Original Paper

Neuropsychobiology

Neuropsychobiology 2005;51:226–233
DOI: 10.1159/000085724

Published online: May 12, 2005

Effects of Different Subanesthetic Doses of (S)-Ketamine on Neuropsychology, Psychopathology, and State of Consciousness in Man

Torsten Passie[a] Matthias Karst[b] Birgitt Wiese[c] Hinderk M. Emrich[a] Udo Schneider[a]

Departments of [a]Clinical Psychiatry and Psychotherapy, [b]Anesthesiology, Pain Clinic, and [c]Biometry, Medical School Hannover, Germany

Key Words

Ketamine · (S)-ketamine · N-methyl-*D*-aspartate antagonists · Altered states of consciousness · Attention · Memory · Hallucinogens · Schizophrenia

Abstract

This is the first neuropsychological study using the S-enantiomer of the noncompetetive N-methyl-D-aspartate antagonist ketamine. In 2 randomized placebo-controlled trials we studied effects of two different doses of (S)-ketamine (low dose/high dose) on neuropsychological functions and psychopathology in 12 healthy male volunteers. Impairment was measured via standardized neuropsychological tests. Results indicate that both subanaesthetic doses produce only nonsignificant impairment in most of the tasks. Tasks involving divided and sustained attention as well as scores for objective and subjective psychopathology show significant impairment in a dose-dependent manner. Implications of these findings for the neuropsychology of attention and schizophrenia are discussed.

Introduction

For the past few years examination of the influences of the glutamatergic or N-methyl-*D*-aspartate (NMDA) neurotransmitter system has gained more attention [1]. This approach lead to the experimental application of the glutamatergic antagonists phencyclidine and ketamine to healthy subjects to induce a temporary psychotic symptomatology [2]. These substances are known to induce a broad range of psychopathological symptoms in many respects similar to those seen in schizophrenic patients. The spectrum of psychopathological symptoms, including negative symptoms, makes this kind of model psychosis the most similar to schizophrenia. Positron emission tomography studies during ketamine application showed brain activity patterns similar to those seen in acutely hallucinating schizophrenic patients [3, 4]. Consequently, it was concluded that reduced glutamatergic activity in the brain may be involved in the etiology of schizophrenia [5].

Ketamine is a widely used anesthetic drug. Its pharmacological profile is characterized by the so-called 'dissociative anesthesia' with activation of the limbic system

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0302–282X/05/0514–0226$22.00/0

Accessible online at:
www.karger.com/nps

Dr. Torsten Passie, MD
Department of Clinical Psychiatry and Psychotherapy, Medical School Hannover
Carl-Neuberg-Strasse 1
DE–30625 Hannover (Germany)
Tel. +49 511 1235699 12 or 22 , Fax +49 511 5322415, E-Mail dr.passie.@gmx.de

and simultaneous depression of the thalamoneocortical systems [6]. Its profound analgesic and moderate hypnotic properties are accompanied by sympathicomimesis and psychotic symptomatology. Its effects cannot be explained by a single mechanism. The most important neuropharmacological mechanism of ketamine is the NMDA-receptor antagonism, but interactions with opioid receptors, monoaminergic and cholinergic transmission are also known [7].

Newer experimental studies found subanesthetic doses of ketamine to induce specific psychotomimetic effects [2] and cognitive deficiencies [8–10], and to stimulate psychotic symptomatology in schizophrenics [11, 12].

