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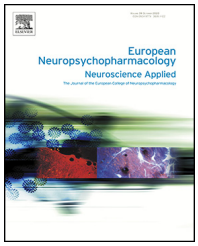

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Comparative effects of (*S*)-ketamine and racemic (*R/S*)-ketamine on psychopathology, state of consciousness and neurocognitive performance in healthy volunteers

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Abstract
Ketamine and its (*S*)-enantiomer show distinct psychological effects that are investigated in psychiatric research. Its antidepressant activity may depend on the extent and quality of these psychological effects which may greatly differ between the enantiomers.
Previous data indicate that the (*S*)-ketamine isomer is a more potent anesthetic than (*R*)-ketamine. In contrast, in subanesthetic doses (*R*)-ketamine seems to elicit fewer dissociative and psychotomimetic effects compared to (*S*)-ketamine.
In this randomized double-blind placebo-controlled trial the effects of (*R/S*)-ketamine and (*S*)-ketamine on standardized neuropsychological and psychopathological measures were compared. After an initial bolus equipotent subanesthetic doses of (*R/S*)- and (*S*)-ketamine or placebo were given by continuous intravenous infusion to three groups of 10 healthy male volunteers each ($n = 30$).

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(*R*/*S*)-Ketamine and (*S*)-ketamine produced significant psychopathology and neurocognitive impairment compared to placebo. No significant differences were found between (*R*/*S*)-ketamine and (*S*)-ketamine. (*S*)-Ketamine administration did not result in reduced psychopathological symptomatology compared to (*R*/*S*)-ketamine as suggested by previous studies. However, this study revealed a somewhat more "negatively experienced" psychopathology with (*S*)-ketamine, which opens questions about potential "protective effects" associated with the (*R*)-enantiomer against some psychotomimetic effects induced by the (*S*)-enantiomer.

As the antidepressant effect of ketamine might depend on a pleasant experience of altered consciousness and perceptions and avoidance of anxiety, the ideal ketamine composition to treat depression should include (*R*)-ketamine. Moreover, since preclinical data indicate that (*R*)-ketamine is a more potent and longer acting antidepressant compared to (*S*)-ketamine and (*R*/*S*)-ketamine, randomized controlled trials on (*R*)-ketamine and comparative studies with (*S*)-ketamine and (*R*/*S*)-ketamine are eagerly awaited.

1. Introduction

Psychopharmacological research carried out with the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine included the investigation of schizophrenia-like psychotic states (model psychosis) (Gouzoulis-Mayfrank et al., 2005; Honey et al., 2006) modeling of dissociative states of consciousness (Chambers et al., 1999). Furthermore, several studies have shown that treatment resistant depression (TRD) improves significantly during and after infusions of subanesthetic doses of (*R*/*S*)-ketamine (Berman et al., 2000; Kudoh et al., 2002; Rasmussen et al., 2013) either as single-dose or repeated doses (Zarate et al., 2006; aan het Rot et al., 2010; Murrough et al., 2013; Shiroma et al., 2014).

Ketamine is usually used as a racemic mixture, i.e. (*R*/*S*)-ketamine. For over 20 years, use of the more potent (*S*)-enantiomer (White et al., 1985) (Ketanest S®) by anesthesiologists has become a preferred option due to the assumption of increased anesthetic and analgesic properties, a more suitable control of anesthesia, and of an improved recovery from anesthesia (Hempelmann and Kuhn, 1997). In TRD response rates after infusions of (*S*)-ketamine (0.4 and 0.2 mg/kg) or (*R*/*S*)-ketamine (0.5 mg/kg) were as high as 67% (Singh et al., 2016) or 91.6% (Shiroma et al., 2014), respectively, but "response" has been defined differently in these studies. An intransal (*S*)-ketamine preparation was developed and in 2019, the US FDA and EMA approved for TRD (FDA, https://www.fda.gov, 2019, EMA, https://www.ema.europa.eu, 2019). However, as only two of the five approval studies demonstrated positive results and due to the risk of serious adverse effects, approval was restricted under the Risk Evaluation and Mitigation Strategy (FDA, https://www.fda.gov, 2019, EMA, https://www.ema.europa.eu, 2019).

The use of ketamine in anesthesia and psychiatry may be accompanied by the manifestation of somatic and especially psychotomimetic symptoms such as perceptual disturbances, experiences of dissociation, euphoria, and anxiety (Short et al., 2017).

There is an ongoing and controversial debate whether the amount extent of dissociative symptoms might be a clinical biomarker to predict ketamine's efficacy in TRD (Aust et al., 2019; Ballard and Zarate Jr., 2020). A recent study using a large sample size showed that "floating" as a subtype of dissociation was not associated with its antidepressant response (Acevedo-Diaz et al., 2020). In a systematic review only three of eight trials (37.5%) found a correlation between ketamine's dissociative and psychotomimetic effects with depression changes (Mathai et al., 2020). Therefore, as a very recent review on this topic frames, the relationship between dissociation and ketamine is still an unresolved issue and needs a broader research approach across preclinical models, neural systems, and cognitive processes (Ballard and Zarate Jr., 2020).

For the purpose of anesthesia, these dissociative and psychotomimetic symptoms are managed by simultaneous application of benzodiazepines so that complete unconsciousness is induced. In cases where sub-anesthetic doses are employed within the psychopharmacological research setting and the treatment of depression, however, co-administration of other substances might be undesirable as ketamine's acute psychological effects are a prerequisite of answering the research question and may help to produce the antidepressant response (Aust et al., 2019), respectively. Aust et al. (2019) showed in a cohort of 31 patients with TRD, who were treated with three ketamine infusions per week (0.5 mg/kg over 40 min) administered for two consecutive weeks, that the 14 non-responders experienced significant ketamine-induced anxiety. Moreover, Stocker et al. (2019) observed that ketamine-induced feeling of lightness according to breaking through emotional barriers were associated with antidepressant benefits. Therefore, in these circumstances, ketamine preparations and doses associated with a balanced mixture of psychological effects are even more important and desirable.

