patients with schizophrenia. Some authors stressed that nicotine does not appear to have a long-lasting therapeutic effect on schizophrenia's symptoms.

Impact of smoking on patients with schizophrenia who are on antipsychotic medications : Smoking increases the metabolism of the antipsychotic medications by inducing the cytochrome P450 1A2 isoform. Smoking lowers the blood levels of typical or atypical antipsychotic medications.

Treatment: Although patients with schizophrenia have low motivations to quit smoking, smoking cessation treatment can be effective for these patients. Atypical antipsychotic medications, in combination with the nicotine transdermal patch, or bupropion significantly enhanced the rate of smoking cessation.

INTRODUCTION

It is well established that patients with schizophrenia are markedly prone to smoke tobacco. However, the reasons for the widespread smoking behaviours seen in these patients are not well understood. In this chapter, we will review the epidemiological, clinical and treatment data about the links between smoking and schizophrenia. Evidence suggests that smoking could be a form of self-medication to alleviate psychotic or cognitive symptoms of schizophrenia or to reduce medications side-effects.

EPIDEMIOLOGICAL DATA

Frequency of Tobacco Consumption in Patients with Schizophrenia

Many studies have shown that patients with schizophrenia consume tobacco much more often than the general population (table 1), or than patients with other psychiatric diseases. In the United States, as in other countries, the prevalence of cigarette smoking is significantly higher among patients with schizophrenia (60-90%) than in the general population (23%) [5, 9, 11, 13, 20, 33, 75]. In the meta-analysis of De Leon and Diaz of 42 studies including 7,593 patients with schizophrenia from 20 countries, the prevalence of tobacco consumption was 62% [13]. Moreover, while tobacco smoking decreases in general population (from 45% in the 1960's to 23-30% in the 2000's), smoking in patients with schizophrenia remains high [5, 33].

The figures noted for the general population come from studies on the general population at the time and in the countries in which the studies on tobacco consumption in patients with schizophrenia took place.

Characteristics of Tobacco Consumption in Patients with Schizophrenia

Patients with schizophrenia are heavy smokers: a mean of 22 to 27 cigarettes per day [20, 41, 47, 58, 59, 88, 90]. Patients with schizophrenia smoke more cigarettes: 29 to 46% smoke

more than 30 cigarettes per day vs 6 to 29 % in controls [13]. Tobacco consumption is more frequent in men than in women: 71% and 44% respectively in a recent meta-analysis [13]. Ninety per cent of patients with schizophrenia began smoking before the psychotic disorder started [47]. Patients smoke more deeply, thereby increasing their exposure to harmful elements in tobacco smoke [88]. They extract more nicotine from each cigarette than controls, and as a result have higher blood levels of nicotine and cotinine, a nicotine metabolite, and higher urinary levels of cotinine, for the same tobacco consumption [73, 88].

Table 1. Frequency of tobacco consumption in patients with schizophrenia

	N	Lifetime	Current	General population Current
Masterson et O'Shea 1984 (Ireland)	100	83 %	-	56 %
Hughes et al. 1986 (USA)	24	-	88%	30 %
Menza et al. 1991 (USA)	99	-	56%	-
Goff et al. 1992 (USA)	78	86 %	74 %	24 %
El-Guebaly and Hodgins 1992 (Canada)	106	-	61 %	32 %
Ziedonis et al. 1994 (USA)	265	76 %	68 %	22 %
De Leon et al. 1995 (USA)	237	-	85 %	24 %
Diwan et al. 1998 (USA)	63	95 %	86 %	28 %
Taiminen et al. 1998 (Finland)	88	-	56 %	23 %
Kelly and McCreadie 1999 (United Kingdom)	168	73 %	58 %	28 %
Mc Evoy and Brown 1999 (USA)	22	-	77 %	25-30 %
Herran et al. 2000 (Spain)	64	-	64 %	51 %
Itkin et al. 2001 (Israel)	64	55 %	45 %	28 %
Beratis et al. 2001 (Greece)	406	61 %	58 %	42 %
Patkar et al. 2002 (USA)	87	81 %	76 %	24 %
De Leon et al. 2002 (USA)	66	92 %	83 %	26 %
De Leon et al. 2002 (USA)	120	-	75 %	-
Llerena et al. 2002 (Spain)	100	-	70%	37 %
Srinivasan et al. 2002 (India)	286	52 %	38 %	40-45 %
McCreadie et al. 2002 (United Kingdom)	316	79 %	65%	40 %
McCreadie et al. 2003 (United Kingdom)	102	84 %	70 %	-
Poirier et al. 2002 (France)	207	70 %	66%	34 %
Mori et al. 2003 (Japan)	137	-	34 %	37 %
Margolese et al. 2004 (Canada)	207	-	66 %	22 %
Etter et al. 2004 (Switzerland)	151	85 %	70 %	28 %
Himelhoch et al. 2004 (USA)	199	-	61 %	27 %
Dervaux et al. 2004 (France)	100	78 %	67 %	30 %
Aguilar et al. 2005 (Spain)	250	73 %	69 %	27-44 %

The Fagerström Test for Nicotine Dependence is widely used to assess nicotine dependence and to predict success in stopping smoking. High nicotine dependence is defined as a total Fagerström Test for Nicotine Dependence score of 6 or higher [13]. Tobacco addiction, evaluated using the Fagerström scale, is severe in patients with schizophrenia, with a mean score between 6 and 7, according to several studies [13, 17, 20, 44, 74, 82, 88, 91]. However, some authors have recently thrown some doubt on the validity of the Fagerström scale in patients with schizophrenia, since this scale can underestimate tobacco addiction in

this population [82]. It should also be noted that in some studies, the level of nicotine dependence in patients with schizophrenia is similar to those found in patients with other serious psychiatric disorders [13].

IMPACT OF TOBACCO CONSUMPTION ON THE PHYSICAL HEALTH OF PATIENTS WITH SCHIZOPHRENIA

Mortality

As in the general population, smoking contributes to the reduced life expectancy in patients with schizophrenia [36]. The risk of mortality from cardiovascular disease is 2.2 to 5 times higher in patients with schizophrenia than in the general population, and 3.2 times higher for respiratory disease [27, 36, 88].

Cardiovascular Diseases

The reduction in life expectancy from tobacco in schizophrenic patients is mainly due to an increase in cardiovascular disease risk [36, 68]. In the Department of Mental Health of the commonwealth of Massachussetts, cardiovascular disease was the factor the most strongly associated with excess mortality. Cardiac deaths were elevated more than 6-fold. Tobacco consumption in fact increases inflammation, thrombosis and LDL-cholesterol oxidation, which increase the risk of coronary heart disease and myocardial infarction [4]. Tobacco consumption also increases oxygen consumption by the heart muscle. Weight gain, insulin resistance, metabolic syndrome, and diabetes mellitus are frequent in patients with schizophrenia, and may worsen the risk of cardiovascular diseases [19, 36, 78].

Cancers

Premature death in patients with schizophrenia from tobacco is more often caused by cardiovascular disease than tobacco-related cancer. It has been reported that the risk for lung cancer in patients with schizophrenia is lower from that of the general population, despite increased smoking [12, 38, 68]. However, in a study conducted in Finland, a slightly increased cancer risk was found in 27000 patients with schizophrenia. Half of the excess cases were attributable to lung cancer [52].

Chronic Obstructive Pulmonary Disease

In a study of 200 adults with serious mental illness, the prevalence of chronic obstructive pulmonary disease, in particular chronic bronchitis and emphysema was significantly higher among those with serious mental illness than in comparison subjects [42].

EFFECT OF TOBACCO CONSUMPTION ON SCHIZOPHRENIC PATIENTS' SYMPTOMATOLOGY

Effect of Tobacco Consumption on the Psychotic Symptoms

Positive and Negative Symptoms

Several studies have compared the symptomatology of smoking and non-smoking patients with schizophrenia. These studies looked for correlations between psychotic symptoms and tobacco consumption, rather than studying causality. Most of these studies did not find any difference between the smoking and the non-smoking patients, on the evaluation scales used, such as the PANSS score for positive, negative and general psychopathological symptoms [3, 20, 41, 47, 83]. However, in a study by Paktar et al., the smokers obtained higher scores for negative symptomatology with PANSS than the non-smokers [74]. On the other hand, Ziedonis et al. found lower negative symptomatology scores and higher positive symptomatology scores in the smokers than the non-smokers [91]. In a study by Goff et al., the smokers had higher negative and positive symptoms subscales scores than the non-smokers [37]. Finally, Herran et al. found a link between anxiety and the number of cigarettes smoked per day [41].

Cognitive Symptoms

Several studies have shown that nicotine increases the cognitive capacity of healthy individuals, in particular for attention and working memory [Review: 11, 55, 77, 85, 86]. Many studies have shown that tobacco consumption can improve certain specific cognitive disorders found in schizophrenia. However, some authors stressed that nicotine does not appear to have a long-lasting therapeutic effect on schizophrenia symptoms [39].

- Patients with schizophrenia demonstrate a smooth pursuit eye movement dysfunction, involuntary reflexive saccades to a prepotent stimulus during saccadic tasks, and increased response to the second of two identical auditory stimuli, the P50 evoked potential response [1, 2]. Sensory gating deficits and abnormalities in smooth pursuit eye movements associated with schizophrenia are transiently normalized with the administration of nicotine. High-dose nicotine also transiently normalizes the abnormality in P50 inhibition in patients with schizophrenia and in their relatives [1, 2].
- Nicotine also improves prepulse inhibition abnormalities, another sign of a deficit in processing auditory information, found in patients with schizophrenia [49].
- Nicotine normalizes certain smooth pursuit eye movement abnormalities, found in patients with schizophrenia, which according to Olincy et al., could be a sign of a disorder of the inhibitory capacity of the prefrontal cortex [6, 71, 72].
- Cigarette smoking may selectively enhance visuospatial working memory and attentional deficits, assessed with the Continuous Performance Test, in smokers with schizophrenia [33, 79].
- However, Harris et al. found that nicotine affects only the attention without effects of nicotine on learning, memory or visuospatial/constructional abilities [39]. Another recent study found an improvement in delayed recognition memory in patients with schizophrenia by nicotine, but no effect on the working memory [69].

- A functional MRI study showed that nicotine improved attention and working memory in patients with schizophrenia by enhancing activation of and functional connectivity between brain regions, in particular the anterior cingular cortex, the thalamus, that mediate task performance [45]. Nicotine also modulated thalamocortical functional connectivity to a greater degree in patients with schizophrenia than in control subjects [45].
- In addition, smoking could facilitate disinhibition in schizophrenic patients [20].

The effects of tobacco consumption on cognition are independent of the withdrawal symptoms caused by tobacco consumption [39]. The effects of smoking on cognition in patients with schizophrenia remains slight [1, 39]. These are also transitory, because of desensitization of the nicotinic receptors produced by addiction [1].

Neurobiological Aspects

Nicotine fixes on the nicotinic acetylcholinergic receptors in the brain. It then has a modulating action on the dopaminergic, glutamatergic and serotoninergic receptors [33, 50]. In particular, nicotine increases the dopaminergic activity in the prefrontal cortex, the amygdala, the nucleus accumbens and the cingular gyrus [11, 81].

The alpha-7 et alpha 4-beta 2 nicotinic receptors in the hippocampus, play an important role in cognitive functions [77]. A post-mortem study showed that patients with schizophrenia have fewer nicotinic receptors [32]. Adler et al. made a link between a deficit in filtering auditory sensations in patients with schizophrenia and alteration in the expression and function of the alpha-7 nicotinic receptors, whose gene is coded for on chromosome 15 [1, 31].

A transitory improvement in cognitive abnormalities due to nicotine, and perhaps also in negative symptomatology, may be due to its stimulatory action on presynaptic nicotinic receptors of the glutamatergic and dopaminergic neurones, thus enhancing glutamatergic and dopaminergic transmission in the prefrontal cortex [22, 35, 35].

IMPACT OF SMOKING ON ANTIPSYCHOTIC TREATMENTS

Patients with schizophrenia who smoke, receive higher doses of antipsychotics than non-smokers [13, 15, 64, 75, 83, 91]. The frequency of tobacco consumption appears to be just as high in patients with other psychiatric disorders treated by antipsychotics, as in treated patients with schizophrenia (75). Smoking increases the metabolism of the antipsychotic medications by inducing the cytochrome P450 1A2 isoform [8, 22, 93]. Hence, smoking lowers the blood levels of typical or atypical antipsychotic medications, in particular haloperidol, chlorpromazine, olanzapine and clozapine [22, 46, 33]. Therefore, abstinence can increase many psychotropics' blood levels. Olanzapine clearance is between 37% and 48% lower in non-smokers than in smokers [22]. Nevertheless, there does not appear to be an interaction between tobacco, Risperidone and Aripirazole, which are metabolized by cytochromes P450 CYP2D6 and CYP3A [14].

In addition, administration of nicotine improves the cognitive disorders caused by Haloperidol, in particular on working memory disorders [37, 51]. Tobacco consumption also increases the metabolism of most benzodiazepines and some antidepressants, like Imipramine and Clomipramine.

Effect of Tobacco Consumption on Extrapyramidal Side Effects from Antipsychotic Treatment

Several studies have shown that tobacco consumption reduces the extra-pyramidal side effects of antipsychotic treatment [33, 37, 48, 51, 75]. This may be due to a reduction in the neuroleptic blood levels, to an increase in subcortical dopaminergic transmission and/or to nicotine acting on the GABAergic and glutamatergic systems [33].

However, tardive dyskinesia was found to be more frequent in smokers treated with antipsychotic medications [22, 46, 70]. Nevertheless, these results were not found in all the studies [47]. The differences between the studies may be due to the fact that tardive dyskinesia occurs more frequently in patients who smoke more than 20 cigarettes per day, in particular in patients with the C-->A) genetic polymorphism in the CYP1A2 gene [47, 7]. No interaction was found between tobacco consumption and anticholinergic treatment [3, 18].

WHY IS TOBACCO CONSUMPTION SO HIGH IN PATIENTS WITH SCHIZOPHRENIA ?

Self-Medication Hypothesis

Although it was previously thought that patients with schizophrenia smoke mainly because of boredom or because their lifestyle is not stimulating enough, several authors have suggested that tobacco consumption is a type of self-medication, in particular for the cognitive symptoms in schizophrenia, by encouraging glutamatergic and dopaminergic transmission in the prefrontal cortex [1, 37, 45, 74, 77, 83].

Tobacco consumption may also be encouraged by antipsychotic treatment, since tobacco attenuates some of the extra-pyramidal and cognitive side effects caused by antipsychotics [51]. McEvoy et al. showed that starting treatment with Haloperidol was followed by an increase in tobacco consumption [63]. However, other authors have underlined that tobacco consumption started in 90% of cases before the drug treatment began [18, 17, 60].

Other Hypotheses

Other factors may have a role in encouraging tobacco consumption in patients with schizophrenia. The high frequency of comorbidity may be linked to the low rate of stopping smoking in these patients [17, 13, 53]. This may also be linked to abnormalities in the cerebral reward pathways in schizophrenia, which would encourage tobacco consumption [10, 48]. The complexity of the links between tobacco consumption and schizophrenia is

illustrated by the differences found in prospective studies, which evaluated smoking in young people, and the later appearance of schizophrenia. In a cohort study of 50,000 Swedish conscripts followed up for 27 years, Zammit et al. recently found a linear relationship between the number of cigarettes smoked and a reduction in the risk of schizophrenia later on (OR= 0.8 [CI= 0.3-0.9]) [89]. On the other hand, in another prospective study on more than 14,000 adolescents, Weiser et al. found a link between tobacco consumption and an increase in the risk of schizophrenia [87].

Role of Genetic Factors

Some authors have suggested that common genetic factors may make individuals vulnerable both to tobacco addiction and to schizophrenia [13, 54]. Freedman et al., in particular, described a genetic abnormality on the locus of the gene coding for the alpha-7 nicotinic receptor on chromosome 15, which would cause neurophysiological disorders, temporarily corrected by nicotine, in schizophrenic patients and in some members of their family [31].

Role of Personality Factors

Several studies on the general population have shown that certain personality traits encourage tobacco consumption, in particular sensation or novelty seeking, impulsivity and antisocial personality traits [23, 66, 92]. As in the general population, patients with schizophrenia who smoke have higher scores than non-smokers on Zuckerman's Sensation Seeking Scale, in particular on the disinhibition subscale scores [20]. They also have higher scores for novelty-seeking on the Tridimensional Personality Questionnaire [84]. However, impulsivity does not seem to encourage tobacco consumption, as is the case in the abuse of alcohol, cannabis or other drugs in patients with schizophrenia [20, 21].

Role of Cultural Factors

The predominant influence of biological factors is suggested by the fact that the high frequency of the schizophrenia/tobacco consumption comorbidity is found in many cultures [13]. However, the frequency of smoking amongst schizophrenic patients in India and Japan is similar to that found in the general population (table 1), which underlines the influence of cultural factors [67, 80]. The role of cultural factors may be linked to the fact that in some countries, smoking initiation is less widespread, especially in women. Tobacco restriction for economic reasons and family customs seems to be particularly predominant in India [80].

THERAPEUTIC ASPECTS

The rate of smoking cessation in patients with schizophrenia is about half that of the general population [13, 88]. There is little to motivate patients with schizophrenia to quit smoking [33]. A recent Swiss study did however show that the motivating factors for smoking cessation were similar to those of a control group [28]. The amount of cognitive disorders seems to play a role in succeeding smoking cessation: patients with schizophrenia with the lowest performances on the Wisconsin Card Sorting Test, assessing executive functions in the prefrontal cortex, and on the Visuospatial Working Memory task, assessing

the visuospatial working memory, were also those who had the most difficulty in smoking cessation [25]. On the other hand, the Stroop Color Word Test and the Continuous Performance Test, assessing other cognitive functions, did not influence these patients in stopping smoking [25]. Some studies found that there was a temporary worsening of certain disorders linked to schizophrenia after stopping smoking, in particular disorders of the working memory [11, 34]. However, studies assessing psychotic symptomatology after administration of nicotine patches or Bupropion, did not show any worsening of the psychotic symptomatology after smoking cessation [33, 35, 29, 36, 40]. It should be underlined that once patients with schizophrenia have given up smoking, they can remain abstinent for a long time [30].

Strategies for Stopping Smoking

The best time to envisage smoking cessation is a period of stabilization of the psychotic symptoms. Atypical antipsychotic medications associated with Bupropion or nicotine transdermal patch, can help motivated patients to quit smoking (35). The doses of conventional and atypical anti-psychotic medications should be reassessed systematically after stopping smoking. In fact, an increase in the plasma levels of these drugs is frequently observed after smoking cessation, due to removal of the interaction by tobacco with cytochrome P450 CYP1A2. For example, in a study of 11 patients, the mean plasma level of Clozapine increased by 57% after stopping smoking [65]. Clinically, overdosage of anti-psychotic drugs is seen by the appearance of sedation and/or extrapyramidal symptoms [22, 93]. It should however be noted that there are no systematic studies with large numbers of patients, in which plasma levels of anti-psychotic drugs have been measured after smoking cessation [65].

Atypical Antipsychotic Drugs

Several studies have shown that administration of atypical anti-psychotic drugs reduced tobacco consumption in patients with schizophrenia, although administration of conventional neuroleptics increased it [33, 62]. In a study including 45 patients, an association of atypical antipsychotic drugs and nicotine transdermal patches was more effective for reducing tobacco consumption (56% stopped smoking at 12 weeks), than an association of conventional neuroleptics and nicotine transdermal patches (22% stopped smoking at 12 weeks) [35]. Several studies have suggested that Clozapine reduced tobacco consumption, in a dose-dependent manner, especially in heavy smokers [33, 61, 62].

Many reasons have been put forward to explain the effect of atypical antipsychotic drugs on tobacco consumption: these medications may produce fewer anti-pyramidal side effects, they may improve the cognitive disorders of schizophrenia which are improved by consuming tobacco, in particular deficits of the P50 wave, and they can improve the negative symptoms. These effects may be linked to an increase in dopaminergic transmission in the prefrontal cortex [1, 62]. Another hypothesis is the inhibitory action of atypical anti-psychotic drugs on the reward pathways in the brain, which are activated by drug-taking and on the reinforcement produced by drugs of abuse in patients with schizophrenia [90].

Nicotine Substitutes

The use of nicotine transdermal patches can help in giving up smoking [33]. The rate of abstinence at 12 weeks after substitution by nicotine transdermal patches are, however, lower in patients with schizophrenia (36%-56%) than in the general population (50%-70%) [33]. The patients must be told that it could be weakly compatible to continue smoking and to use nicotine transdermal patches. They can be used for 8 to 24 weeks or more.

