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Experiences of Awe Mediate Ketamine's Antidepressant Effects: Findings From a Randomized Controlled Trial in Treatment-Resistant Depression

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ABSTRACT

BACKGROUND: Ketamine, an NMDA receptor antagonist, provides rapid antidepressant effects. Although much research has focused on neural and molecular mechanisms of action, it is critical to also consider psychological mechanisms that may contribute to its therapeutic efficacy. The construct of an awe-inducing experience, which is a well-validated psychological phenomenon tied to emotional well-being, had not been applied previously in ketamine research.

METHODS: One hundred sixteen participants with depression, 77 of whom received a ketamine infusion (0.5 mg/kg over 40 minutes) and 39 patients who received saline placebo, completed a validated measure of awe (the Awe Experience Scale [AWE-S]) at 40 minutes postinfusion. AWE-S scores were examined as potential mediators of depression outcomes (% improvement in Montgomery–Åsberg Depression Rating Scale score) at 5 postinfusion time points (24 hours and 5, 12, 21, and 30 days). Dissociative effects, measured by Clinician-Administered Dissociative States Scale scores, were tested in parallel mediation models for comparison.

RESULTS: We found that the psychological experience of awe was strongly reported by participants during ketamine infusion, but not saline infusion, and there were significant associations between total AWE-S scores and Montgomery–Åsberg Depression Rating Scale score improvement (% change) in the ketamine arm at all 5 time points. Furthermore, at all 5 time points, total AWE-S scores statistically mediated the relationship between ketamine and Montgomery–Åsberg Depression Rating Scale scores. By contrast, Clinician-Administered Dissociative States Scale scores did not mediate outcomes at any time point.

CONCLUSIONS: Ketamine infusion strongly induced heightened feelings of awe, and these experiences consistently mediated depression outcomes over a 1- to 30-day period, unlike general dissociative side effects. The specific awe-inspiring properties of ketamine may contribute to its antidepressant effects.

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Depression is a leading cause of morbidity and mortality worldwide and is the projected leading cause of global disease burden in the next decade (1). Ketamine, an NMDA receptor antagonist, shows great promise for patients who are resistant to first-line therapies or in need of immediate relief (2–4). However, feasibility and safety concerns (5) as well as the drug's rapidly dissipating antidepressant effects following each infusion (i.e., 1 to 2 weeks duration of relief) (6), have thus far limited ketamine's clinical impact (7). Esketamine, a Food and Drug Administration–approved ketamine nasal spray, is increasingly used to treat treatment-resistant depression but presents similar challenges.

Ketamine's antidepressant mechanisms are multifactorial. In part, its mechanisms may be related to the role of glutamate in neuroplasticity including downstream effects on synaptogenesis (8,9). Recent data also suggest that ketamine impacts burst firing in lateral habenular circuits that are relevant to reward processing (10). Given the potential benefits of ketamine, it is critical to consider mechanisms by which its effects can be prolonged and/or heightened. One such mechanism may relate to ketamine's psychological properties including possible psychedelic or mystical elements. Such effects have been linked to other beneficial outcomes after ketamine, such as promoting abstinence among people with alcohol and substance use disorders (11–13). It remains unclear whether these properties similarly play a role in its antidepressant effects. Recent work suggests a relationship between ketamine's psychedelic properties and depression outcomes (14), but small sample sizes and a paucity of studies have limited the conclusions that can be drawn from these studies.

The Clinician-Administered Dissociative States Scale (CADSS) was originally created to measure dissociation in individuals experiencing psychosis. Recently, it has been adopted to assess dissociative side effects of ketamine. It is

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currently unclear whether CADSS is an appropriate tool to capture the experience of ketamine fully (15), and there are conflicting results about its ability to predict clinical outcomes (16,17). Rather than assuming that such findings indicate that ketamine's acute psychedelic properties are not strongly relevant to its antidepressant effects, it is important to recognize that a novel measurement tool may be useful to more sensitively capture the unique experience of a ketamine infusion. One such relevant aspect may be an experience of "awe"—defined as a constellation of cognitive, affective, and physiological reactions that occur when we encounter vast mystery or a need for accommodation to rearrange knowledge structures to make sense of what has been encountered (18,19). The current study sought to explore the role of awe in the administration of ketamine using the Awe Experience Scale (AWE-S) (20), an instrument developed to capture the acute state of awe. The AWE-S has been widely used and validated in the field of social and cognitive-affective psychology, but rarely in clinical research (see the Supplement for additional background and rationale). To examine the potential role of experiencing awe in ketamine's antidepressant mechanisms of action, we leveraged a randomized design and temporally separated measurements (awe experiences measured immediately after the infusion; depression outcomes measured repeatedly at later, postinfusion time points) to perform statistical mediation analyses, which can provide a rigorous test of mechanisms in the context of clinical trials (21).

