An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression

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Abstract

Amino-acid neurotransmitter system dysfunction plays a major role in the pathophysiology of major depressive disorder (MDD). We used proton magnetic resonance spectroscopy (¹H-MRS) to investigate whether prefrontal levels of amino-acid neurotransmitters predict antidepressant response to a single intravenous infusion of the N-methyl-D-aspartate (NMDA) antagonist ketamine in MDD patients. Fourteen drug-free patients with MDD were scanned 1–3 d before receiving a single intravenous infusion of ketamine (0.5 mg/kg). We measured gamma aminobutyric acid (GABA), glutamate, and Glx/glutamate ratio (a surrogate marker of glutamine) in the ventromedial prefrontal cortex (VM-PFC) and the dorsomedial/dorsal anterolateral prefrontal cortex (DM/DA-PFC). Correlation analyses were conducted to determine whether pretreatment GABA, glutamate, or Glx/glutamate ratio predicted change in depressive and anxiety symptoms 230 min after ketamine administration. Pretreatment GABA or glutamate did not correlate with improved depressive symptoms in either of the two regions of interest ($p > 0.1$); pretreatment Glx/glutamate ratio in the DM/DA-PFC was negatively correlated with improvement in depressive symptoms [$r_s(11) = -0.57, p < 0.05$]. Pretreatment glutamate levels in the VM-PFC were positively correlated with improvement in anxiety symptoms [$r_s(11) = 0.57, p < 0.05$]. The findings suggest an association between lower Glx/glutamate ratio and greater improvement in response to ketamine treatment. Because glutamine is mainly contained in glia, the decreased Glx/glutamate ratio observed in this study may reflect the reduction in glial cells found in the same regions in post-mortem studies of individuals with MDD, and suggests that the presence of this neuropathological construct may be associated with antidepressant responsiveness to ketamine.

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Introduction

Amino-acid neurotransmitter system abnormalities are thought to play a major role in the pathophysiology and treatment of major depressive disorder (MDD) (Skolnick et al. 2009).

Support for the importance of glutamatergic system dysregulation in mood disorders stems in part from the results of clinical trials showing that glutamatergic modulators had antidepressant properties (Zarate et al. 2004, 2006); from post-mortem evidence of abnormal expression of glutamatergic signalling genes (Bernard et al. 2011) in individuals with depression; and from post-mortem evidence of reduced pyramidal cells and/or g-aminobutyric acid (GABA)-ergic interneurons in regions of the prefrontal cortex (PFC) in...
individuals with depression (Choudary et al. 2005; Rajkowska et al. 2007).

Proton magnetic resonance spectroscopy (MRS) at 3 T allows the in-vivo quantification of amino-acid neurotransmitters in the brain; therefore it has been used to obtain insights into the pathophysiology of MDD (Walter et al. 2009) and the mechanisms underlying antidepressant treatment. Previous MRS studies have demonstrated that GABA and Glx – a composite peak formed by glutamate and glutamine – levels are reduced in the medial and dorsal anterolateral prefrontal cortices of patients with MDD (Hasler et al. 2007), whereas post-mortem studies have provided evidence of reduced glial cell numbers and gene expression in the same regions (Price & Drevets, 2010). Glial cells take up glutamate released by pyramidal neurons and convert it to glutamine through the enzyme glutamine synthetase. Glutamine is then released by glia and recycled back to neurons where it is hydrolysed into glutamate and replenishes the neuronal glutamate pool. Glutamine is also the major source for GABA synthesis. A reduction in glial cell number or function might therefore result in reduced glutamate transport and elevated intrasynaptic glutamate concentrations, which may ultimately lead to apoptosis and neuropil reshaping, as well as decreased GABA levels (Rajkowska & Miguel-Hidalgo, 2007; Sanacora et al. 2008).

Despite the increased attention directed towards developing glutamatergic agents for the treatment of MDD, little research has been conducted exploring whether pretreatment amino-acid neurotransmitter levels in the PFC might be a viable biomarker of clinical improvement for this class of drugs, especially those that directly target the N-methyl-D-aspartate (NMDA) receptor, such as ketamine.

