ARCHIVAL REPORT

Synaptic Potentiation Is Critical for Rapid Antidepressant Response to Ketamine in Treatment-Resistant Major Depression

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Background: Clinical evidence that ketamine, a nonselective *N*-methyl-D-aspartate receptor (NMDAR) antagonist, has therapeutic effects within hours in people suffering from depression suggests that modulating glutamatergic neurotransmission is a fundamental step in alleviating the debilitating symptoms of mood disorders. Acutely, ketamine increases extracellular glutamate levels, neuronal excitability, and spontaneous γ oscillations, but it is unknown whether these effects are key to the mechanism of antidepressant action of ketamine.

Methods: Twenty drug-free major depressive disorder patients received a single, open-label intravenous infusion of ketamine hydrochloride (.5 mg/kg). Magnetoencephalographic recordings were made approximately 3 days before and approximately 6.5 hours after the infusion, whereas patients passively received tactile stimulation to the right and left index fingers and also while they rested (eyes-closed). Antidepressant response was assessed by percentage change in Montgomery-Åsberg Depression Rating Scale scores.

Results: Patients with robust improvements in depressive symptoms 230 min after infusion (responders) exhibited increased cortical excitability within this antidepressant response window. Specifically, we found that stimulus-evoked somatosensory cortical responses increase after infusion, relative to pretreatment responses in responders but not in treatment nonresponders. Spontaneous somatosensory cortical γ-band activity during rest did not change within the same timeframe after ketamine in either responders or nonresponders.

Conclusions: These findings suggest NMDAR antagonism does not lead directly to increased cortical excitability hours later and thus might not be sufficient for therapeutic effects of ketamine to take hold. Rather, increased cortical excitability as depressive symptoms improve is consistent with the hypothesis that enhanced non-NMDAR-mediated glutamatergic neurotransmission via synaptic potentiation is central to the antidepressant effect of ketamine.

Key Words: Cortical excitability, γ oscillation, ketamine, magnetoencephalography, major depression, NMDA antagonist

Interest in identifying potential glutamatergic system dysfunction in mood disorders is gaining momentum (1,2). Mounting evidence, from postmortem (3,4) and magnetic resonance spectroscopy studies (2), points to abnormalities in glutamatergic neurotransmission in depressed individuals. Clinical research has established a range of compounds that have antidepressant properties through their direct action on the glutamatergic system. A major discovery in this context is the finding that a single subanesthetic dose of the nonselective *N*-methyl-D-aspartate receptor (NMDAR) antagonist ketamine can produce a sustained antidepressant effect within hours in patients with treatment-resistant major depressive disorder (MDD) (5) and bipolar disorder (BD) (6,7). Because conventional antidepressants that target monoaminergic systems typically take weeks to be effective, an understanding of the mechanism of the rapid antidepressant action of ketamine would significantly expedite the development of fast-acting and more effective drug therapies for depressive illness.

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Preclinical work has provided critical insight into candidate synaptic and intracellular phenomena underlying rapid antidepressant-like effects of NMDAR blockage. For instance, the antidepressant-like effects of ketamine can be neutralized by pretreatment with NBQX, an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) antagonist (8). This finding, which has been replicated (9–11), suggests that AMPA-mediated neurotransmission is centrally involved in the rapid effects of ketamine, and indeed, other glutamatergic-modulating compounds with antidepressant-like properties have been shown to increase AMPAR trafficking to the postsynaptic membrane (12). Ketamine administration also triggers rapid increases (i.e., at 2 hours) in activity of the mammalian target of rapamycin pathway (11), which is followed by increased expression of synaptic proteins as well as increased density and function of spine synapses (reviewed in Duman and Voleti [13]). Notably, these effects are abolished by pretreatment with AMPAR antagonists (11). More recently, it has been demonstrated that NMDAR blockage initiates a cascade of intracellular processes that boosts translation of brain-derived neurotrophic factor (BDNF), which, in turn, promotes synaptic plasticity (9). A key role for BDNF translation is further highlighted by the finding that BDNF Val66Met knock-in mice have impaired synaptogenesis and lack an antidepressant-like response to ketamine in the forced swim test (14). Beyond a study of serum BDNF levels that did not show any change after ketamine administration or a relation to antidepressant response (15), these findings await translation to patient populations.

