



Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects

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Abstract

Ketamine's mechanism of action was assessed using gamma power from magnetoencephalography (MEG) as a proxy measure for homeostatic balance in 35 unmedicated subjects with major depressive disorder (MDD) and 25 healthy controls enrolled in a double-blind, placebo-controlled, randomized cross-over trial of 0.5 mg/kg ketamine. MDD subjects showed significant improvements in depressive symptoms, and healthy control subjects exhibited modest but significant increases in depressive symptoms for up to 1 day after ketamine administration. Both groups showed increased resting gamma power following ketamine. In MDD subjects, gamma power was not associated with the magnitude of the antidepressant effect. However, baseline gamma power was found to moderate the relationship between post-ketamine gamma power and antidepressant response; specifically, higher post-ketamine gamma power was associated with better response in MDD subjects with lower baseline gamma, with an inverted relationship in MDD subjects with higher baseline gamma. This relationship was observed in multiple regions involved in networks hypothesized to be involved in the pathophysiology of MDD. This finding suggests biological subtypes based on the direction of homeostatic dysregulation and has important implications for inferring ketamine's mechanism of action from studies of healthy controls alone.

Introduction

Over half of patients with major depressive disorder (MDD) fail to respond to first-line treatments [1], and residual symptoms are common. In addition, the neurobiological basis for MDD and the mechanism of action of existing antidepressant drugs are only partially understood. Controlled studies of subjects with treatment-resistant MDD and

bipolar depression have shown that the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine has rapid antidepressant and anti-suicidal effects [2–8]. Convergent evidence supports the conclusion that enhanced α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity, concomitant with increased synaptic potentiation, is critical to ketamine's mechanism of action and may be crucial to developing similar rapid-acting antidepressants [9–12].

Both animal [13–16] and human [17, 18] studies indicate that acute, sub-anesthetic ketamine infusion is associated with robust increases in gamma power. Multiple synaptic mechanisms play a role in regulating gamma oscillations, including AMPA receptor-mediated depolarization and gamma aminobutyric acid (GABA)_A receptor-mediated inhibition. Ketamine may influence both of these systems, both by silencing GABAergic inhibitory synapses and by increasing glutamate release, thereby activating AMPA receptors [19]. The decreased activity in GABAergic interneurons and the disinhibition of excitatory pyramidal neurons [20] presumably provides the mechanism for increased gamma oscillations [21]. The antidepressant mechanism is likely more complex, however, given that

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blockade of NMDA receptors on interneurons and the subsequent disinhibition of pyramidal neurons does not consistently produce an antidepressant effect [22]. Notably, acute administration of the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine (HNK) also increases gamma oscillations, despite the fact that the metabolite does not inhibit NMDA receptors at concentrations that increase gamma power [23]. Because AMPA receptor blockade can attenuate HNK-induced gamma oscillations, enhanced AMPA receptor activity is likely to be the mechanism by which HNK increases gamma power, although the mechanism of increased AMPA receptor activity is not known [24]. Importantly, gamma oscillations have been associated with cognition [25], attention [26], the hemodynamic blood oxygen level dependent (BOLD) response [27, 28], and functional connectivity [29], and are extremely sensitive to metabolic stress due to their influence on neuronal oxygen consumption [30]. Taken together, these findings underscore the close relationship between gamma oscillations and inhibition/excitation balance [31, 32].

Recent evidence suggests that disruptions in synaptic homeostasis may underlie MDD [33]. In this context, homeostasis refers to the stable functioning of neuronal networks in response to changes in excitatory input, alterations in neuronal excitability, and metabolic stressors, ensuring that an appropriate inhibition/excitation balance is maintained. Neurons respond to disruptions in function by altering their synaptic strength, a process known as homeostatic plasticity [34]. For example, to maintain homeostasis, mice with GABA receptor $\gamma 2$ subunit deficits (a model for anxious depression) manifest reduced function of both NMDA and AMPA receptors [35]. Notably, ketamine administration reverses both the glutamatergic adaptations to the intrinsic GABA $\gamma 2$ deficits and the abnormal behavioral phenotype [19]. Chronic stress in rodents also downregulates AMPA and NMDA receptor function, and similar genetic and environmental mechanisms may lead to depressive symptoms in humans [36]. Disruptions in inhibition/excitation balance and receptor function may lead to neuronal atrophy, synaptic loss, altered network level connectivity, and altered volume of brain structures involved in emotional processing [33], all of which have been associated with MDD [37, 38]. These findings support the importance of homeostatic control of mood circuits and form the basis of a synaptic hypothesis of MDD and antidepressant response [33].

In addition to electrophysiological effects, preclinical studies have shown that ketamine rapidly induces synaptogenesis and reverses synaptic deficits caused by chronic stress, thus restoring network connectivity [33], while clinical studies support enhanced plasticity in response to ketamine [39]. However, the hypotheses of homeostatic dysregulation in MDD patients and restoration of

homeostasis by ketamine have not yet been demonstrated. The present study is part of a larger Ketamine Mechanism of Action (Ket-MOA) Study designed to identify clinical and neurobiological correlates of ketamine treatment in unmedicated inpatients with treatment-resistant MDD. This report focuses on the effects of ketamine on mood and resting gamma power (as a surrogate marker of inhibition/excitation balance) measured at baseline, at 6–9 h post-ketamine/post-placebo infusion, and at 11–13 days post infusion. We hypothesized that sustained increases in gamma power would be associated with ketamine administration, commensurate with the degree of improvement in depressive symptoms.

Materials and methods

Subjects

Eligible participants included men and women, ages 18–65 years. Subjects with MDD had been diagnosed with recurrent MDD without psychotic features using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID)-Patient Version [40]. Subjects were required to have a score ≥ 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at screening and before each infusion. Subjects had to have not responded to at least one adequate antidepressant trial during their current episode, as assessed using the Antidepressant Treatment History Form [41], and the current episode had to have lasted at least four weeks. Subjects were free from psychotropic medications in the two weeks before randomization (5 weeks for fluoxetine, 3 weeks for aripiprazole). A patient sample size of 34 individuals was necessary to have 80% power to detect an antidepressant effect of ketamine ($d = 0.5$) with $p < 0.05$, two-tailed.