Ketamine is a non-selective NMDA antagonist that produces rapid antidepressant and anti-anxiety effects in patients with MDD and bipolar depression (Diazgranados et al. 2010; Zarate et al. 2006). The biological mechanisms underlying ketamine’s antidepressant properties remain unclear; preclinical studies show that acute ketamine treatment blocks the NMDA receptor and facilitates glutamate release by decreasing GABAergic inhibitory feedback in pyramidal cells (Homayoun & Moghaddam, 2007; this effect translates into increased 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) receptor throughput, which is key to ketamine’s behavioural antidepressant effects (reviewed in Duman et al. 2011). Additional downstream events essential to ketamine’s antidepressant properties include the increased release of brain-derived neurotrophic factor (BDNF) (Autry et al. 2011) and stimulation of the mammalian target of rapamycin (mTOR) (Li et al. 2010).

Evidence regarding the neurobiology of treatment response to ketamine in humans is more limited; interestingly, consistent with evidence obtained using conventional antidepressants, recent studies have implicated anterior cingulate cortex activity and its functional connectivity with the amygdala as novel predictors of clinical improvement to ketamine (Salvadore et al. 2009, 2010).

The present study investigated whether pretreatment concentrations of GABA, glutamate, or the Glx/glutamate ratio in the PFC might be related to rapid clinical improvement in response to a single intravenous infusion of ketamine in drug-free patients with MDD. To quantitatively assess glutamate, we used a TE-averaged spectrum acquisition technique that allows reliable measurement of glutamate by resolving the C4 proton signal of glutamate at 2.35 ppm (Hurd et al. 2004; Umhau et al. 2010; Zhang et al. 2007).

We hypothesized that GABA, glutamate, and Glx/glutamate ratio levels would correlate with improvement in depressive symptoms 230 min after ketamine infusion. Given the high comorbidity of MDD with anxiety disorders and the overlapping pathophysiology between those two disorders, we also performed an exploratory analysis to investigate whether pretreatment GABA, glutamate, or Glx/glutamate ratio would correlate with a decrease in anxiety symptoms following ketamine infusion.

Methods

Participants

Fourteen patients with a diagnosis of MDD, currently depressed without psychotic features, participated in this study ($n=9$ male, $n=5$ female); diagnosis was confirmed by the Structured Clinical Interview for Axis I DSM-IV Disorders – Patient Version (First et al. 2002). All subjects were studied at the National Institute of Mental Health (NIMH) Clinical Research Center Mood Disorders Research Unit in Bethesda, Maryland, between January 2008 and January 2010. Inclusion and exclusion criteria have been described previously (Salvadore et al. 2009). Four of the 14 subjects had also participated in our previously published magnetoencephalography studies (Salvadore et al. 2009, 2010). All subjects had been drug-free from any psychotropic drugs for at least 2 wk (or 5 wk for fluoxetine). Patients’ demographic and clinical characteristics are summarized in Table 1.
The study was approved by the Combined Neuroscience Institutional Review Board (IRB) at the National Institutes of Health (NIH). All subjects provided written informed consent.

Ketamine administration

Ketamine infusion procedures were similar to those used in our previous studies (Zarate et al. 2006). Briefly, MDD patients received a single, open-label intravenous infusion of 0.5 mg/kg of ketamine hydrochloride over 40 min. Symptoms were reassessed 230 min following ketamine infusion, a time-point consistent with our previous studies of functional predictors of early antidepressant response (Salvadore et al. 2009, 2010).

Baseline and post-ketamine scores for depressive and anxiety symptoms were obtained using the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) and the Hamilton Anxiety Scale (HAMA; Hamilton et al. 1959). Changes in psychiatric symptoms were expressed as percentage change from baseline according to each individual’s scores, with positive percentages reflecting a reduction in symptoms (Salvadore et al. 2009, 2010).

MRS

Subjects were scanned using a GE 3-T (General Electric Medical Systems, USA) whole-body scanner with a transmit-receive head coil 1–3 d before openly receiving a single intravenous infusion of ketamine hydrochloride. Based on our previous MRS studies in patients with MDD and anxiety disorders (Hasler et al. 2007, 2009), proton MRS spectra were acquired from two voxels placed in the dorsomedial/dorsal anterolateral prefrontal cortex (DM/DA-PFC) (5 × 3 × 2 cm) and the ventromedial prefrontal cortex (VM-PFC) (3 × 3 × 2 cm) (Fig. 1). Segmentation of the images was based on a histogram of intensities of the anatomical image within the spectroscopy voxel only. The maxima in the histogram determined the ranges of intensities for the grey- and white-matter fractions. Pixels with intensity lower than the grey-matter fraction were attributed to cerebral spinal fluid (CSF) space.

