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Archival Report

Effects of Ketamine on Brain Activity During Emotional Processing: Differential Findings in Depressed Versus Healthy Control Participants

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ABSTRACT

BACKGROUND: In the search for novel treatments for depression, ketamine has emerged as a unique agent with rapid antidepressant effects. Experimental tasks involving emotional processing can be used during functional magnetic resonance imaging scanning to investigate ketamine's effects on brain function in major depressive disorder (MDD). This study examined ketamine's effects on functional magnetic resonance imaging activity during an emotional processing task.

METHODS: A total of 33 individuals with treatment-resistant MDD and 24 healthy control participants (HCs) took part in this double-blind, placebo-controlled crossover study. Participants received ketamine and placebo infusions 2 weeks apart, and functional magnetic resonance imaging scans were conducted at baseline and 2 days after each infusion. Blood oxygen level–dependent signal was measured during an emotional processing task, and a linear mixed-effects model was used to analyze differences in activation among group, drug, and task-specific factors.

RESULTS: A group-by-drug interaction was observed in several brain regions, including a right frontal cluster extending into the anterior cingulate cortex and insula. Participants with MDD had greater activity than HCs after placebo infusion but showed lower activity after ketamine infusion, which was similar to the activity in HCs after placebo. A group-by-drug-by-task condition interaction was also found, which showed further differences that varied between implicit and explicit emotional conditions.

CONCLUSIONS: The main results indicate that ketamine had differential effects on brain activity in participants with MDD versus HCs. The pattern of activation in participants with MDD after ketamine infusion resembled the activation in HCs after placebo infusion, suggesting a normalization of function during emotional processing. The findings contribute to a better understanding of ketamine's actions in the brain.

Keywords: Brain activity, Depression, Emotion, Face processing, fMRI, Ketamine

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Depression is a highly prevalent mental illness estimated to affect more than 300 million people worldwide, and it is thought to have the largest impact on disability of all disorders (1). Nevertheless, most treatments for major depressive disorder (MDD) benefit only a fraction of all individuals with the disorder, and current antidepressants often take weeks to have an effect. Recent research has shown that ketamine, a glutamatergic modulator, has rapid antidepressant effects in MDD and in treatment-resistant depression (2–5).

Broadly, neuroimaging research has been used to study differences between individuals with MDD and healthy control participants (HCs), particularly in relation to emotional processing. Previous functional magnetic resonance imaging (fMRI) research found increased activation in prefrontal and limbic regions in participants with MDD during emotion regulation, along with differences in areas of the anterior cingulate cortex (ACC), as shown by a review of various emotion-related tasks (6). Specifically, studies found increased activity in ventrorostral ACC and decreased activity in dorsal ACC during the viewing of emotional stimuli, including pictures, faces, and words (7). With regard to valence of emotion, increased response to negative stimuli in emotional processing regions in participants with MDD, and decreased response to positive stimuli, have been found in a meta-analysis of multiple types of emotion processing tasks (8) and in a review of emotional face processing tasks (9). This may represent a bias toward negative stimuli and has even been observed with implicit viewing of emotional faces in a backward masking task (10). It should be noted, however, that varied findings in the literature suggest that both increases and decreases in activation are associated with valence of emotional stimuli. Behaviorally, emotional processing biases have often been found in MDD, with greater attention toward negative emotional stimuli and away from positive emotional stimuli (11,12).

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fMRI has also been used in depressive disorders–related research to investigate the effects of pharmacological treatment on blood oxygen level–dependent (BOLD) signal in the brain. In general, traditional antidepressants have been found to normalize brain function in areas of under- or overactivation in participants with MDD (as compared with HCs) (13,14). Decreased activation during emotional processing has been shown in the amygdala, anterior and posterior cingulate, insula, and precuneus, and increased activation has been observed in mainly prefrontal regions after antidepressant use (15,16). An attenuated response to negative stimuli and an increased response to positive stimuli have also been found in conjunction with implicit processing of emotion after antidepressant treatment in the ACC (17).

In this context, neuroimaging studies—and fMRI in particular—are a valuable way to explore how ketamine affects brain function in MDD. To date, only a few studies have investigated ketamine's effects on brain activity during emotional processing. In one study, ketamine increased activation in the right caudate of participants with MDD while they viewed positive faces (14), although it should be noted that this study lacked a placebo control. In emotion-related tasks in HCs, ketamine was found to decrease activity in the amygdala (18), hippocampus (18), insula (19), dorsolateral prefrontal cortex (19), and pregenual ACC (20). While these previous studies provide some information on ketamine's effects, none included both participants with MDD and HCs and most lacked a placebo control, thereby limiting the conclusions that can be drawn from the findings. A recent study by our research group using an attentional bias task with emotional faces found that ketamine normalized brain activity in several regions, such that the pattern of activation in participants with MDD after ketamine infusion was similar to the activation in HCs after placebo infusion (21). Moreover, the activation in HCs post-ketamine was also more similar to the activation in participants with MDD post-placebo.

