Ketamine, but Not the NMDAR Antagonist Lanicemine, Increases Prefrontal Global Connectivity in Depressed Patients

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Abstract

Background: Identifying the neural correlates of ketamine treatment may facilitate and expedite the development of novel, robust, and safe rapid-acting antidepressants. Prefrontal cortex (PFC) global brain connectivity with global signal regression (GBCr) was recently identified as a putative biomarker of major depressive disorder. Accumulating evidence have repeatedly shown reduced PFC GBCr in major depressive disorder, an abnormality that appears to normalize following ketamine treatment.
Methods: Fifty-six unmedicated participants with major depressive disorder were randomized to intravenous placebo (normal saline; n = 18), ketamine (0.5 mg/kg; n = 19), or lanicemine (100 mg; n = 19). PFC GBCr was computed using time series from functional magnetic resonance imaging scans that were completed at baseline, during infusion, and at 24-h posttreatment.
Results: Compared to placebo, ketamine significantly increased average PFC GBCr during infusion ($p = 0.01$) and at 24-h posttreatment ($p = 0.02$). Lanicemine had no significant effects on GBCr during infusion ($p = 0.45$) and at 24-h posttreatment ($p = 0.23$) compared to placebo. Average delta PFC GBCr (during minus baseline) showed a pattern of positively predicting depression improvement in participants receiving ketamine ($r = 0.44$; $p = 0.06$; $d = 1.0$) or lanicemine ($r = 0.55$; $p = 0.01$; $d = 1.3$) but not those receiving placebo ($r = -0.1$; $p = 0.69$; $d = 0.02$). Follow-up vertex-wise analyses showed ketamine-induced GBCr increases in the dorsolateral, dorsomedial, and frontomedial PFC during infusion and in the dorsolateral and dorsomedial PFC at 24-h posttreatment (*corrected* $p < 0.05$). Exploratory vertex-wise analyses examining the relationship with depression improvement showed positive correlation with GBCr in the dorsal PFC during infusion and at 24-h posttreatment but negative correlation with GBCr in the ventral PFC during infusion (*uncorrected* $p < 0.01$).
Conclusions: In a randomized placebo-controlled approach, the results provide the first evidence in major depressive disorder of ketamine-induced increases in PFC GBCr during infusion and suggest that ketamine's rapid-acting antidepressant properties are related to its acute effects on prefrontal connectivity. Overall, the study findings underscore the similarity and differences between ketamine and another N-methyl-D-aspartate receptor antagonist while proposing a pharmacoimaging paradigm for the optimization of novel rapid-acting antidepressants prior to testing in costly clinical trials.

Introduction

The discovery of the rapid-acting antidepressant (RAAD) effects of ketamine has generated considerable interest in academia and industry about the prospect of targeting N-methyl-D-aspartate receptors (NMDARs) for the treatment of refractory depression.[1,2] However, the results from clinical trials failing to achieve their primary outcomes,[3,4] combined with recent preclinical evidence

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proposing NMDAR-independent mechanisms of ketamine,[5,6] have cast doubts about the potential utility of this line of research.[1,7] Therefore, it is essential to establish a rigorous and reproducible in vivo biomarker of the RAAD ketamine. First, to better understand the underlying mechanisms of action in humans and second, perhaps most importantly, to facilitate and expedite the development of novel, robust, and safe RAADs. Central nervous system (CNS) drug development is increasingly challenging with high failure rates in large clinical trials, and many stakeholders abandoning their CNS division or significantly reducing their clinical trials funding.[8] High failure rates are especially relevant to depression research considering the urgent need for RAADs and the failure of many clinical trials.[9]

