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Neural correlates of rapid antidepressant response to ketamine in bipolar disorder

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Abstract

Objectives—Ketamine, an N-methyl D-aspartate (NMDA) antagonist, has rapid antidepressant effects in depressed subjects with bipolar disorder (BD). Evidence supports a role for the glutamatergic system in the pathophysiology of BD. This double-blind, randomized, cross-over study sought to determine cerebral metabolic correlates of antidepressant response to ketamine.

Methods—Twenty-one subjects with BD currently in a depressed state underwent [¹⁸F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging after receiving a placebo infusion as well as after receiving a ketamine infusion. Metabolism was compared between ketamine and placebo infusions, and correlated with clinical response. Regional metabolic rate of glucose (rMRGlu) in regions-of-interest (ROIs) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores were the main outcome measures.

Results—The study found that change in metabolism between sessions was significantly correlated with percentage change in MADRS scores in the right ventral striatum; subjects who showed the greatest improvement had the largest metabolic increase after ketamine infusion compared to placebo. In a voxel-wise analysis, subjects with BD had significantly lower glucose metabolism in the left hippocampus following the ketamine infusion than the placebo infusion. In

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Disclosures

A patent application for the use of ketamine in depression has been submitted listing CAZ among the inventors; he has assigned his rights on the patent to the U.S. government, but will share a percentage of any royalties that may be received by the government. WCD is now a full-time employee of Johnson & Johnson. ACN, ND, PJC, LI, DAL, NB and PH have no conflicts of interest to disclose, financial or otherwise.

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addition, metabolism in the subgenual anterior cingulate cortex (ACC) following the placebo infusion was positively correlated with percentage improvement in MADRS score following the ketamine infusion.

Conclusions—Taken together, the results suggest that higher activity in the subgenual ACC may predict antidepressant response to ketamine. Ketamine administration altered glucose metabolism in areas known to be involved in mood disorders; these alterations may partially underlie ketamine's mechanism of action.

Keywords

bipolar disorder; imaging; ketamine; NMDA antagonist; PET; positron emission tomography

The development of pharmacologic agents characterized by a rapid onset of antidepressant effects has been the focus of recent research in the treatment of bipolar disorder (BD). Because individuals with BD frequently present in an emergency setting with life-threatening suicidal behavior and/or ideation, the need for such agents is clear. Notably, the N-methyl D-aspartate (NMDA) antagonist ketamine has been shown to have rapid antidepressant effect in depressed subjects with BD (1, 2). Although ketamine interacts with other neurotransmitter systems, its primary action is selective antagonism of the NMDA receptor.

Evidence implicates the glutamatergic system in general—and NMDA receptors in particular—in the pathophysiology of BD, although the exact mechanism and neural correlates of this effect are unknown. For example, alterations in genetic coding for the NMDA receptor subunit 1 (GRIN1) and subunit 2B (GRIN2B) genes have both been shown to confer risk for BD (3, 4), although the effect of these genetic abnormalities on receptor density or function is unclear. In addition, postmortem studies have found reduced NMDA receptor subunit expression in the hippocampus (5) and anterior cingulate cortex (ACC) (6) of subjects with BD. There is also evidence to implicate the glutamate transmission system; studies have shown alterations in frontal cortical mRNA (7) levels of excitatory amino acid transporters (EAATs) as well as decreased striatal EAAT3 and EAAT4 mRNA expression (8) in subjects with BD compared to healthy controls. Interestingly, levels of EAAT1 are upregulated by chronic exposure to the mood stabilizer valproate (9).

Few studies have examined functional neuroimaging biomarkers as potential predictors of clinical response to pharmacological treatments targeted specifically for bipolar depression, let alone controlled studies of glutamatergic agents with a rapid onset of action. A few studies have, however, investigated neurobiological responses to drugs that affect glutamatergic neurotransmission or turnover. For example, Brennan and colleagues (10) found that six weeks of treatment with the glutamatergic modulator riluzole significantly increased glutamate/glutamine ratio in the ACC, and suggested that this might reflect increased glutamate-glutamine cycling. Cytidine, an agent that alters glutamate cycling, was shown to decrease the Glx peak [glutamate + glutamine + gamma aminobutyric acid (GABA)] (11), which may reflect altered cycling of the metabolites, although relative concentrations are difficult to infer from this measure. Although multiple studies have examined the neurobiological correlates of acute ketamine administration [e.g., (12)], these

studies focus primarily on ketamine's acute psychotomimetic effects, and involve only healthy subjects or subjects with schizophrenia. To date, no study has investigated the neural correlates of antidepressant response to ketamine.