In the context of a randomized controlled trial involving a single infusion of ketamine (0.5 mg/kg over 40 minutes) or saline, we sought to measure 1) whether ketamine infusion involves awe-like experiences (relative to saline infusion); 2) whether such experiences are correlated with acute (24 hours) and longer-term (up to 30 days) antidepressant effects following ketamine and/or saline infusion; and 3) whether acute AWE-S scores statistically mediate antidepressant outcomes. For comparison, we sought to contrast findings on the AWE-S with those acquired using the CADSS to index general dissociative side effects. Our sample of 116 patients with depression comprises the largest randomized controlled trial to date that has explored acute psychological effects of ketamine in the setting of depression treatment.

MATERIALS AND METHODS

This study utilized data from a parent study (Clinicaltrials.Gov: NCT03237286) investigating 1) the neurocognitive mechanisms of ketamine treatment, and 2) the efficacy of ketamine combined with a novel digital therapy (automated self-association training [ASAT]) (22). All patients reported moderate to severe levels of depression (indicated by a score $\geq$ 25 on the Montgomery–Åsberg Depression Rating Scale [MADRS]) and had previously undergone at least one unsuccessful trial of a U.S. Food and Drug Administration–approved antidepressant (45% had failed 3 or more trials). Patients' existing depression treatment regimens were required to remain stable for at least 4 weeks before screening and throughout the 30-day trial. See the Supplement for additional trial details including full inclusion/exclusion criteria and CONSORT (Consolidated Standards of Reporting Trials) information.

Participants were randomly assigned at a 2:1 ratio (stratifying randomization on sex and level of prior treatment resistance) to receive either ketamine (at a dose of 0.5 mg/kg) or saline (50 mL of 0.9% sodium chloride) through a 40-minute infusion. The assessment of awe (detailed below) was completed approximately 40 minutes after infusion start. The following day, patients began 4 consecutive days of an additional, digital intervention (either active ASAT or sham ASAT, delivered by computer, according to the patient's random assignment). Due to our principal interest in the impacts of ketamine on awe, the current analyses focus on comparisons of the ketamine versus saline groups, irrespective of ASAT allocation. Please refer to the Supplement for additional details of the active and sham ASAT conditions and sensitivity analyses exploring the impact of ASAT allocation on the current findings.

To measure the specific psychological experience of awe during ketamine infusion, we utilized the AWE-S, which was added to the trial's assessment battery midstudy (after approximately 25% of participants had enrolled) based on the authors' growing familiarity with and interest in this construct. The AWE-S is a 30-item, validated tool designed to quantify the feeling of awe using 6 different subdomains: connectedness, time, vastness, accommodation (representing the need to mentally attempt to accommodate unusual experiences into existing mental schemas), self-diminishment (representing a shrinking of self in the setting of something larger), and physiological changes (20). Of the total of 154 participants who were randomized in the parent study, 116 (n = 77 for ketamine arm, n = 39 for saline) were administered the AWE-S at a 40-minute postinfusion time point and were subsequently included in this substudy. Immediately prior to the administration of the AWE-S (i.e., also at the 40-minute timepoint), the CADSS was administered by a trained rater. The CADSS quantifies general dissociative symptoms (e.g., out-of-body sensations, derealization, shifts in the perception of time and surroundings), measuring a range of possible cognitive experiences without specific links to the subjective experience of awe, and has been used widely in prior ketamine research to measure dissociative side effects.

The primary clinician-rated clinical outcome for the trial was the MADRS, which was administered by a single experienced masters-level rater, blinded to treatment condition, at preinfusion baseline and the following 5 time points postinfusion: +24 hours, +5, +12, +21, and +30 days. Total MADRS scores were used to calculate the percentage improvement from preinfusion baseline at each time point to enhance the clinical relevance and interpretability of post-treatment scores.

