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Preliminary communication

Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder

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ABSTRACT

Background: Electroencephalographic (EEG) sleep slow wave activity (SWA; EEG power between 0.6 and 4 Hz) has been proposed as a marker of central synaptic plasticity. Decreased generation of sleep slow waves – a core feature of sleep in depression – indicates underlying plasticity changes in the disease. Various measures of SWA have previously been used to predict antidepressant treatment response. This study examined the relationship between baseline patterns of SWA in the first two NREM episodes and antidepressant response to an acute infusion of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine.

Methods: Thirty patients (20M, 10F, 18–65) fulfilling DSM-IV criteria for treatment-resistant major depressive disorder (MDD) who had been drug-free for two weeks received a single open-label infusion of ketamine hydrochloride (.5 mg/kg) over 40 min. Depressive symptoms were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) before and after ketamine infusion. Sleep recordings were obtained the night before the infusion and were visually scored. SWA was computed for individual artifact-free NREM sleep epochs, and averaged for each NREM episode. Delta sleep ratio (DSR) was calculated as SWA_{NREM1}/SWA_{NREM2}.

Results: A significant positive correlation was observed between baseline DSR and reduced MADRS scores from baseline to Day 1 ($r=.414$, $p=.02$).

Limitations: The sample size was relatively small ($N=30$) and all subjects had treatment-resistant MDD, which may limit the generalizability of the findings. Further studies are needed to replicate and extend this observation to other patient groups.

Conclusions: DSR may be a useful baseline predictor of ketamine response in individuals with treatment-resistant MDD.

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1. Introduction

Mood disorders are among the most debilitating and widespread psychiatric illnesses. Novel and more effective therapeutics are urgently needed, given the delayed onset and poor response associated with currently available monoamine-based therapies. Towards this end, the development of new treatments for mood disorders would be greatly facilitated by the identification of biomarkers to predict treatment outcomes and assist in treatment selection (Li et al., 2012; Wiedemann, 2011).

Recent studies have shown that the *N*-methyl-D-aspartate (NMDA) antagonist ketamine produces significant antidepressant effects in patients with treatment-resistant major depressive disorder (MDD), with the largest effect observed within one day (Ibrahim et al., 2012; Zarate et al., 2006). Several neurobiological correlates have been associated with ketamine response, including markers of pre-treatment prefrontal glutamine levels and neural activity of the anterior cingulate cortex (Salvadore et al., 2009, 2010, 2011).

Slow wave sleep has long been observed to be decreased in individuals with depression (Ehlers et al., 1996; Gillin et al., 1979; Kupfer and Ehlers, 1989; Reynolds et al., 1993). Delta Sleep Ratio (DSR) – the ratio of sleep slow wave activity (SWA; or wave count) between the first two non-REM sleep episodes – is lower in depressed patients than healthy controls (Kupfer et al., 1990). Furthermore, some traditional antidepressant treatments have been found to normalize slow wave sleep and DSR (Argyropoulos et al., 2009; Ehlers et al., 1996; Jindal et al., 2003). Relatedly, preclinical EEG studies have shown that the NMDA antagonists ketamine and dizocilpine-maleate (MK-801) both increased SWA in rats (Feinberg and Campbell, 1993), and clinical studies have identified DSR as a

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useful predictor of treatment outcome in individuals with MDD (Ehlers et al., 1996; Nissen et al., 2001).

This study examined whether baseline SWA (and DSR specifically) would predict rapid response to ketamine infusion in individuals with treatment-resistant MDD. We hypothesized that pre-treatment DSR would be associated with improved depressive symptoms in response to ketamine.

2. Methods

2.1. Patients

Thirty patients (20M, 10F, 18–65 years (mean age=47.3 SE ± 13.3)) participated in the study from January 2007 through December 2010 at the National Institute of Mental Health (NIMH) Clinical Research Center (CRC) Mood Disorders Research Unit in Bethesda, MD. All patients met DSM-IV criteria for treatment-resistant MDD as assessed by the Structured Clinical Interview for Axis *I* DSM-IV Disorders (SCID; (First et al., 2001) and the Antidepressant Treatment History Form (ATHF)-modified (Sackeim, 2001). Inclusion criteria included a Montgomery Asberg Depression Rating Scale (MADRS) score ≥ 22 at baseline and previous failure to respond to at least two antidepressants. Exclusion criteria included a diagnosis of substance abuse or dependence in the last 90 day as determined by the SCID, or unstable medical illness. All patients were free of all psychotropic medications for at least two weeks (five weeks for fluoxetine) prior to ketamine infusion. Patients' average MADRS score at baseline was 32.5 ± 4.8 (SEM). The study was approved by the Combined Neuroscience Institutional Review Board (IRB) of the National Institutes of Health (NIH). All subjects provided written informed consent before entry into the study.

