

E. Gouzoulis-Mayfrank¹K. Heekeren^{1,2}A. Neukirch^{1,2}M. Stoll²C. Stock²M. Obradovic³K.-A. Kovar³

Psychological Effects of (S)-Ketamine and N,N-Dimethyltryptamine (DMT): A Double-Blind, Cross-Over Study in Healthy Volunteers

Introduction: Pharmacological challenges with hallucinogens are used as models for psychosis in experimental research. The state induced by glutamate antagonists such as phencyclidine (PCP) is often considered as a more appropriate model of psychosis than the state induced by serotonergic hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and N,N-dimethyltryptamine (DMT). However, so far, the psychological profiles of the two types of hallucinogenic drugs have never been studied directly in an experimental within-subject design. **Methods:** Fifteen healthy volunteers were included in a double-blind, cross-over study with two doses of the serotonin 5-HT_{2A} agonist DMT and the glutamate N-methyl-D-aspartate (NMDA) antagonist (S)-ketamine. **Results:** Data are reported for nine subjects who completed both experimental days with both doses of the two drugs. The intensity of global psychological effects was similar

for DMT and (S)-ketamine. However, phenomena resembling positive symptoms of schizophrenia, particularly positive formal thought disorder and inappropriate affect, were stronger after DMT. Phenomena resembling negative symptoms of schizophrenia, attention deficits, body perception disturbances and catatonia-like motor phenomena were stronger after (S)-ketamine.

Discussion: The present study suggests that the NMDA antagonist model of psychosis is not overall superior to the serotonin 5-HT_{2A} agonist model. Rather, the two classes of drugs tend to model different aspects or types of schizophrenia. The NMDA antagonist state may be an appropriate model for psychoses with prominent negative and possibly also catatonic features, while the 5-HT_{2A} agonist state may be a better model for psychoses of the paranoid type.

Introduction

Healthy subjects in hallucinogenic drug states exhibit phenomena which resemble symptoms of schizophrenia or schizophrenia spectrum disorders. Therefore, pharmacological challenges with hallucinogenic drugs such as mescaline, lysergic acid diethylamide (LSD), psilocybin and N,N-dimethyltryptamine (DMT) have been used traditionally as models for psychosis in experimental research [6,14,15,20,22,24,32,52,64,66,73]. However, some authors argued that subjects in hallucinogen states are more differ-

ent from patients with schizophrenia than alike: they are rarely withdrawn and emotionally blunted like schizophrenia patients are, they have more frequently visual rather than auditory hallucinations, which are typical of schizophrenia, and they rarely show real delusions and catatonic features [32]. In the 50s, some researchers reported that sub-anaesthetic doses of the new anaesthetic drug phencyclidine (PCP) induce a more schizophrenia-like psychotic state with prominent thought disorder, negativism, hostility, attention abnormalities, bodily sensations and apathy, and less visual phenomena than the other hallucino-

Affiliation

¹ Department of Psychiatry and Psychotherapy, University of Cologne, Kerpener Strasse 62, Cologne, Germany

² Department of Psychiatry and Psychotherapy, University of Technology, Aachen (RWTH), Pauwelsstrasse 30, Aachen, Germany

³ Institute of Pharmacy, University of Tübingen, Auf der Morgenstelle 8, Tübingen, Germany

Correspondence

Professor Euphrosyne Gouzoulis-Mayfrank, MD · Department of Psychiatry and Psychotherapy · University of Cologne · Kerpener Straße 62 · 50924 Cologne · Germany · Phone: +49 221 478 4825 · Fax: +49 221 478 3738 · E-Mail: e.gouzoulis@uni-koeln.de

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gens [47,60]. Today we know that the predominant action of subanaesthetic doses of PCP and PCP-like drugs is an antagonism at glutamate N-methyl-D-aspartate (NMDA) receptors [34,55] whereas “classic” hallucinogens such as LSD and psilocybin act as agonists or partial agonists at serotonin 5HT_{2A} receptors [59].

Due to the growing insight into serotonergic and glutamatergic mechanisms of schizophrenia, research interest in hallucinogens has been again on the rise since the beginning of the 90 s. Several studies were performed using both serotonergic substances [9,10,17,21,24–26,28,29,61,62,65,67–69,72,77–79] and the PCP-like drug ketamine [2,3,7,13,27,30,31,35,36,38–46,48–51,53,54,56,63,70,71,75,76,80,81]. Interestingly, the recent literature frequently perpetuated the old view that the NMDA antagonist model is the best model of schizophrenia [e.g. 45], although empirical studies with ketamine yielded inconsistent results. In line with the old reports from the 50 s [60], some recent studies found that ketamine induces both positive and negative symptoms in healthy humans and exacerbates both positive and negative symptoms in patients with schizophrenia [39,48,49]. However, another study reported only an exacerbation of positive symptoms after ketamine [44]. In addition, Krystal et al. [40,41] reported that phenomena resembling negative symptoms of schizophrenia are difficult to disentangle from the sedative effects of the drug. Abi-Saab et al. [1] argued that no single drug can possibly mimic the entire spectrum of symptoms of schizophrenia and suggested that the PCP and ketamine states may serve as models for the disorganized or undifferentiated subtype, while the LSD-type drug states may be more adequate models for the paranoid subtype of schizophrenia. Indeed, some authors performed both studies with NMDA antagonists and with serotonergic psychotomimetics and reported on different psychological and/or neurobiological responses to these drugs in humans [11,71–74]. Nevertheless, so far, the psychological effects of ketamine have not been directly compared to the effects of a serotonergic hallucinogen in an experimental within-subject design.

The aim of our experiment was to compare the psychological effects in humans of the 5-HT_{2A} agonist hallucinogen N,N-dimethyltryptamine (DMT) and the NMDA antagonist hallucinogen (S)-ketamine in a randomized, double-blind, cross-over design. Both drugs can be given intravenously and have similar pharmacokinetics with rapid onset and rapid fading of action after the end of the infusion, thus making it possible to study the qualitative differences of the two drug states in a double-blind design. In line with the view by Abi-Saab et al. [1] we hypothesized that no drug state is an overall better model of psychosis than the other. Rather, we predicted that the ketamine induces more phenomena which resemble the negative and cognitive symptoms, while DMT induces more phenomena which resemble positive symptoms of schizophrenia.