Statistical analyses were performed using JMP16.0 and MATLAB (version 2019b; The MathWorks, Inc.). Nonparametric tests were used to compare AWE-S results (total scores and each subdomain score) for study participants who received ketamine with saline-treated control participants. Additionally, the relationship between awe-inspiring experiences of ketamine (defined by higher AWE-S total scores, collapsing across the 6 subscales) and percentage improvement in MADRS scores at each available time point was assessed with Spearman's correlations to assess the clinical significance and impact of acute experiences of awe during the infusion. To

assess for possible statistical mediation effects of the AWE-S in mediating the relationship between the ketamine intervention and MADRS outcomes, the Multilevel Mediation and Moderation Toolbox implemented in MATLAB was used to perform mediation analyses based on a standard 3-variable path model with a bootstrap test of the statistical significance of the mediational pathway (path a × b). A statistically significant a × b mediation pathway indicates the presence of mediation, reflecting that the indirect effect of treatment group on the outcome (MADRS % improvement) when controlling for the mediator (path c′) is significantly reduced compared to the total effect of treatment on MADRS improvement (path c). See Figure 1 for a depiction of the hypothesized mediational model that was tested in these analyses.

Each set of analyses was corrected for multiple comparisons across the 5 discrete MADRS outcome time points using false discovery rate correction.

To probe the specificity of findings to the experience of awe versus general dissociation effects of ketamine, all analyses above were repeated using CADSS scores in place of AWE-S scores. In the ketamine-treated group, the strength of correlation coefficients linking MADRS improvement to each measure (AWE-S vs. CADSS) was compared using Fisher's *r*-to-*z* transformation tests within dependent samples.

RESULTS

Sample characteristics at baseline and treatment response were comparable to the total sample in the parent trial (22) and are detailed in Table S1.

Impact of Ketamine Versus Saline on AWE-S Scores

AWE-S scores in the ketamine group were normally distributed (Shapiro-Wilk, $p = .239$; Anderson-Darling $p = .383$); however, in the total sample and the saline group, the data were not normally distributed ($p < .001$). As a result, nonparametric statistical tests were used. In a Wilcoxon rank-sum test comparing ketamine and saline arms, both total AWE-S score and subdomain scores differed significantly ($p < .0001$) between groups. Table 1 and Figure 2A depict AWE-S scores as a function of treatment group. The highest reported AWE-S score subscale in both groups was for the accommodation subscale.

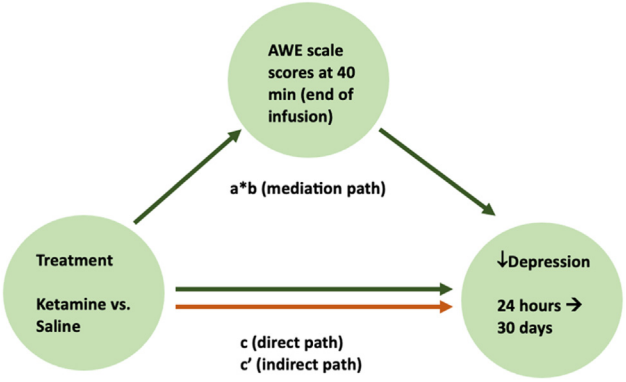

Figure 1. Form of hypothesized mediational models tested in the current analyses. AWE, Awe Experience Scale.

Associations Between AWE-S Scores and Depression Outcomes

Using Spearman's nonparametric correlations to account for the non-normal distributions of scores (detailed above), we found a significant association between total AWE-S scores and MADRS improvement (% change) in the treatment arm at all 5 time points after correcting for multiple comparisons (false discovery rate–corrected $p < .05$). There were no significant associations in the control group. Additionally, in exploratory follow-up analyses, all 6 AWE-S subscales were significantly associated with MADRS improvement (% change) in the treatment group at one or more time points (see Supplement). Figure 3 (left panels) depicts the linear relationships between AWE-S scores and depression improvement in the ketamine arm.

