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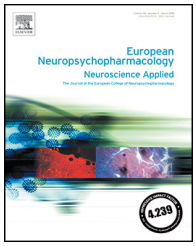

Anxiety during ketamine infusions is associated with negative treatment responses in major depressive disorder

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Abstract
About 20 to 30 percent of patients with Major Depressive Disorder (MDD) do not respond to standard treatment and are considered treatment-resistant. The N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine has demonstrated rapid antidepressant effects in treatment-resistant MDD, but it is unknown whether its acute psychological effects are related to the later antidepressant effect. Therefore, we investigated the association between antidepressant responses to ketamine and the quality of ketamine-induced psychological experiences in MDD. A total of 31 patients ($M = 49.5 \pm 11.2$ years, 16 women) were treated with three ketamine infusions per week (0.5 mg/ kg over 40 min) administered for two consecutive

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weeks. Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, after four and 24 h and at end of treatment. The 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) was applied four hours after the first infusion to assess the subjective quality of acute psychological effects. Patients with a $\geq$ 50% MADRS reduction from baseline to end of treatment were considered as responders. After six infusions, 17 of 31 patients (55%) showed a response to ketamine treatment, while 14 patients (45%) had no response. Anxiety-related experiences induced by ketamine were significantly higher in non-responders. Percentage MADRS reduction after four hours and individual levels of ketamine-induced anxiety were predictive of a response at end of treatment. The study demonstrated the considerable impact of ketamine-induced anxiety on the antidepressant efficacy of ketamine. It underpins the importance of considering patients' subjective experiences and underlines the possibility of a phenotypic response predictor.

1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent disorders worldwide (Whiteford et al., 2013). MDD does not only cause significant suffering but also leads to a growing economic burden (Greenberg et al., 2015). Despite years of intensive research, our current knowledge of its pathophysiology and aetiology remains limited (Otte et al., 2016). Albeit well treatable with psychopharmacological and psychotherapeutic approaches, about 20 to 30 percent of patients do not respond to standard treatment and are considered treatment-resistant (Olchanski et al., 2013). According to the National Institute of Mental Health STAR*D study (Warden et al., 2007), 33 percent of depressed patients do not achieve remission after four consecutive treatments with antidepressants. Although responses might be present within the first week (Taylor et al., 2006), the average time to remission is seven weeks, which is still considered one of the main limitations of antidepressants (Zarate et al., 2006). This points out the urgent need for pharmacological treatment alternatives and the necessity of developing strategies to reduce the delay of response and remission onset (Krystal et al., 2002).

The N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant MDD (Murrough et al., 2013a). Previous studies have shown that antidepressant effects induced by a single dose of ketamine can be observed within four hours with peak effects at 24 h lasting for several days (Bobo et al., 2016). There is growing evidence that repeated administrations can prolong antidepressant effects and are equally well tolerated as single-dose interventions (Andrade, 2017). Furthermore, there are data indicating that a rapid response to the first ketamine infusion assessed within four hours after treatment is predictive of a sustained antidepressant effect after a series of multiple infusions (Murrough et al., 2013b). Typical acute psychological side effects of intravenous ketamine administration (0.5 mg/kg over 40 min) include transient perceptual disturbances, experiences of dissociation (e.g. depersonalization or derealisation), euphoria, and anxiety (Short et al., 2017). These effects subside within several minutes after stopping a ketamine infusion and usually fully remit within two hours (Abdallah et al., 2016).

Although ketamine's antidepressant efficacy has been demonstrated by several randomized controlled trials (Murrough et al., 2013a; Price et al., 2014; Wan et al., 2015), little is yet known about its antidepressant mechanisms. Also clinical and behavioural patient factors predictive of a response are widely unknown. Based on the notion of a "psychedelic treatment model" (Roseman et al., 2018), the question whether the quality of acute treatment experiences is associated with treatment efficacy has been addressed recently. Some studies reported that dissociative side effects were positively correlated with depressive symptom reduction within four hours and at seven days post-infusion (Luckenbaugh et al., 2014; Niciu et al., 2018). It was suggested that dissociation might result from an enhancement of glutamate release induced by ketamine. Given the important role of glutamate in the pathophysiology of depression and ketamine's assumed glutamate-based mode of action (Krystal et al., 2013), it was concluded that the amount of dissociative side effects might be a clinical biomarker to predict ketamine's efficacy. Other studies, however, were not able to replicate a significant association between ketamine-induced dissociation and antidepressant efficacy (Valentine et al., 2011; Wan et al., 2015), whereas the question of a direct link between ketamine's acute psychological effects and an antidepressant response is raised continuously in the literature (Walter et al., 2014).

