ORIGINAL ARTICLE

Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder

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INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability worldwide and current treatments fall short of what is required to meet this large-scale public health problem.1-3 The discovery that the glutamate N-methyl-D-aspartate receptor antagonist ketamine produces rapid and robust antidepressant effects within one day of a single administration4—even in patients with treatment-resistant depression (TRD)5-9—has spurred research and treatment development focused the glutamate system and the N-methyl-D-aspartate receptor in depression. In this context, human in vivo neuroimaging research provides a unique opportunity to examine the neurocircuit functions regulated by ketamine relevant to its putative antidepressant mechanism of action.10

MDD is characterized by dysfunctional processing of social, emotional and reward-related information, leading to the cardinal clinical symptoms of pervasive depressed mood, anhedonia (i.e., reduced capacity to experience pleasure) and a negative cognitive bias.11-14 In particular, neuropsychological and neuroimaging investigations have confirmed a negative emotion processing bias as a central feature of MDD.12,15 Patients with MDD demonstrate increased attention and memory for negative social information (for example, pictures of human facial expressions) and a bias away from positive information.11,16-18 For example, depressed patients show a bias away from positive facial expressions16,19 and require a greater intensity of emotional expression to correctly identify happy (but not sad) emotion.11

Functional neuroimaging studies provide convergent evidence for valence-specific alternations in emotion processing in MDD.13,20,21 Increased neural responses to negative stimuli within anterior cingulate cortex, amygdala and paralimbic regions are observed in MDD, coupled with reduced responses to positive stimuli within regions of prefrontal cortex (PFC) and striatum, among other regions.13,20-23 Hypo-responsiveness to positive self-referential, social or reward-related information within the striatum and related PFC regions in particular is observed across multiple studies in MDD.24-27

Studies examining the effects of antidepressant treatment on neural responses to social and emotional stimuli are broadly consistent with the hypothesis that treatment leads to improvement in clinical symptoms by normalizing dysfunctional circuit activation.28,29 Previous studies have reported attenuated responses to negative stimuli within the amygdala or anterior cingulate cortex following treatment with a selective serotonin reuptake inhibitor,22,30 as well as increased responses to positive

The glutamate N-methyl-D-aspartate receptor antagonist ketamine has demonstrated antidepressant effects in individuals with treatment-resistant major depressive disorder (TRD) within 24 h of a single dose. The current study utilized functional magnetic resonance imaging (fMRI) and two separate emotion perception tasks to examine the neural effects of ketamine in patients with TRD. One task used happy and neutral facial expressions; the other used sad and neutral facial expressions. Twenty patients with TRD free of concomitant antidepressant medication underwent fMRI at baseline and 24 h following administration of a single intravenous dose of ketamine (0.5 mg kg−1). Adequate data were available for 18 patients for each task. Twenty age- and sex-matched healthy volunteers were scanned at one time point for baseline comparison. Whole-brain, voxel-wise analyses were conducted controlling for a family-wise error rate (FWE) of P < 0.05. Compared with healthy volunteers, TRD patients showed reduced neural responses to positive faces within the right caudate. Following ketamine, neural responses to positive faces were selectively increased within a similar region of right caudate. Connectivity analyses showed that greater connectivity of the right caudate during positive emotion perception was associated with improvement in depression severity following ketamine. No main effect of group was observed for the sad faces task. Our results indicate that ketamine specifically enhances neural responses to positive emotion within the right caudate in depressed individuals in a pattern that appears to reverse baseline deficits and that connectivity of this region may be important for the antidepressant effects of ketamine.

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Ketamine treatment
Following an overnight fast and admission to a clinical research unit, an indwelling catheter was placed in the antecubital vein of the nondominant arm, and pulse, blood pressure, digital pulse oximetry and ECG monitoring were instituted. Ketamine hydrochloride (0.5 mg kg\(^{-1}\)) was administered by an anesthesiologist via an infusion pump over 40 min as previously described. Patients remained overnight or were discharged home following a 4-h recovery period and underwent the second fMRI session ~24 h following the treatment.