This preliminary study of the neurobiological correlates of ketamine's rapid antidepressant effect was a double-blind, randomized, crossover study examining 21 patients with BD who underwent [¹⁸F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging after receiving both placebo and ketamine infusions. The FDG PET measure of glucose metabolism is primarily determined by glial uptake of glucose in response to glutamate release from neurons, and therefore reflects glutamatergic transmission (13); FDG PET was specifically chosen as the only modality that could provide a quantitative measure of cerebral glutamate throughout the entire brain. Subjects were imaged two hours after receiving either ketamine or placebo, a time when the dissociative symptoms associated with ketamine are no longer present, but the antidepressant effect is measurable. Study details regarding clinical response were previously published (1, 2). Given that this is the first study of the neural correlates of antidepressant response to ketamine, we hypothesized that we would see alterations in brain regions known to be implicated in mood and anxiety disorders. Thus, we applied a region-of-interest (ROI) approach using regions selected a priori from the neuropsychiatric imaging literature, as well as a more comprehensive voxel-wise analysis, stringently corrected for multiple comparisons.

Materials and methods

Subjects

Twenty-one subjects between the ages of 18 and 65 years, meeting DSM-IV-TR criteria for BD type I or type II participated in the study. Subjects were a subset from two identical controlled studies for which efficacy and other clinical results have already been reported (1, 2). Diagnosis was established by the Structured Clinical Interview for DSM-IV-TR (SCID) (14) and an unstructured interview with a psychiatrist. All subjects were required to currently meet criteria for a major depressive episode lasting at least four weeks, and have a score of > 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at screening and at the start of each ketamine or placebo infusion. In addition, subjects were required to have previously not responded to at least one adequate antidepressant trial, and to have failed a prospective open trial of a mood stabilizer while at the National Institute of Mental Health (NIMH) [either lithium or valproate for at least four weeks at therapeutic levels (serum lithium, 0.6–1.2 mEq/L; or valproic acid, 50–125 µg/mL)].

Subjects with major medical or neurological illnesses—as assessed by medical history, physical examination, blood tests, echocardiogram, drug screen, and urinalysis—were excluded. Additional exclusion criteria included pregnancy, breastfeeding, meeting DSM-IV-TR criteria for substance abuse/dependence within the past three months, current symptoms of psychosis, and contraindications to magnetic resonance imaging (MRI). All subjects were maintained on either lithium or valproic acid monotherapy during the study. Subjects had been free of additional psychotropic drugs for a minimum of two weeks before imaging (five weeks for fluoxetine). As noted above, study details regarding clinical response were previously published (1, 2). Written informed consent was obtained from all

subjects, and the study was approved by the Combined Neuroscience Institutional Review Board and the Radiation Safety Committee of the National Institutes of Health (NIH).

Pharmacologic intervention

As previously noted, subjects were required to not have responded to a prospective open trial of therapeutic levels of either lithium or valproate at the NIMH for a minimum of four weeks. Patients took either lithium or valproate within the specified range for the entirety of the study, and were not allowed to receive any other psychotropic medications (including benzodiazepines) or structured psychotherapy. Following non-response to open treatment with lithium or valproate and a two-week drug-free period (except for treatment with lithium or valproate), subjects received intravenous infusions of saline solution or 0.5 mg/kg ketamine hydrochloride two weeks apart using a randomized, double-blind, crossover design. For this report, we used MADRS score at baseline (60 minutes before the infusion) and at 230 minutes post-infusion; all references to clinical improvement refer to change in MADRS scores.

Imaging acquisition

PET scanning was initiated 120 minutes after both infusions, with the brain emission scan occurring approximately 200 minutes post-infusion. PET imaging was performed on a GE Advance PET scanner (GE Medical Systems, Waukesha, WI, USA) in 3D mode (35 contiguous slices, 4.25 mm plane separations; reconstructed resolution = 6 mm full-width at half-maximum in all planes) following infusion of 4.5 mCi of [¹⁸F]-FDG over two minutes. Subjects were at rest during PET scans. Quantitative images of regional cerebral glucose metabolism (rMRGlu) were calculated using a cardiac input function derived from a dynamic left ventricular scan collected prior to the brain emission scan and venous sampling, as previously validated (15), and according to the method of Brooks and colleagues (16). MRI images were acquired on a 3.0-Tesla (T) scanner (Signa, GE Medical Systems) using a 3D MPRAGE sequence [echo time length (TE) = 2.982 msec, repetition time (TR) = 7.5 msec, inversion time = 725 msec, voxel size = 0.90 × 0.90 × 1.2 mm) to allow anatomic localization of PET activity.