A valid tool to assess different qualities of altered states experiences is the five-dimensional altered states of consciousness self-rating scale (5D-ASC; Dittrich, 1998). It has been applied in various clinical and non-clinical studies that are overviewed in an online database (http://alteredstatesdb.org/chart/). The 5D-ASC has also been shown to reliably measure ketamine-induced consciousness alterations and experiences (Vollenweider and Kometer, 2010) while clearly distinguishing between different qualities of experience such as oceanic boundlessness, anxious ego-disintegration or anxiety (Dittrich, 1998; Studerus et al., 2010).

Based on these considerations, the present study was designed to investigate the association between individual responses to a ketamine infusion series and the quality of ketamine-induced psychological experiences in MDD patients. It was hypothesized that responders and non-responders reported significantly different subjective experiences to ketamine. In addition, we aimed at replicating the previous finding (Murrough et al., 2013b) that an early response to the first ketamine infusion is predictive of the antidepressant effect at the end of treatment.

2. Experimental procedures

2.1. Sample

Female and male patients with a primary diagnosis of MDD in accordance with DSM-V criteria were recruited between April 2014 and December 2015. At the time of enrolment, all participants were inpatients at the Department of Psychiatry at Charité – Universitätsmedizin Berlin on two wards primarily specializing in the treatment of chronic and/or severe affective disorders. Patients were "treatment-resistant" being defined as two or more sufficient antidepressant treatment trials during the current episode without achieving remission. There were no restrictions regarding antidepressant medication at the time of enrolment, however, medication intake was documented. Exclusion criteria comprised lifetime antidepressant treatment with ketamine, lifetime recreational use of ketamine, cardiovascular diseases such as hypertension, cardiac insufficiency or myocardial infarct in the past six months, insufficiently treated anemia, hyper- or hypothyroidism, lifetime increased intracranial pressure or glaucoma, chronic physical diseases, in particular hepatorenal dysfunction, recent heart or head surgery, current pregnancy, as well as any relevant psychiatric or neurological comorbidity, in particular dementia, epileptic seizures (lifetime), schizophrenia (lifetime), psychosis (lifetime), or post-traumatic stress disorder (current). The data presented here were part of a larger antidepressant prediction study carried out in accordance with the latest version of the Declaration of Helsinki (clinicaltrials.gov identifier NCT02099630). The study was approved by the Institutional Review Board of Charité – Universitätsmedizin Berlin and all patients gave written informed consent before participation.

2.2. Treatment with ketamine

Ketamine treatment is part of the clinical routine in the treatment of chronic and/or severe affective disorders at the Department of Psychiatry, Charité – Universitätsmedizin Berlin. It can be offered to patients as an alternative to electroconvulsive therapy (ECT). Three ketamine infusions per week (0.5 mg/ kg over 40 min) were administered for two consecutive weeks. Thus, patients usually received a total of six infusions. Based on clinical evaluation, treatment was extendable to three weeks with a total of nine infusions.

2.3. Psychological assessment

All study procedures are listed in the schedule of enrolment, treatment, and assessments (see Table 1).

Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). The 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC; Dittrich, 1998) was used to assess the quality of acute psychological effects of the ketamine infusion. This self-report tool measures individual reactions to psychedelic substances on 96 items and comprises five dimensions (according to Dittrich, 1998): 1) oceanic boundlessness (referring to a loss of ego boundaries associated with changes in the sense of time and emotions), 2) anxious ego-disintegration (including experiences of negative derealization, disturbed thinking and loss of body- and/or self-control), 3) visionary restructuralization (referring to perceptual alterations such as visual illusions and hallucinations), 4) acoustic alterations and 5) altered vigilance. A newer approach followed by Studerus and colleagues (2010) favors eleven lower order subscales instead: 1) experience of unity, 2) spiritual experience, 3) blissful state, 4) insightfulness, 5) disembodiment, 6) impaired control and cognition, 7) anxiety, 8) complex imagery, 9) elementary imagery, 10) audio-visual synesthesiae, and 11) changed meaning of percepts. Patients indicate the subjective alteration of consciousness compared to their general condition on a visual analogue scale.