Methods

Subjects

Fifteen healthy volunteers (9 men, 6 women; mean age 38.0 years, range: 28–53) with no current physical and no current or previous history of neurological or psychiatric disorder (Axis I

according to DSM-IV criteria) were included in the study. Subjects with a positive family history of severe psychiatric disorder in first-degree relatives (schizophrenia, other psychotic disorders and major affective disorders: DSM-IV codes 295.xx, 297.x, 298.x, 296.xx), a personal history of current or previous alcohol or drug related disorder, or under regular medication were excluded. All subjects were screened with a medical history, a standardized psychiatric interview (SCID) and a physical examination, ECG and a routine laboratory testing. Twelve volunteers reported single or sporadic experiences with hallucinogens and/or stimulants and thirteen volunteers reported single or sporadic experiences with cannabis several years prior to the study (hallucinogens and/or stimulants: range from one to maximum 15 experiences; cannabis: range from one single experience to once or twice per month, period of use: mostly during high school education). One subject had no prior experience with psychotropic substances. No subject had been under medication or subject to excessive caffeine intake and/or stressful life events in the four weeks prior to the study. All subjects were either physicians or psychologists or psychiatric nursing staff and, therefore, involved in work with psychiatric patients. They had a scientific or clinical interest in the study and did not receive any payment for their participation.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee at the Medical Faculty of the University of Technology Aachen and the Federal Health Administration (Bundesinstitut für Arzneimittel und Medizinprodukte, Bundesopiumstelle, Berlin). Written informed consent was obtained from all subjects following detailed description of the experimental procedures and assurance that they could withdraw from the study at any time, if they wish so, without having to explain the reasons.

Drugs

N,N-Dimethyltryptamine fumarate (DMT) was synthesized in the Pharmaceutical Institute, University of Tübingen (Germany) and prepared as a solution for intravenous use by Wülfig Pharma (Gronau, Germany). The (S)-ketamine solution (Ketanest® S, Parke-Davis, Karlsruhe, Germany) was purchased from the hospital pharmacy. The S-isomer of ketamine has 2–4 times greater affinity for the NMDA receptor and stronger hallucinogenic potency than the R-isomer [57,58,75]. The appropriate dosages for both DMT and (S)-ketamine were determined in a previous open study with six subjects (unpublished results). In this study we observed considerable inter-individual differences in the sensitivity to the drug effects. We determined a low dose range so as to evoke relatively subtle psychopathological alterations, below the threshold of psychotic symptoms (a so called “prepsychotic” state), and a high dose range so as to evoke more profound alterations including true psychotic symptoms such as hallucinations and transient delusional misinterpretations of the experimental situation. For the double-blind study we decided not to give the same fixed doses to every subject, but rather to titrate the doses within the defined ranges so as to obtain more comparable psychopathological profiles (in terms of the overall intensity of effects) within the low and high dose regimens.

The four dose regimens were: (1) low DMT: a bolus injection of 0.15 or 0.2 mg/kg over 5 min followed by a break of one minute,

followed by continuous infusion with 0.01125 or 0.015 mg/kg*min over 84 minutes, (2) high DMT: bolus injection of 0.2 or 0.3 mg/kg, break of one minute and continuous infusion with 0.015 or 0.02 mg/kg*min, (3) low (S)-ketamine: bolus injection of 0.1 or 0.15 mg/kg over 5 min, followed by a break of one minute, followed by continuous infusion with 0.0066 or 0.01 mg/kg*min over 54 minutes, followed by continuous infusion at a rate of 75% of the previous dose over 30 minutes, and (4) high (S)-ketamine: bolus injection of 0.15 or 0.2, break of one minute, continuous infusion with 0.01 or 0.015 mg/kg*min over 54 minutes, followed by continuous infusion at a rate of 75% of the previous dose over 30 minutes.

Hence, the first dose was always on the maximum of the dose range of the low dose that equaled the minimum of the dose range of the high dose. The second dose was higher or lower than the first one depending on the intensity of effects during the first infusion period. The decision regarding the second dose (should it be higher or lower than the first one?) was not made on the basis of ratings of hallucinations or other single symptoms, but rather on the basis of the overall intensity of drug effects which was operationalized in a binary way as: a) occurrence of delusional misinterpretations vs. preservation of insight into the experimental nature of the situation throughout the first infusion period, and b) reported feelings of being able to cope with vs. being anxious and (nearly) overwhelmed by the experience. This procedure enabled us to obtain psychological effects of comparable intensity within each dose regimen despite the inter-individual differences in responsiveness to these drugs. For example: We always started the first DMT dose with a bolus of

0.2 mg/kg and continued with an infusion rate of 0.015 mg/kg*min. In case of overall intense effects with the first dose [transient delusional misinterpretations of the experimental nature of the situation, or reported feelings of being anxious and (nearly) overwhelmed by the experience], we started the second dose with the lowest possible bolus of 0.15 mg/kg and continued with the lowest infusion rate of 0.01125 mg/kg*min. In case of overall moderate effects with the first dose (preservation of insight into the experimental nature of the situation, reported feelings of being able to cope with the experience), we started the second dose with the highest possible bolus of 0.3 mg/kg and continued with the highest infusion rate of 0.02 mg/kg*min. The adjustment of the infusion rate of (S)-ketamine after 60 minutes to a rate of 75% of the previous one was required in order to avoid a cumulation of plasma levels and gradual intensification of clinical effects [16,33]. Due to the faster elimination rate of DMT, a reduction of the DMT infusion rate over the 90 minutes administration period was not required [67,69]. The dose regimens for the nine subjects who completed both experiments with both doses of the two drugs (see also section **Results**) are summarized in Table 1. With these dose regimens the psychological effects of both drugs developed fully within about 15 minutes from the start of the injection and were then kept relatively constant over the remaining 75 minutes of the infusion.