ROI analysis

Given that this was the first investigation of the neurobiological correlates of ketamine infusion, we chose to apply both a more powerful ROI analysis in regions known to be involved in mood disorders, as well as a less powerful voxel-wise analysis to reduce type II errors. For the ROI analysis, non-brain tissues were removed from the MRI brain images using the AFNI function 3dSkullStrip (Analysis of Functional NeuroImages, NIH, Bethesda, MD, USA). The resulting whole brain images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) components using the FMRIB automated segmentation tool (FAST) and separate binary mask images were created for each component. The MRI images were then spatially normalized to the Montreal Neurological Institute (MNI) IICBM 152 template, and ROIs previously defined on the template image were transferred to the individual MRIs. Region placement was adjusted on each individual subject's MRI to accommodate inter-individual anatomical variations. Regions were

subsequently transformed back to the native MRI space, multiplied by a binary grey matter mask, and applied to the rMRGlu PET images. Mean values were then calculated.

The *a priori* ROIs were chosen based on previously published studies indicating each region's involvement in mood disorders. These included left and right amygdala, hippocampus, ventrolateral prefrontal cortex (PFC), anteromedial PFC, dorsolateral PFC, ventral striatum, pregenual ACC, subgenual ACC, medial thalamus, posterior cingulate cortex, lateral orbital cortex, superior temporal gyrus, frontal polar cortex, habenula, and anterior insula. A single midline infralimbic cortex was also used. Details regarding the method of region placement have been previously reported (17, 18). Regional mean rMRGlu values were normalized by the mean rMRGlu over all grey matter for all statistical analyses. All future references to metabolic differences refer to normalized metabolism. Paired *t*-tests were used to assess the metabolic effects of ketamine versus placebo in each ROI. Three correlation analyses were performed. First, Pearson correlations between the rMRGlu in each ROI for individuals receiving placebo, and percent improvement in MADRS scores following ketamine infusion (using the post-placebo infusion MADRS score as a baseline), were calculated to determine whether metabolism in the ROI predicted response. Second, change in metabolism between the placebo and ketamine sessions was correlated with the percent difference in MADRS scores acquired during the two sessions. Third, to assess the impact of mood state on metabolism, rMRGlu in each ROI was correlated with absolute MADRS score within the placebo and ketamine sessions separately. Results indicate those findings that survived Bonferroni correction for multiple comparisons over the 31 ROIs tested.

Whole brain analysis

PET images were also analyzed post hoc using SPM5 (Statistical Parametric Mapping, FIL, University College London, UK) within the MATLAB (MathWorks Inc, Natick, MA, USA) platform. The rMRGlu images acquired during the placebo and ketamine sessions were independently co-registered to the MRI scan. MRI scans were normalized to the MNI atlas template supplied with SPM5, and the transformation was applied to the co-registered PET scans. PET images were then smoothed by an 8mm Gaussian kernel. Normalization was applied such that regional rMRGlu values were scaled by the global mean rMRGlu (as calculated in SPM). For one subject, modeling of the cardiac input function failed for the scan following the ketamine infusion; this subject was therefore only included in some of the comparisons, as indicated below. Paired *t*-tests were performed using placebo and ketamine session scans ($n = 20$). As with the regional analyses, three regression analyses were performed. First, multiple regression analysis was performed on images acquired after the placebo infusion with percent improvement in MADRS scores following ketamine infusion (using the post-placebo infusion MADRS score as a baseline), in order to assess potential predictors of response ($n = 21$). Second, images of rMRGlu in the placebo and ketamine sessions were divided by global mean rMRGlu (as calculated in SPM) and subtracted; these difference images were correlated with the percent difference in MADRS scores acquired during the two sessions ($n = 20$). Third, to assess metabolic correlates of mood state, regressions were performed for rMRGlu with total MADRS scores within each session (ketamine session: $n = 20$; placebo session: $n = 21$). MNI coordinates were

nonlinearly translated to the stereotaxic spatial array of Talairach and Tournoux (19) using the `mn2tal` routine. Gaussian random field theory was used to correct cluster-level statistics for voxel-level results at $p < 0.05$ uncorrected. For clusters significant at $p < 0.05$ corrected, the peak voxel and the next two sub-peaks with the highest t -test values are reported.

Results

Subjects

The mean (\pm standard deviation) age of the 21 subjects was 46 ± 12 years; 15 were female. Five subjects were receiving valproic acid monotherapy at the time of the infusions, and the rest were maintained on lithium monotherapy. The subjects taking valproate had a mean dose of 1500 mg (± 395), and a mean blood level of 82 $\mu\text{g/mL}$ (± 15). The subjects maintained on lithium had a mean dose of 928 mg (± 113) and a mean blood level of 0.81 mEq/L (± 0.13). A statistically significant difference was found between mean MADRS ratings obtained 230 minutes after the placebo infusion and mean MADRS ratings 230 minutes following the ketamine infusion (29 ± 6.5 versus 18 ± 10.5 ; $t = 4.64$, $p < 0.001$). Nine subjects showed a reduction of at least 50% in MADRS score between placebo and ketamine infusions; these subjects were classified as ketamine *responders*. Additional details regarding the clinical characteristics of the larger sample that this subset of patients was drawn from were previously published (1, 2).

