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Effects of different subanaesthetic doses of (S)-ketamine on psychopathology and binocular depth inversion in man

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The role of the *N*-methyl-D-aspartate (NMDA) neurotransmitter system in relation to psychoses is not completely understood, but represent a challenge in neurobiological research. The psychotic states induced by NMDA antagonists such as phencyclidine and ketamine have been described as being most similar to schizophrenia and the NMDA system has been implicated in the pathogenesis of schizophrenia. Binocular depth inversion, an illusion of visual perception, has been shown to be impaired in psychotic and psychotomimetic states in healthy and schizophrenic subjects. In this study, pictures of natural and artificial objects were presented stereoscopically to 12 healthy male volunteers and depth perception assessed using an operationalized method. The effects of the psychotomimetic S-enantiomer of the anaesthetic ketamine in two different subanaesthetic doses were compared with those of a placebo. In spite of dose dependence and grave subjective and significant objective psychopathology, no significant impairment of binocular depth perception was found with (S)-ketamine. Implications related to memory function, perceptogenesis and 'bottom-up' processing in ketamine model psychosis and schizophrenia are discussed.

Key words: altered states of consciousness, binocular depth inversion, hallucinogens, memory, model psychosis, NMDA receptors, psychopathology, schizophrenia, (S)-ketamine

Introduction

In recent years, research into the influence of the glutamatergic or *N*-methyl-D-aspartate (NMDA) neurotransmitter system has gained more attention. The glutamatergic antagonists phencyclidine (PCP) and ketamine have been used in healthy subjects to induce a temporary psychotic symtomatology (Krystal *et al*., 1994; Jaritt, 1999). These substances can induce a broad range of psychopathological symptoms similar to those seen in schizophrenic patients. Their spectrum includes negative symptoms and provides a model psychosis which is most similar to schizophrenia. Consequently, reduced glutamatergic activity in the brain has been suggested to be involved in the aetiology of schizophrenic symptomatology (Breier *et al*., 1997; Abi-Saab *et al*., 1998; Vollenweider, 1998).

Ketamine is a widely used anaesthetic drug. The pharmacological profile of ketamine is characterized by the so-called 'dissociative anaesthetic state' with profound analgesic and moderate hypnotic properties and marked sympathomimetic reactions accompanied by psychotic symptomatology (Domino *et al*., 1965). Ketamine effects several receptor classes that might contribute to its behavioural effects. However, the most important action of ketamine is the uncompetitive blockade of NMDA receptors (Adams, 1998).

Newer experimental studies demonstrated that subanaesthetic doses of ketamine induce specific psychotomimetic effects (Krystal *et al*., 1994) and cognitive impairment (Malhotra *et al*., 1996; Krystal *et al*., 2000; Oranje *et al*., 2000), and exacerbate psychotic symptomatology in schizophrenics (Lahti *et al*., 1995).

Binocular depth inversion represents a well-known model of illusionary perception. It has been shown that binocular depth perception is influenced by various factors. Wheatstone (1838) postulated binocular disparity to be the most effective one. Wheatstone also discovered that interchanging the view of the left and the right eye using a stereoscope leads to a reversed depth experience of most objects ('pseudoscopic vision') (Wheatstone, 1852).

Under certain circumstances, the sensory information regarding a pseudoscopically presented three-dimensional object may differ from its individual perception. The so-called binocular depth inversion especially occurs when hollow faces are displayed. In this case, hollow faces will be perceived normally despite depth cues indicating the opposite. This happens because of the strong influence of top-down processing from memory and perceptual mechanisms in brain structures. Current theories in visual perception suggest an interaction of bottom-up and top-down processing, resulting in the conscious experience of an object.

Binocular depth inversion is understood to be a process that involves the generation of hypotheses about the three-dimensional shape of objects by interpreting the bottom-up signals received from the eyes using conceptual and perceptual knowledge (top-down), as well as general rules of perception, such as Gestalt laws of organization and perspective (Yellott Jr, 1981; Ramachandran 1988; Hill and Bruce, 1993; Gregory, 1998). Knowledge or experience is recalled from memory by reactivation of the neural representations in the cerebral cortex. Referring to this concept, binocular depth perception results from a domination of top-down object knowledge over bottom-up data. We previously suggested that a disturbance of binocular depth inversion is due to an impairment of top-down processing (Emrich, 1989; Schneider *et al*., 1996b). Thus, a reduction or reversal of binocular depth inversion by (S)-ketamine would also be caused by an impairment of top-down processing, and this would be strongest for those stimuli which use the most top-down processing. To investigate this hypothesis, binocular depth inversion for different natural objects was assessed in 12 healthy volunteers after administration of two different doses of (S)-ketamine. Additionally, psychopathology was rated using subjective (OAVAV-questionnnaire) and objective measures (Brief Psychiatric Rating Scale, BPRS).