At the circuit level, NMDAR antagonists such as ketamine are known to increase glutamate release and neuronal excitability, acute effects attributed to disinhibition of pyramidal excitatory neurons due to reduced γ-aminobutyric acid(GABA)-ergic inhibitory feedback (16,17). Thus, extracellular glutamate levels might surge and promote plastic changes such as increased AMPAR sur-

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face expression (18). Ketamine also directly induces spontaneous γ synchrony (30–80 Hz oscillations) within cortical networks. This is a well-replicated phenomenon across species, which might be driven by reduced NMDAR-mediated input specifically to fast-spiking parvalbumin-expressing GABAergic interneurons (19–23). This latter effect might be relevant to the psychotomimetic symptoms experienced during ketamine administration (24–26) and has received ample attention in schizophrenia studies (27). Whether the effects of ketamine on cortical excitability and/or spontaneous cortical γ activity last long after dissociative symptoms have dissipated is unknown but might provide critical insight into the link between modulating glutamatergic neurotransmission and reducing depression. This question can be readily addressed noninvasively in depressed patients with whole-head magnetoencephalography (MEG) to determine whether these effects are related to rapid changes in depressive symptoms after ketamine.

In the present study, we administered a single open-label intravenous infusion of ketamine hydrochloride (.5 mg/kg over 40 min) to drug-free patients with treatment-resistant MDD. The MEG data were collected (on average) 3 days before and 6.5 hours after the infusion, to compare baseline cortical activity with cortical activity within the antidepressant response window of ketamine. For pre- and postinfusion MEG sessions, we recorded neuromagnetic activity while patients received tactile stimulation of the left and right index fingers to measure stimulus-evoked somatosensory cortical (SS ctx) excitability and also during rest (eyes-closed) to measure spontaneous SS ctx activity. The focus on SS ctx was based on evidence that synaptic plasticity (i.e., potentiation and depression) can be induced relatively easily in this cortical region (28,29). We hypothesized that enhanced cortical excitability, consistent with synaptic potentiation, rather than enhanced spontaneous cortical γ-band activity would be specifically linked to rapid antidepressant responses after ketamine.

Methods and Materials

Patients

All patients were studied at the National Institute of Mental Health in Bethesda, Maryland, between January 2007 and December 2009. Twenty right-handed patients (5 women, 46 ± 14 years of age) with a DSM-IV diagnosis of MDD (30) without psychotic features met the following inclusion criteria: current major depressive episode of at least 4-week duration, current or past history of lack of response to two adequate antidepressant trials (19 of 20 patients met this criterion for the current episode), and a Montgomery-Åsberg Depression Rating Scale (MADRS) (31) score of ≥ 22. Diagnosis was determined by Structured Clinical Interviews for Axis I DSM-IV Disorders—Patient Version (32). Patients were hospitalized for the study duration and drug-free from psychotropic medications for at least 2 weeks before MEG testing (5 weeks for fluoxetine). To establish treatment resistance, adequacy of past antidepressant trials was determined with the Antidepressant Treatment History Form—modified (33). All patients were physically healthy as determined by medical history, physical examination, electrocardiogram, chest x-ray, urinalysis, and toxicology screen. The study was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health. All subjects provided written informed consent before enrollment and were assigned a clinical research advocate from the National Institute of Mental Health Subject Protection Unit to monitor the consent process and research participation.

Drug Administration

Patients received a single open-label infusion of .5 mg/kg of ketamine hydrochloride (Abbott Labs, North Chicago, Illinois) over 40 min via a Baxter infusion pump by an anesthesiologist. After the infusion, patients entered a randomized, double-blind placebo-controlled 4-week clinical trial of riluzole to determine whether effects of ketamine can be modified through long-term modulation of glutamatergic neurotransmission. Clinical outcome data are reported elsewhere (34). Riluzole, which has been shown to have antidepressant effects after 2 weeks (35), is thought to inhibit presynaptic glutamate release rather than act on postsynaptic receptors (36). Responders and nonresponders to ketamine were equally likely to receive riluzole or placebo. The first oral dose of riluzole (50 mg, $n = 12$) or placebo ($n = 8$) was administered 5–6 hours after ketamine to ensure that antidepressant effects had not begun to dissipate and approximately 1 hour before the postketamine MEG recordings (Figure 1). Given evidence that peak serum levels of orally administered riluzole are achieved after 1–1.5 hours in healthy volunteers (37), we did not expect riluzole to significantly influence the MEG recordings but tested this possibility. Moreover, although single doses of ≥ 250 mg can produce dizziness/vertigo, no central or peripheral side effects (e.g., changes in electrocardiogram) at a 50-mg dose have been reported previously (37). In the present sample, side effects did not differ between the riluzole and placebo groups over the course of treatment (34).

