

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

Brian R. Cornwell, Giacomo Salvatore, Maura Furey, Craig A. Marquardt, Nancy E. Brutsche, Christian Grillon, and Carlos A. Zarate Jr.

**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  $\gamma$  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  $\gamma$ -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,  $\gamma$  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.

From the Section on Neurobiology of Fear and Anxiety (BRC, CG); Experimental Therapeutics and Pathophysiology Branch (GS, MF, CAM, NEB, CAZ), National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland; and Johnson and Johnson (GS), Pharmaceutical Research and Development, Titusville, New Jersey.

Address correspondence to Brian R. Cornwell, Ph.D., Section on Neurobiology of Fear and Anxiety, National Institute of Mental Health, National Institutes of Health, 15K North Drive, Room 200, MSC 2670, Bethesda, MD 20892; E-mail: cornwellb@mail.nih.gov.

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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  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) 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  $\gamma$ -aminobutyric acid (GABA)-ergic inhibitory feedback (16,17). Thus, extracellular glutamate levels might surge and promote plastic changes such as increased AMPAR sur-

face expression (18). Ketamine also directly induces spontaneous  $\gamma$  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  $\gamma$  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  $\gamma$ -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,  $46 \pm 14$  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  $\geq 22$ . 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

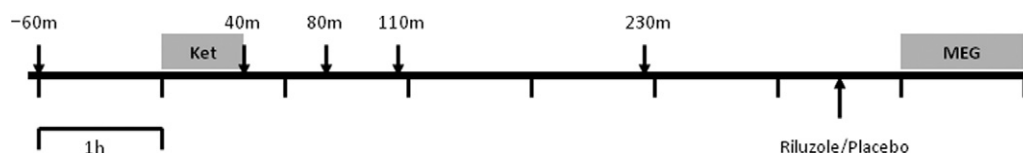
Patients received a single open-label infusion of .5 mg/kg of ketamine hydrochloride (Abbott Labs, North Chicago, Illinois) over 40 min via a Baxter infusion pump by an anesthesiologist. After the infusion, patients entered a randomized, double-blind placebo-controlled 4-week clinical trial of riluzole 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 pre-synaptic 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  $\geq 250$  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  $\geq 50\%$  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**

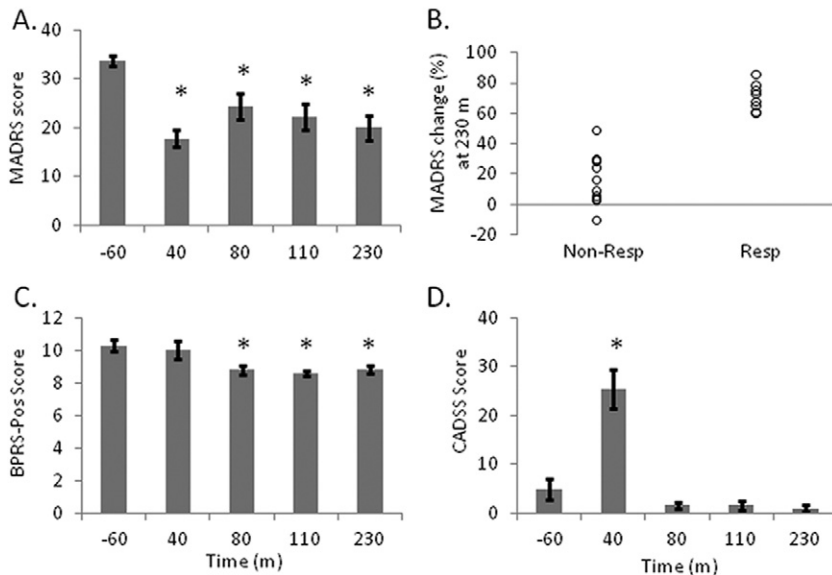
A minimum-variance adaptive beamformer algorithm (41) was used to determine sources of the stimulus-evoked  $\gamma$ -band responses (for similar methods, see Cornwell *et al.* [42] and Salvatore *et al.* [43]). For each dataset (2 runs  $\times$  2 sessions), a single covariance matrix was calculated 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  $\gamma$  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 overlaid 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  $\times$  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



**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).

previous analyses of stimulus-evoked responses were used to extract mean  $\gamma$ -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)  $\times$  2 (Hemisphere: left vs. right)  $\times$  2 (Stimulation: contralateral vs. ipsilateral)  $\times$  2 (Time: preketamine vs. postketamine) mixed-effects ANOVA was conducted. For resting activity, a 2 (Group)  $\times$  2 (Hemisphere)  $\times$  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 ( $\alpha = .05/16 = .0031$ ).