Additional measures were used to characterize the sample of MDD patients and to explore potential differences between ketamine responders and non-responders. **BDI-II.** The Beck Depression Inventory, second version (Beck et al., 1996), is an improved revision of the original BDI, one of the most widely used self-report instruments to assess depression severity. Each of the 21 items is scaled from 0 to 3 with higher scores indicating more severe depression. **SHAPS-D.** The Snaith-Hamilton Pleasure Scale (Snaith, 1993) assesses the hedonic capacity of the participants during the course of the treatment. It relies on self-report information and consists of 14 items. **BHS.** The Beck Hopelessness Scale (Beck et al., 1974) was designed to measure three major aspects of depression-associated hopelessness: feelings about the future, loss of motivation, and expectations. It is a self-report scale and consists of 20 items. **RSQ-D.** The Response Styles Questionnaire (Kühner et al., 2007) assesses individual cognitive and behavioral styles to cope with depressed or dysphoric mood. It comprises 23 items on two subscales: rumination and distraction. **NEO-FFI.** Personality traits were assessed using the NEO five-factor inventory (Costa and McCrae, 1992) with the following five dimensions: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. It has 60 items. **STAI.** The State Trait Anxiety Inventory (Spielberger et al., 1983) consists of 40 questions on a self-report basis. The STAI measures state anxiety, i.e. anxiety about an event, and trait anxiety, i.e. anxiety as an individual characteristic. **MWT-B.** The multiple-choice word test (Lehrl, 2005), which is functionally equivalent to the widely used National Adult Reading Test (Nelson and O'Connell, 1978), is a measure for intelligence.

2.4. Statistical analysis

The percentage change in MADRS scores from baseline to the end of ketamine treatment was calculated for each patient. Patients were considered as "responders" if they had a $\geq$ 50% MADRS reduction at the end of treatment. All other patients were considered as "non-responders". We also calculated the percentage change in MADRS scores from baseline to 4 and 24 h after the first ketamine infusion as a measure for rapid treatment response. Chi-squared tests were used to assess associations between categorical variables. A repeated measures ANOVA was applied to test for significant changes in MADRS scores over time (baseline, after 4

Table 1 Schedule of enrolment, treatment, and assessments.

	Enrolment phase		Treatment phase		
	Screening Visit	Baseline Visit	4 h after 1st infusion	24 h after 1st infusion	after the last infusion (= end of treatment)
Informed consent	X				
Inclusion/exclusion criteria	X				
MADRS		X	X	X	X
5D-ASC			X		
BDI-II		X	X	X	
SHAPS-D		X		X	
BHS		X		X	
RSQ-D		X		X	
NEO-FFI		X			
STAI		X			
MWT-B		X			

MADRS = Montgomery-Åsberg Depression Rating Scale, 5D-ASC = 5-Dimensional Altered States of Consciousness Rating Scale, BDI-II = Beck Depression Inventory, SHAPS-D = Snaith-Hamilton Pleasure Scale, BHS = Beck Hopelessness Scale, RSQ-D = Response Styles Questionnaire, NEO-FFI = NEO five-factor inventory, STAI = State Trait Anxiety Inventory, MWT-B = multiple-choice word test.

and 24 h, end of treatment) within the two groups (responders/ non-responders). Two-sample t-tests were used to assess baseline differences on all psychological assessment scales and group differences (responders/ non-responders) in subjective experiences of ketamine infusions. Bonferroni correction was applied to correct for multiple comparisons. Pearson's correlation coefficients were calculated to explore the association of subjective experiences with additional patient characteristics. Linear regression analysis was used to investigate the predictive value of rapid treatment response for the overall MADRS change (from baseline to end of treatment).

3. Results

3.1. Sample

Between April 2014 and December 2015, N = 56 patients with MDD were treated with ketamine at the Department of Psychiatry at Charité – Universitätsmedizin Berlin and screened for eligibility. A total of N = 31 patients (16 females, 15 males) fulfilled the inclusion criteria, agreed to participate and were included in the study. Clinical characteristics of the sample are displayed in Table 2.

3.2. Treatment with ketamine

Patients received a total number of 6.0(±1.7) ketamine infusions. N = 3 patients requested to stop treatment after the 2nd or 3rd infusion due to a subjective lack of efficacy, N = 1 patient requested to stop after the 3rd infusion due to full remission, and all other N = 27 patients received between 6 and 9 infusions. Thus, end of treatment can be different across patients depending on the individual duration of treatment (i.e. number of ketamine infusions received). The number of ketamine infusions received, however, was not associated with the percentage change in MADRS scores from baseline to the end of treatment ($r = 0.16$, $p = .378$).