Materials and methods

The appropriate ethical committee of the Medical School Hannover approved the study protocol, as outlined below. Twelve healthy male volunteers (physicans/medical students) participated in the study. They signed an informed consent form and were able to withdraw from the study at any time without disclosure of their reasons. The mean (SD) age of participants was 26.8 (3.31) years and mean IQ was 118, as measured with the MWT-B (score 32.50 ± 2.50). All subjects reported normal health, normal or corrected to normal vision and were entirely unremarkable on medical and neurological examination before entry into the study. Stereoscopic vision was tested using the TNO test (Lameris, Utrecht, Netherlands). Subjects with a history of recurrent abuse of illegal drugs or other psychiatric or neurological, and medical diseases, were not included in the study.

All subjects were treated in randomized order under double-blind conditions either with placebo (group 1), low-dose (group 2) or high-dose (group 3) of S-ketamine. The washout period between each of the three phases for every subject was a minimum of 7 days. All experiments were conducted at the same hour each day (afternoon).

In this study, only the S-enantiomer of the racemic ketamine mixture was used. The analgesic, anaesthetic and psychopharmacological potency of (S)-ketamine is approximatively two-fold superior to that of (R)-ketamine. Pharmacokinetic properties of (S)-ketamine are generally comparable with the racemic mixture (Way *et al*., 1990). In each group, a peripheral port system was initially inserted into a cubital vein. Subjects received placebo or S-ketamine by a continuous intravenous infusion using a computer-controlled system to obtain constant plasma ketamine levels throughout the experiment. Commercially available (S)-ketamine (Ketanest S, Parke Davis, Freiburg, Germany) was used. This dosing was below the range of the recommended dosing of the anaesthetic drug (0.01–0.04 mg/min/kg). The (S)-ketamine was diluted in 50 ml NaCl 0.9% solution. Intravenous application was started with a bolus of 5 mg over 5 min for the low- and the high-dose groups. Subsequently, the permanent infusion with 0.003 mg/min./kg (low-dose), respectively, 0.005 mg/min./kg (high-dose) was started. NaCl 0.9% solution was used as placebo. Ketamine and norketamine blood levels were not measured. During the whole course of the experiment, an anaesthesiologist was present. Binocular depth inversion was assessed once, 30 min after starting the administration of (S)-ketamine/placebo.

Psychopathology was measured using the BPRS (Overall and Gorham, 1962). Total score, as well as subscale scores were recorded: anxiety/depression (four items: 1, 2, 5, 9), anergia (four items: 3, 13, 16, 18), thought disorder (four items: 4, 8, 12, 15), activation (three items: 6, 7, 17) and hostile-suspiciousness (three items: 10, 11, 14). Mental status ratings were conducted blindly to the agent administered by a single research clinician (T.P.). Moreover, detailed clinical notes were taken by the blind clinician to describe the responses.

Subjective psychopathology was measured using a newer, psychometrically improved version (OAVAV-questionnaire) of the standardized 94 item 'APZ'-questionnaire developed in experiments and validation studies on different 'altered states of consciousness' (ASC) at the Psychiatric University Clinic Zürich. It was developed in order to explore hypotheses on ASCs by 11 experiments using different induction methods for ASCs in healthy subjects (n = 393) (Dittrich, 1985). The common denominator of ASCs is described by three oblique dimensions, designated as 'Oceanic Boundlessness (OSE)', 'Dread of Ego Dissolution (AIA)' and 'Visionary Restructuralization (VUS)'. The reliability and validity of the scales are satisfactory. In an international study in six countries (n = 1133), the external validity was proven (Dittrich *et al*., 1985). The OAVAV is a new 94-item visual analog scale evolved from the APZ-questionnaire, adding items related to new dimensions: 'Reduction of Vigilance (VIR)' and 'Auditive Alterations (AWV)'. The APZ- and, respectively, OAVAV-questionnaire has become the international standard for the assessment of ASCs (Dittrich, 1998).