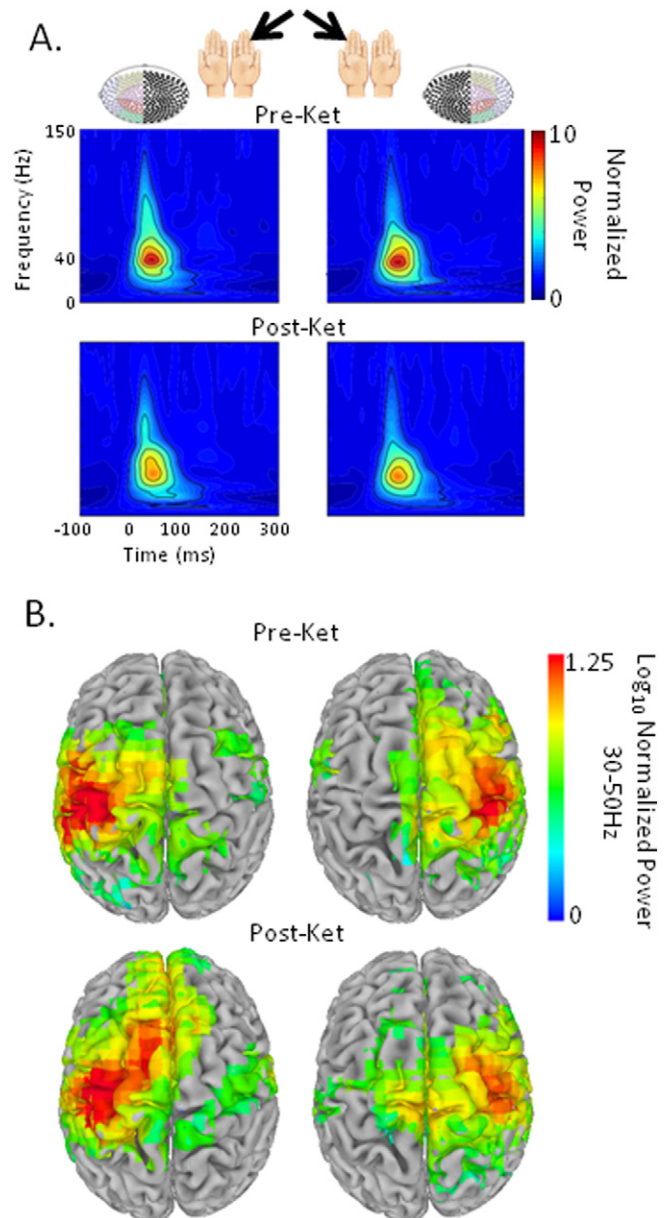
## Results

### 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  $\geq 50\%$  symptom improvement (“responders”) at 230 min; 11 patients 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  $\gamma$  band over contralateral hemisphere (Figure 3A). Group analyses revealed peak evoked power in left and right cen-



**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 overlaid on a standardized brain template.

tral sulci (Brodmann area 3/4) after contralateral and ipsilateral stimulation (Figure 3B), confirming that early stimulus-evoked  $\gamma$ -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).