3.3. Responses to treatment

At the end of ketamine treatment, N = 17 patients (55%) showed a response and N = 14 (45%) showed no response. Responders and non-responders did not differ with regard to medication status [$X^2(1) = 0.14$, $p = .709$] and other clinical characteristics (see Table 3).

In the group of responders, there was a significant effect of ketamine on depression severity at 4 and 24 h as well as at the end of treatment (Wilk's Lambda = 0.080, $F(3,13) = 49.7$, $p = .000$). MADRS scores changed from M = 28.4 ± 5.5 (baseline) to 15.9 ± 7.5 (after 4 h), 14.9 ± 7.3 (after 24 h), and 8.5 ± 4.6 (end of treatment). Post-hoc tests showed that the reduction of MADRS scores was significant from baseline to all subsequent measures (all $p < .001$). In the group of non-responders, the effect of ketamine was also significant (Wilk's Lambda = 0.306, $F(3,11) = 8.3$, $p = .004$). MADRS scores changed from M = 26.1 ± 4.6 (baseline) to 20.1 ± 6.7 (after 4 h), 21.7 ± 7.3 (after 24 h), and 19.3 ± 5.9 (end of treatment). The reduction of MADRS scores was also significant from baseline to after 4 h ($p < .005$), 24 h ($p < .05$) and end of treatment ($p < .001$).

Between groups (responders/ non-responders), MADRS scores did not differ at baseline ($p = .216$) and 4 h after the first ketamine infusion ($p = .120$), however, there were significant group differences after 24 h ($p < .05$) and at the end of treatment ($p < .001$). Also, MADRS scores at baseline were not significantly correlated with the percentage of MADRS reduction from baseline to 4 h, 24 h and end of treatment (all $p > .05$). MADRS reductions across groups (responders/ non-responders) are visualized in Fig. 1.

3.4. Group differences on psychological measures

At baseline, two-sample t-tests revealed that responders and non-responders did not differ on the following measures: self-reported depression severity, anhedonia, personality (neuroticism, extraversion, openness to experience, agreeableness, conscientiousness), state and trait anxiety,

Table 2 Clinical sample characteristics.

	M	SD	sign.
age at inclusion (years)	49.5	11.2	n.s.
Years of education	11.7	1.4	n.s.
IQ	101.9	6.9	n.s.
number of previous depressive episodes	5.5	4.2	n.s.
duration of current episode (months)	27.8	19.0	n.s.
number of previous antidepressant trails in the current episode	4.1	1.4	n.s.
total number of ketamine infusions received	6.0	1.7	n.s.
	N (of 31)	**%**	
lifetime history of ECT	11	35.5	
currently medication free	10	32.3	
current medication SSRI	5	16.1	
current medication SNRI	6	19.4	
current medication tricyclic antidepressants	4	12.9	
current medication monoamine oxidase inhibitors	1	3.2	
current medication buproprion/ mirtazapine/ trazodone	4	12.9	
current medication mood stabilizers	4	12.9	
current medication atypical neuroleptics	4	12.9	
current medication benzodiazepines	3	9.7	
current medication others (such as agomelatine or pregabaline)	5	16.1	
comorbid social phobia	2	6.5	
comorbid panic disorder	1	3.2	
comorbid generalized anxiety disorder	2	6.5	
comorbid alcohol dependence	2	6.5	
comorbid obsessive-compulsive personality disorder	2	6.5	
comorbid avoidant personality disorder	2	6.5	
comorbid Borderline personality disorder	1	3.2	
comorbid combined personality disorder	1	3.2	

M = mean, SD = standard deviation, sign = significant group difference between responders and non-responders (Bonferroni-corrected alpha levels of 0.5/7), n.s. = not significant.

Table 3 Psychological measures (total sample and comparison between responders/ non-responders).