ROI analyses

Mean MADRS scores and rMRGlu for all ROIs following placebo and ketamine infusions, as well as differences between conditions, are given in Supplementary Table S1. Metabolism was increased in the left subgenual ACC following ketamine infusion as compared to placebo infusion, although this finding did not remain significant after correction for multiple comparisons ($t = 2.27$, $p = 0.035$). No areas showed a significant decrease following ketamine infusion as compared to placebo infusion. Change in rMRGlu between placebo and ketamine sessions was inversely correlated with percentage improvement on the MADRS in the right ventral striatum ($r = -0.720$, $p < 0.001$), and this result remained significant after correction for multiple comparisons (Fig. 1). In addition, change in rMRGlu was positively correlated with clinical improvement in the right medial thalamus, although this finding did not remain significant after correction for multiple comparisons ($r = 0.502$, $p = 0.024$).

In the right posterior cingulate, metabolism following the placebo infusion was positively correlated with absolute MADRS score ($r = 0.510$, $p = 0.022$). In addition, in both the left ($r = 0.524$, $p = 0.018$) and right ($r = 0.569$, $p = 0.009$) posterior cingulate cortices, metabolism following the ketamine infusion was positively correlated with MADRS score, although these findings did not remain significant after correction for multiple comparisons.

Whole brain analysis

Individuals with BD had significantly lower rMRGlu uptake in the ketamine session as compared to the sham session in a cluster encompassing the left hippocampus, lingual gyrus, and right parahippocampal gyrus ($p_{\text{corrected}} < 0.001$ for cluster) (Table 1, Fig. 2). The cluster

also extended into the superior temporal gyrus and anterior insula. No significant areas were observed where rMRGlu was greater following ketamine infusion. Results for the correlation between rMRGlu under placebo infusion and percentage improvement on the MADRS following ketamine infusion appear in Table 2 and Figure 3. Subjects with the greatest rMRGlu under placebo in the subgenual ACC showed the highest magnitude of clinical improvement following ketamine administration ($p_{\text{corrected}} = 0.007$ for cluster). No area was identified where the difference in rMRGlu between the placebo and ketamine sessions correlated significantly with percent improvement in MADRS score.

Following ketamine administration, a trend was observed towards inverse correlation between rMRGlu and total MADRS score in the left hippocampus (coordinate: $x = -26$, $y = -21$, $z = -1$; $t = 4.48$, cluster corrected $p = 0.083$). We report this trend here due to the finding in the whole-brain paired t -test showing reduced rMRGlu in the left hippocampus following ketamine. Lower metabolism correlated with more depressive symptoms (higher MADRS score). No significant correlations were seen between rMRGlu and MADRS score following the placebo infusion.

Discussion

As previously noted, in this group of subjects with bipolar depression receiving mood-stabilizer monotherapy, ketamine produced a rapid antidepressant response (1, 2). In the ROI analysis conducted for the present preliminary study, the improvement in depressive symptoms after ketamine administration correlated with a corresponding increase in rMRGlu in the right ventral striatum. The most notable findings from the voxel-wise analysis included a significant reduction in rMRGlu in the left hippocampus following ketamine infusion, and a positive correlation between antidepressant response to ketamine infusion and rMRGlu in the subgenual ACC and dorsal cingulate cortex following the placebo infusion, potentially suggesting that activity in this region may predict antidepressant response. Each of these brain regions is known to play a significant role in the pathophysiology of mood disorders.

Specifically, the ventral striatum plays a major role in reward processing and in the anhedonia often associated with the depressed phase of BD (20). Although reward processing in the striatum involves dopaminergic transmission, the extant evidence also supports a role for glutamate, acting at both NMDA (21) and 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) (22) receptors to inhibit striatal dopamine release. Indeed, some neuroimaging studies of the acute psychotomimetic effects of ketamine found increased striatal dopamine release (23) as well as increased dopamine transporter (DAT) availability (24). In contrast, other studies found no acute ketamine-induced changes in D2 receptor availability as measured with [^{11}C]raclopride PET (25, 26); no studies have yet investigated dopaminergic response to ketamine after acute psychotomimetic effects have subsided.

In the present study, ketamine administration was associated with decreased hippocampal metabolism when compared to placebo. Interestingly, Deakin and colleagues (12) reported an acute increase in blood oxygen level-dependent (BOLD) signal in the hippocampus,

although it is difficult to interpret these disparate findings without both acute and delayed measurements of hippocampal activity in the same group. Although in the present study the ROI analysis showed no findings in the hippocampus, the ROI analysis looked at only a relatively small portion of the anterior hippocampus. Notably, functional and structural hippocampal abnormalities have been well documented in mood disorders. Nevertheless, while significant evidence exists linking reduced hippocampal volumes and major depressive disorder (MDD), less evidence exists for BD, possibly because many mood stabilizers exert neurotrophic effects [reviewed in (27)]. Furthermore, studies indicate that rMRGlu is greater in the hippocampus of individuals with BD than controls (28, 29). Because it has been shown that rMRGlu measured with FDG pet is primarily accounted for by glial uptake of glucose in response to glutamate release from neurons, and is thus a proxy measure of glutamatergic neurotransmission (13), these results are consistent with the hypothesis that volumetric deficits in the hippocampus may be mediated by glutamatergic excitotoxicity, although that cannot be established without further studies.