The current study used an emotional processing task to examine the effects of ketamine versus placebo on BOLD signal in participants with MDD and HCs. This task involved both explicit and implicit emotional processing, along with positive and negative stimuli. Building on our previous work that used a different type of emotion-related task [an attentional bias dot probe task with emotional stimuli (21)], we hypothesized that ketamine would affect BOLD activity differentially in participants with MDD versus HCs. Specifically, we expected that ketamine would generally decrease activation across the brain in participants with MDD and that their activity patterns would become more similar to those of HCs after placebo. This finding would be consistent with ketamine's putative ability to normalize brain function. In HCs, we expected to find a different pattern, including areas of increased activation post-ketamine, which would also be consistent with findings from our previous study. We also expected that ketamine's effects would vary depending on the condition of explicit versus implicit emotional processing. Specifically, we predicted that participants with MDD would generally be more attuned to the emotions depicted in the facial expressions associated with the task, regardless of whether they were processed explicitly or implicitly, and that HCs would be less sensitive to the emotional component in the implicit processing condition; thus, we expected to observe greater differences in brain activity between the explicit and implicit conditions in the HC group versus the MDD group. Relatedly, we hypothesized that, post-ketamine, BOLD response in participants with MDD would be more similar to the activity patterns observed in HCs post-placebo, resembling a normalization of brain function during emotional processing.

METHODS AND MATERIALS

Participants

In total, 33 participants with treatment-resistant MDD (13 male and 20 female; mean age = 35.9 ± 9.8 years) and 24 HCs (9 male and 15 female; mean age = 34.4 ± 10.7 years) were included in the analyses for this study. Diagnoses were ascertained using the Structured Clinical Interview for DSM-IV-TR (patient edition for participants with MDD and nonpatient edition for HCs). Participants ranged in age from 18 to 65 years. Data regarding the participants in this study have been previously reported as part of a larger study on ketamine's mechanism of action (21–23) (NCT identifier number: NCT00088699). For inclusion and exclusion criteria, see the Supplement.

Participants took part in the study as inpatients on the research unit at the National Institutes of Health Clinical Research Center. Before study procedures began, participants with MDD were tapered off medications (if applicable) and had a drug-free period of at least 2 weeks. All participants gave written informed consent to participate in the protocol, which was approved by the National Institutes of Health Combined Neuroscience Institutional Review Board.

Study Design

The study was part of a randomized, double-blind, placebo-controlled crossover trial (21–23) (Figure 1) to explore ketamine's mechanism of action. A baseline fMRI scan was performed at the beginning of the study. Participants were then randomized to receive an infusion of ketamine (0.5 mg/kg over 40 minutes) or placebo (saline solution) and received the other treatment condition 2 weeks later. After each infusion, an fMRI scan was conducted 1 to 3 days post-infusion (with 95% of scans at the 2-day time point). Severity of depressive symptoms was measured at several time points using the Montgomery–Åsberg Depression Rating Scale (MADRS). MADRS scores were compared between groups and between pre-infusion (60 minutes before) and scan day time points (baseline, post-ketamine, and post-placebo) using a mixed model with group, time, and drug as factors.

Some participants did not have usable data for all three scans (baseline, post-ketamine, and post-placebo), either because they did not complete all scans or because scans were excluded for too much motion, poor alignment of functional data with structural data, or low accuracy (<50%) on the task. The number of usable scans for each session was 33 MDD and 20 HC for baseline, 28 MDD and 15 HC for post-ketamine, and 26 MDD and 15 HC for post-placebo (Figure 1). The gender distribution for the usable data for each of the scan sessions was 58% female and 42% male for

