

Increased Anterior Cingulate Cortical Activity in Response to Fearful Faces: A Neurophysiological Biomarker that Predicts Rapid Antidepressant Response to Ketamine

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Background: Most patients with major depressive disorder (MDD) experience a period of lengthy trial and error when trying to find optimal antidepressant treatment; identifying biomarkers that could predict response to antidepressant treatment would be of enormous benefit. We tested the hypothesis that pretreatment anterior cingulate cortex (ACC) activity could be a putative biomarker of rapid antidepressant response to ketamine, in line with previous findings that investigated the effects of conventional antidepressants. We also investigated patterns of ACC activity to rapid presentation of fearful faces compared with the normal habituation observed in healthy subjects.

Methods: We elicited ACC activity in drug-free patients with MDD ($n = 11$) and healthy control subjects ($n = 11$) by rapidly presenting fearful faces, a paradigm known to activate rostral regions of the ACC. Spatial-filtering analyses were performed on magnetoencephalographic (MEG) recordings, which offer the temporal precision necessary to estimate ACC activity elicited by the rapid presentation of stimuli. Magnetoencephalographic recordings were obtained only once for both patients and control subjects. Patients were subsequently administered a single ketamine infusion followed by assessment of depressive symptoms 4 hours later.

Results: Although healthy subjects had decreased neuromagnetic activity in the rostral ACC across repeated exposures, patients with MDD showed robust increases in pretreatment ACC activity. Notably, this increase was positively correlated with subsequent rapid antidepressant response to ketamine. Exploratory analyses showed that pretreatment amygdala activity was negatively correlated with change in depressive symptoms.

Conclusions: Pretreatment rostral ACC activation may be a useful biomarker that identifies a subgroup of patients who will respond favorably to ketamine's antidepressant effects.

Key Words: Anterior cingulate, antidepressant response, ketamine, biomarker, fearful faces, habituation, magnetoencephalography (MEG), major depressive disorder (MDD), predictor

Major depressive disorder (MDD) is a severe, recurrent, and disabling medical illness that is highly prevalent worldwide and often associated with a negative impact on quality of life and productivity. In recent years, considerable effort has been spent trying to define more homogenous subgroups and identify putative endophenotypes associated with MDD. Identifying biomarkers to predict response to antidepressants would be enormously beneficial to patients with MDD, as it would minimize the lengthy trial-and-error process that currently occurs when trying to find the most optimal treatment.

Evidence from in vivo functional imaging suggests that enhanced activity in the anterior cingulate cortex (ACC) may be a biomarker for a subset of patients who subsequently respond to antidepressant treatment (1-3). Most of these studies have demonstrated this putative link with conventional antidepressants (i.e., selective serotonin reuptake inhibitors [SSRIs]), which nor-

mally take several weeks to reach their full therapeutic effect and, despite long-term treatment, are only effective for a minority of patients (4).

In the search for rapid-acting therapeutics for MDD, recent studies have shown that ketamine, a nonselective *N*-methyl-D-aspartate (NMDA) antagonist, results in rapid and sustained (1 to 2 weeks) antidepressant effects in patients with treatment-resistant MDD (5,6). We therefore investigated whether pretreatment ACC activity would be a putative biomarker of rapid antidepressant response to ketamine. We elicited ACC activity in drug-free MDD patients and healthy control subjects by rapidly presenting fearful faces, a paradigm known to activate rostral regions of the ACC among other structures (7). There is also evidence that ACC activity shows habituation to repeated exposure to aversive stimuli in healthy subjects (8).

To measure ACC response to rapid fearful face presentation, spatial-filtering analyses were performed on magnetoencephalographic (MEG) recordings (9). Spatial-filtering algorithms have been shown to yield source distributions highly consistent with functional magnetic resonance imaging (fMRI) data (10,11); with the current procedure, they offer the temporal precision necessary to estimate ACC activity elicited by the rapid presentation of fearful faces. We hypothesized that patients with MDD would display an aberrant pattern of ACC activity to rapidly presented fearful faces compared with the normal habituation observed in healthy subjects. We also hypothesized that ACC activity elicited by fearful faces in MDD patients would predict rapid antidepressant response to ketamine. Finally, given the emerging evidence that amygdala reactivity might predict antidepressant response in

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MDD patients, we conducted exploratory analyses of amygdala activity. Given the links between both hypoactivation and hypoactivation and antidepressant response (3,12,13), we had no specific *a priori* hypotheses regarding how pretreatment amygdala activity might be associated with antidepressant response in patients with MDD.