Study design and experimental procedures

Each subject participated in one experiment with DMT and one experiment with (S)-ketamine in a double-blind, cross-over design and pseudo-randomized order. The two experiments were two to four weeks apart. They were performed in a quiet labora-

Table 1 Intravenous dose regimens for (S)-ketamine (KET) and N,N-dimethyltryptamine (DMT) for the nine subjects who completed both experiments

Subject	Sex	Day	Drug	1. Dose	2. Dose				
					Bolus (mg/kg)	Infusion (mg/min *kg)	Bolus (mg/kg)	Infusion (mg/min *kg)	
1	m	1	KET	low	0.15	0.01*	high	0.2	0.015**
		2	DMT	low	0.2	0.015	high	0.3	0.02
2	m	1	DMT	low	0.2	0.015	high	0.3	0.02
		2	KET	high	0.15	0.01*	low	0.1	0.0066***
3	m	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	high	0.2	0.015	low	0.15	0.01125
4	m	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	low	0.2	0.015	high	0.3	0.02
5	f	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	high	0.2	0.015	low	0.15	0.01125
6	f	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	high	0.2	0.015	low	0.15	0.01125
7	m	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	low	0.2	0.015	high	0.3	0.02
8	m	1	DMT	high	0.2	0.015	low	0.15	0.01125
		2	KET	high	0.15	0.01*	low	0.1	0.0066***
9	m	1	KET	high	0.15	0.01*	low	0.1	0.0066***
		2	DMT	low	0.2	0.015	high	0.3	0.02

m = male, f = female

*: infusion rate reduced to 0.0075 for the last 30 minutes of the infusion

**: infusion rate reduced to 0.01125 for the last 30 minutes of the infusion

***: infusion rate reduced to 0.00495 for the last 30 minutes of the infusion

tory room in the Department of Psychiatry at the Technical University of Aachen. The subjects were instructed to take a light breakfast in the morning of the experiment including one cup of coffee or tea and to come to the hospital between 8:00 and 9:00 a.m. As soon as they arrived intravenous catheters were placed in the forearm veins of both arms. During the experiment subjects were lying comfortably in a bed with their head and upper trunk elevated. They were at all times in the company of an experienced psychiatrist and a medical student, who were both blind as to the substance used [DMT or (S)-ketamine]. On each experiment the low and high dose of one of the two substances [DMT or (S)-ketamine] were administered with a two hours break between the two doses in a single-blind order design (see above). The drugs were administered by a second physician, who was a member of the research team and was not blind as to the substance. Therefore, this physician had no other role in these experiments and did not communicate with the subjects and the other members of the research team.

Drugs were administered intravenously by an automatic infusion pump (Perfusor®, B. Braun, Melsungen, Germany) between 10:00 and 11:30 a.m. and again between 1:30 and 3:00 p.m. Cardiovascular parameters (systolic and diastolic blood pressure, heart rate) were monitored automatically (Dinamap®, Critikon Tampa, FL, USA) throughout the experiment. Between 10:30 and 11:30 a.m. and again between 2:00 and 3:00 p.m. we studied modulation of the startle reflex and attentional performance. These data will be reported separately. Psychiatric interviews were performed in the first 30 minutes of each infusion (10:00 to 10:30 a.m. and again 1:30 to 2:00 p.m.) as well as in the breaks between the assessments of the modulation of the startle reflex and attentional performance (about 10:55 to 11:05 a.m. and 2:25 to 2:35 p.m.). Within 10 to 30 minutes of stopping the drug infusion the psychological effects vanished. Blood samples for plasma levels of DMT and (S)-ketamine were drawn at -10, +15, +60, +90 and +150 minutes from the beginning of each infusion and were analyzed in the Institute of Pharmacy of the University of Tübingen. At 0:30 p.m., i.e. during the break between the two drug doses, subjects were served a light standardized meal. Throughout the experiment they were allowed to drink only water at will. The subjects remained in the hospital under medical supervision during the break between the two doses and for at least two hours after termination of the second dose. During that time we completed the interviews on the drug effects if necessary, and both subject and researcher completed the psychometric ratings relating to the period during which significant effects from the drugs were experienced. One rater performed all interviews and psychometric ratings. At discharge, subjects were instructed to contact the researcher whenever problems such as anxiety, flash back etc. should occur during the following days. On the day after the experiment all subjects were interviewed on possible delayed effects. In addition, seven days and 10 to 12 months after the experiments we carried out semi-structured interviews with all subjects on possible delayed effects, psychological well-being and substance use.

Psychopathological evaluations

Psychological effects were assessed using the following standardized instruments:

Self-assessment inventories

Subjects completed two scales for the assessment of hallucinogen effects.

The *Hallucinogen Rating Scale HRS* [68] consists of 99 items each rated on a scale of 0 to 4. The 99 items form 6 subscales: somesthesia, affect, perception, cognition, volition and intensity. High scores in each subscale indicate stronger deviation from the normal state without indicating the quality or direction of the alteration (i.e. a high score for affect may indicate depressive or mania-like mood alterations).

The *APZ-OAV questionnaire* (*Abnormer Psychischer Zustand = altered state of consciousness*) [11,12] describes the common nucleus of experiences in hallucinogenic drug induced and other similar altered states of consciousness (e.g. meditation, sensory deprivation states etc). The *APZ-OAV* consists of 66 items each rated on an analogue scale of 0 to 100. Together they form a global score and three subscales: *OSE* (*Ozeanische Selbstentgrenzung = oceanic boundlessness*) measures pleasant, ecstatic experiences and feelings of eternity and unity (e.g. "I felt totally free and released from all responsibilities"; "it seemed to me that there were no more conflicts and contradictions in the world"; "I experienced past, present and future as a unity"; "it seemed to me that my environment and I were one"); *AIA* (*Angst vor der Ich-Auflösung = dread of ego-dissolution*) describes a disintegrative, anxious state (e.g. "I felt threatened without realizing by what"; "I felt isolated from everything and everyone"; "I had the feeling that I no longer had a will of my own"); *VUS* (*Visionäre Umstrukturierung = visionary restructuring*) includes visual phenomena and experiences of altered meaning and significance (e.g. "I saw things that I know were not real"; "things around me had a new, strange meaning for me"; "the colors of the things I saw were changed by sounds and noises").