Baseline measures	Total sample (N = 31)	Responders (N = 17)	Non-responders (N = 14)	sign.
BDI-II	M = 36.7 ± 9.1	M = 34.7 ± 9.1	M = 39.0 ± 8.7	n.s.
SHAPS-D	M = 9.3 ± 3.6	M = 8.5 ± 4.3	M = 10.1 ± 2.8	n.s.
BHS	M = 70.2 ± 11.9	M = 64.3 ± 9.9	M = 77.4 ± 10.4	.002*
RSQ-D rumination	M = 57.7 ± 10.5	M = 59.0 ± 8.8	M = 56.4 ± 12.2	n.s.
RSQ-D distraction	M = 20.2 ± 4.5	M = 19.5 ± 2.5	M = 20.9 ± 6.0	n.s.
NEO-FFI neuroticism	M = 34.0 ± 7.2	M = 33.4 ± 8.1	M = 34.6 ± 6.3	n.s.
NEO-FFI extraversion	M = 14.3 ± 6.2	M = 12.3 ± 6.7	M = 16.6 ± 4.7	n.s.
NEO-FFI openness to experience	M = 25.8 ± 7.6	M = 25.8 ± 6.6	M = 25.8 ± 8.9	n.s.
NEO-FFI agreeableness	M = 33.5 ± 4.7	M = 31.7 ± 4.6	M = 35.6 ± 4.0	n.s.
NEO-FFI conscientiousness	M = 28.8 ± 8.3	M = 27.9 ± 8.9	M = 29.9 ± 7.6	n.s.
STAI state	M = 63.1 ± 7.4	M = 61.4 ± 7.7	M = 65.3 ± 6.8	n.s.
STAI trait	M = 62.7 ± 8.9	M = 61.4 ± 8.1	M = 64.1 ± 9.8	n.s.
Measures after 4 h	Total sample (N = 31)	Responders (N = 17)	Non-responders (N = 14)	sign.
BDI-II	M = 26.2 ± 12.3	M = 25.4 ± 11.7	M = 27.1 ± 13.5	n.s
Measures after 24 h	Total sample (N = 31)	Responders (N = 17)	Non-responders (N = 14)	sign.
BDI-II	M = 26.7 ± 12.6	M = 23.4 ± 12.6	M = 31.4 ± 11.5	n.s
SHAPS-D	M = 7.6 ± 4.3	M = 6.9 ± 5.2	M = 8.5 ± 4.2	n.s
BHS	M = 64.9 ± 16.9	M = 59.0 ± 15.9	M = 71.3 ± 16.2	n.s
RSQ-D rumination	M = 54.8 ± 11.2	M = 55.4 ± 11.9	M = 53.9 ± 10.7	n.s
RSQ-D distraction	M = 21.4 ± 4.9	M = 21.1 ± 4.9	M = 21.6 ± 5.1	n.s

M = mean (± standard deviation).

* sign = significant group difference between responders and non-responders (baseline comparison: Bonferroni-corrected alpha levels of 0.05/12), n.s. = not significant; BDI-II = Beck Depression Inventory, SHAPS-D = Snaith-Hamilton Pleasure Scale, BHS = Beck Hopelessness Scale, RSQ-D = Response Styles Questionnaire, NEO-FFI = NEO five-factor inventory, STAI = State Trait Anxiety Inventory.

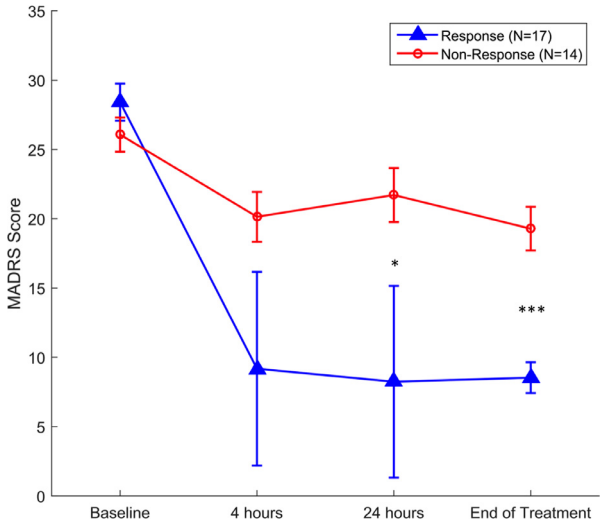

Fig. 1 Reduction of depression severity as measured by MADRS in the course of ketamine treatment by group (responders vs. non-responders), $^{*}p<.05$, $^{***}p<.001$.

rumination and distraction. A significant group difference at baseline was found with regard to hopelessness ($p<.004$). Here, non-responders reported more hopelessness before the first ketamine infusion than responders.

Four hours after the first infusion, responders and non-responders did not differ in self-reported depression severity.

