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Short communication

Synaptic potentiation and rapid antidepressant response to ketamine in treatment-resistant major depression: A replication study

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ABSTRACT

Preclinical and clinical evidence has demonstrated that ketamine has rapid antidepressant effects. Studies using pre-treatment with an AMPA inhibitor suggest that enhancing AMPA throughput is crucial to ketamine's effects, including increases in both basal and evoked gamma power. This study sought to replicate previous findings of increased gamma response to a somatosensory stimulus at 230 min and Day 1 in ketamine responders versus non-responders in 31 depressed subjects and 25 healthy controls. A significant difference in peak gamma power was seen in the depressed ketamine responders versus non-responders. These results implicate AMPA throughput in ketamine's mechanism of antidepressant action.

1. Introduction

Preclinical and clinical studies indicate that enhanced plasticity and synaptic potentiation are key to ketamine's rapid (within hours) antidepressant effects. A preclinical study (Zanos et al., 2016) demonstrated that the metabolism of (*R,S*)-ketamine to (2*S,*6*S;*2*R,*6*R*)-hydroxynorketamine (HNK) is crucial to ketamine's antidepressant effects, and that the (2*R,*6*R*)-HNK enantiomer produces behavioral, neurophysiological (gamma power increases), and cellular antidepressant-related actions in mice. Gamma oscillations can be enhanced either through N-methyl-D-aspartate (NMDA)-mediated disinhibition through gamma aminobutyric acid (GABA)ergic interneurons, or AMPA throughput on pyramidal neurons. While other NMDA antagonists increase gamma power, behavioral and cellular antidepressant-related effects are not induced by other NMDA antagonists, and thus ketamine's effects are likely to be at least partly NMDA-independent. Pre-treatment with an AMPA inhibitor abolishes ketamine and HNK's antidepressant effects in animal models (Zanos et al., 2016), thus implicating AMPA receptor (AMPAR)-mediated maintenance of synaptic potentiation as crucial to ketamine's antidepressant mechanism. Clinically, subjects who responded to ketamine at 230 min had significantly greater increases in stimulus-evoked somatosensory cortical gamma-band responses (cortical excitability) than non-responders; results were obtained six to seven hours post-infusion, far beyond the half-life of ketamine (Cornwell et al., 2012).

This study sought to replicate our finding of increased gamma response at 230 min and also at Day 1 in ketamine responders versus non-responders in a sample of 31 subjects with major depressive disorder (MDD) and 25 healthy controls (HCs).

2. Methods

Subjects were enrolled in a double-blind, crossover trial of 0.5 mg/kg IV ketamine versus normal saline placebo; efficacy results were previously published (Nugent et al., 2018). Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) scores were obtained at both 230 min and Day 1 post-ketamine infusion, and response to ketamine was calculated as percent change in MADRS score from baseline (60 min pre-infusion). Six to nine hours post-infusion, data were acquired on a CTF 275 channel system at 1200Hz using synthetic third order gradient balancing for active noise cancellation. During the recording, subjects received tactile stimulation on the index finger of the left and right hands using a pneumatic stimulating device (500 stimuli, 25 ms bursts of air at 30 psi, 2 Hz average rate of stimulation), as previously described (Cornwell et al., 2012). Subjects completed two runs of the somatosensory task, with recordings performed during right- and left-hand stimulation, respectively; order was counterbalanced. Recordings were visually inspected and trials occurring during artifacts were removed. Note that not all subjects had usable data for both right- and left-hand stimulation or for each session (baseline, placebo, and ketamine), generally due to artifacts, technical issues, or study withdrawal. Subjects also had a T1-weighted anatomical MRI, which was used to construct a multisphere headmodel. The gamma power response (30–50 Hz) averaged over all stimuli was