A significant barrier to the development of psychotropic agents is the lack of reliable, clinically relevant biomarkers that could guide early stages of drug development.[10] For example, the low-trapping NMDAR antagonist lanicemine (AZD6765) has shown promise in early small studies[11] but failed to reach primary antidepressant end points in follow-up large, costly clinical trials using 50 mg and 100 mg doses,[3] leading to the termination of its development. Establishing rigorous and reproducible human biomarkers of RAADs may play a critical role in these early stages of drug development[1,2]: (1) by expediting the in human screening of novel potential agents prior to conducting expensive trials and (2) by determining the therapeutic window and identifying the optimal drug administration regimen, which could ultimately reduce the failure rate of clinical trials. In the current study, we investigated a novel biomarker of RAADs, termed global brain connectivity with global signal regression (GBCr). Prior studies have shown reduced prefrontal cortex (PFC) GBCr in depression,[12–14] and open-label trials showed significant increases in PFC GBCr 24-h postketamine administration in depressed patients.[13,14] However, the 24-h effects were not previously tested in randomized placebo-controlled depression studies, and the effects of ketamine on PFC GBCr during infusion in depressed patients remain unknown.

Over the past decade, GBCr and other graph theory functional connectivity strength (a.k.a. degree) measures have been used extensively in neuroscience research to investigate normal brain functions as well as pathophysiology.[15] In major depressive disorder (MDD), studies have repeatedly shown reduced global connectivity within the PFC using GBCr[12–14] or other functional connectivity strength measures.[16,17] The reduction in PFC GBCr was shown to be due to a dysconnectivity between the PFC and the rest of the brain in MDD subjects.[13] Open-label ketamine enhanced the connectivity between the PFC and the rest of the brain as well as normalized average PFC GBCr (24-h postadministration)—particularly in responders to

treatment.[13] Considering glutamate models of MDD linking depression to prefrontal synaptic loss and dysconnectivity, and relating the RAAD effects of ketamine to increased synaptic density and enhanced connectivity,[18] the pilot human data suggested a temporal relationship between glutamate synaptic connectivity and PFC GBCr changes in MDD and following ketamine infusion.[13] Supporting the putative relationship between GBCr and glutamate synaptic connectivity is the known coupling between brain energy needs and glutamate neurotransmission,[19] combined with the positive correlation between GBCr and indices of brain energy consumption.[20] This relationship is also supported by the recent evidence from nonhuman primates showing a strong relationship between functional and invasive electrophysiological and anatomical connectivity.[21,22] Recent mechanistic investigation in healthy volunteers has provided additional evidence directly relating PFC GBCr to glutamate neurotransmission.[14] First, by showing reduced PFC GBCr following the administration of an inhibitor of glutamate transmission. Second, by demonstrating a ketamine-induced surge in PFC GBCr during infusion, which was modulated by the glutamate transmission inhibitor.[14] The latter finding, combined with substantial preclinical evidence relating the RAAD effect of ketamine to its ability to induce an acute glutamate surge,[23,24] raised the question whether ketamine produces an acute PFC GBCr surge in MDD patients.

The primary aim of the current report is to determine whether ketamine induces a PFC GBCr surge in MDD patients during infusion. In addition, we aimed to provide confirmatory evidence that the previously reported PFC GBCr changes following open-label ketamine would remain significant compared to placebo in a randomized controlled design. To accomplish these aims, we conducted a secondary analysis on previously collected data.[25] In contrast to the current report aims, which are focused on ketamine and recent GBCr findings, the original trial was a pharmaco-magnetic resonance imaging (MRI) study investigating the blood oxygen level dependent (BOLD) activation during lanicemine compared to ketamine and placebo. It was found that ketamine evoked activations of BOLD signal in the anterior cingulate cortex (ACC) greater than lanicemine but both predicted improvement in mood 24 h later.[25]

To expand the scientific benefit and to inform future studies, we conducted secondary analyses examining the effects of lanicemine on PFC GBCr. These analyses are conducted separately, deemed secondary, and their results should be regarded as pilot in nature. Finally, we performed exploratory analyses investigating the GBCr correlates of ketamine-induced symptoms improvement compared to placebo.

Methods

All imaging data and analyses, at the 24-h time point, are new and have not been previously published. The imaging study during the infusion day is a novel connectivity analysis of a previously published pharmaco-MRI data set.[25] None of the reported connectivity measures and analyses in the current report overlap with the previous study. The details of the clinical trial and the behavioral effects of the study drugs have been reported previously[25] and are not included in the current paper.