Healthy control subjects consisted of males and females, 18–65 years old with no Axis I disorder as determined by SCID-NP, and no family history of Axis I disorders in first degree relatives. Healthy control subjects were free of medications affecting neuronal function or cerebral blood flow or metabolism. Subjects in both groups were in good physical health as determined by medical history, physical exam, blood labs, electrocardiogram, chest x-ray, urinalysis, and toxicology. The study was approved by the National Institutes of Health (NIH) Combined Neuroscience Institutional Review Board. All subjects provided written informed consent before entry into the study (NCT00088699).

Data collection

Ketamine and placebo infusions were administered two weeks apart using a double-blind, placebo-controlled, crossover design, with infusion order randomized. Subjects were

rated 60 min prior to each infusion and at 40, 80, 120, and 230 min as well as at 1, 2, 3, 7, 10, and 11 days after the infusion.

The MADRS was the primary outcome measure. Additional secondary outcome measures included the 17-item Hamilton Depression Rating Scale (HAM-D17) [42], the reduced Hamilton-Bech designed to probe rapid changes in depressive symptoms [43], the Snaith-Hamilton Pleasure Scale (SHAPS) [44], and the Temporal Experience of Pleasure Scale (TEPS) [45]. Additional secondary outcome measures administered only through Day 3 included the Hamilton Anxiety Rating Scale (HAM-A) [46], Beck Depression Inventory (BDI) [47], PTSD Checklist Civilian Version (PCL-C) [48], Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) [49], Clinical Global Impression-Severity Scale (CGI-S) [50], and Scale for Suicide Ideation-5 items (SSI5) [51]. Additional scales intended for use in an exploratory analysis of symptom clusters included the Profile of Mood States (POMS) [52], and a seven-item visual analog scale (VAS) [53]. The Clinician-Administered Dissociative States Scale (CADSS) was used as the primary assessment of side effects [54], and the Brief Psychiatric Rating Scale-positive symptoms (BPRS) [55] and Young Mania rating scale (YMRS) [56] were also administered.

Resting state magnetoencephalography (MEG) recordings were obtained at baseline (two to four days before the first infusion), the day of the infusion (KET-Day0 and Placebo-Day0, ~6–9 h post infusion), and 11–13 days post infusion (KET-Day12 and Placebo-Day12). Up to two 250-s resting state recordings per time point were analyzed; in general, one recording occurred at the beginning of the session, and the second was acquired ~30 min–1 h later after a series of tasks. For the resting state recordings, subjects were instructed to relax with their eyes closed and remain still. All data were acquired on a 275-channel CTF system (Coquitlam, BC) at 1200 Hz. Background environmental magnetic noise was attenuated by synthetic third gradient balancing. T1 weighted magnetic resonance imaging (MRI) scans were acquired on a 3 T GE scanner for co-registration. MEG, rather than EEG, recordings were obtained because MEG is associated with enhanced spatial specificity due to the lack of distortion of neuronal magnetic fields by the skull or scalp [57].

Clinical data analysis

IBM SPSS 23.0.0.3 (Armonk, NY) was used to analyze clinical outcome measures. Participants were included in the clinical analyses as long as at least one pre- and one post-infusion measure were available for at least one phase. All time points were analyzed, and the –60 min time point was used as the baseline. Linear mixed models with restricted

maximum likelihood estimation were estimated for each outcome measure. Time and drug factors were within-subjects repeated measures, and the interaction was included in the model along with the phase-specific baseline score as a main effect only. A fixed intercept was included. Post hoc tests with Bonferroni adjustment were used to compare ketamine and placebo at individual time points if the main effect of drug or drug by time interaction was significant. For primary outcome measures, significance was evaluated at $p < 0.05$, two-tailed.

Magnetoencephalography data analysis

MEG data were processed using CTF software (<http://www.ctf.com>), MNE-python [58], Analysis of Functional NeuroImages (AFNI) [59], and routines developed in house. This work used the computational resources of the NIH HPC Biowulf cluster (<http://hpc.nih.gov>). Each MEG dataset was filtered using a high pass filter of 2 Hz and visually inspected to identify and mark time periods with significant muscular, ocular, or movement artifacts. Up to 10 segments of 15-s duration outside marked artifacts were identified in an automated fashion. Datasets were discarded if at least five 15-s artifact-free segments could not be defined. All further described imaging analyses and quality control measures were carried out on the clean epochs.

Data were localized to source space on a 5 mm grid using synthetic aperture magnetometry [60], and a multisphere head model was calculated from co-registered MRI scans. MRI and MEG images were co-registered using MRI-visible fiducial markers placed on the head at the time of MRI scanning. Beamformer weights were calculated using a bandpass frequency of 2–100 Hz, and power was normalized by the projected noise floor of the virtual sensor. The resulting images represented root-mean-square (RMS) power in the gamma band (30–50 Hz). All images were warped to Talairach space using AFNI and masked to remove non-brain matter and cerebellum. The final gamma band images were then normalized by the square root of the sum of squared images for six canonical bands between 2–100 Hz (delta, theta, alpha, beta, gamma, and high gamma). From this point forward, “gamma power” refers to the normalized RMS gamma power.