Methods and Materials

Subjects

The patient group comprised 11 right-handed patients (7 male patients, 4 female patients) with a diagnosis of MDD, currently depressed without psychotic features; diagnosis was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Version (14). All subjects were studied at the National Institute of Mental Health (NIMH) Clinical Research Center Mood Disorders Research Unit in Bethesda, Maryland, between January and December 2007. Inclusion criteria were a Montgomery-Asberg Depression Rating Scale (MADRS) (15) score of at least 22, a current or past history of lack of response to two adequate antidepressant trials, and a current major depressive episode of at least 4 weeks duration. Patients with a DSM-IV (16) diagnosis of drug or alcohol dependence or abuse within the past 3 months; serious, unstable illness; or uncorrected hypothyroidism or hyperthyroidism were excluded. All subjects had been drug-free from any psychotropic drugs for at least 2 weeks (or 5 weeks for fluoxetine). The patients had a mean age of 43.8 ± 15.2 years and mean baseline MADRS scores of 31.9 ± 3.3 . Eight (73%) of the 11 patients had a current comorbid anxiety disorder.

Eleven healthy age- and gender-matched subjects (mean age = 35.9 ± 14.3 years; 7 male subjects, 4 female subjects) were recruited through advertisements on campus and in local newspapers. Healthy subjects underwent a screening visit at the NIMH that included a medical history and physical exam performed by a physician and a Structured Clinical Interview for DSM-IV (17). Exclusion criteria included current medical illness or major psychiatric disorder; any lifetime history of mood disorders, psychosis, or substance use disorders; or first-degree relatives with a history of psychiatric disorders. No subject could be currently taking psychotropic medications. The study was approved by the NIMH Institutional Review Board. All subjects provided written informed consent.

Measures

Raters who trained together to establish reliability performed MADRS ratings before ketamine infusion and at 230 minutes postinfusion. MEG data was obtained at the end of the drug-free period, 1 to 2 days before the ketamine infusion. Antidepressant response was expressed as percentage change score from baseline according to each individual's MADRS score. Baseline and postketamine scores for anxiety symptoms and psychotic symptoms were obtained with the Hamilton Anxiety Scale (HAM-A) (18) and with the Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale (19).

Ketamine Administration

The ketamine infusion procedure was similar to a previously described procedure (6). Briefly, MDD patients openly received a single intravenous infusion of saline solution and .5 mg/kg of ketamine hydrochloride (Abbott Laboratories, Abbott Park, Illinois) over the course of 40 minutes. Depressive, anxiety, and psychotic symptoms were reassessed 230 minutes following ketamine infusion (6). Changes in psychiatric symptoms were expressed as percentage change from baseline, with positive

percentages reflecting a reduction in symptoms. Post-assessment for anxiety symptoms was missing for one patient. We did not assess treatment response later because further analysis of previous data (6) showed that most patients with treatment-resistant MDD who demonstrate a significant treatment response to ketamine do so at the 230-minute postinfusion time point (15/17, 88.2%).

Stimuli and Procedure

The experiment involved presentation of four different stimuli: two fearful faces (one male face, one female face) and two geometric shapes (one blue circle, one red circle) (20). Participants received 130 consecutive exposures of each stimulus with a 15-second break between each exposure set. Within each set, the stimulus appeared for 250 msec with a 650 msec to 850 msec interstimulus interval. Half the participants in each group were presented with a repeating fearful face first and the other half with a repeating shape first. On 10 trials within each set, a plus sign was superimposed on the face or shape, and participants responded by button press. These trials ensured that participants maintained attention. There were no reaction time differences between groups ($F < 1$).