Participants

The parent clinical trial randomized 58 participants to normal saline (n = 19; mean age = 25.7 years), 0.5 mg/kg ketamine (n = 21; mean age = 27.1 years), or 100 mg lanicemine (n = 20; mean age = 26.7 years) infused intravenously over 60 min (Table S1). Study procedures were conducted at two sites (Manchester, UK and Oxford, UK) and were approved by the institutional review boards, and informed consent were completed before participation (ClinicalTrials.gov identifier: NCT01046630). The study criteria were previously reported.[25] Briefly, unmedicated depressed patients between the age of 18 and 45 years (mean 27 years, 24 men) were randomized, provided they met criteria for a current MDD diagnosis (Structured Clinical Interview for DSM IV); were not taking psychoactive drugs for at least two weeks; had no lifetime history of psychosis, bipolar disorder, or alcohol/substance use disorder; had no unstable medical condition; were all left handed; women were not pregnant; were not consuming more than 10 cigarettes or eight cups of caffeinated drinks per day; had a negative drug screen; and had no magnetic resonance (MR) contraindications. Beck Depression Inventory (BDI) was used to assess depression severity correlates of the neuroimaging measures.[25]

Neuroimaging

The details of the neuroimaging acquisition were previously reported.[25] Briefly, resting-state functional MRI (*f*MRI) scans (voxel size = $3 \times 3 \times 2.5$ mm; repetition time (TR) = 3000 ms; echo time (TE) = 30 ms) were acquired for 5 min prior to the infusion, for 40 min during the infusion, and for 25 min 24-h following the infusion. High-resolution structural scans (voxel size = $1 \times 1 \times 1$ mm) were acquired for coregistration. The Human Connectome Pipeline was adapted to conduct surface-based preprocessing and optimize registration.[26] Details of the image processing are provided in the Supplemental Information. GBCr calculation followed our previous reports,[13,14,27] that is, they were computed as the average of the correlations between each voxel and all other voxels in the brain gray matter (see Supplemental Information).

Statistical Analyses

Statistical Package for the Social Sciences (version 24) was used for analyses. The distribution of outcome measures was examined using probability plots and test statistics. Transformations and nonparametric tests were used as necessary. Estimates of variation are provided as the standard error of the mean. Baseline BDI differed between the study groups (Supplemental Information—Table S1). Therefore, it was included as a covariate. To demonstrate the effects of ketamine on average PFC GBCr, a repeated-measure general linear model (GLM) examined the effects of treatment (placebo vs. ketamine), time (baseline vs. during infusion vs. 24-h posttreatment), and treatment-by-time interaction, with study sites and baseline BDI as covariates. Secondary analyses examined the effects of lanicemine using similar GLM. Significance was set at $p \leq 0.05$, with two-tailed tests.

Vertex-wise *f*MRI analyses used FMRIB Software Library (FSL). Permutation Analysis of Linear Models, with tail approximation and threshold-free cluster enhancement for type I error correction (corrected $\alpha = 0.05$).[28] Independent *t* tests compared PFC delta GBCr (during infusion—baseline and 24 h—baseline) between treatment groups (ketamine vs. placebo and lanicemine vs. placebo), with study sites and baseline BDI as covariates. All vertex-wise analyses were limited to the PFC, and only vertices surviving correction for multiple comparisons are reported in the main text and figures.

Exploratory analyses without correction for multiple corrections examined the correlation between BDI percentage improvement at 24-h posttreatment and PFC GBCr during and 24 h following treatment.

Results

As previously reported,[25] there was significant reduction in BDI scores at 24 h following ketamine (32%), placebo (27%), and lanicemine treatments (26%). However, there were no significant differences in BDI improvement between treatment groups (treatment by time: $F_{(2,52)} = 0.47$, $p = 0.63$).