The finding that subgenual ACC rMRGlu following placebo infusion correlated with antidepressant response to ketamine suggests that this brain region may be a useful predictor of response, although only a baseline scan acquired before either infusion could unequivocally establish this. Extensive evidence implicates the subgenual ACC in the pathophysiology of BD [for a review, see (30)]. Glucose metabolism in this area was shown to be reduced in the depressed phase of BD, and is at least partially explained by a reduction in gray matter volume in this area (31). Thus, our results may suggest that subjects exhibiting the fewest abnormalities in subgenual ACC function are also the most likely to respond to ketamine, although the specificity of this effect could not be determined from our study. In general, effective antidepressant treatment with a variety of agents decreases glucose metabolism in the subgenual ACC [reviewed in (30)]. Similar to our finding that subgenual ACC rMRGlu may predict response to ketamine, Salvatore and colleagues (32), using magnetoencephalograph (MEG), found that increased pregenual ACC beta-band activity during a working memory task predicted later response to ketamine in subjects with MDD. The relationship between ACC activity and response to other antidepressant interventions has also been examined; Wu and colleagues (33) found that subgenual ACC hypermetabolism predicted later response to sleep deprivation in MDD (33). Other studies found that increased cerebral blood flow (34) and increased low-theta power (35) in the subgenual ACC correlated with better response to transcranial magnetic stimulation. In contrast, one study found that non-responders to cognitive behavioral therapy or venlafaxine exhibited higher glucose metabolism in the subgenual ACC as compared to responders (36). Functional MRI studies in which subjects performed a variety of cognitive tasks have also shown that subgenual ACC activity predicted later antidepressant response, and that the exact relationship between cingulate function and treatment response was task specific (see, for example (37)). Consistent with these results, subjects with larger ACC volumes had a more favorable clinical course (38). Given the evidence that subgenual ACC metabolism predicts antidepressant response to a wide variety of agents, our finding is most likely not specific to ketamine, but may indicate a common neurobiological correlate of many successful treatments for mood disorders. It is notable that these prior findings were all in

subjects with MDD rather than BD. The present study is thus a significant extension of these findings to bipolar depression.

Collectively, the regions found to be significantly involved in the neurobiological and clinical response to ketamine in this study implicate a circuit previously characterized in terms of anatomic connections. The subgenual ACC, in which post-placebo metabolism significantly predicted response to ketamine, and in which metabolism differed pre- and post-ketamine (non-significantly after correction), is a key region in the medial prefrontal 'visceromotor' network outlined by Ongur and Price (39) in both non-human primates and humans. The subgenual ACC projects directly to the hippocampal subiculum, and the medial caudate, ventral putamen, and accumbens nucleus within the ventromedial striatum (39), as well as the parahippocampal gyrus (40), and posterior cingulate (41). In particular, evidence exists that activity in the posterior cingulate is functionally correlated to the subgenual ACC, both at rest and during the performance of emotional tasks (42). The ACC also shares dense, reciprocal connections with the thalamus (43, 44), thus it is not surprising that ACC metabolism changed post-ketamine relative to post-placebo, and that thalamic metabolism was correlated with clinical improvement following ketamine, although neither these results are significant after controlling for multiple comparison.

Previous neuroimaging studies investigating ketamine have focused on its acute psychotomimetic effects in either healthy subjects or individuals with schizophrenia, and the relevance of those findings to ours are unclear. Notably, however, Deakin and colleagues (12) found that intravenous ketamine acutely decreased BOLD signal in the subgenual cingulate and hippocampus, and that the decrease in the subgenual ACC was associated with the severity of dissociative symptoms. This, along with our data, suggests that the subgenual cingulate may play a significant role in both acute and sustained response to ketamine.

Despite these important findings, this study had several limitations. First, the sample size was fairly small and prohibited stratification of the subject population into responders and non-responders to ketamine. Also, this preliminary study did not include healthy controls. Before exposing additional research subjects to ionizing radiation, we felt that it was important to demonstrate a change in rMRGlu in response to ketamine in patients; changes in rMRGlu between healthy subjects and those with BD at baseline have already been established. Follow-up studies should also enroll healthy subjects. Although the neurobiological response to ketamine in control subjects may have revealed effects not related to changes in mood state, it is reasonable to hypothesize that a healthy brain may respond differently to ketamine than the brain of a BD subject. In addition, the lack of a control group prevented us from ensuring that the BD subjects in this study showed similar abnormalities to those reported in the literature, compared to controls. This limitation was partly remedied by the cross-over design, which enabled each subject to serve as his or her own control. This design also increased the power to detect differences between conditions, thus minimizing the number of subjects needed. Nevertheless, results from this study may justify future studies incorporating healthy subjects.