Data Acquisition

Neuromagnetic data were recorded at 1200 Hz with a 0 Hz to 300 Hz bandwidth using a CTF 275 MEG system (CTF Systems, Inc., Coquitlam, Canada) composed of a whole-head array of 275 radial first-order gradiometers housed in a magnetically shielded room (Vacuumschmelze, Hanau, Germany). Synthetic third-gradient balancing removed background noise online. Anatomical magnetic resonance images (MRIs) were obtained for coregistration with the MEG data in a separate session using a 1.5 T or a 3 T GE Signa scanner (Milwaukee, Wisconsin).

Source Analysis

We performed adaptive spatial filtering to estimate source activity evoked by fearful faces compared with shapes (for similar analyses, see 21). An adaptive spatial filter is derived from the sensor data covariance. It is optimized to suppress all activity except at the location of interest in source space (by minimizing the output of the filter with the constraint of unity pass or gain at the location of interest) (reviewed in 9). Volumetric images of power can be produced by constructing spatial filters at each point in a three-dimensional grid encompassing the brain. Spatial-filtering analyses have successfully captured activity in structures involved in emotional face processing, including the amygdala, fusiform gyrus, and ACC (22,23).

Because we expected that ACC responses to fearful faces would change across rapid, repeated exposures (e.g., habituation), we divided the 120 exposures into four blocks of 30 exposures and performed our source analyses on these blocks separately (trials for reaction time assessment were excluded). Covariance matrices were calculated over 30 unaveraged 500-msec epochs from the first face exposure set and the first shape exposure set (60 total epochs), from -250 msec to $+250$ msec relative to stimulus onset, with a 2 Hz to 30 Hz bandwidth. Spatial filter coefficients were calculated with a linearly constrained minimum-variance beamformer algorithm (24) in 7 mm steps across source space using a multisphere head model. At each voxel, spatial filter output was time-domain averaged to maximize signal-to-noise ratios (i.e., event-related spatial filtering) (25,26). Source activity was quantified as the \log_{10} transformed ratio of power on face epochs over shape epochs in correspond-

ing 50-msec time bins (e.g., 0–50 msec postface onset relative to 0–50 msec postshape onset). A sliding window analysis with 50% overlap captured source power from stimulus onset to offset (i.e., 0–250 msec). The same procedures were carried out for the second face and second shape exposure sets.

AFNI software (27) was used to spatially coregister source images to participants' MRIs. Source images were within-volume normalized to compensate for intersubject variability in global power and spatially warped into Talairach space. Two-way analyses of variance (ANOVAs), with group (two levels) and block (four levels) as factors, were conducted on each time window to identify regions that showed different patterns of change to repeating faces between groups. This was done for volumetric source power averaged across both repeating faces and for each face individually. Significant interactions were followed up with linear trend analyses within groups. Statistical thresholds were set at $p < .001$, uncorrected for multiple comparisons, given our a priori hypothesis of group differences in ACC activity. For the omnibus analysis, we did calculate the false discovery rate (FDR) (28) using a region of interest approach encompassing the ACC/Brodmann area (BA) 24/32 (i.e., 125 voxel-wise tests) that also incorporated multiple tests done across time windows. For exploratory analyses of amygdala activity, we used a less conservative criterion of $p < .01$ to establish statistical significance.

Correlation analyses were conducted to determine whether ACC and amygdala activity predicted change in depressive symptoms following ketamine administration. We used nonparametric Spearman correlations following inspection of the distribution of MADRS percentage change scores showing a nonnormal distribution. Given the small sample, these analyses were likely to be underpowered, and thus we elected to use a less conservative criterion of $p < .05$.

Results

Treatment Response

Significant improvement in depressive symptoms occurred 230 minutes after the infusion based on change in MADRS score [mean MADRS pretreatment score 31.9 ± 3.3 ; MADRS mean score 230 minutes after ketamine 20.4 ± 12 ; $t(10) = 3.74$, $p < .005$]. We also observed a significant decrease in anxiety symptoms [mean HAM-A pretreatment score 23.4 ± 6.5 ; HAM-A mean score after 230 minutes 14.3 ± 7.8 ; $t(9) = 3.39$, $p < .01$] and a marginally significant decrease in psychotic symptoms [mean BPRS positive symptoms subscale pretreatment score 10.2 ± 1.4 ; BPRS positive symptoms mean score after 230 minutes 9.1 ± 1.2 ; $t(10) = 2.08$, $p < .10$].