Bupropion

Administration of Bupropion also seems to be useful in smoking cessation, but the results are not as good, compared to those in general population [29, 33, 34]. Up to date, 2 studies did not find that the positive signs of schizophrenia were worsened by Bupropion, despite its property of enhancing dopaminergic transmission, including at doses of 150 to 300 mg/day [29, 33, 34].

Psychosocial Aspects

In general, medical advice and evaluation of motivation for smoking cessation, even when brief or when the patients with schizophrenia do not ask for it, encourage cessation later on [36]. Psychotherapeutic management is based on evaluation of motivation and prevention of relapsing [76]. The educational aspect is particularly important, because patients with schizophrenia have little knowledge of the dangers of tobacco [33]. The patients can be helped to weigh the advantages and disadvantages of continuing smoking or quitting, in particular the reduction of the cardiovascular and pulmonary risks, as well as the money that can be saved by stopping smoking. The cardiovascular risk is close to that of non-smokers 5 years after stopping smoking [4]. It is important to take into account peer pressure, in particular that of other patients, and especially in institutions.

CONCLUSION

There is a high frequency of tobacco consumption in patients with schizophrenia. Unlike other addictions, tobacco consumption seems to be linked to self-medication, particularly for certain cognitive abnormalities linked with abnormalities of cholinergic, dopaminergic and glutamatergic transmission. Smoking cessation in stabilized patients with schizophrenia is helped by associating atypical anti-psychotic drugs with nicotine transdermal patches or with Bupropion.

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Chapter 15

PERIPHERAL BIOLOGICAL MARKERS AND TREATMENT RESPONSE IN SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a severe, chronic mental disorder that appears in 1% of the population. The abnormal neurotransmission of serotonin (5-hydroxytryptamine, 5-HT), dopamine, noradrenalin, and altered neuroendocrine function are implicated in the pathophysiology of schizophrenia. Peripheral biochemical markers might be used to improve the understanding of the underlying neurobiology of schizophrenia, for the preclinical screening, diagnosis, disease staging, and monitoring of treatment. Since there are striking similarities how both central nervous system and platelets store and metabolize 5-HT, blood platelets have been widely used as a peripheral model for the central serotonergic synaptosomes. The dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity and altered secretion of prolactin (PRL) and plasma lipids levels are frequently found in schizophrenia.

Clinical diagnosis of schizophrenia was made according to the DSM-IV criteria. Main outcome measures were scores in Positive and Negative Syndrome Scale, Clinical Global Impression of Severity (CGIS) or Change (CGIC), Hamilton Rating Scale for Depression (HAMD), and HAMD subscale for suicidal behavior. Control group consisted of drug free healthy persons with no personal or family history of psychopathology. Biomarkers studied were: platelet 5-HT concentration, platelet monoamine oxidase (MAO) activity, serum lipids levels: cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoproteins cholesterol (LDL-C), plasma PRL levels and cortisol levels at baseline and after dexamethasone suppression test (DST). Biomarkers were determined using spectrofluorimetric, radioimmunoassay, immunoradiometric methods, enzymatic color test and enzymatic clearance assay.

Schizophrenic patients had higher values of platelet 5-HT, cortisol and PRL, abnormal cortisol response to DST, and lower values of cholesterol, HDL-C and LDL-C

than healthy controls. Platelet 5-HT concentration was correlated to plasma levels of cortisol and PRL in healthy, but not in schizophrenic subjects. There was no significant relationship between plasma PRL and cortisol levels in all groups. Age had no influence on biochemical parameters. Our results suggest an altered relationship between 5-HT system, HPA axis activity and PRL secretion, and abnormal DST response in schizophrenia.

The effects of different neuroleptics (fluphenazine, haloperidol) or atypical antipsychotic (olanzapine) on peripheral biochemical markers, clinical response and safety were studied in naturalistic, comparative or double-blind studies in schizophrenic patients.

Our data suggest that the evaluation of the peripheral biological markers might improve the characterization of the baseline group characteristics, might be used to predict a suicidal risk, to help to differentiate particular symptoms, or syndromes, and to predict the treatment response in schizophrenia.

Keywords: biomarkers, platelets, serotonin, monoamine oxidase, cortisol, prolactin, plasma lipid levels, schizophrenia, treatment response

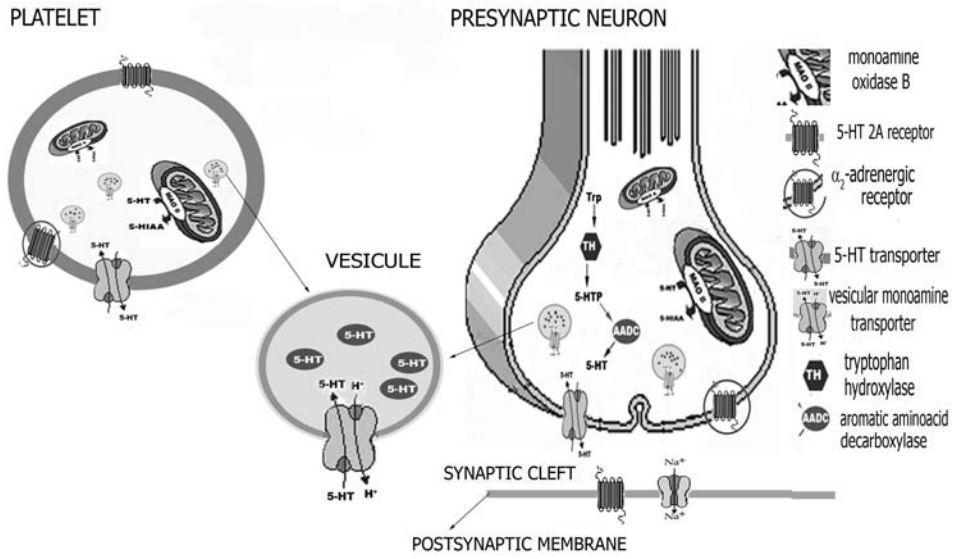
1. INTRODUCTION

Various neuropsychiatric disorders are defined by the pathological or biochemical abnormalities, which include dysfunction of the specific or multiple neurotransmitter and neuromodulatory systems, with consequent characteristic clinical manifestations, specific risk factors, particular genes involved, and death of neurons. Targeting strategies for the studies investigating the physiological and pathological processes or dysfunctions in the central nervous system are limited to the few methods, such as functional imaging techniques, including single photon emission computerized tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (FMRI), macroscopic neuropathology (computed tomography (CT), and neurochemical and genetic studies, and these methods can provide direct in vivo assessment of the expression and function of the particular neurotransmitters, enzymes or transporters, thought to be involved in the etiology of schizophrenia. In addition, histological studies on the post mortem brain tissue can gain some insight in the pathophysiology of schizophrenia (Wong and Van Tol, 2003). All these methods have their advantages and limitations, since brain disorders are usually complex, polygenic in nature, and neurochemical systems altered in these devastating diseases are interdependent and interconnected. The methods such as PET, or SPECT, CT or magnetic resonance imaging need sophisticated equipment, and some of them require an administration of the radioactive ligands, such as -[^{123}J]- for SPECT studies (Kugaya et al., 2004), or the short living -[^{11}C]-labeled ligands, that have to be synthesized immediately before the administration in a radioisotope laboratory (Nishizawa et al., 1997). Besides the complexity and multiplicity of the neurobiological alterations in neurochemical systems responsible for the particular mental disease, the methods utilizing tissue fragments obtained during neurosurgery or biopsy, or the postmortem tissues, are confounded by the various factors such as the time elapsed from the extraction of the tissue to the time of determination, age of the subjects, the radioligand used, regional area examined, previous medication, and for postmortem tissues all the above factors and the time elapsed from death to the extraction of

the tissue, the difference in the storage of the tissue samples, the confounding diagnosis, etc. Hence the neurochemical and genetic studies in living patients are still the first choice for the evaluation of different mental disorders. Neurochemical studies use biomarkers, biological molecules that might be used in the preclinical screening, diagnosis, disease staging, and predicting and monitoring of treatment. However, there is a need for the suitable, easy obtainable, peripheral model for the studies of the biochemical processes in the central nervous system.

1.1. Blood Platelets and Serotonin

In the search for the biomarkers, blood platelets have been used as a limited peripheral model for the central serotonin (5-hydroxytryptamine, 5-HT) synaptosomes, since they share similar pharmacodynamics of 5-HT with central 5-HT neurons (Stahl, 1985; Andres et al., 1993; Camacho and Dimsdale, 2000; Mendelson, 2000; Goveas et al., 2004; Muller-Oerlinghausen et al., 2004). Namely, central 5-HT is a master control neurotransmitter that regulates the formation and integration of neural networks, acting through its multiple 5-HT receptor subtypes. Central 5-HT modulates a wide variety of physiological functions. When impaired, deficits in the 5-HT neurotransmission lead to diverse behavioral and physiological abnormalities and different mental disorders. The similarities between neurons and platelets (Scheme 1) lay in the similar processes such as uptake, storage and release of 5-HT, platelet monoamine oxidase (MAO) type B, 5-HT transporters (Lesch et al., 1994), 5-HT2 receptors (Andres et al., 1993), α_2-adrenergic receptors, and binding sites for ^{3}H-imipramine and ^{3}H-paroxetine, which share identical pharmacologic and kinetic characteristics with the central nervous receptors and binding sites, and resemble the corresponding counterparts and biological processes in the central serotonergic neurons. Platelet MAO shares similar biochemical and pharmacological characteristics, and has identical amino acid sequences with brain MAO-B (Coccini et al., 2005). Platelet MAO has been proposed to represent a genetic marker for the size or functional capacity of the central serotonergic system (Oreland, 2004). Platelet 5-HT concentration (Oreland, 2004), and platelet MAO activity (Schalling et al., 1987; Garpenstrand et al., 2000; Oreland, 2004; Kozaric-Kovacic et al., 2000), have been proposed to serve as biological, even trait markers for particular mental disturbances. Serotonergic alterations might contribute to the cognitive disturbances and deficits in the memory systems occurring in schizophrenia, and platelet 5-HT has been reported to be altered in aggression (Goveas et al., 2004), impulsivity (Askenazy et al., 2000), and suicidal behavior (Muck-Šeler et al., 1996a, Pivac et al., 1997a). For almost 30 years numerous investigators have used blood platelets as the peripheral model for the central 5-HT synaptosomes, and study platelet 5-HT markers in different psychiatric disorders and personality disturbances, with the aim to elucidate the association between these biomarkers, especially platelet 5-HT, and particular mental disturbances.



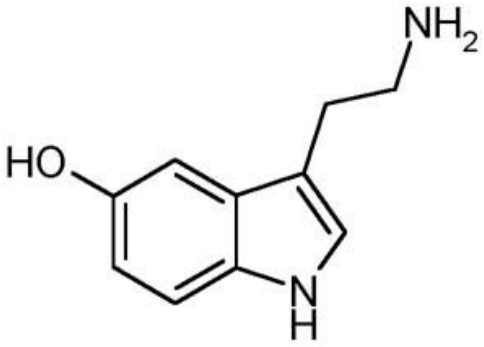
Scheme 1. Similarities/ differences between blood platelets and serotonergic synaptosomes.

Serotonin

Central 5-HT is a main controller of the formation and integration of neural networks, which modulates a myriad of physiological and pathological functions and behaviors. Serotonin regulates important functions and behaviors: hallucinatory behavior, wet-dog shake, feeding behavior, control of mood and emotion, control of sensory pathways, including nociception, control of body temperature, sleep, sexual functions, vomiting (Lucki, 1998; Stahl, 1998). The main action of 5-HT in the central nervous system is the regulation of the synaptic function, neurite outgrowth, synaptogenesis and cell survival. Serotonin has a major role also in the processes of learning and memory, i.e. on the cognitive functions (Mattson et al., 2004). The impaired 5-HT neurotransmission elicits a variety of behavioral and physiological abnormalities and psychiatric disorders, including depression, autism, eating disorders, schizophrenia, obsessive/compulsive disorder, premenstrual syndrome, anxiety, panic disorder, seasonal affective disorder, extreme violence, hostility and aggression, suicide, migraine, manic depression, addiction, and more. Serotonin is produced by the cells groups that are localized in the brainstem raphe nucleus (dorsal and median raphe nucleus), and project diffusely to limbic structures and neocortex. Serotonergic neurons from dorsal raphe innervate amygdala, nucleus accumbens and other forebrain regions, and mediate anxiety and emotional reactions. The projections from medial raphe into forebrain innervate also hippocampus and they mediate tolerance to aversive stimuli, and exert relaxation. Projections from dorsal and medial raphe, synergistically with serotonergic neurons from hypothalamus, innervate corticotrophin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus, and vice versa. The stimulation of the CRH release leads to the activation of the hypothalamic-pituitary-adrenal (HPA) axis, with consequent release of ACTH and glucocorticoids (cortisol) secretion. Hence 5-HT system positively controls the HPA axis activity, and glucocorticoids and catecholamines mediate

changes of the central 5-HT system induced by stress. Serotonin acts via seven subtypes of 5-HT receptors, that activate either GTP-binding proteins and adenylate cyclase pathways or phospholipase C and inositol (1,4,5)-trisphosphate and diacylglycerol pathways.

Serotonin is ubiquitously distributed in nature, it can be found in plants (edible fruits, vegetables and nuts), and in animals (intervertebrates and vertebrates). Serotonin is a heterocyclic amine (Scheme 2) that is synthesized from the amino acid tryptophan (Scheme 3). The biosynthesis of 5-HT starts from the tryptophan, which is hydroxylated by tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP), and 5-HTP is decarboxylated by aromatic-L-amino acid decarboxylase (AADC) with pyridoxal 6-phosphate as a coenzyme. The biosynthesis of 5-HT is dependent on the availability of tryptophan and 5-HTP formation. Tryptophan is bound to plasma albumins. Metabolism of 5-HT is achieved by oxidative deamination with MAO, conjugation with sulfuric and glucuronic acids, N-acetylation, 5-O-methylation. The catabolism by MAO converts 5-HT to 5-hydroxyindole acetaldehyde, most of which is dehydrogenated to form 5-hydroxyindole acetic acid (5-HIAA) which is excreted in urine (Scheme 3).

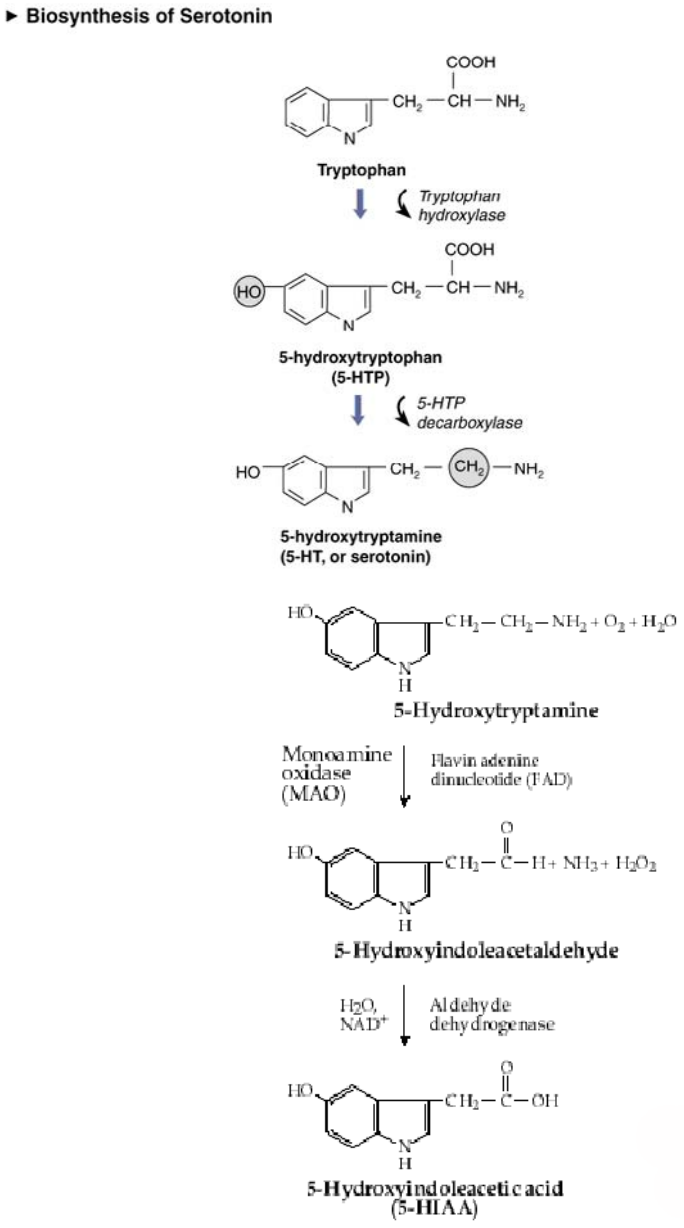


Scheme 2. Serotonin

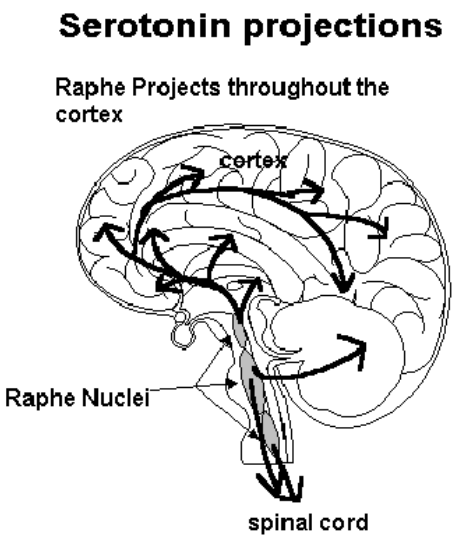
Serotonin Receptors and Functions

Serotonin achieves its multiple actions by acting through several 5-HT receptors and multiple subtypes. There are three main serotonin receptors: 5HT1, 5HT2, 5HT3. The 5HT-1 and 5HT-2 receptors are of a greater interest for psychiatry. The main receptors in the CNS are: $5HT_{1A}$ (raphe nuclei, hippocampus), $5HT_{1B}$ (substantia nigra, globus pallidus, basal ganglia), $5HT_{1D}$ (brain), 5HT2, 5HT3 (area postrema, sensory and enteric nerves). Raphe nuclei contain $5H_{1A}$ receptors, expressed as autoreceptors by the 5-HT neurons. From raphe they project to the cortex and amygdala. Serotonergic neurons are the main target of antianxiety and antidepressant drugs. Cortex and hippocampus contain 5-HT2 receptors which exert an excitatory post-synaptic effect. These receptors are the target of hallucinogenic drugs. D-lysergic acid diethylamide inhibits the firing of 5-HT neurons in the raphe nuclei, apparently by acting as an agonist on the inhibitory autoreceptors of these cells. Gastrointestinal tract and the vomiting center of the medulla (area postrema) contain 5-HT3 receptors, that modulate the vomiting reflex, stimulate emesis, and these receptors are modulated by anticancer chemotherapeutic drugs. The 5HT1 receptors have been subtyped by

DNA cloning and differential pharmacology into four major subtypes. The most important is the $5HT_{1A}$, an autoreceptor located in the raphe and hippocampus. Its function is a modulation of the 5-HT release from presynaptic neurons, and has a role in thermoregulation, arteriolar vasomotor responses, hypotension, sexual behavior, and sleep. The 5HT-2 receptors are located throughout the cortex and have been implicated in platelet aggregation, vasomotor contraction, head twitches, and sleep. These receptors are targets for butyrophenones and phenothiazines.



Scheme 3. Biosynthesis and degradation of serotonin



Scheme 4. Serotonin projections

The scheme shows 5-HT neurons: the cell bodies are in nuclei raphe (dorsal raphe and the raphe magnus), and its diverse projections.

Schizophrenia

Schizophrenia is, according to the DSM-IV criteria (APA, 1994), a chronic, severe, debilitating brain disease, which affects around 1% of population. Schizophrenia is a psychotic disorder, characterized primarily by the impaired thinking and emotion, deviant behavioral and emotional responses, and disturbances in judgement. These severe symptoms lead to the lack of contact with reality and a severe personal, social and occupational dysfunction. The symptoms in schizophrenia are delusions, hallucinations and other alterations in psychological and physical function. It has a great impact on social, political, and economical level. The symptoms in schizophrenia can be divided into positive or psychotic symptoms, negative or deficit symptoms, and cognitive impairment (Wong and Van Tol, 2003). Positive symptoms consist of delusions, hallucinations, disorganized thinking and speech, and inappropriate affect. Negative symptoms, that are more difficult to treat than positive symptoms, include social withdrawal and isolation, and consist of alogia (poverty of speech), blunted and flat affect, loss of volition, social withdrawal (anhedonia) and psychomotor symptoms (catatonia). The symptoms occurring in schizophrenia are listed in the Positive and Negative Syndrome scale (PANSS), in the positive subscale (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility), negative subscale (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking), general psychopathology subscale (somatic concern, anxiety, guilt feeling, tension, mannerism and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control,

preoccupation, active social avoidance), and supplementary items subscale (anger, difficulty in delaying gratification, affective liability).