Facial emotion perception task
All study participants underwent event-related fMRI during two separate emotion perception tasks. During each 8-min experiment, participants were presented with stimuli consisting of high emotion, low emotion or neutral facial expressions drawn from a standardized series of prototypical facial expressions. Subsets of the prototypical facial expressions were morphed to depict expressions of 50 or 100% affect intensity along the neutral-emotional expression continuum. The final stimuli set for each experimental session consisted of 21 prototypically happy or sad expressions (100% emotion); 21 mildly happy or sad expressions (50% emotion) and 21 neutral facial expressions presented in pseudorandomized order using E-prime software (Psychology Software Tools). Each facial stimulus was displayed for 2 s with an interstimulus interval varying from 3 to 13 s, with an average interval of 4.29 s. Participants were instructed to rate the emotional valence experienced in each stimulus by making a response using a fiber optic button system located under the right hand. Response options ranged from 1 to 5 with 1 indicating a very negative affect; 3 indicating a neutral affect and 5 indicating very positive affect. The order of the two experiments was randomized across participants.

Neuroimaging data acquisition
Participants were scanned with a Philips Achieva 3.0 T X-series MRI using an eight-channel birdcage headcoil for radio frequency transmission and reception. Functional data were acquired using a T2*-weighted gradient echo-planar imaging sequence (repetition time 2000 ms; echo time 26.6 ms; voxel dimensions: 2.2 mm × 2.2 mm × 2.5 mm; field of view 210 mm × 210 mm; flip angle = 90°) and 38 contiguous and ascending near-axial planes parallel to the AC–PC plane. For co-registration, high-resolution T1-weighted anatomical images were collected using a three-dimensional turbo field echo sequence (repetition time: 7.5 ms; echo time: 3.5 ms; voxel dimensions: 1 mm × 1 mm × 1 mm; field of view 224 mm × 224 mm; flip angle = 8°) and 172 sagittal planes.

Neuroimaging data analysis
Preprocessing. The functional imaging data preprocessing was completed using the Statistical Parametric Mapping software (SPM8) and Matlab (Mathworks, Natick, MA, USA) and included slice scan time correction, voxel-wise linear de-trending, intensity normalization, high-pass filtering, motion correction, co-registration, normalization to the Montreal Neurological Institute template, and three-dimensional smoothing (6 mm full width at half maximum).

fMRI modeling of brain activity. Whole-brain, voxel-wise general linear modeling was conducted separately for the two experiments using Neuroelf version 9c (http://neuroelf.net/). Models included three stimulus-type (100% emotion, 50% emotion, neutral) and six nuisance (motion) regressors convolved with a canonical hemodynamic response function. To identify brain regions specifically engaged by emotion perception, single-subject whole-brain maps reflecting the difference between the blood oxygen level-dependent signals recorded during 100% emotion and neutral stimuli (100% happy or 100% sad > neutral) were computed. Although the 50% morph condition was included in the model, our analyses focused on the 100% emotion vs neutral contrast as this contrast is expected to isolate the largest effect of emotion. To identify differences in neural responses between healthy volunteers and TRD participants at baseline (Time 1), difference maps were utilized in independent sample t-tests. To identify changes in neural responses following ketamine, difference maps for TRD participants were used in paired sample t-tests to identify voxels displaying significant changes in the blood oxygen level-dependent contrast between the pre- and posttreatment scans (Time 1 and Time 2, respectively). To control for multiple comparisons, Alphasim...
was implemented in Neuroelf to identify cluster size thresholds ensuring a whole-brain family-wise error (FWE) rate of $P < 0.05$.

To identify relationships between neural responses and depressive symptom severity, we followed up on the analyses above using significant cluster(s) as functionally defined regions of interest. Percent signal change for the contrast of interest (for example, happy 100% > neutral) within regions identified in the primary analyses was extracted and subjected to linear correlation analysis using either baseline MADRS score or % change in MADRS score. Finally, we examined potential associations between functional connectivity and symptom severity at baseline and following ketamine (see below).

Functional connectivity analyses. We investigated the functional connectivity of regions before and after ketamine that demonstrated main effects of time in the above analyses and the relationship between connectivity and change in depression symptoms following treatment. Following a psychophysiological interaction procedure, we constructed general linear models consisting of the three stimuli-type and six motion correction regressors previously described as well as the time course extracted from the seed, and the product of the seed time course and the 100% emotion stimuli regressor. This last regressor enabled the estimation of the degree of covariation between the seed’s time course and any voxel’s time course during 100% emotion trials only. We next inserted into the model each subject’s MADRS score percent change, and generated a second-level statistical map representing regions that showed significant correlations between MADRS score percent change and seed-functional connectivity values.

RESULTS

Participant characteristics and clinical outcomes

Twenty individuals with TRD underwent fMRI at baseline and 24 h following ketamine, and adequate data were available for 18 individuals for each fMRI task; 20 healthy volunteers underwent a single fMRI session (Table 1). The clinical characteristics and treatment response of a subset of individuals in the current study have been previously reported.8,9

See Supplementary Information for behavioral results of the neuroimaging tasks.