Clinical Measures

Patients were rated 60 min before ketamine infusion and at multiple time points after infusion (40 min, 80 min, 110 min, 230 min). Rating scales included the MADRS (31), which was the primary outcome measure. Values for items on this scale that do not change over brief time periods (e.g., sleep, appetite) were carried forward from the baseline ratings. Responders were defined as patients exhibiting ≥50% reduction in MADRS scores at 230 min relative to baseline scores. Secondary outcome measures were the Brief Psychiatric Rating Scale positive symptoms subscale (BPRS-pos) (38) and the Clinician Administered Dissociative States Scale (CADSS) (39), which measure psychotic and dissociative symptoms, respectively.

Plasma Measurements

Ketamine and norketamine plasma levels were obtained along with clinical ratings after the infusion. Analyses were performed by

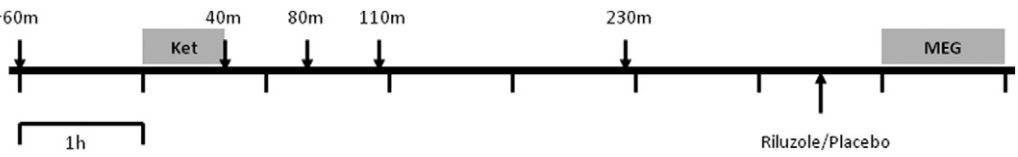

Figure 1. Timeline of ketamine (Ket) session. Patients received a single open-label infusion of Ket (.5 mg/kg) over 40 min. The depressive, dissociative, and psychotic symptoms of patients were assessed before the infusion and at several time points afterwards (arrows). Depressive symptom change at 230 min was used to define responder and nonresponder groups. Blood draws to measure plasma metabolite concentrations were taken at approximately the same times after the infusion. Post-Ket magnetoencephalography recordings (MEG) were made approximately 6.5 hours after the start of infusion. An oral dose of riluzole (50 mg) or placebo was administered approximately 1 hour before MEG recordings.

Gas Chromatograph-Mass Spectrometer (Agilent Technologies, Santa Clara, California) at NMS Labs (Willow Grove, Pennsylvania); for detailed methods, see DiazGranados *et al.* (6).

MEG and Magnetic Resonance Image Acquisition

Baseline MEG recordings were made 1–6 days before the infusion, and postketamine MEG recordings were made 6–7 hours after the infusion. Patients completed two runs (250 sec/run) while receiving tactile stimulation of the left and right index fingers (500 stimuli, 25-msec duration, 2-Hz average rate). Tactile stimulation was controlled by a pneumatic stimulating device that uses a brief burst of air (30 psi) to displace a plastic membrane resting against the skin of the distal phalange. Patients also completed two runs (250 sec/run) in which they rested with their eyes closed.

For each run, neuromagnetic activity was recorded by a CTF-OMEGA 275-channel whole-head magnetometer (VSM MedTech, Coquitlam, British Columbia, Canada) in a magnetically shielded room (Vacuumschmelze, Hanau, Germany), with synthetic third order balancing for active noise cancellation. Data were acquired at 1200 Hz with a bandwidth of 0–300 Hz. Anatomical T1-weighted magnetic resonance images (MRIs) were obtained from each patient with a 1.5-T or 3-T GE whole-body scanner (GE Healthcare, Milwaukee, Wisconsin) in a separate session.

Time-Frequency Analysis

All MEG analyses were done by an experimenter (B.R.C.) who was blind to the clinical ratings of patients and session information. Time-frequency analyses were conducted on the sensor data to examine stimulus-evoked response characteristics. Stimulus epochs (−100 to 300 msec, locked to stimulus onset) were time-domain averaged before applying a Stockwell transform (40) to the data. Plots of evoked power were normalized by prestimulus power and averaged across sensors overlying the hemisphere contralateral to stimulation. Source analyses were tailored to the response characteristics shown in these plots.

Source Analysis: Stimulus-Evoked Responses

A minimum-variance adaptive beamformer algorithm (41) was used to determine sources of the stimulus-evoked γ-band responses (for similar methods, see Cornwell *et al.* [42] and Salvadore *et al.* [43]). For each dataset (2 runs × 2 sessions), a single covariance matrix was calculated from 500 unaveraged epochs, from -100 to 300 msec relative to stimulus onset, with a 30–50 Hz bandpass filter. A multi-sphere source space model derived from MRIs of patients was used for source power estimation. Beamformer weights were calculated with a normalized vector formulation that determines optimal source orientation in three-dimensional space for computing the biomagnetic forward solution at each voxel (44). Virtual sensor time series were projected by vector multiplication of the raw data by the beamformer weights and subsequently averaged in the time domain to attenuate noise and extract the stimulus-locked evoked response at each voxel (implemented by SAMerf [45]). From the time course of evoked γ power observed in the time-frequency plots, we contrasted power in the 30–60 msec poststimulus window with power in a 30-msec prestimulus window.