Although schizophrenia has been investigated for over 100 years, there is still no consensus on the neuropathology that causes schizophrenia. The main neuropathological findings in schizophrenia are decreased cortical volume in temporal cortex and increased ventricular size, decreased hippocampal and cortical neuron size, gliosis absent as an intrinsic feature, abnormal laminar distribution of neurons in temporal cortex, decreased perfusion and metabolism in frontal regions, increased striatal D2 receptors, increased dopamine content or metabolism, decreased $5HT_{2A}$ receptors, decreased expression of synaptic and neuronal marker genes and proteins (Wong and Van Tol, 2003). The studies investigating postmortem brains of schizophrenic patients are confounded by the various factors that affect the results, primarily the cause of death and the effects of antipsychotics. Since schizophrenia is not a lethal disease, besides suicide, which has a fatal outcome, in non-suicidal schizophrenic patients the cause of death is usually not related to schizophrenia itself, but to other causes, such as various diseases of the old age in older patients.

Neurobiology of Schizophrenia

Neurochemical theories of schizophrenia are based on the persistent impairment/s in catecholamine (primarily dopamine), serotonin, glutamate, GABA, neuropeptide, signal transduction, and developmental/synaptic systems (Fuller Torrey et al., 2005). A main cause of schizophrenia, an alteration in dopaminergic neurotransmission, was confirmed by the pharmacological properties of the antipsychotic drugs, since all available antipsychotics block D2 receptors. "Dopamine hypothesis" in schizophrenia is based also on the fact that antipsychotics reduce psychotic symptoms, acting via dopaminergic receptors. In addition, the hyperactivity of the dopaminergic system, presumably in mesolimbic system, which can be mimic by the drugs such as amphetamine of cocaine (which induce psychosis) is responsible for the psychotic symptoms in schizophrenia (Wong and Van Tol, 2003). It has been assumed that the cerebrospinal fluid or plasma homovanillic acid (HVA) level has been associated to treatment response in schizophrenia (Altamura et al., 2005).

Serotonin and Schizophrenia

Schizophrenia is associated with the 5-HT dysfunction (Meltzer and Nash, 1991; Abi-Dargham et al., 1997), and changes of the central 5-HT system have been detected in the altered cerebrospinal fluid concentration of the 5-HT metabolite, 5-Hydroxyindol acetic acid (5-HIAA) in schizophrenic patients, in the decreased concentration of 5-HT in the postmortem brains, with increased 5-HT neurotransmission in the putamen, accumbens and pallidus, and decreased 5-HT neurotransmission in cortical regions of the schizophrenic patients, in the decreased density of the 5-HT transporters in the frontal cortex of schizophrenic patients, in the altered (decreased, but also unchanged) density of the frontal 5-HT2 receptors in schizophrenic patients (Abi-Dargham et al., 1997), in the decreased cortical $5\text{-}HT_{2A}$ density, increased $5\text{-}HT_{1A}$ receptor density, or unchanged 5-HT6 receptor binding (Wong and Van Tol, 2003). In schizophrenic patients a downregulation of the $5\text{-}HT_{2A}$

receptors in cortical and subcortical regions of the postmortem brain tissue was detected (du Buis et al., 2005).

Since 5-HT is involved in the control of different physiological (cardiovascular, respiratory, thermoregulatory) and behavioral (circadian rhythm, sleep-wake cycle, appetite, aggression, sexual behavior, sensory motor reactivity, pain sensitivity and learning) functions and behaviors (Stahl, 1998; Lucki, 1998) that are disturbed in schizophrenia, and newer antipsychotic drugs act also by blocking 5-HT_{2A} receptors (Meltzer and Nash, 1991), a new "serotonin hypothesis of schizophrenia" has been postulated. Meltzer proposed that antipsychotic with a high 5-HT_{2A} relative to D2 receptor affinity should induce less extrapyramidal side effects, and reduce negative symptoms in schizophrenia. Newer antipsychotics have low affinity and low occupancy of the striatal D2 receptors, and occupy 70-80% of the cortical 5-HT_{2A} receptors, and are characterized by the lower incidence of the extrapyramidal side effects. The exact mechanism by which the blockade of 5-HT_{2A} receptors protects the patients of developing extrapyramidal side effects is still not clear, since some antipsychotics (sulpiride, remoxipride) block D2, but do not affect 5-HT_{2A} receptors, and do not elicit extrapyramidal side effects. The additional receptor blockade (D4, histaminergic, noradrenergic, cholinergic), or atypical antipsychotic-induced delicate balance between 5-HT and dopamine, and not a potency for these receptors, might be responsible for the antipsychotic action and might prevent the development of extrapyramidal side effects. The poor treatment response to atypical antipsychotics (olanzapine, sertindole, quetiapine) has been associated with lower plasma or platelet concentration of 5-HT in schizophrenic patients (Altamura et al., 2005).

Drug Treatment in Schizophrenia

Antypsychotic Drugs

Conventional Antipsychotics

The first drugs used in the treatment of schizophrenia were phenotiazine neuroleptics. Conventional antipsychotics or classical neuroleptics have high affinity to D2 receptors and low affinity to other types of receptors, affect mainly positive symptoms of schizophrenia, and induce extrapyramidal side effects, or have lower affinity to D2 receptors and higher affinity to other receptor types, and therefore affect positive and affective symptoms of schizophrenia. They induce sedation, anticholinergic, antihistaminic and cardiovascular side effects, and extrapyramidal symptoms. The main representative was chlorpromazine, improving the positive symptoms in schizophrenia. After that, other families of the drugs were discovered (butyrophenone and benzamide), with haloperidol, perphenazine, trifluoperiazine and fluphenazine, that were effective in decreasing psychotic symptoms in schizophrenia. The most commonly used drugs are chlorpromazine, chlorprotixene, clopenthixole, levopromazine, periciazine, thioridazine, droperidole, flupentixol, fluphenazine, fluspirilene, haloperidol, melperone, oxyprothepine, penfluridol, perphenazine, pimozide, prochlorperazine, trifluoperazine, etc. These drugs reduce dramatically the positive symptoms and the length of the hospitalizations, but conventional neuroleptics induce serious side effects (neurological, gastrointestinal and cardiovascular), are ineffective in 30% of patients, sometimes induce an exacerbation of the symptoms, and do not affect negative or

cognitive symptoms in schizophrenia. Their mechanism of action is achieved through the blockade of the dopaminergic D2 receptors in the mesolimbic pathways, but this mechanism is connected with the induction of the extrapyramidal side effects, and higher D2 affinity results in more extrapyramidal side effects and akathisia (Wong and Van Tol, 2003).

Clozapine

Clozapine was the first atypical antipsychotic drug, effective especially in schizophrenic patients refractory to chlorpromazine (Kane et al., 1988). It was used for the treatment of positive symptoms such as hallucinations, delusions, bizarre behavior and hostility, negative symptoms such as withdrawal, blunted emotions, lack of motivation, and inability to experience pleasure or enjoyment. Clozapine is an antipsychotic that does not cause extra pyramidal side effects. Clozapine affects negative symptoms better than traditional antipsychotics. It has a rare but potentially fatal side effect, agranulocytosis, hence the patients on clozapine have to control their white blood cell count before treatment and weekly for the first six months of treatment, and every 2 weeks thereafter. Clozapine has higher affinity for the dopamine D4 receptor than for D2 and D3 receptors, lower affinity for D2 receptors in the striatum, and it binds to the D1, D3 and D5 receptors. Clozapine shows also a high affinity for 5-HT receptors (5-HT2, 5-HT3, 5-HT6 and 5-HT7 subtypes), for $\alpha 1$, $\alpha 2$ and muscarinic receptors, while it also affects GABA-ergic and glutamatergic mechanisms.

Atypical Antipsychotics

Atypical antipsychotics or antipsychotics of the 2nd generation are dual 5-HT / dopamine antagonists. They are antagonists of D2 and 5-HT_{2A} receptors, but they can affect also other types of receptors, listed in Table 1. Their mechanism of action is a D2 receptor blockade in the mesolimbic pathway (to reduce positive symptoms), enhanced dopamine release and 5-HT_{2A} receptor blockade in the mesocortical pathway (to reduce negative symptoms), while other receptor-binding properties may contribute to their efficacy in treating cognitive symptoms, aggressive symptoms and depression in schizophrenia. These drugs reduce positive symptoms (hallucinations, delusions), negative symptoms (amotivation, emotional and social withdrawal), cognitive impairment, mood problems, and persistent aggressive behavior. Atypical antipsychotics are more efficient in the treatment of negative symptoms of schizophrenia, when compared to conventional antipsychotics. Their main advantage is that atypical antipsychotics have lower side effects, especially lower extrapyramidal side effects, such as rigidity, tremor, and akathisia, or tardive dyskinesis. These drugs include amisulpiride, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride, and newer drugs, ziprasidone and aripiprazole. Their pharmacological receptor profile is shown in Table 1. However, these new second-generation antipsychotics have been associated with weight gain, and might elicit hyperglycemia and diabetes, and also hyperprolactinemia and a measurable prolongation of the QT interval. Because of these side effects, patients should be monitored regularly for the weight gain, blood glucose and serum lipid profile, and new-onset type 2 diabetes.

Table 1. Receptor systems affected by atypical antipsychotics

D2, 5-HT_{2A}, 5-HT_7, α_1, α_2	risperidone
D2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D3, α_1	sertindole
D2, 5-HT_{2A}, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2C}, 5-HT_7, D3, α_1, NRI, SRI	ziprasidone
D2, 5-HT_{2A}, 5-HT_6, 5-HT_7, D1, D4, α_1, M_1, H_1, NRI	loxapine
D2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D1, D3, D4, α_1, H_1, NRI	zotepine
D2, 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7, D1, D3, D4, α_1, α_2, M_1, H_1	clozapine
D2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, D1, D3, D4, D5, α_1, $M_{1\text{-}5}$, H_1	olanzapine
D2, 5-HT_{2A}, 5-HT_6, 5-HT_7, α_1, α_2, H_1	quetiapine

2. METHODS

2.1. Subjects

Schizophrenic male (N=211) and female (N=95) patients were diagnosed according to DSM-IV criteria (American Psychiatry Association, 1994). All 306 schizophrenic patients were evaluated by structured clinical interview, conducted by two psychiatrists. The severity of the symptoms occurring in schizophrenia was evaluated using Positive and Negative Syndrome scale (PANSS) (Guy, 1976): positive symptoms (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility), negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking), general psychopathology symptoms (somatic concern, anxiety, guilt feeling, tension, mannerism and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance), and supplementary items (anger, difficulty in delaying gratification, affective liability). The scores in total PANSS scale was 100.92 ± 11.74, while patients had 32.68 ± 4.83 scores in the PANSS positive subscale and 26.47 ± 5.85 scores in the PANSS negative subscale, respectively. The patients were not treated with psychotropic drugs before the samples were selected for baseline data. All participants gave their informed consent. The local Ethic committee approved this protocol. All subjects had a medical evaluation and routine laboratory screening tests prior to entry into the study, gave written informed consent to participate in the trial.

Control group consisted of 326 (155 men and 171 women) healthy persons (mainly medical stuff), with no personal or family history of psychopathology and no medical treatments. All participants gave their informed consent.

2.2. Drug Treatment and Study Design

In a randomized, double blind 5 months study, 22 female schizophrenic (DSM-IV criteria) patients were treated with either olanzapine or fluphenazine. Psychiatric and physical

examinations were made during the first interview. Patients with substance abuse, or serious suicidal risk, or pregnant or lactating women were excluded (Dossenbach et al., 2004). All inclusion/exclusion criteria were verified at the second interview, and patients were randomly and in a double-blind manner allocated in two different treatment groups. On admission, 12 patients had been drug free for about 1 year, none received depot neuroleptics, and the others were medicated with different neuroleptics (haloperidol, clozapine). Before blood sampling patients were not treated with any neuroleptics or antidepressants for at least 7 days. Blood samples from schizophrenic and control women were collected between 1st and 7th day of the menstrual cycle. Twelve patients received olanzapine (5-20 mg/day), and 10 patients were treated with fluphenazine (6-21 mg/day). This study was part of the larger study evaluating the efficacy of olanzapine in a larger multicentre parallel clinical trial (Dossenbach et al., 2004). Before treatment schizophrenic patients who were later assigned into olanzapine or fluphenazine groups had similar values of the severity of clinical symptom, as shown in the total PANSS scores (107.7 ± 19.1 and 96.9 ±15.4) and CGI scores (5.3 ± 0.75 and 5.2 ± 0.78), respectively.

In and open 6-months comparative trial, 34 male schizophrenic (DSM-IV criteria) patients with suicidal behavior (Clinical Global Impression for Severity of Suicidality, CGI-SS), 17 patients received olanzapine in a dose of 5-20 mg/day (N=17) and 17 were treated with haloperidol (5-20 mg/day). Main outcome measures were reductions from baseline to endpoint (last observation carried forward) in the total scores on the Clinical Global Impression (CGI), Clinical Global Impression-Severity of Suicidality (CGI-SS), and Hamilton rating scale for depression (HAMD) (Guy, 1976; Hamilton, 1960).

2.3. Determination of Platelet 5-HT Concentration

At baseline (before treatment, i.e. after 1 week of washout) and 5-6 months after treatment with different antipsychotic drugs, a forearm vein was cannulated for blood sampling at 08.00 a.m., after an overnight fasting. Blood samples (8 ml) were drawn in a plastic syringe with 2 ml of acid citrate dextrose anticoagulant. Platelet rich plasma (PRP) was obtained after centrifugation of whole blood at 950g for 30 sec at room temperature and platelets were sedimented by further centrifugation of PRP at 10,000g for 5 min in a refrigerated centrifuge. The platelet pellet was washed with saline and centrifuged again. Sedimented platelets were frozen and stored at -20°C no longer than 7 days before being assayed for 5HT concentration. Platelet 5-HT concentration was determined by the spectrofluorimetric method, as previously described (Pivac et al., 2001). Briefly, platelets were destroyed by sonication (20 kHz, amplitude 8 x 10^{-3} mm for 30 sec). Specimens of standard, blank (water) and platelet sonicates were analyzed in duplicate. All samples were deproteinized with 1 ml of 10% $ZnSO_4$ and 0.5 ml of 1 N NaOH. For the preparation of fluorophore, 0.2 ml of L-cysteine (0.1%) and 1.2 ml of orthophthalaldehyde (0.05%) were added to deproteinized samples. The measurement of the 5-HT fluorescence was performed on a Varian Spectrophotofluorimeter Cary Eclipse, on an exciting wavelength of 345 nm and emitted wavelength of 485 nm. Platelet protein concentrations were measured by the method of Lowry et al. (1951).

After a drug-free interval, platelet 5-HT and plasma cortisol concentration were determined at 8.00 a.m. At 11.00 p.m., 1 mg of dexamethasone was administered orally to

each patient. On the following day, platelet 5-HT and plasma cortisol concentrations were determined at 8.00 a.m. and at 4.00 p.m. Abnormal response of plasma cortisol levels to dexamethasone, or nonsuppression to dexamethasone, was defined when plasma cortisol levels exceeded 138 nmol/l after dexamethasone. According to the response to dexamethasone (or dexamethasone suppression test or DST), patients were divided into responders and nonresponders (Pivac et al., 1997b; Jakovljevic et al., 1998; Muck-Seler et al., 1999a).

2.4. Determination of Platelet MAO Activity and other Biochemical Analyses

Platelet MAO-B activity was determined spectrofluorimetrically using kynuramine as a substrate, by a slight modification of the method of Krajl (1965), as previously described (Pivac et al., 2002; Muck-Seler et al., 2002). Briefly, 100 μl of standard (4-hydroxyquinoline, 4-HOQ), blank (water) and platelet sonicates were incubated with 100 μl of kynuramine (final concentration 73.6 μM) at 37°C for 1 hour. The reaction was stopped with 1 N NaOH. The measurement of 4-HOQ fluorescence, a product of kynuramine, was performed on Varian Spectrophotofluorimeter Cary Eclipse, with an exciting wavelength of 310 nm and emitted wavelength of 380 nm. Platelet protein levels were measured by the method of Lowry et al. (1951).

For the kinetic constants of the platelet MAO: platelet MAO activity was measured using ^{14}C-phenylethylamine (^{14}C- PEA, specific activity 48.26 mCi/mmol, New England Nuclear) as a substrate by the method of Muck-Šeler et al.(1991). Platelet sonicates (0.05ml) and 0.1 ml Sörensen phosphate buffer were preincubated at 37°C in a shaking water bath for 5 min. The reaction was started by the addition of 0.05 ml of ^{14}C- PEA in final concentrations of 2, 4, 5, 6, 8, and 10μM. Two types of blanks were used. The first blank was prepared by thermic inactivation of enzyme activity (specimens of blanks were heated in a boiling water bath for 10 min). In the second blank, platelet sonicate was replaced by saline. In both cases, blank values were near 0.1% of total added radioactivity. After 30 min, the enzyme reaction was stopped by addition of 0.2 ml of 0,5 M perchloric acid. Pasteur pipettes filled with Amberlit CG 50 (100-200 mesh) were used for the separation of substrate and anionic and neutral reaction products. Immediately before separation, the acidified samples were mixed with 0,2 ml of water and 0,5 ml of methanol. The content of each tube was transferred to the top of the Pasteur pipette, which was positioned above a scintillation vial. After the reaction mixture ran into the column, the tube was rinsed two times with 0,5 ml methanol diluted with water (1:1) which also was then passed through the column. The radioactivity of the column eluates was determined after the addition of Aquasol (10 ml) using an LKB scintillation counter.

K_m and V_{max} were calculated from Lineweaver-Burk plots using computer analysis of the data. K_m was expressed as μM of ^{14}C- PEA and V_{max} as nmol products formed / mg protein / hour. Platelet protein was determined by the method of Lowry et al. (1951).

Serum lipid levels: serum total cholesterol, high-density lipoprotein (HDL), or triglycerides (TG) levels, in patients with PTSD and in healthy control subjects, were determined by the enzymatic color test, while serum low-density lipoprotein (LDL) levels were measured using enzymatic clearance assay. Cortisol levels were determined using a commercially available radioimmunoassay kit from Diagnostic Products Cooperation, CA,

USA, with detection limit of 5.5 nmol/l. Intra- and inter-assay coefficients of variation (CVs) were 4.7% and 5.2%, respectively, as previously described (Pivac et al., 1997b). PRL was measured by a immunoradiometric assay using commercially available kit (Diagnostic Product Corporation, USA). The detection limit was 0.1 ng/ml. Intra- and inter-assay CVs were 1.6% and 2.8%, respectively.

2.5. Determination of Active Transport of ^{14}C-5-HT into Platelets

For the uptake experiments, PRP (0.1 ml) and phosphate buffer (0.89 ml, 0.055 M, pH 7.35) were pre-incubated at 37°C in a shaking water bath for 5 min. The reaction was started by the addition of ^{14}C-5-HT (specific activity 47 mCi/mmol; New England Nuclear, Boston, MA, USA), in final concentrations from 3.0 to 10.0 x 10^{-7}M (Muck-Šeler et al., 1988). Blank values were obtained by adding ^{14}C-5-HT to PRP samples kept in an ice-water bath. After 5 min, the uptake of ^{14}C-5-HT was stopped with adding ice-cold buffer and transferring the test tubes to ice water. Platelets were sedimented by centrifugation in a refrigerated centrifuge at 10,000g for 5 min. The platelet pellets were washed with saline and centrifuged again. The radioactivity of the samples was determined after addition of Aquasol using a Beckman scintillation counter. K_m and V_{max} were calculated from Lineweaver-Burk plots using computer analysis of the data.

2.6. Data Analysis

The statistical analysis of the data was conducted with Statistica, release 6, Statsoft (Tulsa, Oklahoma, USA), and with Sigmastat 2.0 (Jandell Scientific Corp. San Raphael, California, USA). The results, expressed as means ± SD, were evaluated using one-way analysis of variance (ANOVA) followed by followed by Newman Keuls or Tukey multiple comparison test. The results were also evaluated with Kruskal-Wallis ANOVA by ranks, followed by a Mann Whitney test for the pairwise comparison, when distribution of the data was not normal. Pearson coefficient of correlation was used to test the correlations between two variables. For two groups comparison Student's t-test was used. The significance was accepted when $p<.05$.

3. RESULTS

Platelet 5-HT Concentration in Schizophrenic Patients and Healthy Controls

Platelet 5-HT concentration differed significantly ($F=15.32$; $df=3,628$; $p<0.001$, ANOVA) between 211 male and 95 female schizophrenic patients and 155 male and 171 female healthy controls (Fig. 1). The between group comparisons revealed (Newman Keuls test) that schizophrenic male and female patients had significantly ($p<0.05$) increased platelet 5-HT concentration when compared to corresponding control men and women. Platelet 5-HT concentration was also significantly ($p<0.05$) different between male and female persons.