Effects of Study Drugs—Average Prefrontal GBCr

Primary Analysis. The GLM examining the effects of ketamine revealed a treatment-by-time interaction ($F_{(1,32)} = 5.7$; $p = 0.02$), showing a significant increase in PFC GBCr—in the ketamine group compared to the placebo group—during infusion ($F_{(1,32)} = 6.3$; $p = 0.02$; Figure 1(a)) and at 24-h posttreatment ($F_{(1,32)} = 5.7$; $p = 0.02$; Figure 1(b)). We found no treatment effect ($p = 0.59$), but a significant time effect ($F_{(1,32)} = 7.0$; $p = 0.01$), reflecting a significant increase in PFC GBCr during infusion and at 24-h posttreatment compared to baseline ($p \leq 0.01$) with no significant differences between
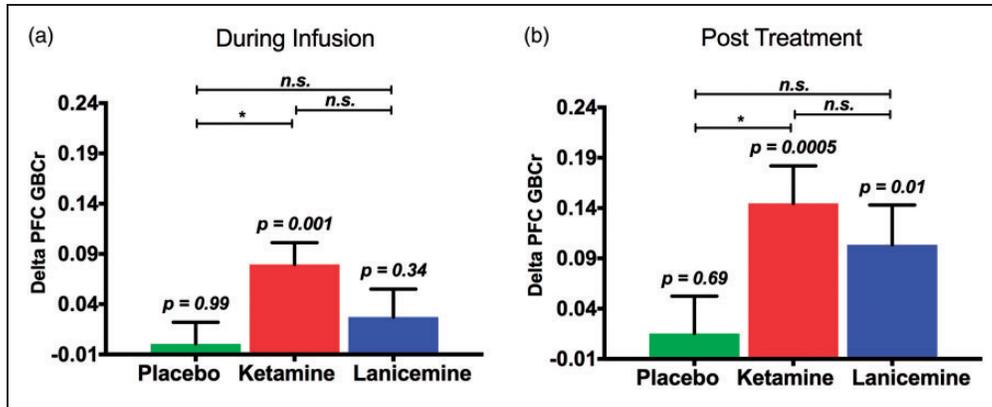
Figure 1. The effects of the study drugs on average prefrontal global connectivity. Compared to placebo, ketamine significantly increased PFC GBCr during infusion (a) and at 24-h posttreatment (b). PFC GBCr changes during and following lanicemine did not significantly differ from PFC GBCr changes in the placebo group (a and b). Delta PFC GBCr (time point minus baseline) values are the estimated marginal means covarying for study site and baseline depression severity; p values reflect the results of the time effect within each group (i.e., during/post infusion vs. baseline); and *($p < 0.05$) and *n.s.* ($p > 0.05$) reflect the comparison of delta PFC GBCr between groups (i.e., drug vs. placebo). PFC: prefrontal cortex; GBCr: global brain connectivity with global signal regression.
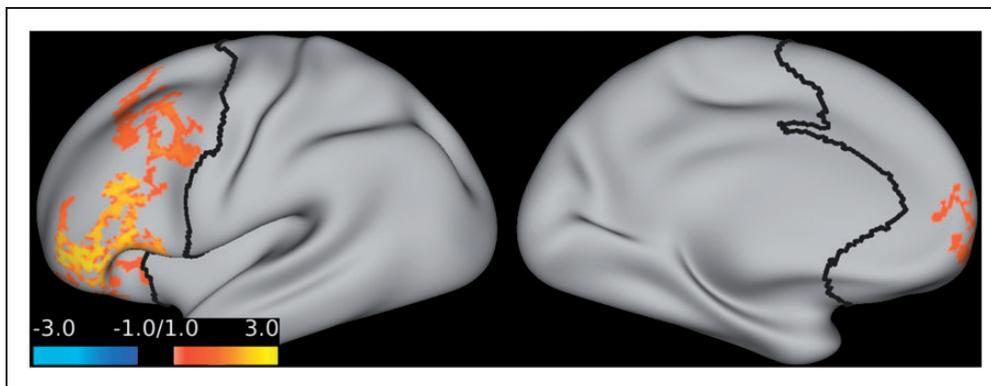

Figure 2. The effects of ketamine on prefrontal global connectivity during infusion. Compared to placebo, ketamine significantly increased GBCr in the red/yellow clusters.