Statistical Mediation Models

Furthermore, in a series of mediation analyses (depicted in Figure 1), we found that at all 5 MADRS time points, total AWE-S scores mediated the relationship between ketamine and MADRS scores (a × b mediation effects 24 hours: $p = .0028$; day 5: $p = .0154$; day 12: $p = .0027$; day 21: $p = .0018$; day 30: $p = .0052$; false discovery rate–corrected $p < .05$ for all time points). At both 24 hours and 5 days postinfusion, there was also a significant main (direct) effect of ketamine on MADRS scores (24 hours: $p < .0001$; day 5: $p < .001$), while from day 12 forward there was no longer a main effect of group on MADRS scores ($ps > .10$). Because a main (direct) treatment effect is not necessary to accurately identify a mediator (23), these results suggest that for a specific subset of ketamine-treated patients who reported particularly strong responses of awe, larger antidepressant effects began within 24 hours and then endured over a 30-day period, well beyond the time period when a significant main group-level effect of ketamine was observed. Refer to the Supplement for exploratory post hoc mediational analyses conducted separately in the ketamine+ASAT and ketamine+sham training subgroups.

Parallel Analyses for General Dissociative Symptoms (CADSS Scores)

The data were not normally distributed ($p < .001$); therefore, nonparametric testing was used including Wilcoxon rank-sum tests and Spearman's correlations. We found that the CADSS total score obtained at 40 minutes was significantly higher in study participants who received ketamine than in saline control participants ($p < .0001$) (Table 1; Figure 2B). In contrast to the AWE-S, we did not find a significant association between CADSS scores and MADRS improvement in the ketamine arm at any of the 5 time points (Table 2). AWE-MADRS correlations were significantly stronger than CADSS-MADRS correlations from the day 12 time point onward (Table 2). Figure 3 (right panels) depicts the lack of any linear relationships between CADSS scores and depression improvement in the ketamine arm. There were a few modest positive correlations in the CADSS analyses in the control group, but none survived multiple comparisons correction (Table 2). Lastly, in a parallel

Table 1. AWE-S and CADSS Scores by Treatment Group

Measure	Total, *n* = 116	Ketamine Group, *n* = 77	Saline Group, *n* = 39	*p* Value for Group Comparison
Total AWE-S Score at 40 Minutes	84.9 (42.9)	104.6 (35.5)	46.2 (26.8)	<.0001
Physical	11.9 (6.9)	13.9 (6.9)	8 0.0 (4.9)	<.0001
Self-diminishment	14.4 (8.5)	17.6 (7.7)	7.9 (6.1)	<.0001
Accommodation	19.6 (10.6)	25.0 (7.7)	8.9 (6.2)	<.0001
Connectedness	13.9 (9.2)	17.5 (8.9)	6.7 (4.2)	<.0001
Time	11.9 (6.9)	13.9 (6.9)	8.0 (4.9)	<.0001
Vastness	13.3 (8.5)	16.7 (8.2)	6.7 (3.6)	<.0001
CADSS Score at 40 Minutes	9.8 (12.2)	13.8 (12.9)	1.3 (3.1)	<.0001

Data are reported as mean (SD).

AWE-S, Awe Experience Scale; CADSS, Clinician-Administered Dissociative States Scale.

mediation analysis of the effect of ketamine on MADRS scores, in contrast to total AWE-S scores, which mediated outcomes at all 5 time points, we found that CADSS scores did not mediate outcomes at any time point (a × b mediation effect *p*s >.372).

DISCUSSION

In this study, we found that ketamine strongly induced heightened feelings of awe in patients with depression. In addition, the self-reported strength of the experience of awe during a ketamine infusion statistically mediated ketamine's effect on clinician-rated improvements in depression symptoms. Mediation effects were present both for rapid depression outcomes (at 24 hours and 5 days, when robust group-level effects of ketamine were observed) as well as mediating the level of enduring antidepressant effects observed up to 30 days postinfusion. Despite the fact that a notable improvement in symptoms due to ketamine was no longer evident (in the entire group) at this point in time, patients who reported experiencing a high level of awe immediately after the infusion continued to exhibit greater persistent antidepressant benefits (Figure 3, left panel). In contrast, CADSS, a tool often used to capture the dissociative effects of ketamine, did not mediate depression outcomes, and correlations with depression improvements among ketamine-treated patients were nonsignificant and substantially weaker than for the AWE-S, particularly at later time points (postinfusion day 12–30). Our results highlight the potential role of awe, a specific component of the psychological experience during the infusion, in the efficacy of ketamine treatment for depression.