To evaluate specific psychopathological effects of the high NMDA receptor-specific S-enantiomer of ketamine, we evaluated effects of two different doses on neuropsychological performance and objective/subjective psychopathology in healthy young men. We were especially interested in attentional functions which were discussed to be central in neuropsychological aberrations during ketamine-induced states [9, 13]. Some previous studies lead to conflicting results in this regard [8, 11, 13, 14]. Our study may contribute to a further understanding of glutamatergic influences on psychopathological measures and aberrations in human information processing during psychotic states. The focus of our study is how different doses of (S)-ketamine, which has a more specific affinity to the NMDA receptor than racemic ketamine, influence different dimensions of attentional functioning. Specifically, the question of a threshold dose is addressed as well as the question whether specific correlations of psychopathology with neuropsychological measures can be obtained. In pilot experiments we established a low dose, inducing changes which are little above the threshold of subjectively perceivable effects, and a high dose which was close to the point where neuropsychological testing would become impossible.

Subjects and Methods

Subjects were recruited from medical staff of the hospital and from medical students. All subjects were medically screened and excluded from the study if either a history of serious medical or psychiatric problems including alcohol and drug abuse, psychopharmacological medication, seizures, or an IQ < 90 were present. A physical examination was performed, and volunteers with neurological, cardiac, pulmonary, hepatic or renal diseases were excluded. All subjects reported normal or corrected-to-normal vision. The appropriate ethics committee of the Medical School Hannover approved the study-protocol as outlined below. Twelve healthy male volunteers (physicians/medical students) participated in the study. They signed an informed consent form and were allowed to withdraw from the study at any time without disclosure of their reasons. The mean age of the subjects was 26.8 years (± 3.31 SD).

Table 1. Order of application of (S)-ketamine to experimental subjects

Number	Condition 1	Condition 2	Condition 3
1	Placebo	High dose	Low dose
2	High dose	Placebo	Low dose
3	Low dose	Placebo	High dose
4	Placebo	Low dose	High dose
5	High dose	Placebo	Low dose
6	Low dose	Placebo	High dose
7	Placebo	High dose	Low dose
8	Low dose	Placebo	High dose
9	Placebo	Low dose	High dose
10	Placebo	Low dose	High dose
11	Low dose	Placebo	High dose
12	Placebo	High dose	Low dose

Experimental Design

Three randomized, placebo-controlled crossover trials were conducted. Subjects were treated in randomized order with placebo, low dose and high dose of (S)-ketamine. In this way all three conditions were applied to each subject (distribution of cases to order of drug application see table 1). The washout period between each of the three drug conditions for every subject was 7 days as a minimum. All experiments were conducted at the same hour each day (afternoon).

In this study only the S-enantiomer of the ketamine racemat was used. The analgesic, anesthetic and psychopharmacological potency of (S)-ketamine is approximately 2-fold superior to (R)-ketamine. Pharmacokinetic properties of (S)-ketamine are generally comparable with the racemic mixture [6]. In each group, a peripheral port system (14G Introcan®) was initially inserted into an antecubital 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. The (S)-ketamine was diluted in 50 ml NaCl 0.9% solution. Intravenous application was started with a bolus of 5 mg in 5 min for the low- and the high-dose conditions. This dosing was within the range of the recommended dosing as an anesthetic drug (0.01–0.04 mg/min/kg). Afterwards the permanent infusion with 0.003 mg/min/kg for the low-dose and 0.005 mg/min/kg for the high-dose was started, a dose very much lower than the clinical range mentioned above. NaCl 0.9% solution was used as a placebo. During the whole course of the experiment an anesthesiologist was present. Volunteers were told that they might receive a placebo or an active drug.

Since our study used a mode of application similar to Vollenweider et al. [15] pharmakokinetics were known from their study,

and no ketamine or norketamine plasma level evaluation was performed in order to minimize distracting effects on the subjects.

Objective psychopathology was measured using the Brief Psychiatric Rating Scale (BPRS) [16]. The BPRS total score was evaluated. Mental status ratings were conducted by a single research clinician (Torsten Passie) who was blind with respect to the agent administered. Moreover, detailed clinical notes were taken by the above mentioned clinician to describe the responses. Subjective psychopathology was measured using a psychometrically improved version of the standardized 94-item 'APZ'-questionnaire described below [17, 18].