PFC GBCr during infusion and at 24-h posttreatment ($p = 0.15$). Exploratory analyses examining the time effects within each group showed a significant increase in PFC GBCr during infusion ($p = 0.001$; Figure 1(a)) and at 24-h posttreatment ($p = 0.0005$; Figure 1(b)) in the ketamine group but not in the placebo group ($p \geq 0.69$).

Secondary Analysis. The GLM of the lanicemine effects found no significant treatment-by-time interaction ($p = 0.23$), reflecting the absence of differences between the changes in the PFC GBCr in the lanicemine group compared to the placebo group during infusion ($p = 0.45$) and at 24-h posttreatment ($p = 0.23$). Also, we found no significant treatment ($p = 0.57$) or time effects ($p = 0.43$). Exploratory analyses examining the time effects within the lanicemine group showed a significant increase in

PFC GBCr at 24-h posttreatment ($p = 0.01$; Figure 1(b)) but not during infusion ($p = 0.34$; Figure 1(a)). We further explored whether the changes in PFC GBCr during or following lanicemine differed from ketamine, which showed no statistically significant differences between the two drugs ($p > 0.05$; Figure 1(a) and (b)).

Effects of Study Drugs—Vertex-Wise Prefrontal GBCr

Primary Analysis. Compared to placebo, ketamine significantly increased GBCr in multiple clusters within the PFC during infusion and at 24-h posttreatment. No reduction in PFC GBCr was observed. The GBCr increases were found in the dorsolateral, dorsomedial, and frontomedial PFC during infusion (Figure 2) and in the dorsolateral and dorsomedial PFC at 24-h posttreatment (Figure 3).
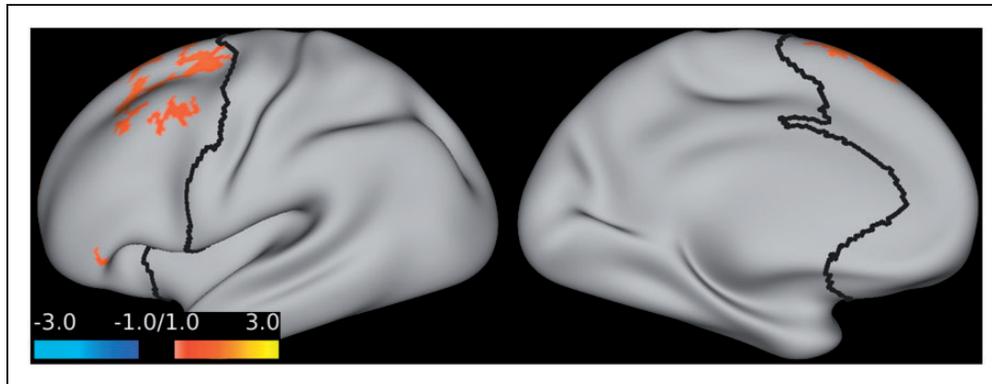
Figure 3. The effects of ketamine on prefrontal global connectivity at 24-h posttreatment. Compared to placebo, ketamine significantly increased GBCr in the red/yellow clusters.
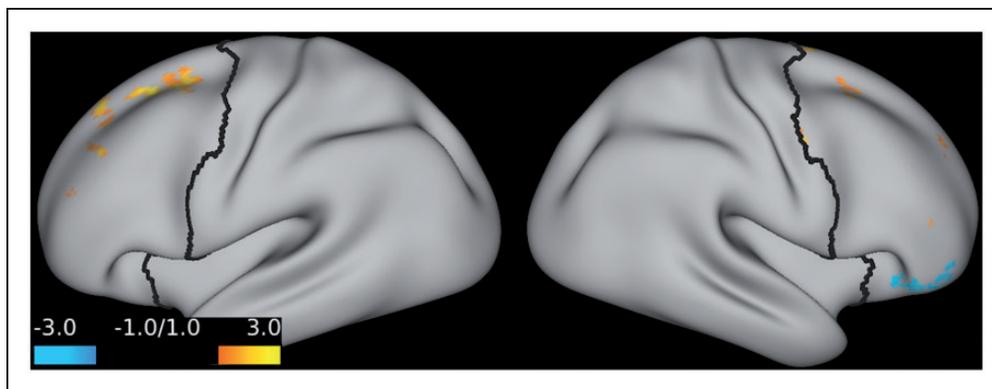