Over the past 20 years, there has been mounting evidence that ketamine is a fast-acting and effective treatment option for treatment-resistant depression (2,24–27). Research aimed at understanding this therapeutic effect has focused largely on the molecular-, cellular-, and circuit-level mechanisms of action, while relatively few studies have thoroughly explored potential psychological components. As a result, there has been widespread adoption in the academic research community of a biological model in which the acute cognitive and psychological (e.g., dissociative) experiences of ketamine are often seen as undesirable side effects. Studies that have examined ketamine's acute psychological or cognitive impacts among patients with depression have largely focused on general dissociative or psychotomimetic symptoms, such as those captured by the CADSS. Studies using the CADSS have yielded inconsistent results, with some finding that dissociative experience is correlated with lower depression scores following ketamine (28,29) and others finding no association at all (30,31). Unexpectedly, CADSS scores in the current trial

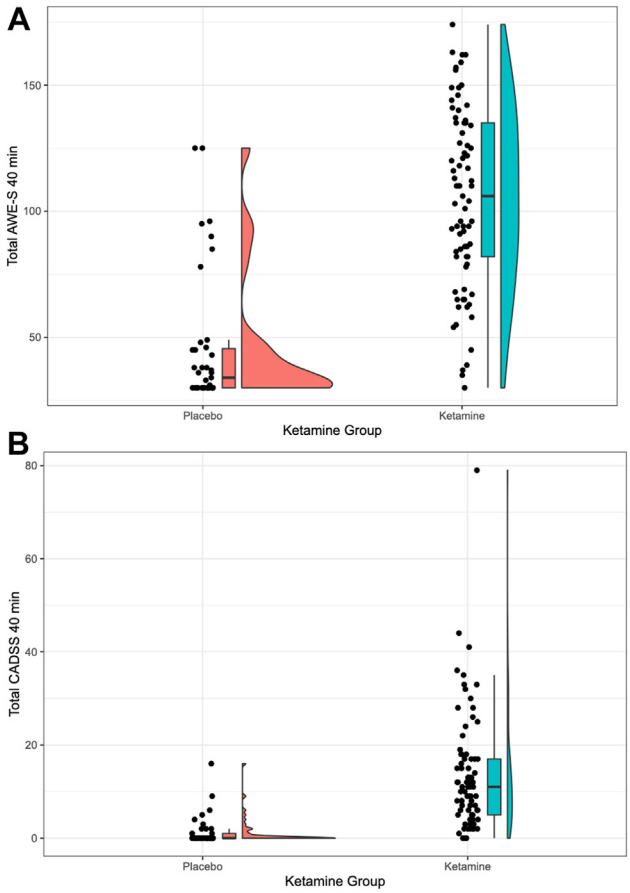

Figure 2. **(A)** Individual participant scores, boxplots (group median marked by horizontal line), and violin plots for the Awe Experience Scale (AWE-S) collected at the 40-minute postinfusion time point in the placebo (saline) arm and the treatment (ketamine) arm. **(B)** Individual participant scores, boxplots (group median marked by horizontal line), and violin plots for the Clinician-Administered Dissociative States Scale (CADSS) collected at the 40-minute postinfusion time point in the placebo (saline) arm and the treatment (ketamine) arm.