There were significant ($p<0.05$) sex-related differences, i.e. higher platelet ($p<0.05$) 5-HT concentration in male than in female schizophrenic patients, and higher platelet ($p<0.05$) 5-HT concentration in male than in female healthy control persons.

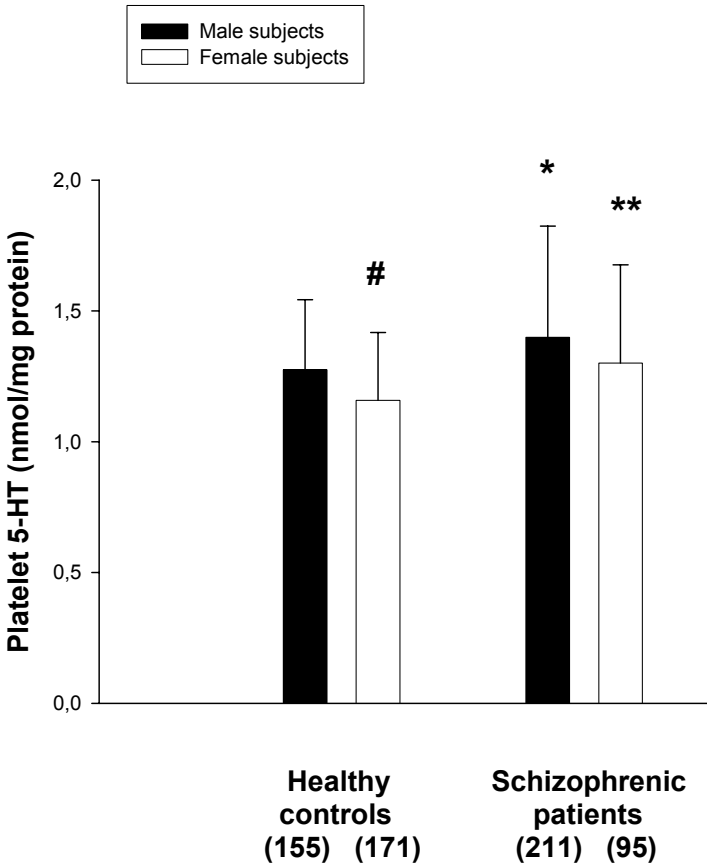


Figure 1. Platelet 5-HT concentration in healthy persons and schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. healthy male and vs. female schizophrenics; **P<0.05 vs. healthy female subjects; #P<0.05 vs. healthy male subjects.

Platelet 5-HT Concentration in Schizophrenic Patients and Healthy Controls Divided According to their Season of Birth

Platelet 5-HT concentration differed significantly between female ($F=3.64$; $df=7,187$; $p<0.001$, ANOVA) or male ($F=2.83$; $df=7,301$; $p<0.007$, ANOVA) schizophrenic patients and control women and men, who were divided according to their season of birth (Fig. 2). Female schizophrenic patients born in winter had significantly ($p<0.05$) higher platelet 5-HT concentration than schizophrenic women born in all other seasons, and when compared to female healthy persons born in all seasons (Fig 2A). The similar increase in platelet 5-HT concentration was detected in male subjects: male schizophrenic patients born in winter had significantly ($p<0.05$) higher platelet 5-HT concentration than schizophrenic men born in all other seasons, and than male healthy persons born in spring, summer and fall (Fig. 2B).

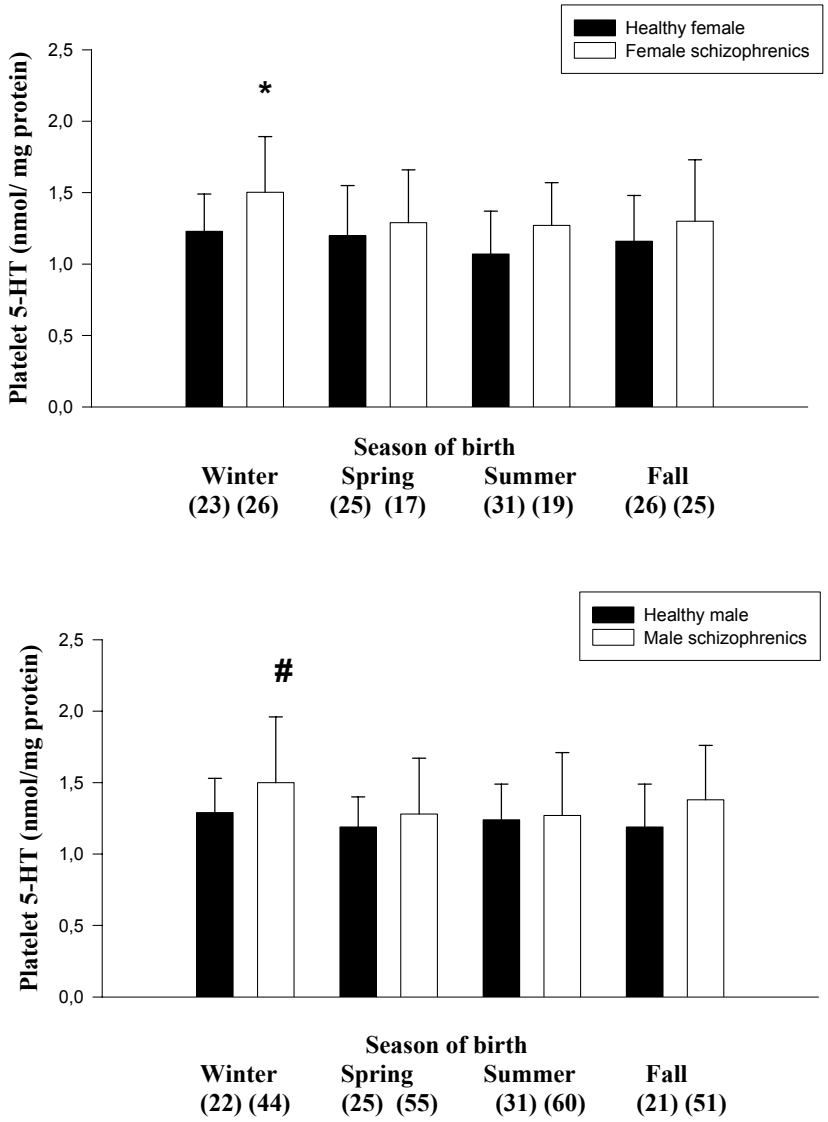


Figure 2. Season of birth and platelet 5-HT concentration in female and male healthy persons and schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. female schizophrenics born in winter and all other seasons and vs. healthy female born in different seasons; #P<0.05 vs. male schizophrenics born in winter and all other seasons and vs. healthy male born in different seasons (ANOVA followed by Newman Keuls test).

Platelet 5-HT Concentration in Healthy Controls, Schizophrenic Patients and their Healthy Relatives

Platelet 5-HT concentration did not differ significantly (t=0.56; df=69; p>0.50, Student t-test) between healthy controls and healthy relatives of schizophrenic patients (Fig 3A). As expected (Fig 3B), platelet 5-HT concentration was significantly higher in schizophrenic patients than in healthy controls (t=2.54; df=69; p<0.02, Student t-test). Platelet 5-HT

concentration was significantly (t=2.15; df=36; p<0.05, Student t-test) increased in schizophrenic patients when compared to their healthy relatives (Fig 3C).

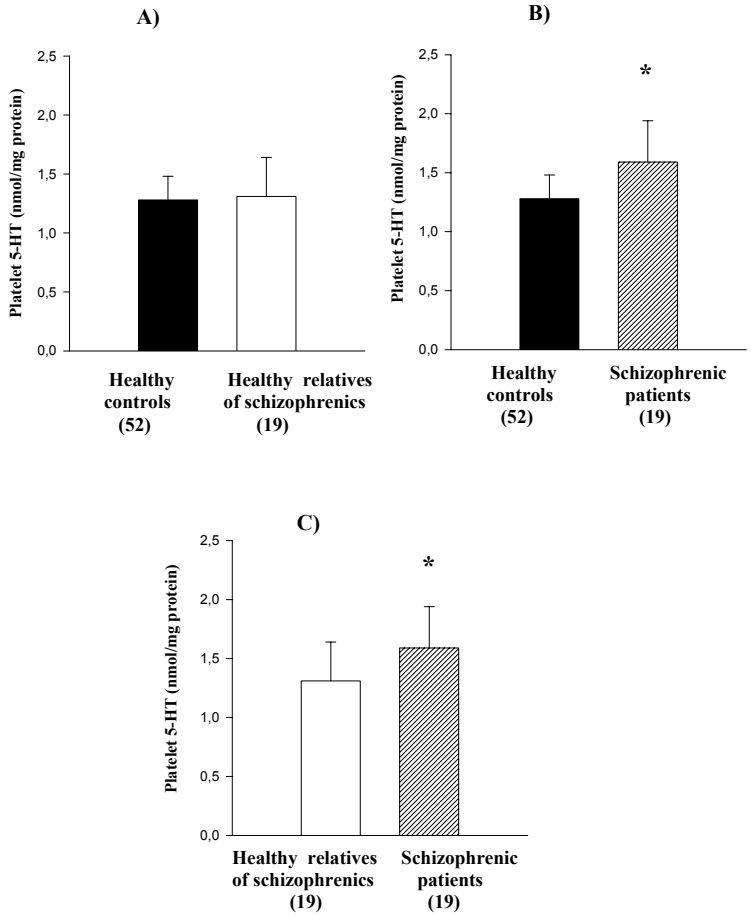


Figure 3. Platelet 5-HT concentration: A) in healthy controls and healthy relatives of schizophrenic patients; B) in healthy controls and schizophrenic patients; C) in healthy relatives of schizophrenic patients and schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. healthy controls and healthy relatives (Student's t-test).

Platelet 5-HT Concentration in Paranoid and Non-Paranoid Schizophrenic Patients

Platelet 5-HT concentration was significantly (t=2.93; df=74, p<0.005, Student t-test) higher in paranoid than in non-paranoid schizophrenic patients (Fig. 4).

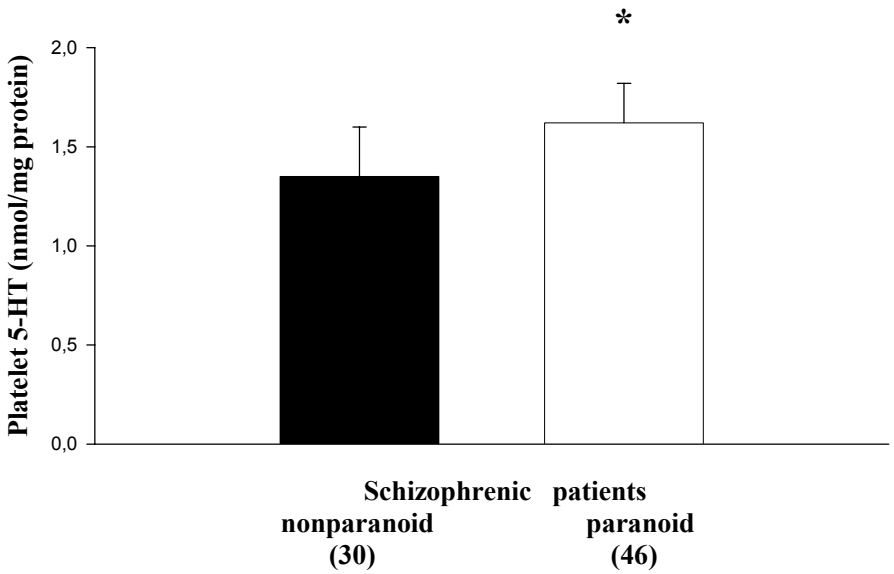


Figure 4. Platelet 5-HT concentration in paranoid and non-paranoid schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.005 vs. non-paranoid schizophrenic patients (Student's t-test).

Platelet 5-HT Concentration in Schizophrenic Patients and Healthy Controls Divided According to the Season of Sampling

To elucidate the effect of seasonality on platelet 5-HT concentration, we sampled simultaneously male and female healthy controls (Fig. 5) and male and female schizophrenic patients (Fig. 6) in different (spring, summer, fall, winter) seasons. Although platelet 5-HT concentration differed significantly between healthy control subjects sampled during different seasons ($F=3.36$; $df=7,168$; $p<0.002$, ANOVA), no significant effect of seasonality was detected within healthy male or female subjects sampled in spring, summer, fall or winter (Fig. 5). In schizophrenic patients platelet 5-HT concentration did not differ significantly ($F=1.32$; $df=7,220$; $p=0.241$, ANOVA) between male or female patients sampled in spring, summer, fall or winter (Fig. 6).

Platelet 5-HT Concentration in Schizophrenic Patients with Predominantly Positive and Negative Symptoms

When male schizophrenic patients were divided according to the subtype of schizophrenia, into those with predominantly positive or those with predominantly negative symptoms (Fig. 7A), their platelet 5-HT concentration differed significantly ($t=4.71$; $df=78$; $p<0.001$, Student t-test). Namely, schizophrenic patients with predominantly positive symptoms had significantly higher platelet 5-HT concentration than schizophrenic patients with predominantly negative symptoms (Fig. 7A). After dexamethasone suppression test (DST), male schizophrenic patients with predominantly positive and negative symptoms were

subdivided further according to the results of the DST into suppressors and nonsuppressors (Fig. 7B). Their platelet 5-HT concentration differed significantly ($F=6.71$; $df=3,76$; $p<0.001$, ANOVA), and schizophrenic patients with predominantly positive symptoms who were either suppressors or nonsuppressors had significantly ($p<0.05$) higher platelet 5-HT concentration that schizophrenic patients with negative symptoms (suppressors and nonsuppressors). Schizophrenic suppressors or nonsuppressors with predominantly negative symptoms had significantly ($p<0.05$) lower platelet 5-HT concentration that schizophrenic suppressors or nonsuppressors with predominantly positive symptoms (Fig. 7B).

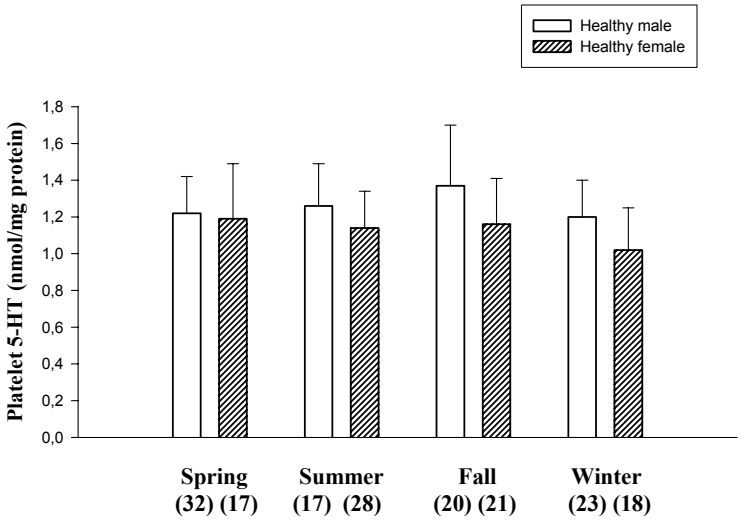


Figure 5. Platelet 5-HT in healthy male and female subjects sampled in different seasons. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

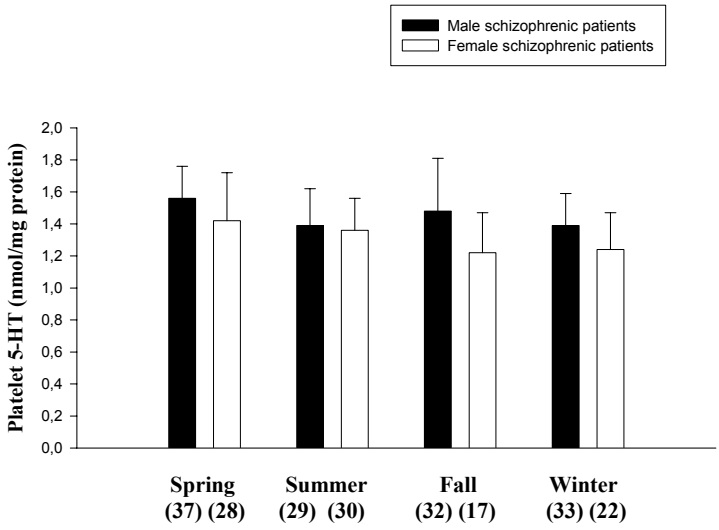


Figure 6. Platelet 5-HT in schizophrenic male and female patients sampled in different seasons. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

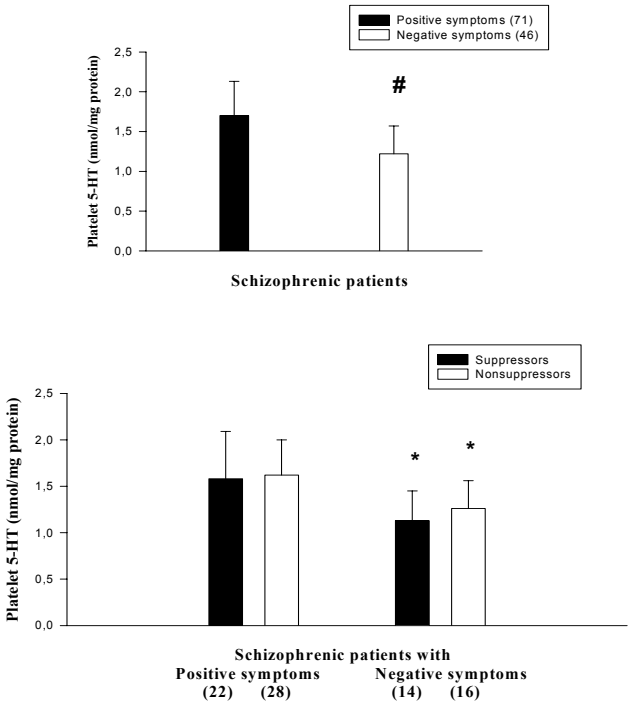


Figure 7. Platelet 5-HT concentration in schizophrenic patients with predominantly positive or negative symptoms. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. # P<0.05 vs. schizophrenic patients with predominantly positive symptoms (Student's t-test); * P<0.05 vs. corresponding schizophrenic patients with predominantly positive symptoms (ANOVA followed by Newman Keuls test)

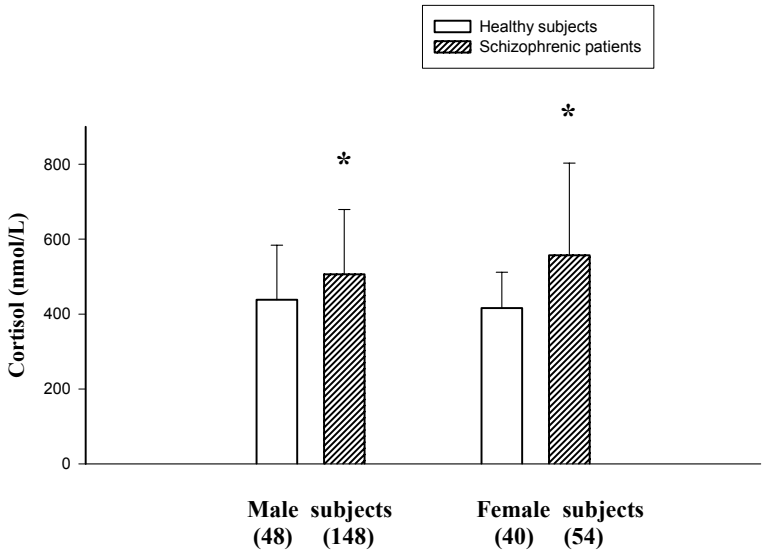


Figure 8. Plasma cortisol levels in male and female healthy subjects and schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. corresponding healthy subjects (ANOVA followed by Newman Keuls test).

Plasma Cortisol Levels in Schizophrenic Patients and in Healthy Controls

Plasma cortisol levels were significantly different between female or male ($F=6.65$; $df=3,286$; $p<0.001$, ANOVA) schizophrenic patients and control women and men. Plasma cortisol levels were significantly ($p<0.05$) higher in schizophrenic male patients than in healthy men, and was also significantly ($p<0.05$) increased in schizophrenic female patients when compared to values in healthy women (Fig. 8).