Figure 4. Statistical maps examining the correlation between percentage improvement of depression and GBCr changes during infusion of ketamine (*uncorrected* $p \leq 0.01$). Compared to placebo, treatment response—as measured by the Beck Depression Inventory at 24-h posttreatment—is associated with increased GBCr in the dorsal PFC (red/yellow), but reduced GBCr in the ventral PFC (blue).

Secondary Analysis. There were no clusters with significant changes in PFC GBCr in the lanicemine group compared to the placebo group.

Relationship to Treatment Response—Exploratory Analyses

Exploring the relationship between delta PFC GBCr during infusion and percentage improvement of depression, we found a pattern of positively predicting depression improvement in participants receiving ketamine ($r = 0.44$; $p = 0.06$; $d = 1.0$) or lanicemine ($r = 0.55$; $p = 0.01$; $d = 1.3$) but not those receiving placebo ($r = -0.1$; $p = 0.69$; $d = 0.02$). We found no significant correlations between depression improvement and average delta PFC GBCr at 24-h posttreatment ($p \geq 0.60$). However, vertex-level exploratory analyses examining the relationship with depression improvement showed positive correlation with GBCr in the dorsal PFC during infusion (Figure 4) and at 24-h posttreatment (Figure 5) but negative correlation with GBCr in the

ventral PFC during infusion (Figure 5; *uncorrected* $p < 0.01$).

Discussion

Consistent with the study hypotheses, the results provide evidence of a prefrontal global connectivity surge during the infusion of an antidepressant dose of ketamine in MDD patients. Furthermore, the prefrontal connectivity changes were sustained at 24-h postketamine administration, a finding that reproduced prior open-label evidence while providing strong support of the rigor and reproducibility of the PFC GBCr biomarker in the context of ketamine treatment. Follow-up vertex-wise analyses have localized the GBCr changes to prefrontal clusters primarily overlapping with the central executive and salience networks.[29–31] Of note, the corrected statistical maps (Figure 2 and 3) showed hemispheric lateralization and limited overlap between the significant clusters during infusion and at 24-h postketamine. However, it is important to note that this lateralization and time-dependent
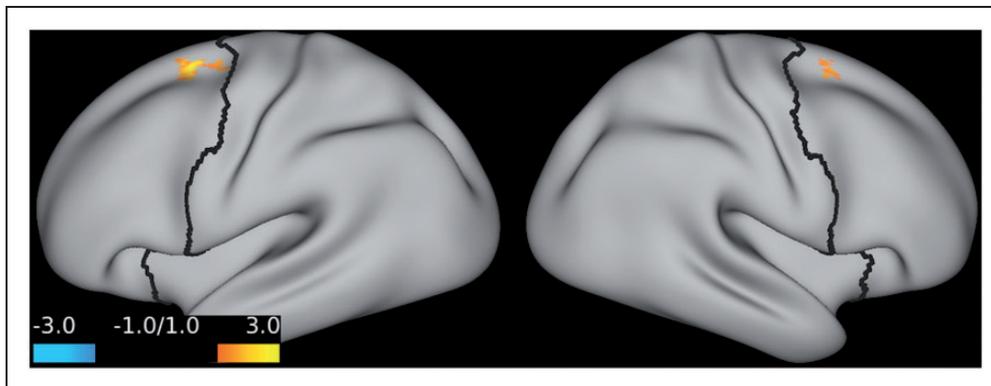
Figure 5. Statistical maps examining the correlation between percentage improvement of depression and GBCr changes at 24-h posttreatment with ketamine (*uncorrected p* ≤ 0.01). Compared to placebo, treatment response—as measured by the Beck Depression Inventory at 24-h posttreatment—is associated with increased GBCr in the dorsal PFC (red/yellow).

localization may be due to varying effect size, considering the significant effects on average prefrontal connectivity (Figure 1) and the bilateral effects on the uncorrected maps (Figure S1).