Images were analyzed using a linear mixed model implemented in the AFNI routine 3dLME [61]. If more than one usable recording existed for a given subject and session, both were included and coded as having occurred before or after tasks. Session (baseline, Placebo-Day0, Placebo-Day12, KET-Day0, KET-Day12), diagnosis, and the pre-post task factor were included in the model, along with the interaction between session and diagnosis. Gender and age were initially included as main effects and removed if non-

Table 1 Demographic and clinical characteristics for the sample

	MDD (<i>N</i> = 35) ^b		HC (<i>N</i> = 26) ^a	
	<i>N</i>	%	<i>N</i>	%
Female	21	60.0	16	61.5
Race (Caucasian)	32	94.1	19	73.1
History of psychiatric hospitalization	19	54.3		
History of suicide attempt	14	40.0		
History of substance abuse	8	22.9		
<i>Family history</i>	<i>N</i>	%		
Alcohol abuse (first degree)	13	37.1		
Anxiety disorder	12	34.3		
Mood disorder	25	71.4		
Suicide attempt	6	17.7		
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Age	35.5	9.6	33.9	10.4
Age of onset	15.8	6.6		
Length of current episode (months)	41.4	68.0		
Mean number of failed trials (lifetime, <i>N</i> = 34)	6.4	3.4		
MADRS	33.4	4.7	1.5	1.6
HDRS	21.6	4.3	1.6	1.4
BDI	29.0	7.6	0.2	0.6
CADSS	2.8	4.5	0.0	0.0
BPRS positive	10.1	1.9	8.0	0.2
HAMA	22.6	6.3	1.4	1.3
SHAPS	39.5	3.9	18.5	4.3
SSI (five items)	1.6	1.8	0.0	0.0
TEPS consummatory	23.4	4.6	39.6	5.2
TEPS anticipatory	23	7.3	46.9	5.5
PCLC	42	12.3	17.6	1.1
QLESQ	30.8	7.2	64.1	5.2

^aNote that one healthy control subject was excluded prior to infusion and thus only baseline MEG recordings are included in the analysis. Mean values on rating scales are given for *N* = 25

^bAll patients had failed to respond to at least one antidepressant trial in the current episode. MDD subjects and healthy controls did not differ on the basis of age or gender composition (*p* > 0.05)

MDD major depressive disorder, *HC* healthy control, *MADRS* Montgomery Åsberg Depression Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *BDI* Beck Depression Inventory, *BPRS* Brief Psychiatric Rating Scale, *CADSS* Clinician-Administered Dissociative States Scale, *HAM-A* Hamilton Anxiety Rating Scale, *SHAPS* Snaith-Hamilton Pleasure Scale, *SSI* Scale for Suicide Ideation, *TEPS* Temporal Experience of Pleasure Scale, *PCLC* PTSD Checklist, Civilian Version, *QLESQ* Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form

significant. Post hoc tests were performed within the 3dLME routine to assess individual contrasts. Images are shown at a voxel uncorrected threshold of *p* < 0.01 only if the false discovery rate (FDR)-corrected *p* value was < 0.05, with the voxel uncorrected threshold lowered to *p* < 0.001

as necessary to better distinguish clusters. Additional descriptive analyses were performed on regions of interest (ROIs), as described in the Supplementary Methods. Note that because these clusters were defined from the functional images, effect size estimates could not be made from extracted values.

As a secondary analysis, an additional mixed model was carried out using 3dLME using only the KET-Day0 and Placebo-Day0 recordings, with an additional covariate of absolute change in MADRS, centered within group and session, to determine if regional gamma power was associated with response to ketamine. Contrasts were performed to assess the relationship between gamma power and change in MADRS score within each diagnosis and session, as well as any differences between diagnostic groups with regard to the relationship between gamma power and change in MADRS score. In order to increase sensitivity, additional mixed models were performed in SPSS using the ROIs defined from the primary analysis of KET-Day0 vs. Placebo-Day0 recordings (supplementary Methods). The mean gamma power in each ROI during the KET-Day0 session was examined, with the pre-post factor as a repeated measure and diagnoses as a factor. The absolute change in MADRS response at *t* = +40 min was entered as a covariate, and the diagnosis by MADRS interaction was modeled. As before, age and gender were included as main effects and retained only if significant. These models were repeated using the change in CADSS at *t* = +40 min.

After the initial findings that gamma power in the MDD cohort did not correlate with MADRS response, we performed additional exploratory analyses using data previously defined ROIs. The purpose of these exploratory analyses was to determine if baseline gamma power moderated the relationship between post-ketamine gamma power and MADRS response. Seventeen subjects had both baseline and post-ketamine data; for subjects with two recordings in a session, we used mean gamma power. Mixed models were performed on post-ketamine gamma power using baseline gamma power and change in MADRS score from *t* = -60 to *t* = +40 min as main effects, with the effect of interest being the interaction between baseline gamma power and MADRS response. As in previous analyses, age and gender were included as main effects and removed if non-significant. Identical models were then repeated using the MADRS percent change from *t* = -60 to *t* = +230 min, as this is a more common measure of antidepressant response.

Code availability

All scripts and routines used for analyzing data are available from the corresponding author upon request.

Results

Subjects

Thirty-five unmedicated treatment-resistant subjects who met DSM-IV criteria for MDD and 26 healthy control subjects were included. One healthy control subject had a baseline MEG but was not randomized. Supplementary Figure S1 illustrates subject flow through the study, and demographic and clinical characteristics are summarized in Table 1.

Effects of ketamine on mood—MDD

Antidepressant effects were assessed using the MADRS, and acute psychotomimetic effects were assessed via the CADSS. In MDD subjects, MADRS scores were significantly lower post-ketamine infusion compared to placebo ($F_{1,77} = 84.5$, $p < 0.001$; Supplementary Table S2, Fig. 1a). The interaction with time was not significant ($p = 0.24$), although placebo and ketamine scores approached convergence by the end of Day 11. CADSS scores showed significant effects of drug ($F_{1,414} = 57.66$, $p < 0.001$), time ($F_{6,380} = 43.61$, $p < 0.001$), and a drug by time interaction ($F_{6,380} = 45.59$, $p < 0.001$; Fig. 1a). Ketamine significantly improved symptoms across a wide variety of domains including anhedonia, anxiety, post-traumatic stress disorder (PTSD), suicidality, and quality of life (Supplementary Tables S2 and S3). Results from the independent ratings acquired by raters who were not present for the entire infusion (infusion-blinded ratings) as well as results exploring carryover effects appear in the Supplementary Materials (Supplementary Table S1).