Neuroimaging results

Baseline comparison between TRD and healthy groups. During the positive emotion task, both groups demonstrated main effects of emotion (happy 100% > neutral) and there was a significant group × emotion interaction within the left insula and right caudate (Table 2). In both regions, the TRD group demonstrated hypoaactivity for the emotion > neutral contrast compared with the healthy group. In the right caudate, mean blood oxygen level-dependent percent signal for each condition show that responses to positive emotion are reduced in the TRD compared with healthy group, whereas the responses to neutral stimuli are similar (Figure 1). There were no significant results for the happy 50% > neutral contrast.

During the negative emotion task, no main effects of emotion or group × emotion interactions survived correction. See Supplementary Material for additional results.

Effects of ketamine treatment in TRD

For the positive emotion task, there was a significant interaction between emotion (happy 100% > neutral) and time yielding a large cluster centered in the right caudate (peak coordinates: 12,21,3; $k > 589$, FWE $P < 0.05$; Table 2, Figure 2). Mean blood oxygen level-dependent signal for each condition at Time 1 and Time 2 show that neural responses to positive emotion increased following ketamine whereas responses to the neutral stimuli remained approximately unchanged. There were no significant results for the happy 50% > neutral contrast.

During the negative emotion task, there was a significant time × emotion interaction within the left middle frontal gyrus. See Supplementary Material for additional results.

Relationships between brain activity and depressive symptoms

Since our primary hypotheses were not supported for the negative emotion task, no further analyses were performed. For the positive emotion task, no correlation was found between brain activation during the main contrast of interest (happy 100% > neutral) and depressive symptoms at baseline or following treatment within the functionally defined regions of interest (for example, insula or caudate) or in a follow-up whole-brain analysis.

Connectivity analysis revealed a significant correlation between right caudate connectivity following ketamine and clinical improvement using the functionally defined seed region identified in the primary analysis ($k > 451$, FWE $P < 0.05$; Figure 3). The analysis was repeated using an anatomically defined right caudate region and similar whole-brain corrected results were obtained (data not shown). At baseline, there was no association between caudate connectivity and depression symptom severity or subsequent improvement following treatment.

Table 1. Sample characteristics

|                        | TRD group (n = 18) | Healthy volunteers (n = 20) |
|------------------------|-------------------|---------------------------|
| Age, years             | 38.1 (13.8)       | 35.0 (8.9)                |
| Gender, male           | 10 (55.6%)        | 11 (55%)                  |
| Race                   | W: 13, AA: 2, A: 3 | W: 7, AA: 8, A: 1         |
|                        | M: 0, O: 0        | M: 3, O: 1                |
| Education, years       | 15.8 (2.0)        | 16.6 (2.5)                |
| Age at illness onset   | 14.3 (5.3)        |                           |
| Duration of illness, years | 24.2 (15.7)       | —                         |
| Duration of episode, years | 16.3 (18.1)       | —                         |
| Number of episodes     | 2.4 (1.7)         | —                         |
| Lifetime ADT failures  | 4.8 (2.0)         | —                         |
| Baseline MADRS score   | 29.9 (6.8)        | —                         |
| Posttreatment MADRS score | 16.4 (11.1)       | —                         |

Abbreviations: A, Asian; AA, African-American; ADT, antidepressant treatment; M, multiple; MADRS, Montgomery-Asberg Depression Scale; MDD, major depressive disorder; O, other; TRD, treatment-resistant depression; W, white. *Values based on participants completing the positive emotion perception task. Values shown are means (s.d.) or count (%).

Table 2. Brain responses during positive emotion task at baseline and following treatment with ketamine

| Brain region          | X (mm) | Y (mm) | Z (mm) | Cluster extent |
|-----------------------|--------|--------|--------|----------------|
| Baseline comparison between TRD and healthy groups |        |        |        |                |
| L insula              | -24    | 24     | 18     | 398            |
| R caudate             | 12     | 24     | 6      | 334            |
| Change in TRD group following ketamine              |        |        |        |                |
| R caudate             | 12     | 21     | 3      | 951            |

Abbreviations: FWE, family-wise error; L, left; R, right; TRD, treatment-resistant depression. Clusters indicate regions in which there are significant group (TRD > healthy) × emotion (happy 100% > neutral) or time (Time 2 > Time 1) × emotion (happy 100% > neutral) interactions. Coordinates describe location of cluster peak based on the Montreal Neurological Institute template. For baseline comparison, uncorrected $P < 0.05$, $k > 170$, FWE $P < 0.05$; for treatment effect, uncorrected $P < 0.05$, $k > 574$, FWE $P < 0.05$. 