BPRS ratings were performed at 0, 30, 60, 90, 120, 150 min of the experiment, but were afterwards averaged across the experiment, since pharmacokinetic aspects were not addressed in this evaluation. BPRS baseline rating was done at 0 min. Cognitive testing took place in a laboratory located in the Department of Clinical Psychiatry and Psychotherapy. The test sessions started 20 min after beginning of (S)-ketamine infusion. Each session lasted 80–100 min plus 30–60 min until drug effects were completely gone.

Description of Tests

Benton Visual Retention Test. This is a standardized test of visuomotor coordination for children and adults [19]. The test material consists of 10 separate line drawings, adapted from those used by Max Wertheimer in his studies in Gestalt psychology. Each design is printed against a white background on a separate card. The most frequently used testing condition involves the presentation of each geometric figure for 10 s, after which the subject attempts to draw the figure from memory without a time limit. The Benton Visual Retention Test is probably used most frequently as a screening device for signs of organic cerebral dysfunction [20].

Go/No Go Test. This is a standardized test to evaluate attentional functioning and the ability to suppress an inadequate reaction. This ability attributed to the frontal cortex, will lead to erroneous reactions when frontal cortical functioning is disturbed. We used a paradigm with 5 different stimuli presented in the middle of a computer screen of which 2 are defined as critical. Fifty stimuli are presented in random order for some seconds from which 20 have to be correctly selected by pushing a button [21].

Divided Attention. In this computer-based binary choice reaction test, the subjects have to react differentially to a distinct tone and a specific pattern of white squares on a black screen. The tones and the white squares are presented in random order. Reaction time and mistakes reflect not only motor speed but also the decision-making process [22].

Vienna Reaction Time. Reaction time and discriminatory function were assessed by asking subjects to press a button in response to successive presentations of 15 single or combined visual/auditory stimuli. They were presented in randomized sequence as light (single visual stimulus) or tone (single auditory stimulus, 2,400-Hz tones). This test measures both motor- and recognition-reaction time as well as total-reaction time [23].

Signal Detection. A computerized visual searching task, based on the signal-detection theory was used. On a black screen many white squares are presented. Single squares appear and disappear in randomized order. If the squares form a specific pattern the subjects have to press a response button. The test indicates speed of information processing and vigilance [24].

Although learning or practice effect on the psychomotor tests may have occurred during this study, the randomized design should have controlled for this potentially confounding variable.

The sequence of neuropsychological tests was as follows: (1) Benton visual retention test, (2) Go/No Go, (3) divided attention (4) reaction time and (5) signal detection.

Objective psychopathology was measured using the Brief Psychiatric Rating Scale [25]. Psychopathological status ratings were conducted blindly by a single research clinician (Torsten Passie). Moreover detailed clinical notes were taken by the above mentioned clinician to describe the responses.

Subjective psychopathology was measured with the OAVAV-questionnaire [18]. It is a 94-item-questionnaire developed from the questionnaire on altered states of consciousness APZ. It assesses the following dimensions of subjective experience retrospectively by using a visual analog scale for each item with the two end points: 'not more than usual'/'much more than usual').

For rating of subjective psychopathology the actual version of the 94-item 'APZ' questionnaire was used. It was developed in studies on altered states of consciousness (ASC) to explore hypotheses on ASCs in experiments with healthy subjects (n = 393) [17]. 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 assessed [26]. In this study a psychometrically improved version (OAVAV) was used. This new 94-item scale is based on visual analog scales for each item and includes two new subscales named 'Reduction of Vigilance (VIR)' and 'Auditive Alterations (AWV)'. The APZ- or OAVAV-questionnaire respectively have become the international standard for the assessment of ASCs [18]. A description of the major features of this scale is given below.

OSE

This subscale tries to assess structural changes in the experience of the self and the body, the relation to the environment, alterations in time experience and mood changes in the direction of elevation and sublimity.

An example item is: It seemed to me that my environment and I were one.