Clinician ratings

We used three psychiatric scales for the assessment of schizophrenia-like psychotic symptoms:

1. The *Scale for the Assessment of Negative Symptoms SANS* [5] consists of 24 items each rated from 0 to 5. They form a global score and five subscales: affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and attention.
2. The *Scale for the Assessment of Positive Symptoms SAPS* [4] consists of 35 items each rated from 0 to 5. They form a global score and five subscales: hallucinations, delusions, bizarre behavior, positive formal thought disorder, and inappropriate affect.
3. The *Schizophrenia Prediction Instrument-Adult Version SPI-A* [37] consists of 49 items which describe subtle, subclinical subjective symptoms, complaints and perceptual alterations occurring in prodromal stages of psychosis. Ratings on a scale from 0 to 6 are performed by the clinician based on a standardized, structured interview with the patient. The items form six subscales: overstrain, emotional deficits, cognitive impediments, cognitive disturbances, body perception disturbances, and perception and motor disturbances and estrangement. The rationale for using the SPI-A in addition to the SAPS and SANS was that similarities between hallucinogen induced states and schizophre-

nia tend to be more pronounced for the early stages of psychoses [18–20]. Accordingly, some of the SPI-A items describe experiences which seem to be rather similar to the effects of hallucinogenic drugs (e.g. *bodily sensations of movement, feeling overwhelmed by stimuli, photopsia, micro- or macropsia, changed perception of the face or body of others, changes in the perceived intensity or quality of acoustic stimuli*), but are not included in the SANS and SAPS.

In order to assess motor and behavioral phenomena that resemble catatonic symptoms of psychosis we selected the most suitable single items from the psychometric scales. These were two items from SPI-A and three items from APZ-OAV: 1) *Motor interference (SPI-A)*: refers to spontaneous and unintended movements or utterances that interfere with intended motor actions or speech, and are not due to thought disturbances and are not regarded by the person as being made by external forces (pseudo-spontaneous movements, movement stereotypes, automaton syndrome), 2) *motor blockages (SPI-A)*: refers to impediment or complete blockage of intended motor actions which may occur suddenly and vanish quickly and may be regarded as counterpart of the automaton syndrome, 3) *"I felt like a marionette" (APZ-OAV)*, 4) *"I felt as though I were paralyzed" (APZ-OAV)*, and 5) *"I stayed frozen in a very unnatural position for quite a long time" (APZ-OAV)*.

Data analysis

We analyzed the psychometric data by means of repeated measures analyses of variance (ANOVA) with the factors substance [DMT, (S)-ketamine] and dose (high, low). All analyses were performed using the SPSS software (version 11.0). Statistical significance was set at $p \leq .05$.

Results

From the fifteen subjects who entered the study twelve subjects completed the experiment with both doses of DMT and ten subjects completed the experiment with both doses of (S)-ketamine. Dropouts were due to intense, unpleasant psychological effects [one male and one female subject under (S)-ketamine, one male subject under DMT], nausea (one female subject under DMT) and hypotonia (one female subject under DMT). In the entire dropout cases undesirable effects vanished within a few minutes from stopping the infusion. No additional medication was given to these subjects thereafter and no lasting sequelae were observed. Finally, one more female subject decided to abstain from the second experiment because of unpleasant aftereffects in the evening and next day after the first experiment (headache and mild orthostatic complaints after an experiment with DMT that was carried out without acute complications). In that case the unpleasant aftereffects lasted up to 24 hours and resolved spontaneously without lasting sequelae. Nine subjects completed both experiments with both doses of DMT and (S)-ketamine. Data are reported for these nine subjects. Plasma levels for both substances showed little variation between +60 and +90 minutes after start of infusion and a fast decline after termination of the infusion. Mean plasma levels for (S)-ketamine were: low dose: 169.8 ± 29.9 ng/ml, high dose: 197.4 ± 31.6 ng/ml (mean values of plasma levels at +60 and +90 minutes after start of infusion). Mean

plasma levels for DMT were: low dose: 42.8 ± 26.1 ng/ml, high dose: 60.0 ± 28.0 ng/ml. Ten minutes before the start of the second dose infusion plasma levels had dropped to 5.1 ± 3.1 ng/ml for DMT and to 49.1 ± 12.2 ng/ml for (S)-ketamine.

There were no spontaneous reports of psychological or physical problems in the days following the experiments. The interview on the day after each experiment, revealed tiredness and headache in the evening after the experiment in 10 out of the 13 subjects who received DMT, and in 4 out of 11 subjects who received (S)-ketamine. One subject reported persisting nausea until the next morning after (S)-ketamine and another subject reported sleep disturbance in the night after DMT. Finally, one subject reported mild orthostatic complaints and another subject reported two very short episodes of visual perceptual distortions (less than one minute each) in the morning after the DMT experiment. The interviews conducted seven days and ten to twelve months after the experiments revealed no aspects of psychopathology or substance abuse that might be related to participation in our study.

Psychometric scores

The descriptive statistics for the two self-assessment inventories are illustrated in Fig. 1.

