Original Article

A qualitative and quantitative account of patient's experiences of ketamine and its antidepressant properties

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Abstract

Background: Ketamine is central to one of the most rapidly growing areas of neuroscientific research into novel treatments for depression. Limited research has indicated that the psychedelic properties of ketamine may play a role in its antidepressant effects.

Aim: The aim of the current study was to explore the psychedelic experiences and sustained impact of ketamine in major depressive disorder.

Methods: In the current study, ketamine (0.44 mg/kg) was administered to 32 volunteers with major depressive disorder in a crossover design with the active-placebo remifentanil, in a magnetic resonance imaging (MRI) environment. The 11-dimension altered states of consciousness questionnaire and individual qualitative interviews were used to capture the acute psychedelic experience. The Montgomery-Asberg Depression Rating Scale and further interviewing explored lasting effects. The second qualitative interview took place ⩾3 weeks post-ketamine.

Results: Greater antidepressant response (reduction in Montgomery-Asberg Depression Rating Scale at 24 h) correlated with the 11-dimension altered states of consciousness dimensions: spirituality, experience of unity, and insight. The first qualitative interview revealed that all participants experienced perceptual changes. Additional themes emerged including loss of control and emotional and mood changes. The final interview showed evidence of a psychedelic afterglow, and changes to perspective on life, people, and problems, as well as changes to how participants felt about their depression and treatments.

Conclusions: The current study provides preliminary evidence for a role of the psychedelic experience and afterglow in ketamine's antidepressant properties. Reflexive thematic analysis provided a wealth of information on participants' experience of the study and demonstrated the psychedelic properties of ketamine are not fully captured by commonly used questionnaires.

Keywords

Ketamine, depression, qualitative research, thematic analysis, psychedelic

Introduction

Ketamine has been dominant in the growing field of research into rapid-acting antidepressants. This is partly because ketamine is an established, safe and widely used medication in surgery and pain management (Kohrs and Durieux, 1998). Its potential as an antidepressant was first reported by Berman et al. (2000), and has gained considerable momentum since a larger replication by Zarate et al. (2006) demonstrated significant antidepressant effects within 3 h of treatment in 70% of a group of participants with treatment resistant depression, that lasted for around 1 week. Ketamine is often discussed alongside the classic serotonergic psychedelic psilocybin due to their rapid action as antidepressants and the psychedelic nature of their acute effects (Majić et al., 2015; Vollenweider and Kometer, 2010). Therefore, an area of research interest has been whether the psychedelic effects of these drugs and the content of the acute experiences are related to their antidepressant properties (Mathai et al., 2020). A second area of interest has been determining the nature of the lasting changes in perspective or perception of oneself or one's depression after taking just a single dose of these drugs, both in consideration of and beyond alleviation of the symptoms of depression (Griffiths et al., 2016; Majić et al., 2015; Roseman et al., 2018; Watts et al., 2017).

There is less research in this area for ketamine compared to psilocybin, despite there having been considerably more studies investigating the antidepressant effects of ketamine (see Schenberg (2018)). Compared to ketamine, classic serotonergic psychedelics (like psilocybin) have highly distinct pharmacological, phenomenological, and therapeutic profiles (see Vollenweider

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and Kometer (2010) for a brief review). It is not the purpose of the current study to provide a critical comparison of ketamine and classic psychedelics, however it is the case the there is real need for unique research to be conducted evaluating ketamine because of these differences.

Existing research investigating the relationship between the acute experience of ketamine and its antidepressant properties typically explores the dissociative, hallucinogenic, and psychotomimetic effects of doses around 0.5 mg/kg. However, describing sub-anesthetic ketamine using each of these terms in isolation is insufficient (Bowdle et al., 1998). Psychotomimesis describes alterations in perception and thought (e.g. paranoia and delirium) brought on by drugs such as ketamine but also phencyclidine hydrochloride (PCP) and, lysergic acid diethylamide (LSD) among others, particularly in relation to pathological psychosis (Krystal et al., 1994). The related construct of dissociation refers to the disruption of perception primarily in terms of connection with one's senses and body. Hallucinogen implies ketamine always or exclusively causes hallucination. Instead the term psychedelic[1] is preferred to describe ketamine, to allow and explore fluidity in people's experiences of the above properties of ketamine in varying quantities, and where the alteration of consciousness crosses and transcends multiple sensory and perceptual domains, often giving way to a rich experience. During the acute experience of ketamine, symptoms such as hallucinations or dissociations may manifest themselves as emotionally or spiritually important or meaningful, occurring alongside higher level or transcendent experiences, such as a dissolution of the ego (Jansen, 2004; Krupitsky and Grinenko, 1997). Such experiences are widely referred to as "peak experiences", which is a term introduced by Maslow (1961) and developed in the psychedelic field by Pahnke (1966; 1969) to refer to the most intense point of the psychedelic state and specifically encompass "mystical" experiences (e.g. a sense of unity, transcendence of time and space). Empirical research on classic psychedelics demonstrate that it is these more meaningful and insightful experiences that are often associated with therapeutic effects (Carhart-Harris et al., 2018b; Haijen et al., 2018; Watts et al., 2017; Watts and Luoma, 2020).

The psychedelic afterglow refers to a persistent "elevated and energetic mood with a relative freedom from concerns of the past and from guilt and anxiety," as well as enhanced willingness "to enter into close interpersonal relationships" (Pahnke, 1966). The psychedelic afterglow of ketamine (Jansen, 2004; Krupitsky and Grinenko, 1997; Majić et al., 2015), may be emergent in people undergoing ketamine infusions to alleviate major depressive disorder (MDD). While the afterglow of ketamine has been reported in the context of ketamine-assisted psychotherapy (KAP) (Dore et al., 2019; Krupitsky and Grinenko, 1997), how these experiences emerge unprompted, intrinsically to the ketamine experience has not been explored.

Further motivating thorough and unique investigation into the acute and lasting experience of different psychedelics, ketamine and classic psychedelics have differing and apparent domain specific effects on memory and cognition (Healy, 2021; Krystal et al., 1994; Morgan and Curran, 2006; Passie et al., 2005). Ketamine is known to cause dose-dependent negative impacts on memory encoding (Honey et al., 2005) and working memory manipulation (Adler et al., 1998; Morgan and Curran, 2006). However, people who have had ketamine still report a detailed psychedelic experience (Bowdle et al., 1998; Krupitsky and Grinenko, 1997). Ketamine's effects on memory may impact how people report their psychedelic experience, and therefore uniquely interact with psychedelic related therapeutic outcomes in depression.

A recent meta-analysis (Mathai et al., 2020) reported that of eight included studies, only three demonstrated a relationship between the acute psychedelic effects of ketamine and the antidepressant response (Luckenbaugh et al., 2014; Phillips et al., 2019; Sos et al., 2013). However, limitations identified included the common use of the Clinician-Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS) (Mathai et al., 2020). These scales test only symptoms of dissociation and psychotomimesis respectively. In contrast the Altered States of Consciousness (ASC) questionnaire provides a more detailed interrogation of the phenomenology of the psychedelic experience, importantly targeting mystical experiences (Dittrich, 1998; Studerus et al., 2010). The single study included in the meta-analysis that used the ASC found no relationship with the antidepressant response, though it only had 10 participants (Mathai et al., 2020; Vidal et al., 2018).

In combination with quantitative questionnaires, qualitative research can be useful to allow participants to explore and explain meaningful experiences and changes that scales are not sensitive to. The aim of the current study was to understand participant's memory of their experience of the ketamine infusion in terms of changes to mood and perception that may be intrinsic to the antidepressant properties of the drug. This was investigated in both the acute stages of the ketamine infusion, and also in the longer-term changes that were sustained for the week-long therapeutic window of ketamine's antidepressant effects and beyond. In particular, ketamine was considered in terms of how the qualitative changes compare with classic serotonergic psychedelic drugs such as psilocybin. This aim was investigated with a combination of qualitative and quantitative techniques. Qualitative interviews were carried out both directly after the infusion, and as part of the debrief at the conclusion of the study approximately 3–8 weeks post ketamine. In addition, quantitative data were collected on the acute effects of ketamine using the 11-dimensional altered state of consciousness (11D-ASC) questionnaire (Dittrich, 1998; Studerus et al., 2010). Also, in a broader sense, the aim was to investigate the impact of rapid but short-lived alleviation of each participant's symptoms (if it occurred), as well as the impact of participation in the trial more generally on participants' perceptions of their depression and of receiving future treatment. This was incorporated into the same interview as part of the debrief and included only qualitative questioning.