With the Analysis of Functional Neuroimages program (46), individual-subject source volumes, which represent distributions of baseline-normalized stimulus-evoked power, were co-registered to their anatomical MRIs and spatially warped to a Talairach template for group-level analyses. For visualization, group-averaged maps for baseline and postketamine sessions were overlayed on a standardized MRI and statistically thresholded on the basis of one-sample *t* tests at a false discovery rate (47) of .001. Peak responses were identified in left and right sensorimotor cortices for contralateral stimulation after averaging group-maps across baseline and postketamine sessions. Spherical masks of 5-mm radii were centered at each source to extract mean power estimates. The same source identified in each hemisphere for contralateral stimulation was used for extracting individual mean power estimates for ipsilateral stimulation.

Source Analysis: Resting-State Activity

A similar minimum-variance adaptive beamformer algorithm was employed to determine changes in cortical resting-state (eyes-closed) activity before and after ketamine (for similar methods, see Rutter *et al.* [48]). For each dataset (2 runs × 2 sessions), a single covariance matrix was calculated over 4 min of rest, with a 30–50 Hz bandpass filter. Source power at each voxel was estimated over the single 4-min epoch and normalized by a constant noise estimate, which is derived from the same covariance matrix, to correct for the depth bias in beamformer power estimates (pseudo-*Z* deviate [41]). The same spherical masks defined by the previous analyses of stimulus-evoked responses were used to extract mean γ-band power from left and right SS ctx before and after ketamine.

Statistical Analyses

Mixed-effects analyses of variance (ANOVAs) were conducted on extracted data in SPSS 18 (SPSS, Chicago, Illinois) ($\alpha = .05$). For stimulus-evoked responses, a 2 (Group: responders vs. nonresponders) × 2 (Hemisphere: left vs. right) × 2 (Stimulation: contralateral vs. ipsilateral) × 2 (Time: preketamine vs. postketamine) mixed-effects ANOVA was conducted. For resting activity, a 2 (Group) × 2 (Hemisphere) × 2 (Time) mixed-effects ANOVA was conducted. We also ran these analyses by replacing the Group variable with MADRS percentage change scores as a continuous between-subjects variable to ensure that any null effects related to treatment response were not due to loss of power after dichotomization. The same statistical outcomes were obtained and thus are not reported. Both models were also expanded by the additional grouping factor of Riluzole (riluzole vs. placebo) to determine whether administration of this drug affected the results.

For responders and nonresponders separately, Pearson correlations were calculated to test for relationships between mean stimulus-evoked SS ctx responses and plasma concentrations of ketamine and norketamine taken at four time points. The aim of these correlation analyses was to provide evidence for a direct link between ketamine administration and postketamine cortical responses, given the absence of a placebo control. Due to positive skew in plasma concentration levels, a $\log_{10}$ transformation was applied to these data. Statistical significance (two-tailed) was determined with a Bonferroni correction for multiple correlation tests ($\alpha = .05/16 = .0031$).

Results

Symptomatic Change

Paired *t* tests (Bonferroni-corrected) were conducted to assess symptom change at each time point after ketamine, relative to baseline scores taken 60 min before the infusion. One patient was missing a MADRS score at 40 min, a BPRS-pos score at 40 min and 80 min, and a CADSS score at 80 min. A second patient was missing a CADSS score at 40 min. The MADRS scores were significantly reduced at all time points (all *t* values > 4.7, *p* values $< .001$) (Figure 2A). Nine patients reached a response criterion of ≥50% symptom improvement ("responders") at 230 min; 11 pa-