Plasma Cortisol Levels in Schizophrenic Patients with Predominantly Positive and Negative Symptoms

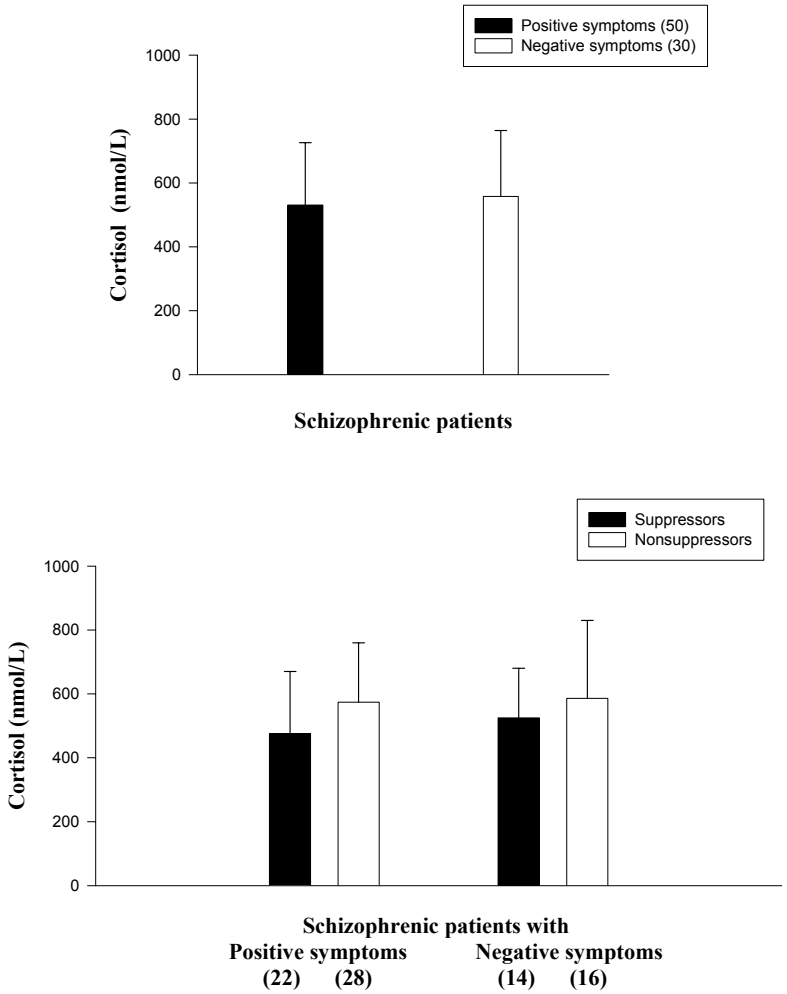


Figure 9. Baseline plasma cortisol levels in schizophrenic patients with predominantly positive and negative symptoms. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

Plasma cortisol levels did not differ significantly (t=0.579; df=78; p>0.05, Student t-test) between schizophrenic patients with predominantly positive symptoms versus patients with predominantly negative symptoms (Fig 9). When male schizophrenic patients with either predominantly positive or predominantly negative symptoms were subdivided according to the DST response into suppressors and nonsuppressors (Fig. 9), their plasma cortisol levels did not differ significantly (F=1.41; df=3,76; p>0.05, ANOVA).

Platelet 5-HT Concentration in Healthy Controls and Schizophrenic Patients with Different Time Course of Schizophrenia

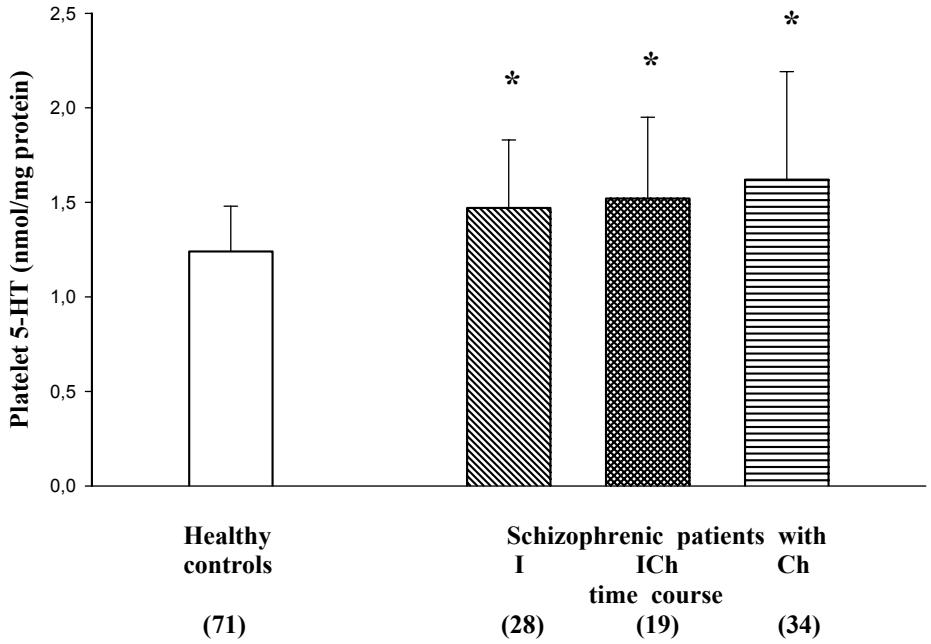


Figure 10. Platelet 5-HT in healthy control subjects and schizophrenic patients with intermittent (I), intermittent-chronic (ICh) and chronic (Ch) time course of schizophrenia. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P <0.05 vs. healthy controls (ANOVA followed by Newman Keuls test).

Platelet 5-HT concentration differed significantly (F=8.74; df=3,148; p<0.001, ANOVA) in male healthy controls and in male schizophrenic patients subdivided according to the time course of illness into those with intermittent, intermittent-chronic and chronic time course of schizophrenia (Fig. 10). Schizophrenic patients with intermittent, intermittent-chronic and chronic time course of schizophrenia had all significantly p <0.05) higher platelet 5-HT concentration than healthy subjects.

Platelet 5-HT Concentration in Schizophrenic Suppressors and Nonsuppressors with Different Time Course of Schizophrenia

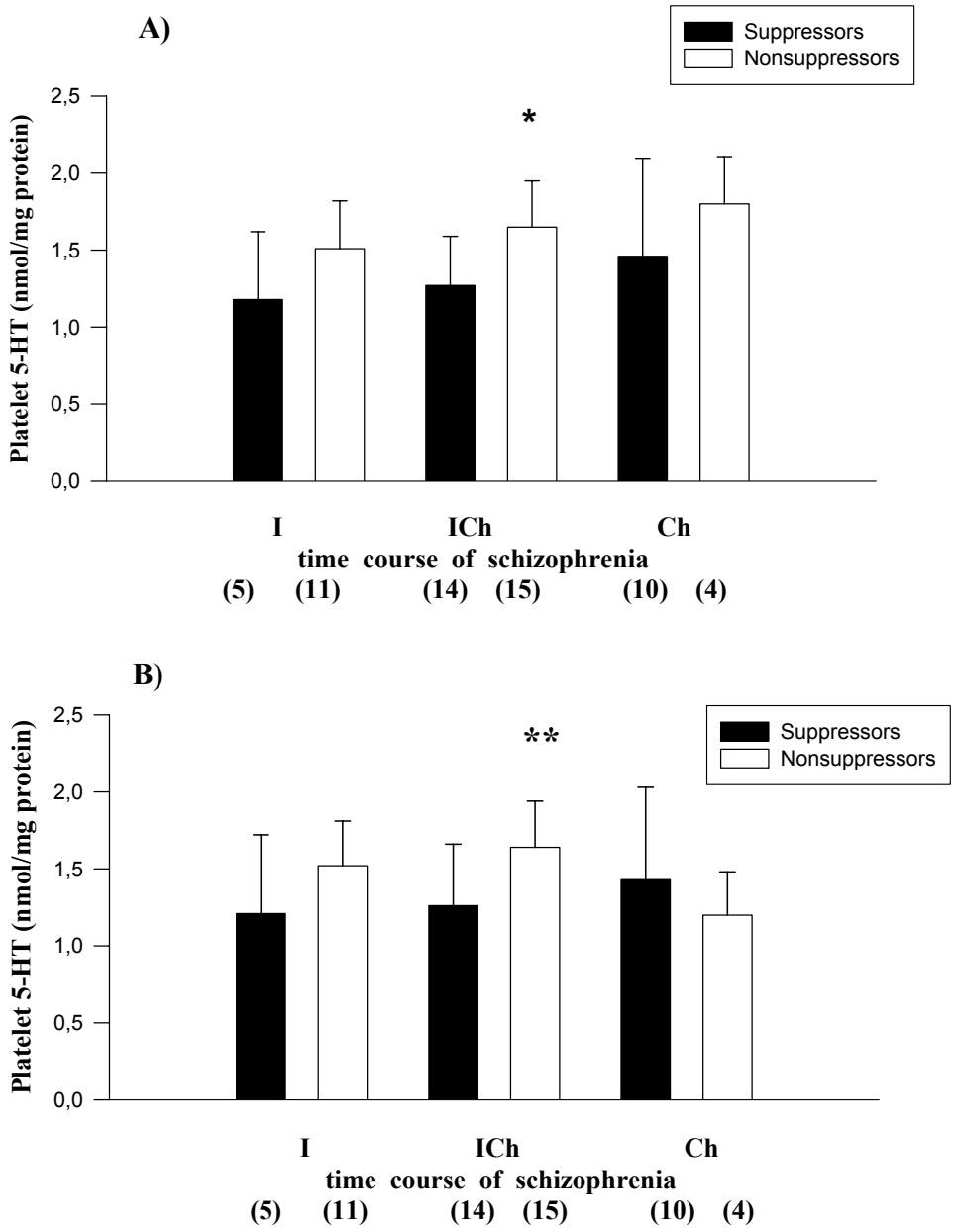


Figure 11. Platelet 5-HT in healthy controls and schizophrenic patients with intermittent (I), intermittent-chronic (ICh) and chronic (Ch) time course of the illness at baseline (A) and after dexamethasone (B). Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P <0.002 vs. suppressors; ** P <0.002 vs. suppressors (Mann-Whitney test).

There was a significant difference (H=24.90; df=11, P=0.009, Kruskal-Wallis ANOVA by ranks) in platelet 5-HT concentration between schizophrenic suppressors and nonsuppressors with intermittent, intermittent-chronic, and chronic time course of

schizophrenia at baseline (Fig. 11A) and after DST (Fig. 11B). Before DST (Fig. 11A), nonsuppressors with intermittent, intermittent-chronic, and chronic time course of schizophrenia to DST had significantly higher ($p<0.003$; Mann-Whitney test) platelet 5-HT concentration than suppressors. After DST (Fig 11B), nonsuppressors with intermittent-chronic had significantly ($p<0.002$: Mann-Whitney test), while nonsupressors with intermittent or chronic time course of schizophrenia had marginally higher platelet 5-HT concentration than suppressors.

Plasma Cortisol Levels in Schizophrenic Patients with Different Time Course of Schizophrenia

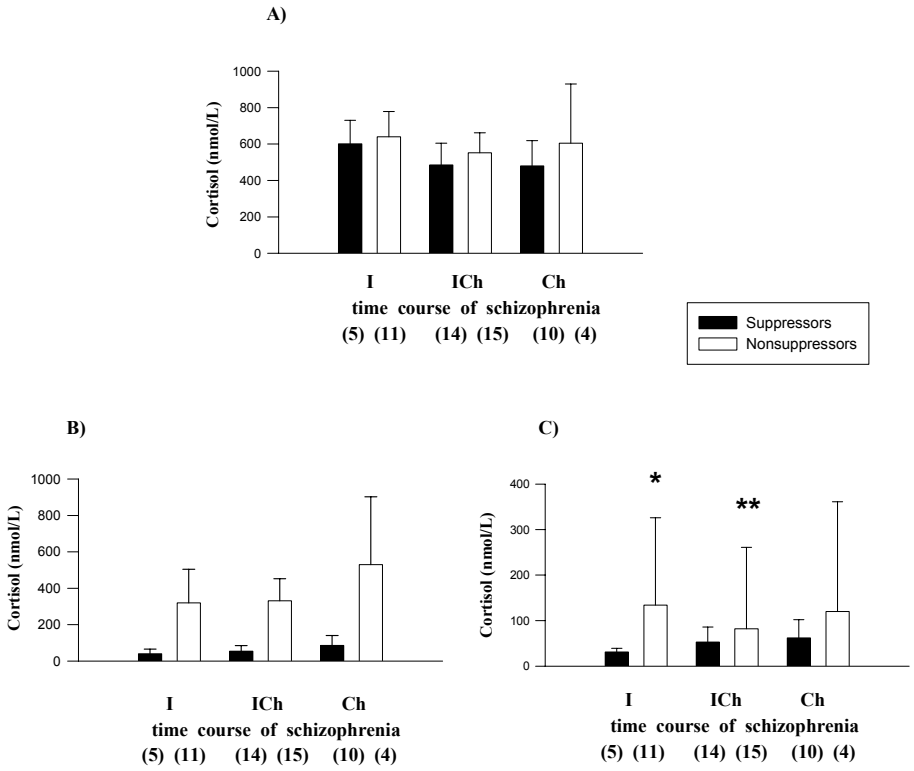


Figure 12. Plasma cortisol levels in schizophrenic patients with intermittent (I), intermittent-chronic (ICh) and chronic (Ch) time course of schizophrenia at baseline (A) and at 8h (B) or 16h (C) after dexamethasone. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.*P <0.05 vs. nonsuppressors at 8 h; ** P <0.002 vs. nonsuppressors at 8 h (Mann-Whitney test).

The values of plasma cortisol levels in male schizophrenic patients with different time course of schizophrenia, divided into suppressors and nonsuppressors according to the DST response, are shown in Fig. 12. There was no significant difference in plasma cortisol levels in schizophrenic suppressors and nonsuppressors with intermittent, intermittent-chronic and chronic time course of schizophrenia before DST ($H=6.52$; $df=5$, $P=0.26$, Kruskal-Wallis ANOVA by ranks). Between schizophrenic suppressors with different time course of the illness, no difference ($H=7.18$; $df=5$, $P=0.21$, Kruskal-Wallis ANOVA by ranks) in plasma

cortisol levels were detected when measured 8 h after DST. However, nonsupressors with intermittent ($p < 0.05$; Mann-Whitney test) or intermittent-chronic ($p < 0.002$; Mann-Whitney test) time course of schizophrenia had significantly higher plasma cortisol levels after DST at 8 h than at 16 h (Fig. 12).

Clinical Rating Scores (Clinical Global Impression of Severity (CGIS),Clinical Global Impression for Severity of Suicidality (CGI-SS), or Hamilton Rating Scale for Depression (HAMD) Scores in Schizophrenic Patients before and after Treatment with Haloperidol or Olanzapine

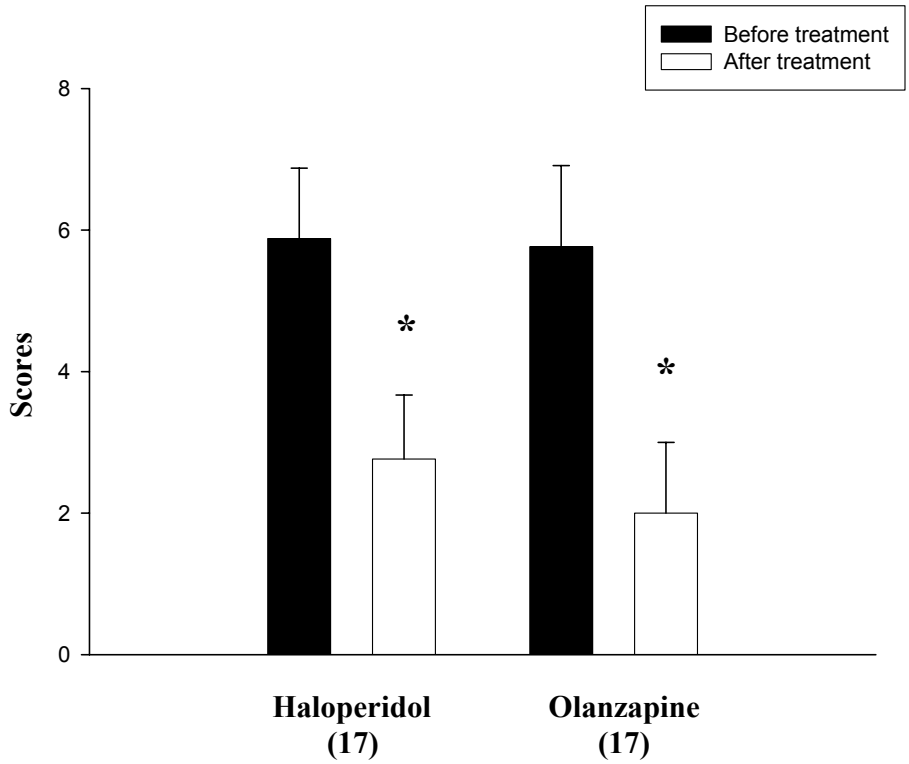


Figure 13. Scores in Clinical Global Impression of Severity (CGIS) in schizophrenic patients treated with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. corresponding scores before treatment (ANOVA followed by Tukey's test)

In 34 male schizophrenic patients with suicidal behavior, the scores in Clinical Global Impression of Severity (CGIS), Clinical Global Impression for Severity of Suicidality (CGI-SS), and Hamilton Rating Scale for Depression (HAMD) at baseline and after 6 months treatment with olanzapine or haloperidol are shown in Figures 13-15. There was a significant difference in the scores in CCI-S ($F=66.80$, $df=3,64$; $p<0.001$), and olanzapine and haloperidol similarly reduced the scores after treatment. The suicidal symptoms, listed in CGI-SS scores, were significantly ($F=7.09$, $df=3,64$; $p<0.001$) different after both drugs, but olanzapine decreased significantly ($p<0.05$), while haloperidol did not alter significantly these scores after treatment. HAMD scores differed slightly but significantly between olanzapine or

haloperidol treated patients (F=4.35, df=1,32; p=0.045), and were significantly (p<0.05) lower after olanzapine than after haloperidol treatment.