Effects of ketamine on mood—healthy controls

Healthy control subjects exhibited an unexpected increase in depressive symptoms, with significant main effects of drug ($F_{1,328} = 61.87$, $p < 0.001$), time ($F_{9,314} = 14.31$, $p < 0.001$), and a drug by time interaction ($F_{9,313} = 9.87$, $p < 0.001$). The increase in depressive symptoms was significant at 40, 80, and 120 min post infusion and at Day 1; by Day 2, only one healthy control subject exhibited a MADRS score five points greater than at baseline. To understand which symptoms were driving the increase in MADRS score, we examined individual MADRS and HAM-D17 items (Supplementary Table S5 and Fig. 2). Items showing the greatest increase in healthy controls (but decreases in MDD subjects) included inner tension, lassitude, inability to feel, psychic anxiety, and somatic anxiety. We also found significant increases in SHAPS, TEPS-Anticipatory, HAM-A, and BDI scores. Notably, every item on the SHAPS and TEPS (aside from those relating to food

and appetite) showed increases in healthy controls and decreases in MDD subjects post-ketamine. These findings suggest that ketamine's mood-lowering effect on healthy control subjects occurred primarily in the domains of anxiety, emotional blunting, and anhedonia.

Consistent with MDD patients, healthy controls demonstrated significant but acute increases in CADSS scores post-ketamine, with main effects for drug ($F_{1,274} = 26.21$, $p < 0.001$), time ($F_{6,261} = 27.50$, $p < 0.001$), and a drug by time interaction ($F_{6,259} = 26.01$, $p < 0.001$). In post hoc tests, only the 40-min time point was significant ($F_{1,261} = 187.54$, $p < 0.001$). Importantly, CADSS scores at 40 min post infusion were only weakly correlated with MADRS scores ($R = 0.358$, $p = 0.086$), indicating that the increase in depressive symptoms extended beyond that associated with dissociative side effects.

Electrophysiology—MEG results

Resting state MEG recordings were obtained at baseline, the day of the infusion, and 11–13 days post infusion. Data were analyzed using linear mixed models, and post hoc contrasts examining differences between diagnostic groups and sessions are reported.

Figure 2a shows the contrasts for Ketamine-Day0 vs. Placebo-Day0 for the MDD group, and Fig. 2b shows the same contrast in the healthy control group. Regions include those involved in the central executive (CEN), salience (SN), and default mode (DMN) networks (see figure legend). Figure 2c illustrates the estimated marginal means from mixed models of RMS gamma power extracted from selected ROI defined on the Ketamine-Day0 vs. Placebo-Day0 contrast across both groups. While unbiased effect sizes cannot be estimated from functional ROIs, they suggest that MDD subjects exhibited increases post-ketamine to levels commensurate with those seen in healthy control subjects following placebo infusion. Additional contrasts are described in the Supplementary Materials.

To examine the relationship between gamma power and MADRS response, we used absolute change in MADRS score from the $t = -60$ to the $t = +40$ min time point as a covariate in a mixed model including both ketamine and placebo recordings. Although the +230-min time point was closer to the MEG recording, there was no difference between placebo and ketamine MADRS scores in the healthy control group at this time point. We observed no significant relationship between MADRS response and gamma power in either group in the ketamine session. Similar mixed models carried out on ROIs derived from the data presented in Fig. 2 produced equivalent results, with no relationship between gamma power and either MADRS or CADSS observed in either group.