Earlier studies indicated lower psychotomimetic activity of (*S*)-ketamine versus equipotent doses of (*R*/*S*)-ketamine (Adams et al., 1992a; Engelhardt et al., 1994). (*S*)-Ketamine showed increased hypnotic and analgesic potency and reduced recovery time versus (*R*)-ketamine (White et al., 1980, 1985). Furthermore, compared to (*R*/*S*)-ketamine, (*S*)-ketamine showed less drowsiness, less lethargy and less impairment of cognitive capacity (Muller et al., 2016; Pfenninger et al., 2002). For this reason, (*S*)-ketamine is widely used in anesthesia.

The pharmacodynamics of ketamine cannot be fully explained by a single mechanism alone. A complex pattern of interactions involving opioid receptors, monoaminergic and cholinergic systems is known. NMDA receptor antagonism, however, is understood to play a key role in its mechanism of action (Adams, 1998). Ketamine's interactions with opioid receptors have a possible role in the induction of psychotomimetic effects. (*S*)-Ketamine has a higher affinity to the sigma receptor than (*R*)-ketamine, which implies some action on this receptor at subanesthetic doses (Hustveit et al., 1995).

More recently, activation of the brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) signaling and synaptogenesis via AMPA receptors are identified as the proposed cellular mechanisms for antidepressant effects (Yang et al., 2018). Both, (*S*)-ketamine and (*R*)-ketamine and their relevant metabolites, activate AMPA receptors, although they seem to engage different intracellular pathways. Moreover, from animal data it can be assumed that in contrast to (*S*)-ketamine, (*R*)-ketamine elicit a more sustained antidepressant effect through increased synaptogenesis in selected brain regions (Yang et al., 2015). In fact, a small open-label pilot study suggested that (*R*)-ketamine might be associated with rapid-acting antidepressant and sustained antidepressant actions in TRD patients (Leal et al., 2020).

The present study was designed to systematically compare the psychological effects of equipotent doses of (*R*/*S*)- and (*S*)-ketamine using validated psychopathological rating scales and neurocognitive tests. An intravenous administration route was used because of a very high first pass metabolism of ketamine and a much higher production of one of the major (active) metabolite nor-ketamine, when ketamine is given by the oral route. In contrast to other studies, it was avoided to consider declining plasma levels during testing by employing a steady infusion technique after administration of an initial bolus.

2. Experimental

2.1. Subjects

The ethical committee of Hannover Medical School (IRB) approved the study-protocol as outlined below. Thirty healthy male volunteers (physicians/medical students) were recruited by notice within the university. Written informed consent was provided and the option to withdraw from the study was available at any time without disclosure of reasons. Subjects were aged 25.83 years ($\pm$ 3.41 SD) and had a mean IQ of 120 as determined with the multiple-choice vocabulary intelligence test (Mehrfachwahl-Wortschatz-Intelligenztest B (MWT-B)) (Lehrl, 2005) (score 33.00 $\pm$ 2.03; percent range 88.6). All subjects were medically screened and excluded from the study, if either a history of serious medical or psychiatric problems were present, such as alcohol and drug abuse, psychopharmacological medication, seizures, or an IQ $<$ 90. 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 before entry into the study.

2.2. Experimental design

A double-blind placebo-controlled study was performed (n = 30). Sample size calculations were modelled on the BPRS scores of the Krystal et al. (1994) study. Based on this we hypothesized a Cohen's d of 0.4. Assuming 3 groups, an alpha of 0.05, and a power of 80% sample size calculation resulted in a number of 6 participants per group. Due to the equivalent doses of (*R*/*S*)-ketamine and (*S*)-ketamine we presumed fewer differences between the groups compared to the model of "low dose" and "high dose". Therefore, we increased the sample size to 10 healthy volunteers in each group, a magnitude, which is also in line with our earlier cross-over trial (Passie et al., 2005). However, in respect to psychopathological and neurocognitive measures the magnitude of the differences between the subanesthetic doses of (*R*/*S*)-ketamine and (*S*)-ketamine were largely unknown, what complicates sample size calculations.

Subjects received placebo (group 1, n = 10), (*R*/*S*)-ketamine (group 2, n = 10) or (*S*)-ketamine (group 3, n = 10) in a randomized order. All experiments were conducted in the early afternoon. Commercially available (*S*)-ketamine (Ketanest S®, Parke-Davis, Freiburg, Germany) and (*R*/*S*)-ketamine (Ketanest®, Parke-Davis, Freiburg, Germany) was used. In all subjects, an intravenous catheter (14 G Introcan®) was initially inserted into a cubital vein. (*S*)-Ketamine was diluted in 50 ml NaCl 0.9% solution. Continuous intravenous infusion was achieved using a syringe pump. Because of the large distribution volume of ketamine in the body, intravenous infusion commenced with a bolus of 0.1 mg/kg (*S*)-ketamine or 0.2 mg/kg (*R*/*S*)-ketamine, applied during a 5 min period and followed by a continuous infusion at 0.006 mg/kg/min (*S*)-ketamine or 0.012 mg/kg/min (*R*/*S*)-ketamine for 60 min. The 2:1 ratio of racemic to (*S*)-ketamine dosing was based on previously published pharmacodynamic studies, which evaluated the clinical potency for (*S*)-ketamine twice compared to (*R*/*S*)-ketamine (Schüttler et al., 1987; Vollenweider et al., 1997a; White et al., 1980, 1985). For the purpose of anesthesia, half the dose is used for (*S*)-ketamine compared to (*R*/*S*)-ketamine (Geisslinger et al., 1993; White et al., 1980).

In the context of TRD the 2:1 ratio of racemic to (*S*)-ketamine dosing is only weakly established. However, Singh et al. (2016) showed a robust antidepressant effect after 0.20 mg/kg IV (*S*)-ketamine similar to 0.40 mg/kg. Moreover, in a head-to-head comparative study of (*S*)-ketamine (0.25 mg/kg IV) and racemic ketamine (0.5 mg/kg IV) using the 2:1 ratio non-inferiority of (*S*)-ketamine in this dose was observed (Correia-Melo et al., 2020). The (*S*)-ketamine/(*R*/*S*)-ketamine dose was employed at subanesthetic levels to enable subjects to perform tests. NaCl 0.9% solution was used as placebo.