For testing binocular depth inversion, the following technique was used. Stereoscopic pictures were taken from different natural objects: flowers, some other ordinary objects (e.g. a chair; n = 6) and faces of middle-aged males (n = 4). Faces were photographed as frontal views. Objects of stimuli thus differed in their everyday familiarity (Hill and Bruce, 1994). A score of 1 is constituted by objects with a lower degree of familiarity (e.g. flowers) and a score of 2 by objects with a higher degree of familiarity (faces). The stereoscopic pictures were scanned and transferred to an Apple Macintosh computer. Depth information of most of the pictures was manipulated by exchanging the left and the right images, thus resulting in a change in disparity indicating an inverted object ('pseudoscopic vision').

The corresponding pictures were presented on a computer monitor with high resolution (overall stimulus size 800 × 600 points, 30.0 × 22.5) and colour depth (16 bits) for a maximum of 60 s. A Wheatstone stereoscope (Wheatstone, 1838) was used to achieve stereoscopic vision. The mirror stereoscope used four semisilvered trapezoid mirrors with two central right and left eye display mirrors (25 cm^2), and two larger lateral right and left mirrors (160 cm^2) each with a vertical axis of rotation. The distance between the presentation unit and the mirror stereoscope

in front was 50 cm. The lateral mirrors reflected the corresponding part of the stereoscopic to the corresponding central mirror. The ability to rotate the lateral mirrors enabled adjustment of the stereoscope to the individual interocular distance of each participant.

Subjects were told that the presented objects might either have a more convex or a more concave shape. Each inverted image displayed was preceded by the same non-inverted image. Images without binocular depth information or without a corresponding inverted image were randomly presented as distracting stimuli. The volunteers were instructed that the depth perception of each object might vary or not. Using an operationalized description, they reported their visual perception of the overall shape of the object and of a selected part of each object (e.g. faces as very concave, concave, flat, convex and very convex). This was achieved using a five-step rating scale. When depth perception was totally inverted completely (e.g. if a subject perceived a hollow face as a normal convex face), a score of zero points was given. A complete matching between depth perception and the veridical view of the object was scored as 4 points. Six (Score 1; ordinary objects) and four (Score 2; faces), respectively, objects of each class were presented and the ratings for the overall shape of the object, and for a selected part of each object, were averaged and divided by the maximum possible score. Thus, a maximum of 1 point was applicable for each class of objects. This score is referred to as 'inversion score'.

Statistical analysis of the data was performed using SPSS statistical software package (SPSS Inc., Chicago, IL, USA). An analysis of variance (ANOVA) model with healthy volunteers as random effect and phase and dose as fixed effects was used. In this study, each subject served as his own control to minimze the effect of inter-individual variation. Post-hoc Scheffé tests were used to determine significant differences between the drug conditions. Differences were considered significant if the probability of error was $p < 0.05$ and the phase effect was not significant.

Results

Subjects' individual reactions to ketamine reactions ranged from mild euphoria or dysphoria to more pronounced reactions. Discrete anxiety related to possible loss of self-control was reported by two of the subjects. Body image distortions, thought disorders and visual illusions and, rarely, delusional thoughts also occurred. One subject felt nauseated when looking at the presented pictures and the infusion was stopped, which lead to a normalization of the state in a few minutes. This subject did not contribute data to the study.

BPRS scores are given in Table 1. Total BPRS scores increased dose dependently with S-ketamine. There was no significant phase effect. Upon analysis of BPRS subscores, (S)-ketamine had significant dose-dependent effects (high dose) on anxiety/depression, thought disorder, activation and hostility/suspiciousness. For these subscores, the low dose produced no significant effects. The factor anergia was significantly increased on low dose, as well as on high dose, compared to placebo. Measurement of the subjective psychopathology using the OAVAV-questionnaire showed similar results. The OAVAV total score was increased dose dependently and showed evidence of a significant psychotomimetic activity of (S)-ketamine. The scale-dimensions OSE, AWV and VUS were significantly increased only on high doses; the scale-dimensions AIA, VIR were significantly increased using high-dose as well as