Methods

Study design

This study was a randomised, double-blind, active placebo-controlled crossover trial of ketamine in MDD (Figure 1). Participants were required to meet the Diagnostic and Statistics Manual of Mental Disorders (DSM-V) criteria for MDD (American Psychiatric Association, 2013). The current study was part of a larger imaging trial that has been reported elsewhere (McMillan et al., 2020; Sumner et al., 2020a). A summary of demographics can be found in Table 1. Full screening criteria, inclusion and exclusion criteria is published in Sumner et al. (2020a). Of the 32 participants who

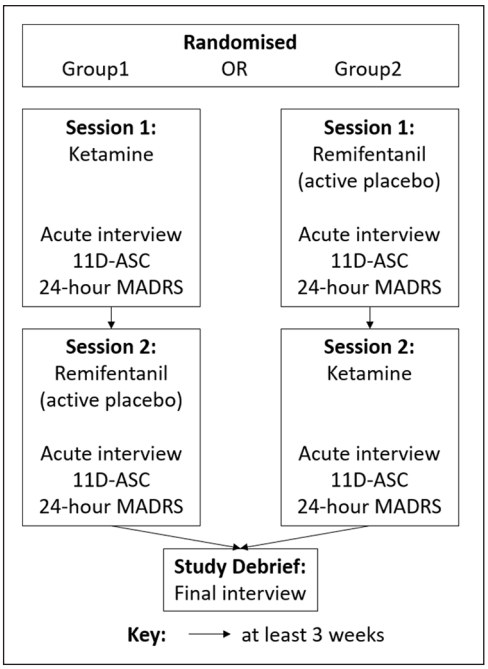

Figure 1. Depiction of the randomised, double blind, active placebo crossover study design and the measures of interest including the acute qualitative interview that took place immediately after the infusion, the 11-dimensional altered state of consciousness (11D-ASC) completed 3 h post-infusion and the Montgomery-Asberg Depression Rating Scale (MADRS) 24 h post-infusion. The final study debrief was at least 3 weeks post-ketamine depending on the crossover order.

volunteered, 30 completed the study, while two only completed the ketamine study day (discontinuation was due to one antidepressant medication change and one personal circumstance change). Participants received racemic ketamine (Biomed, Auckland, New Zealand) intravenously as a 0.25 mg/kg bolus and 0.25 mg/kg/h infusion for 45 min on one study visit, and the active placebo remifentanil hydrochloride (Ultiva, GlaxoSmithKline) using a target controlled infusion to achieve 1.7 ng/mL plasma concentration over 9 min using the Minto pharmacokinetic model (Minto et al., 1997a, 1997b) on the other day. Drugs were administered in the left antecubital fossa while undergoing an MRI. Participants with a body mass index over 30 were dosed according to their ideal body weight. The drug order was randomized and counterbalanced. Participants provided informed written consent. All procedures were approved by the Health and Disabilities Ethics Committee of New Zealand (Reference number: 15NTB53, Trial Registration: ACTRN12615000573550). Refer to Figure 1 for a summary of the study phases and interview schedules used.

The purpose of selecting an active placebo over an inert placebo such as saline was to improve blinding to the profound psychoactive effects of ketamine. A known issue for double-blinded trials investigating treating depression with psychoactive drugs is how to maintain blinding when their effects are so intense. As an active placebo, remifentanil offered several advantages over other options such as midazolam (for example, as used by Murrough et al. (2013)) such as no known antidepressant/anxiolytic properties. Further, Sanacora and Schatzberg (2015), recommended the use of an opioid as an alternative placebo to midazolam around the time the current study was conceptualized. An assessment of remifentanil in maintaining blinding, as well as a table of side-effects for both drugs, is provided in Sumner et al. (2020a).

Table 1. Cohort demographics.

Demographics		
Sex	Male	17
	Female	15
Age (years μ(SD))		30.4 (8.91)
MADRS on entry[a] (total score μ(SD))		29.7 (5.47)
Number with comorbid anxiety		23
Duration of depression[b]	<5 years	7
	5–10 years	11
	>10 years	12
	Unknown	2
Current treatment[c]	SSRI (SERT)	10
	SNRI (SERT and NET)	6
	Tricyclic (SERT and NET)	1
	Other antidepressant (NET, DAT), releaser (NE, DA); MM)	3
	Augmentative (glutamate)	1
	Counselling	2
	Nil	10
Mean treatments failed (μ(SD))		3.5[d] (1.21)

MADRS: Montgomery-Asberg Depression Rating Scale; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; SERT: serotonin transporter; SNRI: serotonin and norepinephrine reuptake inhibitor; NET: norepenephrine transporter; DAT: dopamine transporter; DA: dopamine; NE: norepinephrine; MM: multi-modal.
[a]Minimum MADRS on entry was 20, classified as moderate to severe depression.
[b]Approximate only and based on self-report of lifespan of depression, not only current episode.
[c]Four participants were taking both an SNRI and other medication (n=1), SSRI and other medication (n=1), SNRI and counselling (n=1), or other medication and augmentative treatment (n=1).
[d]Underestimates actual number as it only includes those that could specifically be recalled. Includes counselling.

MADRS

The primary outcome measure in the study was change in MADRS (Williams and Kobak, 2008) at 1 day post-infusion compared to the baseline (pre-infusion). Responders were classified as demonstrating a 50% or greater decrease in depression symptoms.

11D-ASC

To assess the acute psychoactive effect of ketamine the 11D-ASC questionnaire (Dittrich, 1998) was administered approximately 3.5 h following drug administration. While the full 96-question ASC was administered (Dittrich, 1998) the analyses used the Studerus et al. (2010) validated subset of 42 questions. The subscales assess participants' experiences and attempt to quantify spirituality, blissfulness, insight, disembodiment, impaired cognition, anxiety, complex imagery, simple imagery, audiovisual hallucinations, changed meaning, and experiences of unity. The questionnaire is completed on the computer using a visual analogue sliding scale from 0–100. Relationship between the 11D-ASC and the antidepressant response to ketamine was established using Spearman's Rho correlations corrected for multiple comparisons using the false discovery rate (FDR) (Benjamini and Hochberg, 1995).

Qualitative interviews

The methods are reported according to the consolidated criteria for reporting qualitative research (COREQ) checklist for qualitative research (Tong et al., 2007). The interview schedule was initially and deliberately broad, to allow participants to describe their experiences. Some prompting was provided based on likely experiences derived from the literature (for example: Krupitsky and Grinenko (1997); Majić et al. (2015); Bowdle et al. (1998)). This is commonly referred to as "field testing" (Kallio et al., 2016). A more structured interview schedule was developed after the first three interviews, incorporating the themes that emerged leading to both a targeted exploration of psychedelic experiences (such as detachment and hallucinations), but also colloquial themes as described by participants, such as feeling "high." The full schedules can be found in the Supplementary Material.

Two types of qualitative interviews were carried out, each lasted on average 15–20 min. The first probed the acute effects of ketamine and the active placebo remifentanil and took place within an hour of the infusion. This interview was carried out face-to-face by author RM. It included questions such as: "What was is like for you when you received the infusion? What are you experiencing now? Did you experience any distortions of time, space or body?" And if yes, they were encouraged to describe these. The interviewer audio-recorded and transcribed all of the acute interviews.

The second interview specifically explored the longer-term effects of ketamine and took place between 3–8 weeks post infusion (depending on whether the participant received ketamine or placebo as the first intervention). This interview was carried out over the phone and audio-recorded by authors RLS (16 interviews), and SDM (13 interviews). The interview took place after unblinding and included questions such as: "What do you remember of your experience of the ketamine infusion? Has the ketamine you received changed the way you felt or still feel about problems?" Perspectives on the wider purpose of these sorts of research trials with ketamine were gathered using questions such as: "Has the ketamine you received changed the way you felt or still feel about future treatments? What were your expectations going into the study? Did the study meet these?"

Qualitative analysis was carried out utilizing a reflexive thematic analysis approach which has been developed to explore people's experiences (Braun and Clarke, 2006, 2019). Themes were coded in the transcripts using an iterative process of identifying and reviewing data-driven and theory-driven themes at the semantic level. The incorporation of inductive and deductive analysis reflects our consideration of the existing documentation on ketamine's psychedelic and therapeutic effects as well as the novelty of the specific context this data was collected in that may have led to the emergence of undocumented themes and experiences. Each coded theme was grouped or combined as subthemes under a main theme where the narrative that emerged captured the rich acute and lasting experience of the ketamine infusion, and the personal impact of participation in the trial.