AIA

This dimension describes a very unagreeable experience or state, which may be called 'bad trip' by psychedelic drug users. The AIA dimension is characterized by an accentuation of the subject/object barrier, which is experienced with great distress. The unity of the person is split, and control over ego functions is diminished.

An example item for AIA is:

I felt threatened without realizing by what.

VUS

It comprises elementary, amorphous 'primitive' optical phenomena. Following this, there may be organized scenic hallucinatory phenomena, sometimes accompanied by hypnagogic imagery and synesthesias A third category consists of alterations in the meaning of things perceived in the environment.

Example items for VUS are:

I saw light or flashes of light in total darkness or with closed eyes.

VIR

This dimension consists of items characterizing reduction of sensory experience, less alertness up to clouding of consciousness. The decrease in vigilance is typically accompanied by reduced self-control and cognitive performance. Examples of items for VIR are:

My thoughts and actions were slowed.

I felt sleepy.

AWV

This dimension measures acoustic phenomena. It consists of items like hearing clicks or amorphous low noise, hearing music or voices, possibly commenting on the thinking or behavior of the subject.

An example is:

I heard words without knowing where they came from.

The OAVAV questionnaire was applied 90 min after termination of the drug infusions.

Statistical Analysis

Statistical analysis of the data was performed using Statistical Package for the Social Sciences. A mixed model of repeated measurement ANOVA with healthy volunteers as random effect and phase and dose as fixed effects. Phase means that even when the wash-out period is completely effective, the psychophysical state induced by the first treatment may to some extent persist, so that the subjects may be no longer comparable in their clinical state at the start of the next experiment. In this study, each subject served as his own control to minimize the effect of interindividual variation. Since no systematic, but a random permutation of order of dosages was applied, phase effect and dosages could not be evaluated as tested factors, but had to be tested separately. 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

General observations: Subjects' individual reactions ranged from mild euphoria or dysphoria to more pronounced reactions. Anxiety, related to feelings of loss of self-control, was reported by two subjects. Body image distortions, thought disorders, visual illusions and delusional thinking also occurred. One subject felt nauseated 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.

The ANOVA revealed significant effects of drug dosage for BPRS total score (F = 11.929, 2 df), OAVAV subscores (OSE: F = 5.175, 2 df; AIA: F = 14.015, 2 df; VUS: F = 5.257, 2 df; VIR: F = 50.309, 2 df; AV: F = 42.110, 2 df).

Table 2. Effects of different doses of (S)-ketamine on BPRS scores in healthy volunteers (post-hoc Scheffé tests)

Dose	Mean ± SD	p (vs. placebo)
BPRS total score		
Placebo	23.08 ± 5.79	
Low dose	28.08 ± 3.65	0.072
High dose	33.00 ± 5.32	<0.001

Low dose: 0.003 mg/min/kg; high dose: 0.005 mg/min/kg.

Table 3. Effects of different (S)-ketamine doses on subjective psychopathology in healthy volunteers (post-hoc Scheffé tests)

OAVAV Subscores	Mean ± SD	p vs. 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 (AWV)		
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

Results of the BPRS scores are given in table 1. We evaluated total psychopathological symptoms (mean of 6 BPRS ratings during time course). Measurement of the subjective psychopathology using the OAVAV questionnaire showed similar results. The OAVAV total score was dose dependent and showed evidence for significant psychotomimetic activity of (S)-ketamine. The OAVAV subscales OSE, AWV and VUS were only significantly increased in high-dose sessions, the subscales AIA and VIR

Table 4. Effects of different (S)-ketamine doses on different neuropsychological tests in healthy volunteers (post-hoc Scheffé tests)