Group Differences in Changes in ACC Activity

Source analyses revealed a significant group by block (2×4) interaction in the rostral ACC (BA 32) between 125 msec to 175 msec poststimulus onset for the average response to fearful faces [Figure 1A; peak: 5, 45, 9 mm, $F(3,30) = 8.22$, $p < .001$, FDR < 10%], suggesting group differences in evoked ACC response over repeated exposures to fearful faces. This interaction was driven by a strong linear increase in ACC activity over several repetitions in MDD patients [peak: 5, 46, 12 mm, $t(10) = 4.55$, $p < .002$], together with a decrease over several repetitions in healthy control subjects [$t(10) = -2.59$, $p < .05$]. Further analyses that considered each repeating fearful face separately indicated that this linear increase in ACC activity in MDD patients over several repetitions was observed for the first repeating face [Figure 1B;

peak: 5, 46, 7 mm, $t(10) = 4.93$, $p < .001$] but not the second [Figure 1C; $p > .05$].

Correlation Between ACC Activity and Symptom Change Following Ketamine

We calculated source images for each patient that reflected the linear contrast presented above to explore whether the increase in poststimulus ACC activity from early to late presentations of the first repeating face correlated with change in depressive symptoms following ketamine administration. These analyses were performed for only the first fearful face because of the clear differential change in ACC activity between patients and healthy subjects for the first but not the second face (Figure 1). Correlation analyses revealed local maxima ($p < .05$) in ACC across several poststimulus time windows. Collapsed across poststimulus time windows, we observed that change in ACC activity following repeated exposure to the first fearful face was positively correlated with antidepressant response [peak: 5, 27, -3 mm, $r_s(9) = .68$, $p < .05$], suggesting greater increases in ACC activity to repeated exposures of a fearful face in those who showed a more positive change in depressive symptoms (i.e., greater reduction) (Figure 2). A similar positive correlation was observed for ACC activity during the last block of exposures to the first fearful face [peak: 5, 32, -3 mm, $r_s(9) = .75$, $p < .01$]. Partial correlation analyses demonstrated little change in the positive associations between ACC peak activations and MADRS percentage change scores when controlling for HAM-A percentage change scores [linear change, $r(7) = .64$, $p < .07$, and last block, $r(7) = .60$, $p < .10$].

Exploratory Analyses of Amygdala Activity

Source analyses failed to reveal group differential patterns of amygdala activity across repeated presentations. For both groups, there was an overall linear decrease in right amygdala activity between 125 msec to 175 msec poststimulus onset across repeated presentations for the average response to both faces [peak: 21, -12, -8 mm, $t(20) = -3.05$, $p < .01$]. Correlation analyses revealed local minima ($p < .05$) in right amygdala across multiple poststimulus windows. Collapsed across poststimulus time windows, we found that change in right amygdala activity following repeated exposure to the first fearful face was negatively correlated with antidepressant response [peak: 21, -7, -20 mm, $r_s(9) = -.72$, $p < .05$]. Those who showed relatively larger decreases in right amygdala activity over repeated exposures also showed better improvement in depressive symptoms (Figure 3). We also observed a strong negative correlation between right amygdala activity during the last block of the exposures to the first fearful face and antidepressant response [peak: 16, -7, -14 mm, $r_s(9) = -.82$, $p < .005$]. Similar to the ACC results, partial correlation analyses revealed that the magnitudes of negative association between right amygdala peak activations and MADRS percentage change scores remained high when controlling for HAM-A percentage change scores [linear change, $r(7) = -.58$, $p < .10$, and last block, $r(7) = -.69$, $p < .05$].