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  $\gamma$  activity in responders (i.e., increased stimulus-evoked  $\gamma$ -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://clinicaltrials.gov/ct2/show/NCT00088699?term=NCT00088699&rank=1;NCT00088699>.*

*Supplementary material cited in this article is available online.*

- Sanacora G, Zarate CA Jr, Krystal JH, Manji HK (2008): Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 7:426–437.
- Yüksel C, Öngür D (2010): Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry* 68:785–794.
- Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD, *et al.* (2011): Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. *Mol Psychiatry* 16:634–646.
- Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, *et al.* (2005): Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proc Natl Acad Sci U S A* 102:15653–15658.
- Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al.* (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63:856–864.
- DiazGranados N, Ibrahim L, Brutsche N, Newberg A, Kronstein P, Khalife S, *et al.* (2010): A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 67:793–802.
- Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, *et al.* (2012): Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial [published online ahead of print January 30]. *Biol Psychiatry*.
- Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, *et al.* (2008): Cellular mechanisms underlying the antidepressant effects of ketamine: Role of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors. *Biol Psychiatry* 63:349–352.
- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng P-F, *et al.* (2011): NMDA receptor blockage at rest triggers rapid behavioural antidepressant response. *Nature* 475:91–95.
- Koike H, Iijima M, Chaki S (2011): Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behav Brain Res* 224:107–111.
- Li N, Lee B, Liu R-J, Dwyer JM, Iwata M, Li X-Y, *et al.* (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329:959–964.
- Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, *et al.* (2007): The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: Relationship to clinical effects in mood disorders. *Neuropsychopharmacol* 32:793–802.