Neuropsychological′ tests	Hits ± SD	p (vs. placebo)	Errors ± SD	p (vs. placebo)
Benton test				
Placebo	8.00 ± 1.04		2.75 ± 1.17	
Low dose	7.33 ± 1.83	0.629	3.58 ± 2.47	0.674
High dose	7.08 ± 1.73	0.424	4.25 ± 2.56	0.294
	Hits	p (vs. placebo)	Mean	p (vs. placebo)
Go/No Go				
Placebo	22.83 ± 2.52		579.40 ± 43.30	
Low dose	22.08 ± 3.65	0.740	558.60 ± 88.52	0.692
High dose	23.08 ± 1.44	0.976	601.16 ± 60.81	0.669
	Omissions	p (vs. placebo)	Mean	p (vs. placebo)
Divided attention				
Placebo	0.83 ± 0.83		650.65 ± 51.03	
Low dose	1.58 ± 1.62	0.309	649.21 ± 62.07	0.994
High dose	2.75 ± 2.01	0.003	666.61 ± 45.78	0.510
	Decision time	p (vs. placebo)	Motor time	p (vs. placebo)
Reaction time				
Placebo	424.83 ± 77.60		147.17 ± 66.40	
Low dose	439.58 ± 75.17	0.693	128.08 ± 22.06	0.508
High dose	431.58 ± 88.23	0.925	161.00 ± 52.84	0.697
	Hits	p (vs. placebo)	Detection time median	p (vs. placebo)
Signal detection				
Placebo	51.83 ± 7.00		0.8525 ± 0.1367	
Low dose	50.33 ± 558	0.772	0.9700 ± 0.2592	0.047
High dose	46.42 ± 7.13	0.053	0.9933 ± 0.1614	0.016

were significantly increased during high- as well as low-dose sessions (table 2).

Table 3 shows the effects of (S)-ketamine on different neuropsychological tests. The ANOVA revealed significant effects of drug dosage for some neuropsychological tests (Benton Test hits: F = 1.839, 2 df; Benton Test errors: F = 2.639, 2 df; Go/No Go Test hits: F = 0.782, 2 df; Go/No Go mean: 2.331, 2 df; Divided Attention errors: F = 1.572, 2 df; Divided Attention omissions: F = 5.921, 2 df; Reaction Time Test decision time: F = 0.620, 2 df; Reaction Time Test motor time: F = 3.097, 2 df; Signal Detection hits: F = 6.221, 2 df).

In the *Benton Visual Retention Test* no significant difference in correct responses for the low dose (p = 0.629) and the high dose (p = 0.424) compared to placebo was found. In regard to Benton Test errors no significant difference for low dose (p = 0.674) and high dose (p = 0.294) compared to placebo was found.

In the *Go/No Go Test* for frontal suppression of inadequate visuomotor responses no significant difference regarding correct responses for low dose (p = 0.740) or high dose (p = 0.967) sessions compared to placebo was found. The Go/No Go Test mean score showed no significant difference for low-dose (p = 0.692) and high-dose (p = 0.669) (S)-ketamine to placebo.

The *Divided Attention* task mean score showed no significant difference for the low- (p = 0.994) and the high- (p = 0.510) dose ketamine condition compared to placebo. In the omission score no significant difference for the low-dose session (p = 0.309), but a highly significant difference for the high-dose session (p = 0.003) compared to placebo was demonstrated.

The results of the *Vienna Reaction Time* as attention-related combined visuo-audio-motor speed task showed no difference in decision time for low- (p = 0.693) and high- (p = 0.925) dose ketamine compared to placebo. In

regard to motor time no significant difference of low ($p = 0.508$) and high ($p = 0.697$) dose to placebo was found.

In the *Signal Detection* task for sustained attention no significant difference in correct responses for the low-dose condition ($p = 0.772$), but a trend for the high-dose condition ($p = 0.053$) compared to placebo was found. The detection time median for the low dose ($p = 0.047$) and the high dose ($p = 0.016$) were significantly higher compared to placebo. Validity of results in this test may be limited by interfering exercise effects when in the random order of application more subjects received their low and high dose after the placebo (table 1).