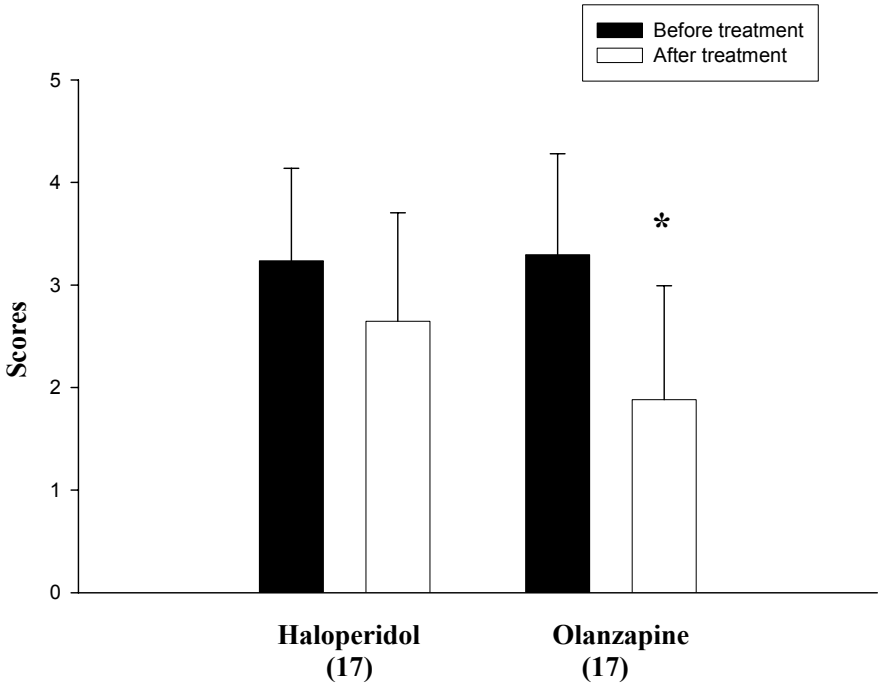


Figure 14. Clinical Global Impression for Severity of Suicidality (CGI-SS) scores in schizophrenic patients before and after treatment with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. baseline scores in olanzapine treated patients (ANOVA followed by Tukey's test)

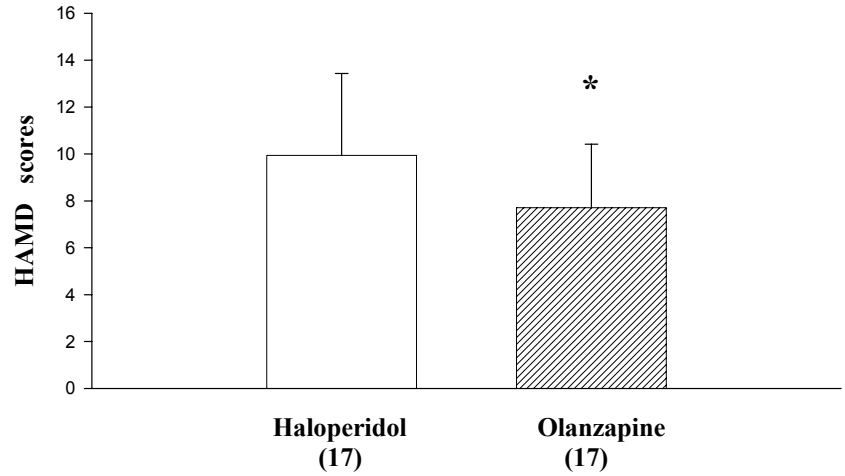


Figure 15. Hamilton Rating Scale for Depression (HAMD) scores in schizophrenic patients treated with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. scores in haloperidol treated patients (ANOVA followed by Tukey's test)

Peripheral Biochemical Markers (Platelet 5-HT Concentration, Platelet MAO Activity, Plasma Cholesterol) in Schizophrenic Patients after Treatment with Haloperidol or Olanzapine

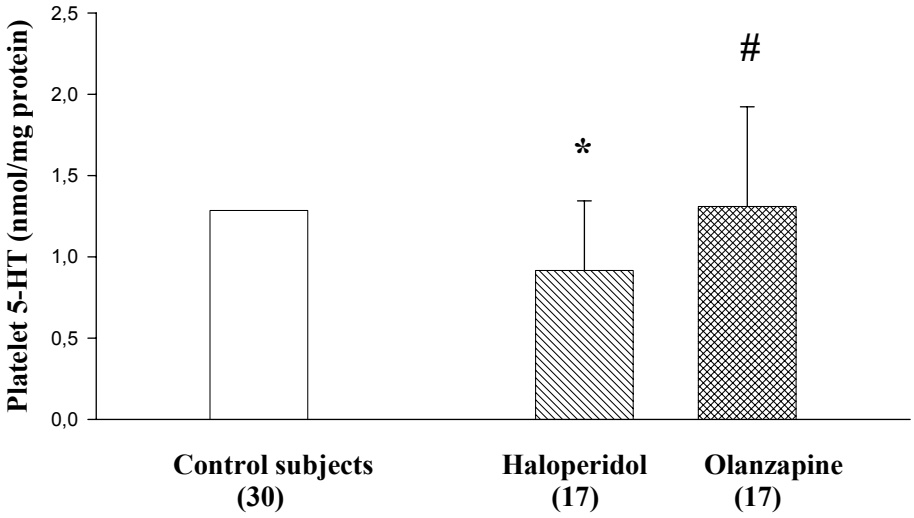


Figure 16. Platelet 5-HT concentration in healthy control subjects and in schizophrenic patients treated with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. control subjects; # P<0.05 vs. haloperidol treated patients (ANOVA followed by Tukey's test)

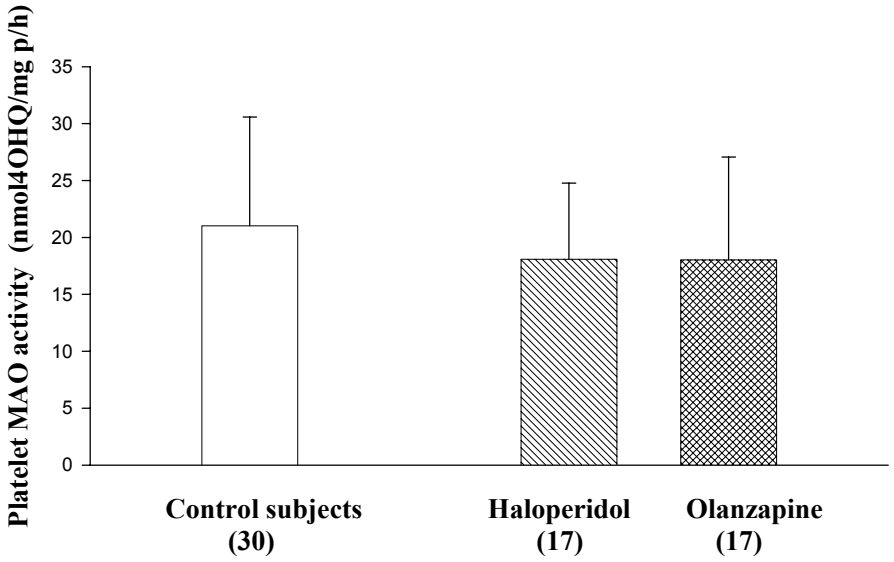


Figure 17. Platelet MAO activity in healthy control subjects and in schizophrenic patients treated with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

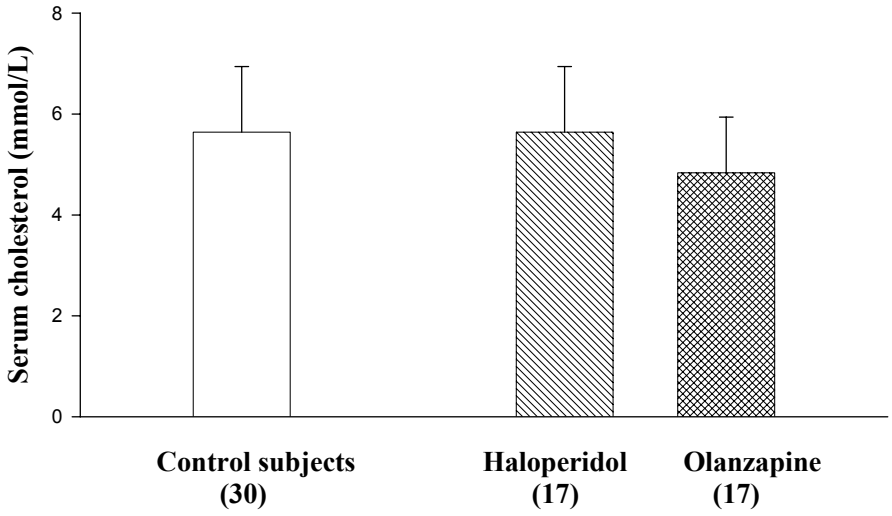


Figure 18. Serum cholesterol in healthy control subjects and in schizophrenic patients treated with haloperidol or olanzapine. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

The values of platelet 5-HT, platelet MAO activity and plasma cholesterol in male suicidal schizophrenic patients are shown in Figures 16-18. Platelet 5-HT concentration differed significantly ($F=4.58$, $df=2,61$; $p=0.014$) in suicidal schizophrenic patients treated with haloperidol or olanzapine (Fig. 16). Significantly ($p<0.05$, Tukey's test) lower platelet 5-HT concentration was found in suicidal schizophrenic patients treated with haloperidol than in patients treated with olanzapine or than in healthy controls (Fig. 16). The values of platelet 5-HT did not differ significantly ($p> 0.05$, Tukey's test) between schizophrenic patients treated with olanzapine and healthy control subjects (Fig. 16). Platelet MAO activity did not differ significantly ($F=0.90$, $df=2,60$; $p=0.416$) between healthy control men and suicidal schizophrenic patients treated with olanzapine or haloperidol (Fig. 17). Serum cholesterol levels ($F=2.22$, $df=2,61$; $p=0.118$) were not significantly different between schizophrenic patients treated with haloperidol or olanzapine and healthy subjects (Fig. 18).

Platelet MAO activity was significantly ($F= 10.59$, $df= 3,204$; $p<001$) different between male and female healthy controls and male and female schizophrenic patients. Both male and female schizophrenic patients had significantly ($p<0.05$) lower platelet MAO activity than their corresponding (male and female) control subjects. Sex differences in platelet MAO activity were found in healthy subjects, and healthy women had significantly ($p<0.05$) higher platelet MAO activity than healthy male subjects (Fig. 19).

Kinetic Constants Km and Vmax for Uptake of ^{14}C-5-HT into Platelets of Healthy Controls, Drug Free or Medicated Schizophrenic Patients with Different Time Course

Kinetic constants Km and Vmax for uptake of ^{14}C-5-HT into platelets in healthy controls and schizophrenic patients with different time course of schizophrenia are shown in nontreated and in treated schizophrenic patients (Fig. 20). The values for the uptake of ^{14}C-5-HT into platelets were similar ($p>0.05$) between schizophrenic patients and healthy control subjects, and did not differ between schizophrenic patients with different time course of schizophrenia (Fig. 20).

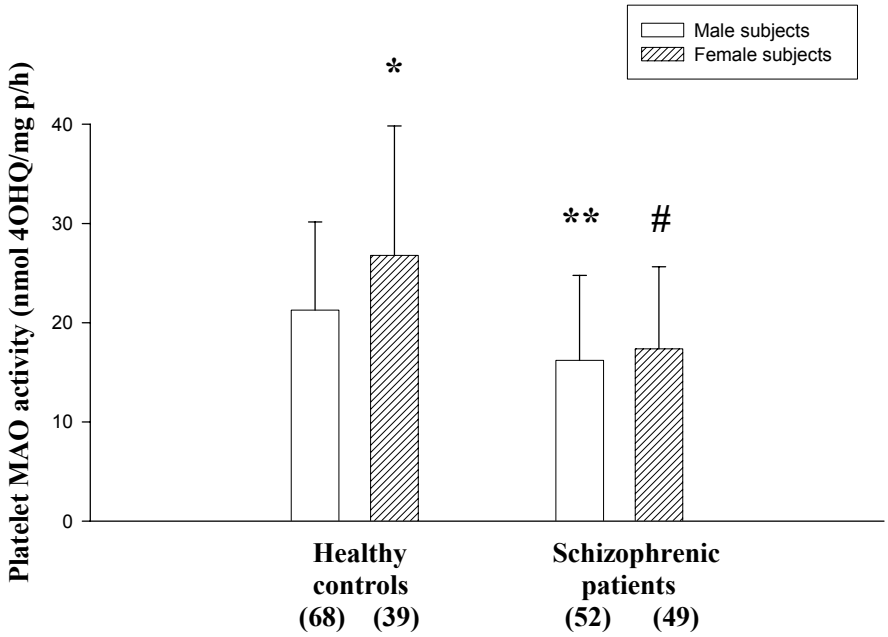


Figure 19. Platelet MAO activity in male and female healthy controls and in schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs healthy male persons; **P<0.05 vs healthy male persons; # P<0.05 vs. healthy female persons.

Kinetic Constants Km and Vmax for Platelet MAO Activity in Healthy Controls and Paranoid and Nonparanoid Schizophrenic Patients

The maximal velocity (Vmax) of platelet MAO activity (Fig. 21) was significantly higher in healthy control women than in healthy men ($t=2.68$; $df=26$, $p<0.02$, Student t-test. The affinity constant (Km) for platelet MAO activity did not differ significantly ($t=0.35$; $df=26$, $p>0.05$, Student t-test) between male or female healthy subjects. There was no significant difference ($p>0.05$, Student t-test) in the Vmax and Km for platelet MAO activity between male or female schizophrenic patients. Values for Vmax or Km for platelet MAO activity did not differ significantly ($p>0.05$) between paranoid and nonparanoid schizophrenic male or female patients (Fig. 21).

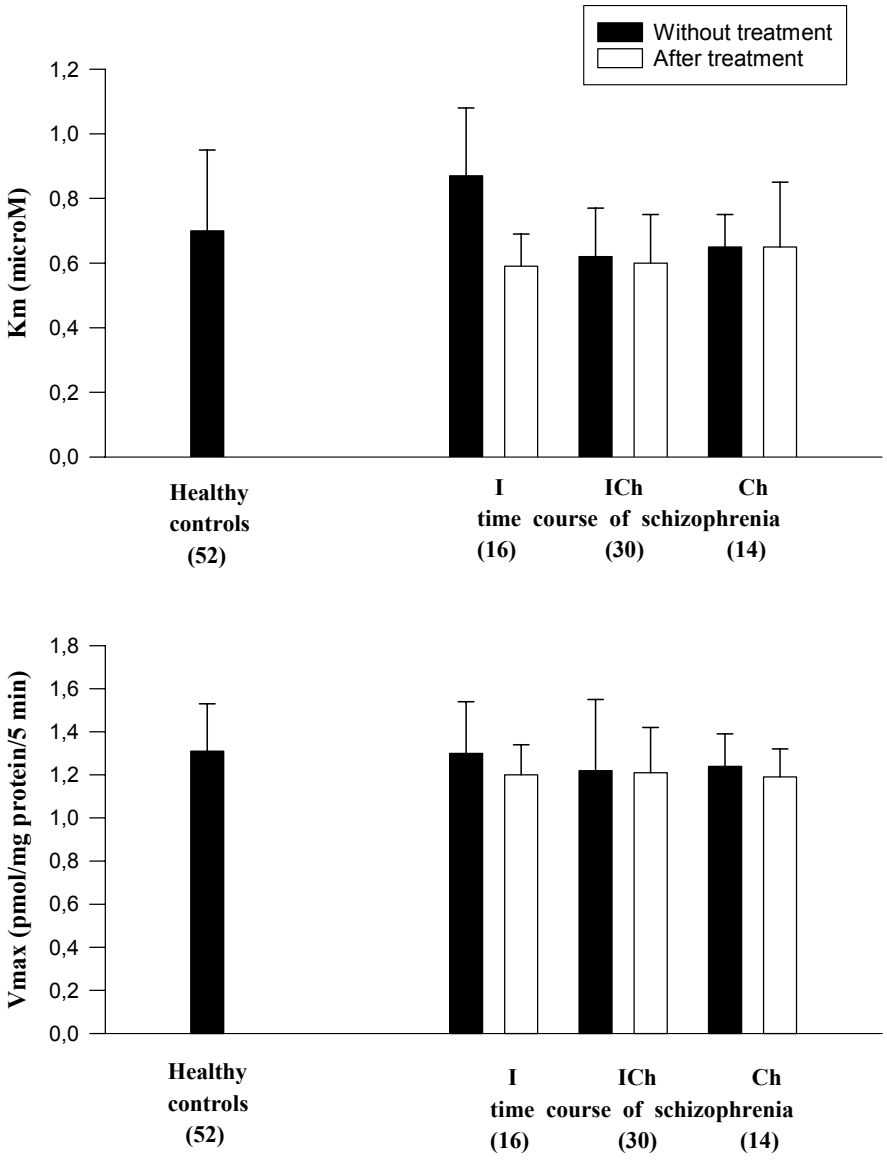


Figure 20. Kinetic constants Km and Vmax for uptake of ^{14}C-5-HT into platelets of healthy controls and schizophrenic patients with intermittent (I), intermittent-chronic (ICh) and chronic (Ch) time course of schizophrenia without treatment and after treatment with antipsychotics. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects.

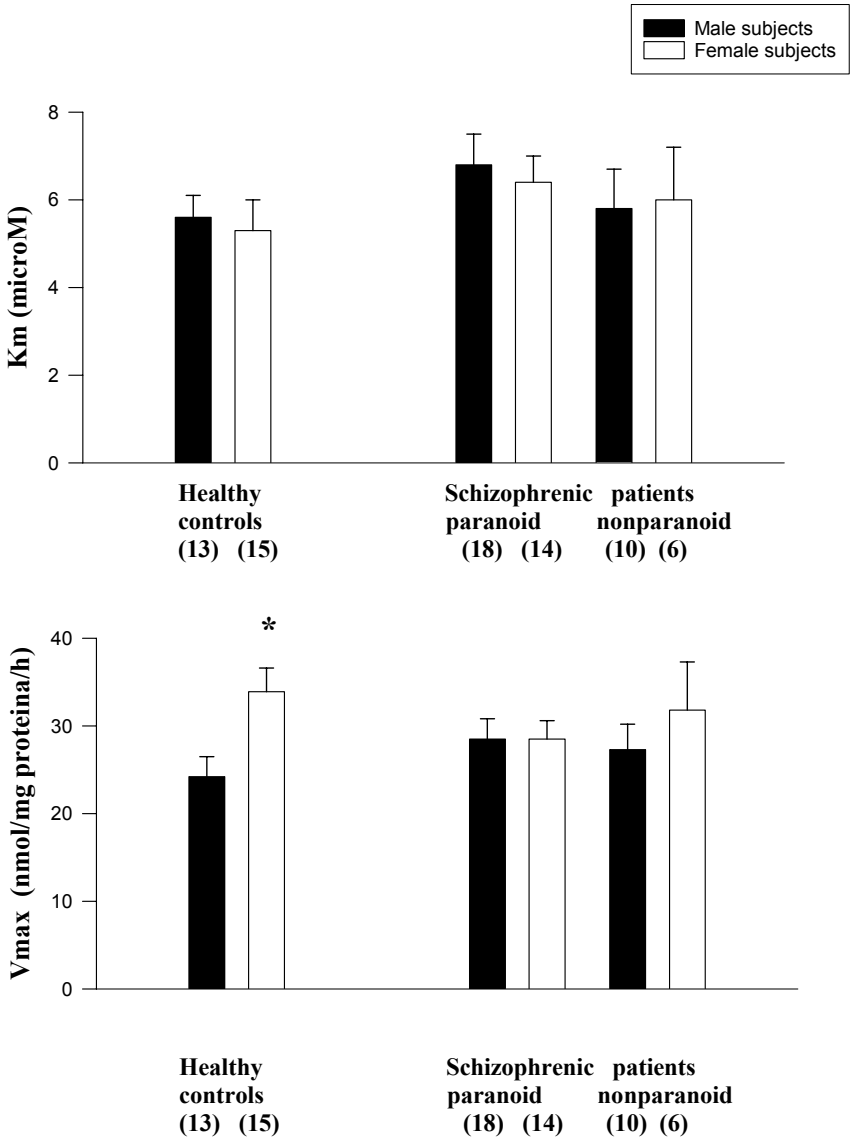


Figure 21. Kinetic constants Km and Vmax for platelet MAO activity in healthy controls and paranoid and nonparanoid schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs. healthy male subjects (Student's t-test).

Baseline plasma PRL levels differed significantly (ANOVA F= 20.815; df=3,209; P<0.001) between male and female healthy controls and schizophrenic men and women. Both schizophrenic male and female patients had significantly ($p<0.05$) higher plasma PRL levels than the corresponding male or female healthy controls. Female healthy and schizophrenic subjects had significantly ($p<0.05$) higher plasma PRL levels than their corresponding male subjects (Fig. 22).

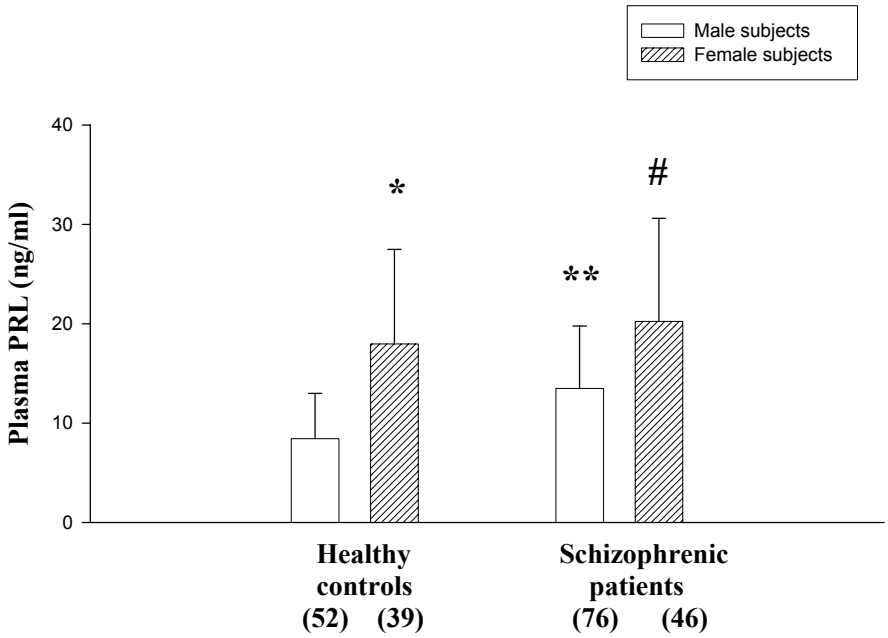


Figure 22. Plasma PRL in male and female healthy controls and in schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.05 vs healthy male persons; **P<0.05 vs healthy male persons; # P<0.05 vs. healthy female persons (ANOVA followed by Newman Keuls test)

Serum lipid profile (cholesterol, triglycerides, high density lipoprotein-cholesterol (HDL) and low density lipoprotein-cholesterol (LDL) in healthy controls and schizophrenic patients is shown in Fig. 23. Serum cholesterol (t= 4.99; df= 152), HDL (t=4.162; df=152) and LDL (t=3.814; df =152) levels were significantly (p<0.001, Student t-test) reduced in schizophrenic patients when compared healthy control subjects. Serum triglyceride levels did not differ significantly (t= 1.299; df= 152; p=0.196, Student t-test) between schizophrenic patients and healthy control subjects (Fig. 23).