After 24 h, groups did also not differ with regard to self-reported depression severity, anhedonia, hopelessness, rumination and distraction. For details please see Table 3.

3.5. Group differences in subjective experiences induced by ketamine (5D-ASC)

Two-sample t-tests showed that there was a significant difference between responders and non-responders on one of the five 5D-ASC subscales (according to Dittrich, 1998), the scale "anxious ego-disintegration" ($p<.01$, Bonferroni corrected alpha-level of 0.05/5). Non-responders ($M=41.4\pm32.5$) had significantly higher scores than responders (17.8 ± 18.3) indicating more anxiety-related experiences in response ketamine (see Fig. 2). When looking at the different subdimensions of "anxious ego-disintegration" in more detail, responders and non-responders did not differ with regard "thought disorder" ($p=.220$) and "paranoid thinking" ($p=.062$), however, non-responders scored higher on experiences of "negative derealization", "reduced self-control" and "reduced body control" (all $p<.01$, Bonferroni corrected alpha-levels of 0.05/5). We replicated this finding using the eleven lower order 5D-ASC subscales as proposed by Studerus and colleagues (2010). Using this approach, responders and non-responders only differed on the subscale "anxiety" ($p<.004$, Bonferroni-corrected alpha-level of 0.05/11), while there were no differences on the other ten dimensions (e.g. "experience of unity", "blissful state" or "disembodiment").

Post-hoc exploratory analyses showed that there was a significantly negative correlation between the amount of experienced anxiety and openness to experience ($r=-0.54$, $p<.005$) indicating more ketamine-induced anxiety in patients with lower openness to experience, while there were no significant correlations with state or trait anxiety at baseline ($p=.784$, $p=.883$).

3.6. Prediction of treatment response

Linear regression analysis revealed that percentage of MADRS reduction from baseline to 4 h after the first ketamine infusion significantly predicted the percentage of MADRS reduction from baseline to end of treatment ($\beta=0.49$, $p=.005$). Percentage of MADRS reduction from baseline to after 4 h explained 24% ($R=0.49$, $p=.009$) of the variance in the sample. Adding the degree of ketamine-induced self-reported anxiety ($\beta=-0.33$, $p=.045$) and hopelessness at baseline ($\beta=-0.39$, $p=.024$) to the model increased the amount of explained variance from 24 to 49% ($R=0.70$, $p=.001$).

4. Discussion

In the present sample of 31 MDD patients, 17 (55%) had a response and 14 (45%) showed no response at the end of ketamine treatment. The numbers are widely consistent with the average response rate of 59% reported in recent review articles (Kraus et al., 2017). We were able to replicate the previous finding from Murrough and colleagues (2013b) that a rapid response four hours after the first ketamine infusion was predictive of a sustained antidepressant effect in a series of multiple infusions. However, our data also indicated that evaluating ketamine effects 4 h after the first infusion might still be too early since MADRS reduction after four hours only explained 24% of the variance of the percentage MADRS reduction from baseline to end of treatment. Furthermore, significant differences in MADRS scores between responders and non-responders were first detectable 24h after the first infusion. MADRS scores also significantly decreased within both groups irrespective of meeting the criteria for response at the end of treatment. Thus, it might be beneficial to continue ketamine treatment also in patients who only show a mild response after the first infusion.

Previous studies have demonstrated that a variety of patient characteristics and variables such as rumination and distraction (Bagby et al., 1999), trait anxiety (Min et al., 2012), depression severity (Friedman et al., 2012), hopelessness (Papakostas et al., 2003, 2007) and the amount of provided information about potential side effects (in the sense of a "nocebo effect", Meister et al., 2017) can have a significant impact on antidepressant treatment outcome. Therefore, all patients were given standardized information about ketamine treatment including the most typical side effects, their usual duration and the applied preventive procedures, such as close monitoring of vital parameters during the infusion. Information was always provided by the same person (S.A.). Additional patient characteristics were assessed to differentiate between responders and non-responders to ketamine. At baseline, groups did not differ