Conversely, the study failed to demonstrate a significant overall or localized effect of lanicemine on PFC GBCr compared to placebo. However, two observations are worth considering in future studies. First, the acute prefrontal connectivity surge positively correlated with depression improvement postlanicemine treatment. Second, the PFC GBCr changes following the administration of lanicemine (100 mg) appeared to be numerically in between those of placebo and ketamine, raising the question whether future optimization of the lanicemine dose or administration regimen could lead to successful modulation of prefrontal global connectivity. In addition, lanicemine was administered as fixed dose, while ketamine dose was based on body weight. Thus, considering the larger error bars in the lanicemine versus ketamine (Figure 1), it is plausible that administering lanicemine dose based on weight may reduce the variance across subjects and improve its effect on prefrontal global connectivity.

In our previous studies,[13,14] we have demonstrated both reduced depression severity and increased prefrontal GBCr following ketamine treatment. These findings raised at least two possibilities: (1) ketamine increases prefrontal synaptic plasticity and global connectivity, leading to reduction in depression (i.e., consistent with the preclinical models), or (2) reduction in depression, regardless of treatment modality (i.e., placebo or ketamine), leads to an increase in prefrontal GBCr. While it is unfortunate that the current clinical trial failed to show significant behavioral differences between ketamine and placebo, it did offer a unique mechanistic opportunity to distinguish the pharmacodynamic effects of ketamine from the nonspecific behavioral effects of reducing depression symptoms (i.e., to the rule out hypothesis 2).

In fact, the current results provide strong evidence against hypothesis 2, by demonstrating that the GBCr increases are only evident after ketamine, but not placebo; despite the fact that depression improvement was comparable in both arms. This is further supported by the lack of correlation between GBCr changes and depression improvement in the placebo arm. Together, the results are consistent with the preclinical hypothesis that ketamine induces its antidepressant response through enhancing prefrontal synaptic and functional connectivity,[1,2] while the antidepressant effects of placebo are through unknown mechanisms—independent of prefrontal global connectivity. In summary, there is extensive evidence in the literature that both placebo and ketamine significantly reduce depression severity. The current study results provide mechanistic evidence that the neural mechanisms underlying the placebo antidepressant effects are not related to prefrontal connectivity. In contrast, the results show a pattern of positive association between improvement in depression symptoms and increases in prefrontal connectivity following ketamine and lanicemine treatment.

Based on extensive preclinical evidence and suggestive clinical findings, it was proposed that prefrontal synaptic loss and dysconnectivity underlie the pathophysiology of depression.[1,18,23,32,33] In this model, the altered synaptic connectivity affects large-scale networks precipitating and perpetuating depressive symptomatology.[34] Moreover, the reversal of synaptic dysconnectivity appears to be a necessary step to exert antidepressant effects.[18] Ketamine has been found to robustly reverse the prefrontal synaptic dysconnectivity in animal models of depression and to normalize related network disturbances in humans.[18,34,35] At the molecular level, it is believed that ketamine and other RAADs (e.g., scopolamine) exert their effects primarily through induction of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-dependent glutamate neurotransmission surge and

subsequent enhancement of neurotrophic factors and synaptogenesis.[2,36,37] Yet the role of NMDAR antagonism in inducing this glutamatergic synaptogenesis remains contested.[1,6,7,38,39] The current study findings show a remarkable temporal parallel between the ketamine-induced acute glutamate surge and sustained synaptogenesis in rodents and the ketamine-induced acute and sustained PFC GBCr in depressed patients.