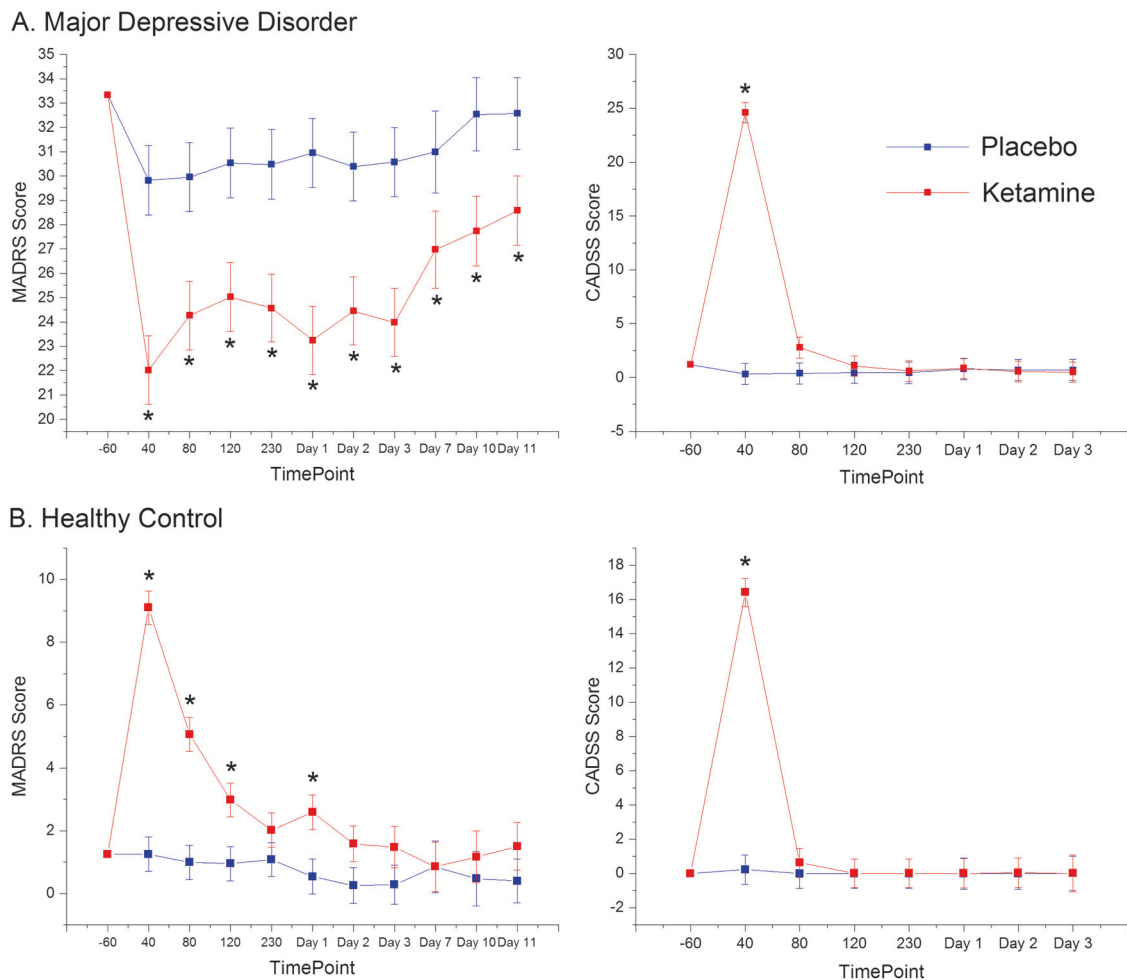


Fig. 1 Effects of ketamine on mood. Graphs of the marginal means derived from the linear mixed models for the Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinician-Administered Dissociative States Scale (CADSS) time points significant at $p < 0.05$ after Bonferroni correction are indicated with an asterisk. **a** In major depressive disorder (MDD) subjects, MADRS scores demonstrated a significant main effect of drug ($F_{1,559} = 140.70$, $p < 0.001$; Supplementary Table S2). CADSS scores indicated significant main effects of drug ($F_{1,414} = 57.66$, $p < 0.001$), time ($F_{6,380} = 43.61$, $p < 0.001$), and a drug by time interaction ($F_{6,380} = 45.59$, $p < 0.001$). CADSS scores peaked at 40 min post-ketamine ($F_{1,389} = 326.7$, $p < 0.001$); the effect of the drug was not significant at any other time point. **b** In healthy controls, MADRS scores indicated significant main effects of drug

($F_{1,328} = 61.87$, $p < 0.001$) and time ($F_{9,314} = 14.31$, $p < 0.001$) and a significant drug by time interaction ($F_{9,313} = 9.87$, $p < 0.001$). The increase in depressive symptoms was significant at 40, 80, and 120 min post infusion and at Day 1. Seventeen of 24 healthy controls receiving ketamine (71%) showed an increase of at least five points on the MADRS at any time point, compared to only one of 23 healthy controls receiving placebo (4%). By Day 2, only one healthy control subject still scored above 5 on the MADRS. CADSS scores in healthy controls demonstrated significant main effects of drug ($F_{1,274} = 26.21$, $p < 0.001$), time ($F_{6,261} = 27.50$, $p < 0.001$), and a drug by time interaction ($F_{6,259} = 26.01$, $p < 0.001$), with significant differences between ketamine and placebo observed only at the 40-min time point

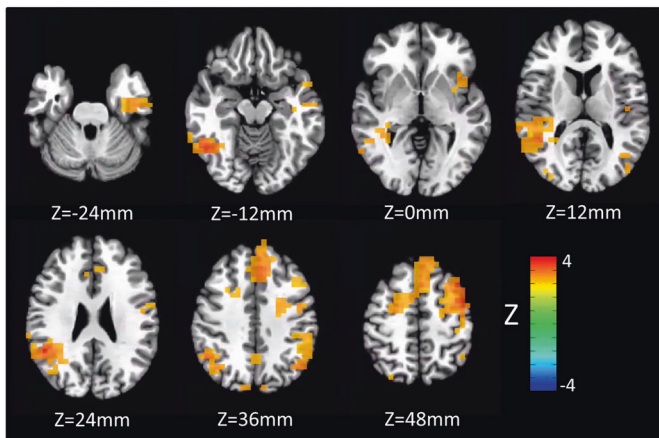
Electrophysiology—exploratory analysis of gamma power and antidepressant response

We hypothesized that heterogeneity within the MDD sample might have contributed to the lack of association between antidepressant response and gamma power; in particular, we hypothesized that if response to ketamine depended on homeostatic regulation, as has been suggested previously [33], baseline gamma power might modulate the interaction. To investigate this, we used the ROIs where we observed significant increases in gamma power post-

ketamine in the combined depressed and healthy groups (Supplementary Table S7).

The first exploratory model examined gamma power at the Day0 post-ketamine time point using baseline gamma power and absolute change in MADRS score from the -60 to the +40-min time points as covariates; the effect of interest was the interaction between baseline gamma power and MADRS response. As expected, there were significant main effects for baseline gamma power in all ROIs. Additionally, after controlling for baseline gamma power, we observed a main effect of MADRS response, as

A. MDD: Ketamine > Placebo



B. HC: Ketamine > Placebo

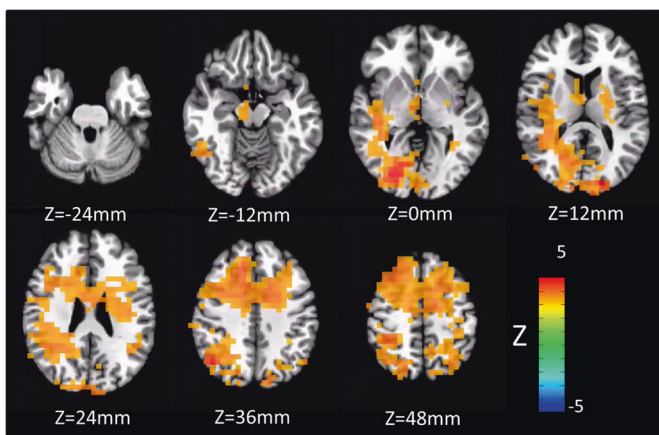
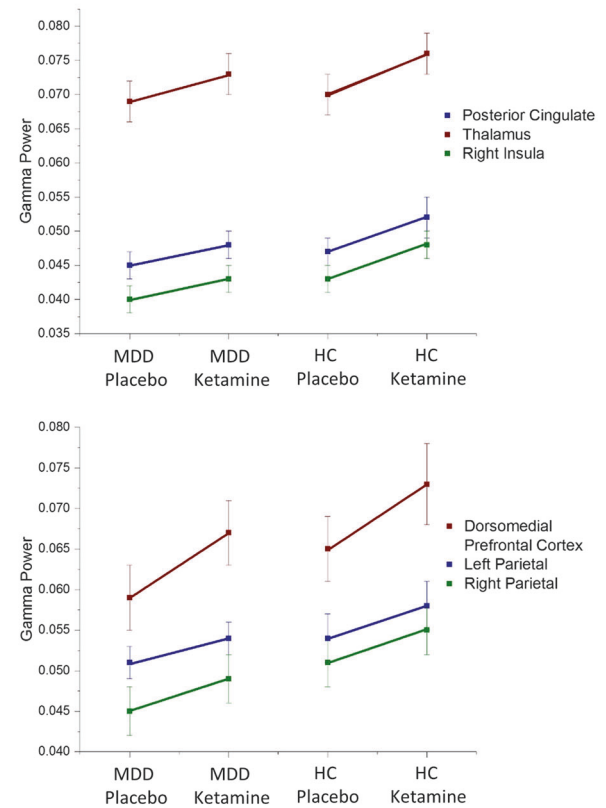