Clinical Results of the Total and Subscale Scores in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) in Schizophrenic Patients before and after Treatment with Fluphenazine or Olanzapine

No significant difference in the severity of symptoms was found between schizophrenic patients subdivided into groups treated with olanzapine or fluphenazine for 5 months (Table 2). Treatment with olanzapine for 5 months decreased significantly the scores in total PANSS and in the positive subscale of PANSS, and CGI scores. Treatment with fluphenazine for 5 months did not alter significantly total and subscale scores listed in PANSS and CGI. The scores in the negative subscale of PANSS were not significantly affected either by olanzapine or by fluphenazine (Table 2).

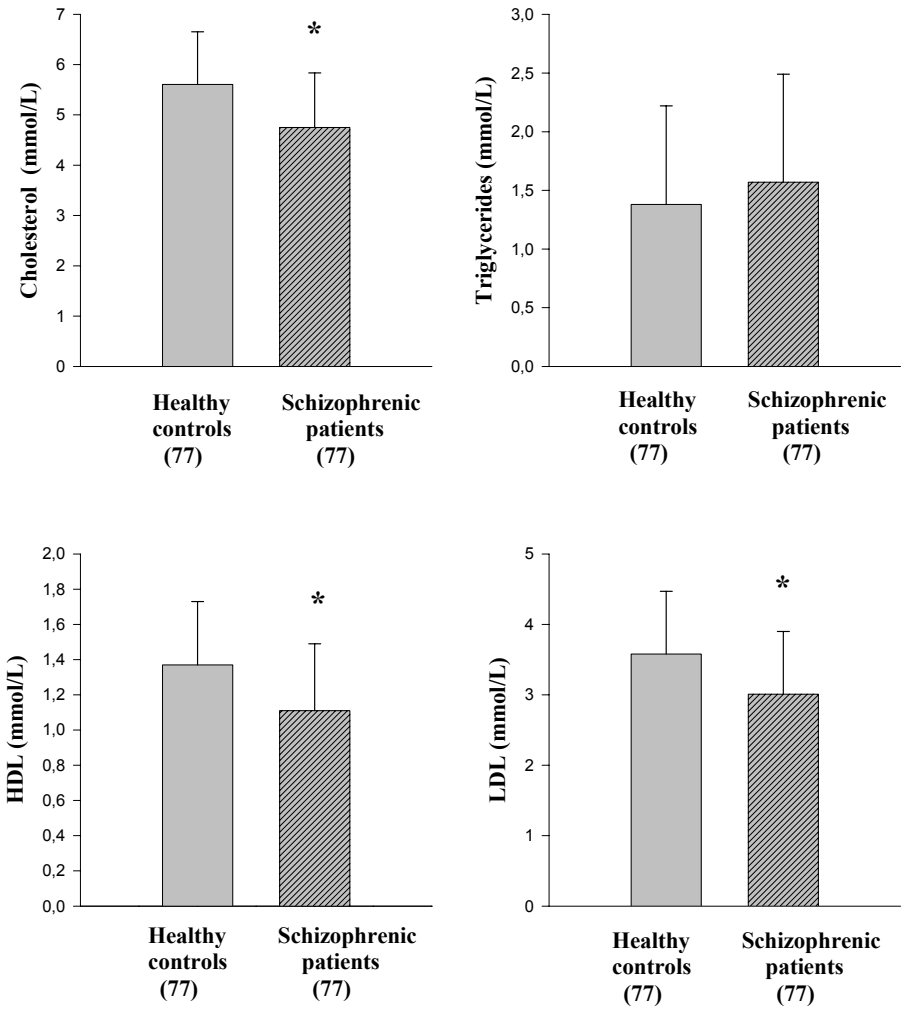


Figure 23. Serum lipids levels in healthy controls and schizophrenic patients. Each column represents mean ± SD. The numbers in parentheses represent the number of subjects. *P<0.001 vs. corresponding values in healthy controls (Student's test)

Table 2. Scores in different clinical scales in female schizophrenic patients before and after 5 months of treatment with fluphenazine or olanzapine. Results are expressed as mean ± SD. N is the number of patients. *p<0.05 vs. scores before treatment with olanzapine (Newman Keuls test)

	Fluphenazine (N=10)		Olanzapine (N=12)		ANOVA df= 3,42 F p
	Before treatment	After treatment	Before treatment	After treatment	
	Scores				
PANSS total	96.9 ±15.4	94.0 ± 30.7	107.7 ± 19.1	77.0 ±22.9*	4.12 <0.012
PANSS positive	26.2 ± 8.0	24.3 ± 9.7	27.8 ± 4.8	18.4 ± 9.6 *	3.24 <0.031
PANSS negative	23.2 ± 9.3	23.1 ± 9.4	27.5 ± 8.9	20.7 ± 6.4	1.39 n.s.
CGI	5.2 ± 0.78	4.7 ± 1.56	5.3 ± 0.75	3.1 ± 1.51*	3.03 <0.04

Table 3. Platelet 5-HT, plasma PRL and cortisol levels in female schizophrenic patients before and after 5 months of treatment with fluphenazine or olanzapine. Results are expressed as mean ± SD. N is the number of patients

	Platelet 5-HT (nmol/mg protein)	PRL (nmol/ml)	Cortisol (nmol/ ml)
Healthy controls (22)	1.18± 0.36	14.2 ± 5.8	397 ± 107
Fluphenazine (10):			
Before treatment	1.54 ± 0.60	34.2 ± 19.8	580 ± 218*
After treatment	1.52 ± 0.74	68.7 ± 41.5 *, #, **	724 ± 189*, **
Olanzapine (12):			
Before treatment	1.37 ± 0.42	27.3 ± 15.2	586 ± 187*
After treatment	1.56 ± 0.75	39.7 ±19.2	502 ± 134

* $p<0.05$ vs. corresponding healthy controls; ** $p<0.05$ vs. olanzapine after treatment,
# $p<0.05$ vs. fluphenazine before treatment, (ANOVA, followed by Newman Keuls test)

Schizophrenic patients subdivided into groups treated with olanzapine or fluphenazine for 5 months had similar values of platelet 5-HT concentrations ($F=1.57$; $df=4,61$; $p=0.19$), and significantly different plasma PRL ($F=10.98$; $df=3,42$; $p<0.001$) or plasma cortisol ($F=8.85$; $df=4,61$; $p<0.001$) levels (Table 3). Fluphenazine treatment increased significantly ($p<0.05$) plasma PRL levels when compared to values before treatment, or to values after treatment with olanzapine, or to control values. Fluphenazine treatment for 5 months increased significantly ($p<0.05$) plasma cortisol and did not affect platelet 5-HT levels. Five-months of olanzapine treatment did not affect significantly platelet 5-HT concentration or plasma cortisol or PRL levels (Table 3).

Table 4. Pearson's coefficient of correlation (r) between platelet 5-HT, plasma cortisol and plasma PRL in male healthy controls and male schizophrenic patients.

	Healthy male controls (N=52)	Male schizophrenic patients (N=76)
Platelet 5-HT (nmol/mg protein)	1.28 ± 0.28	1.41 ± 0.48
Plasma cortisol (nmol/l)	437 ± 140	472 ± 186
Plasma PRL (ng/ml)	8.4 ± 4.6	17.9 ± 9.5
Platelet 5-HT vs. plasma cortisol	r = - 0.140 ; p = 0.321	r = - 0.011 ; p = 0.927
Platelet 5-HT vs. plasma PRL	r = 0.127 ; p = 0.368	r = - 0.081 ; p = 0.485
Plasma cortisol vs. plasma PRL	r = - 0.109 ; p = 0.440	r = 0.129 ; p = 0.265

Platelet 5-HT concentration was marginally ($t=1.73$; $df=126$; $p=0.087$, Student t-test), and plasma PRL levels significantly ($t=6.72$; $df=126$; $p<0.001$, Student t-test) increased in male schizophrenic patients when compared to male healthy control subjects (Table 4). Plasma cortisol levels did not differ significantly ($t= 1.17$; $df=126$; $p=0.246$, Student t-test) between healthy men and male schizophrenic patients. There was no significant correlation ($p>0.05$, Pearson's coefficient of correlation) between platelet 5-HT concentration and plasma cortisol levels, or between platelet 5-HT concentration and plasma levels of PRL, or between plasma cortisol and plasma PRL levels in either healthy men or in schizophrenic male patients (Table 4).

4. DISCUSSION

Platelet 5-HT Concentration in Schizophrenic Patients and Healthy Controls

The results from the present study, obtained on a large groups of male and female schizophrenic patients and healthy subjects, show that schizophrenic patients had significantly higher platelet 5-HT concentration than the corresponding healthy controls, and confirm our previous (Muck-Seler et al., 1988; 1991; 1999a; 1999b; 2004; Jakovljevic et al., 1997, 1998), and other (Iqbal and Van Praag, 1995) data. Platelet 5-HT concentration did not differ between healthy controls and healthy relatives of schizophrenic patients, suggesting that only schizophrenic patients have increased platelet 5-HT concentration. Our data about the increased platelet 5-HT concentration in schizophrenia are confirmed also by other groups that used different methods for the platelet 5-HT determination and had different population of patients (Pavlova et al., 2005; Brusov et al., 2005). These data might support the hypothesis that platelet 5-HT concentration, among other markers, might be used as a limited peripheral model for the central serotonergic synaptosomes, since indicators of the central 5-HT activity (post mortem assays, 5-HT concentration in various regions of the brain, density of the 5-HT receptors and 5-HT transporter (Egan and Hyde, 2000), and maximum number of the 5-HT transporter sites in platelets of untreated schizophrenic patients (Govitrapong et al., 2002) were reported to be altered in schizophrenia.

In line with our previous data, higher platelet 5-HT concentration was a characteristic feature of schizophrenia with predominantly positive symptoms (Jakovljevic et al., 1997; Pivac et al 1997b), and paranoid schizophrenia (Muck-Seler et al., 1991). These data indicate that platelet 5-HT concentration might be used as a peripheral serotonergic marker for the subtypes of schizophrenia, since it was significantly increased in schizophrenic patients with predominantly positive, when compared to patients who had schizophrenia with predominantly negative symptoms (Jakovljevic et al., 1997; Pivac et al 1997b), and in patients with paranoid schizophrenia, when compared to non-paranoid (catatonic, disorganized or undifferentiated) schizophrenia (Muck-Seler et al., 1991). This finding agrees with the proposal that platelet serotonergic markers, such as platelet 5-HT, are closely related to particular basic psychopathological characteristics, i.e. trait markers (Askenazy et al., 2000; Muller-Oerlinghausen et al., 2004), and confirm the presumption that platelet 5-HT is associated with aggression (Goveas et al., 2004), impulsivity, and high degree of violence (Askenazy et al., 2000), psychotic symptoms of depression (Muck-Seler et al., 1996a; Pivac et al., 1997a), severe loss of appetite in chronic renal female patients (Pivac et al., 2001) or in male war veterans with posttraumatic stress disorder (Muck-Seler et al., 2003), anxiety and cognitive disturbances in male patients on hemodialysis (Barisic et al., 2004), suicidal behavior (Muck-Seler et al., 1996a; Pivac et al., 1997a), and specific subtype of schizophrenia (present study, Muck-Seler et al., 1991; Jakovljevic et al., 1997; Pivac et al 1997b).

Sex-related differences in platelet 5-HT concentration, with higher values in male than in female subjects, found before in healthy subjects (Oxenkrug, 1979; Muck-Seler et al., 1996a; 1999b; Pivac et al., 2001; 2004), depressed (Oxenkrug, 1979; Muck-Seler et al., 1996a), suicidal (Muck-Seler et al., 1996a; Muller-Oerlinghausen et al., 2004), alcoholic (Pivac et al., 2004) and schizophrenic (Muck-Seler et al., 1999b; Brusov et al., 2005) patients, were detected also in the present study. All our data show that female subjects had significantly

lower platelet 5-HT concentration than male subjects. This finding agrees with the lower plasma free tryptophan, and lower 5-HT synthesis in the brain of female when compared to male healthy subjects (Nishizawa et al., 1997). The decreased rate of the 5-HT synthesis in healthy women (Nishizawa et al., 1997) and in depressed female patients (Rosa-Neto et al., 2004) might indicate that women are more prone than men to react to the stressful situations with a decline in central 5-HT, and this reduced 5-HT synthesis might lead to vulnerability to different psychiatric disorders (Nishizawa et al., 1997). Decreased platelet 5-HT concentration in women, found in different diagnostic groups and healthy controls, might be attributed to a different phases of the estrus cycle, or to different levels of estrogens. Namely, it has been shown that estro-progestative treatment affected platelet and blood 5-HT concentration (Guicheney et al., 1988), however estrogen replacement therapy did not change plasma 5-HT levels in postmenopausal women (Blum et al., 1996), and we have recently shown that pre- or post-menopausal status does not affect platelet 5-HT concentration (Muck Seler et al., 2004). In addition, whole blood 5-HT levels did not differ between healthy women during follicular, ovulatory or luteal phase of the menstrual cycle (Rasgon et al., 2000). Since the reports on the possible effect of the menstrual cycle on platelet 5-HT concentration are contradictory (Leibenluft et al., 1994), the possible effect of estrus cycle on platelet 5-HT concentration might be neglected.

Platelet 5-HT concentration might be affected by the older age, but conflicting results regarding the effect of age on platelet 5-HT concentration have been reported, with increased (Kumar et al., 1998), or unchanged platelet 5-HT concentration in older subjects (Pivac et al., 2004). No significant relation between age and platelet 5-HT was consistantly found in our and other previous works, either in healthy persons (Muck-Seler et al., 1996b; Franke et al., 2000; Pivac et al., 2001; 2003; 2004) or in a large number of depressed and schizophrenic patients (Muck-Seler et al., 1996a; 1996b; 1999a; 1999b; Pivac et al., 1997b; 2003; Franke et al., 2000), hence the possible effect of age on platelet 5-HT content might be neglected. To avoid the possible influence of meals on platelet 5-HT concentration, blood was sampled in fasting subjects, and in addition, platelet 5-HT content was not affected by nutrition (Anderson, 1985).

In line with our previous data in male healthy, depressed and schizophrenic subjects (Jakovljevic et al., 1997), platelet 5-HT concentration was not affected by the sampling in different seasons, since there was no significant difference in platelet 5-HT concentration between fairly large groups of male or female schizophrenic patients and male or female healthy persons, when sampled in different seasons. However, to avoid the possible seasonal influence on platelet 5-HT parameters (Muller-Oerlinghausen et al., 2004), we sampled schizophrenic patients and healthy controls simultaneously. To prevent the influence of the diurnal rhythm on the platelet 5-HT concentration, subjects were sampled always between 8.00-9.00 a.m. (Wirtz-Justice et al., 1977).

Platelet 5-HT concentration was significantly higher both in male, as well as in female schizophrenic patients born in winter, than in healthy subjects or schizophrenic patients born in spring, summer and fall. This finding, obtained on the larger number of subjects, is in line with our previous data (Muck-Seler et al., 1999b). We did not measure the occurrence of schizophrenia in the present study, but our previous study (Muck-Seler et al., 1999b) found similar occurrence of schizophrenia in subjects born in winter, spring, summer or fall. Since platelet 5-HT concentration differed among schizophrenic patients born in different seasons, increased platelet 5-HT concentration, which is postulated to represent a characteristic feature

of schizophrenia, might indirectly add further support to the hypothesis that schizophrenia is a neurodevelopmental disorder. However, the cause of schizophrenia is still unknown. Schizophrenia might be explained by the complex interaction between genetic factors, disturbances in brain and nervous system during gestation, with persistent impairment in one or more neurotransmitter systems, and other factors, such as infections (which might be associated with season of birth), diet, social and environmental factors, or severe bleeding during pregnancy (Kelly, 2005).

In agreement with our previous data obtained on the smaller groups of schizophrenic subjects (Muck-Seler et al., 1988; Jakovljevic et al., 1998), platelet 5-HT concentration was higher in male patients with intermittent, intermittent-chronic and chronic time course of schizophrenia, than in healthy control men. The data suggest that chronic time course of schizophrenia is associated with elevated platelet 5-HT concentration. This finding suggests that these patients are severely impaired, and increased platelet 5-HT indicates the presence of positive or paranoid symptoms. Since the kinetic characteristics for the uptake of ^{14}C-5-HT into platelets were similar between healthy controls and non-treated and treated schizophrenic patients, with different time course of schizophrenia, no correlation has been found between uptake of 5-HT and platelet 5-HT concentration in schizophrenic patients (Muck-Seler et al., 1988).

Besides the disrupted activity of the 5-HT system, schizophrenia is characterized also with a hyperactive hypothalamic-pituitary-adrenal (HPA) axis (Tandon and Halbreich, 2003). In addition, 5-HT has been implicated in the stress-related regulation of the HPA axis (Dinan, 1996). Previously (Pivac et al., 1997b; Jakovljevic et al., 1998; Muck-Seler et al., 1999a), we have found abnormal response of the HPA axis to administration of dexamethasone (i.e. nonsuppression to DST) in schizophrenic patients. To elucidate the relationship between the activity of the HPA axis and platelet 5-HT, we determined platelet 5-HT concentration in schizophrenic patients with different time course of schizophrenia, subdivided into suppressors and nonsuppressors to DST. In agreement with our previous studies (Pivac et al., 1997b; Jakovljevic et al., 1998; Muck-Seler et al., 1999a), before, as well as after DST, nonsuppressors with intermittent-chronic time course of schizophrenia had higher platelet 5-HT concentration than suppressors. All schizophrenic nonsuppressors had higher platelet 5-HT concentration than suppressors. Platelet 5-HT concentration did not differ between schizophrenic patients with predominantly positive or negative symptoms, subdivided further into suppressors and nonsuppressors to DST. Namely, platelet 5-HT was decreased in schizophrenic patients with negative symptoms, regardless of the suppression or nonsuppression to DST. Our present and previous data (Pivac et al., 1997b; Jakovljevic et al., 1998) suggest that DST was not associated significantly with the time course, or the subtype of the illness, and question the proposed association between DST and severity of illness.

Platelet MAO Activity in Schizophrenic Patients

Monoamine oxidase is a flavoenzyme that has two types: type A and type B, and both are important since they deaminate different neurotransmitters and xenobiotic amines in the central nervous system and in the periphery. Platelets contain only MAO-B type, which shares the identical amino acid sequence, and similar biochemical and pharmacological characteristics with MAO-B in the brain (Billett, 2004; Oreland, 2004; Coccini et al., 2005).

The substrates for MAO-B are phenyletylamine and benzylamine, and dopamine and tyramine are substrates for both MAO types. It has been reported that platelet MAO might be used as a genetic marker for the size or functional capacity of the central 5-HT system (Oreland et al., 2002), and a biological marker for psychopathology and personality (Oreland and Shaskan 1983; Kozaric-Kovacic et al., 2000; Oreland, 2004). In our study platelet MAO activity was decreased in male and female schizophrenic patients when compared to male and female healthy control subjects. In addition, in support to our previous results (Muck-Seler et al., 1991; Pivac et al., 2005), we have found significant sex-related differences in platelet MAO activity, and female healthy and schizophrenic subjects had higher platelet MAO activity than their corresponding male subjects. In conformation to these results, the affinity constant (Vmax) of platelet MAO activity was increased in female compared to male healthy subjects. Although values of Vmax and affinity constant for platelet MAO activity in male or female schizophrenic patients were similar, and Vmax or Km for platelet MAO activity did not differ between paranoid and non-paranoid schizophrenic male or female patients, these results might be explained by the small number of schizophrenic patients when divided into subgroups, or the different method used to detect kinetic characteristics of platelet MAO. Hence, sex differences, observed in healthy (present study, Muck-Seler et al., 1991; Pivac et al., 2005), or alcoholic (Pivac et al., 2005) subjects, were now detected also in schizophrenic patients.

Platelet MAO activity might be affected by sex (Muck-Seler et al., 1991; Verkes et al., 1998; Snell et al., 2002; Oreland, 2004; Coccini et al., 2005), and increased platelet MAO activity in women might be due to the increased concentration of the platelet MAO-B protein in women (Snell et al., 2002). Other factors that increase platelet MAO activity in women might be estrogens and/or ovulation, however, the opposite findings were reported, showing ovulation-induced fall and/or elevation of platelet MAO activity (Leibenluft et al., 1994), but also no variations in platelet MAO activity during the menstrual cycle in control women (Hallman et al., 1987).

Smoking is another factor that affects platelet MAO activity (Oreland et al., 2002), and smokers have decreased platelet MAO activity (Berlin et al., 1995; Fowler et al., 2003). In support to these findings, we have found reduced platelet MAO activity in healthy smokers (Pivac et al., 2005), but the number of cigarrettes smoked per day did not affect platelet MAO activity (Pivac et al., 2005). The limitation of the present study is that we did not matched the results according to the smoking status, because data were not available for the smoking status for all subjects. Since both schizophrenic and healthy groups consisted of smokers and nonsmokers, we might assume that reduced platelet MAO activity is more related to schizophrenia than to the effect of smoking. However, the studies that would covariate platelet MAO activity and smoking in schizophrenia are underway to clarify this finding.

