CHRONIC STRESS

Chronic Stress
Volume 3: 1–3

DOI: 10.1177/2470547019861417
journals.sagepub.com/home/css
SAGE

Neurophysiological Effect of Ketamine on Prefrontal Cortex in Treatment-Resistant Depression: A Combined Transcranial Magnetic Stimulation–Electroencephalography Study

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Treatment-resistant depression (TRD) represents a substantial clinical and economic burden. A single subanesthetic dose of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine improves TRD depression symptoms within hours.[1] The rapid response points to a fundamentally different mechanism which, while well modeled in preclinical studies, has yet to be translated into clinically relevant biomarkers. Transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) are a direct index of the neurophysiological state of the stimulated cortical and cortico-thalamic network.[2] TEPs have also previously shown a relationship with glutamatergic and Y-amino butyric acid (GABA)-ergic neurotransmission suggesting that concurrent TMS–electroencephalography (EEG) can also be an index of local cortical excitability/inhibition balance.[2] Animal studies suggest that ketamine not only increases glutamatergic excitatory drive in the prefrontal cortex (PFC) and limbic regions of the brain[1] but also demonstrates $GABA_AR$ agonism.[3] This study aimed to observe changes in PFC cortical excitability measures indexed by a pharmaco-TMS–EEG approach by evaluating alterations in its component structure up to 24 hours post-ketamine infusion.

Four TRD patients (mean age: 38.3 ± 10.6 years; N = three females) provided written informed consent to participate. They received open-label intravenous infusion of 0.5 mg/kg ketamine over 40 minutes. Patient's depression levels were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HAM-D) at pre-ketamine baseline, and 4 hours and 24 hours post-ketamine infusion. Concurrent TMS stimulation and EEG recording were performed at all sessions. Biphasic single-pulse TMS (MagVenture MagPro) was presented at the left dorsolateral prefrontal cortex (DLPFC), for N = 200 pulses. The cortical response to TMS was recorded using 64-channel EEG (BrainAmp DC, BrainProducts), sampled at 5000 Hz, with electrode wires reoriented to avoid direct contact with the TMS coil. Stimulation intensity was 120% of baseline resting motor threshold. EEG data were analyzed by replacing the TMS pulse period (0–20 ms) with linear interpolation. Artifacts were removed using a two-tiered independent components analysis routine (ARTIST).[4] This algorithm automatically identifies artifactual components based on features capturing the spatiotemporal profile of both neural and artifactual activities. Additional noise suppression employed the source-estimate-utilizing noise-discarding algorithm (SOUND).[5] We utilized the local mean field amplitude–area under the curve (LMFA–AUC) from a subset of electrodes (Figure 1(d)) around the stimulation site as our primary outcome measure. This has previously been reported as a reliable index of cortical reactivity or excitation.[6] We applied the SOUND correction to individual trials to test within-subject differences from session to session using nonparametric Kruskal–Wallis tests. Overall, patients showed a reduction in the LMFA–AUC at 4 hours that increased back at 24 hours but remained lower than baseline. We also found an overall reduction in peak-to-peak measures at