Fig. 2 Images of Ketamine-Day0 vs. Placebo-Day0 contrasts derived from the mixed model are shown for **a** patients with major depressive disorder (MDD). Images are thresholded at a voxel-level threshold of $p < 0.01$, which corresponds to $p_{FDR} = 0.049$. The same images are shown for **b** healthy controls, where in order to differentiate regions of peak change, images are thresholded at a more restrictive voxel-level threshold of $p < 0.001$, which corresponds to $p_{FDR} = 0.0014$. Gamma power was robustly increased in regions of the central executive network (CEN; Fig. 2a, b, $Z = 36$ mm), including bilateral parietal cortex, dorsomedial prefrontal cortex, and dorsolateral prefrontal cortex (DLPFC) in both groups. The MDD group exhibited increases in the insula, which is involved in the salience network (SN; Fig. 2a, $Z = 0$ mm). Healthy control subjects exhibited increases in gamma power in

well as a significant interaction between baseline gamma power and MADRS response in 8 of our 11 regions (supplementary table S7). The interaction between baseline gamma power and MADRS response was most notable in the thalamus ($F_{1,12} = 47.46$, $p < 0.001$) and the right insula ($F_{1,13} = 22.24$, $p < 0.001$). We repeated these models using percent change in MADRS score from the -60 to $+230$ -min time point, as this is a more common measure of antidepressant response. The moderating effect of baseline gamma power on MADRS response was evident only at a trend level for the dorsomedial prefrontal

C.



the posterior cingulate and thalamus (Fig. 2b, $Z = 0$ mm–12 mm), regions related to the default mode network (DMN). MDD subjects exhibited increases under ketamine in the inferior temporal cortex extending into the parahippocampal cortex (Fig. 2a, $Z = -24$ mm to -12 mm). **c** The plots of estimated marginal means from mixed models performed on regions of interest (ROIs) defined on the Ketamine-Day0 vs. Placebo-Day0 contrast collapsed across groups. Coordinates are given in Supplementary Table S7. Because these are functionally defined ROIs, effect sizes cannot be interpreted, although the general trend of MDD subjects exhibiting increases in gamma power following ketamine infusion to a level commensurate with that of the healthy controls following placebo infusion can be observed. HC healthy control

cortex and right parietal cortex (supplementary table S7). Figure 3a illustrates the difference in the relationship between gamma power post-ketamine and MADRS response as baseline gamma power increases; it should be noted that subgroup stratification was performed for visualization purposes only, and that baseline gamma power was a continuous variable in the statistical model. Figure 3b plots the change in gamma power between the post-ketamine and baseline sessions vs. MADRS response for patients divided by the magnitude of their baseline gamma power.