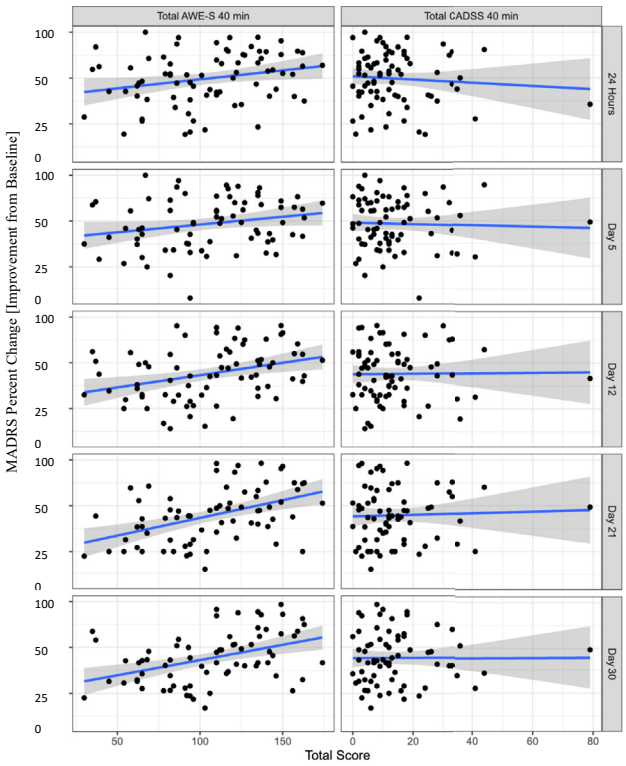

Figure 3. Scatterplots depicting linear associations (with standard error bands) in the group of ketamine-treated participants for the relationship between depression improvement (Montgomery–Åsberg Depression Rating Scale [MADRS] % improvement) at 24 hours and at 5, 12, 21, and 30 days postinfusion and 2 psychological measures collected on infusion day at the 40-minute postinfusion time point: Awe Experience Scale (AWE-S) total scores (left panels) and Clinician-Administered Dissociative States Scale (CADSS) total scores (right panels). For visualization purposes, original (raw) total scores are presented. However, nonparametric (for group comparisons and correlations) and bootstrapping (for mediation) tests were used for statistical inferences, which are robust tests that can be applied even when scales are non-normally distributed or skewed, including to manage the presence of outliers. These tests minimize the impact of anomalies or discrepancies in the range and distribution of the absolute (raw) scores because prior to analysis, all raw values are first converted to rank-ordered values.

Table 2. Correlation of Depression Improvement Across MADRS Time Points in Relation to AWE-S and CADSS Scores at 40 Minutes in the Total Sample and Separately by Treatment Group

Depression Outcomes	Ketamine Group, n = 77	Saline Group, n = 39
Correlations With AWE-S Scores at 40 Minutes		
24-Hour MADRS	0.2540[a]	0.1888
5-Day MADRS	0.2312[a]	0.0445
12-Day MADRS	0.6586[a,b]	−0.0096
21-Day MADRS	0.4703[a,b]	−0.0005
30-Day MADRS	0.4404[a,b]	0.1889
Correlations With CADSS Scores at 40 Minutes		
24-Hour MADRS	0.0075	0.2035
5-Day MADRS	−0.0449	0.2865
12-Day MADRS	−0.0370[b]	0.2771
21-Day MADRS	0.0054[b]	0.4233
30-Day MADRS	0.0095[b]	0.3148

Data are reported as Spearman's coefficients.

AWE-S, Awe Experience Scale; CADSS, Clinician-Administered Dissociative States Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

[a]Values indicate correlation is significant with false discovery rate–corrected $p < .05$.

[b]Values show a significantly different ($p < .05$) strength of relationship for AWE-S relative to CADSS among ketamine-treated participants, per Fisher's r-to-z transformation and comparison tests of correlations drawn from dependent samples.

were modestly (and nonsignificantly) correlated with reductions in depression in the saline group only (Table 2), suggesting that nonspecific factors (e.g., demand characteristics, placebo effects), rather than specific drug actions, may sometimes result in CADSS responses and depression outcomes being linked.

Other work suggests that ketamine's acute effects on consciousness extend beyond dissociation. In a recent qualitative exploration of the experience of ketamine based on patient interviews (14), the researchers posited that ketamine may cause psychedelic experiences, which in turn helps participants improve their outlook on challenges in their lives. Additionally, the interviews suggested that the psychological and mystical properties of ketamine are not fully captured by scales that measure dissociative symptoms. The same study also found that 3 subfactors of the 11-dimensions Altered States of Consciousness rating scale, unity, spirituality, and insight, were correlated with improved antidepressant outcomes among patients treated with ketamine. These findings are consistent with studies that have compared ketamine to psilocybin, a known psychedelic. Vollenweider and Kometer (32) administered the 5-dimensions Altered States of Consciousness rating scale to healthy participants alongside different dosages of ketamine and psilocybin. Both substances caused dose-dependent psychological experiences ranging from feelings of connectedness and an enjoyable blurring of ego boundaries to a more fear-invoking ego dissolution similar to psychosis (32). Studerus *et al.* (33) later found more nuanced differences between the 2 substances using the 11-dimensions version of the Altered States of Consciousness scale. Importantly, ketamine enabled spiritual and unitive experiences on par with psilocybin (33).