GABA was quantified using an interleaved point resolved spectroscopy (PRESS)-based J editing method, as described in further detail elsewhere (Hasler et al. 2007) (TE 68 ms, TR 1.5 s, number of excitations 2, number of acquisitions 1024). Individual peak areas were fitted using an in-house-written Interactive Data Language (IDL) (ITT Visual Information Solutions, USA) program that performs time-domain spectral analysis. At experimental conditions optimized for GABA editing, a small fraction of Glx-2 at 3.8 ppm and Glx-4 at 2.4 ppm were co-edited because of their J couplings to the Glx-3 signal at 2.1 ppm. The clean co-edited Glx-2 signal was used to measure Glx, as its intensity is proportional to the total concentration of Glx (Hasler et al. 2007) (Fig. 2) and was also included in the Glx/glutamate ratio calculation.

Glutamate was quantified using a 1D variant of the 2D J-resolved spectroscopy method, which was previously validated both in vitro and in vivo, and which is described in more detail elsewhere (Hurd et al. 2004; Umhau et al. 2010; Zhang et al. 2007). Briefly, the methylene signal of glutamate C4 protons was resolved by averaging different echo-time spectra (Hurd et al. 2004) (TR 3 s, number of excitations 4, number of acquisitions 128, echo interval 6 ms, echo number 32). The quantification program was also developed in-house using IDL, as previously described (Zhang et al. 2007). It used individually simulated spectra as basis spectra that were linearly combined to fit the experimental data, yielding the relative ratio of glutamate to creatine (Cr). The sequence was optimized and used an echo interval of 6 ms and 32 incremental steps, resulting in negligible macromolecule contaminations and further improved baselines in the regions of interest. The fitting used the sub-region from 1.9 to 3.3 ppm and thus only included the proton spins of glutamate, glutamine, NAA, Cr and choline. The raw data were preprocessed with eddy-current correction (Zhang et al. 2007).

The data of TE-averaged spectra were acquired with a scan number of 128 and finished in about

<table>
<thead>
<tr>
<th>Table 1. Patients’ demographic and illness characteristics</th>
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<tr>
<td>N (%)</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Gender (male)</td>
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<td>9 (64)</td>
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<tr>
<td>Ethnicity (Caucasian)</td>
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<td>14 (100)</td>
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<tr>
<td>Employed</td>
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<td>2 (15)</td>
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<tr>
<td>Mean S.D.</td>
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</tr>
<tr>
<td>Age</td>
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<tr>
<td>50.1 10.4</td>
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<tr>
<td>MADRS score at baseline</td>
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<tr>
<td>33.4 5.9</td>
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<tr>
<td>Age of onset (yr)</td>
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<tr>
<td>21.4 12.9</td>
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<tr>
<td>Length of illness (yr)</td>
</tr>
<tr>
<td>28.9 14.2</td>
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<tr>
<td>Length of current episode (months)</td>
</tr>
<tr>
<td>158.1 179.0</td>
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<tr>
<td>Number of previous episodes</td>
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<td>1.9 1.9</td>
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MRS predictors of improvement to ketamine
8 min for each voxel. Figure 3 shows a TE-averaged spectrum and the corresponding simulated spectrum from a single subject participating in this study. The co-edited Glx/Cr to glutamate/Cr ratio (Glx/glutamate) was also obtained for each of the two voxels as a potential surrogate marker of glutamine.

Quantification of the MRS measures of interest was performed by two investigators (J.W.v.d.V. for GABA and Glx; Y.Z. for glutamate) blind to the clinical ratings obtained both before and after ketamine infusion.

Statistical analysis

Separate ANCOVAs were conducted for each metabolite and each voxel using GABA, glutamate or Glx/Glu as the dependent variable, gender as a factor, and age, duration of illness, and percentage of grey matter as covariates. Significant variables were included in the primary correlation analysis between baseline MRS measures and clinical improvement to ketamine.