Ketamine plasma levels were assessed during the experiment. During the course of the experiment an anesthesiologist was present. Volunteers were told that they might receive a placebo or an active drug. Following initiation of infusion, subjects were instructed to take a supine position on a bed and be quiet to simulate a post-anesthetic situation. After 25 min, subjects changed to a sitting position to begin neurocognitive testing. After completion of the assessments, the infusion was stopped after 60 min and subjects were observed for the following hours.

2.3. Measurements

2.3.1. Analysis of (R/S)-ketamine and (S)-ketamine plasma levels

Venous plasma concentrations of (*R*/*S*)-ketamine and (*S*)-ketamine were measured by high performance liquid chromatography and ultraviolet detection (HPLC-UV) at 5, 30 and 60 min of the experiment using an established method (Adams et al., 1992b).

2.3.2. Clinician administered psychopathology

Clinician administered psychopathology was measured using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The BPRS scores were assessed blind by a single educated research psychiatrist at −15, 5, 30, 60, and 120 min of the experiment. BPRS baseline rating was done at −15 min. As described in Passie et al. (2005), total psychopathological symptoms were evaluated using the mean values of the five BPRS ratings. Clinical notes on the general reaction of the subjects were also taken by the blind clinician.

2.3.3. Self-administered psychopathology

Self-administered psychopathology was measured retrospectively with the five-dimensional questionnaire for the assessment of altered states of consciousness (5D-ASC) (Dittrich, 1998; Dittrich et al., 2006, 2010). Measurements took place 90–100 min after infusion was stopped. The 5D-ASC is a 94-item-questionnaire developed from the 3-dimensional questionnaire on the Abnormal Mental States questionnaire (APZ) (Dittrich, 1998), which was introduced for the quantitative assessment of altered states of consciousness (ASCs) in healthy subjects ($n = 393$) (Dittrich, 1985). External validation was obtained from an international study carried out in six countries ($n = 1133$) (Dittrich et al., 1985). The 5D-ASC questionnaire assesses 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'). The common denominator of the 5D-ASC is described by five oblique dimensions, designated as 'oceanic boundlessness (OSE)', 'dread of ego dissolution (AIA)', 'visionary restructuralization (VUS)', 'vigilance reduction (VIR)', and 'auditory alterations (AWV)'. Beneficial effects are associated with OSE and VUS (Studerus et al., 2010; Vlisides et al., 2018). OSE is referring to positively experienced ego dissolution and VUS to perceptual alterations and altered meaning of percepts. In contrast, AIA, VIR, and AWV may be associated with adverse effects (Studerus et al., 2010; Vlisides et al., 2018). AIA is referred to anxious ego dissolution, VIR to sleepiness and reduction in self-control, and AWV to often distressing acoustic phenomena. A further description of the five oblique subscales of the 5D-ASC is given in Table 1. The reliability and validity of the scales are satisfactory (Dittrich, 1998; Dittrich et al., 2006, 2010)). The 5D-ASC is one of the most widely used self-report questionnaires for assessing subjective experiences of ASC (Studerus et al., 2010). Further, its advantage has been shown in evaluating subjective ketamine-induced consciousness alterations and experience (Vollenweider and Kometer, 2010). The 5D-ASC was applied 90–100 min after termination of the drug infusions.

2.3.4. Neurocognitive measures

The *Benton Visual Retention Test* is a standardized paper and pencil test of visual memory and visuomotor coordination (Benton, 1945). 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 testing condition involves the presentation of each of the ten geometric figures for 10 s, after which the subject attempts to draw the figure from memory (without time limit). The Benton Visual Retention Test is the most frequently used screening device for signs of organic cerebral dysfunction (Kuzis et al., 1999).

The computerized neurocognitive testing sessions started at around 3.00 p.m. Tests were presented on a 17 inch computer screen. The subjects sat upright in front of the screen on a chair, which was adjusted to a level, which insured that the subject was placed at a distance of 50 cm in front of the center of the screen. The screen was set on a table, on which the two response panels for the two tests were positioned so that the subjects could easily handle the response buttons by using the dominant hand.

The *Go/NoGo Test* is standardized test to evaluate attentional functioning and the ability to suppress an inadequate reaction to a given stimulus. This ability attributed to the frontal cortex, will lead to erroneous reactions when frontal cortical functioning is disturbed. The test consisted of little squares filled with five different patterns. These squares were presented one at a time in a row for a short time on a computer screen. The subjects were then asked to react only to the two critical of the five patterns by pushing a button. Fifty different stimuli are presented (20 critical). Both errors and reaction time were assessed (Müller-Vahl et al., 2001).

The *Divided Attention Test* is 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 (Zimmermann and Fimm, 1989).

The *Reaction Time Test* measures motor and recognition reaction time, as well as total reaction time. It is part of the "Wiener Testsystem", a recognized neurocognitive testing battery. Reaction time and discriminatory function were assessed by asking subjects to press a button in response to the successive presentation of 15 specific single or combined visual/auditory stimuli. They were presented in randomized sequence as light (single visual stimulus) or tone (single auditory stimulus, 2400 Hz tones) or both. Subjects were instructed to push a button as quickly as possible when a specific constellation of combined stimuli (light plus tone) was present (Hasse-Sander et al., 1982).

The Signal Detection Test is a computerized visual searching task, based on the signal-detection theory. The test used is part of the "Wiener Testsystem". A varying pattern of dots is presented on the computer screens. A small portion of all dots disappears on one site and reappears on another at intervals of 750 ms. This leads to a stepwise change of the pattern of dots. The target stimulus is a square of dots within the overall pattern of dots; all other dot configurations are non-target stimuli or „noise". The target stim-

Table 1 A description of the five oblique subscales of the 5D-ASC.

