Commentary

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The Role of Awe and Other Psychological Factors in Ketamine's Mechanism of Antidepressant Action

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As the use of ketamine and psychedelic-like treatments grows in psychiatry, a better understanding of the psychological experiences associated with these treatments becomes increasingly important. To date, research on ketamine's mechanisms of antidepressant action has focused on its specific pharmacological and neurobiological actions, such as the modulation of glutamatergic neurotransmission, neuroplastic effects generating long-term changes in synaptic structure and functional connectivity, and effects on cognitive processes such as reward sensitivity. However, ketamine also induces transient psychological experiences that may, independently of the specific pharmacology, mediate a portion of the antidepressant effect. Although these transient psychological experiences are frequently cited in relation to ketamine's mechanism of antidepressant action, studies have only recently rigorously explored the unique role that these psychological states play in relation to the antidepressant effect. The study by Aepfelbacher *et al.* (1) contributes to the field by identifying a psychological experience as a potential mediator of ketamine's antidepressant effects.

Awe, defined as an emotional response to something vast or beyond the ordinary, can lead to a sense of something larger than oneself. Awe was previously purported to be a mechanism underlying the antidepressant effects of psychedelic-like agents (2), and the work by Aepfelbacher *et al.* now suggests that it may also play a role in ketamine's mechanism of antidepressant action. However, we should be careful not to overinterpret the study's findings in relation to the specificity of awe in generating the clinical benefit because other factors related to one's ability to experience awe and prior expectations may also moderate and mediate the effect.

The study's findings have some similarities to the recent report by Lii *et al.* (3). That study sought to determine whether functional unblinding could be contributing to ketamine's large treatment effects. To ensure treatment blinding, the investigators conducted a placebo-controlled trial involving 40 adults with major depressive disorder undergoing routine surgery. The participants were administered either a single dose of intravenous ketamine (0.5 mg/kg) or saline-placebo while under general anesthesia, with the primary outcome being depression severity measured by the Montgomery–Åsberg Depression Rating Scale at several time points after infusion. The design proved effective at masking the treatment allocation because less than half of the patients in both groups were able to guess their treatment allocation correctly. Under these conditions, no significant difference in antidepressant response was observed between the ketamine and placebo groups, leading the authors to suggest that functional unblinding had markedly contributed to ketamine's large effect sizes in previous clinical trials. Surprisingly, however, participants in both groups responded remarkably well, with nearly 60% of participants in the ketamine group and 40% of participants in the placebo group meeting the remission criteria by day 2 after the infusion (3). The fact that so many people responded to the treatment while not being able to consciously experience the acute psychological effects induced by ketamine suggested that the transiently induced psychological effects were not necessary for many to benefit from the treatment. Moreover, the fact that the longer-term benefit of the treatment in the Lii *et al.* study was more closely associated with the participants' belief about their assignment to the active or placebo group further suggested that expectations could be a powerful component of the overall antidepressant response.

Given the findings of Lii *et al.*, it is important to consider the possibility that the experience of awe identified in this current article may be a proxy for other psychological mechanisms acting to enhance and alter treatment response. Contextual effects are increasingly being recognized as major factors contributing to treatment response rates in major depressive disorder (4), as they are across most areas of medicine (5). Many contextual factors likely contribute to the ultimate response, but the placebo effect, which is driven largely by expectations, conditioning, and therapeutic alliances, is believed to play a large role in generating the overall response. In relation to expectation effects, we see the power of perceived group assignment in randomized controlled trials across many fields of medicine (6).