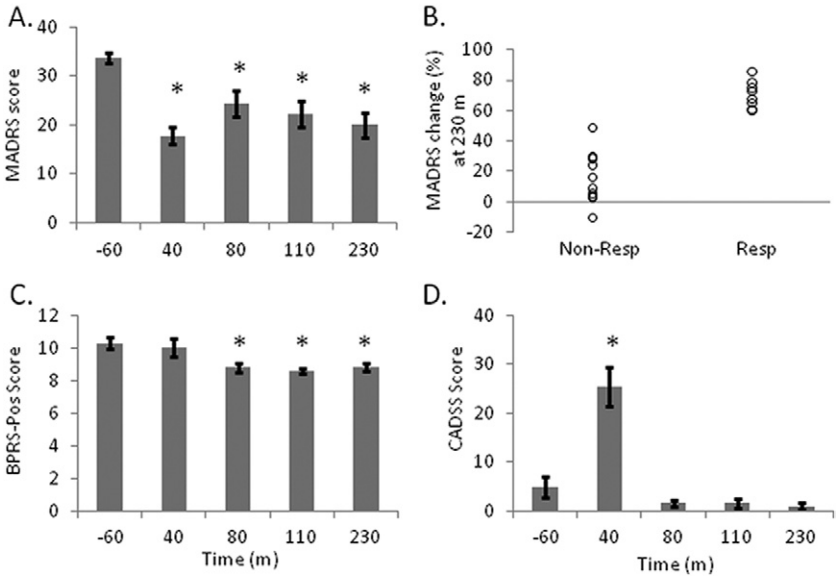

Figure 2. Depressive symptoms improve after ketamine. **(A)** Depressive symptoms measured by the Montgomery-Åsberg Depressive Rating Scale (MADRS) decrease 40 min after the infusion and remain low through 230 min. **(B)** Patients were divided into responders (Resp) ($n = 9$) and nonresponders (Non-Resp) ($n = 11$) on the basis of percentage change in MADRS scores. **(C)** Psychotic symptoms measured by the Brief Psychiatric Rating Scale-positive symptoms subscale (BPRS-pos) decrease after 80 min and remain low through 230 min. **(D)** Dissociative symptoms measured by the Clinician Administered Dissociative States Scale (CADSS) spike at 40 min but return to baseline by 80 min after infusion. *Significantly different than baseline (−60 min, Bonferroni-corrected).

tients showed little to no improvement at this time point ("nonresponders") (Figure 2B). Antidepressant response was not associated with participant gender: of the 9 responders, 2 were female patients and 7 were male patients; and of the 11 nonresponders, 3 were female patients and 8 were male patients [$\chi^2(1) = .07, p = .80$]. Responders and nonresponders were also equally randomly assigned to receive riluzole (6 of 9 responders received riluzole, and 6 of 11 nonresponders received riluzole) [$\chi^2(1) = .30, p = .58$]. The BPRS-pos scores were significantly reduced at 80 min [$t(18) = 4.63$, $p < .001$], 120 min [$t(19) = 4.59$, $p < .001$], and 230 min [$t(19) = 3.88$, $p = .001$] but not at 40 min [$t(18) = .73$, $p = .47$] (Figure 2C). The CADSS scores were significantly increased at 40 min [$t(18) = -5.95$, $p < .001$] (Figure 2D) but not at later time points (all t values < 2.64, p values $> .015$).

Stimulus-Evoked SS ctx Responses

Time-frequency analyses revealed that stimulation elicited an evoked response approximately 45 msec after stimulus with a spectral peak in the γ band over contralateral hemisphere (Figure 3A). Group analyses revealed peak evoked power in left and right central sulci (Brodmann area 3/4) after contralateral and ipsilateral stimulation (Figure 3B), confirming that early stimulus-evoked γ-band responses (GBRs) observed before and after ketamine reflect bottom-up sensory processing in left and right primary SS ctx. Spherical regions of interest for extracting individual stimulus-evoked responses were centered at group-averaged peak locations after averaging pre- and postketamine data (for left SS ctx: −37, 17, 47 mm in Talairach space; for right SS ctx: 43, 17, 52 mm).

A four-way mixed-effects ANOVA revealed that responders showed significantly increased SS ctx GBRs after ketamine relative to baseline [$F_{Time}(1,8) = 12.19, p = .008$]; nonresponders showed no change [$F_{Time}(1,10) = 1.51, p = .25$; $F_{Response \times Time}(1,18) = 8.38, p = .01$] (Figure 4A). This interaction effect was neither lateralized to one hemisphere [$F_{Hemisphere \times Response \times Time}(1,18) = 2.81$, $p = .11$] nor driven differentially by contralateral or ipsilateral stimulation [$F_{Stimulation \times Response \times Time}(1,18) < 1$]. No acute effect of riluzole on stimulus-evoked SS ctx GBRs was detected [$F_{Riluzole \times Time}(1,16) < 1$]. Moreover, the significant response × time interaction effect was not modulated by riluzole [$F_{Riluzole \times Response \times Time}(1,16) < 1$] (Figure S1 in Supplement 1). Effect sizes for the Response × Time interaction for patients receiving placebo ($n = 8$, partial $\eta^2 = .42$) versus riluzole ($n = 12$, partial $\eta^2 = .24$) further suggest that riluzole did not significantly influence the results.

