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Ketamine normalizes brain activity during emotionally valenced attentional processing in depression

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ABSTRACT

Background: An urgent need exists for faster-acting pharmacological treatments in major depressive disorder (MDD). The glutamatergic modulator ketamine has been shown to have rapid antidepressant effects, but much remains unknown about its mechanism of action. Functional MRI (fMRI) can be used to investigate how ketamine impacts brain activity during cognitive and emotional processing.

Methods: This double-blind, placebo-controlled, crossover study of 33 unmedicated participants with MDD and 26 healthy controls (HCs) examined how ketamine affected fMRI activation during an attentional bias dot probe task with emotional face stimuli across multiple time points. A whole brain analysis was conducted to find regions with differential activation associated with group, drug session, or dot probe task-specific factors (emotional valence and congruency of stimuli).

Results: A drug session by group interaction was observed in several brain regions, such that ketamine had opposite effects on brain activation in MDD versus HC participants. Additionally, there was a similar finding related to emotional valence (a drug session by group by emotion interaction) in a large cluster in the anterior cingulate and medial frontal cortex.

Conclusions: The findings show a pattern of brain activity in MDD participants following ketamine infusion that is similar to activity observed in HCs after placebo. This suggests that ketamine may act as an antidepressant by normalizing brain function during emotionally valenced attentional processing.

Clinical trial: NCT#00088699: https://www.clinicaltrials.gov/ct2/show/NCT00088699

1. Introduction

Currently available FDA-approved pharmacological treatments for major depressive disorder (MDD) take several weeks to achieve their full antidepressant effects, thus significantly impacting patient function and well-being and underscoring the urgent need for faster-acting medications to treat this disorder. The glutamatergic modulator ketamine has rapid antidepressant effects (Berman et al., 2000), even in treatment-resistant MDD (Zarate Jr. et al., 2006). However, much remains unknown about ketamine's precise mechanism of action in the brain, including its effects on neurobiology and specific depressive symptomatology.

In this regard, it would be valuable to examine the effects of ketamine on cognitive and affective processing domains, with particular interest in those previously found to differ in MDD, such as emotion processing. Specifically, numerous behavioral studies have suggested that, compared to healthy controls (HCs), individuals with MDD demonstrate a cognitive bias towards negative emotional information (Dalgleish and Watts, 1990; Mathews and Macleod, 1994). For instance, studies have reported biases for stimuli including depression- and anxiety-related words (Mogg et al., 1995), socially threatening words (Mathews et al., 1996), and sad faces (Gotlib et al., 2004; Joormann and Gotlib, 2007). However, some studies have also noted the absence of a behavioral bias in depression, such as with angry, sad, happy (Mogg et al., 2000), or fearful (Amico et al., 2012) facial expressions.

Dot probe attentional bias tasks have been used with emotion-related word and face stimuli to assess cognitive biases in depressed participants (Peckham et al., 2010). Generally in a dot probe task, two

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different stimuli are presented for a short time, followed by a dot in the same location as one of the prior stimuli. The participant responds to indicate the location of the dot, and reaction time is measured to analyze attentional bias towards a specific type of stimulus. Thus, the task can span both attentional and emotional processing domains. Notably, the administration of dot probe tasks during functional magnetic resonance imaging (fMRI) can identify brain regions associated with attentional bias towards or away from certain emotional stimuli. In general, neuroimaging findings may also be more stable (based on test-retest reliability) and sensitive than behavioral measures of attentional bias using this type of task (White et al., 2016). For example, fMRI results associated with a dot probe task showed activation differences between MDD participants and HCs associated with fearful stimuli in the absence of behavioral differences that would be consistent with an attentional bias; specifically, MDD participants had less activation in the left middle cingulum and left insula (Amico et al., 2012). Other fMRI research using dot probe tasks showed increased activation in temporo-parietal and occipito-parietal regions in response to fearful versus happy faces in HCs (Pourtois et al., 2006). In addition, decreased anterior cingulate cortex activation was found during incongruent trials across healthy and anxious youth participants (Price et al., 2014).

In addition to probing baseline differences in emotional processing, dot probe tasks can also be used to investigate neuroimaging changes associated with the influence of treatment. For instance, multiple dot probe studies have demonstrated the effects of anxiolytic treatments on attentional biases and related changes in the brain (Britton et al., 2015; Ironside et al., 2016); to date, however, research into treatment approaches for depression using dot probe tasks has been limited.