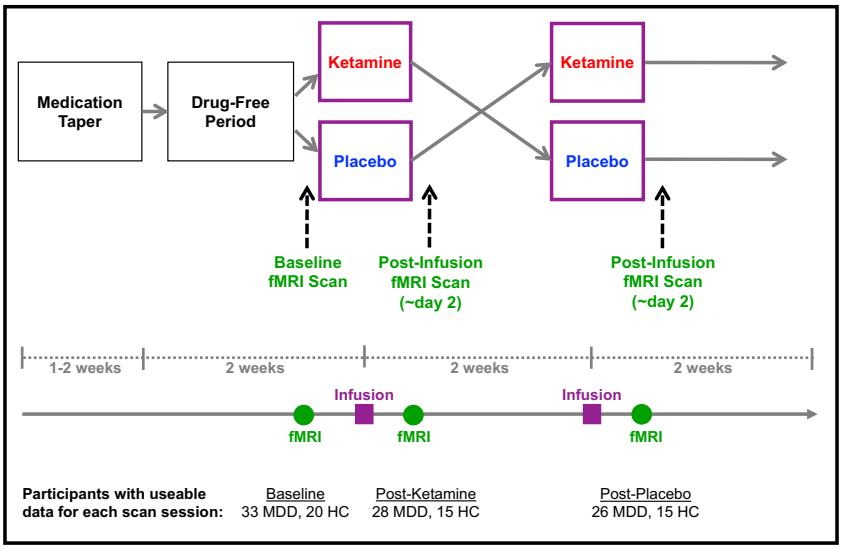

Figure 1. Study design. A representation of the double-blind, placebo-controlled crossover protocol is shown. Time points for the functional magnetic resonance imaging (fMRI) scans used in the current study are indicated in green. The number of participants with usable data for each time point is listed at the bottom. HC, healthy control group; MDD, major depressive disorder group.

baseline, 65% female and 35% male for post-ketamine, and 56% female and 44% male for post-placebo.

Experimental Task

In the emotional processing task (Supplemental Figure S1), faces with emotional expressions (sad, angry, happy, or neutral) were randomly presented, either right side up or upside down (to increase task difficulty). Each face was presented individually for 750 ms, with a 2500-ms interstimulus interval during which a fixation cross appeared. There were two runs of the task—each 4.8 minutes long—and each run comprised two blocks of about 1.75 minutes each along with instruction screens for each block and fixation periods. In one block—the explicit emotion processing condition—participants pressed a button to judge the emotion of the face (one button for sad or angry [classified as negative] and the other button for neutral or happy [classified as positive]). The emotions were grouped in this way so as to have only two response options, making it consistent with having two options for the implicit emotion processing condition of the task. In this block, participants identified the gender of the face (one button for male and the other button for female). Because limited prior research exists regarding ketamine's effects on emotional processing (and particularly on any specific component of such processing), this task was used to explore ketamine's effects on multiple factors, including valence of emotion and explicit versus implicit processing, with upside-down faces included to examine whether the increased difficulty of these trials would affect any such effects.

Imaging Acquisition and Analysis

fMRI data were acquired on a 3T General Electric HDx scanner (GE Signa, Milwaukee, WI) using an eight-channel head coil. BOLD signal was measured using echo-planar imaging with a T2*-weighted sequence (echo time = 23 ms, repetition time = 2500 ms, voxels = 3.75 × 3.75 × 3.5 mm, flip angle = 90°, matrix = 64 × 64, 45 sagittal slices, phase encode direction = anterior–posterior, interleaved acquisition). For each run, the first four repetition times were discarded for time-series stabilization. A high-resolution anatomical scan was acquired for alignment. Data were preprocessed with AFNI (24) using afni_proc.py (specific procedures are described in the Supplement).

For the first-level analyses, regressors were created for each participant to model individual trial types categorized by each combination of the three task-related factors: negative or positive emotion, right-side-up versus upside-down face direction, and judging emotion or gender. Regressors were also included for instruction screens, and fixation periods were used as baseline. For the group-level analysis, a whole-brain analysis was conducted using a linear mixed-effect model to analyze activation estimates from the event-related findings from each participant's first-level analysis that corresponded to each of the different individual trial types. The model included the following factors: emotion (negative or positive), face direction (right side up or upside down), condition (judging emotion or gender), scan session (baseline, post-ketamine, or post-placebo), and diagnostic group (MDD or HC). 3dClustSim with the autocorrelation function method in AFNI (25) was used to calculate a familywise error (FWE)-corrected threshold of $p < .05$ starting with an initial voxel-level threshold of $p < .001$. This resulted in a cluster size of at least 11 voxels for significant clusters. *F*-test results were initially examined for each factor and interaction; general linear tests (from within the same overall model) were then used to further investigate the directionality of significant results. For results associated with session, we focused on the contrast between ketamine and placebo sessions because our main aim was to study drug-related effects. For interaction effects, we extracted and graphed BOLD percentage signal change for each combination of factors involved in the interaction so as to examine the directionality of the interaction.