The transcripts were entered into NVivo 12 Pro (QSR International Pty Ltd, 2018) to facilitate manual coding and thematic analysis. As a "first pass," thematic analysis was divided between authors CA, JC, AF, SJ, AR, and RS. Themes were identified with no knowledge of the participant's antidepressant responder status. Themes/subthemes were discussed and refined until consensus was achieved between raters on final coding. The use of consensus in maintaining consistency of coding in the group diverges from a purely reflexive thematic analysis method (Braun and Clarke, 2020). We note this was not used to develop a structured coding framework however (Braun and Clarke, 2020), rather we aimed to maintain a reflexive approach through collaborative ongoing discussion while actively ensuring the entire dataset could be interpreted as a single piece. Thus, for consistency and to reduce the likelihood of error, as an entire piece, as a final step the thematic analysis was reviewed by RS. This approach overall allowed for the number of people who commented on each theme to be accounted for, and tallies to be made to facilitate clear qualitative comparison between responders and non-responders to ketamine according to the main aims of this study.

Results

Montgomery-Asberg depression rating scale results

The MADRS results are summarized in Figure 2 and Table 2 for the 32 participants, only 30 of which had a corresponding active placebo (remifentanil) session. These data are reported in full in Sumner et al. (2020a), where a linear mixed models (LMM) analysis revealed a significant main effect of drug and a significant drug by time interaction. In summary, ketamine significantly reduced MADRS score relative to the active placebo by 3 h post-dose. This effect remained significant at 1 day and 7 days post-dose. By 14 days, there was no significant difference. Furthermore, the LMM analysis demonstrated there were no significant carry-over effects from counterbalancing the crossover design.

Of additional note, Figure 2 shows evidence of a short-term reduction in MADRS following remifentanil as well as ketamine

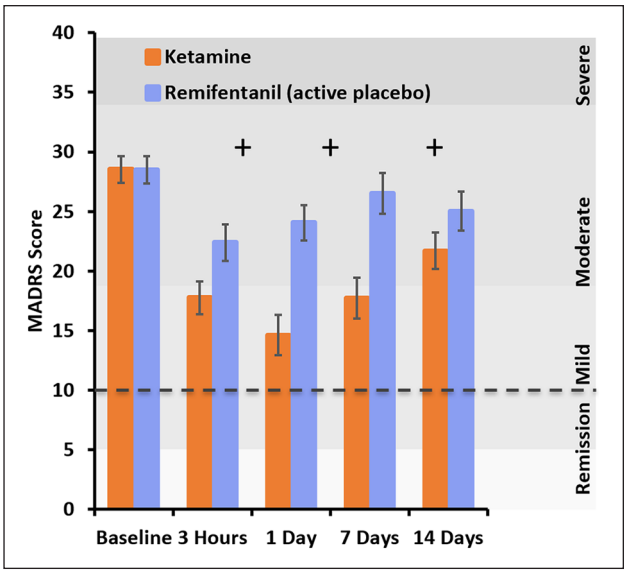

Figure 2. Montgomery-Asberg Depression Rating Scale (MADRS) results for the 32 ketamine sessions, and 30 active placebo (remifentanil) sessions (two participants did not complete the placebo session). The + sign indicates where a significant difference between ketamine and placebo was found as reported in Sumner et al. (2020a). Note: the analysis only incorporated the 30 participants that completed both sessions as in Sumner et al. (2020a), as the linear mixed model was not rerun as this would have introduced missing cases into the model.

(though to a significantly lesser extent). To explore this, uncorrected paired sample *t*-tests were performed comparing baseline MADRS to the MADRS at 3 h ($t(29)=5.16$, $p=0.00002$) and at 1 day ($t(29)=4.07$, $p=0.0003$) post-remifentanil. Unlike ketamine, there was no significant difference to baseline by 7 days.

11D-ASC

There was a significant relationship between percentage change in MADRS at 24 h and participant's experience of unity ($r_s=-0.440$, $p=0.039$ FDR), spirituality ($r_s=-0.429$, $p=0.039$ FDR), and insight ($r_s=-0.398$, $p=0.044$ FDR) during the ketamine infusion (see Figure 3). The other factors of feeling blissful, disembodied, impaired cognition, anxiety, complex imagery, simple imagery, audiovisual hallucinations, or changed meaning were not significantly related to antidepressant response, both uncorrected and corrected (all p values>0.05).

A figure comparing ketamine and the active placebo, remifentanil, is provided in the Supplementary Material. The average global scores demonstrate that the sub-anesthetic dose of ketamine (M=28.53%, standard deviation (SD)=16.94) produced a marked psychedelic response, whereas the placebo remifentanil (M=5.52%, SD=7.59), produced a much smaller response – inconsistent with a psychedelic experience, as expected.

Acute qualitative interview

The thematic analysis of the acute qualitative interview led to the identification of five (A–E) major themes (Table 3).

Thirty-one participants took part in the acute interview. All participants reported a change in perception of some kind (the first theme). Within this theme, several subthemes were identified including distortions of body, space, and time. Dreams and dreamlike experiences were common, as were feelings of detachment. Hallucinations and pseudo-hallucinations captured sensory perceptual disturbances. Most also experienced emotional or mood changes (the second theme); this theme incorporated the subthemes of positive or negative feelings, as well as feelings of being high, and a gentle return back to normal after the infusion (a come down). The third theme included reports of losing control. Less commonly, the fourth theme included mention of death or the existence of the self. The final and fifth theme included any physiological symptoms that did not fit in the previous themes. This interview captured the myriad of experiences, both psychedelic and more plainly physiological, of ketamine in the trial. While themes were clearly clustered closely around the interview schedule, some unique themes emerged also. Themes and subthemes are discussed below, with quotes from the participants when relevant.[2]

Theme A. Change in perception. All participants reported a change in perception. This is as expected given the properties of ketamine as a dissociative hallucinogen.

A.1 Distortion of body. For 18/31 participants this was expressed as a distortion of their body. For some this was a distortion of limbs, how their body was positioned or where each part was.

> It felt like my hands were on backwards for a while, which was a really weird feeling! (Participant 5)

Others spoke of a change in the constitution of their body.

> Just my head, itself. Inside the mind felt a lot more, I don't know, voluminous. (Participant 20)

> Yes. I was telling my cartoon self, what's the point in moving my legs, I'm made of paper. (Participant 22)

A.2 Distortion of space. Of the participants, 26/31 spoke of a distortion of space which was often expressed as being dropped somewhere in a space, or space itself, and floating.

> I started to feel as if, I don't know, like I lost, I was just floating in the emptiness or something. Things like that. Floating in different spaces and different rooms. I wasn't there anymore. (Participant 8)

Others spoke to a more grounded sense of change in space, such as the sensation of moving, or falling backward.

> The crosshairs seemed to go, become more distant and it felt like I was peeling back a little bit from the contraption around me. (Participant 13)

A.3 Distortion of time. Thirty of 31 participants described a distortion in their sense of time. This included a mix of losing track

Table 2. Participant number, responder status, and interview contribution.

Participant Number	% change MADRS 24-hour	Responder	MADRS	11D-ASC	Early interview	Final interview
Participant 1[a]	−90.91%	Yes	✓	✓	×	×
Participant 2	−61.76%	Yes	✓	✓	✓	×
Participant 3	−56.00%	Yes	✓	✓	✓	×
Participant 4	0.00%	No	✓	✓	✓	✓
Participant 5	−73.33%	Yes	✓	✓	✓	✓
Participant 6[a]	−40.63%	No	✓	✓	✓	✓
Participant 7	−16.22%	No	✓	✓	✓	✓
Participant 8	−60.71%	Yes	✓	✓	✓	✓
Participant 9	−54.17%	Yes	✓	✓	✓	✓
Participant 10	−33.33%	No	✓	✓	✓	✓
Participant 11	−77.78%	Yes	✓	✓	✓	✓
Participant 12	−77.78%	Yes	✓	✓	✓	✓
Participant 13	−4.35%	No	✓	✓	✓	✓
Participant 14	−36.00%	No	✓	✓	✓	✓
Participant 15	−13.16%	No	✓	✓	✓	✓
Participant 16	−69.23%	Yes	✓	✓	✓	✓
Participant 17	−55.18%	Yes	✓	✓	✓	✓
Participant 18	−71.43%	Yes	✓	✓	✓	✓
Participant 19	−64.29%	Yes	✓	✓	✓	✓
Participant 20	−69. 07%	Yes	✓	✓	✓	✓
Participant 21	14.29%	No	✓	✓	✓	✓
Participant 22	−6.67%	No	✓	✓	✓	✓
Participant 23	−62.50%	Yes	✓	✓	✓	✓
Participant 24	−56.00%	Yes	✓	✓	✓	✓
Participant 25	−13.79%	No	✓	✓	✓	✓
Participant 26	−60.00%	Yes	✓	✓	✓	✓
Participant 27	−65.63%	Yes	✓	✓	✓	✓
Participant 28	−60.00%	Yes	✓	✓	✓	✓
Participant 29	−57.14%	Yes	✓	✓	✓	✓
Participant 30	−57.14%	Yes	✓	✓	✓	✓
Participant 31	−42.86%	No	✓	✓	✓	✓
Participant 32	−86.11%	Yes	✓	✓	✓	✓

11D-ASC: 11-dimensional altered state of consciousness; MADRS: Montgomery-Asberg Depression Rating Scale.
[a]Did not complete placebo session.