Our findings that awe experiences, but not general dissociation, statistically mediated improvements in depression are also consistent with findings from studies that were not focused on depression treatment. Ketamine-induced mystical experiences, measured by the Hood Mysticism Scale, have been shown to be associated with improved outcomes in cocaine use disorder (13,34) and alcohol use disorder (12). Similar to our findings, both these studies found that the Hood Mysticism Scale mediated the relationship between ketamine and improvements in symptoms of substance disorders, while CADSS scores did not.

More broadly, our findings are consistent with a growing literature documenting the therapeutic and/or quality-of-life benefits of awe experiences, which can be invoked through a wide range of stimuli, including contact with nature, art, moral

courage illustrated by others, and even everyday surroundings. Pioneers in this field have argued that awe is a fundamental human emotion, and its expression plays a critical role in our social behavior and sense of self (18,19,35). In addition, experiences of awe have been posited to have profound evolutionary importance by connecting individuals to collectives and helping them gain awareness of the systems around them. Humans have a natural tendency toward a narrow focus on both the self and cause-effect relationships, which may be further exacerbated in the context of depression (36). The experience of awe challenges this by bringing forth a systems view of life, which can have important implications for survival and provide a potential path to improved mental and physical health (18). In a study that explored the effects of a daily "awe-walk," where participants are taught to shift attention outward instead of inward and orient intentionally toward experiences of awe, results showed that compared with participants who took control walks, those who took awe walks exhibited greater self-diminishment (i.e., a beneficial lessening of hyper self-focus), joy, prosocial positive emotions, increasing objective smile intensity over the study, and decreases in daily distress (37). Additionally, in a representative national sample, dispositional tendencies to experience awe predicted greater generosity in an economic game above and beyond other prosocial emotions, such as compassion (35). Given that negative emotions are often found in a self-focused state, awe-inducing events may be an effective and rapid tool to aid individuals in connecting to something greater than themselves, with potential transformative impacts on life outlook, mental state, and social relationships.

Notably, the current findings, which suggest a therapeutic mechanism of ketamine captured at the psychological level of analysis, do not negate or contradict the wealth of findings regarding ketamine's neurobiological and molecular mechanisms of action, which have been studied extensively in both animal models and human patients, [including in overlapping subsets of patients drawn from this very clinical trial (9)]. As theorized previously (8,38), ketamine-induced enhancements in neuroplasticity—a key mechanism implicated in this robust literature (8,39)—may in fact be apparent across numerous levels of analysis in an integrated and/or synergistic fashion. Thus, ketamine's neuroplasticity mechanisms may include plasticity appearing in the form of psychological flexibility in human patients, and the immediate subjective experience of awe could be one manifestation (and/or accelerant) of such psychoplastogenic effects. Awe has previously been linked to enhanced cognitive flexibility (19) and related changes in neural network activation and connectivity (40–42), which suggests its potential relevance to the neurocognitive substrates of depression across multiple levels of analysis. The current findings encourage more work that adopts an integrative conceptualization of neuroplasticity, spanning traditionally separate literatures and methodologies. In addition to neuroplasticity, several alternative mechanisms that could relate to the current findings (e.g., lateral habenula/reward function, contextual factors) are outlined in the Supplement.

Our findings may have treatment implications for expanding on ketamine's therapeutic potential. Combining ketamine with mindfulness is a potential method by which the acute subjective psychological experience can be fostered in a clinical setting. Given that the experience of awe mediates the relationship between ketamine and improved depression scores, ketamine adjunctive therapies as well as the treatment context (set and setting) can both explicitly and implicitly encourage and support this subjective experience for patients. While such practices are routinely incorporated into clinical care in real-world ketamine clinics and other ketamine treatment modalities [e.g., at-home ketamine telehealth services (43)] and are supported by work that suggests a correlation between incorporation of psychotherapeutic techniques and beneficial outcomes (44) and certain preliminary clinical trial findings (34,45–47), studies with randomized designs are lacking to robustly validate the value gained through such adjunctive techniques. Additional research is needed to elucidate the role of mindfulness, postinfusion integration work, and other practices (e.g., cognitive behavioral therapy) that may support and encourage an experience of awe in the setting of ketamine infusion.