A series of Pearson correlations revealed that norketamine levels at 40 min after infusion positively correlated with postketamine SS ctx responses in responders [$r(7) = .85$, $p = .003$] (Figure 4B); no such correlation was found in nonresponders [$r(9) = -.01$, $p = .977$]. Plasma ketamine and norketamine at later time points were not significantly correlated with postketamine SS ctx responses in either group (all p values $> .11$).

Spontaneous SS ctx γ Activity

A three-way mixed-effects ANOVA revealed greater spontaneous γ-band power, averaged over two runs, in the left (dominant) SS ctx compared with the right SS ctx [$F_{Hemisphere}(1,18) < 10.27, p = .005$] but no evidence of an increase after ketamine relative to baseline [$F_{Time}(1,18) < 1$] or a relation to antidepressant response [$F_{Response \times Time}(1,18) < 1$]. Spontaneous γ-band activity in SS ctx during rest was also not affected by riluzole [$F_{Riluzole \times Time}(1,16) < 1$].

Discussion

Here we investigated cortical changes associated with ketamine administration in the context of treatment response in treatment-resistant MDD patients. Stimulus-evoked responses and spontaneous SS ctx activity were measured with MEG before and after a single infusion of ketamine to extend our previous work that focused exclusively on pretreatment brain-based predictors of treatment response (43,49–50). For those patients exhibiting a rapid and robust reduction in depressive symptoms (responders), we found a uniform increase in stimulus-evoked SS ctx responses after the infusion (Figure 4A). Among these responders, we also found a positive correlation between increased cortical excitability and plasma norketamine levels (Figure 4B), a major active metabolite of ketamine with a relatively long half-life (approximately 5 hours) compared with ketamine (approximately 2 hours) (51). Patients exhibiting little or no improvement in depressive symptoms within hours after the infusion (nonresponders), on average, showed no change in stimulus-evoked responses and no correlation with plasma metabolite levels. These results show that enhanced cortical excitability differentiates responders from nonresponders to ketamine, as opposed to spontaneous cortical γ activity that

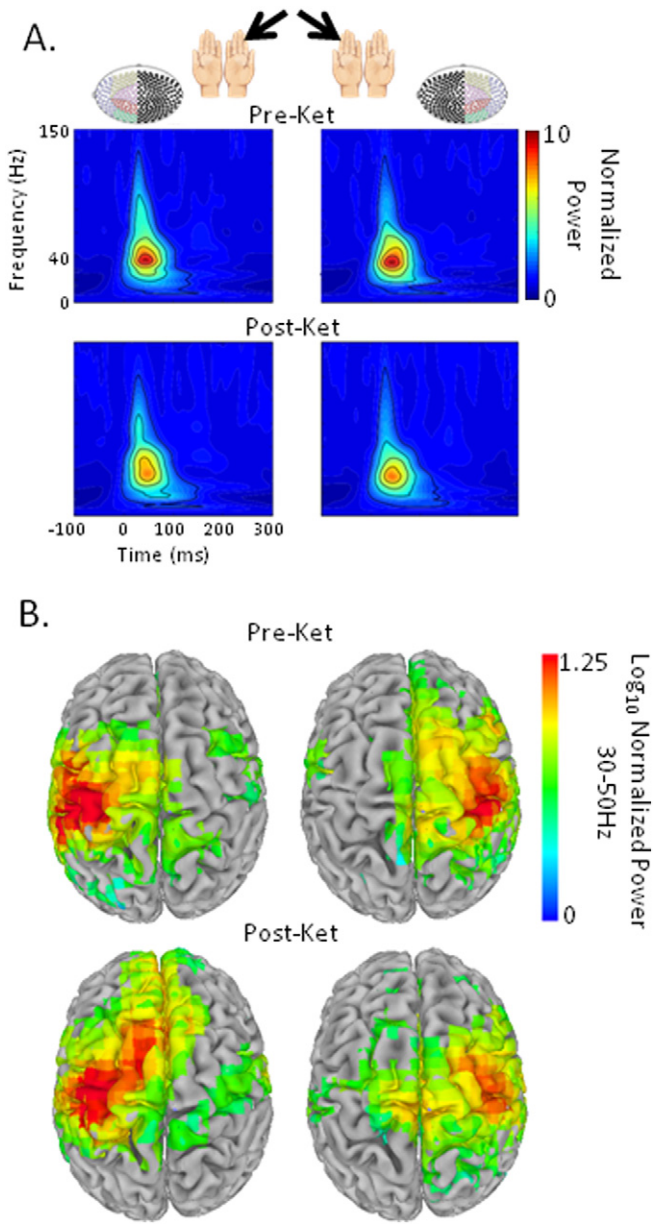

Figure 3. Tactile stimulation of the left and right finger elicits an early stimulus-evoked response that is localized to left and right primary somatosensory cortex. **(A)** Grand-averaged ($n = 20$) Stockwell time-frequency plots before (Pre-Ket) and after (Post-Ket) ketamine administration show robust stimulus-evoked power to the tactile stimulus (relative to a prestimulus baseline) in sensors overlying the contralateral hemisphere (colored circles). **(B)** Source analyses of evoked power (relative to prestimulus power) revealed peaks in left and right central sulci (Brodmann area 3/4). Whole brain maps of evoked power are statistically thresholded on the basis of one-sample *t* tests (false discovery rate = .001) and overlayed on a standardized brain template.