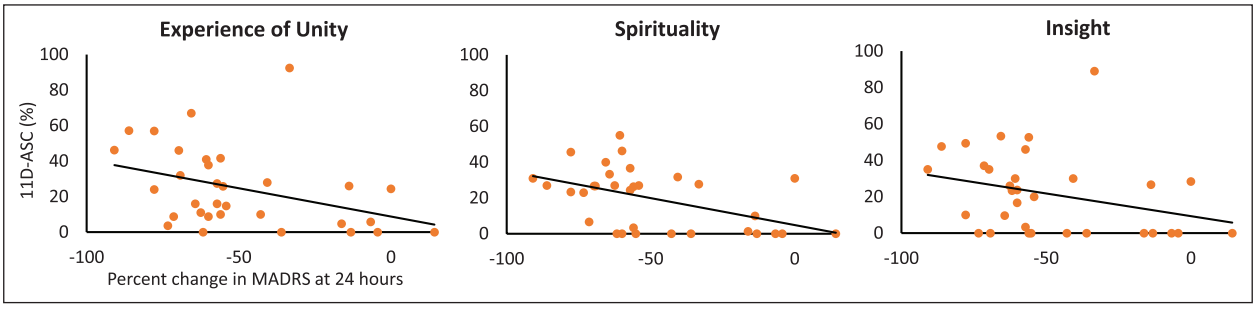

Figure 3. 11-Dimensional altered state of consciousness (11D-ASC) results demonstrating a significant relationship between great antidepressant response to ketamine at 24 h and participants experience of unity, spiritual experiences and insight. A more negative score corresponds with greater percent reduction in MADRS.

of time entirely, and even the concept of time itself. Others provided descriptions of the infusion feeling like an eternity or just much longer than it was (days or hours). Others said it went really fast.

A.4 Dreams or dream-like experiences. Of the participants, 15/31 described the experience as being dreamlike, as if they were asleep, or experiencing déjà vu. When prompted to describe

Table 3. Acute qualitative interview themes.

	Total (% of 31)	Responders (% of 20)	Non-responders (% of 11)
A. Change in perception	31 (100%)	20 (100%)	11 (100%)
A.1 Distortion of body	18 (58.06%)	14 (70%)	4 (36.36%)
A.2 Distortion of space	26 (83.87%)	17 (85%)	9 (81.82%)
A.3 Distortion of time	30 (96.77%)	19 (95%)	11 (100%)
A.4 Dreams or dream-like experiences	15 (48.39%)	11 (55%)	4 (36.36%)
A.5 Feelings of detachment	18 (58.06%)	11 (55%)	7 (63.63)
A.6 Hallucinations	18 (58.06%)	12 (60%)	6 (54.55%)
A.6.1 Auditory	6 (19.35%)	4 (20%)	2 (18.18%)
A.6.2 Taste and smell	11 (35.48%)	7 (35%)	4 (36.36%)
A.6.3 Visual	11 (35.48%)	6 (30%)	5 (45.45%)
A.7 Pseudo-hallucinations	28 (90.32%)	19 (95%)	9 (81.82%)
A.7.1 Auditory	14 (45.16%)	11 (55%)	3 (27.27%)
A.7.2 Visual	26 (83.87%)	18 (90%)	8 (72.73%)
B. Emotional or mood changes	30 (96.77%)	19 (95%)	11 (100%)
B.1 Feeling a gentle come down	22 (70.97%)	13 (65%)	9 (81.82%)
B.2 Feeling high	23 (74.19%)	17 (85%)	6 (54.55%)
B.3 Positive feelings	24 (77.42%)	16 (80%)	8 (72.73%)
B.4 Negative feelings	12 (38.71%)	10 (50%)	2 (18.18%)
C. Loss of control	21 (67.74%)	18 (90%)	3 (27.27%)
D. Questioning of existence or self	7 (22.58%)	6 (30%)	1 (9.09%)
D.1 Near-death	4 (12.90%)	3 (15%)	1 (9.09%)
E. Physiological	24 (77.42%)	15 (75%)	9 (81.82%)

the dreamlike experience four of these participants spoke of thinking about a specific person in their life.

> When I closed my eyes, I saw lots of things. Like a screen, thinking of my mother, scrolling through photos and it's like ah! There's my mum. And then it went off onto another tangent. And yeah, it was really vivid. There were paths and colors and yeah... (Participant 32)

A.5 Feelings of detachment. Eighteen of 31 participants spoke of feelings of detachment. While there was a lot of overlap between detachment and distortion of space, detachment included some reference to no longer feeling connected to their body either entirely or almost entirely.

> I didn't feel my body at all. And I felt a little bit weird because I thought I could see myself from outside. (Participant 10)

A.6 Hallucinations. Hallucinations were experienced by 18/31 participants. Few experienced auditory hallucinations (6/31), and where present these tended to be substantial distortions of the sounds of the MRI machine they were lying in. MRI scanners make mechanical, high, and low-pitched sounds that pulse, beep, and move around the head of the person.

> While the machine [referring to the MRI] was going, sometimes. It sounded like words... sounded like they were repetitively saying something.. . . It sounded like a specific word but I can't remember what that specific word is. (Participant 30)

Eleven of the 31 participants reported hallucinations of taste and smell that could not be attributed to the equipment.

> I'd say like almost like, it's not something I've ever tasted before but it's what I imagine eating some weird plant in the rainforest or something would taste like. Like it was a very, um, very, very pronounced in my saliva. Like it was like my saliva was flavored. (Participant 12)

> Yeah there was a definite smell that I associated with it but I couldn't really describe it. It wasn't like a solvent or chemically but I just couldn't put my finger on it. (Participant 7)

Visual hallucinations were experienced by 11/31 participants.

> It felt like there were like black and white birds, like the seagulls that you kind of draw when you're a kid, like you know. And they were just kind of flying at me while I was falling and they were all speaking some weird language that I've never heard before [laughs]. Yup, it was very weird. (Participant 14)

A.7 Pseudo-hallucinations. Pseudo-hallucinations were mild to moderate distortions of existing sensory information and were differentiated from hallucinations as such. Twenty-six of 31 participants reported visual distortions, most included a distortion of the small cross they were asked to look at while in the MRI, that was projected on a screen.

> Just like a general sense of movement. Like there were things moving in my peripheral vision that I wasn't looking at but they were there. The cross seemed like it was a very, very long way away. Like down a hallway or something. (Participant 3)

Auditory distortions were experienced by 14/31 and were almost always related to the sounds of the MRI scanner.

> While the MRI, all the sounds of the MRI were I suppose, and this is my first experience of it so to me. . . it was distorted and moving the sound and making it quite meditative or something. They were so rhythmic the sounds. (Participant 8)

B. Emotional or mood changes. Almost all participants (30/31) experienced emotional or mood changes acutely, while receiving ketamine.

B.1 Feeling a gentle comedown. Participants were asked about whether they experienced a comedown from ketamine. Twenty-two of the 31 participants described a gradual return to normal. Only one person referred to a sudden return or crash back to normal.

B.2 Feeling high. Of the participants, 25/31 described themselves as high during the experience. For some this was in reference to how similar it was to previous experiences taking drugs recreationally, or while in hospital.