Spearman correlations were conducted to determine the relationship between pretreatment GABA, glutamate, and Glx/glutamate ratio and the percentage change from baseline in depressive symptoms at 230 min after ketamine administration according to each individual’s MADRS score. Given the high degree of comorbidity between MDD and anxiety disorders in the clinical population and in our sample, exploratory correlation analyses between pretreatment GABA, glutamate, and Glx/glutamate ratio and percentage change in anxiety symptoms measured using the HAMA rating scale were also conducted. Significance was set at $p < 0.05$, two-tailed.

Results

Depressive symptoms were significantly improved 230 min after ketamine infusion, as assessed by changes in mean MADRS scores ($t_{13} = 3.26$, $p = 0.006$; the mean pre-treatment MADRS score was $33.4 \pm 5.9$, and the mean MADRS score 230 min after ketamine was $25.1 \pm 11$). In addition, change in MADRS score was significant at day 1 ($t_{13} = 2.97$, $p = 0.01$). Measurement of glutamate from the VM-PFC was unavailable for one subject because of poor spectral quality; metabolite...
levels in the DM/DA-PFC were not available for another subject due to technical difficulties. Overall, GABA measurements were available for 14 subjects in the VM-PFC and 13 subjects in the DM/DA-PFC, while glutamate and Glx/glutamate ratio data were available for 13 subjects in both regions of interest. The mean percentage of grey matter in the VM-PFC and the DM/DA-PFC voxels was 53.1 and 44.5, respectively. No significant effect was noted for age, duration of illness, gender, or percentage of grey matter on the concentration of any outcome measure ($p > 0.1$). Therefore, none of those variables were used as a covariate in the main correlation analyses.

Pretreatment GABA and glutamate concentrations did not correlate with improvement of depressive symptoms in either region of interest. Pretreatment Glx/glutamate ratio in the DM/DA PFC was negatively correlated with clinical improvement to ketamine [$r_s(11) = -0.572, p = 0.041$] (Table 2 and Fig. 4).

Ketamine administration was also associated with a significant improvement in anxiety symptoms, as assessed by change in HAMA scores ($t_{13} = 5.28, p < 0.001$; mean HAMA pretreatment score: 20.9 ± 4.1; mean HAMA score 230 min after ketamine: 13.64 ± 4.5). Glutamate levels in the VM voxel revealed a significant association with reduction in anxiety symptoms 230 min after ketamine administration [$r_s(11) = 0.569, p < 0.05$]. Twenty-four hours post-infusion, no significant correlation with change in MADRS score was observed; however, correlation with glutamate in the VM voxel was significant [$r_s(11) = 0.561, p < 0.05$].

### Discussion

This study is the first to investigate whether pretreatment levels of amino-acid neurotransmitters in the
PFC of individuals with MDD predict rapid antidepressant response to a drug that specifically targets the glutamatergic system.

The past few years have witnessed increasing interest in drugs that modulate the glutamatergic system as potential novel treatments for MDD (reviewed in Sanacora et al. 2008); positive clinical trials have been conducted using ketamine (Zarate et al. 2006), riluzole (Sanacora et al. 2004; Zarate et al. 2004), and the NR2B subunit selective NMDA antagonist CP-101,606 (Preskorn et al. 2008). In-vivo assessment of central glutamate levels measured using proton MRS may afford a novel and valuable approach to elucidate the pathophysiology of MDD and the mechanisms of action of novel glutamatergic modulators (Salvadore & Zarate, 2010).

Herein, we used a relatively novel averaged echo-time sequence to quantify levels of glutamate and Glx/glutamate ratio – a putative surrogate marker of glutamine – in patients with MDD before they received a single intravenous infusion of ketamine. Pretreatment Glx/glutamate ratio in the DM/DA-PFC was found to be inversely correlated with the magnitude of antidepressant response 230 min after ketamine administration. According to Cohen’s guidelines, a correlation coefficient greater than 0.50 – such as the one reported here – corresponds to a large effect size (Cohen, 1988).