Behavioral Data Analysis

Accuracy and reaction time on the task were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY). If a participant

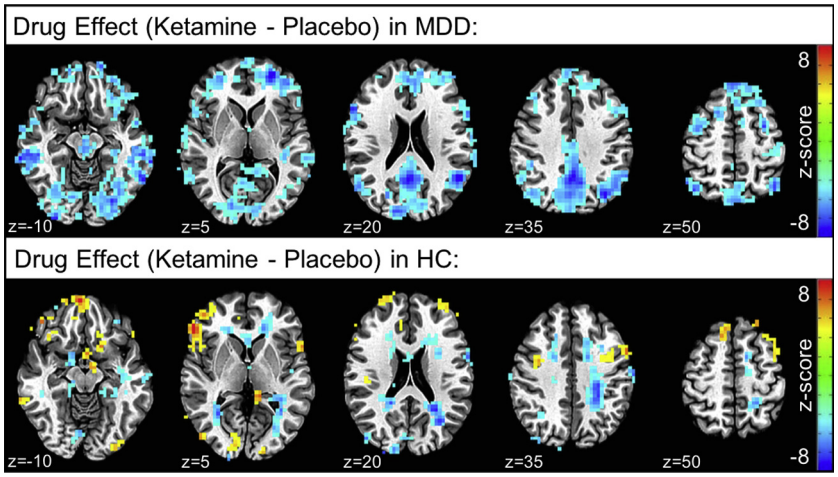

Figure 2. Drug effect in each group separately. Regions of activity that differed between post-ketamine and post-placebo scan sessions in the major depressive disorder group (MDD) (top) and the healthy control group (HC) (bottom) (left = right) are shown. Contrast is post-ketamine minus post-placebo (with yellow indicating greater activity post-ketamine and blue indicating less activity post-ketamine).

performed with less than 50% accuracy (chance accuracy for the two-option response) for a session, the participant's data for that session were excluded from both imaging and behavioral analyses. Baseline behavioral data from one participant were missing owing to an issue with response recording, but that participant's imaging data were included in fMRI analysis because of acceptable behavioral responses at the other time points. To include only valid responses, reaction times less than 200 ms were excluded. All reaction times were less than 3000 ms. A mixed model was used for each of the accuracy and reaction time analyses, with the same factors as the imaging analysis (emotion, face direction, condition,

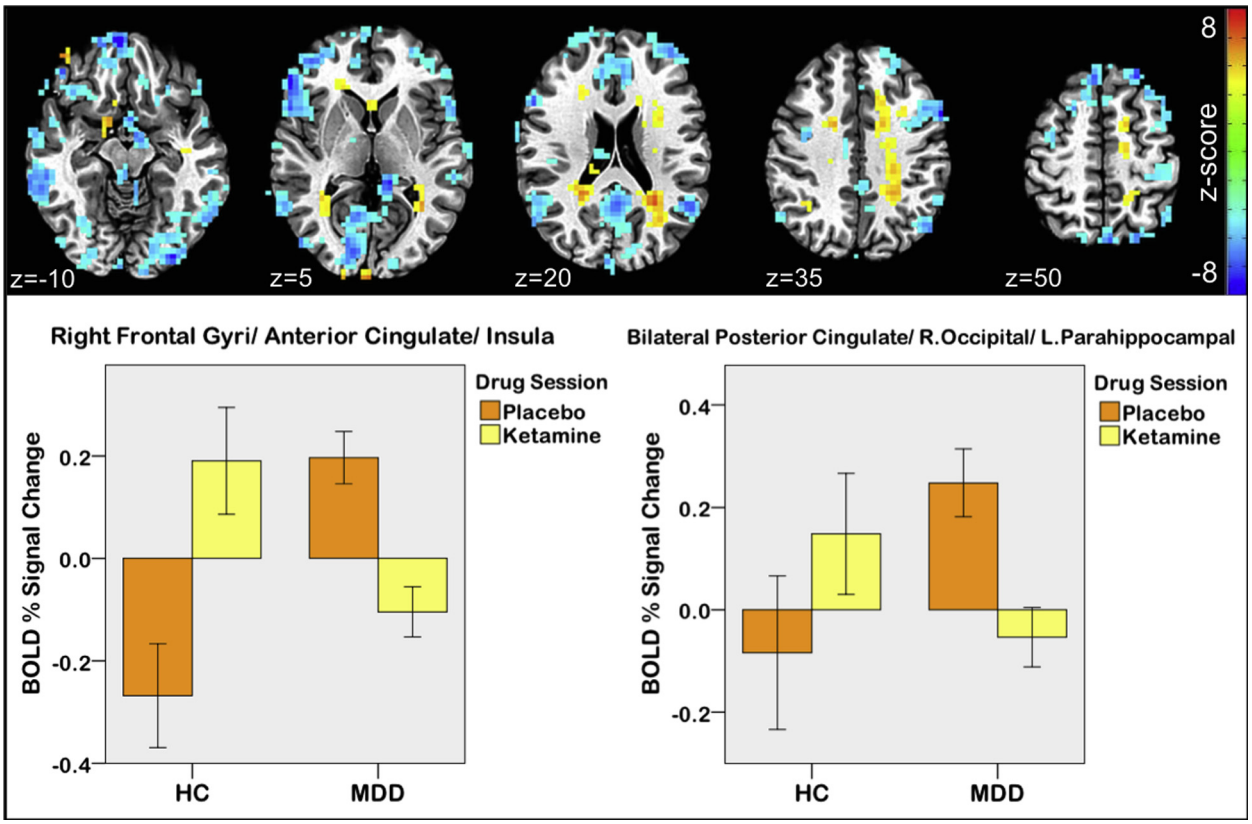

Figure 3. Drug (post-ketamine or post-placebo)-by-group interaction. Regions of activity for the drug-by-group interaction are displayed on brain images (left = right). Extracted values from two clusters are graphed to visualize the directionality of interaction effects. BOLD, blood oxygen level–dependent; HC, healthy control group; L., left; MDD, major depressive disorder group; R., right.