Another limitation to those results specifically suggesting subgenual ACC metabolism as a biomarker of response is the lack of a baseline scan acquired before either the placebo or

ketamine infusions. We chose to conduct two, rather than three, scans in part to minimize exposure to ionizing radiation for subjects involved in this study. Because of the chosen design, however, we cannot rule out either a placebo effect or carry-over effects when ketamine is received before placebo. It should be noted, however, that no significant differences were observed between baseline MADRS scores and MADRS scores acquired 14 days post-ketamine or post-placebo infusion (1). Nevertheless, further studies incorporating baseline scans are warranted, in particular to unequivocally demonstrate the predictive power of subgenual ACC activity. Another limitation of this study involves clinical heterogeneity; specifically, we did not have enough subjects to examine differential effects between subjects with BD-I versus BD-II. Most subjects in the study were female, and we did not attempt to scan subjects during a specific time within the menstrual cycle, thus our study did not take into account cycle related changes in glutamate. In addition, subjects were maintained on one of two mood stabilizers, which may have interacted differently with ketamine. We did not have sufficient subjects in each medication group to carry out a subgroup analysis; however, when the ROI analyses were repeated in the subjects maintained on lithium only, the results were consistent with those reported herein. In future studies, it may also be useful to correlate neural response with absolute blood levels of ketamine or its metabolites to aid in interpreting observed neurobiological effects. Future studies may also employ multiple PET modalities to elucidate the complex effects of ketamine on other neurotransmitter systems.

Despite these limitations, this preliminary study was the first to examine the neurobiological correlates of ketamine administration in BD. The findings of this study, consistent with prior work on the neurobiology of BD, may contribute to our understanding of the mechanism of action of ketamine, and may aid in developing other treatments for BD that act on the glutamatergic system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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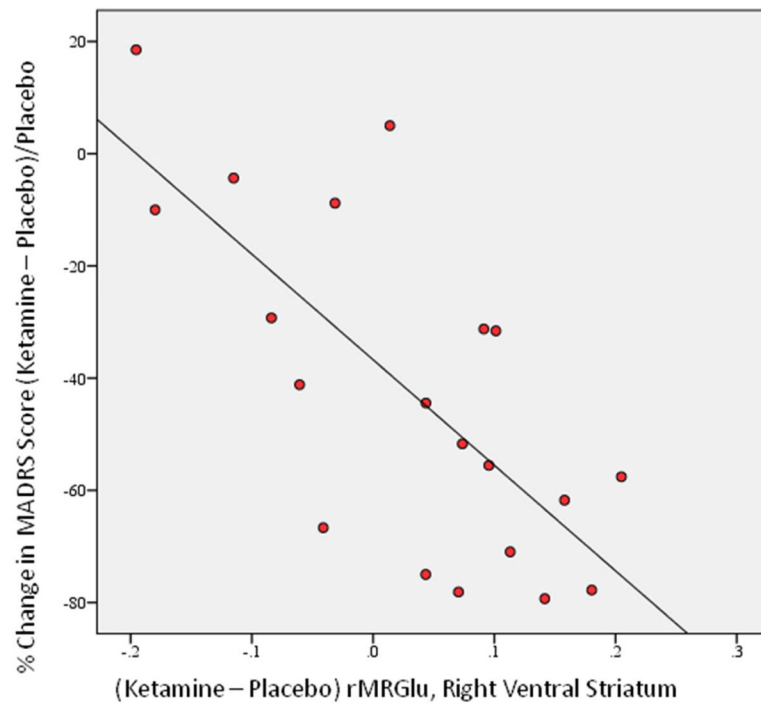


Fig. 1. The relationship between change in regional metabolic rate of glucose (rMRGlu) in the right ventral striatum and change in Montgomery-Åsberg Depression Rating Scale (MADRS) score between the placebo and ketamine conditions.