Discussion

Psychopathology

In previous studies racemic ketamine was shown to produce an acute psychotic state including ego dissolution, visual illusions, paranoid thinking and changes of mood and body image [2, 25, 27]. Ketamine-induced loss of self-control and emotional withdrawal, blunting of affects and perceptual alterations of time and space are highly reminiscent of schizophrenic symptomatology [28–30].

Results of psychopathological ratings in the present study support the assumption that (S)-ketamine is also able to mimic schizophrenic psychopathology in healthy humans.

Neuropsychology

With respect to NMDA-receptor blockage as the main cause of ketamine-induced psychotic states it has to be noted that at submicromolar plasma levels as used in this study, ketamine has been reported to bind selectively to the phencyclidine-binding site of the NMDA-receptor complex [31]. The potency of both ketamine enantiomeres correlates positively with their relative affinity to the phencyclidine-binding site [32]. Breier et al. [3] demonstrated (within the same dosage range as in the present study) selective forebrain activation compared to more generalized metabolic activation with higher doses [15]. Because attentional functions are predominantly located in the frontal cortex we used some tests specific for different attentional functions.

As known from previous studies NMDA antagonists like ketamine can have adverse effects on memory and psychomotor performance [33]. More recent studies examined mainly influences of racemic ketamine on memory functions, but involvement of other cognitive functions in memory functions was discussed as critical [2, 8]. Specific features of deficits suggest that mainly the acquisition of material was disturbed. Oye et al. [32] found recall of material learned before ketamine administration to be unimpaired during its infusion, but recall of material originally learned under its influence to be impaired, which means that the drug does not impair retrieval but memory consolidation.

To gain further insight into neurocognitive alterations during ketamine infusion we examined neuropsychological functions with the more NMDA-receptor specific S-enantiomere of ketamine. (S)-ketamine was found to have a 4:1 ratio of NMDA receptor binding affinity compared to the R-ketamine [32].

Neuropsychological testing with (S)-ketamine in low- and high-dose sessions in the present study produced some significant effects. The effects on more complex attentional tasks, as divided attention and signal detection, were significant compared to placebo. In spite of a high score in the VIR subscale of the OAVAV no impairment was shown in the audio-visual reaction time test and the Go/No Go Test or visual memory in the Benton Test.

Krystal et al. [2] found significant impairment of sustained attention as measured with the Continuous Performance Test of Vigilance, especially with the higher dosage used. Our study confirmed significant deficits in sustained attention with the Signal Detection paradigm for the high dose (S)-ketamine group. We also found a significant impairment of the divided-attention task for the high-dose group, especially in regard to omissions. Oranje et al. [9] found no influence of racemic ketamine (one bolus i.v. 0.3 mg/kg) on human selective attention using an auditory stimulus discrimination task. But this and some others studies [14, 34] were possibly compromised by neuropsychological testing during decreasing plasma levels of a one-bolus application of ketamine in contrast to the constant infusion regimen of the present and other studies [2,12]. The nonsignificant results of the Go/No Go task, sensitive for suppression of inadequate visuomotor responses, may be interpreted as no grave influence of (S)-ketamine on prefrontal functioning. But the executive functions necessary for this task may represent a more primitive mode of prefrontal functioning than the more complex mode of functioning for complex tasks as the Wisconsin Card Sorting Test (WCST), which was found severely impaired during ketamine infusion [2]. In all other neuropsychological tests for visual short-term memory (Benton Test), and reaction time (Vienna Reaction Time) used in the present study no significant

difference of both ketamine dosages to placebo was found. In relation to the severe psychopathological aberrations, especially in the VIR and the VUS scores for both ketamine groups it may seem surprising that neuropsychological functioning is not more impaired, especially in regard to visuomotor and other attention- or speed-related tasks.