did not change in either responders or nonresponders, and thus provides the first cortical marker of the rapid antidepressant action of ketamine.

Notably, our findings fill a critical gap in our understanding of the mechanism underlying the effects of ketamine. *N*-methyl-D-aspartate receptor blockage is known to acutely increase spontaneous γ activity (19–25), and computational modeling supports the hypothesis that these abnormal oscillations result directly from reducing NMDAR-mediated input to fast-spiking GABAergic interneurons (26). We, however, did not observe increases in spontaneous SS ctx γ activity hours after the infusion in either responders or nonresponders. This could reflect the dose used here (.5 mg/kg), which is substantially lower than doses used in most preclinical work, as well as the timing of our measurements. To our knowledge, evidence that NMDAR antagonists increase spontaneous γ is limited to the period just after drug intake when psychotomimetic symptoms are most prominent. Thus, ketamine-related increases in spontaneous cortical γ might be more relevant to the acute, dissociative effects than the antidepressant effects of NMDAR antagonism. Resting-state measurements obtained during or directly after ketamine infusion could evaluate this possibility. Nevertheless, because changes in spontaneous γ in our patients were not apparent hours after the infusion and did not correlate with changes in their depressive symptoms, the immediate effects of NMDAR antagonism might not be sufficient to elicit rapid clinical improvements. Additional processes must account for the sustained profile of increased cortical excitability in responders.

We should also note that increased cortical excitability 6–7 hours after ketamine administration is not likely due to lingering differences in extracellular glutamate levels between responders and nonresponders. In animals, glutamate levels return to baseline within 2 hours after variable doses of ketamine (17). Likewise, recent magnetic resonance spectroscopy studies in humans have reported evidence of a surge of glutamate during ketamine administration (52,53) but not after its administration; more importantly, they have not revealed a link between glutamate level and antidepressant response (54,55). We can

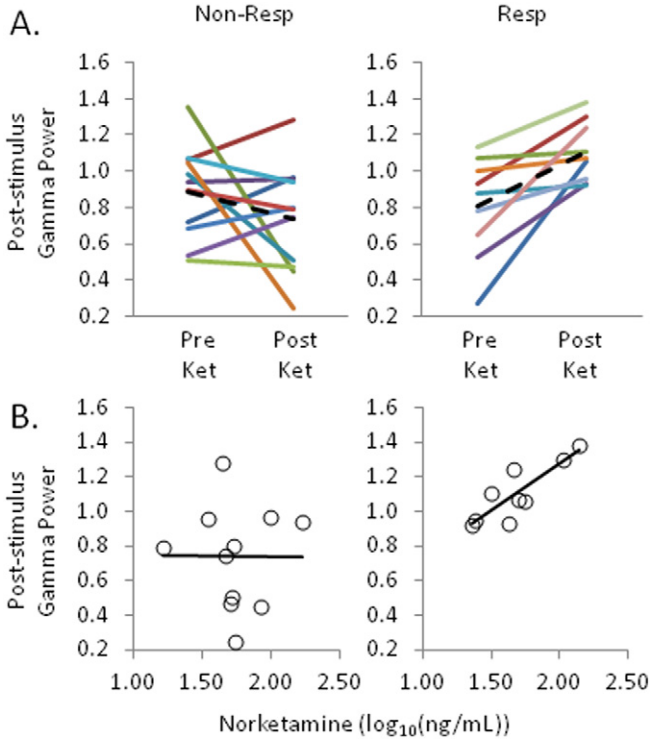

Figure 4. Rapid improvement in depressive symptoms after ketamine (Ket) is linked to increased somatosensory cortex (SS ctx) excitability. **(A)** Stimulus-evoked SS ctx γ-band responses from pre- to post-Ket infusion, collapsed across left and right hemispheres and contralateral and ipsilateral stimulation, were selectively increased in responders (Resp) ($n = 9$, right) but not nonresponders (Non-Resp) ($n = 11$, left). Solid lines represent individual patients, and dotted lines represent the group means. **(B)** Post-Ket SS ctx responses were positively correlated with plasma norketamine levels (40 min relative to the start of infusion) in Resp (right) but not Non-Resp (left).