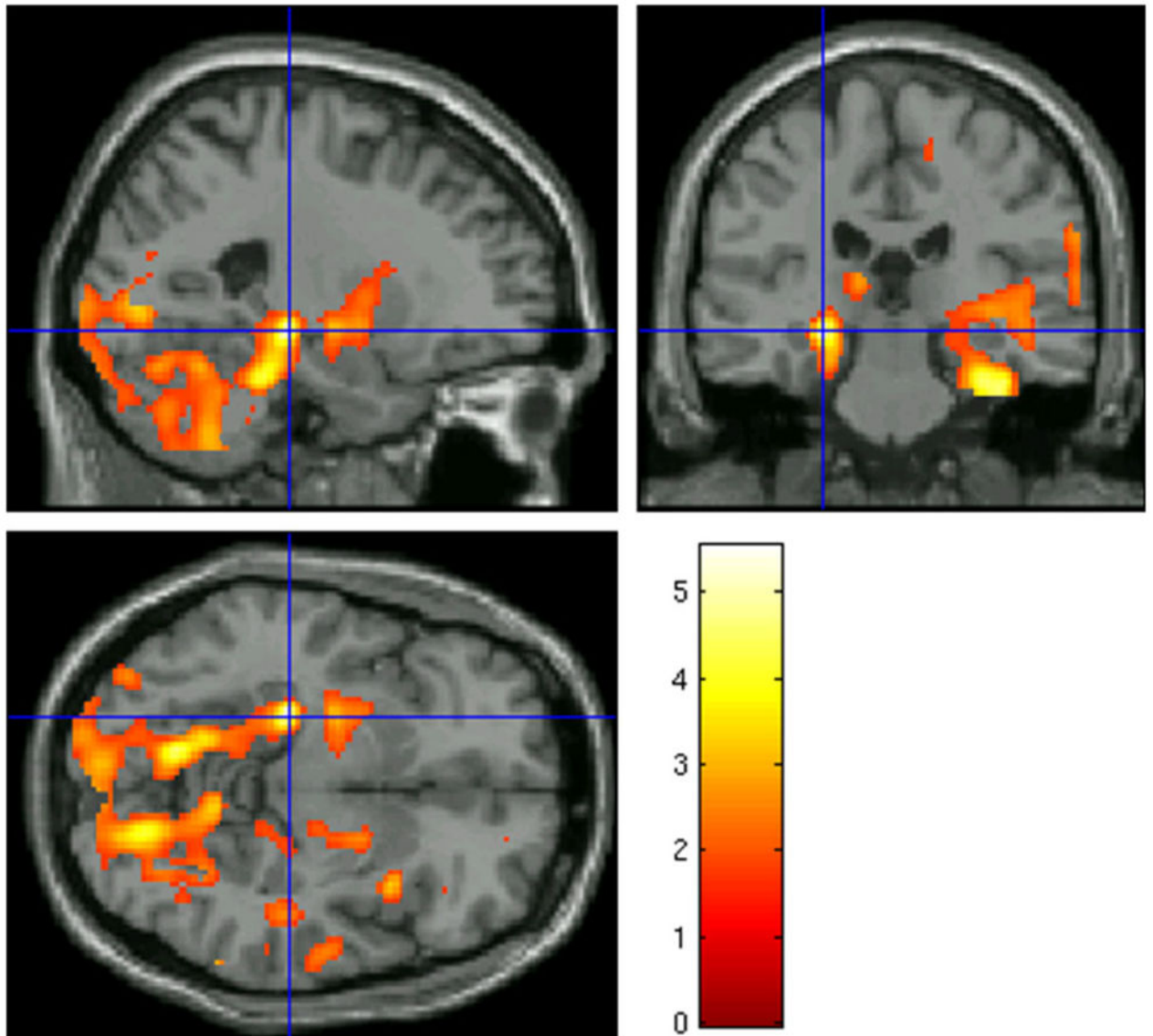


Fig. 2. Regional metabolic rate of glucose (rMRGlu) was significantly lower following ketamine infusion in these regions as compared to placebo infusion. Cross-hair is centered on the finding in the left hippocampus, but the extension of the cluster into the lingual gyrus, right anterior insula, right parahippocampal gyrus, and cerebellum are also evident. Image thresholded at $p < 0.05$ uncorrected. The extent threshold was set such that only the cluster remaining significant after correction for multiple comparisons ($p_{\text{corrected}} < 0.001$) is shown.