Limitations

The effect size for observed relationships between AWE-S scores and depression outcomes ranged from small to medium, which suggests that multiple additional sources of variance in depression outcomes were likely influential. For example, the parent clinical trial from which participants were drawn tested an adjunctive digital therapy (ASAT) designed to enhance and extend ketamine's impact on depression. This introduces an additional variable to the ketamine group that was not utilized in this secondary study due to the discrete goals of the current analysis (see the Supplement for sensitivity analyses exploring the potential impact of an ASAT condition). While the double-blind, randomized controlled design of this study is a strength, saline (an inert placebo) was selected for the control infusion so that all group differences in measured mechanisms would be fully attributable to ketamine's effects, as opposed to being confounded by the (potentially different or opposing) impacts of an alternate, psychologically and neurobiologically active substance [e.g., midazolam, which has been used to provide improved, but still imperfect, patient blinding in some ketamine trials (48,49)]. Saline offers inadequate protection against functional unblinding of participants in the context of a potent psychoactive medication such as ketamine (22), which leaves open the possibility that expectancy effects contributed to both self-reported awe experiences and clinical improvements in symptoms. The addition of a measure of expectancies would help minimize this limitation in future studies. Nevertheless, irrespective of the origin of patients' acute experiences of awe (whether expectancies, ketamine's psychopharmacological actions, or both), our findings link awe experiences prospectively during an isolated 40-minute period to improvements in depressive symptoms over a subsequent, much more enduring (30-day) period.

In this study, we did not randomize the order of administration of CADSS and AWE-S, and thus the prior administration of the CADSS might have affected patients' ratings on the AWE-S. Furthermore, the AWE-S was not part of the initial study design and was introduced after 25% of the sample had been recruited. Our methods did not include a measure of a participant's baseline propensity to experience awe or

inclination toward experiencing awe, but only captured participant's experiences during a specific event (an infusion of saline vs. ketamine). While our stratified, randomized design provides protection against baseline group differences, it is possible that unmeasured pre-existing personality traits or other psychological factors differed across groups or that such propensities helped to amplify (i.e., moderate) ketamine's acute effects in a subset of patients. Our design also did not include other active treatments and thus cannot delineate the specificity of our findings to ketamine per se; other antidepressant treatments (particularly those that exhibit acute psychoactive properties) may likewise involve changes in awe. Some additional factors may further limit the generalizability of our findings. First, our eligibility criteria, while designed to broadly reflect ketamine-treated patients in clinical practice, did not include individuals with bipolar depression or common comorbid psychiatric conditions including ongoing moderate-severe substance use disorders. Secondly, there is a lack of racial and ethnic diversity in our sample, which reflects both the geographic locale of study recruitment as well as the larger systemic issue of minority underrepresentation in research studies. Future studies with more diverse participants are needed to delineate the generalizability and applicability of ketamine infusion experiences across diverse populations.

Conclusions

In conclusion, our study suggests that the experience of awe during ketamine infusion may play a mediating role in both rapid and more sustained antidepressant effects over the course of 1 month. These enduring statistical mediation effects were observed even beyond the period when a significant overall impact of ketamine was noted across all ketamine-treated individuals, which suggests that individuals who do not report experiencing strong awe-like experiences during the infusion are more likely to experience a rapid return of depression. By contrast, individuals who reported very strong experiences of awe during the infusion were relatively buffered against depression's return for at least 1 month after a single infusion. In contrast, a commonly used tool aimed at capturing the general dissociative side effects of ketamine did not mediate depression outcomes. Awe is a multifaceted, foundational human emotion that has previously been tied to mental health and well-being (18,19,35). Our findings, obtained using a randomized controlled design, help illuminate the potential significance of awe as a component of the subjective psychological experience that unfolds during a ketamine infusion, which may contribute to ketamine's efficacy as a treatment for depression.

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RBP and BP conceived and designed the study and collected the data. JA and RBP analyzed and interpreted the data. JA drafted the manuscript. All authors critically revised the manuscript for important intellectual content, provided final approval, and agree to be accountable for all aspects of the work.

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RBP is the named inventor on a University of Pittsburgh–owned patent filing related to the combination intervention that was used in the parent clinical trial. All other authors report no biomedical financial interests or potential conflicts of interest.

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