> Kind of something that I dabbled in, in my younger years so I'm familiar with the feeling. So, I was like oh dude, you're really high (Participant 32)

B.3 Positive feelings. Positive feelings were reported by 24/31 participants. Commonly experienced positive feelings included being relaxed, calm, content. Feelings of amusement, or as if something was funny and they wanted to laugh were also common.

B.4 Negative feelings. Conversely, negative experiences were reported by 12/31 participants. Several reported significant anxiety at the intensity of the experience, for example when they felt they experienced loss of control (Theme C). Participants also expressed anxiety as to whether they were doing well, or "messing up" the study results in some way. No references were consistent with a psychotomimetic type paranoia. Although paranoia was referred to by some participants, this was often synonymous with anxiety or concern.

> Yeah, anxiety and I was quite paranoid. (Participant 14)

> About anything in particular? (Experimenter prompt)

> No. I think it was just falling made me feel weird. (Participant 14)

C. Loss of control. Most participants reported some kind of loss of control (21/31). This was commonly reported as a short feeling of being overwhelmed by ketamine initially and then an ability to go with it, or control it afterwards.

For some the feeling of loss of control lasted longer and was related to a sense of distortion or detachment from their body, or a loss in their ability to control all or parts of their body.

> It kind of felt like I was moving but I, obviously I wasn't moving. It felt like my body was a bit numb like I felt like I couldn't move my arms. I felt like I was clenching my jaw at one point but I'm not sure if I was. (Participant 21)

D. Questioning of existence or self. Several (7/31) spoke of questioning their existence or their self, which in four people included comments around thoughts that they might have died or that this experience may be what dying is like.

> As soon as I heard a voice I was like "oh!" There's real life, this is real life. I'm not, you know. . . (Participant 11)

> I did wonder, I did have a little flickering thought there, maybe you'd have to kick my heart into gear or I might have died on the table. But I kind of reconciled it, you know. So, it wasn't really anything bad. (Participant 27)

E. Physiological. Physiological effects of ketamine were reported by 24/31 during the interview, and included feelings such as nausea, dizziness, and a cold sensation in their arm when the infusion started. Numbness or tingling was reported, particularly around the lips and tongue.[3]

Final qualitative interview

The thematic analysis of the final qualitative interview lead to the identification of six (F–K) major themes (Table 4).

Twenty-nine participants took part in the final interview. For this interview, six major themes were identified. Again, themes were often closely linked to the interview schedule, with some unique themes emerging. The first theme was changes in perspective. Subthemes that were identified included changes to how participants thought about, interacted with or felt with people, how they thought or felt about their life in general, and also with regard to how they approached, solved or felt about problems. A subtheme also incorporated changes to how participants perceived their depression. A second theme was change in mood. A third theme included emotional changes. For these change-based themes while some spoke of experiencing a change, several also identified not experiencing a change related to that theme, and therefore these were tallied separately within subthemes as "presence of a change" and "absence of a change" respectively (Table 4).

The fourth theme, time, captured specific references to any effect that lasted for 3 weeks or more, or 3 weeks or less. Moreover, many participants came into the study with expectations (fifth theme). The study also affected how participants felt about ketamine as a future treatment option, and engaging in treatments more generally (sixth theme)

F. Change in perspective. Participants were asked about different ways in which ketamine may have changed their perspective on issues such as people, their life in general, and problems. Twenty-eight out of 29 participants indicated that it had.

F.1 People. Participants who experienced a change in how they felt about people, reported increased feelings of closeness, connectedness, and ability to relate.

> Straight afterward um. . . I felt like it was easier to hold a conversation, or be more engaged in the conversation. Um. . . like I was a bit connected with the person I was talking to (Participant 30)

For others this was a reduction in their focus on how they were being judged or thought of by other people.

Table 4. Final qualitative interview themes.

	Total (% of 29)	Responders (% of 18)	Non-responders (% of 11)
F. Change in perspective	28 (96.55%)	18 (100%)	10 (90.90%)
F.1 People	19 (65.52%)	16 (88.89%)	3 (27.27%)
Presence of change	13 (44.83%)	13 (72.22%)	0 (0%)
Absence of change	6 (20.69%)	3 (16.67%)	3 (27.27%)
F.2 Life	23 (79.31%)	17 (94.44%)	4 (36.36%)
Presence of change	19 (65.52%)	15 (83.33%)	4 (36.36%)
Absence of change	4 (13.79%)	2 (11.11%)	2 (18.18%)
F.3 Problems	17 (58.62%)	11 (61.11%)	6 (54.54%)
Presence of change	15 (51.72%)	12 (66.67%)	3 (27.27%)
Absence of change	5 (17.24%)	2 (11.11%)	3 (27.27%)
F.4 Re-evaluating their own depression	12 (41.38%)	9 (50.00%)	3 (27.27%)
G. Change in mood	28 (96.55%)	17 (94.44%)	11 (100%)
Presence of change	23 (79.31%)	17 (94.44%)	6 (54.54%)
Absence of change	5 (17.24%)	0 (0%)	5 (45.45%)
H. Change in emotion	16 (55.17%)	11 (61.11%)	5 (45.45%)
Presence of change	13 (44.83%)	10 (55.56%)	3 (27.27%)
Absence of change	3 (10.34%)	1 (5.56%)	2 (18.18%)
I. Time	26 (89.66%)	18 (100%)	8 (72.72%)
I.1 Short (<3 week)	12 (41.38%)	4 (22.22%)	2 (18.18%)
I.2 Lasting (>3 week)	24 (82.76%)	17 (94.44%)	7 (63.63%)
J. Expectations	27 (93.10%)	18 (100%)	9 (81.81%)
J.1 Had expectations	17 (58.63%)	13 (72.22%)	4 (36.36%)
J.2 No expectations	10 (34.48%)	6 (75.00%)	4 (36.36%)
K. Future treatments	26 (89.66%)	18 (100%)	8 (72.72%)
K.1 Increase in hope or willingness to try future treatments	22 (75.86%)	17 (94.44%)	5 (45.45%)

> Normally I worry about what other people think about me a lot. So, I won't do anything to change their opinion of me but um. . . yeah I guess in the last couple of weeks I haven't actually really cared, they can think whatever they want I suppose. (Participant 32)

Some reported an increase in thinking of what others may be thinking or feeling.

> I've noticed I have got a lot more mindful of other people again. I guess, thinking about how things, rather than just thinking about myself and how things impact on me, I've been able to externalize that a bit more and think about how other people are thinking by my actions or word. (Participant 23)

F.2 Life. When asked about changes to their life in general, the 19/29 of those who reported presence of a change spoke of increased hope, motivation, feelings of well-being and optimism. This was usually spoken of in terms of lasting changes. Most spoke of a feeling that having experienced relief from their depression gave them the opportunity to see a future without their depression, or just a greater sense of control over their depression.

> I suppose it's because you can kind of see a way out of it, it helps you sort of actually start working towards the future rather kind of than being stuck where you are? (Participant 17)

However, for some, that experience was now inaccessible to them.

> You know, it was a wonderful experience and the way I felt for the few weeks after it, I wish I could tap back into it. I can still think about the experience and I can still somewhat recreate in my mind what things were looking like and I can try to feel the way I felt after it by thinking about the experience that happened, but I can't get that sense of momentum and inner change that came with it. I can't really explain but I don't feel good at the moment. (Participant 8)

F.3 Problems. Seventeen out of 29 participants spoke of a change in their feelings around problems in life. For some this was an increased ability to cope with them. For many this was also a reframing of what problems were, or their weight.

> Problems felt far away, didn't feel as pressing and important or didn't as um, what's the right word, um, yeah it's just that the problems didn't seem um as bad, intense. . . (Participant 30)

Some also spoke of a shift in how they viewed their own role in problems.

> I felt like I was able to deal with the issues in a self-nurturing way. Just that I accepted that all of the stuff that happened, happened and it's not the end of the world, don't need to hate myself over things that I haven't done right. (Participant 27)

Again, while some had experienced a change that was lasting, several participants expressed thoughts around not being able to access this experience anymore.

> I wish that I could say it had [changed how they felt about problems] but I feel like um, I certainly think it would have the power to, with more work on that sort of thing, but having a one off experience like that and falling back into life and patterns and habits and situations I think that ultimately it's um, it hasn't really changed the way I feel on a situation or anything like that in the long run. . . (Participant 8)

F.4 Re-evaluating their own depression. Twelve of 29 participants made comment on how ketamine changed how they felt about their depression. This was most often about feeling their depression as something that can change or that might not last forever.