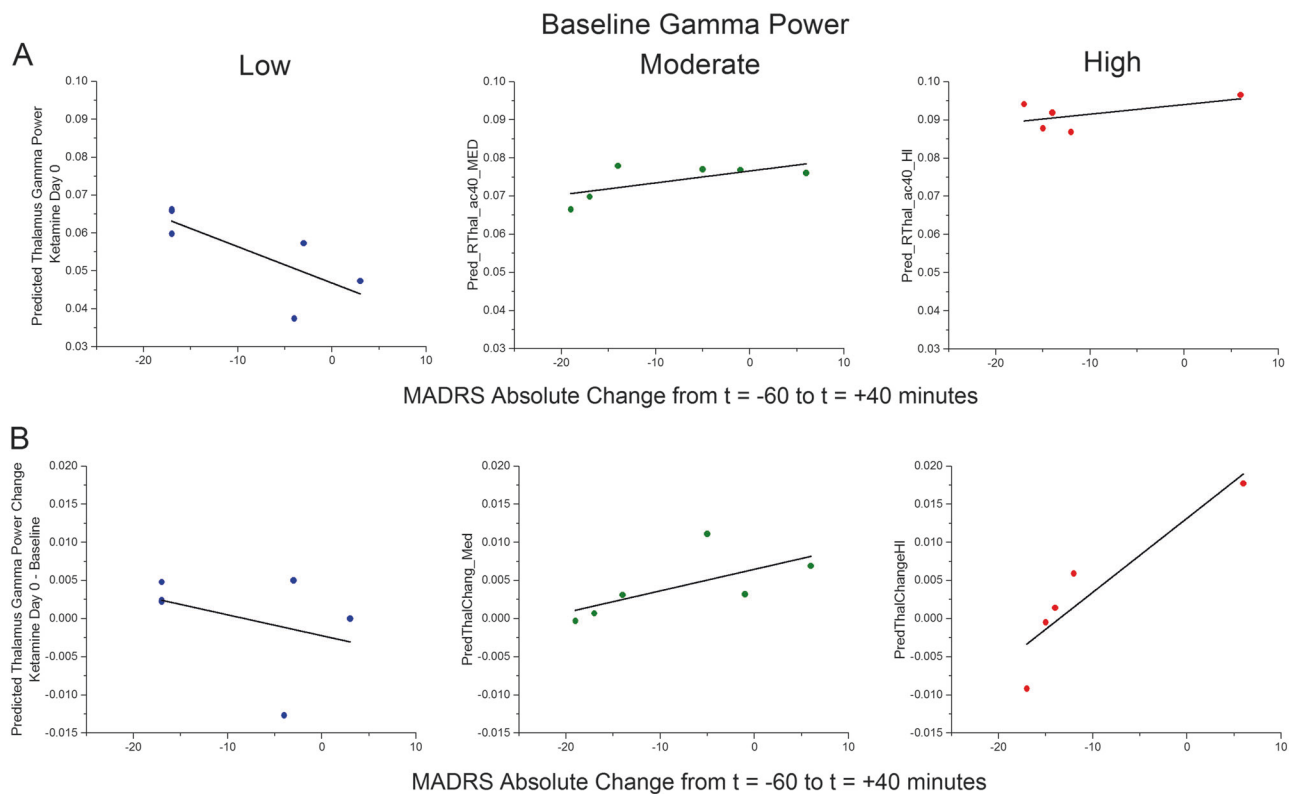


Fig. 3 a Exploratory results in major depressive disorder (MDD) patients from a mixed model examining post-infusion gamma power in the right thalamus with baseline gamma power and change in Montgomery Åsberg Depression Rating Scale (MADRS) score as a covariate. Significant main effects were noted for both baseline gamma power ($F_{1,12} = 224.8$, $p < 0.001$) and MADRS response ($F_{1,12} = 32.6$, $p < 0.001$), as was a significant interaction between baseline gamma power and MADRS response ($F_{1,12} = 47.46$, $p < 0.001$). The predicted

values are plotted vs. change in MADRS score from $t = -60$ to $t = +40$ following ketamine infusion for three groups of patients stratified by baseline gamma power to visualize the interaction. Note that subgroup stratification was performed here for visualization purposes only; baseline gamma power was a continuous variable in the statistical model. **b** The same data from **a** (above), except with change in gamma power from baseline to ketamine sessions plotted along the y axis; note that the statistical effects are the same

Discussion

In this study, and consistent with prior work [2–6], we report a robust, rapid, and relatively sustained antidepressant response to a single dose of ketamine in MDD patients. Unexpectedly, we also observed significant increases in depressive symptoms in healthy control subjects lasting up to 24 h post infusion, primarily in the domains of anxiety and anhedonia. Importantly, increased MADRS scores only weakly correlated with CADSS scores, indicating that depressive symptoms were not entirely accounted for by increased dissociative symptoms. We also observed increased gamma power following ketamine infusion compared to placebo infusion in widespread cortical and subcortical areas in both healthy control and MDD groups 6–9 h post infusion. Contrary to our a priori hypothesis, we did not observe a simple relationship between gamma power post-ketamine infusion and antidepressant response. Our post hoc exploratory models, however, revealed a more complex interaction. In MDD subjects, these models showed that baseline gamma power

moderated the relationship between change in gamma power post-ketamine and antidepressant response in multiple regions; subjects with higher baseline gamma power who experienced larger increases in gamma power showed a worse antidepressant response, while subjects with lower baseline gamma power who also experienced larger increases in gamma power showed a better antidepressant response. Taken together, these data suggest that alterations to homeostatic balance may be a crucial piece of ketamine's mechanism of action and, potentially, the pathophysiology of MDD, at least in a treatment-resistant population.

Although ketamine infusion in psychiatrically healthy control subjects has been used extensively as a model for schizophrenia [62], only one study specifically assessed depressive symptoms, reporting a small but significant increase in HAM-D17 scores in eight subjects [63]. Acute increases in BPRS-negative (dysphoric) and anxiety symptoms in healthy controls have also been reported [64], a measure that was acutely reduced in our MDD subjects. Multiple studies have also reported increased anhedonia following ketamine infusion in healthy volunteers [65–67].

While sad mood was not among the most robust symptom domains affected by ketamine infusion in healthy controls in the present study, it is important to note that diagnosing a major depressive episode requires the presence of either sad mood or anhedonia, not both. The short duration of depressive symptoms in response to ketamine in healthy controls may indicate a rapid adaptation to the actions of ketamine; this would be analogous to resiliency in response to stressors, a process known to be altered in individuals with MDD [36]. However, because gamma power was still elevated at the 6–9-h post-ketamine time point compared to placebo, this indicates that synaptic homeostasis was not yet fully restored.

Notably, the extant literature investigating ketamine's influence on resting gamma oscillations has primarily examined acute response. Studies have reported acute increases in gamma power in widespread frontal, temporal, and parietal areas [17, 68], as well as thalamic gamma oscillations [17]. Acute increases in gamma power in cortical areas associated with visual and motor tasks have also been reported [18]. Although few studies have investigated time points occurring hours or days post infusion, gamma band synaptic potentiation has been observed 6–7 h post infusion, although only the motor cortex was examined [39]. The only functional MRI (fMRI) study measuring the non-acute effects of ketamine found reduced resting state functional connectivity 24 h post infusion between the medial prefrontal cortex and the posterior cingulate [69], regions where we observed increased gamma power 6–9 h post infusion. Because gamma synchrony typically correlates positively with functional connectivity, taken together, these results may indicate that—after a relatively acute phase of increased gamma synchrony and functional connectivity—there may be a rebound phase as homeostasis is restored. Longitudinal studies at multiple time points following ketamine infusion are needed to confirm this hypothesis. Consistent with this notion, an magnetic resonance spectroscopy (MRS) study in healthy control subjects showed an increase in the glutamine/glutamate ratio 24 h following ketamine infusion that was partly driven by decreases in glutamate [70]; notably, no increase in glutamate was found 1 h post infusion, and other spectroscopy studies in healthy control subjects failed to find differences in glutamate immediately following ketamine infusion [63].