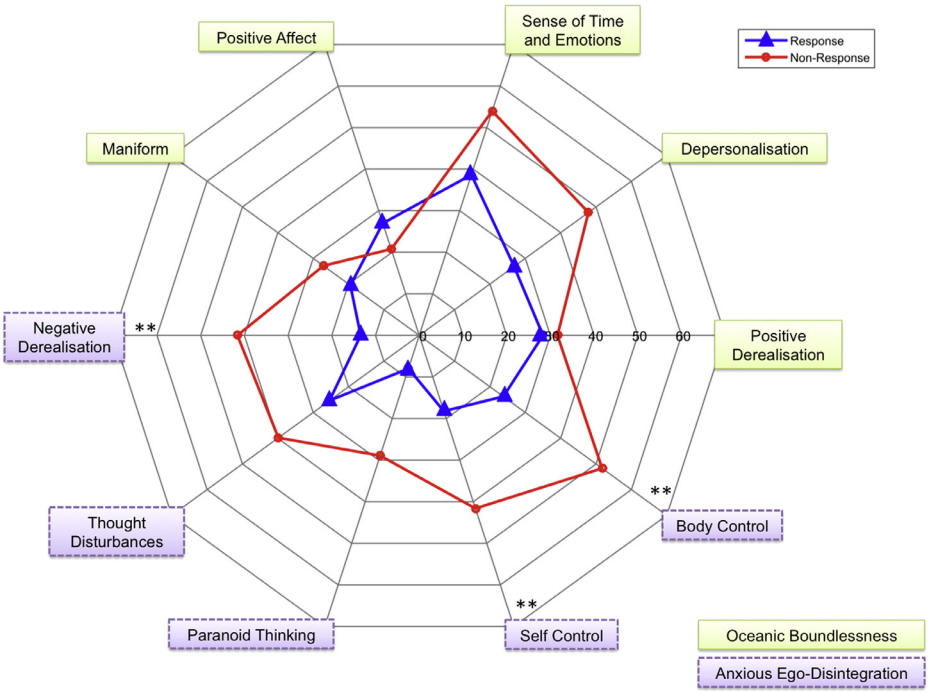

Fig. 2 Group differences in subjective experiences during the first ketamine infusion as measured by 5D-ASC (responders vs. non-responders), $^{**}p<.01$.

on most assessed variables such as years of education, intelligence, number of previous episodes, duration of current episode or medication status. Groups also showed comparable levels of depression severity, anhedonia, state and trait anxiety, rumination and distraction and did not differ with regard to personality dimensions. However, non-responders reported significantly more hopelessness than responders. Interestingly, groups did not differ with regard to the number of ketamine infusions administered. Moreover, the number of infusions received did not significantly correlate with hopelessness at baseline or 24 h after the first infusion (indicating that a patient's degree of hopelessness did not affect the clinicians' decision to discontinue treatment ahead of schedule). Possibly, hopelessness could have induced a greater tendency to underestimate the benefits of a ketamine treatment in non-responders. As shown by an extensive body of literature on placebo and context effects in psychopharmacology (Rief et al., 2016), patients' efficacy expectations are a critical factor for the actual treatment outcome.

The present study showed for the first time that non-responders had more anxiety-related experiences induced by the first ketamine infusion than responders confirming our initial hypothesis of significantly different subjective experiences as a function of treatment response. Specifically, we found that it was the extent of ketamine-induced anxiety that was negatively predictive of a treatment response after a series of six infusions on average. This result could be replicated using a newly validated 5D-ASC model with eleven instead of five subscales (Studerus et al., 2010). Dissociative experiences such as a perceived loss of ego boundaries associated with changes in the sense of time and emotions or an experience of blissful state showed no association with antidepressant response. It is important to note that in the present study, patients received a series of ketamine infusions and that percentage MADRS reduction from baseline to the end of treatment were defined as primary outcome measures. Here, the appearance of anxiety-related experiences induced by ketamine might represent a clinical biomarker for increased treatment resistance in non-responding patients (along the lines of Godlewska et al., 2016). Alternatively, anxiety-related experiences combined with increased hopelessness as well as a negative information processing bias (Gotlib et al., 2004) might have contributed to a lower treatment expectation in ketamine non-responders.