Discussion

Biological markers, or biomarkers, are quantitative measurements that provide information about biological processes, a disease state, or response to treatment (29). Biomarkers thus hold the potential to provide a better understanding of the etiology and pathophysiology of a complex and heterogeneous disorder like MDD; ultimately, particular target-based therapies could be matched to particular markers in subgroups of patients.

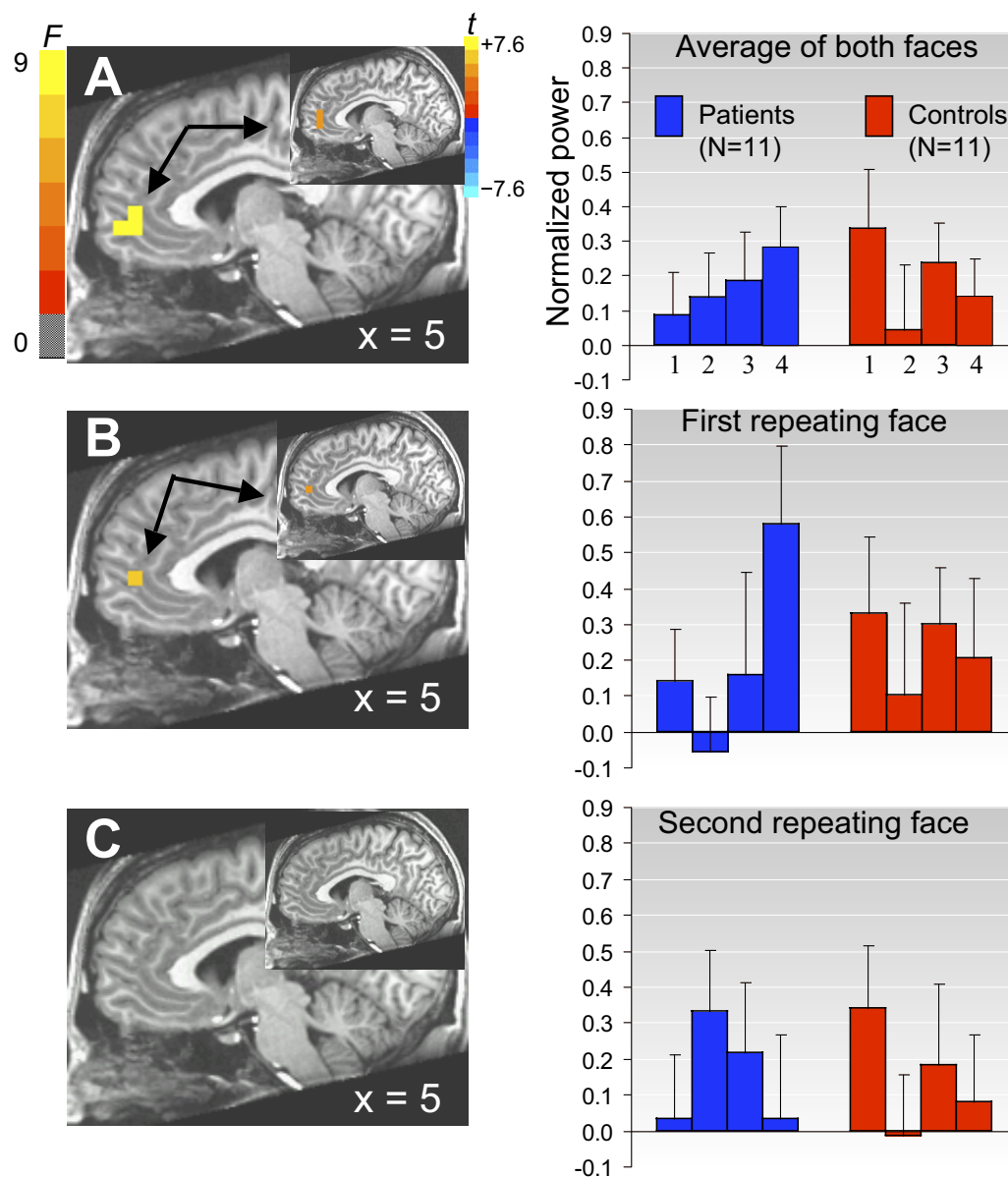


Figure 1. ACC shows contrasting changes in activity (i.e., increasing or decreasing for 120 repeated presentations) in patients with MDD versus healthy control subjects for the average of both faces (A) and separately for the first face (B) but not the second face (C). Sagittal images show the omnibus F statistics for the 2×4 interaction between group and block (blocks 1, 2, 3, 4) between 125 msec and 175 msec poststimulus onset ($p < .001$); insets show the t statistics for the linear contrast across blocks in the patient group ($p < .002$). Bar graphs show average power increase averaged across 125 voxels within an ACC region of interest (BA 24,32) as a function of group and blocks. Errors bars are standard errors of the means. ACC, anterior cingulate cortex; BA, Brodmann area; MDD, major depressive disorder.