Older age has been proposed to increase platelet MAO (Veral et al., 1997; Oreland, 2004), and increased values of MAO-B have been detected in platelets (Nicotra et al., 2004), or brain (Fowler et al., 2003; Karolewitz et al., 2005). On the other hand, no significant effect of age on platelet MAO activity was reported (Coccini et al., 2005), and we have not found increased platelet MAO values in older subjects (Pivac et al., 2005). Since the present study included a mixed population of older and younger subjects, the possible influence of age on platelet MAO activity might be neglected.

Although platelet MAO activity might be increased in Alzheimer's disease (Mimica et al., 2005), pernicious anemia, Parkinson's disease and Huntington’s chorea (Oreland, 2004), since

our schizophrenic patients had decreased platelet MAO activity, we might presume that they were free of these disorders.

Plasma Cortisol Levels in Schizophrenic Patients

Schizophrenia is associated with a dysregulated HPA activity and elevated ACTH (Ryan et al., 2004), and cortisol (Lee and Meltzer, 2001; Tandon and Halbreich, 2003) levels, hippocampal abnormality and cognitive impairment. In agreement with our previous data obtained on male (Pivac et al., 1997b; Jakovljevic et al., 1998; Muck-Seler et al., 1999a; Marcinko et al., 2005) or female (Muck-Seler et al., 2004) schizophrenic patients, plasma cortisol levels were significantly increased in male and female schizophrenic patients when compared to corresponding control men and women. In the present study there was no sex-related difference in plasma cortisol levels, a result that adds to the controversies regarding the gender related differences in cortisol secretion (Schmidt et al., 2002). Dexamethasone suppression test (DST) has been used as a probe of the abnormal response of the HPA axis to suppression induced by dexamethasone, and nonsuppression to DST has been proposed to be an indicator of the altered activity of the HPA axis in depression (Carroll et al., 1981). We have previously shown that schizophrenic patients also have an abnormal response to DST, and 50% or more schizophrenic patients were non-suppressors to DST (Jakovljevic et al., 1998; Pivac et al., 1997b; Muck-Seler et al., 1999a). It is assumed that nonsupression to DST might occur as a result of the withdrawal from antipsychotics, since antipsychotic "normalize" overactive HPA axis due to the modulation of the glucocorticoid receptors (Ryan et al., 2004). To further evaluate plasma cortisol levels in the subtypes of schizophrenia, we divided schizophrenic patients into groups with predominantly positive and predominantly negative symptoms. We have found in the present and in our previous (Pivac et al., 1997b) study that plasma cortisol levels did not differ between schizophrenic patients with predominantly positive symptoms and patients with predominantly negative symptoms. This finding does not confirm the hypothesis (Tandon et al., 2001) that plasma cortisol levels are associated with psychotic symptoms, and suggests that plasma cortisol level can not differentiate between the subtypes of schizophrenia, at least not in our sample of patients. Plasma cortisol levels did not differ in schizophrenic patients with positive or negative symptoms, subdivided according to the DST response into suppressors and nonsuppressors (Pivac et al., 1997b), or in schizophrenic suppressors with different time course of the illness (Jakovljevic et al., 1998). After DST, there was an expected fall of plasma cortisol levels in suppressors, but nonsuppressors, with intermittent or intermittent-chronic time course of schizophrenia, had decreased plasma cortisol values 16 h after DST when compared to values in nonsuppressors 8 h after DST (Jakovljevic et al., 1998; Muck-Seler et al., 1999a). The basal cortisol findings suggest that hypercortisolemia is independent of the time course of the illness. This unexpected decrease 16 h after DST in nonsuppressors indicates that schizophrenic patients with intermittent or intermittent-chronic time course may have a moderate, but delayed reaction of the HPA axis to DST. They suppress plasma cortisol after DST, but need longer time for the reaction, which is not a complete one.

Although plasma cortisol was not a good marker of the subtype or time course of schizophrenia, plasma cortisol levels differed were significantly between violent and non-violent suicide attempters among male schizophrenic patients (Marcinko et al., 2005).

Increased plasma cortisol was a characteristic feature of the violent suicide attempters with schizophrenia (Marcinko et al., 2005). Our data suggest that plasma cortisol levels, or HPA axis abnormalities, might be used to differentiate between schizophrenic and non-schizophrenic subjects, and between violent and non-violent suicide attempters, but not between positive or negative subtype of schizophrenia, or between different time course of schizophrenia.

Plasma Prolactin Levels in Schizophrenic Patients

In the present study, male and female schizophrenic patients had significantly higher plasma PRL levels than male or female healthy subjects. The higher values in plasma PRL levels in our schizophrenic patients agreee with some (Halbreich et al., 2003), but not all published data (Muck.Seler et al., 2004). The differences between our previous (Muck-Seler et al., 2004) and present study might be explained by the much larger patient group in the present study, divided according to the gender. In addition, there was a slight but nonsignificant rise of plasma PRL levels in the previous study (an increase of 20% versus control women) that did not reach the statistical significance. Other reasons that might explain the discrepancies between studies might include the residual effects of the previous drug treatment (Canuso et al., 2002), different estrus phases of the subjects (Lebenluft et al., 1994), age, or the presence of different molecular forms of PRL between schizophrenic patients and healthy controls (Warner et al., 2001). The limitation of this study is that groups were not matched according to the age. However, no correlation was found between age and plasma PRL and cortisol levels in healthy (Sagud et al., 2002) or schizophrenic (Muck-Seler et al., 2004) women. Hyperprolactinemia was observed after treatment with traditional antipsychotics like haloperidol (Crawford et al., 1997; Esel et al., 2001). To exclude the effect of previous antipsychotics, that all affect plasma PRL levels (Canuso et al., 2002), our baseline PRL data were obtained in schizophrenic patients after a washout period (of 7 days). In addition, since depot neuroleptics increase plasma PRL levels (Wistedt et al., 1981), we excluded these patients from our study. Since the increased pretreatment plasma PRL levels were associated with a good therapeutic response (Yazici et al., 2002), our data might indirectly suggest that our schizophrenic patients, with elevated baseline PRL levels, comprised of groups that would later respond good to antipsychotics.

We have found significant sex differences in plasma PRL levels in both healthy and schizophrenic subjects, with higher values in female when compared to male subjects. While PRL is controlled by the gonadal hormones, it appears that PRL levels in women are not under influence of the menstrual status. No differences in basal PRL levels were found between women in follicular and luteal phase of menstrual cycle (Schwartz et al., 1999), between young women and postmenopausal women with or without estrogens hormone replacement therapy (van Amelsvoort et al., 2001), and in premenopausal or postmenopausal females (Huerta et al., 1995; Muck-Seler et al., 2004).

The Lack of Correlation between Platelet 5-HT, Plasma Cortisol and Prolactin Levels in Healthy Men and Male Schizophrenic Patients

In contrast to our previous data obtained on female subjects (Muck-Seler et al., 2004), in the present study no significant correlation was found between the concentration of platelet 5-HT and plasma cortisol, or between platelet 5-HT and plasma PRL, or between plasma cortisol and plasma PRL in healthy men. Namely, it has been suggested that serotonergic receptors, particularly 5-HT_{1A} and 5-$HT_{2A/2C}$, are involved in the regulation of HPA axis activity (Dinan, 1996) and PRL secretion (Palazidou et al., 1995). Meltzer and Maes (1994) implied that stimulation of PRL release is dependent on the activation of both 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors. Since there is a complex relationship between central 5-HT, the activity of the HPA axis, and PRL secretion, and 5-HT regulates the release of cortisol and PRL (Dinan, 1996; Balsa et al., 1998), the lack of relationship in healthy subjects is an unexpected finding. However, there was also no association between hypercortisolemia and platelet 5-HT concentration in schizophrenic patients (Muck-Seler et al., 1999). At present it is not clear why we failed to detect a significant correlation between platelet 5-HT, plasma cortisol and PRL concentration, and did not replicate our findings on the female healthy subjects (Muck-Seler et al., 2004). The discrepancies between the present and our previous (Muck-Seler et al., 2004) study might be explained with the different gender of the subjects. Although the pre- or post-menopausal status did not affect significantly platelet 5-HT, plasma cortisol or PRL levels in female subjects, as shown in previous study (Muck-Seler et al., 2004), gonadal steroids have their role in the control of cortisol and PRL secretion in male and female subjects, and gender and gonadal steroids also modulate serotonergic system function (Schmidt et al., 2002). In line with that, moderate gender related differences in the mCPP (m-chlorophenylpiperazine), a serotoninergic stimulus-induced release of cortisol and ACTH, were observed in healthy subjects in a hypogonadal model (Schmidt et al., 2002). Although these results were not significant, and were obtained in experimentally induced hypogonadal and hormone replaced conditions, and after a challenge test, they suggest a relationship between gonadal steroids and serotonergic system in healthy men and women (Schmidt et al., 2002). On the other hand, the lack of significant relationship, i.e. no significant association between platelet 5-HT, plasma cortisol and PRL concentration, was detected in male schizophrenic patients. This finding was expected (Muck-Seler et al., 2004), since schizophrenic patients have a dysregulated HPA axis activity and PRL secretion (Tandon et al., 1991; Halbreich et al., 2003), with increased plasma cortisol levels (Jakovljevic et al., 1998: Muck-Seler et al., 1999a), and PRL (Halbreich et al., 2003) levels.

Serum Lipid Levels in Schizophrenic Patients

The lipid profile in schizophrenic patients showed decreased serum cholesterol, high density lipoprotein-cholesterol (HDL) and low density lipoprotein-cholesterol (LDL) levels when compared to values in healthy controls, a finding in agreement with the previous studies (Ryan et al., 2003; Marcinko et al., 2004). There was no difference in serum triglyceride levels between schizophrenic patients and healthy control subjects. The lower plasma lipid (cholesterol, HDL and LDL) levels in schizophrenia might be associated with a hyperactive state of these patients, or the low dietary intake. In line with our data, lower cholesterol

(Marcinko et al., 2004) or lower HDL (Huang and Chen, 2005) levels were detected in drug free schizophrenic patients (Huang and Chen, 2005). Since lower serum cholesterol levels have been associated with a violent suicidal attempt (Marcinko et al., 2004), schizophrenic patients in our study might consisted of a subgroup of patients with suicidal behavior. Other lipid data (serum cholesterol or LDL levels) were lower in Croatian population (present study) and higher in Taywaneese population (Huang and Chen, 2005). The reason for the opositte results might be sought in the acute-phase schizophrenia compared to chronic schizophrenia in our study. In addition, it should be stressed out that higher values of serum levels of cholesterol or triglycerides might be a consequence of the conventional or atypical antipsychotic treatment in schizophrenic patients (Saari et al., 2004). Remission to antipsychotic treatment is associated with normalization of plasma lipid levels. Although we have not shown the pretreatment data for the plasma lipid levels in a double blind haloperidol versus olanzapine study, our data showing no differences in serum cholesterol levels between healthy controls and schizophrenic patients after treatment with both drugs, might be interpreted in terms that responders after antipsychotic treatment had «normalized» values of serum cholesterol levels.

Clinical Rating Scores and Peripheral Biological Markers in Schizophrenic Patients Treated with Haloperidol or Olanzapine

In an open 6 months comparative prospective study with 34 male schizophrenic patients who had pronounced suicidal behavior, atypical antipsychotic (olanzapine) or conventional neuroleptic (haloperidol) decreased, in a similar manner, the symptoms of schizophrenia, as shown by the reduced scores listed in CGIS scale. However, suicidal symptoms, listed in CGI-SS scores, and depressive symptoms, listed in HAMD scores, were significantly reduced after olanzapine, but not after haloperidol treatment. Namely, in our study suicidal schizophrenic patients treated with haloperidol had decreased platelet 5-HT concentration which was associated with higher suicidal scores. Treatment with olanzapine reduced suicidal scores, and these patients had higher platelet 5-HT concentration. In line with the recent study showing lower values of plasma and platelet 5-HT in schizophrenic patients, associated to poor response to atypical antipsychotic (Van der Heijden et al., 2004), in our study platelet 5-HT concentration was significantly lower in suicidal schizophrenic patients treated with haloperidol than in patients treated with olanzapine, or than in healthy controls. These results show that olanzapine showed a beneficial effect in the treatment of schizophrenia with suicidal behavior, and suggest that better therapeutic response to olanzapine was associated with increased platelet 5-HT concentration. Since we have previously shown that suicidal behavior is characterized with the reduced platelet 5-HT concentration in either suicidal psychotic or nonpsychotic depressed patients (Muck-Seler et al., 1996a, Pivac et al., 1997a), our present data confirm our hypothesis that decreased platelet 5-HT concentration is a characteristic feature of suicidal behavior, but extend our findings to different diagnostic group, i.e. schizophrenia. These data indicate that reduced platelet 5-HT, but not other markers such as platelet MAO or serum cholesterol, might be used as a peripheral biochemical marker of suicidal behavior, not only in depression, but also in suicidal schizophrenia. The lack of changes in platelet MAO activity between suicidal schizophrenic patients treated with haloperidol or olanzapine, or between these two groups of schizophrenic

patients and control subjects, agrees with the data showing no differences in platelet MAO activity between suicidal and nonsuicidal subjects (Engstorm et al., 1997; Muller-Oerlinghausen et al., 2004). Although the role of platelet serotonergic markers in suicidal behavior has been questioned (Muller-Oerlinghausen et al., 2004), and confounded by the different samples such as small sample size, sex, age and season-differences, various comorbidities (Muller-Oerlinghausen et al., 2004), our data, obtained before on the large groups of age, sex and season-matched psychotic and nonpsychotic, male and female depressed patients (Muck-Seler et al., 1996a, Pivac et al., 1997b), and present data, obtained on smaller groups of male schizophrenic patients, confirm that reduced platelet 5-HT is associated with suicidal behavior (Muck-Šeler et al., 1996a, Pivac et al., 1997a). In addition, the data showing lower platelet 5-HT concentration in schizophrenic patients that were poor responders to olanzapine suggest a relationship between platelet 5-HT concentration and treatment response in schizophrenia (Van der Heijden et al., 2004). Our data are not in contradiction with previous, opposite finding in depression (Muck-Seler et al., 2002; 2005; Pivac et al., 2003), where decreased platelet 5-HT concentration was associated with a remission in depression, but add further support to the hypothesis that platelet 5-HT concentration might be used as a predictor to the treatment response.

Clinical Rating Scores and Peripheral Biological Markers in Schizophrenic Patients Treated with Fluphenazine or Olanzapine

In a double blind, 5 months multicentric study, superior efficacy of olanzapine when compared to fluphenazine in the treatment of schizophrenia was described previously (Dossenbach et al., 2004). Fluphenazine is a conventional antipsychotic with D_1 and D_2 receptors blocking properties (Coirini et al., 1997), and a moderate affinity for 5-HT_2 receptors (Meltzer and Nesh, 1991). Olanzapine is an atypical antipsychotic, with potent serotonergic 5-HT_{2A} and dopaminergic D_2 blocking receptors, and a higher affinity for 5-HT_{2A} than for D_2 receptors (Richelson and Souder, 2000). The severity of the symptoms, listed in PANSS scale and PANSS positive and negative subscale and in CGI, was similar in schizophrenic patients before treatment. After 5 months of treatment with olanzapine, the scores in total PANSS and in the positive subscale of PANSS, and CGI scores were all significantly decreased. In contrast to olanzapine treatment, the treatment with fluphenazine for 5 months did not reduce total and subscale scores listed in PANSS and CGI. This lack of effect of fluphenazine might be explained by the small number of patients, hence they might have all been non-responders, or by the noncompliance of the patients, presumably due to the undesirable side-effects (Tandon and Jibsen, 2003).

The present study showed that chronic treatment with olanzapine and fluphenazine did not change platelet 5-HT concentration in schizophrenic patients. These results are similar to the lack of effect of clozapine and haloperidol on platelet 5-HT concentration in schizophrenic patients (Muck-Seler et al., 1988). Neuroleptics and atypical antipsychotics do not affect platelet 5-HT concentration since they inhibit platelet 5-HT uptake only very weakly (Richelson and Pfenning, 1984). Regarding the undesirable neuroendocrine effects of antipsychotics (Halbreich et al., 2003), fluphenazine treatment elicited a greater increase of plasma PRL levels than olanzapine treatment. In contrast to olanzapine, fluphenazine treatment elevated also plasma cortisol levels in schizophrenic patients. This difference in

presumably induced by a different mechanism of action: fluphenazine blocks D2 receptors, which stimulate PRL secretion (Coirini et al., 1997), in contrast to olanzapine, which blocks 5-HT2A/2C receptors and to a lesser extent D2 receptors. Hence, the increased cortisol and PRL secretion, induced by fluphenazine, was associated with a non-response to fluphenazine (Duval et al., 2003), and the "normalization" of the increased cortisol levels after olanzapine treatment was associated with remission (Duval et al., 2003).

CONCLUSION

The cause of schizophrenia is still unknown. The multiple impairments of the multitude of neurotransmitter and neuromodulatory systems, complex interaction between genetic factors, environmental and neurodevelopmental, and other factors, might cause schizophrenia (Kelly, 2005). Despite the large body of evidence pointing to the alteration in dopamine system, other systems, such as 5-HT, glutamate, or acetylcholine, have their role in the neurobiology of schizophrenia. Genetic studies involve the research of the couple of candidate genes, i.e. genes in the 5-HT, dopamine and glutamate systems, and the identification of the genetic loci on the chromosomes 8p, 14q and 22q. Genetic research has been slow because of the biologically diverse neurodevelopmental abnormalities, biological and genetic heterogeneity, complex inheritance and diagnostic definition.

Multiple neurochemical markers for schizophrenia and other brain disorders have been investigated (Fuller Torrey et al., 2005). Biomarkers have their use in the preclinical screening, diagnosis, disease staging, and monitoring of treatment. Evaluation of complex biological signals might improve the characterization of the baseline group characteristics, even predict a suicidal risk, differentiate between particular symptoms, or improve the understanding of the underlying neurobiology of schizophrenia.

Our previous and present data suggest that platelet 5-HT concentration might be used as a platelet serotonergic marker in schizophrenia, and for the subtypes and time course of schizophrenia. The data indirectly support the theory that serotonergic system plays an important role in schizophrenia (Iqbal and van Praag, 1995; Abi-Dargham et al., 1997).

Our results, showing decreased platelet MAO activity in schizophrenic patients, support the hypothesis that platelet MAO might be a biological marker of the psychopathology and personality (Oreland, 2004). The results are in agreement with the proposed role of platelet MAO activity as a trait dependent factor for the increased vulnerability to particular psychopathology and personality (Farren et al., 1998), impulse and affect dysregulation (Verkes et al., 1998), personality traits such as sensation seeking and impulsivity, disinhibition and excessive risk-taking behavior (Oreland et al., 2002), which increase the vulnerability for drug-abuse, social mal-adaptation or different psychiatric disturbances (Schalling et al., 1987; Oreland et al., 2002; Longato-Stadler et al., 2002; Oreland, 2004). Altered platelet MAO activity was a constant finding in different personality and temperamental traits, and our data show that platelet MAO activity is reduced in schizophrenia.

Schizophrenic patients in our study had multiple neuroendocrine disturbances: altered activity of the HPA axis, hypercortisolemia, increased secretion of PRL, abnormal response to DST in more than 50% of patients, fluphenazine-induced hypersecretion of cortisol and

PRL, and the "normalization" of the increased cortisol levels after olanzapine treatment, associated with remission.

The results of the present study, showing higher values of platelet 5-HT, cortisol and PRL, abnormal cortisol response DST, and lower values of platelet MAO activity, cholesterol, HDL and LDL in schizophrenic patients, suggest an altered relationship between 5-HT system, HPA axis activity and PRL secretion in schizophrenia. Although there is a dispute over the role of platelet serotonergic markers in suicidal behavior (Muller-Oerlinghausen et al., 2004), our present and previous data (Muck-Seler et al., 1996a, Pivac et al., 1997b) confirm the association between reduced platelet 5-HT and suicidal behavior. Our data support the hypothesis that decreased platelet 5-HT concentration is related to poor therapeutic response in schizophrenia (Van der Heijden et al., 2004).

The research of biological markers, which reflect the activity of the central neurotransmitter and/or neuroendocrine systems, should further be conducted to expand the knowledge of the neurobiology of schizophrenia, to facilitate new drug development, and to find out the possible predictors of the suicidal behavior, and possible predictors of the therapeutic response, in order to prevent suicide, and to target an aim of the modern medicine, which is a proper treatment for an individual patient at a given stage of disease.

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INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Y

Z