session, and group) and a threshold of $p < .05$. For the reaction time analysis, only correct trials were included.

RESULTS

Participants

Participant groups did not significantly differ with regard to gender or age. The analysis of MADRS scores resulted in a significant group-by-time-by-drug interaction ($p = .002$). This interaction effect showed that in participants with MDD, MADRS scores decreased significantly from 60 minutes pre-ketamine infusion to the day of the scan (pre-infusion mean score = 33.8; post-infusion mean score = 24.0). No such association was observed post-placebo infusion (pre-infusion mean score = 32.5; post-infusion mean score = 30.7).

Neuroimaging Results

Main Effects. Main effects were found for session and condition, but not for group, emotion, or face direction. With regard to the main effect of session, we focused on the contrast between the post-ketamine and post-placebo scan sessions as the drug effect (as per our hypothesis). For the drug effect, significant differences were found in several regions throughout the brain ($p_{FWE} < .001$), primarily showing less activation post-ketamine. These areas included the bilateral middle/medial frontal gyri, anterior and posterior cingulate, and parietal and occipital regions. The main effect of condition ($p_{FWE} < .001$) showed widespread areas in which greater activation was observed during the emotion (explicit) condition versus the gender (implicit) condition. Some regions also showed the opposite finding, including the bilateral medial frontal gyri and precuneus/posterior cingulate. Although no main effect was observed for group, a group effect was specifically noted during the baseline scan ($p_{FWE} < .001$) (Supplemental Figure S2). Participants with MDD showed greater activity than HCs in the bilateral cuneus/lingual gyrus, left temporal and medial frontal gyri, and right parietal cortex, and less activity was observed in the left cingulate gyrus and right lentiform nucleus.

Drug effect (post-ketamine vs. post-placebo) was also examined separately in each group across all task-related factors (emotion, face direction, and condition) (Figure 2). In the MDD group, large areas showing less activation after ketamine were observed, including the bilateral frontal, temporal, precuneus, and posterior cingulate regions ($p_{FWE} < .001$); no areas showing greater activation were found. In the HC group, some regions showed less activation post-ketamine, including the bilateral cingulate cortex, while other regions showed greater activation, including a large frontal cluster ($p_{FWE} < .001$).

Group-by-Drug Interaction Effects. A significant group-by-drug interaction (across all task-related factors) was found in a large cluster that included areas of the right frontal gyri, ACC, and insula as well as a cluster in the bilateral posterior cingulate (extending into the right occipital cortex and left parahippocampal gyri) and numerous other regions ($p_{FWE} < .001$) (Figure 3 and Table 1). When this interaction was graphed to examine its directionality, most of the regions showed that, post-placebo, participants with MDD had greater activation than HCs. Post-ketamine, this pattern was reversed, with activation decreasing in participants with MDD and increasing in HCs (Figure 3).

Table 1. Drug (Post-ketamine or Post-placebo)-by-Group Interaction

Region	x	y	z	Number of Voxels
Right Frontal Gyri/Anterior Cingulate/Insula	54	31	3	1144
Bilateral Posterior Cingulate/Right Occipital/Left Parahippocampal	−12	−36	7	532
White Matter Near Left Cingulate Gyrus	−26	−47	17	433
Right Temporal Gyri	61	−12	−15	374
Left Superior Temporal/Inferior Frontal Gyri	−37	20	−25	287
Left Fusiform/Temporal Gyri	−54	−61	−15	204
Left Occipital/Lingual Gyri	−30	−85	−11	199
Left Middle Frontal Gyri	−54	10	38	169
Left Cerebellum	−19	−29	−46	147
Right Cerebellum	33	−26	−43	116
Left Precuneus	−23	−71	49	95
Left Superior Temporal Gyrus	−47	−50	17	71
Left Superior Frontal Gyrus	−23	34	49	70
Left Postcentral Gyrus	−47	−26	56	67
Left Cerebellum	−12	−61	−50	59
Bilateral Precuneus	−5	−75	49	57
Bilateral Subcallosal Gyri	−2	6	−11	56
Left Superior Temporal/Inferior Frontal Gyri	−51	10	−4	51
Bilateral Cerebellum	2	−33	−15	50

Brain regions found in the drug-by-group interaction effect are shown. Coordinates indicate peak activity of cluster. Owing to the extensive list of significant findings, only clusters of at least 50 voxels are listed. For clusters in the table: voxel-level $p < .001$; cluster-level $p_{familywise\ error} < .001$.