Part of an explanation for less impairment of neuropsychological functioning during (S)-ketamine application may be the more circumscribed activation of brain metabolism induced by (S)-ketamine compared to a more generalized brain metabolic activation through the racemic mixture of ketamine as used in all previous studies. This difference in neurometabolic activation by (S)-ketamine may leave some neurocognitive functions more intact. This may be especially significant when low doses as in the present study were used, because of the preferential activation of the prefrontal cortex during low-dose ketamine infusions [3]. This effect could also be caused by effects on cortical networks involving the frontal, parietal and temporal lobes as well as subcortical structures, because frontal lobe function is modulated via effects on circuits involving cortex, striatum, globus pallidus, subthalamic nucleus, and thalamus [35].

In conclusion our data suggest severe effects of (S)-ketamine on psychopathology in healthy humans. In contrast to the significant psychopathological aberrations, no impairment on some simple attentional tasks and a visual memory task (Benton Test) was found. In more complex attention-related tasks, as divided attention and the signal detection paradigm, a significant impairment especially in the high dose condition could be demonstrated. This generally little impairment in attentional and visual memory functioning marks a difference to alterations of these functions in schizophrenics [36]. Our findings may be interpreted as intactness of simple attentional, psychomotor and memory functions during ketamine psychosis, while more complex attention-related tasks, especially if they involve a capacity for abstract thinking, e.g. WCST, were found consistently impaired [2]. Other results are the dose-dependency of neuropsychological aberrations and that the high NMDA-receptor specific (S)-enantiomere of ketamine leads to equivalent psychopathological and neuropsychological disturbances as the racemic mixture of ketamine, which implies much lower effects of the (R)-enantiomere on psychopathology and neuropsychological performance.

References

1 Bunney BG, Bunney WE, Carlsson A: Schizophrenia and glutamate; in Bloom FE, Kupfer DJ (eds): Psychopharmacology: The Fourth Generation of Progress. New York, Raven Press, 1995, pp 1205–1214.

2 Krystal JH, Karper LP, Saibyl JP, Freeman GK, Delaney R, Brenner JD, Heninger GR, Bowers MB, Charney DS: Subanesthetic effects of the noncompetetive NMDA antagonist ketamine in Humans. Arch Gen Psychiat 1994;51:199–214.

3 Breier A, Malhotra AK, Pinals DA, Weisenfels NI, Pickar D: Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. Am J Psychiatry 1997;154:805–811.

4 Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J: Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). European Neuropsychopharmacology 1997a;7:25–38.

5 Abi-Saab WM, D'Souza DC, Moghaddam B, Krystal JH: The NMDA antagonist model of schizophrenia: Promise and pitfalls. Pharmacopsychiatry 1998;31:104–109.

6 Way WL, Trevor AJ, White PF: Pharmacology of the ketamine enantiomorphs; in Domino EF (ed): Status of Ketamine in Anaesthesiology. Ann Arbor, 1990, pp 101–108.

7 Adams HA: Wirkmechanismen von Ketamin. Anaethesiol Reanimat 1998;23:60–63.

8 Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A: NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996;14:301–307.

9 Oranje B, van Berkel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN: The effects of a sub-anaesthetic dose of ketamine on human selective attention. Neuropsychopharmacology 2000;22:293–302.

10 Krystal JH, Bennett A, Abi-Saab D, Belder A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS: Dissociation of ketamine effects on rule acquisition and rule implementation: Possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiatry 2000;47:137–143.

11 Lahti AC, Koffel B, LaPorte D, Tamminga CA: Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995;13:9–19.

12 Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A: Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 1997;17:141–150.

13 Newcomer JW, Krystal JH: NMDA receptor regulation of memory and behavior in humans. Hippocampus 2001;11:529–542.

14 LaPorte DJ, Lahti AC, Koffel B, Tamminga CA: Absence of ketamine effects on memory and other cognitive functions in schizophrenic patients. J Psychiatr Res 1996;30:321–330.