Effect of ketamine on brain activity in depression

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DISCUSSION

The current study used positive and negative emotion perception tasks and fMRI to investigate the neurocircuitry effects of ketamine and associations with antidepressant response in unmedicated patients with TRD. At baseline, patients with TRD compared with healthy volunteers showed reduced responses to positive emotion within the caudate and insula. Following ketamine, responses to positive emotion were increased within the right caudate on the basis of whole-brain analyses. Functional connectivity of the right caudate during positive emotion was positively correlated with improvement in depression severity following ketamine. We did not find an association between baseline connectivity and change in symptom severity following ketamine. Taken together, our results demonstrate that ketamine regulates neural responses to positive emotion within the right caudate in depressed individuals and that increased caudate connectivity during positive emotion perception is associated with antidepressant effect following ketamine.

Our finding of reduced brain responses within the caudate to positive emotion in TRD is consistent with prior studies showing reduced striatal (caudate or putamen) activation in response to positive social and nonsocial stimuli in MDD and in the context of reward processing. A recent meta-analysis identified a cluster of hypoactivation in response to positive stimuli within the right caudate and putamen in MDD patients compared with a control group. The reason for the laterality of our finding is not completely clear, although we note that our right-sided caudate finding is consistent with the recent meta-analysis by Hamilton et al. Prior studies have suggested a general right lateralization of emotional functioning (reviewed in Wager et al.), although more recent investigations suggest a more complex picture. Although our study did not address reward processing per se, it is notable that reduced responses to rewarding stimuli are observed within the caudate and putamen in depressed patients and that smaller caudate volume has been associated with more severe depressive symptoms.

Our finding of reduced brain responses within the insula to positive emotion in MDD is partially consistent with prior reports, although there is considerable variability in the published literature. A recent meta-analysis found reduced activation within anterior insula in MDD to negatively valenced stimuli, whereas a separate meta-analysis found that insula responses were increased to negative (but not positive) stimuli in MDD. The reason for these disparate findings is not completely clear. The insula is known to have a key role in emotion processing, visceral awareness and, in particular, is linked to anxiety and disgust states. Future studies using task-based fMRI focused on specific cognitive emotional processes will likely be required to more fully elucidate the role of the insula in depression.

Contrary to our hypotheses, we did not observe robust differences in brain responses to negative emotion between the
TRD and healthy control groups. Prior individual studies using emotional faces tasks have found group differences\textsuperscript{22,23} and abnormal responses to negative stimuli in MDD more generally are well documented in meta-analyses.\textsuperscript{13,20,42} Although the reason for the absent finding in the current study is not fully known, it is noteworthy that the current study utilized an explicit facial emotion perception task, whereas the study by Surguladze et al.\textsuperscript{23} and other studies\textsuperscript{22} utilized an implicit processing task. We chose to use an explicit emotion perception task to allow us to measure the subjective judgment that subjects made regarding the emotion of the face, although this may have rendered the task less robust in probing limbic activation (for example, amygdala) in response to negative emotion. Another factor that may have contributed to our negative finding is suggested by a recent study showing that heightened amygdala responses to sad faces in depression was confined to a subgroup of patients with histories of childhood trauma.\textsuperscript{48} Although systematic measurement of childhood trauma was not available in the present study, the influence of trauma history on neurocircuit activation in depression will be an important direction for future research.