The glutamine concentration measured using the MRS technique applied here reflects mostly glial intracellular content, given that glutamine synthetase, the key enzyme in glutamine synthesis, is almost exclusively localized in glial cells in the brain (Martinez-Hernandez et al. 1977); decreased glutamine levels in MDD may reflect the reduction in glial cells reported in post-mortem studies of MDD (reviewed in Price & Drevets, 2010). The types of glial cells implicated in these studies include satellite (perineuronal) oligodendrocytes and astrocytes, both of which contain glutamine synthetase (D’Amelio et al. 1990).

Because Glx/glutamate ratio is a putative marker of glutamine, our results appear compatible with the hypothesis that the MDD patients who show the greatest clinical improvement following ketamine administration are characterized by reduced glial concentrations. If so, then responsiveness to ketamine may reflect a relationship with the pathological construct that underlies the glial reductions. While the aetiology of glial cell reduction in MDD remains unclear, it is noteworthy that in rodents a similar reduction in oligodendroglia has been observed following repeated stress (Banasr & Duman, 2007). This effect may conceivably arise because elevated glucocorticoid levels reduce the proliferation of oligodendrocyte precursors (Alonso, 2000). In addition, oligodendrocytes express AMPA and kainite-type glutamate receptors, and are sensitive to excitotoxic damage from excess glutamate as well as to oxidative stress (Hamidi et al. 2004). Thus, a potential explanation for the relationship between the Glx/glutamate ratio and the improvement in depressive symptoms is that subjects who hypersecrete cortisol and/or have elevated glutamatergic transmission respond preferentially to ketamine.

![Fig. 4. Scatter plot representing Spearman correlations between DM/DA-PFC Glx/Glu ratio and improvement in depressive symptoms 230 min after a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) (rs = −0.572, p < 0.05).](http://ijnp.oxfordjournals.org/)}
In addition, glutamine might not only predict the therapeutic effects of drugs that target the glutamatergic system, it might also represent a putative biomarker capable of identifying more homogenous subgroups of patients with depression. Walter & colleagues (2009) found decreased pregenual anterior cingulate cortex levels of glutamine in highly anhedonic inpatients with MDD, but not in such patients with low levels of anhedonia; glutamate and GABA concentrations did not differ significantly between the two groups.

Despite accumulating evidence of reduced GABA levels in the PFC of patients with MDD (Bhagwagar et al. 2008; Hasler et al. 2007), our results do not support the hypothesis that GABA levels might be a surrogate marker of clinical improvement to the NMDA antagonist ketamine. This result is not entirely surprising, given that a previous MRS study of patients with MDD found that while antidepressants increased GABA concentrations in the occipital cortex, pretreatment GABA levels did not correlate with the magnitude of subsequent clinical improvement (Sanacora et al. 2002).

We also found that pretreatment glutamate levels in the VM-PFC were positively correlated with the magnitude of improvement of anxiety symptoms 230 min after ketamine administration.

The VM-PFC region of interest included the frontal polar cortex (BA 10) and portions of the perigenual anterior cingulate cortex, which was previously implicated as a strong predictor of antidepressant and anxiolytic response to ketamine using functional imaging (Salvadore et al. 2009, 2010). Thus, the present results are consistent in indicating that the pregenual anterior cingulate cortex is a key area for predicting symptom improvement to ketamine, as suggested by previous magnetoencephalography studies (Salvadore et al. 2009, 2010). The biological underpinnings of the present finding are unclear; however, as glutamate measured with MRS assesses mainly the glutamate intracellular pool present in glutamatergic neurons, with a negligible contribution from extracellular glutamate (Hasler et al. 2007), it could be argued that higher glutamate levels might reflect greater neuronal viability. As brain glutamate is also tightly related to fMRI BOLD response (Bonvento et al. 2002), this interpretation is consistent with evidence of hyperactivity of the anterior cingulate cortex as a predictor of symptomatic improvement following venlafaxine in patients with generalized anxiety disorder (Whalen et al. 2008). Interestingly, ketamine was found to acutely decrease subgenual anterior cingulate cortex BOLD response in healthy volunteers (Deakin et al. 2008); however, whether this effect correlates with a decrease in depressive symptoms in a clinical sample remains to be seen.