speculate that ketamine-induced disinhibition and increased glutamatergic activity are too transient to figure directly into rapid alleviation of depressive symptoms. Nevertheless, these processes could trigger critical plastic changes at excitatory synapses that mediate the relatively long-lasting increases in cortical excitability in patients exhibiting symptomatic improvement. An upregulation of AMPAR surface expression is a strong candidate mechanism underlying this effect, as emerging preclinical work indicates (8–11). Given a critical role for AMPAR-mediated neurotransmission in recruitment of fast-spiking GABAergic interneurons (56), greater sensory-driven perturbation of γ activity in responders (i.e., increased stimulus-evoked γ-band responses) after ketamine might reflect enhanced AMPAR-mediated glutamatergic drive of interneuronal networks.

Importantly, although our findings are consistent with enhanced AMPAR-mediated glutamatergic neurotransmission via synaptic potentiation, we did not specifically test the effects of an AMPAR antagonist (or agonist) and thus cannot exclude other mechanisms. Moreover, despite positive preclinical findings (reviewed in Sanacora *et al.* [1]), there is currently no clinical proof of concept data for AMPAR potentiators in depressed patients. Nonetheless, we can raise the question of whether NMDAR antagonism is a necessary starting point for modifying cortical circuitry in a way that proves to be clinically beneficial. If not, the possibility of triggering synaptic potentiation directly rather than indirectly by NMDAR antagonists remains a promising target for the development of potent, rapid-acting antidepressants. Alternatively, although enhanced non-NMDAR glutamatergic transmission might be an important endpoint, NMDAR antagonism might be a critical antecedent to all downstream cellular phenomena, such as local BDNF translation (9), which ultimately support the reduction of depressive symptoms.

Despite clear results, the administration of riluzole before the postketamine MEG recordings introduces potential complications in interpreting effects of ketamine on cortical responses. We found no evidence to indicate that riluzole contributed to postketamine changes in stimulus-driven responses (Figure S1 in Supplement 1); indeed, effect sizes for each group (riluzole vs. placebo) were comparable. Thus, we remain confident that the timing of riluzole administration was relatively unproblematic, with regard to our findings. Moreover, the open-label administration of ketamine might leave some doubt regarding the specificity of the effects. In previous clinical trials (5,6), the rate of placebo responding at 230 min was very low (1 of 16 and 1 of 18). Because we used the same patient inclusion criteria for treatment resistance and symptom severity for our sample, nonspecific effects seem unlikely. The fact that, in responders, norketamine levels correlated positively with postketamine stimulus-evoked SS ctx responses provides additional support for a specific link between increased cortical excitability and ketamine administration. Placebo-controlled investigations with larger sample sizes are needed to confirm this link.

To conclude, our findings identify the first cortical marker of the rapid antidepressant effects of ketamine, and they are consistent with the hypothesis that enhanced non-NMDAR-mediated glutamatergic neurotransmission through synaptic potentiation is central to the mechanism of action of ketamine. Further work should examine whether increased cortical excitability persists for the duration of antidepressant response after a single dose of ketamine (e.g., up to 1 week) (5) and whether it attenuates upon relapse. It would also be important to determine whether similar effects of increased cortical excitability can be obtained with other NMDAR antagonists that have antidepressant action, particularly those with milder dissociative effects than ketamine (e.g., NR2B subunit-selective NMDAR antagonist) (57). More generally, whether increased cortical excitability is a state-dependent correlate of depressive mood improvement and thus broadly associated with clinical response to conventional antidepressants and other therapeutic interventions or specific to glutamatergic-modulating drugs should also be considered in future studies. Finally, extending the current results to cortical regions that have been implicated in the pathophysiology of MDD and show activities that are predictive of treatment response to ketamine (e.g., rostral anterior cingulate cortex) (43,49) might be critical to linking local cortical circuit abnormalities to specific phenotypic characteristics of mood disorders.

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This work was conducted at the Intramural Research Program at the National Institute of Mental Health. CAZ is listed as a coinventor on a patent application for the use of ketamine and its metabolites in major depression and has assigned his rights in the patent to the United States government but will share a percentage of any royalties that might be received by the government. GS is now a full time employee of Johnson and Johnson Pharmaceuticals. All other authors declare no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Rapid Antidepressant Effects of Ketamine in Major Depression; http://clinicaltrial.gov/ct2/show/NCT00088699?term=NCT00088699&rank=1; NCT00088699.

Supplementary material cited in this article is available online.

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