We tested the hypothesis that MEG could be used to provide a neurophysiologic biomarker associated with ketamine's antidepressant effects. We measured ACC activity in response to rapid exposure to fearful faces in drug-free MDD patients and healthy control subjects. As expected, healthy subjects showed decreased neuromagnetic activity in the rostral ACC across repeated exposures, consistent with evidence that this region exhibits habituation to negative affective stimuli (8). Patients with MDD showed the opposite pattern, that is, robust increases in ACC activity over repeated exposures. Notably, we found that this increase in ACC activity in MDD patients was positively correlated with rapid antidepressant response to ketamine, an NMDA antagonist recently shown to have rapid and sustained

antidepressant properties in treatment-resistant subpopulations of MDD patients (5,6).

Mayberg *et al.* (2) first reported that higher rostral ACC (BA 24a/b) metabolism differentiated eventual treatment responders from nonresponders to conventional antidepressants at 6 weeks. Higher pretreatment ACC metabolism was subsequently shown to predict antidepressant response to sleep deprivation (30) and paroxetine (3). Using fMRI, other researchers found that stronger ventral ACC response during negative emotional processing predicted antidepressant response to venlafaxine (1), while ACC activation during unsuccessful motor inhibitions predicted response to escitalopram in patients with MDD (13). Finally, theta band activity (i.e., 4–8 Hz neural oscillations) in the rostral ACC,