This study has several limitations; first, given the lack of reliable techniques to measure glutamine in the brain using MRS at 3 T, we had to rely on the Glx/glutamate ratio as a surrogate marker for glutamine; however, the MRS sequences used in this study provide optimal spectral resolution for each of those two individual metabolites and can be confidently interpreted as an indicator of glutamine. In addition, proton MRS provides a measure of total glutamate in the voxel without being able to separate between the intracellular and extracellular pool or between neuronal and glial content.

Future studies with 13C-MRS may prove particularly informative, as this technique allows the quantification of glutamate/glutamine cycling between neurons and glia. Furthermore, the voxels where we measured the concentration of amino-acid neurotransmitters extended beyond individual anatomical areas, as they measured 18 and 30 cc³, respectively; the spatial resolution of MRS is relatively low compared to other imaging techniques. This was determined by the need to obtain enough signal-to-noise ratio to resolve the spectral resonance of GABA and glutamate. Therefore, it is impossible to draw any conclusion about specific anatomical areas that influence clinical improvement in response to ketamine. It is also possible that if amino-acid transmitters in a specific brain area are involved in predicting clinical improvement to ketamine, this effect was not detected in the current study because of a ‘dilution’ effect due to the inclusion in the measurement of non-contributory areas. Correlations between pretreatment glutamate and Glx/glutamate ratio and antidepressant improvement, albeit of different magnitudes (i.e. moderate to large), were in the same direction across the two voxels investigated in the present study (i.e. positive correlations for glutamate and negative correlations for Glx/glutamate ratio), possibly indicating a general PFC effect rather than any regional specificity. Interestingly, we observed a slightly different correlation pattern with the changes in anxiety scores, where a positive correlation with glutamate levels was noted only in the VM-PFC voxel. The VM-PFC voxel encompasses brain areas that previous functional imaging studies implicated in the pathophysiology of anxiety disorders (Whalen et al. 2008). Future studies conducted at higher field strengths will allow the quantification of amino-acid neurotransmitters in smaller voxels and the investigation of...
regional specific effects with proton MRS (Stephenson et al. 2011).

It is also important to note that, because subjects were not scanned after ketamine administration, we could not investigate whether glutamine, glutamate, or GABA concentrations were acutely affected by ketamine treatment, nor could we assess whether change in amino-acid neurotransmitter concentration was correlated with clinical improvement. A recent MRS study in rodents found that acute NMDA blockade induced by phencyclidine triggered a rapid increase in glutamine and decreased glutamate levels, which might indicate a shift in the glutamate–glutamine cycle (Ilis et al. 2009). This is consistent with a previous study in healthy volunteers that showed an acute increase in glutamine levels in the anterior cingulate cortex following ketamine administration (Rowland et al. 2005); a more recent study that tested the effects of ketamine on amino-acid concentrations in the occipital cortex of patients with depression detected no significant glutamine changes in this region after ketamine administration (Valentine et al. 2011). Another recent study found that ketamine had no significant effect on cortical concentrations of glutamate and Glx in healthy volunteers (Taylor et al. 2011). Clearly, further studies are needed to investigate whether MRS is a viable technique for assessing the effects of drugs that target the glutamatergic system, such as ketamine. Moreover, investigating the effects of ketamine on more than one voxel in the same study will be necessary in order to capture region-specific effects.

Finally, some limitations of the present study are related to study design and patient sample. These include the small sample size, the lack of a placebo condition, and the high comorbidity with anxiety disorders. In addition, the analyses exploring the correlation with improvement in anxiety symptoms should be considered exploratory, as the patient population had not been specifically selected for the presence of anxiety, and because the main outcome measure in this clinical trial was change in MADRS score. Therefore, the present findings need to be considered preliminary and warrant replication in a larger, placebo-controlled sample.

Nevertheless, when taken together our results suggest a potential link between markers of glutamatergic function and rapid clinical improvement to a drug that specifically targets the glutamatergic system. Integration of measures drawn from different imaging techniques (e.g. fMRI, magnetoencephalography) might eventually lead to a better understanding of the neural underpinnings of treatment response in depression.

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Statement of Interest

This work was conducted at the Intramural Research Program at the National Institute of Mental Health (NIMH). Dr Salvadore is now a full-time employee of Johnson & Johnson Pharmaceuticals. Dr Zarate is listed as a co-inventor on a patent application for the use of ketamine in major depression. Dr Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government.

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