> There's a lasting feeling of I can live past it. (Participant 27)

> I have been able to see that it's not going to be dark and gloomy forever. (Participant 28)

For some this included a change in the relationship between their sense of self, versus their depression and where these intersect.

> It has changed the way I perceive my own brain and the way I experience reality, in a more realistic way. I also had a strong negative internal dialogue, and didn't see that it was a problem with my brain and thought it was a problem with reality. I think after that experience I am open to the idea that my brain is actually processing things in a negative way .... I view the biology of my brain in a more significant way now. (Participant 12)

G. Change in mood. Most participants identified a change in their mood (23/29), with five reporting no change (5/29). All of those who reported no change were non-responders. Nine of the 23 participants who identified a change in mood directly followed this with a statement on how the change in mood improved their motivation or ability to get started on things such as work, routine chores, or socializing. Four out of the 23 referred to increased optimism.

H. Change in emotion. Of the participants, 13/29 reported a change in how they feel emotions. There was a wide variety in what this change was. For 6/13 this was described as a stripping away of or reduction in negative emotion. Four out of 13 reported an increase in their feeling of positive emotion. Some spoke of feeling "lighter" or less emotional overall. When discussed in terms of reducing emotion, the change wasn't always considered a good thing.

> Like I can watch a sad movie without crying or fall apart from weeping. Not cold hearted like I'm a bitch now. But in a sad situation I used to put myself in the other persons shoes and how they would feel it. But now I kind of look at it from the outside and kind of just say that's really sad. I don't know if that's good or bad. (Participant 11)

> I felt more excited about stuff, I was able to look forward to things and use that as a sort of anchor for not going into a depressive cycle. (Participant 6)

> I woke up and I didn't feel quite so edgy and so grey I guess as I did before, probably more able to cope and analyze what the feelings and things that I was having than I could before. (Participant 14)

I. Time. Twenty-seven out of 29 participants gave some reference to the longevity of the effects they had experienced on their perspective of people, life and problems, or their mood and emotions. Short-term changes were classified as lasting less than 3 weeks, though most spoke of just hours or days of change (15/29). To be considered a short-term change, participants had to have made some reference to how they had returned to how they had felt prior to participating. Twenty-four of the 29 were able to report a lasting change of at least 3 weeks with some reporting a change at the final interview 8 weeks or more post-infusion. Most participants reporting a long-term change spoke in the present tense, indicating this change had not yet returned back to how they had felt prior to participating, the limiting factor being the time of the interview post-ketamine sometimes being as short as 3 weeks post dose.

Unsurprisingly, the most common short-term change experienced was mood (13/15) and only three participants said all effects of ketamine such as mood changes that they experienced were short-term. Long-term changes included mood. For 12/24 this indicated that while the MADRS changes were no longer significant, there were still noticeable changes to many participants. However, two also reported a worsening in their mood since before the study. One expressed disappointment at not being able to continue ketamine. For the other, they were disappointed they had not responded. Ten of 24 participants spoke of a lasting change in their perspective on life, 6/24 experienced an ongoing change in their emotions.

J. Expectations. Twenty-seven of 29 participants spoke of expectations around what they might get out of the study when asked.

J.1 Had expectations. Seventeen of 29 participants said that they had some expectations and these typically included hope or excitement that they would receive antidepressant benefit, or that it would just do "something" to their mood. Common expectations included how the drug would make them feel.

> I was [sic] of course had hopes that ketamine would do something. . . make me feel better. Worst case, you get to see what ketamine feels like even if it doesn't make you feel better? And that's just out of interest. (Participant 9)

J.2 No expectations. Ten out of 27 participants said that they had no expectations going into the study, and several who had set expectations expressed trying not to. In both cases this was often to try and avoid disappointment if it didn't work for them.

> Well I just went in with a really open mind, so if it didn't do anything I wouldn't be absolutely devastated. I definitely wanted it to work but didn't make up in my head that it should work. (Participant 11)

Twenty-one of 27 participants spoke of whether the study met expectations (even if they had none), 15/27 said it had met at least some of their expectations (four of whom reported having none). Five of the 27 said it exceeded their expectations (three reported having none). One non-responder who had said they had thought they had no expectations, realized they must have hoped for an antidepressant response because they were surprised by their disappointment and feeling that ketamine had not met their

expectations. Four non-responders indicated that the study met their expectations, two because it had shifted their mood in a noticeable way to them even if not by a 50% reduction in MADRS (the threshold for determining a responder).

K. Future treatments. Twenty-eight of 29 participants spoke of future treatments, including general comments on ketamine as an option for depression, as well as how the trial had influenced their thoughts on treating their depression going forward. An important consideration for clinical trials is how participation can affect people's engagement with future treatments, especially if the experimental intervention is not available to them as in the current study. Twenty-two of the 29 participants indicated they had increased hope in future treatments or alleviation of their depression, especially if ketamine became available in future. For some this was coupled with an increase in willingness to try further treatments, not just ketamine. This was much more often the case for responders (17/18), than non-responders (5/11). However for one participant not responding had reduced their hope, and for one participant that did respond, they now felt increased frustration with their depression and the thought of trying to find another therapy from the lack of current options available to them.

Discussion

Ketamine has been increasingly researched as an antidepressant in the last decade (Fond et al., 2014; Kishimoto et al., 2016; McGirr et al., 2014). While there has been some interest in the psychedelic properties of ketamine and whether these play a role in ketamine's antidepressant properties, to the best of the authors knowledge, studies to date have only been carried out using quantitative measures. Like other psychedelics, the subjective experiences of ketamine can be broken down into the acute psychedelic state (and the peak psychedelic experience), the afterglow, and the residual effects (Majić et al., 2015). In the current study, we used a combination of a quantitative questionnaire (11D-ASC) and qualitative interviewing to capture the psychedelic state and explore the association with the antidepressant response. From the 11D-ASC, a number of the dimensions (spirituality, experience of unity, and insight) correlated with the magnitude of the antidepressant response. Thematic analysis was applied to the qualitative interviews, with the themes that emerged from the acute qualitative interview supporting and expanding the 11D-ASC correlations. The MADRS and final interview was used to capture the antidepressant response to ketamine and elaborate on this, the psychedelic afterglow, and residual effects. Six major themes emerged in the final interview that demonstrated the profound effects of ketamine on participants' perspective on life, people and problems, as well as changes to how participants felt about their depression and future treatments. Of potential interest to clinicians and researchers, the current study also provides insight into the impact of rapid alleviation of depressive symptoms in the context of a clinical trial.

Experience during and directly after the ketamine infusion

Majić et al. (2015) recommended the use of ASC questionnaires to capture the peak psychedelic experience. In the current study, the results of the 11D-ASC indicate that as well as spiritual experiences, experience of unity, and insight were significantly correlated with the antidepressant response. Interestingly, this is similar to what has been found using the 11D-ASC in psilocybin treatment for depression; in Carhart-Harris et al. (2018a), insight and a combination of unity, spiritual experience and blissful state predicted reduced depressive symptoms. Similarly, using the 5D-ASC, Roseman et al. (2018) found that oceanic boundlessness (which encompasses spiritual experiences, experiences of unity and insight) correlated with antidepressant response to psilocybin. Importantly, these ASC dimensions relate to mystical experiences (Studerus et al., 2010; Majić et al., 2015) and are not captured by the commonly used CADSS or BPRS questionnaires (Luckenbaugh et al., 2014; Valentine et al., 2011; Niciu et al., 2014; Sos et al., 2013; Phillips et al., 2019; Berman et al., 2000) that assess the presence of dissociation and psychotomimesis without revealing the qualities of these. This may explain why relationships between the psychedelic effects of ketamine and the antidepressant response have been unreliable or difficult to capture in the past (Luckenbaugh et al., 2014; Niciu et al., 2014; Sos et al., 2013; Valentine et al., 2011). Further it suggests that Pahnke's (1966; 1969) concept of a psychedelic peak experience (defined in the introduction) may be important to ketamine's antidepressant properties, whereby a more meaningful peak predicts a greater response.

Alongside mystical experiences, emotional breakthrough has also been found to be predictive of improvements in wellbeing following psilocybin induced psychedelic experiences (Roseman et al., 2019). Emotional breakthrough refers to an emotional release associated with the overcoming of difficult emotions during the acute experience of a psychedelic.[4] In the current study, there was emerging evidence for emotional breakthroughs in participant's reports of intense relief and emotional empowerment (captured in the qualitative interview subtheme positive feelings). Furthermore, where these elements of emotional breakthrough were present, it appeared to be explicitly linked to releases from the challenges of participant's depression, and the experiences they face in their lives.