We found that ketamine rapidly reversed the blunted response to positive emotion within the caudate in patients with TRD. At the cellular level, subanesthetic doses of ketamine potentiate glutamate signaling in cortical and subcortical circuits\textsuperscript{49,50} and facilitate dopaminergic responses within the striatum.\textsuperscript{51–53} In vivo human imaging of the D\textsubscript{2} receptor suggests that ketamine potentiates amphetamine-induced striatal dopamine release,\textsuperscript{51} whereas a direct stimulation effect on striatal dopamine is less well supported.\textsuperscript{53} The striatum has a key role in emotion processing and reward learning.\textsuperscript{54} The dorsal striatum—corresponding to the caudate head—in particular is involved in linking motivation to action.\textsuperscript{55,56} The ventral and dorsal striatum receive dense glutamatergic projections from ventromedial PFC and orbitofrontal cortex conveying stimulus value information.\textsuperscript{54,57} Notably, disruption of glutamate signaling between ventromedial PFC and striatum or blockade of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor signaling within striatum results in depressive-like behaviors in animals\textsuperscript{58,59} and ketamine is known to enhance postsynaptic AMPA receptor signaling.\textsuperscript{55} These findings suggest that ketamine may lead to alleviation of depressive symptoms at least in part by reversing impaired glutamate signaling within PFC-striatal pathways.\textsuperscript{57} Ketamine was recently shown to reverse deficit dopamine signaling in a learned helplessness model of depression and normalized synaptic plasticity within the nucleus accumbens via activation of dopamine D1 receptors.\textsuperscript{60} Future studies utilizing fMRI tasks specifically designed to assay reward circuitry in humans will be required to more fully understand the impact of ketamine on reward functioning and its association with antidepressant therapeutic effects.

In the current study, ketamine was observed to alter brain responses during negative emotion processing within the left middle frontal gyrus, extending into the orbitofrontal cortex. Specifically, we observed reduced deactivation to sad faces and greater deactivation to neutral faces following ketamine. Since we did not detect baseline differences between the TRD and healthy control groups during sad compared with neutral faces, however, the meaning of the observed findings is not entirely clear. Ventral PFC and orbitofrontal cortex regions are critically involved in value attribution,\textsuperscript{61,62} reward processing\textsuperscript{27} and emotion regulation,\textsuperscript{63,64} therefore, it will be important for future studies to more specifically examine the impact of ketamine on these processes.

The current findings do not address the question of the specificity of the observed effect of ketamine on neurocircuit activation since alternative putative rapidly acting antidepressants or conventional antidepressants were not included in the study. Prior studies investigating the neural effects of antidepressant treatment in humans have produced somewhat inconsistent results with regard to the striatum.\textsuperscript{28,29,42} Studies have reported both increases and decreases in response to an affective challenge within the putamen following antidepressant treatment\textsuperscript{42} and conventional antidepressants have not been clearly associated with increased striatal responses to positive emotion.\textsuperscript{29} Our current findings suggest that robust regulation of neural responses to positive emotion within the caudate, in contrast to conventional antidepressants, may either be a relatively unique effect of ketamine or may be characteristic of a rapidly acting antidepressant more generally. Future studies directly comparing
ketamine to conventional antidepressants or to other putative rapidly acting agents will be required to further elucidate these issues.

Our study has several limitations. The current study did not include a placebo treatment condition, therefore the potential influence of nonspecific effects related to time or other factors on the observed changes in the TRD group cannot be fully evaluated. The healthy control group did not receive ketamine, therefore, it is not known whether the observed effect of ketamine on caudate activation is specific to depression or if a similar effect would be observed in the absence of depression. Individuals were scanned ~24 h following a single ketamine infusion, thereby limiting interpretations to this timeframe. Image acquisition at the 24-h time point allows us to capture neural changes associated with rapid therapeutic response, while avoiding the confounding effects of acute sedation or dissociation. However, our study cannot address important issues related to durability of antidepressant response. Our healthy control group was scanned at one time point to facilitate the interpretation of baseline brain responses in the TRD group before treatment. However, obtaining repeated scans in the healthy group would have permitted a more thorough evaluation of nonspecific practice effects.

In conclusion, our results show that ketamine rapidly increases brain responses to positive emotion within the caudate in patients with TRD. These changes are consistent with a pattern of normalization of a blunted response to positive emotion in TRD at baseline. Future studies will be required to determine the specificity and duration of this effect and to confirm the specific role of the striatum in the neurobiology of depression and in the antidepressant mechanism of action of ketamine.

CONFLICT OF INTEREST
In the past 3 years, JWM has served on advisory boards for Janssen Research and Development and Genentech, has provided consultation services for ProPhase, LLC and Impel Neuropharma and has received research support from Janssen and Avanir Pharmaceuticals; he is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders. DVI has consulted for Avanir, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, Servier, Sunovion and he has received grant/research support through Mount Sinai School of Medicine from Alkermes, AstraZeneca, Brainway, Euthymics Bioscience, Neosync, Roche and Shire. DSC (Dean of Icahn School of Medicine at Mount Sinai) and Icahn School of Medicine at Mount Sinai have been named on a use patent on ketamine for the treatment of depression. The Icahn School of Medicine has entered into a licensing agreement for the use of ketamine as therapy for treatment-resistant depression. DSC and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approval if ketamine were to gain approval.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)