Table 1 Effects of different (S)-ketamine doses on BPRS scores in healthy volunteers (low dose: 0.003 mg/min/kg; high dose: 0005 mg/min/kg)

BPRS subscores	Dose	Mean ± SD	p (vs. placebo)
Thought disorder	Placebo	4.50 ± 0.90	
	Low dose	5.17 ± 0.72	0.154
	High dose	5.75 ± 1.06	0.004
Hostility/suspiciousness	Placebo	3.25 ± 0.62	
	Low dose	4.08 ± 1.56	0.367
	High dose	4.83 ± 1.53	0.040
Anxiety/depression	Placebo	5.92 ± 2.35	
	Low dose	7.33 ± 1.61	0.176
	High dose	8.83 ± 1.90	0.003
Activation	Placebo	3.83 ± 1.03	
	Low dose	4.50 ± 1.31	0.418
	High dose	5.33 ± 1.61	0.023
Anergia	Placebo	5.58 ± 1.98	
	Low dose	7.00 ± 1.38	0.035
	High dose	8.25 ± 1.76	< 0.001
BPRS total score	Placebo	23.08 ± 5.79	
	Low dose	28.08 ± 3.65	0.072
	High dose	33.00 ± 5.32	< 0.001

Table 2 Effects of different (S)-ketamine doses on subjective psychopathology in healthy volunteers

OAVAV subscores	Dose	Mean ± SD	*p* (versus placebo)
Oceanic Boundlessness (OSE)	Placebo	0.27 ± 7.55	
	Low dose	13.85 ± 26.74	0.184
	High dose	20.28 ± 31.37	0.031
Dread of Ego Dissolution (AIA)	Placebo	1.06 ± 3.36	
	Low dose	8.16 ± 10.04	0.158
	High dose	18.73 ± 16.39	< 0.001
Visual Restructuralization (VUS)	Placebo	0.46 ± 1.53	
	Low dose	3.30 ± 6.29	0.453
	High dose	6.40 ± 10.27	0.042
Reduction of Vigilance (VIR)	Placebo	4.38 ± 6.99	
	Low dose	28.93 ± 18.30	0.001
	High dose	54.80 ± 21.66	< 0.001
Auditive Alterations (AV)	Placebo	0.008 ± 0.003	
	Low dose	0.26 ± 5.33	0.983
	High dose	4.15 ± 5.69	0.022
OAVAV total score	Placebo	6.18 ± 10.35	
	Low dose	54.50 ± 46.42	0.002
	High dose	104.37 ± 63.18	< 0.001

Table 3 Comparison of binocular depth inversion scores for two different classes of objects in healthy volunteers after application of two different doses of (S)-ketamine

	Dose	Mean ± SD	*p* (versus placebo)
Score 1	Placebo	0.44 ± 0.10	
	Low dose	0.45 ± 0.99	0.931
	High dose	0.44 ± 0.60	0.999
Score 2	Placebo	0.51 ± 0.96	
	Low dose	0.53 ± 0.94	0.848
	High dose	0.50 ± 0.96	0.988

The mean values the inversion scores (± SEM) are shown for the two classes of objects presented (score 1, ordinary objects, $n = 6$; score 2, faces, $n = 4$).

low-dose (S)-ketamine (Table 2). The VIR-scale showed a massive dose-dependent reduction of vigilance. Interestingly, subjects exhibited no clear changes in spontaneous behaviour during epochs where they were experiencing grave mood and perceptual alterations, as reflected by the marked difference between the objective psychopathology measured with the BPRS and the subjective psychopathology measured with the OAVAV.

The depth inversion scores for the two classes of objects are shown in Table 3. Binocular depth inversion scores of objects with a higher degree of familiarity (faces), as well as with a lower degree of familiarity (e.g. flowers), were not increased by both doses of (S)-ketamine compared to placebo.