The finding that ketamine induced depressive symptoms in healthy controls, particularly in the domains of anxiety and anhedonia, has important implications. It suggests that ketamine's effects in healthy control subjects may represent a potential model for dysphoria. In addition, while many studies have investigated ketamine infusion in healthy controls in an effort to discern its antidepressant mechanism of action, our findings indicate that one cannot presume that biological findings in healthy subjects will accurately represent the biology of the antidepressant response.

Within our MDD subject group, we found that baseline gamma power moderated the relationship between increased gamma power post-ketamine and antidepressant response in multiple regions, consistent with the notion that resting gamma oscillations may be a proxy measure of inhibition/excitation balance and homeostasis, although these exploratory results should be considered preliminary. As a potential explanation for our findings, we would hypothesize that subjects with low baseline gamma power may be in a state where ketamine-induced increases in gamma power (via decreased interneuron and/or increased AMPA receptor activity) re-establish optimal homeostatic balance; in contrast, subjects with high baseline gamma power may experience a further disruption of the homeostatic balance and thus no antidepressant effect (although it should be noted that thalamic gamma power was nominally although not significantly reduced in MDD subjects compared to healthy controls (Figure S5)). Notably, however, gamma power dysfunction has not been identified as a biomarker for MDD, consistent with the idea that both increases and decreases in gamma power beyond a homeostatic ideal may be pathological. Additionally, it may be difficult to discern an ideal value for gamma power, as there is likely high inter-subject variability, analogous to the high inter-subject variability of the peak alpha frequency [71]. In the present study, gamma power also depended on age and/or gender (Supplementary Results). Further research is needed to determine whether clinical characteristics or secondary biomarkers can differentiate subjects above vs. below their ideal point of inhibition/excitation balance. Substantial evidence for biologically based MDD subpopulations exists, as recently demonstrated in a large sample of resting state fMRI images collected from over 1100 patients with MDD [72]. Given the extant correlations between resting state fMRI connectivity, glucose utilization [73–76], and gamma synchrony [27], these fMRI-based subgroups may potentially reflect altered glutamatergic function as well as inhibition/excitation balance. MRS studies in depression have been inconsistent, with both increases and reductions observed in prefrontal glutamate concentrations relative to controls; this may also be attributable to biological subtypes of MDD that may be poorly distinguished on the basis of clinical features alone (reviewed in ref. [77]).

Increased gamma power in both healthy controls and MDD subjects was observed in regions relating to the SN, CEN, and DMN, a triad of networks hypothesized to be intimately involved in the pathophysiology of MDD [78–80]. Many of these same regions also showed a relationship in MDD patients between MADRS response and gamma power after controlling for baseline gamma power, most notably thalamus and insula (an SN region). Interestingly, an fMRI study in healthy control subjects showed increased

thalamo-cortical connectivity during acute ketamine infusion [81], and Dreisen et al. [82] showed that the magnitude of the increase in global connectivity of the thalamus was negatively associated with negative symptoms experienced during the infusion. Although MEG is less sensitive to subcortical sources than cortical surface sources, it was used to observe cortico-thalamic gamma oscillations as early as 1991 [83]. The beamforming technique used herein enables visualization of deep sources, and prior studies have demonstrated altered gamma power in the thalamus in response to fearful faces in individuals with MDD [84]. Consistent with the idea that prolonged dysrhythmia or deviation from homeostasis can result in neuronal damage, studies have found decreased thalamic volumes in MDD [85], along with abnormally increased blood flow and metabolism [86] and DMN connectivity [87].

Our exploratory results, while tantalizing, should be treated with caution. Due to the assiduous quality control of our scans, the final sample size for exploratory MEG analysis used only 17 MDD subjects. In addition, these results alone do not provide a biomarker for response to ketamine. While subjects with lower baseline gamma who had the greatest increase in gamma power post-ketamine experienced the greatest antidepressant response, we cannot predict who is likely to experience the greatest gamma power increase in response to ketamine. In addition, there is no clear "ideal" value for raw gamma power post-ketamine, and it is unlikely that an ideal value would apply to all subjects, given that the range of resting gamma power in healthy subjects is relatively broad. We should also note that while, for consistency, we chose the measure of response to ketamine to match what we used in our analyses including the healthy controls (absolute change between MADRS score from $t = -60$ to $+40$ min), percent change at other time points is more commonly used as a metric of the antidepressant response. Although results no longer remained significant using percent change at later time points, the antidepressant response in our sample was maximal at 40 min, even in the depressed subjects, and the variance was significantly larger in the percent change at $+230$ and day 1. Finally, because these were post hoc exploratory analyses, further hypothesis-driven investigations are required.

Nevertheless, these data have broad implications. First, we found that ketamine infusion in healthy control subjects robustly and rapidly induced depressive symptoms across multiple symptom domains, complicating the interpretation of studies examining the biological response to ketamine in healthy subjects as well as the applicability of those results to individuals with MDD. Second, our finding that gamma power was increased even six to nine hours post-ketamine infusion in both healthy controls and MDD subjects indicates that the influence of ketamine and its metabolites on

synaptic plasticity persists outside of the acute infusion period. Third, and most importantly, our results potentially identify gamma power as a marker for synaptic homeostasis, which may enable the discovery of more accurate markers pointing to the degree and direction of divergence from ideal synaptic function. Building on this work, future treatments could be tailored to the degree and direction of dysregulation for each subject individually, potentially enabling a personalized approach to psychiatry.

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Compliance with ethical standards

Conflict of interest Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; NCT00088699/04-M-0222/ZIA MH002857), by a NARSAD Independent Investigator Award to C.A.Z., and by a Brain and Behavior Mood Disorders Research Award to C.A.Z. C.A.Z. is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation. C.A.Z. is listed as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain. C.A.Z. is listed as co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and PTSDs; he has assigned his patent rights to the US government, but will share a percentage of any royalties that may be received by the government. The remaining authors declare that they have no conflict of interest.

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