Group-by-Drug-by-Condition Interaction Effects. A significant group-by-drug-by-condition interaction was also observed. This finding included clusters in bilateral medial/superior frontal gyri, temporal gyri, and precuneus/posterior cingulate ($p_{FWE} < .001$) (Figure 4 and Table 2). Graphing this interaction showed slightly different patterns depending on the specific region. Activation from the left temporal gyri and bilateral precuneus/posterior cingulate clusters is shown in Figure 4. In general, the amount of activation varied according to explicit versus implicit condition; this occurred differentially in placebo versus ketamine scans and in the opposite direction for participants with MDD versus HCs. Based on the values in the graph (Figure 4) for the left temporal gyri, the activity pattern showed a greater difference between explicit and implicit processing conditions in HCs than in participants with MDD post-placebo. This comparison was in the opposite direction after ketamine infusion, with greater differences between conditions in participants with MDD.

Behavioral Results

Graphs displaying percentage accuracy and reaction time for each group and session are shown in Supplemental Figure S3.

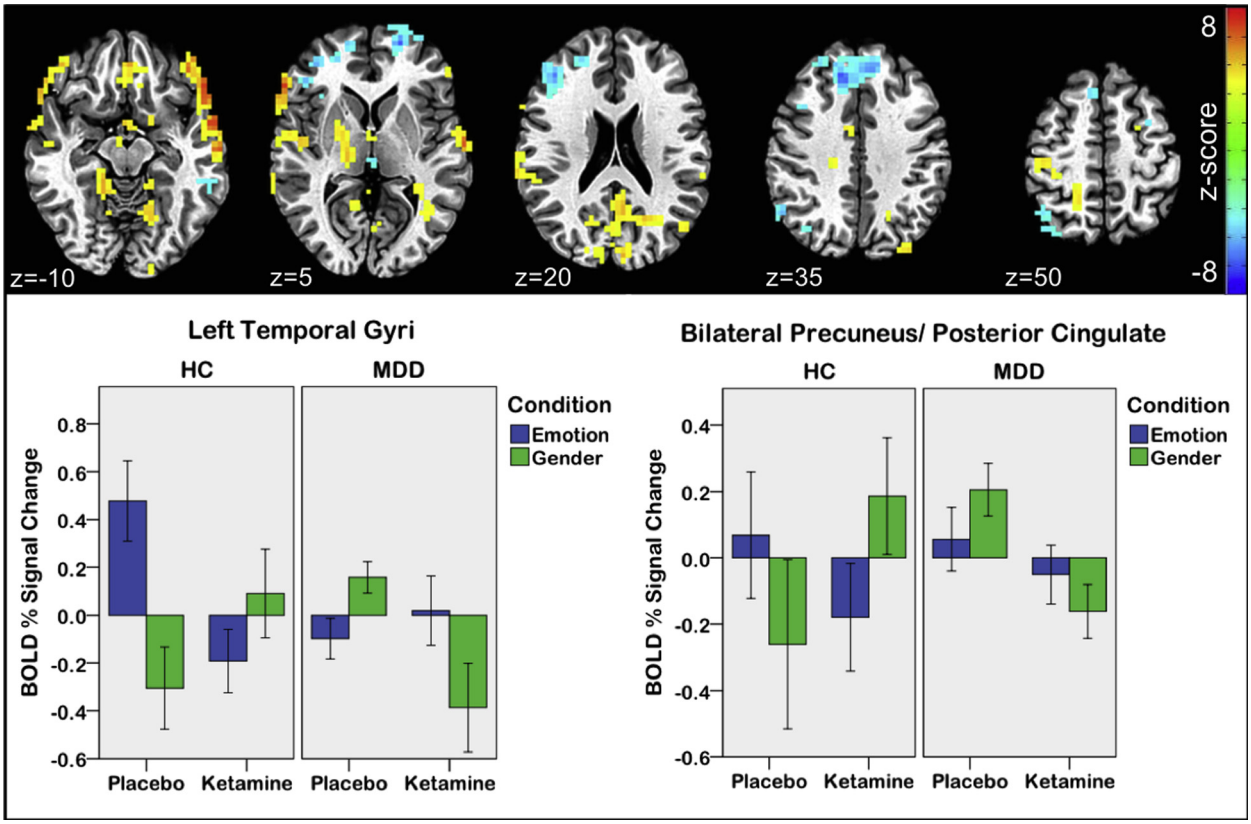

Figure 4. Drug (post-ketamine or post-placebo)-by-group-by-condition interaction. Regions of activity for the drug-by-group-by-condition interaction are displayed on brain images (left = right). Extracted values from two clusters are graphed to visualize the directionality of interaction effects. BOLD, blood oxygen level–dependent; HC, healthy control group; MDD, major depressive disorder group.