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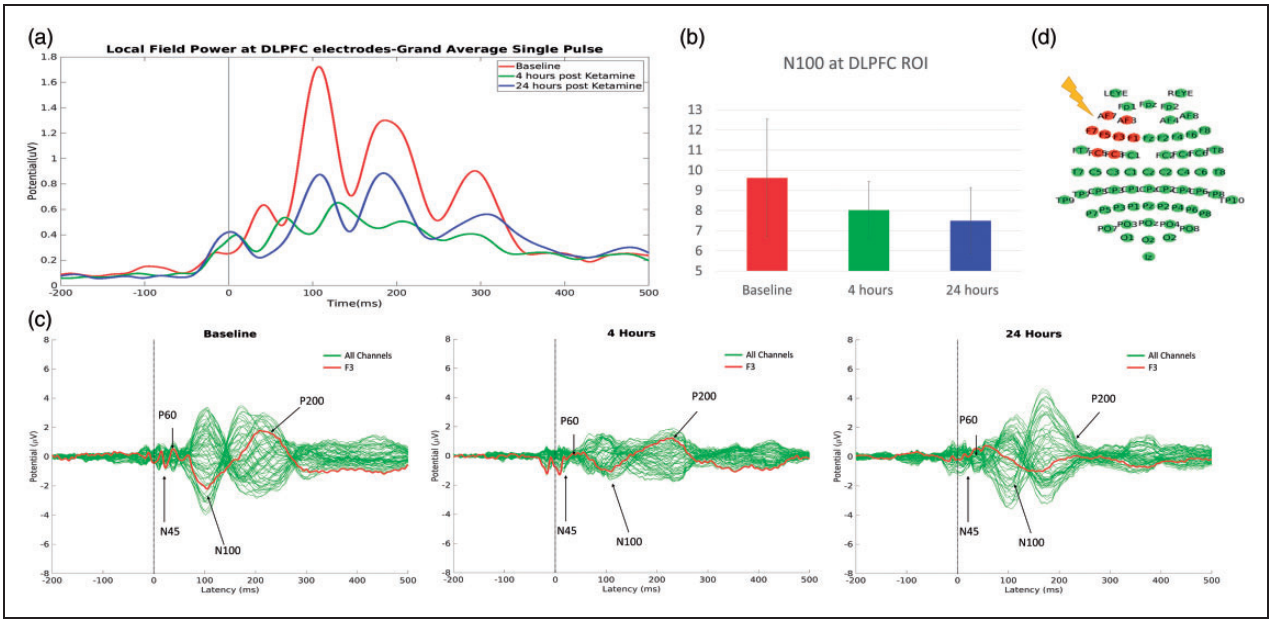

Figure 1. Modulation of TEPs and Local Field Power by single pulse TMS administered to DLPFC. (a) The mean SOUND corrected Local Field Power at DLPFC ROI. LMFA-AUC was calculated by summation of LMFA amplitude from 55 to 275ms after TMS pulse. (b) The mean SOUND corrected N100 peak-to-peak amplitude computed between 55 ms and 275ms after TMS pulse. (c) Butterfly plot of TEPs for all electrodes (green) and electrode F3 (red) with most pronounced TEP components labeled. (d) Schematic of the DLPFC ROI shaded in red.