15 Vollenweider FX, Leenders KL, Scharfetter C, Antonioni A, Maguire P, Missimer J, Angst J: Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG). Eur Neuropsychopharmacol 1997b;7:9–24.

16 Overall JE, Gorham DR: Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812.

17 Dittrich A: Ätiologie-unabhängige Strukturen veränderter Wachbewusstseinszustände. Stuttgart, Enke, 1985.

18 Dittrich A: Standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry 1998;31:280–284.

19 Benton AL: A visual retention test for clinical use. Arch Neurol Psychol 1945;59:273–291.
20 Kuzis G, Sabe L, Tiberti C, Merello M, Leiguarda R, Starkstein SE: Explicit and implicit learning in patients with Alzheimers disease and Parkinson disease with dementia. Neuropsychiatry Neuropsychol Behav Neurol 1999; 12:265–269.
21 Müller-Vahl KR, Koblenz A, Jobges M, Kolbe H, Emrich HM, Schneider U: Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry 2001;34:19–24.
22 Zimmermann F, Fimm B: Neuropsychologische Testbatterie zur Erfassung von Aufmerksamkeitsdefiziten. Freiburg, Psychologisches Institut der Universität Freiburg, 1989.
23 Hasse-Sander I, Gross G, Huber G, Peters S, Schuttler R: Examinations by psychological tests in basic stages and pure residual syndromes of schizophrenic diseases (in German). Arch Psychiat Nervenkr 1982;231:235–249.
24 Schneider U, Bevilacqua C, Jacobs R, Karst M, Dietrich DE, Becker H, Muller-Vahl KR, Seeland I, Gielsdorf D, Schedlowski M, Emrich HM: Effects of fentanyl and low doses of alcohol on neuropsychological performance in healthy subjects. Neuropsychobiology 1999; 39:38–43.
25 Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 1965; 6:279–291.
26 Dittrich A, Arx S, Staub S: International study on altered states of consciousness (ISASC): Summary of the results. German J Psychol 1985;9:319–339.
27 Bowdle TA, Radant AD, Cowley DS, Karash ED, Strassman RS, Roy-Byrne PP: Psychedelic effects of ketamine in healthy volunteers: Relationship to steady state plasma concentrations. Anesthesiology 1998;88:82–88.
28 Gouzoulis-Mayfrank E, Habermeyer E, Hermle L, Steinmeyer A M, Kunert H J, Sass H: Hallucinogenic drug induced states resemble acute endogenous psychoses: Results of an empirical study. Eur Psychiatry 1998;13:399–406.
29 Corssen G, Oget S, Reed PC: Psychic Effects of Ketamine. Anesth Analg 1971;50:397–401.
30 Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301–1308.
31 Oye I, Hustveit O, Moberg ER, Pausen O, Skoglund LA: The chiral forms of ketamine as probes for NMDA receptor function in humans; in Kameyama T, Nabeshima T, Domino EF (eds): NMDA Receptor Related Agents: Biochemistry, Pharmacology, and Behavior. Ann Arbor, NPP Books, 1991, pp 381–389.
32 Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 1992;260:1209–1213.
33 Harris JA, Biersner RJ, Edwards D, Bailey LW: Attention, learning and personality during ketamine emergence: A pilot study. Anesth Analg 1975;54:169–174.
34 Ghonheim MM, Hinrichs JV, Mewaldt SP, Petersen RC: Ketamine: Behavioral effects of subanesthetic doses. J Clin Psychopharmacol 1985;5:70–77.
35 Vollenweider FX, Geyer MA: Systems model of altered consciousness: Integrating natural and drug-induced psychoses. Brain Res Bull 2001;15;56:495–507.
36 Tamlyn D, McKenna PJ, Mortimer AM, Lund CE, Hammond S, Baddeley AD: Memory impairment in schizophrenia: Its extent, affiliations and neuropsychological character. Psychol Med 1992;22:101–115.