A main group effect for accuracy (p = .014) was observed, with higher accuracy in participants with MDD, but no group effect was found for reaction time (p = .700). There was a trend toward a main effect of session for accuracy (p = .075) but no session effect for reaction time (p = .758). Main effects were seen for the three task factors (condition, emotion, and direction) for both accuracy and reaction time (all ps $<$ .005). Participants were more accurate and faster in responding to the gender versus emotion condition, to positive versus negative faces, and to right-side-up versus upside-down faces. A trend toward a group-by-session interaction (p = .055) was observed for accuracy, in which groups differed at baseline (trend level: p = .082) and post-placebo (p = .001) (with higher accuracy in participants with MDD) but not post-ketamine (p = .303). No group-by-session interaction for reaction time was found (p = .791).

DISCUSSION

This double-blind, placebo-controlled crossover study examined the effects of ketamine on BOLD activity during an emotional processing task in both participants with MDD and HCs. Ketamine affected several regions across the brain, and the effects of ketamine versus placebo were often opposite in the MDD versus HC groups. In individuals with MDD, activation was generally lower post-ketamine versus post-placebo, whereas activation was generally higher post-ketamine in HCs. Furthermore, brain activation in some areas varied by task condition (explicit vs. implicit emotional processing).

When comparing activation post-ketamine versus post-placebo, there was generally less BOLD activation after ketamine across groups. This was found in frontomedial regions as well as posteriorly in parietal and occipital areas. When this contrast was examined separately in each group, the findings in participants with MDD were nearly all in this direction (activation post-ketamine $<$ post-placebo) and covered large regions throughout the brain. This included some areas considered to be part of the default mode network (DMN) (26) such as the medial prefrontal cortex, posterior cingulate, and precuneus. The results suggest that decreased activity in these regions during emotional processing may be related to ketamine's mechanism of action in MDD. This finding may be consistent with a previous study finding that DMN deactivation predicted response to another antidepressant (27). Another study by our group using a similar set of participants showed increased connectivity of the DMN with the insula after ketamine in MDD (23). The findings of less activation in regions within this network may suggest greater efficiency in such brain function post-ketamine. Alternatively, it is possible that more deactivation of the DMN during the task could be related to better engagement of task-related processing post-ketamine. In the HC group, greater activation was observed

Table 2. Drug (Post-ketamine or Post-placebo)-by-Group-by-Condition Interaction

Region	x	y	z	Number of Voxels
Bilateral Medial/Superior Frontal Gyri	12	31	31	273
Left Inferior/Middle Temporal Gyri	−44	−8	−36	206
Bilateral Precuneus/Posterior Cingulate	−19	−64	24	203
Right Postcentral Gyrus	23	−33	63	195
Right Superior Temporal Gyrus	65	−33	14	144
Left Inferior Frontal/Superior Temporal Gyri	−51	24	−15	136
Right Inferior Frontal Gyrus	58	27	7	95
Right Inferior Parietal Lobule	40	−68	42	91
Left Superior Frontal Gyrus	−30	59	−1	81
Bilateral Thalamus	−5	−8	−18	66
Right Thalamus	19	−19	14	65
Bilateral Cuneus	−5	−85	21	57
Bilateral Medial Frontal Gyri	−2	41	−22	54

Brain regions found in the drug-by-group-by-condition interaction effect are shown. Coordinates indicate peak activity of cluster. Owing to the extensive list of significant findings, only clusters of at least 50 voxels are listed. For clusters in table: voxel-level $p < .001$; cluster-level $p_{\text{familywise error}} < .001$.

in frontal areas, but less activation was seen in cingulate regions. This result underscores ketamine's differential effects in HCs, including activation increases specific to this group that may represent aberrant overactivation, as suggested previously (21).

Statistically significant differences in drug effects between groups were shown in the drug-by-group interaction findings. Several brain regions showed this interaction, including areas previously related to emotional processing in MDD such as the insula and ACC (28). These areas showed an interaction in which greater activation in the MDD versus HC groups was seen for the placebo condition. However, post-ketamine, the opposite pattern was observed, with less activation in the participants with MDD. Here, the activity pattern in the MDD group post-ketamine became more similar to the activity pattern in the HC group post-placebo. This suggests that ketamine may normalize BOLD activation in MDD, a result previously found in another study from our laboratory that used an attentional bias task (21). Activation in some of the brain regions found in the drug-by-group interaction also differed between groups at baseline, including the frontal, temporal, and cuneus areas. This suggests that regions with different activity at baseline in participants with MDD versus HCs also showed a differential response to ketamine versus placebo. Thus, areas of over- or underactivation in MDD appeared to normalize post-ketamine infusion. This is generally consistent with prior research demonstrating that antidepressants normalize brain function (13,14). However, traditional antidepressants have been shown to both increase and decrease fMRI activity during emotional processing in MDD (15,16). The current study observed only widespread deactivation post-ketamine in the MDD group. This could potentially differentiate effects of ketamine in the brain compared with other pharmacological treatments.