HRS (Hallucinogen Rating Scale): There were no significant effects of substance or dose for somaesthesia, volition and intensity. Affect and perception scores tended to be higher for DMT, however

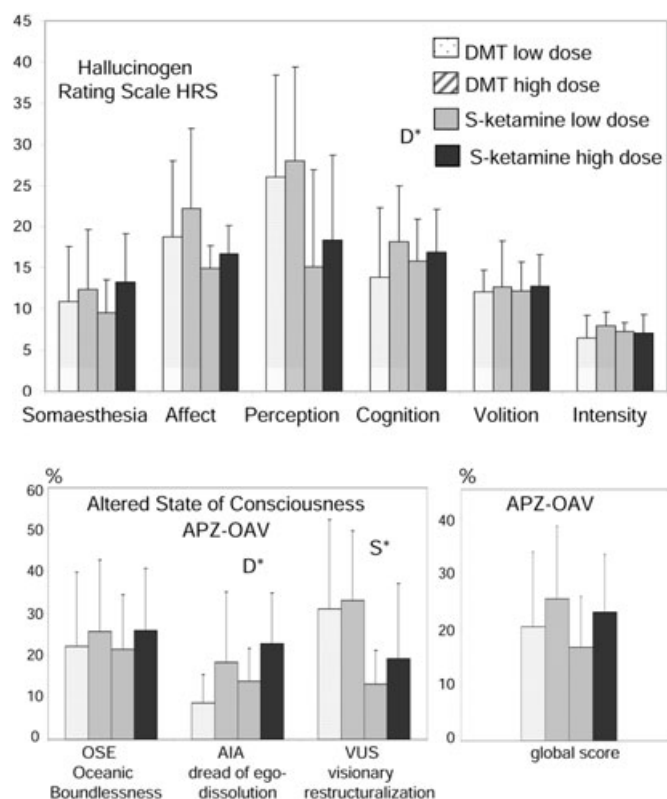


Fig. 1 Mean scores $\pm$ standard deviations of the self assessment inventories HRS and APZ-OAV after N,N-dimethyltryptamine (DMT) and (S)-ketamine (randomized, double-blind, cross-over, $n = 9$). S, D: significant main effects of substance or dose in the ANOVA, level of significance: * $p \leq 0.05$.

these differences were not significant (main effect of substance $F = 3.98$, $p = 0.081$ and $F = 2.61$, $p = 0.145$, main effect of dose $F = 2.64$, $p = 0.143$ and $F = 2.95$, $p = 0.124$, respectively). Regarding cognition, there was a significant main effect of dose ($F = 8.96$, $p = 0.017$), but no effect of substance. There were no significant interactions substance $\times$ dose.

APZ-OAV (Altered state of consciousness): The data for this scale reflect the percentage of the possible maximal scores. For the global score, repeated measures ANOVAs revealed no significant main effect of substance and a marginal effect of dose ($p = 0.057$). There were no significant main effects of substance or dose for OSE. Regarding AIA, there was a significant main effect of dose ($F = 7.69$, $p = 0.024$), but no effect of substance. Regarding VUS, there was a significant main effect of substance ($F = 9.64$, $p = 0.015$), and no effect of dose. There were no significant interactions substance $\times$ dose.

The descriptive statistics for the psychiatric scales are illustrated in Fig. 2.

SAPS (Scale for the Assessment of Positive Symptoms): For the global score, repeated measures ANOVAs revealed significant main effects of substance and dose ($F = 20.76$, $p = 0.002$ and $F = 32.19$, $p < 0.0001$), indicating higher scores for positive symptoms after DMT. Similarly, both main effects were significant for positive formal thought disorder ($F = 29.23$ and $F = 23.84$, both $p = 0.001$). For inappropriate affect, we found a significant effect of substance ($F = 5.76$, $p = 0.043$) and no effect of dose, again indicating more inappropriate affect after DMT. For hallucinations, we found a marginal effect of substance ($p = 0.058$) and a significant effect of dose ($F = 18.68$, $p = 0.003$). For delusions, we found a significant effect of dose ($F = 9.05$, $p = 0.017$), but no effect of substance. Bizarre behavior did not differ between substances and doses. Finally, we found no significant interactions substance $\times$ dose.

SANS (Scale for the Assessment of Negative Symptoms): For the global score, repeated measures ANOVAs revealed significant main effects of substance and dose ($F = 29.41$, and $F = 26.32$, both $p < 0.001$), indicating higher scores for negative symptoms after (S)-ketamine. Significant main effects of substance indicat-