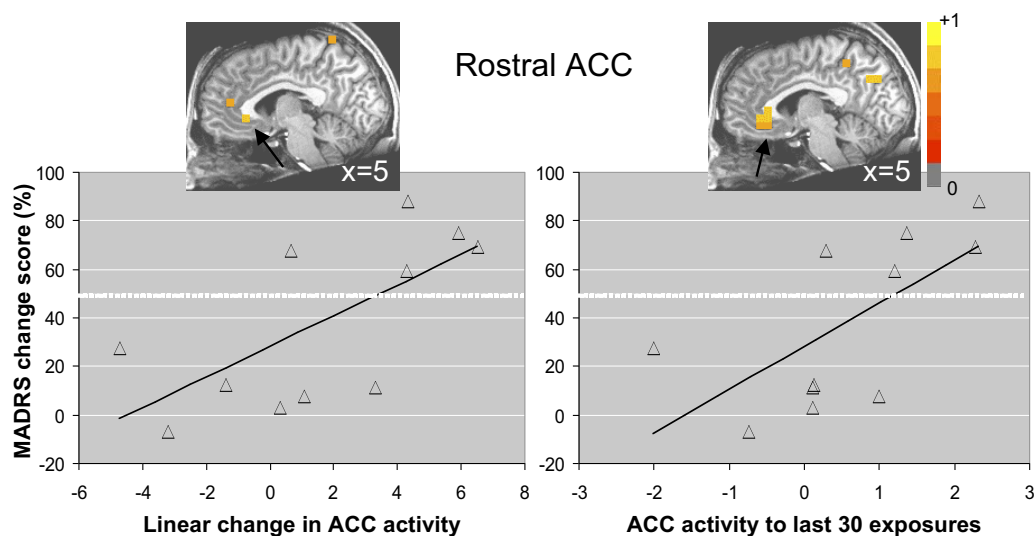


Figure 2. Nonparametric correlation between increased ACC activity (thresholded at $p < .05$) over repeated exposure to a fearful face and change in depressive symptoms 230 minutes after ketamine infusion (left) and for ACC activity to the last 30 exposures only (i.e., block 4, on the right). Scatterplots with least squares lines display ACC activity values, averaged across all poststimulus time windows, at the location of maximal correlations. Change in depressive symptoms is expressed by the percentage change in MADRS score, with positive percentages representing reductions in depressive symptoms. Dotted lines represent the 50% criterion for defining treatment responders. Images are in radiological orientation (left = right, right = left). ACC, anterior cingulate cortex; MADRS, Montgomery-Asberg Depression Rating Scale.

as measured by electroencephalogram (EEG), was found to predict response to the tricyclic antidepressant nortriptyline (31). The present study replicates previous findings and extends them to a novel, nonmonoaminergic drug, ketamine, whose antidepressant effect occurs within hours.

The rapid antidepressant effects of ketamine have been postulated to occur via alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-mediated synaptic potentiation of critical neural circuits (32,33). Increasing preclinical and clinical evidence demonstrates that synaptic plasticity, a fundamental mechanism of neuronal adaptation, is altered in mood disorders (34). A growing body of data also suggests that AMPA receptor

trafficking (including receptor insertion, internalization, and delivery to synaptic sites) plays a critical role in regulating activity-dependent regulation of synaptic strength, as well as various forms of neural and behavioral plasticity (35). It is thus noteworthy that recent studies have shown that the chronic administration of antidepressants can increase synaptic AMPA glutamate receptor subunit 1 (GluR1) receptors (35,36). Sleep deprivation is the only other known strategy that exerts an antidepressant effect as quickly (i.e., within hours or 1 day) and may share common cellular mechanisms with ketamine. Faraguna *et al.* (37) demonstrated that sleep deprivation is also associated with enhanced AMPA-mediated synaptic plasticity. In toto, the data suggest that

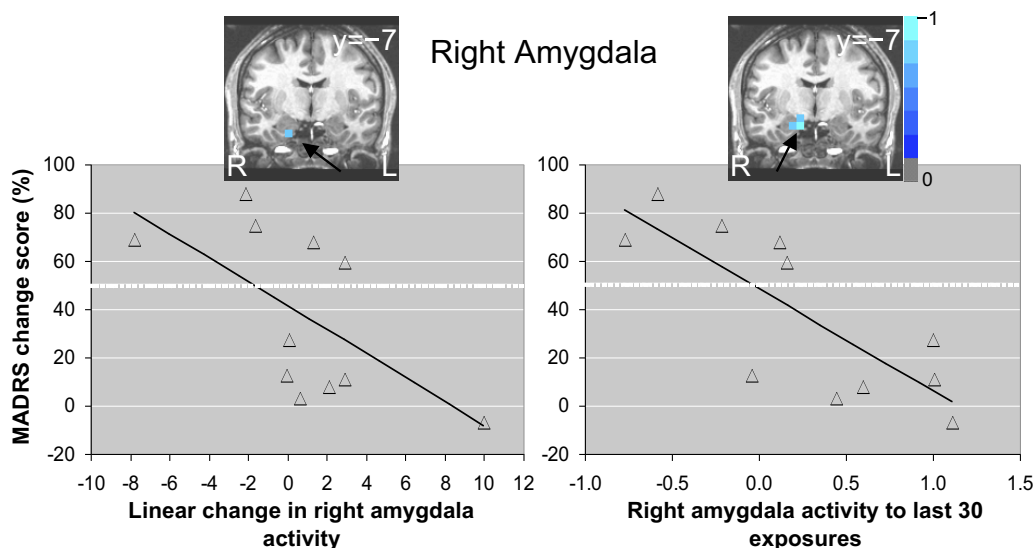


Figure 3. Nonparametric correlation between decreased right amygdala activity (thresholded at $p < .05$) over repeated exposure to a fearful face and change in depressive symptoms 230 minutes after ketamine infusion (left) and for right amygdala activity to the last 30 exposures only (right). Scatterplots with least squares lines display right amygdala activity values, averaged across all poststimulus time windows, at the location of maximal negative correlations. Images are in radiological orientation (left = right, right = left). MADRS, Montgomery-Asberg Depression Rating Scale.