Studying the nature of mystical experiences, and emotional breakthrough in greater detail in future research on ketamine in MDD is warranted by the current results. To achieve this, in addition to the 11D-ASC, Future research should consider implementing the Challenging Experiences Questionnaire (Barrett et al., 2016), Mystical Experience Questionnaire (Barrett et al., 2015; Griffiths et al., 2006), and Emotional Breakthrough Inventory to allow direct comparison with psilocybin research (Roseman et al., 2019) and to facilitate a better understanding of ketamine as a psychedelic therapy for depression.

The qualitative analysis of the acute interview provided an even more detailed account of the psychedelic experience of ketamine than quantitative questionnaires could have achieved alone. Unfortunately, the number of responders and non-responders was too low to conduct any formal analysis, however, a few subthemes showed close to or more than 50% difference between non-responders and responders. These trends support the 11D-ASC results that showed some aspects of the dissociative and psychedelic experiences of ketamine are correlated with antidepressant response. For example, non-responders experienced distortion of their body (36.6%) at around half the rate of responders (70%). Auditory pseudo-hallucinations were also reported more

often in responders (45%) than non-responders (27.27%). 90% of responders reported loss of control, while only 27% of non-responders did. Finally, non-responders (18.18%) did not tend to have more negative experiences such as anxiety than responders (50%). These psychedelic experiences in responders may suggest a relationship between these experiences and the antidepressant response but will need replication in future studies.

Set and Setting

More broadly, even if participant numbers had been sufficient to permit formal analysis, previous and current accounts of ketamine's acute psychedelic experience may be difficult to reliably associate with the antidepressant response because participants in clinical trials largely experience ketamine passively and alone. Carhart-Harris et al. (2018b) extensively reviewed the importance of the context that the psychedelic experience occurs in (referred to as "set and setting"). The psychedelic assisted psychotherapy model emphasizes the importance of both psychological preparation prior to, and psychological integration following the psychedelic session (Watts and Luoma, 2020). Additional aspects of the set and setting such as physical environment (including music, décor and presence of others), intention setting, and a willingness to "let go" to the experience have all been emphasized as important predictors of long-term outcomes both within and outside a therapeutic setting (Carhart-Harris et al., 2018b; Haijen et al., 2018; Watts and Luoma, 2020). In the current study, some participants seemed to be on the cusp of drawing deeper meaning from the psychedelic experience, and yet struggled to access this or use it beyond a sense of knowing that something deep or purposeful was occurring. This included mentioning a difficulty explaining or remembering exactly their experience afterward, despite being clear about how profound it felt.

Furthermore, possibly corresponding to the aspect of "set and setting" of willingness to "let go," – loss of control was one of the themes far more prevalent in responders than non-responders. Learning to let go is a core component to psychedelic therapy (Wolff et al., 2020). There is a growing literature on KAP in a range of mood disorders (including depression, anxiety, and post-traumatic stress disorder (PTSD)) where the experience of ketamine is integrated into the therapy as a mechanism for providing "time-out" from their usual state of mind, and where a therapist assists in expanding and deepening an inward journey and engagement with patient's sense of self (Dore et al., 2019). KAP in different forms has been implemented with some success in addiction therapy (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002). The current study indicates, willingness to "let go," a positive prognostic factor for psilocybin (Carhart-Harris et al., 2018b; Haijen et al., 2018; Watts and Luoma, 2020), may also be to some degree achievable with ketamine. Unfortunately studies using KAP have not been randomized controlled trials. Future studies ought to address this, paying attention to all key elements of "set and setting" and whether in doing so therapy and the infusion are greater than the sum of their parts.

Lasting experience of ketamine

The MADRS results of the current study showed that 70% of participants experienced at least a 50% reduction in global score 24 h post-dose (McMillan et al., 2020; Sumner et al., 2020a). There was a significant decrease in MADRS across the group for at least 1 week. While these results encouragingly replicate the known antidepressant properties of ketamine, the qualitative interview that was conducted at the completion of the study elaborated on and revealed several additional ways in which ketamine affected participants. For example, there were lasting effects on participants >3 weeks post-ketamine, indicating enduring effects of experiencing ketamine and of participation in the trial beyond the therapeutic window of ketamine's antidepressant properties. Participants frequently spoke of changes in perception of themselves and the world with regard to problems, other people, and their depression; similar to that reported by Krupitsky and Grinenko (1997) in KAP for alcoholism. The changes that were reminiscent of a psychedelic afterglow include increased closeness to people, increased energy, and, elevated mood that endured for weeks. Additionally, while at lower rates than responders, non-responders did report changes in perspective, mood, and emotion demonstrating how even small changes that may not be considered statistically significant, can be personally significant for the person receiving treatment.

From a clinical point of view, the interviews also captured more fundamental shifts in thinking, pointing to potential mechanisms by which ketamine may exert its antidepressant effects; again, providing additional insight than the MADRS can alone. From a cognitive theory perspective, helping depressed people switch from a content focused mode of information processing to a "decentered" metacognitive mode is helpful in recovery from depression (Ingram and Hollon, 1986). Many participant comments in the follow-up interview sections exploring changes in perspective and emotion show evidence of this fundamental shift having occurred as a longer-term effect of ketamine. Once negative thinking can be seen in a sufficiently wider perspective, then this can be protective against downward spiraling back into depression. Some participant comments have suggested that whilst decentering has occurred at least briefly, it has been too weak to establish a clinically significant shift. Most models of mind also assume that conscious information processing exists in "limited capacity channels" which suggests that once the mind is decentered, if these limited channels can then be filled with non-ruminative material, then at least for a period of time, the person will experience some relief from rumination (Teasdale et al., 1995). There is evidence of this phenomena also occurring in participant comments where they seem to be able to engage and connect with people and life in general again, and experience less self-referential thinking.

The observed shift in thinking points to an additional channel by which ketamine may be combined with psychological/psychotherapy-based treatments not only in the acute psychedelic phase as in KAP. If, in the days/weeks post-treatment, ketamine opens the mind and improves motivation sufficiently, patients may become more able to engage in therapy. A comprehensive study on the predictors of successful outcomes following cognitive behavioral therapy (CBT) demonstrated only patient's capacity predicted improvement by the end of therapy (Renaud et al., 2014). Patients who had greater capacity to identify and articulate their thoughts and feelings, and who were able to share them in a non-defensive and focused way benefitted most from CBT. Motivation is also a major reason for early drop-out from CBT (Bados et al., 2007). Thus, it is possible to

envisage a synergistic relationship between ketamine treatment and psychological therapies whereby ketamine may facilitate more successful outcomes, and psychological therapy may help sustain and imbed the positive shifts in thinking that occur in the initial week/s following ketamine. Results from a small, but recent study support this (Wilkinson et al., 2017).

The personal impact of participation

The interviews also captured how managing expectations is an important consideration for clinical trials that recruit patient populations. Unsurprisingly, many participants came into the trial with expectations on how ketamine would feel or whether they would receive a benefit (58.63%). Particularly pertinent to clinical trials is the impact of participation which may last after participants are discharged from the study's care. Of the participants, 75.86% reported increases in hope and willingness to try future treatments. However, a non-responder felt a loss of hope because ketamine had not alleviated their depression, even though they remarked they did not realize they had expectations in the first place. While only reported by one participant, it is important to be mindful of this potential outcome. Ketamine also frequently changed how participants viewed their depression (41.38%), with many seeing it as more temporary or changeable after responding to ketamine.

The importance of considering these impacts is substantial from an ethical perspective. At the time of testing ketamine was not available to the participants involved in the trial as a treatment afterward, either privately or publicly funded in New Zealand. This is an even more common scenario internationally for psychedelic treatments such as psilocybin and LSD. Moreover, these single- or limited-trial studies are often conducted in treatment-resistant cohorts (Schenberg, 2018), where the treatments may be seen as a last hope.

The positive reports of met expectations and increased hope in the final interview of the current study likely, at least partially, reflect the study team ensuring that they clearly explained the purpose of the study and the lack of availability of ketamine post-study to participants. Furthermore, clinician input at the initial screening stage also ensured participants were screened as best as possible for resilience to disappointment and had demonstrated relative stability. This rigorous screening is undoubtedly a strength of the current study that likely reduced risk and negative lasting impact on participants. However, notably missing from the literature on ketamine and other drugs (particularly psychedelics) is an empirical assessment of the impact of providing single treatments of drugs that are available recreationally and whether such trials change participant's recreational drug-use or self-medication behaviors. When ketamine is available therapeutically, there is evidence of no influence (Dore et al., 2019).