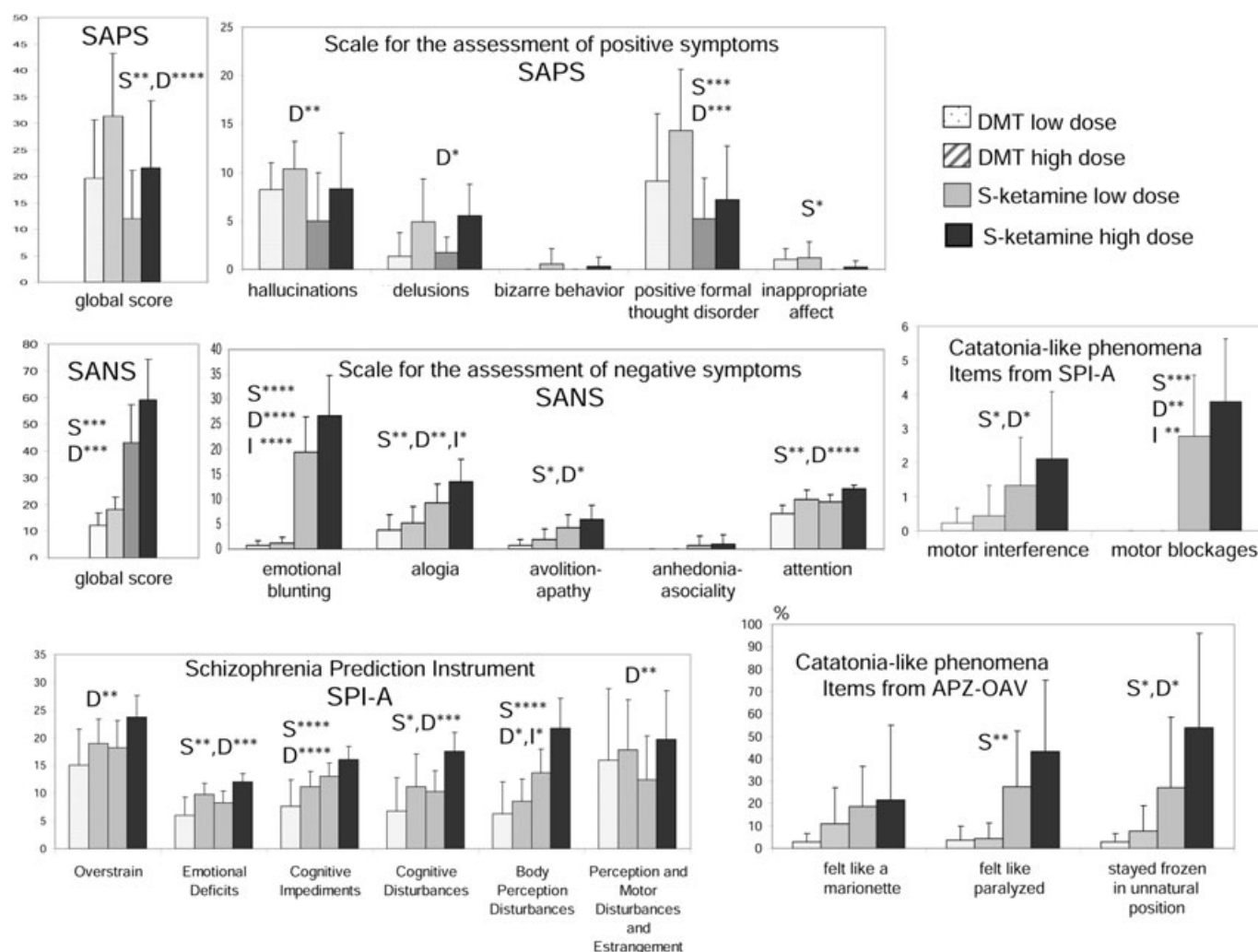


Fig. 2 Mean scores $\pm$ standard deviation of the psychiatric scales SAPS, SANS and SPI-A and single items describing catatonia-like symptoms after N,N-dimethyltryptamine (DMT) and (S)-ketamine (randomized, double-blind, cross-over, $n = 9$). S, D, I: significant main effects of substance or dose, significant interaction substance $\times$ dose in the ANOVA, level of significance: *: $p \leq 0.05$, **: $p \leq 0.01$, ***: $p \leq 0.001$, ****: $p \leq 0.0001$.

ing higher scores after (S)-ketamine were also found for affective blunting ($F = 75.83$, $p < 0.0001$), alogia ($F = 17.44$, $p = 0.003$), avolition-apathy ($F = 8.53$, $p = 0.019$) and attention ($F = 11.30$, $p = 0.010$). In addition, we found significant main effects of dose for the same scores (affective blunting: $F = 47.25$, $p < 0.0001$, alogia: $F = 15.19$, $p = 0.005$, avolition-apathy: $F = 9.32$, $p = 0.016$, attention: $F = 75.62$, $p < 0.0001$). Finally, we found significant interactions of substance $\times$ dose for affective blunting ($F = 52.53$, $p < 0.0001$) and alogia ($F = 7.53$, $p = 0.025$), indicating a stronger increase of effects with the higher (S)-ketamine dose compared to the higher DMT dose.

SPI-A (Schizophrenia Prediction Instrument): Repeated measures of ANOVAs revealed significant main effects of dose for all six subscales of the SPI-A (overstrain: $F = 14.38$, $p = 0.005$; emotional deficits: $F = 23.72$, $p < 0.001$; cognitive impediments: $F = 39.56$, $p < 0.0001$; cognitive disturbances: $F = 31.02$, $p < 0.001$; body perception disturbances: $F = 10.09$, $p = 0.013$; perception and motor disturbances and estrangement: $F = 21.95$, $p = 0.002$). The main effect of substance was significant for emotional deficits ($F = 13.31$, $p = 0.007$), cognitive impediments ($F = 32.58$, $p < 0.0001$), cognitive disturbances ($F = 9.49$, $p = 0.018$) and body perception disturbances ($F = 73.50$, $p < 0.0001$) and marginal for overstrain ($F = 4.07$, $p < 0.078$), indicating overall stronger effects with (S)-ketamine in all subscales except for perception and motor disturbances and estrangement. There was a significant interaction of substance $\times$ dose for body perception disturbances ($F = 5.51$, $p = 0.047$), indicating a stronger increase of effects with the higher (S)-ketamine dose compared to the higher DMT dose.

Catatonia-like items: Repeated measures ANOVAs revealed significant main effects of substance for motor interference ($F = 9.65$, $p = 0.015$), motor blockages ($F = 30.87$, $p < 0.001$), *feel like paralyzed* ($F = 22.04$, $p = 0.002$), and *stayed frozen in an unnatural position* ($F = 8.97$, $p = 0.017$), indicating overall stronger effects with (S)-ketamine. The effect of dose was also significant for motor interference ($F = 7.20$, $p = 0.028$), motor blockages ($F = 12.00$, $p = 0.009$), and *stayed frozen in an unnatural position* ($F = 7.14$, $p = 0.028$). Finally, the interaction of substance $\times$ dose was significant for motor blockages ($F = 12.00$, $p = 0.009$), indicating an increase of effects only for the higher (S)-ketamine dose but not for the higher DMT dose.

High DMT plasma levels were associated with more pronounced positive symptoms and global alteration of consciousness [DMT AUC (Area under the curve)/SAPS global score: $r = 0.629$, $p < .05$; DMT Cmax (peak concentration)/APZ-OAV global score: $r = 0.590$, $p < .05$]. High (S)-ketamine plasma levels were associated with more pronounced negative symptoms, subjective cognitive impediments and body perception disturbances [(S)-ketamine AUC/SANS global score: $r = 0.691$, $p < .01$; (S)-ketamine AUC/SPI-A subscores overstrain, emotional deficits, cognitive impediments, cognitive disturbances and body perception disturbances: $r = 0.643$ to 0.720 , $p < .05$ to $< .01$].