AMPA-mediated synaptic potentiation in critical circuits may play an important role in antidepressant action; ketamine and sleep deprivation bring about AMPA-mediated synaptic potentiation rapidly, whereas conventional antidepressants do so in a delayed manner, through a cascade of intracellular signaling changes (35).

In addition to ACC activity, pretreatment activity in the right amygdala may represent another useful biomarker of treatment response in patients with MDD. In the present study, amygdala response to fearful faces was negatively correlated with the antidepressant response observed 230 minutes after ketamine infusion. Lower amygdala activation was also found to predict treatment response to escitalopram and paroxetine in two previous studies of individuals with MDD (3,13); however, the opposite association (i.e., greater pretreatment amygdala activation predicting antidepressant response) has also been observed (12,38). Several factors could explain these divergent findings, including medication status, treatment response criteria, and duration between pretreatment measurement and symptom assessment.

Healthy subjects showed decreased neuromagnetic activity in the rostral ACC across repeated exposures to fearful faces, consistent with evidence that this region habituates to negative affective stimuli (8). The emotional salience of a fearful face may weaken upon repeated exposures and may require less engagement of regulatory mechanisms supported by the rostral ACC, explaining the decrease in activity observed in healthy subjects. In contrast, MDD patients showed robust increases in ACC activity over repeated presentations. As the correlation analyses suggest, patients who showed significant treatment response were those driving this increased activity at the group level. These findings could reflect two key differences between MDD patients and healthy control subjects. First, the emotional salience of a stimulus may weaken more slowly over time in MDD patients; for instance, there is evidence that MDD patients exhibit sustained amygdala activity to negative words compared with healthy control subjects (39). Second, affective regulatory processes mediated by the rostral ACC may be delayed in MDD patients; that they become engaged eventually in some patients may reflect that the functional integrity of these processes is not entirely compromised. Antidepressants normalize the altered connectivity between the rostral ACC, limbic regions, and subcortical structures in individuals with MDD, suggesting indirectly that this circuit is not fully dysfunctional in treatment responders (40,41). Neurobiological mechanisms in patients might therefore display subtle quantitative abnormalities that are not necessarily qualitatively different from those in healthy individuals.

This study has several limitations. The lack of a placebo group might imply that the correlation between rostral ACC activation and antidepressant response is not directly related to ketamine administration; however, this is unlikely because we found a robust correlation with antidepressant response 230 minutes after ketamine infusion, a time point where we had previously showed that ketamine's clinical effect robustly separates from placebo (6). In addition, we studied patients with very severe and treatment-resistant MDD, and these individuals had a high rate of comorbid anxiety disorders; this may limit the generalizability of our findings. The associations between rostral ACC and right amygdala activity and antidepressant response appeared independent of the concomitant antianxiety response observed following ketamine administration; however, the partial correlation analyses were clearly underpowered and would require a

larger sample size to demonstrate the specificity of these relationships.

Finally, we did not obtain MEG measures after the administration of ketamine, so it cannot be determined here whether ketamine directly regulates rostral ACC and amygdala function in patients who display antidepressant response. However, Deakin *et al.* (42) recently found that ketamine directly regulates orbitofrontal cortex and subgenual ACC blood oxygenation level-dependent (BOLD) activity in healthy individuals, suggesting a direct link with our data.

In conclusion, a growing number of studies suggest that targeting glutamatergically mediated synaptic plasticity could be an effective strategy for treating MDD and other mood disorders (35). Indeed, several therapies targeting this system show substantial early promise for the treatment of mood disorders (35). Continued exploration of the antidepressant-like effects of glutamatergic drugs, like ketamine, may ultimately lead to the development of new treatments for MDD. The results presented here strongly implicate ACC dysfunction in the pathophysiology of MDD and support the idea that pretreatment rostral ACC activation might be a useful biomarker for identifying a subgroup of patients who will respond favorably to ketamine within hours.

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