A group-by-drug-by-condition interaction was also found in multiple clusters. The activation patterns differed somewhat by brain region but again generally showed activity that varied by group according to drug and also by task condition. In the left temporal cortex, the interaction showed more of a difference between the explicit and implicit emotion processing conditions post-placebo in HCs versus participants with MDD. This echoes findings from another study showing less differentiation in BOLD response between explicit and implicit processing in individuals with MDD (29). A somewhat larger difference was observed between conditions post-ketamine for participants with MDD versus HCs. Specifically, the activity pattern in participants with MDD after ketamine more closely resembled the activity pattern in HCs after placebo, further supporting ketamine's putative role in normalizing brain activation.

The behavioral results examining effects of group or session showed a significant effect only of group on accuracy. Across sessions, participants with MDD were more accurate than HCs. A possible explanation for this could be that participants with MDD were more attuned to the emotional expressions in the task. In addition, the HCs may have been less actively engaged in the task and in trying to perform as well as they could. In general, behavioral results differed significantly from neuroimaging results, suggesting that performance- versus brain-based analyses may be differentially sensitive to particular factors explored in this study.

The current study was associated with several limitations and unexpected findings. First, although the total sample size was 57, not all participants had usable data for every scan session, so there were fewer data in the analyses (which varied by session). Second, owing to the number of factors involved in the study (group, session, and three task-specific factors), our analysis model was complex and resulted in numerous types of contrasts that could have been examined in different ways across sessions, which may be a weakness of the design and complicate interpretation of the results. Specifically, the three-way interaction effect of group, drug, and condition may be difficult to interpret because of the complex associations among the multiple factors. Third, we found no effect for emotional valence on brain activation, which would typically be predicted in MDD. This could be because happy and neutral faces were grouped together for one response option, which may have decreased any potential effect of positive emotion and resulted in less differentiation from the negative emotional faces. Relatedly, because the task was limited in the number of trials for each individual emotional expression, it may have been difficult to effectively analyze differences among the four separate emotions for this factor. Fourth, while a placebo condition was included, saline solution is not an ideal control for ketamine given that the dissociative effects often experienced post-ketamine could cause participants to not be fully blinded to which infusion they received. Fifth, our study design did not include a baseline condition for each arm of the study (ketamine and placebo), which could have been useful for controlling for a baseline corresponding to each drug condition. Finally, while our results were consistent with our hypotheses about differential activation in participants with MDD versus HCs and about ketamine's ability to normalize brain activation, we found that in general participants with MDD were not more attuned to emotional stimuli across task

conditions. Rather, both groups had differential activation depending on task condition both post-placebo and post-ketamine, as shown by the drug-by-group-by-condition interaction.

Despite these limitations, our overall findings that ketamine normalized brain function in a post-ketamine MDD versus post-placebo HC comparison are consistent with previous research from our group; one study used a different fMRI task (21), one used resting-state fMRI data (23), and one used magnetoencephalography data (22), but all found that ketamine normalized brain function in MDD. This study used an emotional processing task involving both explicit and implicit processing. Participants with MDD and HCs displayed differential activation in several brain regions post-placebo as well as, and in contrast to, post-ketamine. In addition, variable activity patterns were found according to explicit versus implicit processing. Taken together, the results demonstrate that ketamine affects BOLD activity throughout the brain during emotional processing, with different effects in participants with MDD versus HCs. Our findings suggest that ketamine may act by normalizing emotion-related brain activation specifically in MDD while differentially altering function in healthy individuals, significantly expanding our knowledge of ketamine's impact on brain function.

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CAZ is listed as a coinventor on a patent for the use of ketamine in major depression and suicidal ideation; as a coinventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a coinventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. Dr. Furey is identified as a co-inventor on a patent application for the use of scopolamine in mood disorders. She has assigned her rights on this patent to the U.S. government but will share a percentage of any royalties that may be received by the government. MLF is a full-time employee of Janssen Pharmaceuticals of Johnson & Johnson. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Rapid Antidepressant Effects of Ketamine in Major Depression; https://clinicaltrials.gov/ct2/show/NCT00088699?term=NCT00088699&rank=1; NCT00088699.

ARTICLE INFORMATION

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