In this context, and considering prior evidence linking GBCr to glutamate transmission and neuroenergetics,[14,20] we interpret the acute increases in PFC GBCr during ketamine infusion and its positive relationship to treatment response, as a supportive human evidence (1) that the ketamine-induced acute glutamate surge is putatively present in humans,[40–42] (2) that it contributes to the RAAD of the drug,[43,44] and (3) that PFC GBCr is a clinically relevant rigorous and reproducible biomarker of the underlying glutamate surge.[14] The sustained PFC GBCr increases, 24-h postketamine, are hypothesized to reflect the underlying ketamine-induced glutamatergic synaptogenesis reported in animal models. Consistent with our previous findings,[13] the current study provided exploratory evidence associating depression improvement with increased GBCr in the dorsal PFC 24-h postketamine. However, it is important to caution the reader that these findings would require replication in future studies, considering the trend level of significance during infusion (i.e., $r = 0.44$; $p = 0.06$; $d = 1.0$), the lack of correction for multiple comparisons, and the lack of correlation with overall PFC GBCr. The latter could be due to the low response rate in the parent clinical trial, which reduced the sample power to detect positive correlation between improvement and 24-h GBCr increases. Moreover, as noted in the vertex-wise analysis (Figure 5), it is plausible that at the 24-h time point, a more localized PFC GBCr effect would better map to the antidepressant response. Hence, this exploratory analysis supports the need for larger samples to robustly identify the localized GBCr correlates of treatment response at the 24-h time point.

In the parent pharmaco-MRI trial, ketamine evoked activations of BOLD signal in the ACC greater than lanicemine, but both predicted improvement in mood 24 h later.[25] Evidence suggests that ACC BOLD responses to ketamine also reflect increased glutamate release, considering its modulation by a glutamate release inhibitor.[45] Therefore, the pharmaco-MRI and connectivity analyses reinforce a primary role for a glutamate surge as a mechanism of the observed rapid antidepressant effects. As BOLD signal is linked to neuronal metabolism,[46] it is possible that the glutamate surge occurs in ACC and not in frontal cortex which did not show BOLD responses to ketamine. The major reciprocal innervation between frontal cortex and ACC could then initiate the increased frontal GBCr connectivity, which mediates the antidepressant response.

Limitations and Strengths

A main limitation is the low response rate in the parent trial which may have reduced our ability to detect significant association between depression improvement and 24-h PFC GBCr. It also limits the generalizability of the results to the larger population of ketamine treated patients who show, on average, superior response rate following ketamine treatment. In addition, the study could have benefited from a follow-up time point at 10 to 14 days posttreatment to determine the longevity of the PFC GBCr changes and its relationship to relapse. Of note, the ketamine-induced synaptogenesis lasts for approximately 10 days in rodents, and the majority of depressed patients relapse within two weeks of single ketamine infusion.[47] Another limitation is the use of a self-report measure of depression and the enrollment of nontreatment resistance population in contrast to previous ketamine studies. In addition, the pretreatment *f*MRI acquisition was only 5 min, future connectivity studies may benefit from longer acquisition time. Finally, future studies may particularly benefit from more substantial sample and comprehensive standardized assessments of depression-related constructs, for example, anhedonia and suicidality, to better understand the relationship between alterations in these constructs and better localize the underlying prefrontal GBCr changes. The strengths of the study include (1) a randomized placebo-controlled design, (2) a relatively large sample compared to previous ketamine neuroimaging studies, and (3) the use of GBCr, a well-validated robust biomarker that is based on established graph theory models with extensive prior evidence in health and disease to facilitate the interpretation of the study findings. The robustness of the GBCr measure is further supported by the lack of any notable changes in PFC GBCr in the placebo group in the current study in MDD and in previous studies in healthy subjects.[14]

Conclusions

The study provides evidence of ketamine-induced prefrontal global connectivity during infusion in depressed patients. It also replicates, in a placebo-controlled design, previous open-label evidence of ketamine-induced prefrontal global connectivity at 24-h posttreatment. Lanicemine (100 mg) failed to induce significant prefrontal global connectivity increases during and 24-h posttreatment compared to placebo. However, it is evident that numerically the lanicemine-induced connectivity changes appear to be in the same direction as ketamine, which raises the question for future studies whether optimization of the lanicemine administration regimen could lead to significant prefrontal connectivity normalization—especially considering the positive relationship between prefrontal global connectivity increases and treatment response.

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Declaration of Conflicting Interests

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