Comparing ketamine with other psychedelics

The focus of this article has been exploring ketamine's psychedelic properties and its use as an antidepressant. While it is not in the scope of the current article to provide an extensive comparison with other psychedelics it is worth noting that ketamine is not a classic psychedelic and this raises interesting questions about the mechanisms that may underlie the psychedelic peak and afterglow, if indeed these experiences are important for the antidepressant properties of psychedelic drugs. The pharmacological mechanisms of the major psychedelics used in psychedelic assisted psychotherapy have been reviewed extensively by Reiff et al. (2020). The review considered LSD, psilocybin, ayahuasca (focusing on N,N-dimethyltryptamine (DMT)), and 3,4-methylenedioxy-amphetamine (MDMA; MDMA is also classified as a non-classical psychedelic). These drugs have all shown promising therapeutic effects across a number of psychological conditions. The main mechanisms of LSD, psilocybin, and ayahuasca occur via distributed action on the 5-hydroxytryptamine (5-HT) receptor, primarily 5-$HT2_A$ and 5-$HT2_c$ (Reiff et al., 2020; Vollenweider and Kometer, 2010). It has been proposed that the efficacy of classic psychedelics is due to the modulation of 5-$HT2_A$ opening a window of plasticity and facilitating long-term change and benefit (Carhart-Harris and Nutt, 2017). A wealth of neuroimaging literature has explored mechanisms of entropy, functional, and effective connectivity and plasticity that may mediate the therapeutic benefits of psychedelic experiences (Carhart-Harris et al., 2012; 2014; Gilbert and Zarate Jr, 2020; Johnson et al., 2019; Nutt, 2019; Vollenweider and Kometer, 2010). However, thus far, neuroimaging is heavily focused on the psychedelic state and peak experience and uses same-day testing. To the best of the authors' knowledge no trials to date directly observe the mechanisms of the psychedelic afterglow during the days and weeks that follow using neuroimaging.

Contrastingly to classic psychedelics, the primary pharmacological mechanism of action of ketamine is glutamatergic, via its action as a non-competitive N-methyl-D-aspartate (NDMA) receptor antagonist, and though it does act on 5-$HT2_A$ receptors, the psychedelic effects are attributable to NMDA receptor and hyperpolaraization activated cyclic nucleotide gated potassium channel 1 (HCN1) action (Chen et al., 2009; Sleigh et al., 2014). Similar downstream glutamatergic action and the consequences for neural plasticity provide plausible shared mechanisms by which ketamine, LSD, psilocybin, ayahuasca, MDMA, and other psychedelic drugs may exert their therapeutic effects (Ly et al., 2018; Reiff et al., 2020; Vollenweider and Kometer, 2010). For example, the recently proposed Relaxed Beliefs Under Psychedelics (REBUS) model proposes that the psychedelic peak is an acute entropic state (mediated by increased plasticity) that allows for a relaxation in the precision of top-down prior beliefs, leading to increased sensitization to bottom-up information flow and revision of past beliefs (Carhart-Harris and Friston, 2019). The pharmacological justification for REBUS is heavily serotonin-centered. Thus, as it is, REBUS excludes ketamine. However, this somewhat conflicts the growing evidence on the potential therapeutic benefit of the acute experience of ketamine. Ketamine is also a strong example of the role of plasticity in rapid-acting antidepressant therapy (Gilbert and Zarate Jr, 2020; Sumner et al., 2020a, 2020b). Furthermore, there is evidence that ketamine increases sensitivity to prediction error (consistent with REBUS) and that this is related to improvements in depression (Sumner et al., 2020b). Establishing the relationship between plasticity, the psychedelic peak, afterglow and residual effects, as well as potential mediating impacts on observed changes to entropy, and connectivity (using neuroimaging) in non-classic as well as classic serotonergic psychedelics is required to account for the apparent complex mechanisms underlying psychedelic therapy.

Strengths and limitations

A major strength of the current study is the novel use of qualitative techniques to better understand and explore the early and lasting effects of ketamine's antidepressant and psychedelic properties. The incorporation of the 11D-ASC as a quantitative measure of the psychedelic effect of ketamine follows the recommendation of Majić et al. (2015). However, the correlations with the antidepressant response reported in the current study are only low-to-medium and require replication with a greater sample size to establish reliability. Likewise, quantifying the trends seen from the thematic analysis in non-responders and responders require greater numbers.

As emphasized throughout the above discussion, a limitation of much of the ketamine literature that attempts to explore the role of the acute psychedelic state and peak psychedelic experience in the antidepressant effects, as well as the difficulty in comparing ketamine to classic psychedelic therapy, may be attributable to setting. To date, the impact of the acute drug experience, and its context, have been largely unacknowledged in the ketamine literature. The current study administered ketamine to participants while they were in an MRI setting. The MRI interfered with elements of the acute experience, most evident in the nature of the hallucinations experienced. However, reviewed extensively in Carhart-Harris et al. (2018b) the context that the therapy occurs in provides implicit and explicit priming to the peak experience, and potentially lasting effects on the therapeutic outcome.

The reverse of this limitation is that the current study reveals a potential major strength of ketamine as a psychedelic treatment. Important psychedelic effects that in the classic psychedelic literature are thought to be heavily mediated by the set and setting of the acute experience, such as psychological insight and long-term changes in perspective, occurred when these aspects of the drug experience were not emphasized. This therefore raises two important questions: (a) could the efficacy of ketamine be increased if it was placed inside a therapeutic model similar to other psychedelics (noting that the time-window for psilocybin's efficacy in depression (~3 months) (Carhart-Harris et al., 2018a) is far longer than ketamine's (1–2 weeks)), and (b) if effective and safe without the resource intensive therapeutic model, could this be beneficial toward justifying widespread use of ketamine administered as a psychedelic antidepressant? Reaching a balance of resource intensity and long-term outcomes may be an important avenue for future research both for classic psychedelics and ketamine.

Overall, the assessment of the experience of ketamine largely fits around the neuroimaging protocol in the current study. It is hoped that this study provides strong motivation for research where a qualitative exploration of ketamine is conducted as the central measure, whereby the MRI scanner would not interfere with the reporting of hallucinations, and there is broader questioning, interviewing, and even integration.

Conclusion

In conclusion, ketamine administered in humans for depression produces hallmarks of a psychedelic experience. The current study provides evidence that aspects of the psychedelic peak experience may play a role in the antidepressant properties of ketamine. Furthermore, there may be a rationale for psychotherapeutic guidance as part of ketamine therapy for MDD, as well as greater attention paid to the context in which ketamine is administered. The qualitative interviews revealed aspects of a psychedelic experience, afterglow and residual effects that positively affect people receiving ketamine therapy for depression. A number of these effects are not captured by quantitative measures of depression alone.

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Notes

1. The differences between ketamine and the classic psychedelics have led to some controversy around calling ketamine a psychedelic at all (Jansen, 2004). Relative to classic psychedelics, ketamine has a therapeutically versatile and dose-dependent pharmacological profile of effects that may have led to controversy over classifying ketamine as a psychedelic (for an extensive review by the authors see McMillan and Muthukumaraswamy (2020); and Morgan CJA and Curran (2006)).
2. As the drug was administered in an MRI environment this setting will have influenced the nature of many of the experiences, this was particularly obvious in the first theme: change in perception. The subthemes where the MRI influenced the experience are identified and explained in the extended interpretations (section 3.2: A.6 Hallucinations, A.7 Pseudo-hallucinations). In the MRI participants were passively fixating on a small cross on a screen.
3. For a detailed outline of physiological side-effects see Sumner et al. (2020a).
4. Such emotional breakthroughs are most often coupled with facing challenging emotions or memories during the psychedelic peak, with such "challenging experiences" encompassing feelings such as intense grief, fear, death, insanity, isolation, physical distress, and paranoia (Barrett et al., 2016)

(note that the specificity of the term "challenging experiences" means they are not simply equivalent to the negative experiences theme in the current study). There was no evidence of challenging experiences in the pure sense of the term in the current study, however whether this is reflective of an intrinsic property of ketamine or the absence of specific psychological preparation for facing such emotional challenges is unclear.

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