In the current study by Aepfelbacher *et al.*, people who experienced awe might have been more likely to guess that they had received active ketamine, thus experiencing a greater response to treatment. However, the Clinician-Administered Dissociative States Scale measure of dissociation, which also suggested inadequate masking of treatment assignment, was not highly associated with ketamine response. Does this suggest that functional unblinding of treatment allocation and expectations did not contribute to the observed responses? Expectations can be shaped in different ways, including through social observation, verbal suggestion, anticipation of benefits, and previous experience (7). There may be several layers linking the belief in treatment assignment to clinical response. If participants are specifically primed to believe that

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there is a multistep process that mediates the clinical response, they may need to perceive evidence at each step of the process to receive the full benefit of the expectation effects. For example, if a participant, through previous media exposure or discussions with clinicians, concludes that a certain immediate effect (such as a sense of awe) is necessary to achieve the antidepressant benefit of the treatment, then simply believing that they received the active treatment may be insufficient to generate the expectation effect if they did not experience awe. This is a major concern with the design of many trials exploring the antidepressant benefits of psychedelic treatments that include intense preparatory sessions and prolonged treatment protocols facilitated by therapists. However, the design of the current study did not seem to provide much opportunity to influence participants' expectations about the effect of awe because the parent study was not focused on the effect of awe, there were no specific preparatory sessions to promote the idea, and the Awe Experience Scale was collected as a single questionnaire among many. To better study the effects of expectation in the future, it will be important to collect guess forms shortly after the study treatments are provided that assess not only the degree of confidence in treatment assignment but also the expectation that the treatment will lead to longer-term clinical benefits.

Another possible explanation for the study's findings is that people who experience awe may possess a trait associated with a greater propensity to respond positively to treatments such as ketamine, thus making the ability to experience awe a potential moderating factor and not necessarily demonstrating that the experience of awe is a mediating factor. It is also possible that the experience of awe rendered the participants more likely to respond to the Automated Self-Association Training (ASAT) app in the parent study (8). The ASAT was designed to promote positive self-associations through evaluative conditioning, eventually providing lasting depression relief induced by ketamine. The possible interaction between the ASAT and the experience of awe is highlighted by the fact that the investigators found the effect of awe on antidepressant response to grow over time, while the main effect of ketamine on response dramatically diminished.

It is also possible that the experience of awe and clinical response could be mediated through common mechanisms but not be causally related to each other. Studies have shown that ketamine may normalize the interaction between the default mode network (DMN) and the salience network. These effects on the DMN are commonly proposed as a contributing mechanism underlying ketamine's antidepressant effect (9). Other studies have also recently linked the DMN to the experience of awe (10), suggesting that it may be possible that ketamine's effects on the DMN may independently mediate the effects of awe and antidepressant response (Figure 1). In this sense, the early experience of awe may simply be a proxy marker for the drug's effects on the network. Additionally, it is possible that the ability of ketamine to modulate DMN function may pave the way for the ASAT app to provide optimal benefit.

Other factors such as use of only a single administration of ketamine and the lack of racial, ethnic, and cultural diversity also limit broader interpretation of the study's findings. However, all being said, this study undoubtedly adds an important new perspective to our understanding of how a variety of contextual factors and unique psychological experiences can modulate the response to a treatment beyond the specific pharmacological effects of the drug. An enhanced appreciation of the complex psychological factors that contribute to the therapeutic effects of a medication, whether it be a sense of awe or changes in expectations, can be used not only to better understand mechanism of action but also to optimize trial design and clinical practice more broadly.

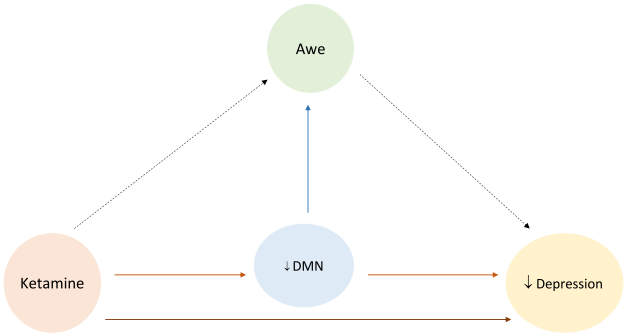

Figure 1. The solid brown and orange lines represent models where ketamine's mechanism of antidepressant action is either directly or partly mediated through decreased activity in the default mode network (DMN). The blue solid line represents an independent ability of DMN changes to mediate the experience of awe separately. The dashed line represents the mechanism proposed in the study by Aepfelbacher *et al.* through which awe mediates the antidepressant effect of ketamine.

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Article Information

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