2.2. Infusion

Patients underwent a single open-label, 40-min infusion of saline solution and ketamine hydrochloride (.5 mg/kg), followed by the double-blind administration of riluzole (100 mg/d; 50 mg BID) or placebo 4 to 6 h post-infusion. These patients were a subgroup of a larger, previously published study investigating the ability of riluzole (another glutamatergic modulator) to maintain ketamine's initial antidepressant response (ketamine/placebo, $n=11$; ketamine/riluzole, $n=19$) (Ibrahim et al., 2012). That study found no difference in efficacy between the ketamine/placebo and ketamine/riluzole groups (Ibrahim et al., 2012), nor was any difference observed in sleep EEG variables between the groups Duncan et al., in press. In the current study, group differences in correlations were examined to exclude the possibility of an early interactive effect between the two compounds.

2.3. Mood assessment

For the initial analysis, depressive symptoms were assessed via the MADRS at baseline (60 min prior to ketamine infusion) and Day 1 post-infusion. Patients exhibiting a ≥ 50% reduction in MADRS scores on Day 1 post-infusion were classified as ketamine responders ($n=12$); non-responders ($n=18$) showed less than 50% improvement. Day 1 was selected as the primary endpoint for this analysis as it represents the time point with the largest clinical effect (Ibrahim et al., 2012).

In addition, daily MADRS ratings for the next seven days were obtained from the larger, previously published study (Ibrahim et al., 2012) and used to examine the relationship between baseline DSR and prolonged response to ketamine.

2.4. EEG analysis

Whole-night sleep recordings were taken following an adaptation night on the baseline night before ketamine infusion. Two electroencephalograms (C3/A2 and C4/A1), two electrooculograms (EOGs), and one submental electromyogram (EMG) were recorded using a Nihon–Khoden system (Neurofax v. 05–50) and Polysmith Acquisition and Review software (v. 4.0.25.0). EEG readings were scored in 30 s epochs according to criteria established by Rechtschaffen and Kales (1968) by reviewers blind to night of study.

EEG signals were first filtered from .5 to 30 Hz. Spectral density analysis (Welch's averaged modified periodogram with a Hamming window, averages of six five-second epochs) was performed on C3/A2 and C4/A1 derivations. Awake, REM, Movement Time, and NREM epochs that exceeded eight times the mean power values in the .75 to 4.5 Hz and 20 to 30 Hz bands were excluded from the analysis. Because SWA values were identical at both C3 and C4, averaged SWA values were used. For each subject the total night SWA was calculated. For each NREM period throughout the night, SWA was normalized using individual total night EEG power estimates. The DSR (Jindal et al., 2003; Nissen et al., 2001) was calculated as the quotient of normalized SWA in the first to the second NREM episode.

2.5. Statistical analysis

Pearson correlations were used to examine the relationship between the baseline DSR and change in depression rating scales from 60 min pre-infusion to Day 1. Partial correlations and Fisher *r–z* transformations controlling for the effect of age and drug (riluzole administered post-ketamine infusion) were also completed. Paired *t*-tests were used to compare baseline sleep data for the responder and non-responder groups. ANOVA was used to examine the predictive effects of baseline DSR on mood response during the first week after dividing the patient group based on DSR threshold ≤ 1.

3. Results

3.1. Baseline sleep measures between ketamine responders and non-responders

No significant group differences were observed for sleep variables (Table 1), although sleep quality was slightly reduced in ketamine responders ($n=12$) versus non-responders ($n=18$), i.e., less total sleep, reduced sleep efficiency, and lower SWA. There was a trend for non-responders to have lower baseline NREM1 SWA and DSR than responders.

3.2. Baseline DSR was associated with changes in depression rating scores after a night of sleep

No significant correlation was observed between baseline DSR and change in MADRS scores from baseline to 230 min post-infusion (Pearson's $r=.217$, $p=.259$). However, after a night of sleep following ketamine infusion, a significant positive correlation ($r=.414$, $p=.02$) was observed between baseline DSR and change in MADRS scores (from baseline to Day 1; Fig. 1). No Day 1 differences were found in mood or gender between the ketamine/placebo and ketamine/riluzole subgroups, and the Fisher *r*-to-*z* transformation (Rosenthal, 1991) found no differences in DSR-MADRS correlations between these two groups. Correlations were significant when controlling for age (Day 1 change: $r=.431$, $p=.02$). Visual inspection of the relationship between baseline DSR and change in MADRS scores at Day 1 indicated that eight of 12 ketamine responders had DSRs ≤ 1, and 15 of 18 non-responders had DSRs > 1 ($\chi^2=7.75$; $p=.0054$).