Oceanic boundlessness (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 Example items: - It seemed to me that my environment and I were one. - I felt very happy and content for no outward reason.
Dread of ego dissolution (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. Example items: - I felt threatened without realizing by what. - I observed myself as though I were a stranger.
Visual restructuralization (VUS)	This subscale tries to assess subjective visual phenomena. It comprises elementary, amorphous 'primitive' optical phenomena. Following this, there may be organized scenic hallucinatory phenomena, sometimes accompanied by hypnagogic imagery and synesthesia. A third category consists of alterations in the meaning of things perceived in the environment. Example items: - I saw light or flashes of light in total darkness or with closed eyes. - I saw things that I knew were not real.
Reduction of vigilance (VIR)	This subscale 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. Example items: - My thoughts and actions were slowed. - I felt sleepy.
Auditory alterations (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. Example items: - I heard words without knowing where they came from. - A voice commented all what I thought.

uli are presented in each quadrant of the screen with the same probability. The subjects are required to respond as quickly as possible to the target stimulus, that is the formation of a square. There are 60 presentations of the target stimulus. The test lasts 15 min. The test indicates sustained attention, speed of information processing and vigilance (Schneider et al., 1999).

Neurocognitive measurements took place in the period between 30 and 60 min after starting the infusion. The sequence of the neurocognitive tests was as follows:

1. Benton Visual Retention Test
2. Go/NoGo
3. Divided attention
4. Reaction time
5. Signal detection

2.3.5. Statistical analysis

Data analyses were performed using SPSS (Statistical Package for the Social Sciences), version 21.0. One-factor ANOVA with Post hoc Bonferroni adjusted tests was used to evaluate differences between groups. The dependent variable in each model is the respective score value of the psychological test and the factor is the group assignment. Differences were considered significant below $p = 0.05$.

3. Results

3.1. General observations

The application of ketamine was well tolerated by most of the subjects but two subjects exhibited undesirable effects. During the first minutes of the bolus application, one subject described the experience as a "very strange altered state", which made it necessary to stop the experiment. The subject recovered very quickly. His-high body weight (100 kg) implied a high bolus dose, which may have been causative. The other subject displayed mutism during the first 15 min and was unable to communicate. The infusion was terminated and he recovered quickly. Nine subjects (7 in the (*R*/*S*)-ketamine and 2 in the (*S*)-ketamine group) developed nausea and vomiting during or shortly after changing from prone to sitting position. One of these subjects preferred to quit the experiment. The other eight subjects insisted on continuing the experiment and interpreted temporary nausea and vomiting as an insignificant affection. The three subjects not completing the experiment did not contribute any data to the study and were replaced by additionally recruited subjects. All subjects recovered completely from perceptible ketamine effects one hour after the end of infusion, i.e. 120 min after the beginning of the experiment.

Table 2 (*S*)-ketamine and (*R*/*S*)-ketamine plasma levels during the experiment ($n = 30$). The mean plasma levels of (*R*/*S*)- and (*S*)-ketamine were within the expected 2:1 equivalent ratio after 60 min.

		5 Min. Mean ± SD	30 Min. Mean ± SD	60 Min. Mean ± SD
ketamine plasma levels (ng/ml)	Placebo	00.00	00.00	00.00
	(*S*)-ketamine	82.43 ± 57.94	109.57 ± 48.18	159.43 ± 73.95
	(*R*/*S*)-ketamine	138.00 ± 45.24	179.89 ± 38.09	300.33 ± 32.86

3.2. Plasma levels

(*R*/*S*)-Ketamine and (*S*)-ketamine plasma levels are shown in Table 2. A steady increase of mean ketamine plasma concentrations was observed during the experiments. The range of plasma levels were in the same range for both ketamine groups, but after 30 min the levels of (*S*)-ketamine where relatively higher compared to the levels for (*R*/*S*)-ketamine. At the 60 min time point, the plasma levels of both substances were within in the expected range. To evaluate possible influence of the ketamine plasma levels an analysis of variance was conducted with psychopathological and neurocognitive scores as target variables, groups as factors and the plasma level mean of the measurements at 30 and 60 min as covariates. The analysis did not show any significant effects of the group and plasma levels on psychopathological and neurocognitive measures.

3.2. Psychopathological measures

Fig. 1 shows ratings obtained for objective psychopathology using the BPRS indicating highly significant psychopathology for the (*S*)-ketamine group and significantly high scores for the (*R*/*S*)-ketamine group when compared to placebo. No significant differences were found in BPRS scores between both ketamine groups.

The self-ratings of subjective psychopathology using the 5D-ASC were highly significant in all subscores for both ketamine groups when compared to placebo. The only exception found was the AWV-subscore where a significant difference to placebo was demonstrated only for (*S*)-ketamine. In the OSE, AIA, VUS, VIR and AWV subscores (and the 5D-ASC total score), no significant differences between the ketamine groups were detected (Fig. 2, Table 3). Whereas (*S*)-ketamine produced (insignificantly) higher scores on AIA, VIR and AWV in comparison to (*R*/*S*)-ketamine, scores of OSE and VUS were highest with (*R*/*S*)-ketamine (Fig. 2, Table 3).

3.3. Neurocognitive measures

All neurocognitive test results are summarized in Table 4. The *Benton Test* for immediate visual recall showed no significant differences for (*S*)-ketamine in hits and errors compared to placebo. In contrast, (*R*/*S*)-ketamine produced a significant difference in hits and errors as compared to placebo. Comparison of both ketamine groups showed no significant difference.

The *Go/NoGo Test* for the ability of the prefrontal cortex to suppress inadequate visual-motor responses showed no significant difference but a trend was observed with regards

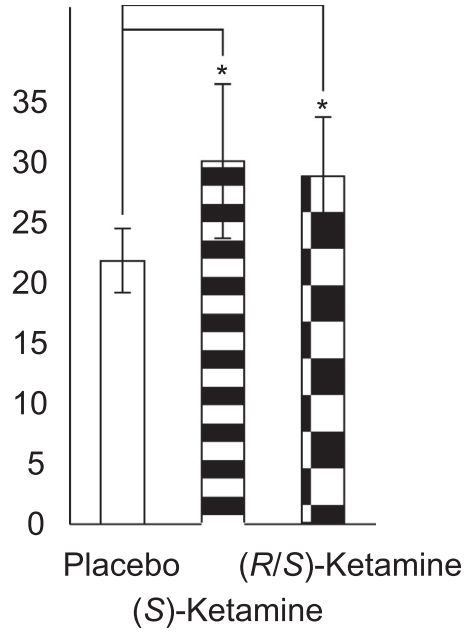

Fig. 1 Psychopathology measurements using the Brief Psychiatric Rating Scale (BPRS). Comparisons between the placebo group with the (*S*)-ketamine group and (*R*/*S*)-ketamine groups showed significant psychopathology. * Denotes significant level $p<0.002$ for placebo/(*S*)-ketamine and $p<0.010$ for placebo/(*R*/*S*)-ketamine using model of ANOVA with *Post hoc* Bonferroni tests. No significant differences were found in BPRS scores between both ketamine groups.