13. Duman RS, Voleti B (2012): Signaling pathways underlying the pathophysiology and treatment of depression: Novel mechanisms for rapid-acting agents. *Trends Neurosci* 35:47–56.
14. Liu R-J, Lee FS, Li X-Y, Bambico F, Duman RS, Aghajanian GK (2011): Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex [published online ahead of print October 28]. *Biol Psychiatry*.
15. Machado-Viera R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, *et al.* (2009): Brain-derived neurotrophic factor and initial antidepressant response to an N-Methyl-D-Aspartate antagonist. *J Clin Psychiatry* 70:1662–1666.
16. Homayoun H, Moghaddam B (2007): NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* 27:11496–11500.
17. Moghaddam B, Adams B, Verma A, Daly D (1997): Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade. *J Neurosci* 17:2921–2927.
18. Song I, Huganir RL (2002): Regulation of AMPA receptors during synaptic plasticity. *Trends Neurosci* 11:578–588.
19. Carlen M, Meletis K, Siegle JH, Cardin JA, Futai K, Vierling-Claassen D, *et al.* (2011): A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior [published online ahead of print April 5]. *Mol Psychiatry*.
20. Lazarawicz MT, Ehrlichman RS, Maxwell CR, Gandal MJ, Finkel LH, Siegel SJ (2009): Ketamine modulates theta and gamma oscillations. *J Cogn Neurosci* 22:1452–1464.
21. Maksimow A, Sfké M, Långsjö JW, Salmi E, Kaisti KK, Yli-Hankala A, *et al.* (2006): Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. *Clin Neurophysiol* 117:1660–1668.
22. Sohal VS, Zhang F, Yizhar O, Deisseroth K (2009): Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 459:698–702.
23. Anver H, Ward PD, Magony A, Vreugdenhil M (2011): NMDA receptor hypofunction phase couples independent  $\gamma$ -oscillations in the rat visual cortex. *Neuropsychopharmacol* 36:519–528.
24. Hong LE, Summerfelt A, Buchanan RW, O'Donnell P, Thaker GK, Weiler MA, *et al.* (2010): Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine. *Neuropsychopharmacol* 35:632–640.
25. Pinault D (2008): N-methyl D-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant  $\gamma$  oscillations in the rat neocortex. *Biol Psychiatry* 63:730–735.
26. Spencer KM (2009): The functional consequences of cortical circuit abnormalities on gamma oscillations in schizophrenia: Insights from computational modeling. *Front Hum Neurosci* 3:33.
27. Ulhaas PJ, Singer W (2010): Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 11:100–113.
28. Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F, Tononi G (2006): A direct demonstration of cortical LTP in humans: A combined TMS/EEG study. *Brain Res Bull* 69:8684.
29. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, *et al.* (2006): Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci* 9:1169–1176.
30. American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: American Psychiatric Association.
31. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
32. First M, Spitzer RL, Gibbon M, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Patient Edition.* New York: Biometrics Research Department, New York State Psychiatric Institute.
33. Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62:10–17.
34. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, *et al.* (2012): Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs. add-on riluzole: Results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacol* 37:1526–1533.
35. Zarate CA Jr, Payne JL, Quiroz J, Sporn J, Denicoff KD, Luckenbaugh D, *et al.* (2004): An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 161:171–174.
36. Urbani A, Belluzzi O (2000): Riluzole inhibits the persistent sodium current in mammalian CNS neurons. *Eur J Neurosci* 12:3567–3574.
37. Le Liboux, Lefebvre P, Le Roux Y, Truffinet P, Aubeneau M, Kirkesseli S, *et al.* (1997): Single- and multiple-dose pharmacokinetics of riluzole in white subjects. *J Clin Pharmacol* 37:820–827.
38. Overall JE, Gorham DR (1962): The brief psychiatric rating scale. *Psychol Rep* 10:790–812.
39. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, *et al.* (1998): Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS). *J Trauma Stress* 11:25–36.
40. Stockwell RG, Mansinha L, Lowe RP (1996): Localization of the complex spectrum: The S transform. *IEEE Trans Signal Process* 44:998–1000.
41. Vrba J, Robinson SE (2001): Signal processing in magnetoencephalography. *Methods* 25:249–271.
42. Cornwell BR, Carver FW, Coppola R, Johnson L, Alvarez R, Grillon C (2008): Evoked amygdala responses to negative faces revealed by adaptive MEG beamformers. *Brain Res* 1244:103–112.
43. Salvatore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate CA Jr, *et al.* (2009): Increased anterior cingulate cortical activity in response to fearful faces: A neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol Psychiatry* 65:289–295.
44. Sekihara, K, Nagarajan SS, Poeppel D, Marantz, A, Miyashita Y (2001): Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique. *IEEE Trans Biomed Eng* 48:760–771.
45. Robinson SE (2004): Localization of event-related activity by SAM(erb). *Neuro Clin Neurophysiol* 2004:109.
46. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.
47. Genovese CR, Lazar NA, Nichols T (2002): Thresholding of statistical maps in functional neuroimaging using false discovery rates. *Neuroimage* 15:772–786.
48. Rutter L, Carver FW, Holroyd T, Nadar SR, Mitchell-Francis J, Apud J, *et al.* (2009): Magnetoencephalographic gamma power reduction in patients with schizophrenia during resting condition. *Hum Brain Mapp* 30:3254–3264.
49. Salvatore G, Cornwell BR, Sambataro F, Latov D, Colon-Rosario V, Carver F, *et al.* (2010): Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacol* 34:819–821.
50. Salvatore G, van der Veen JW, Zhang Y, Marenco S, Machado-Vieira R, Baumann J, *et al.* (2011): An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression. *Int J Neuropsychopharmacol* 1:1–10.
51. Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, *et al.* (1999): Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacol* 20:106–118.
52. Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E, *et al.* (2005): Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: A 4-T proton MRS study. *Am J Psychiatry* 162:394–396.
53. Stone JM, Dietrich C, Edden R, Mehta MA, De Simoni S, Reed JH, *et al.* (2012): Ketamine effects on brain GABA and glutamate levels with 1H-MRS: Relationship to ketamine-induced psychopathology [published online ahead of print January 3]. *Mol Psychiatry*.
54. Taylor MJ, Tiangga, ER, Ni Mhuircheartaigh R, Cowen PJ (2011): Lack of effect of ketamine on cortical glutamate and glutamine in healthy volunteers: A proton magnetic resonance spectroscopy study [published online ahead of print May 26]. *J Psychopharmacol*.
55. Valentine GW, Mason GF, Gomez R, Fasula M, Watzel J, Pittman B, *et al.* (2011): The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by  $[^1\text{H}]$ -MRS. *Psychiatry Res: Neuroimage* 191:122–127.
56. Fuchs EC, Zivkovic AR, Cunningham MO, Middleton S, LeBeau FEN, Bannerman DM, *et al.* (2007): Recruitment of parvalbumin-positive interneurons determines hippocampal function and associative behavior. *Neuron* 53:591–604.
57. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW (2008): An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol* 28:631–637.