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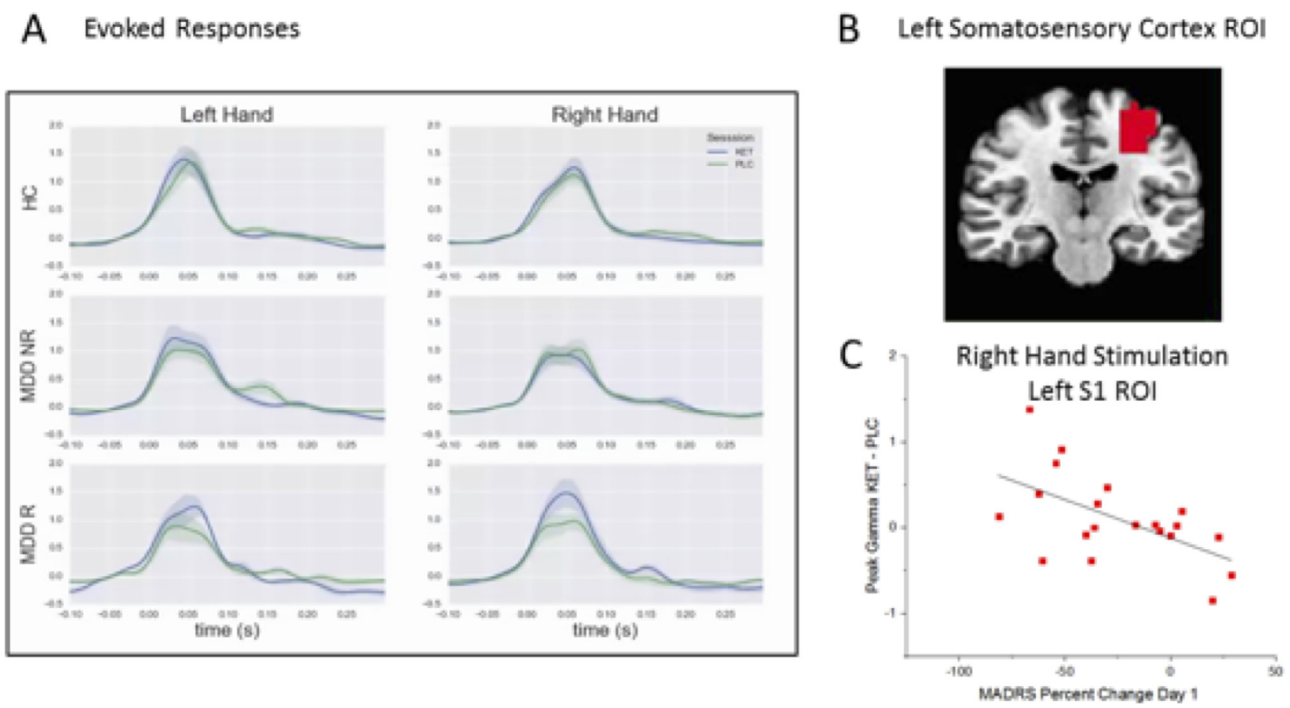

Fig. 1. A) Evoked gamma power response to a somatosensory stimulus delivered to the hand at t = 0 s. Evoked responses are shown separately for healthy control subjects (HCs), subjects with major depressive disorder (MDD) who did not respond to ketamine infusion (MDD-NR), and subjects with MDD who showed an at least 50% reduction in their Montgomery–Asberg Depression Rating Scale (MADRS) scores at Day 1 post-ketamine infusion (MDD-R). B) The left sensorimotor cortex region of interest (ROI) defined at the time point where the evoked response averaged over all subjects and sessions was maximal (image in radiologic orientation). C) Scatter plot showing the difference in peak gamma power between the ketamine and placebo sessions, plotted versus percent change in MADRS score, parametrized such that a negative percentage indicates a reduction in depressive symptoms.

projected into anatomical source space using synthetic aperture magnetometry (Robinson and Vrba, 1999), as implemented in the SAM routine, to produce 3D + time datasets containing the time-locked gamma band response to the stimulus at every voxel. Regions of interest (ROIs) of the left and right sensorimotor cortex were created as a thresholded mask of gamma power response to contralateral stimulation at the timepoint where the average evoked gamma power response peaked (Fig. 1A). For each subject, gamma response was averaged over all voxels in the ROI, and the peak and latency of the peak were extracted. As a quality control measure, datasets where the latency of the gamma response was greater than 100 ms were excluded from further analysis.

Statistical analyses first tested whether or not MDD subjects differed from HCs at baseline (up to several days pre-infusion). A mixed model examining baseline differences between MDD and HC participants was performed first, then repeated with the MDD group subdivided as responders (MDD-R, MADRS response ≥ 50%) and non-responders (MDD-NR) to ketamine at both 230 min and Day 1. Although prior results (Cornwell et al., 2012) dichotomized responders using the 230-min time point only, we analyzed subjects dichotomized by those who responded by Day 1, as we had fewer responders at the 230-min time point. We included the hand stimulated as a repeated factor, as it was reasonable to expect that differences in somatosensory response might exist between dominant and non-dominant hand stimulation.

Second, we tested the hypothesis that synaptic potentiation is crucial to ketamine's antidepressant effects. A mixed model was used to determine whether somatosensory response differed between the placebo and ketamine sessions in MDD-R versus MDD-NR subjects, using a dichotomous variable for these groups (for both Day 1 and 230 min). Session and hand stimulated were included as repeated measures. This response-dichotomized analysis was performed to facilitate comparison to prior results. To isolate drug effect and overcome the weakness of the dichotomized analysis, the final analysis used a mixed model to determine whether change in power between the ketamine and placebo sessions was related to magnitude of response to ketamine, modeled as a continuous variable, with hand stimulated as a repeated measure.

3. Results

No significant differences in mean age or sex were observed between the MDD and HC groups (35.5 ± 9.8 vs. 34.2 ± 10.5 years; 58% vs. 64% females, respectively).

At baseline, no differences between the MDD and HC groups in peak gamma response to the stimulus were observed, nor were differences between MDD-R, MDD-NR, and HC responses. One subject underwent baseline and placebo procedures but did not receive a ketamine infusion, and thus could not be classified as a responder/non-responder.