to hits for the (*R*/*S*)-ketamine group compared to placebo. No significant difference for hits was demonstrated comparing the (*S*)-ketamine to placebo. Comparison of both ketamine groups showed no significant difference. In respect to reaction time, a significant difference for both the (*S*)-ketamine as well as (*R*/*S*)-ketamine compared to placebo was found, but there was no significant difference between both ketamine groups.

The *Divided Attention Test* for sustained attention and psychomotor speed showed a significant difference in speed of reaction between (*S*)-ketamine, as well as (*R*/*S*)-ketamine compared to placebo. A comparison of both ketamine groups showed no significant difference. The omission score was highly significant for (*R*/*S*)-ketamine whereas (*S*)-ketamine showed only a trend in difference to placebo, but there was no significant difference between both ketamine groups.

The *Reaction Time Test*, an attention-related visual-motor speed task, revealed a highly significant difference between (*R*/*S*)-ketamine and (*S*)-ketamine in decision time

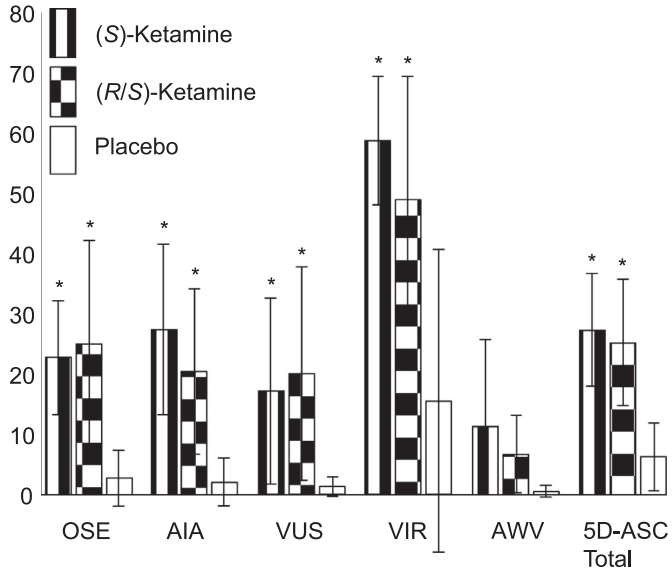

Fig. 2 Effects of (*S*)-ketamine and (*R*/*S*)-ketamine compared to placebo on subjective psychopathology/states of consciousness ($n = 30$) using the 5D-ASC questionnaire. Significant levels are summarized in Table 3.

Table 3 Results of ANOVA (between groups differences) and post hoc Bonferroni tests (multiple comparisons) on subjective psychopathology/state of consciousness.

5D-ASC-Scores	F-value	df	p-value	Substance	Mean	± SD	***Multiple comparisons: Bonferroni adjusted p* values**
Oceanic boundlessness (OSE)	11.079	2	<0.001	(*S*)-ketamine (*R*/*S*)-ketamine Placebo	22.80 25.01 2.79	9.51 17.13 4.68	(*S*)-ketamine/ (*R*/*S*)-ketamine: 1.000 Placebo/(*S*)-ketamine: 0.002 Placebo/(*R*/*S*)-ketamine: 0.001
Dread of ego dissolution (AIA)	12.699	2	<0.001	(*S*)-ketamine (*R*/*S*)-ketamine Placebo	27.37 20.44 2.06	14.10 13.77 3.91	(*S*)-ketamine/ (*R*/*S*)-ketamine: 0.579 Placebo/(*S*)-ketamine: <0.001 Placebo/(*R*/*S*)-ketamine: 0.004
Visual restruc-turalization (VUS)	5.482	2	0.010	(*S*)-ketamine (*R*/*S*)-ketamine Placebo	17.08 19.97 1.28	15.42 17.68 1.69	(*S*)-ketamine/ (R/S)-ketamine: 1.000 Placebo/(*S*)-ketamine: 0.045 Placebo/(R/S)-ketamine: 0.014
Reduction of vigilance (VIR)	13.247	2	0.042	(*S*)-ketamine (*R*/*S*)-ketamine Placebo	58.61 48.81 15.40	10.72 20.49 25.03	(*S*)-Ketamine/ (R/S)-ketamine: 0.826 Placebo/(*S*)-ketamine: <0.001 Placebo/(*R*/*S*)-ketamine: 0.002
Auditory alterations (AWV)	3.558	2	<0.001	(*S*)-ketamine (*R*/*S*)-ketamine. Placebo	11.30 6.68 0.52	14.34 6.33 1.01	(*S*)-Ketamine/ (*R*/*S*)-ketamine: 0.792 Placebo/(*S*)-ketamine: 0.039 Placebo/(*R*/*S*)-ketamine: 0.422
5D-ASC total score	17.411	2	<0.001	(*S*)-ketamine (*R*/*S*)-ketamine Placebo	27.25 25.13 6.30	9.36 10.48 5.63	(*S*)-ketamine/ (*R*/*S*)-ketamine: 1.000 Placebo/(*S*)-ketamine: <0.001 Placebo/(*R*/*S*)-ketamine: <0.001

compared to placebo. No significant was found between both ketamine groups. A significant difference for (*R*/*S*)-ketamine and (*S*)-ketamine groups compared to placebo was found for motor time but no significant difference between both ketamine groups.