Discussion

This study characterized the effects of subanaesthetic doses of the NMDA antagonist (S)-ketamine in healthy human subjects, consistent with previous reports suggesting that NMDA antagonists produce psychotic symptoms in healthy volunteers (Krystal *et al*., 1994). It can alter the form and content of thought in healthy subjects. Ketamine is able to elicit loose associations, concreteness, ideas of reference and unusual thought content (Abi-Saab *et al*., 1998). Using the BPRS (S)-ketamine increased the symptoms anxiety/depression, thought disorder, activation and hostility/suspiciousness only in high doses. The BPRS-subscore anergia was increased in low as well as in high doses. Measurements of subjective psychopathology with the OAVAV-questionnaire revealed altered states in regard to the scale-dimensions AIA and VIR using low and high doses of (S)-ketamine. The scale-dimensions OSE, VUS and AWV were increased only on high doses. This may be interpreted as evidence for a threshold dose to produce hallucinatory activity which is able to transform the whole perceptual system. OSE measures derealization and depersonalization, phenomena associated with a positive basic mood ranging from heightened feelings to sublime happiness, changes in body image and ego experience. The scale-dimension VUS refers to auditory and visual illusions, synesthetic phenomena, as well as to changes in the perceived meaning of various percepts (Dittrich, 1998). Especially significant in the Ketamine induced state are the massive changes in the scale-dimension VIR, consisting of items characterizing alterations of consciousness from tiredeness up to clouding of consciousness, which are not quite usual in naturally occurring psychotic states (Gouzoulis-Mayfrank *et al*., 1998).

The impairment in psychopathology induced by (S)-ketamine is dose dependent. Higher doses showed a greater impairment than low doses. The subjective impairment, measured with the OAVAV-questionnaire, seems to be more marked than the impairment measured with the BPRS. Additionally, subjects exhibited no clear changes in spontaneous behaviour during periods when they were experiencing grave mood and perceptual alterations.

Illusionary perceptions have been a matter of interest for several hundred years. More recently, the underlying mechanisms of binocular depth inversion have been revealed in more detail (Yellott Jr, 1981; Hill and Bruce, 1993; Gregory, 1998). To date, there is no indication for an underlying general disturbance of binocular depth perception (Yellott Jr, 1981). The perceptual experiences of the different classes of objects found in our study are in agreement with previous observations (van den Enden and Spekreijse, 1989; Hill and Bruce, 1994).

Several appealing models and hypotheses regarding the mechanisms involved in binocular depth inversion have been proposed. For example, Gray and Rawlins (1986) postulated a 'comparator system' that gauges incoming sensory data (bottom-up) against conceptual knowledge (top-down). The 'comparator' determines the ultimate conscious experience of the outer world. They postulated hippocampal structures as a possible site of the 'comparator' system. Gregory (1998) has recently presented a further elaboration on this hypothesis. It has been proposed that internal correcting and adaptive systems may be deficient in psychotic states, and that an imbalance in systems responsible for 'concept formation' occurs (Malenka *et al*., 1982; Frith and Done, 1989). It is still controversial as to whether other structures of the temporal lobes and/or prefrontal cortical areas are involved in these processes (Crick and Koch, 1992; Haxby *et al*., 1994). At present, the basic neural mechanism of binocular depth inversion remains a subject for further research.

However, our baseline data (placebo-condition) for different types of objects support the proposed view on internal correcting and adaptive systems. The influence of top-down processing on the depth inversion of objects with a higher degree of everyday familiarity seems to be more pronounced than for objects with a lower degree of everyday familiarity. Interestingly, the top-down processing in the sense of a correcting mechanism is apparently not weakened by the influence of (S)-ketamine.

Schneider *et al*. (2002) investigated 20 schizophrenic inpatients using the binocular depth inversion paradigma. In their study, the performance in the binocular depth inversion test of the schizophenic patients differed significantly from healthy controls and from patients with major depression. The schizophrenic patients were more veridical in their judgements in the binocular depth inversion test. During antipsychotic treatment, BPRS and PANSS scores improved and the inverted faces were seen as more illusionary, possibly driven by an increase in top-down processing. At the end of the treatment, there was no significant difference between the patient group and the healthy volunteers in the score of binocular depth inversion.

Binocular depth inversion was not impaired using (S)-ketamine in subanaesthetic doses in contrast to all other psychotomimetic influences tested (e.g. schizophrenia, sleep deprivation, cannabinoids, alcohol intoxikation and alcohol withdrawal) (Schneider *et al*., 1996a,b; Sternemann *et al*., 1997; Schneider *et al*., 1998; Leweke *et al*., 1999, 2000; Schneider *et al*., 2002), in spite of the fact that BPRS and OAVAV scores were high. Obviously, (S)-ketamine effects mimic psychopathological symptoms of schizophrenia but the binocular depth inversion data suggest that (S)-ketamine in subanaesthetic doses does not produce changes in visual perception that are identical to those seen in schizophrenic subjects using this paradigm (Schneider *et al*., 2002).