Ketamine versus placebo effects were examined next. In the mixed model examining differences between HC (N = 22) and MDD subjects divided by response at 230 min (MDD-R, N = 6 and MDD-NR, N = 24), a significant effect was noted for session ($F_{1,124}$ = 5.04, p = 0.027). In post-hoc tests, MDD-R subjects showed significant increases in gamma power in the ketamine session compared to the placebo session when the right hand was stimulated ($F_{1,121}$ = 4.79, p = 0.031). MDD-NR subjects showed such increases when the left, but not the right, hand was stimulated ($F_{1,109}$ = 4.68, p = 0.033). This result may have been driven primarily by MDD-NR subjects who went on to respond at the Day 1 time point; indeed, three of the four subjects who were non-responders at 230 min but responders at Day 1 showed increased gamma power in the ketamine session as compared to placebo for left hand stimulation.

In the mixed model examining differences between healthy (N = 22) and MDD subjects divided by response at Day 1 (MDD-R, N = 10; MDD-NR, N = 20), a significant effect for session was similarly observed (F_{1117} = 7.53, p = 0.007). In post-hoc effect tests, the difference between ketamine and placebo sessions was significant only in

the MDD-R group ($F_{1120} = 7.38$, $p = 0.008$). Further subdividing by hand stimulated within the MDD-R group, a significant difference in peak gamma power was noted between sessions for right-handed stimulation ($F_{1116} = 5.08$, $p = 0.026$), and a trend towards a difference was seen for left-handed stimulation ($F_{1114} = 3.11$, $p = 0.081$).

The final mixed model using response to ketamine as a continuous variable and difference in peak response between the ketamine and placebo sessions as the outcome measure included only subjects with data for both ketamine and placebo sessions (17 subjects for left hand stimulation and 20 for right). A significant interaction between hand stimulated and antidepressant response was observed at 230 min ($F_{1,15} = 5.17$, $p = 0.038$). Post-hoc tests showed a significant relationship between gamma power response and antidepressant response when the right hand was stimulated ($t = -2.15$, $p = 0.041$). The same interaction using response at Day 1 was not significant ($p > 0.05$), although the post-hoc test examining the relationship between gamma power and antidepressant response when the right hand was stimulated was significant ($t = -2.17$, $p = 0.038$). Finally, when the right hand was stimulated, the difference in peak gamma power between the ketamine and placebo sessions significantly correlated with response at 230 min ($R = -0.556$, $p = 0.011$) and at Day 1 ($R = -0.571$, $p = 0.009$).

4. Discussion

This short report replicated prior findings that ketamine's antidepressant effects are related to successfully inducing synaptic potentiation in the human cortex. These results add to the increasing behavioral, neurophysiological, cellular, and molecular evidence implicating AMPA throughput in ketamine's mechanism of antidepressant action. Studies have consistently shown that altered AMPA trafficking underlies synaptic plasticity (Kessels and Malinow, 2009) and, clinically, the AMPAR antagonist perampanel was found to reduce evoked gamma responses to visual stimuli (Muthukumaraswamy et al., 2016). Our finding of increased synaptic response post-ketamine as compared to post-placebo thus implicates altered AMPA signaling. Interestingly, recent preclinical work demonstrated that while ketamine is a potent NMDA antagonist, its mechanism of action may rely instead on the HNK metabolite. Although the exact mechanism of action of HNK is unknown, its behavioral effects can be abolished by pre-treatment with the AMPAR antagonist NBQX (Zanos et al., 2016). Together, these results point to AMPAR-mediated synaptic potentiation as crucial to ketamine's mechanism of action.

Limitations of the study include the small sample size and the lower response rate to ketamine compared to the previous study. The lower response rate, however, was likely due to the fact that this study was placebo-controlled, unlike the prior study that used open-label ketamine. In addition, multiple data points were missing, which further exacerbated issues related to the relatively small sample size. Because of the uncertainties in spatial localization inherent to MEG, our ROI was necessarily larger than the actual brain area activated by the task, likely adding noise to our results. Despite these limitations, we consider this a successful replication of the prior finding that synaptic potentiation is crucial to ketamine's antidepressant effects. This replication study further suggests that stimulus evoked gamma power might be a useful cross-species biomarker for developing novel therapeutics.

Declaration of interest and role of funding source

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Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; 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; and as a 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 post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

Author contributions

ACN: Helped design the study; oversaw data acquisition; helped conduct the data analysis; performed and interpreted the statistical analyses; provided research supervision; drafted the manuscript.

KEW: Helped acquire data; helped conduct the data analysis; revised and edited the manuscript for critical intellectual content.

JRG: Helped conduct the data analysis; provided research supervision; edited the manuscript for critical intellectual content.

CAZ: Conceptualized the study; designed the study; edited the manuscript for critical intellectual content; provided research supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.09.001.

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