Finally, because the overall number of comparisons between the two drugs was large (33 psychometric scores including three global scores, 25 subscale scores and five single items) and because ANOVAs were conducted separately for each psychometric di-

mension we performed a correction for multiple testing for the effects of substance. Even after applying a conservative Bonferroni correction, the main effects of substance for SAPS positive formal thought disorder, SANS global score, SANS emotional blunting, SPI-A cognitive impediments, SPI-A body perception disturbances and SPI-A motor blockages still passed the significance level ($p < 0.0016$).

Summary of subjective descriptions of the drug states and observations of the researcher

Both the DMT and the (S)-ketamine states were dose-dependently perceived as strong to extremely strong alterations of mind with limited to no possibility at all for the subject to have an influence on what was happening. In general, visual and auditory phenomena were more pronounced with DMT, but body misperceptions were roughly equally frequent and intensive with both drugs (e.g. touch or light pressure on arm or head while taking blood or adjusting electrodes was perceived as deformation of this body part). Individual subjects even described feelings as if the whole body were melting away and/or difficulties to sense the boundaries of their body. There were frequent reports of sensations as if one's arm did not belong to oneself, or as if parts of the body were enlarged or shrunk. Ego-control and insight into the experimental nature of the experience were preserved at the low doses. However, at the high doses all subjects reported experiences of altered meaning or significance and developed at least transient paranoid thoughts and misinterpretations of the experimental situation.

DMT state

Effects of both DMT doses included vivid alterations of visual, auditory and tactile perception, illusions and abnormal somatic sensations. At the high dose auditory hallucinations (music, whispering voices, telephone rings) occurred in two cases. Visual hallucinations (e.g. complex geometric patterns on the walls, moving persons and body parts on the computer screen) were reported by seven subjects already at the low dose and by all subjects at the high dose. One subject reported characteristic synaesthesias. At the high dose, four subjects reported paranoid ideation, e.g. two subjects thought that a higher power was conducting the experiment and that the actions of the researchers were part of the plan of this higher power. Another subject perceived her own mimic action of face muscles as being "made" by somebody else. Most subjects tended to report their experiences during the experiment spontaneously, and they were interested in interpersonal interactions. To some extent positive formal thought disorder (loosening of associations, derailment and distractibility) was observed in virtually every subject even at the low dose. Prominent positive formal thought disorder was observed in five subjects at the high dose. One subject displayed dose-dependent increased energy and drive, and diminished behavioral inhibition. Mood varied from anxious and tense to expansive and euphoric with mostly vivid verbal, mimic and psychomotor expression of emotions. Two subjects reported feeling uncomfortable with the emotional alterations, because they felt that the emotions were not "real", but rather "made by the drug".

(S)-Ketamine state

After (S)-ketamine all subjects displayed dose-dependent hypomimia, psychomotor poverty, poverty of speech, apathy and

withdrawal. Six subjects displayed catatonic-like behavior (e.g. one subject took unnatural postures, another subject held the computer mouse for several seconds in his hand after being told to let it down, a third one kept his hands in mid-air a few centimeters away from the computer keyboard after he was told to touch it). There was almost complete lack of spontaneous verbal communication after (S)-ketamine. Whenever asked about their experiences, subjects answered with single words or short sentences and with a latency of up to five seconds, and they seemed to have no interest in interpersonal interaction. After the action of the drug faded, all subjects reported that they had felt more or less remote, isolated from others and emotionally blunted, and two subjects reported complete "loss of emotions". Four subjects reported that while they had been engaged in the computer tests they had felt as if they were transported to a different "dimension" where nothing and nobody existed apart from themselves and the test. Two subjects reported that they had performed the computer tests like an automaton "running automatically" without personal will. Dream-like alterations of visual perception were common, but only one subject reported visual hallucinations at the high dose (cartoon-like figures moving on the computer screen). There were seven reports of subtle auditory misperceptions, but no reports of auditory hallucinations. By contrast, virtually every subject reported prominent bodily and/or vestibular sensations, e.g. as if the body were moving rapidly in space like a motor vehicle, or like being in a moving elevator. All except one subject found the (S)-ketamine experience more or less unpleasant.

Discussion

The psychological effects of two doses of the serotonergic hallucinogen N,N-dimethyltryptamine (DMT) and the antihypocretinergic hallucinogen (S)-ketamine were studied in a randomized, double-blind, cross-over experimental study with healthy volunteers. Both drugs were administered intravenously by continuous infusion and the doses were titrated within predetermined dose ranges so as to have relatively uniform psychological effects. Overall, most subjects tolerated the procedures and we observed no serious delayed adverse effects after the experiments. In those cases where we stopped drug administration and terminated the experiment because of intense, unpleasant psychological or adverse physical effects, all undesirable phenomena faded rapidly and were never followed by lasting sequelae. Hence, although the participation in this study has been stressful, in our view, the level of distress for the subjects has been acceptable.

Overall, the intravenous administration of both hallucinogens was followed by dose-dependent, powerful alterations of perception, affect and cognition. Interestingly, the dose dependency appeared to be less pronounced for the psychological effects as they were rated by the subjects themselves (HRS and APZ-OAV) compared to the clinician ratings (SAPS, SANS and SPI-A). The most probable explanation for this relative discrepancy is that the effects of the low dose were already so impressive to the subjects that the difference between the low and the high dose was less prominent and failed significance for most subscales. Nevertheless, the global intensity of the hallucinogenic effects of both drugs was similar. This is reflected in the similar global scores of

the APZ-OAV questionnaire and the similar intensity subscale scores of the Hallucinogen Rating Scale HRS. However, there were distinct differences in the psychological profiles of the two drugs: Overall, phenomena that resemble positive symptoms of schizophrenia were more pronounced after DMT, which is reflected by the significant effects of substance for the SAPS global score, as well as SAPS subscores for positive thought disorder and inappropriate affect. Visual phenomena were also more pronounced after DMT, which is reflected by significant or marginal effects of substance for visionary restructuration (VUS subscale of APZ-OAV), the hallucinations subscale of the SAPS and the perception subscale of the HRS. Notably, explorative correlational analyses of these data sets failed to demonstrate significant associations between the scores (data not shown). This may be best explained by the fact that the three subscales (APZ-OAV VUS, SAPS hallucinations and HRS perception) have some overlap, but they also include several items which are unique to them compared to the other two scales. Therefore, the lack of correlations between the scores on these scales does not question the statement that visual phenomena between drugs were different.