The *Signal Detection Test* for sustained attention and vigilance showed a significant difference in hits for (*R*/*S*)-ketamine and (*S*)-ketamine when compared to placebo. There was no significant difference between both ketamine groups. Detection time was significantly different for (*R*/*S*)-ketamine and for (*S*)-ketamine compared to placebo but there was no significant difference between both ketamine groups. As mentioned before, analysis of variance with psychopathological and neurocognitive scores as goal variables and both groups as factors and the plasma level mean of the 30 and 60 min measurements showed no significant

Table 4 Results of ANOVA (between groups differences) and post hoc Bonferroni tests (multiple comparisons) on neuropsychological tests ($n = 30$).

Neurocognitive measures A B		F-value	df	p-value	Substance	Mean A B	± SD A B	*Multiple comparisons: Bonferroni adjusted p* values A/B
Benton Test	Hits	5.706	2	0.009	(*S*)-ketamine	6.50	1.84	(*S*)-ketamine/(R/S)-ketamine:
	Errors	48.933	2	0.006		4.40	2.41	0.437/0.147
					(*R*/*S*)-ketamine	5.30	2.21	
						7.00	3.97	
					Placebo	8.00	1.15	Placebo/(*S*)-ketamine
						2.60	1.51	0.216/0.495
								Placebo/(*R*/*S*)-ketamine:
								0.007/0.005
Go/NoGo	Hits	2.885	2	0.074	(*S*)-ketamine	23.00	0.67	(*S*)-ketamine/(*R*/*S*)-ketamine:
	Mean [ms]	6.594	2	0.005		614.33	75.92	0.348/1.000
					(*R*/*S*)-ketamine	22.30	1.42	
						645.35	92.74	
					Placebo	23.33	0.50	Placebo/(*S*)-ketamine:
						516.96	67.19	1.000/0.040
								Placebo/(*R*/*S*)-ketamine:
								0.082/0.005
Divided attention	Mean [ms]	8.326	2	0.002	(*S*)-ketamine	778.65	61.68	(*S*)-ketamine/(R/S)-ketamine:
	Omissions	11.224	2	<0.001		4.30	2.75	1.000/0.830
					(*R*/*S*)-ketamine	815.78	109.50	
						7.30	4.08	
					Placebo	665.75	78.78	Placebo/(*S*)-ketamine:
						1.20	0.79	0.020/0.069
								Placebo/(R/S)-ketamine:
								0.002/<0.001
Reaction time	Decision time [ms]	6.336	2	0.006	(*S*)-ketamine	519.60	102.42	(*S*)-Ketamine/(R/S)-ketamine:
	Motor time [ms]	5.100	2	0.013		191.20	62.73	1.000/1.000
					(*R*/*S*)-ketamine	501.40	62.27	
						185.80	41.82	
					Placebo	399.80	73.26	Placebo/(*S*)-ketamine:
						122.40	54.08	0.008/0.024
								Placebo/(*R*/*S*)-ketamine:
								0.028/0.040
Signal detection	Hits	7.048	2	0.004	(*S*)-ketamine	46.33	7.37	(*S*)-Ketamine/(*R*/*S*)-ketamine:
	Detection time mean [s]	7.116	2	0.003		1.12	0.23	1.000/1.000
					(*R*/*S*)-ketamine.	43.70	8.73 0.22	
						1.08		
					Placebo	54.60	2.72	Placebo/(*S*)-ketamine:
						0.82	0.09	0.039/0.007
								Placebo/(*R*/*S*)-ketamine:
								0.004/0.014

effect of the group and plasma level on neurocognitive results.

4. Discussion

4.1. Clinician administered outcomes

(*R*/*S*)-Ketamine and (*S*)-ketamine, intravenously given, did not demonstrate different properties on psychopathological (BPRS) or neurocognitive outcomes in young healthy volunteers. It appears that (*S*)-ketamine leaves neurocognitive abilities somewhat more intact than (*R*/*S*)-ketamine (Table 4), which is in line with previous findings (Doenicke et al., 1992; Pfenninger et al., 1994, 2002). A possible explanation lies in the fact that studies have demonstrated more circumscribed alterations of brain activity induced by (*S*)-ketamine compared to with (*R*/*S*)-ketamine (Breier et al., 1997; Malhotra et al., 1996; Vollenweider et al., 1997a, 2000) (see also section 4.4).

Furthermore, in anesthesia settings using *anesthetic* doses of different ketamine preparations, overall, (*S*)-ketamine may lead to a better perioperative performance compared to (*R*/*S*)-ketamine (White et al., 1980). However, when used in *subanesthetic* doses it seems to be reversed (Mathisen et al., 1995). Even in the anesthesia setting,

patients who received (*R*/*S*)-ketamine had more pleasant and fewer unpleasant experiences during dreaming compared to (*S*)-ketamine (White et al., 1980).

In addition, the majority of previous experimental studies implemented a one-bolus administration model (Adams et al., 1994, 1992a; Engelhardt, 1997; Pfenninger et al., 1994, 2002). Due to the large volume of distribution associated with enantiomeric forms of ketamine, rapid (and undetected) declines in plasma levels during the testing period might be expected. This is especially problematic when stereoselective metabolism is taken into account (Persson et al., 2002). A faster elimination of (*S*)-ketamine compared to (*R*/*S*)- or (*R*)-ketamine has been demonstrated (Geisslinger et al., 1993). For this reason, we employed a continuous infusion model followed by the determination of plasma levels.

The dosing scheme was decided based on reports in the literature, which have shown equivalent clinical effects with a 2:1 (*R*/*S*)- to (*S*)-ketamine dosing on EEG (Ihmsen et al., 2001) and in surgical anesthesia (White et al., 1980, 1985; Geisslinger et al., 1993). (*S*)-Ketamine has a higher systemic clearance when given alone compared to the racemic mixture, which suggests an inhibition of (*S*)-ketamine clearance by the (*R*)-enantiomer (Geisslinger et al., 1993; Ihmsen et al., 2001; Persson et al., 2002). In the present study, the plasma level of (*S*)-ketamine was observed to be 10 to 20% higher than expected after 30 min but the mean plasma levels of (*R*/*S*)- and (*S*)-ketamine were within the expected 2:1 ratio after 60 min. Consequently, the major part of the neurocognitive testing was conducted during a period with appropriate plasma levels. An analysis of variance did not show significant effects of group and plasma levels on psychopathological and neurocognitive measures.