Using ERP-experiments, schizophrenics show impairment of early and late information processing (Eikmeier *et al*., 1991). Healthy subjects after administration of ketamine show only impaired late information processing whereas early phases of information processing remain nearly unimpaired with an increase in N_1 peak amplitude but no effect on N_1 peak latency (Umbricht *et al*., 2000). Schizophrenic patients have more deficits in the elemental classification of stimuli, whereas this might not be the case for subjects on ketamine. From this point of view, impairment of binocular depth inversion might be due to the early phases of information processing.

In order to perceive a hollow face as a normal convex face, intact top-down processing is necessary. Only with unbroken top-down processing can the bottom-up signals be 'voted down'. In schizophrenic patients, the top-down processing is weakened (Schneider *et al*., 2002). Unimpaired top-down processing is only possible if knowledge or experiences are unconsciously recalled from memory by reactivation of their neural representations. Non-declarative memory entails a facilitation of memory based on prior exposure and is contrasted with 'declarative' or 'explicit' memory, which is characterized by conscious search and retrieval procedures. Ketamine produces decrements in several memory-related tasks, such as free recall and recognition. These memory impairments do not appear to be secondary to disturbance in attention deficits (Malhotra *et al*., 1996). In contrast, the data from investigations of binocular depth inversion suggest that non-declarative memory functions are not impaired by (S)-ketamine.

There are several possible reasons for the lack of an effect of (S)-ketamine on the binocular depth inversion phenomenon in the study presented.

First, the dose of (S)-ketamine employed was too low to observe this effect. However, the psychopathology induced by (S)-ketamine was highly significant and in the range reported in the literature. Other binocular depth inversion experiments show that much lesser psychopathology induced by other psychotomimetic conditions (e.g. sleep deprivation, alcohol withdrawal, tetrahydrocannabiol) is associated with strong aberrations of binocular depth inversion (Schneider *et al*., 1996b, 1998; Leweke *et al*., 2000). Judging from these results, it is unlikely that the dose used was not high enough.

Second, ketamine alters perception and, as a result, increases the variability (reduces the accuracy) of reports of shape or depth perception. However, this effect cannot explain our results, because the variance measured was lower than the normal range typical for these experiments. If perceptual variance was the key factor, there should be a difference between the different doses, which was not the case.

Third, another hypothetical mechanism may be the tendency of (S)-ketamine to induce a marked reduction of vigilance (i.e. a clouding of sensory perception) as obviously perceived by the subjects. This may lead to a weakening of the stream of sensory data to the brain (bottom-up). This implies that a possible reduction of top-down processing by (S)-ketamine is compensated for by the weakening of bottom-up processing. However, this does not explain the similarity of changes of depth inversion scores between the high and low-dose groups.

There is also the possibility that ketamine fails to effect binocular depth inversion of faces because faces are uniquely processed by specific regions of the accessory visual cortex (Allison *et al*., 1999). Ambiguous stimuli such as faces and inverted faces may be processed at an earlier stage than other visual stimuli, particularly in regard to so-called binding. The absence of a need for binding might reduce the dependence on higher order processing of sensory data. From this point of view, ketamine fails to interact with the organization of information to constitute a face, because faces are organized into whole percepts at the elemental level. This hypothesis may be true for the processing of faces, but not for the other objects presented in our experiment.

A possible implication of our results is that the main neurophysiological mechanisms influenced by (S)-ketamine (i.e. glutamatergic neurotransmission) may only minimally, or even not, be involved in changes of perceptogenesis in schizophrenic psychoses.

One shortcoming of our study is that we did not measure ketamine plasma levels. Vollenweider *et al*. (1997) used a comparable mode of application and assessed ketamine plasma levels. From their data, it was evident that plasma ketamine levels remained within the same range of magnitude after the bolus application had been completed and 15 min after continuous infusion of ketamine was started. Therefore, in the study presented here, binocular depth inversion was measured during the plateau when high constant plasma ketamine levels are reached.

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