In contrast, phenomena that resemble negative symptoms of schizophrenia were clearly more pronounced after (S)-ketamine, which is reflected by the significant effects of substance for the SANS global score, affective blunting, avolition and avolition-apathy and for the SPI-A subscale score for emotional deficits. Similarly, cognitive problems such as difficulties with concentration and short-term memory were more pronounced after (S)-ketamine, which is reflected by the significant effects of substance for the SANS attention subscale score and the SPI-A subscale scores for cognitive impediments and cognitive disturbances. Clearly, the psychometric data alone do not allow us to securely distinguish between negative/cognitive symptoms and sedative effects [40,41], and some of the (S)-ketamine phenomena could be viewed as sedation. However, as in the studies by Krystal et al. [40] the detailed descriptions of the (S)-ketamine state by the subjects suggest that they felt clearly more blunted, isolated and without energy and motivation, and less sedated. Finally, catatonia-like psychomotor phenomena beyond simple psychomotor retardation were prominent after (S)-ketamine, but almost absent after DMT. In most cases, extreme hypomimia, unnatural ways of moving limbs and unnatural postures were the most prominent differences between the DMT and (S)-ketamine state. These observations by the researchers are supported by the subjective descriptions of the (S)-ketamine state by the subjects themselves and they are in line with the psychometric data which showed significant effects of substance for four out of the five single items describing catatonia-like symptoms. Again, the psychometric data alone do not allow us to securely distinguish between catatonic symptoms and sedative effects or negative symptoms. Moreover, it should be noted that in this study we used no validated scale for the assessment of catatonic behavior. Therefore, interpretations of the psychometric data derived from the five single items should be cautious.

Our study is the first direct comparison of the psychological effects of a serotonergic and an antihypocretinergic hallucinogen in a double-blind experimental design. However, this study has methodological limitations that have to be acknowledged: First,

an inherent methodological problem concerns the limitation of comparisons of the effects of the two drugs. This is due to the uncertainty whether the doses used were really equivalent. Although the APZ-OAV global scores were similar for both drugs, this question cannot be answered definitely. Furthermore, due to inter-individual differences in the sensitivity to the effects of hallucinogens we decided to use flexible rather than fixed doses in order to obtain psychological effects of comparable intensity within the two dose regimens. Needless to say, this advantage is coupled with the disadvantage that it is impossible to draw firm conclusions on the effects of certain doses of the drugs. Second, the absence of a placebo condition is a further limitation that we decided to accept due to practical considerations: The fact that we would have needed a third experimental day for the placebo condition would have been critical for the recruitment of volunteers for our study. This problem is very significant because our subjects were full time professionals who had to take time from work to take part in our experiments without payment. Nevertheless, placebo controlled hallucinogen experiments have their own methodological problems, because the effects of hallucinogens are so prominent that blinding is not really possible [23]. Because of this and recognizing that the focus of this study was on the differential effects of the two drugs, we decided that, on balance, it was reasonable and acceptable to omit the placebo condition.

Most importantly, our sample was small and we used psychiatric staff as experimental subjects. This may result in an (unconscious) bias towards reports of effects that might have been known to the subjects from their work with patients and/or from the literature. In addition, most subjects had had some previous experiences with hallucinogenic drugs, which may also have influenced their reports. On the other hand, it is difficult to plan and obtain permissions for human experimental studies with hallucinogens, and the recruitment of suitable experimental subjects is a sensitive issue. Therefore, it would be rather unrealistic to plan studies with larger samples. Also, different samples of volunteers who are not professionals in the psychiatric field would be likely to have their own biases (are people who volunteer to participate in such studies representative, "average" subjects?), and, in fact, it would be impossible to recruit a reasonable number of volunteer subjects to participate in research studies with hallucinogens having no previous experience with such drugs. Finally, we did not perform drug screens on the days of the experiments and this may also be viewed as a methodological limitation of our study. However, the reported period of abstinence from previous experimental use of hallucinogens or stimulants has been several years, and biography as well as social and professional status of all subjects were in line with our impression that their accounts were absolutely plausible and reliable. Nevertheless, the subject-related methodological limitations of our study may account for biases regarding the overall intensity of the drug effects. However, it is rather unlikely that they will account for the differences between the effects of the two hallucinogens, which is the main focus of our study.

Taken together, although methodological caveats have to be taken into account, the data from the present study support our hypothesis that the NMDA antagonist model of psychosis is not globally superior to the LSD-type model. Rather, the two models

portray different aspects of psychoses of the schizophrenia spectrum. In line with our hypothesis, the LSD-type hallucinogen DMT induced more phenomena which resemble positive symptoms, while (S)-ketamine induced more phenomena which resemble the negative and cognitive symptoms of schizophrenia.

Conclusion

The 5HT_{2A} agonist or LSD-type model and the NMDA receptor antagonist or PCP-type model portray different aspects or subtypes of the heterogeneous disorder schizophrenia: the LSD-type drug DMT induced more phenomena which resemble positive symptoms. Therefore, the LSD-type model may refer to paranoid-hallucinatory psychoses and brief psychotic disorders. (S)-Ketamine induced more phenomena which resemble the negative and cognitive symptoms of psychoses. Hence, the PCP-type model may refer to the undifferentiated and possibly also to the catatonic subtypes of schizophrenia. Our data are in line with the view that a heterogeneous disorder like schizophrenia is unlikely to be modeled accurately by a single pharmacological agent. The availability of more than one model for the different subtypes of schizophrenia may provide the basis for laboratory-based explorations into the neurobiological and cognitive bases of different psychotic syndromes and into symptom-specific therapeutic approaches.

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