Since many previous studies have been evaluated through the eyes of anesthesiologists or within anesthesia settings, the research questions have been devoted more to untoward interpretations of altered consciousness and cognitive capacity. This may have led to the use of test instruments unable to explore effects in more depth. For example, neither the APZ nor the 5D-ASC or other self-administered tests have been used and neurocognitive measurements included less validated tests (Pfenninger et al., 2002).

4.2. Self-administered psychopathological outcomes

In the present study 5D-ASC ratings for psychopathology showed a congruent pattern with significant higher scores of both ketamine preparations compared to placebo and no significant differences between (*R*/*S*)- and (*S*)-ketamine. Interestingly, (*R*/*S*)-ketamine administration resulted in higher values reflecting the beneficially attributed dimensions OSE and VUS (Studerus et al., 2010; Vlisides et al., 2018), whereas the adversely assigned dimensions AIA, VIR, and AWV were highest, when (*S*)-ketamine has been given. Thus, it seems that the (*R*)-enantiomer was able to balance the (*S*)-enantiomer's adverse parts of the altered state of consciousness and promoting positive psychedelic experiences, so that a more coherent state of consciousness is experienced. The overall altered state of consciousness includes more than single patterns of subjective experience such as global misrepresentation and the context in which the phenomenal experience emerges (Revonsuo et al., 2009). In the ketamine-evoked altered state of consciousness the adjunct of the (*R*)-enantiomer seems to support the integration and evaluation of the sensory, affective and cognitive environment to a more desirable background mechanism and to mediate the relationship to the outer world more positively.

This conclusion is supported by a negative functional MRI (fMRI) response pattern in conscious rats treated with (*R*)-ketamine (see also section 4.4), and the absence of producing hyperlocomotion, deficits in prepulse inhibition, and maladaptive reward sensitivity compared to rats after administration of (*S*)-ketamine or (*R*/*S*)-ketamine (Masaki et al., 2019; Yang et al., 2015). Compared to (*S*)-ketamine, (*R*)-ketamine seems to produce abuse-related effects at doses much higher than the antidepressant dose (Zanos et al., 2019) and dissociative and psychotomimetic effects has been attributed mainly to the actions of (*S*)-ketamine (overview in Zanos et al., 2018) (see also section 4.3). In addition, (*R*)-ketamine seems to be a more potent and longer acting antidepressant compared to (*S*)-ketamine and (*R*/S)-ketamine (Chang et al., 2019; Hashimoto, 2019; Wei et al., 2020). Furthermore, different research groups demonstrated that the active metabolite (2*R*,6*R*)-hydroxynorketamine (HNK) of (*R*)-ketamine might play a role in the potency and the sustained antidepressant-like effects (overview in Hashimoto, 2019 and Hillhouse et al., 2019). (*R*)-Ketamine has approximately three to four-fold lower affinity for blocking the NMDA receptor compared to (*S*)-ketamine and therapeutically relevant concentrations of (2*R*,6*R*)-HNK do not bind to or directly inhibit NMDA receptors (Jelen et al., 2020). These findings question the role of NMDA receptor antagonism as the only or main mechanism for the antidepressant effects of ketamine. Alternative molecular targets have been suggested, e.g. such as AMPA receptor-dependent signaling cascade resulting in BDNF-TrkB signaling and finally increased synaptogenesis (see also section 4.4) or, for example, improvement of gut microbiota composition resulting in antidepressant actions mediated by the brain-gut-microbiota axis (Hashimoto, 2020). The small open-label pilot study of Leal et al. (2020) is insufficient to prove the antidepressant efficacy of (*R*)-ketamine in TRD patients. Randomized controlled studies (RCTs) on (*R*)-ketamine and direct comparison of the safety and efficacy of (*R*)-ketamine and (*S*)-ketamine in TRD will be of great importance (Jelen et al., 2020).

Taken together, animal and human studies suggest that both (*R*)-ketamine and (*S*)-ketamine might complementarily or synergistically contribute to the antidepressant effects of ketamine based on different neurobiological mechanisms (Jelen et al., 2020). In relation to the experience of psychotomimetic symptoms and their potential contribution to the antidepressant effects, (*R*)-ketamine alone or (*R*)-ketamine dominant variants (e.g. 2:1 to 4:1 ratio of (*R*)-ketamine:(*S*)-ketamine) might therefore be more suitable to produce an anxiety-free and pleasant altered consciousness and perceptions creating profound and long-lasting antidepressant effects.

4.3. Psychopathological outcomes of subanaesthetic ketamine in previous studies

The findings of the present study are consistent with results from a very recent systematic review and meta-analysis including 725 healthy volunteers exposed to racemic ketamine or (*S*)-ketamine compared to placebo (Beck et al., 2020). There were no significant differences observed in the BPRS and the Positive and Negative Syndrome Scale (PANSS). Interestingly, (*S*)-ketamine showed larger effect sizes than (*R*/*S*)-ketamine and psychotomimetic symptoms, mainly symptoms of the positive scale, were more pronounced when ketamine was given as a bolus. However, the clinician administered scores BPRS and PANSS are not adequate to evaluate the altered state of consciousness.