The finding that ketamine-induced experiences of anxiety may be related to lower antidepressant responses to ketamine raises the question of how to reduce or even prevent the occurrence of such anxiety-related experiences. Firstly, it could be beneficial to select patients prior to treatment more carefully. Our data indicate that openness to experience, which was negatively correlated with experiences of anxious ego-disintegration, might be a factor to keep in mind when discussing ketamine as a treatment option with depressed patients. Secondly, a safe and calm treatment environment might also be suitable to reduce patients' anxiety. This could include the assignment of specifically trained medical personnel attentive to creating a climate of well-being and safety, but also the creation of treatment facilities such as comfortable seats and audiovisual shielding of patients via headphones with music or video/ virtual reality goggles. Thirdly, following the path of a recent study (Wilkinson et al., 2017), one might consider cognitive behavioral interventions to better prepare patients for ketamine-induced alterations of consciousness, to explore

individual expectations or concerns and, which might be most important with regard to the results presented here, to reflect on subjective experiences after the first ketamine infusion to reduce anticipatory fear (and hopelessness) of further infusions. The idea of supporting and maintaining patients' responses to psychopharmacological interventions by psychotherapeutic approaches has been proven to be effective in different treatment settings (e.g. Brakemeier et al., 2014). One may also consider other ways of ketamine administration (e.g. intranasal) that might show fewer side-effects related to anxiety and dissociation (Lapidus et al., 2014).

When interpreting the results, the following limitations must be considered. First, there was no follow-up after the end of ketamine treatment, so no conclusions can be drawn on other relevant aspects of ketamine treatment such as time to relapse or beneficial effects of repeated administrations as compared to single dose treatment. Second, subjective experiences were assessed only after the first infusion for reasons of time and effort for patients (the 5D-ASC has 96 items). Thus, the question remains whether there were changes of subjective experience over time (such as a transition from anxious ego-disintegration to a more positive oceanic boundlessness) and if such later changes were associated with an altered response to treatment or a change from the non-responder to the responder group over time. Third, we did not control for medication or medication changes between baseline and end of ketamine treatment due to the high variability of medication. The same applies to other forms of concomitant treatment such as psychotherapy, which were not recorded. As mentioned above, response to treatment was not associated with medication status at baseline. However, the risk of overestimating the percentage of ketamine responders in the present sample remains due to lack of medication control in the course of treatment. One could also argue that responders might have assessed their subjective experiences to ketamine in a different emotional state than non-responders, since the questionnaire was filled out four hours after the first infusion when symptom severity might already have been reduced. This could have led to a slight overestimation of anxiety-related experiences in the group of non-responders (although significant group differences in depression severity were only detectable after 24 h and not as early as 4 h post-infusion, when patients filled out the 5D-ASC). Another limitation is the categorical instead of a continuous approach regarding responders/ non-responders as well as the fact that the present study was designed as an open-label investigation with the lack of a control condition. Finally, it might - at first - seem surprising that no direct association was found between the individual degree of experienced dissociation (e.g. the 5D-ASC subscale disembodiment) and responses to ketamine as reported by some previous studies (e.g. Luckenbaugh et al., 2014; Pennybaker et al., 2017). In these studies, dissociation was assessed by the Clinician Administered Dissociative States Scale (CADSS, Bremner et al., 1998), which was originally developed to discriminate patients with dissociative disorders from patients with other psychiatric disorders and healthy subjects. Its items do not include a valence dimension, however, as the present data show, the valence of ketamine-associated experiences seems to be a critical factor effecting treatment efficacy. Therefore, one cannot compare previous results with our 5D-ASC based findings. Future studies could overcome this methodological shortcoming and apply both questionnaires in the assessment of ketamine-induced experiences and their association with antidepressant responses.

To conclude, the present study demonstrated the considerable impact of anxiety-related ketamine-induced experiences on the antidepressant efficacy of ketamine. It underpins the importance of considering the subjective quality of altered states of consciousness and underlines the possibility of a phenotypic response predictor. At the same time, psychological acute effects of ketamine might be more than just side effects, but rather effects associated with treatment efficacy that need to be acknowledged. Whether and how altered states of consciousness induced by ketamine are directly related to its antidepressant effect needs to be addressed in future studies with larger samples and a placebo-controlled design.

Contributors

Authors SA, MG, SG and MB designed the study and wrote the protocol. Authors SA, MG, LB and SG managed the literature searches and analyses. Authors SA, MG, LB, CO, KW and SG undertook the statistical analysis, and authors SA, MG, SG and MB wrote the first draft of the manuscript. Authors CO, KW, WC, IH, FR, NCC and FvH substantially revised and proofread the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Prof. Dr. Bajbouj was involved in a clinical trial by Johnson and Johnson investigating the antidepressant effects of ketamine. Prof. Dr. Otte has received honoraria from Lundbeck and Neuraxpharm. All other authors reported no biomedical financial or potential conflicts of interest.

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