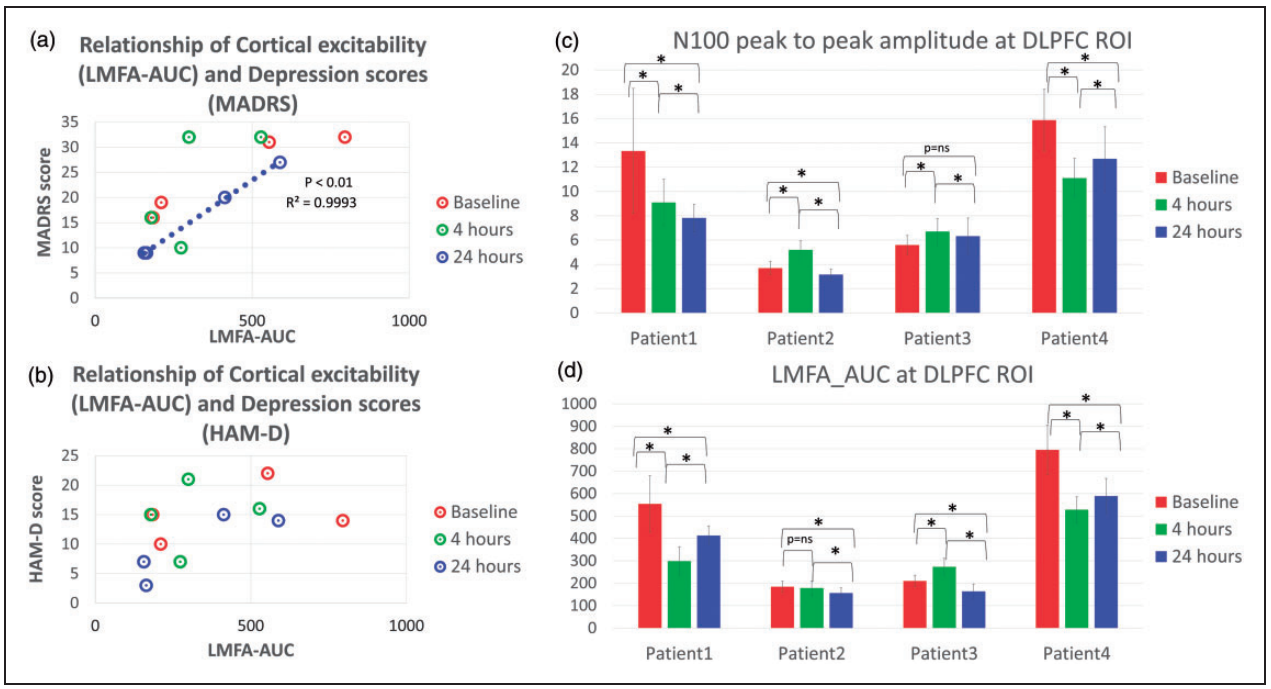

Figure 2. a-b: Relationship of cortical excitability measures (LMFA-AUC) and depression scores (a) MADRS and (b)HAM-D. c-d: Pairwise comparison of the session with significance values adjusted by Bonferroni correction for multiple tests for all patients.

N100, which is known to reflect cortical inhibition.[2,7] The Kruskal–Wallis *H* test showed that there was a statistically significant difference in both N100 amplitude and LMFA–AUC between the sessions for all patients ($p < 0.05$). Follow-up pairwise comparisons of session with significance values adjusted by Bonferroni correction for multiple tests were conducted (Figure 2(c) and (d)). There was a reduction in the MADRS (42.2%) and

HAM-D (47%) total depression scores between baseline and 24 hours for all patients except one (patient 4). There was a significant direct relationship between the depression scores (both HAM-D and MADRS) and LMFA–AUC values at 24 hours ($p < 0.01$) (Figure 2).

These preliminary results show the initial feasibility of the TMS–EEG approach to investigating DLPFC excitability and its relationship with antidepressant response in TRD. Previous studies have focused on motor-evoked potentials from TMS to the motor cortex, but very few have directly investigated TEPs from the DLPFC. Although ketamine has previously been reported to increase TMS-evoked motor cortical excitability,[8] we found reduced PFC excitability 4 hours after 0.5 mg/kg ketamine infusion (Figure 1(a)). This can be interpreted as an alteration in excitatory/inhibitory balance. A recent TMS–EEG study of the DLPFC[9] demonstrated that the N100 amplitude and global mean field amplitude–area under the curve (GMFA–AUC) were higher in patients with major depressive disorder compared to healthy controls. This larger GMFA–AUC in the DLPFC corroborates with early EEG findings that show hyperactivation in endogenous depression patients, which normalizes after antidepressant treatment.[9,10] Our study similarly provides a TMS–EEG paradigm for detecting the neuromodulatory effects of ketamine. Although the specific mechanisms by which excitation-inhibition balance is altered remains unclear, findings of $GABA_AR$ agonism decreasing N100 in motor cortex (while $GABA_BR$ agonism increases it)[7] suggest that effects may include modulation of GABA transmission. We acknowledge the preliminary nature of this small sample, but it could serve as a starting point for identifying clinical and EEG correlates of extended response in single-infusion ketamine studies and inform the design and interpretation of future multiple-infusion protocols. Furthermore, adequately powered studies will investigate whether altered PFC cortical excitability underlies depression and may be a biomarker of antidepressant treatment response in TRD.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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