In a study on 9 patients with acute orofacial pain and 7 patients with chronic neuropathic orofacial pain, subanesthetic doses of both (*R*/*S*)-ketamine (0.9 mg/kg i.m.) and (*S*)-ketamine (0.45 mg/kg i.m.) showed a comparable prevalence of dizziness and illusions, approximately 30% more proprioceptive disturbances and altered hearing with (*S*)-ketamine compared to (*R*/*S*)-ketamine, whereas dreams and hallucinations were only observed with (*R*/*S*)-ketamine and not with (*S*)-ketamine or (*R*)-ketamine (Mathisen et al., 1995). In a group of 6 healthy volunteers, Øye et al. (1992) showed that (*S*)-ketamine at a dose of 0.2 mg/kg i.v. elicited proprioceptive disturbances in all test persons compared to 2 volunteers with (*R*)-ketamine at 0.8 mg/kg i.v.. These proprioceptive disturbances were often characterized as “floating in the air” and appeared to be associated with drowsiness. In another trial, 10 healthy volunteers received a bolus of either 15 mg (*S*)-ketamine or (*R*)-ketamine followed by a continuous infusion of subanesthetic doses (Vollenweider et al., 1997a). (*S*)-Ketamine produced acute psychotic reactions including depersonalization and derealization phenomena, flattened affects and emotional withdrawal (Vollenweider et al., 1997a). Furthermore, the results of the mood rating scale (Eigenschaftswörterliste) showed negative and dysphoric feelings and anxiety. Overall, emotional changes ranged from euphoria (30%), indifference (30%) or heightened anxiety (40%) (Vollenweider et al., 1997a). In contrast, given in equipotent doses (*R*)-ketamine did not produce any psychotic symptoms, but instead a state of relaxation and well-being, that was characterized by facilitated introspection and a slight change in the time, comparable to a meditative state (Vollenweider et al., 1997a).

4.4. Mechanism of ketamine on psychopathological and neurocognitive outcomes

Different effects of (*S*)-ketamine and (*R*)-ketamine on brain metabolism and brain regions may account for their differences in clinical outcomes. In studies on patients diagnosed with schizophrenia with auditory hallucinations, an activation of the temporomedial cortex was demonstrated (Liddle et al., 1992). (*S*)-Ketamine increased metabolism in this brain region (Vollenweider et al., 1997a) whereas (*R*)-ketamine was observed to reduce brain metabolism (Liddle et al., 1992). In humans, (*S*)-ketamine increases metabolic activity in most cortical brain regions, whereas (*R*)-ketamine decreases brain glucose metabolism in the corresponding brain regions (Vollenweider et al., 1997a). In case of (*R*/*S*)-ketamine, however, similar increases in regional brain metabolism comparable to (*S*)-ketamine were reported (Vollenweider et al., 1997a). A potential explanation for the fact that adding the (*R*)-enantiomer to the (*S*)-enantiomer did not lead to increased psychopathology compared to the (*S*)-enantiomer alone, might be reflected in (holistic) dynamics of cortical-subcortical patterns that might be functioning in a more “harmoniously concerted" way, i.e. the balance between different brain activations and deactivations might be closer to the organism‘s usual homeostasis. For example, it appears possible that (*R*)-ketamine indirectly induces a somewhat augmented subcortical arousal ("limbic activation") by suppressing some of the increases of cortical metabolism induced by (*S*)-ketamine as suggested by the results of Vollenweider et al. (1997a; 1997b). Subjectively, this may lead to a more tolerable pattern of psychopathological side effects, which is especially relevant to patients in other than surgical settings involving subanesthetic doses and without the additional administration of benzodiazepines as is commonly the case for the treatment of TRD. In line with these observations are fMRI findings on psilocybin, whose antidepressant effects have been convincingly shown (Romeo et al., 2020). The primary predictor of positively experienced ego dissolution was a reduction in hippocampal glutamate signaling, while the strongest predictor for acute psychedelic-induced anxiety was localized glutamate-induced hyperfrontality (Mason et al., 2020).

As outlined in the introduction, the proposed mechanism of ketamine‘s antidepressant action is conceived to involve a NDMA receptor-dependent glutamatergic AMPA receptor-dependent signaling cascade resulting in BDNF-TrkB signaling and finally increased synaptogenesis (Sanacora and Schatzberg, 2015). However, other mechanisms of action such as dopaminergic/sigma 1 interactions and serotonergic activity have been discussed (Sanacora and Schatzberg, 2015). Preclinical research on antidepressant effects of ketamine indicates that (*R*)-ketamine strongly activates the prefrontal serotonergic system through an AMPA receptor-independent way, whilst (*S*)-ketamine induces both, serotonin and dopamine release AMPA receptor-dependently (Ago et al., 2019).

4.5. Limitations

Several limitations have to be considered. The number of subjects enrolled in this pilot study might not have been large enough to detect small differences. In addition, there were no further study arms with (*R*)-ketamine or different (*R*/*S*)-ketamine-ratios. Therefore, the results of the present study might be used to design a trial with a larger number of subjects including other (*R*/*S*)-ketamine-ratios.

The study population displayed a relatively high mean verbal IQ (mean 120 on the MWT-B), which might have contributed to an improved ability to compensate for drug-induced effects on cognition, thus, limiting the generalizability of the results to larger populations.

Another limitation might be seen in the steadily increasing plasma levels, which may have altered the response of the subjects during the course of the experiment but this

might be counterbalanced by the nearly equivalent increase for both substances.

Lastly, in respect to hallucinatory activity, as measured by the VUS score of the 5D-ASC, (*S*)-ketamine has been demonstrated to have different effects in different settings. If an eyes-open condition is used, VUS scores were more than three times lower (Passie et al., 2003, 2005) than those obtained under eyes-closed condition as used in the present study (Table 3). Therefore, a different setting condition might have had a significant impact on some psychopathological symptoms.

Conclusion

In the present study, clinician administered and self-administered psychopathology as well as neurocognitive performance tests following administration of equipotent doses of (*R*/*S*)-ketamine and (*S*)-ketamine revealed no significant differences. However, compared to (*S*)-ketamine, (*R*/*S*)-ketamine administration resulted in a more pronounced effect that reflected beneficially attributed dimensions of the 5D-ASC. If the antidepressant effect of ketamine is associated with an anxiety-free and pleasant experience of altered consciousness and perceptions, the ideal ketamine preparation used treat TRD should include (*R*)-ketamine. Moreover, since preclinical data indicate that (*R*)-ketamine is a more potent and longer acting antidepressant compared to (*S*)-ketamine and (*R*/*S*)-ketamine, RCTs on (*R*)-ketamine and comparative studies with (*S*)-ketamine and (*R*/*S*)-ketamine are eagerly awaited.

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Contributors

Authors TP and HAA designed the study and wrote the protocol. Authors TP, FL, MK carried out the clinical experiments. Authors TP, MK, SDB managed the literature searches and analyses. Author BW undertook the statistical analysis, and author TP wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing interest

None.

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