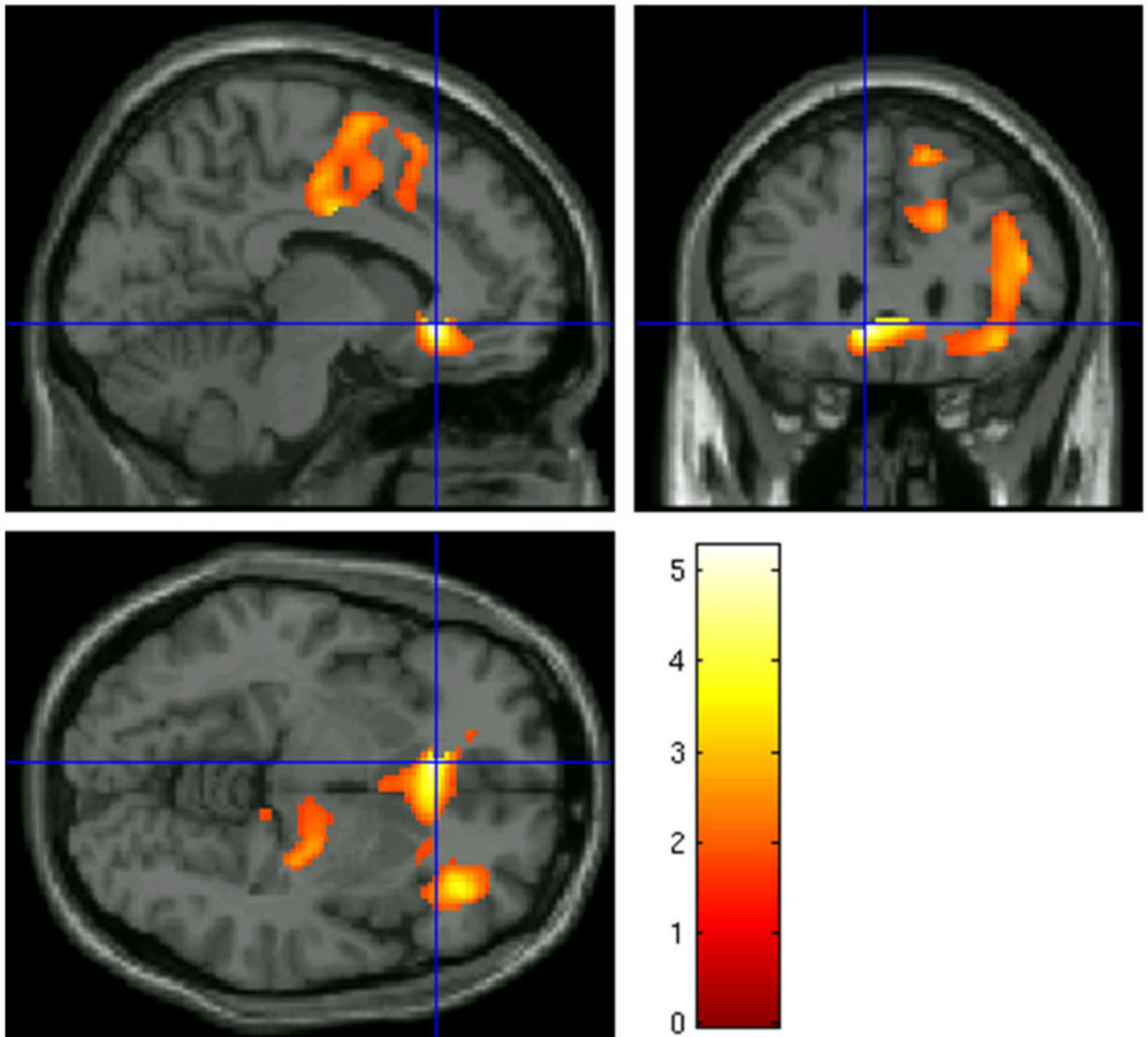


Fig. 3. Areas where regional metabolic rate of glucose (rMRGlu) following placebo infusion was significantly correlated with percent improvement in Montgomery-Åsberg Depression Rating Scale score following ketamine administration. Cross-hair is centered on the finding in the subgenual anterior cingulate, but the cluster with the peak voxel is in the dorsal cingulate. Image thresholded at $p < 0.05$ uncorrected. The extent threshold was set such that only the clusters remaining significant after correction for multiple comparisons ($p_{\text{corrected}} < 0.01$) are shown.

Areas where regional metabolic rate of glucose (rMRGlu) was significantly lower following ketamine infusion compared to placebo infusion

Table 1

Coordinates			Region	t-value	Cluster p (corrected)	Extent
x	y	z				
-24	-26	-5	Left hippocampus	5.53	< 0.001	22808
-12	-64	-5	Left lingual gyrus	4.82	-	-
32	-24	-21	Right parahippocampal gyrus	4.78	-	-

All cluster p-values are corrected for multiple comparisons using Gaussian random field theory as implemented in SPM5. The three most significant sub-peaks are given for each cluster.

Areas where regional metabolic rate of glucose (rMRGlu) following placebo infusion was significantly correlated with percent improvement in Montgomery-Åsberg Depression Rating Scale score following ketamine administration

Table 2

Coordinates			Region	t-value	Cluster p (corrected)	Extent
x	y	z				
-8	27	-6	Subgenual anterior cingulate	5.27	0.007	4300
42	31	4	Ventrolateral prefrontal cortex	4.74	-	-
48	9	33	Inferior frontal gyrus	4.73	-	-
-14	-12	37	Dorsal cingulate	4.60	0.004	4793
28	-34	61	Postcentral gyrus	4.23	-	-
14	20	56	Superior frontal gyrus (BA6)	3.24	-	-

All cluster p-values are corrected for multiple comparisons using Gaussian random field theory as implemented in SPM5. For each cluster, the peak voxel and two sub-peaks with the highest t-values are reported.