Due to its rapid onset and short duration of action, ketamine is uniquely suited to studying antidepressant response using cognitive tasks and fMRI. Indeed, recent research has examined ketamine's effects on cognitive and emotional processing using other cognitive tasks, though no studies have yet examined dot probe tasks specifically. Ketamine would also be expected to affect individuals with treatment-resistant MDD, given its demonstrated effects as a glutamatergic modulator and the potential dysfunctions of the glutamate system associated with depression (Niciu et al., 2014; Zarate Jr. et al., 2010). In an emotion perception task, participants with treatment-resistant MDD showed increased activation in response to positive emotion in the right caudate after ketamine treatment (Murrough et al., 2015), but this study included no placebo condition for comparison. In a working memory task with emotional stimuli in HCs, ketamine decreased activity in the left and right insula and right dorsolateral prefrontal cortex (DLPFC) specifically during negative emotion conditions (Scheidegger et al., 2016a). In HCs who received a single ketamine infusion, reduced activation was observed in an amygdalo-hippocampal area during emotional processing (Scheidegger et al., 2016b), as was greater deactivation in the anterior cingulate cortex (ACC) in response to negative stimuli (Lehmann et al., 2016). While these studies investigated ketamine's effects using fMRI, only limited conclusions can be drawn, given that they did not involve simultaneous longitudinal assessments of both MDD and HC participants, and most lacked a placebo control condition.

The current study is the first to use a dot probe task to investigate fMRI activation during emotion-related attentional bias in treatment-resistant participants with MDD and HCs across multiple time points. Participants were studied first at baseline and then at about two days and eleven days following ketamine and placebo infusions. We hypothesized that ketamine, in contrast to placebo, would alter brain activity in regions associated with emotional processing and depression. This activity could potentially vary in MDD participants versus healthy individuals, given that this has not yet been well-studied in ketamine fMRI research.

2. Method and materials

2.1. Participants

Participants in this study included 33 individuals with treatment-resistant MDD (12 M/21 F, mean age = 36.1 ± 9.7 years) and 26 HCs (10 M/16 F, mean age = 33.9 ± 10.4 years), ages 18 to 65. Diagnoses were made using the Structured Clinical Interview for DSM-IV-TR (SCID-P for MDD participants and SCID-NP for HCs) (First et al., 2002). Inclusion criteria for participants with MDD included an age of onset of < 40 years, a current depressive episode lasting at least four weeks, an initial score of at least 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS), and a past failure to respond to at least one adequate trial of an antidepressant during a depressive episode; on average, MDD participants had failed to respond to six antidepressant trials. All participants had no serious, unstable illnesses, as assessed via a medical screening by a clinician and by laboratory tests that included blood labs and urine drug screens; negative drug screens were also required throughout the study. Exclusion criteria included a history of drug or alcohol dependency/abuse within the past three months for MDD patients or any such diagnosis for HCs, psychotic symptoms, a medical illness likely to affect brain structure or physiology, any contraindications for MRI, and anatomical brain abnormalities found on a clinical MRI. MDD participants with comorbid Axis I disorders or personality disorders were not excluded. For HCs, exclusion criteria included a prior Axis I diagnosis or any psychiatric disorder in a first-degree relative.

Prior to the study, MDD participants were tapered off medications, followed by a drug-free period lasting at least two weeks before study procedures began. Participants were studied as inpatients at the National Institutes of Health (NIH) Clinical Research Center. All participants gave written informed consent to participate in the study, which was approved by the NIH Combined Neuroscience Institutional Review Board. Data drawn from other studies using the same participants have been previously published (Nugent et al., n.d.; Evans et al., 2018).

2.2. Study design

This study was part of a randomized, double-blind, placebo-controlled, crossover protocol (Nugent et al., n.d.); the study design is shown in Fig. 1. Participants first took part in a baseline fMRI scan and were subsequently randomized to receive either a ketamine (subanesthetic dose, 0.5 mg/kg over 40 min) or placebo (saline solution) infusion. Two weeks later, participants crossed over to receive the other treatment condition. MDD participants were required to have a MADRS score of at least 20 to cross over to the second treatment condition.

In order to examine drug effects in each treatment phase (post-ketamine and post-placebo), fMRI scans took place one to three days after each infusion; 95% of scans took place two days post-infusion. Additional interim fMRI scans were performed nine to 13 days after each infusion (interim-ketamine and interim-placebo); 85% of scans took place 11 days post-infusion. There was no between-group difference in the number of scans that took place on days other than the two-day and 11-day post-infusion time points. Thus, the five scan sessions in the study were baseline, post-ketamine, interim-ketamine, post-placebo, and interim placebo. Given that our main hypothesis centered around differences in fMRI activation between the post-ketamine and post-placebo time points, we focused on contrasts specific to these scan sessions, referred to hereafter as drug sessions. Throughout the study, the severity of depressive symptoms was assessed via the MADRS. MADRS scores were compared between pre-infusion and the day two post-infusion time point using paired *t*-tests and between groups at each of these time points using paired *t*-tests.

It should be noted here that not all participants had usable data for all five scan sessions, due to either exclusion for imaging data quality (excessive motion or poor alignment), exclusion for low accuracy on