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## **Ketamine's Acute Effects on Negative Brain States are Mediated through Distinct Altered States in Humans**

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Ketamine commonly and rapidly induces dissociative and other altered states of consciousness (ASCs) in humans. These experiences may involve detaching from negative affective states relevant to withdrawal from substances of abuse. However, the neural mechanisms that contribute to these experiences remain unknown. In a novel double-blinded, randomized, cross-over design, thirteen healthy subjects (mean age=33 years, 54% female) received two doses of IV ketamine including the standard antidepressant dose (0.5mg/kg) and a “low” dose (0.05mg/kg), as well as placebo over 40 minutes, 10 days apart. We used functional neuroimaging to assess key regions of the brain's negative affective circuit during social emotion processing in a facial emotion task. Ketamine-induced experiences were assessed with the Clinician-Administered Dissociative States Scale (CADSS) and 5-Dimensional Altered States of Consciousness Scale (5-DASC).

Ketamine induced a dose-dependent effect on multiple ASCs, including depersonalization, derealization, and amnesia assessed by the CADSS and states of bliss, anxiety, and impaired control rated by the 5-DASC ( $P$ 's<0.001,  $pFDR$ 's<0.05). In a causal mediation model, we showed that the differently valenced ASCs mediate opposing effects of ketamine on anterior insula activity during social fear processing. Participants experiencing relatively higher depersonalization induced by 0.5mg/kg of ketamine showed a reduction in anterior insula activity for social fear indicative of relief from negative brain states ( $a*b=-0.39$ ,  $p=0.004$ ). In contrast, participants experiencing dissociative amnesia ( $a*b=0.32$ ,  $p=0.046$ ) and anxiety ( $a*b=0.46$ ,  $p=0.08$ ) showed an exacerbation of anterior insula activity.

These findings highlight the importance of subject stratification in exploratory therapeutic trials. Additionally, they provide a novel reverse translational neural target for interrogation of causal mechanisms across human and animal models studies. Finally, they have important personalized therapeutic implications, as emerging evidence indicates that ketamine is a promising therapy for substance use disorders and that dissociative experience may be important to its therapeutic benefit in these disorders.

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