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Antidepressant effects of selective slow wave sleep deprivation in major depression: A high-density EEG investigation

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ABSTRACT

Sleep deprivation can acutely reverse depressive symptoms in some patients with major depression. Because abnormalities in slow wave sleep are one of the most consistent biological markers of depression, it is plausible that the antidepressant effects of sleep deprivation are due to the effects on slow wave homeostasis. This study tested the prediction that selectively reducing slow waves during sleep (slow wave deprivation; SWD), without disrupting total sleep time, will lead to an acute reduction in depressive symptomatology. As part of a multi-night, cross-over design study, participants with major depression (non-medicated; $n = 17$) underwent baseline, SWD, and recovery sleep sessions, and were recorded with high-density EEG (hdEEG). During SWD, acoustic stimuli were played to suppress subsequent slow waves, without waking up the participant. The effects of SWD on depressive symptoms were assessed with both self-rated and researcher-administered scales. Participants experienced a significant decrease in depressive symptoms according to both self-rated ($p = .007$) and researcher-administered ($p = .010$) scales, while vigilance was unaffected. The reduction in depressive symptoms correlated with the overnight dissipation of fronto-central slow wave activity (SWA) on baseline sleep, the rebound in right frontal all-night SWA on recovery sleep, and the amount of REM sleep on the SWD night. In addition to highlighting the benefits of hdEEG in detecting regional changes in brain activity, these findings suggest that SWD may help to better understand the pathophysiology of depression and may be a useful tool for the neuromodulatory reversal of depressive symptomatology.

1. Introduction

Sleep disturbances are an integral part of the diagnostic criteria for major depression (American Psychiatric Association, 2000; Peterson and Benca, 2006), and sleep may provide biomarkers for treatment response to antidepressant medication (Steiger and Kimura, 2010). Since the initial investigation of a therapeutic benefit of sleep deprivation (SD) in depression (Pflug and Tölle, 1971), many studies have attempted to understand the link between sleep and depression. SD interventions, including total sleep deprivation (TSD), partial sleep deprivation and selective REM sleep deprivation (REMD) can acutely reverse depressive symptoms in approximately 50–60% of patients with major depression (Gillin, 1983; Wu and Bunney, 1990; Kuhs and Tölle, 1991; Wirz-Justice and Van den Hoofdakker, 1999; Hemmeter et al., 2010). Decreased REM sleep latency and increased REM density are hallmark features of depression (Kupfer and Foster, 1972; Benca et al., 1992). Given these features, and the observation of suppressed REM sleep with antidepressant medication (Riemann et al., 1990; Jobert et al., 1999), it has been postulated that selectively suppressing REM sleep may yield an antidepressant response (Vogel et al., 1975).

Slow wave sleep abnormalities, however, are also prominent in depression (Borbély and Wirz-Justice, 1982; Benca et al., 1992) and likely play a role in the modulation of depressive symptomatology. For instance, Nissen et al. (2001) found that a high delta sleep ratio (quotient of slow wave activity [SWA] in the first to the second NREM sleep cycle) on the night prior to SD predicted the antidepressant response. In addition, Duncan et al. (1980) showed that the participants who responded to SD treatment exhibited a greater rebound of slow wave sleep and total sleep time upon recovery sleep compared to their baseline. Finally, Borbély (1987) proposed that sleep in depression is characterized by abnormal slow wave homeostasis, which may be renormalized by SD therapy.

The current study directly investigated the role of slow wave homeostasis in the antidepressant action of SD by using a selective slow wave deprivation (SWD) technique. As the first study to assess the antidepressant effects of SWD in depression, this exploratory investigation had two primary aims. First, we sought to determine

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the efficacy of the SWD technique in suppressing SWA in depressed participants, to measure the overnight change in depressive symptomatology, and to examine the extent to which these two variables are correlated. Second, we aimed with this initial investigation, using a simple, randomized cross-over design, to provide the foundation for larger, more controlled, comparison-based, double-blinded studies to rigorously assess the usefulness of SWD in treating major depression.

2. Methods

2.1. Participants

17 right-handed individuals (9 female; mean age 23.94 ± 2.31 years, M ± S.E.M.) participated in the study (approved by the Institutional Review Board of the University of Wisconsin–Madison). Participants were medication-free for ≥ 6 months prior to enrollment, diagnosed with Major Depressive Disorder via the Structural Clinical Interview for DSM-IV Axis 1 disorders (SCID) (First et al., 1995) and initially evaluated with the researcher-administered 17-item Hamilton Rating Scale for Depression (score: 14.25 ± 1.31, range 7–25) (Hamilton, 1960). During the informed consent, participants were informed that the study aimed to understand brain waves during sleep in depressed individuals compared to healthy controls, to examine motor learning in depressed individuals, and to track changes in mood over the course of the study, during which tones may or may not be played during sleep. Participants were instructed to maintain regular sleep-wake schedules, avoid napping, and refrain from alcohol, caffeine, and nicotine for the duration of the study. Compliance was verified by sleep diaries and wrist motor actigraphy (Actiwatch, Mini-Mitter, Bend, OR).

2.2. Study design

The current study consisted of 3 overnight sessions in the following order: baseline (BSL), slow wave deprivation (SWD) intervention, and recovery (RCV) sleep nights. Each sleep session was recorded in a sound-attenuated room. These recordings were part of a larger, randomized cross-over design study that involved 2 additional visits to the laboratory, which minimized possible order effects (9 participants underwent SWD on the 2nd visit overall and 8 underwent SWD on the 4th visit). The BSL night included full clinical polysomnography, which was reviewed by an American Board of Sleep Medicine-certified physician. The clinical polysomnography entailed electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), bilateral tibial EMG, and respiratory recordings, as well a position sensor and pulse oximetry. Participants with sleep disorders (including apnea-hypopnea index >10 or periodic limb movement-arousal index >10) or a sleep efficiency < 80% were excluded from the study.

2.3. Data collection and processing

EEG recordings of sleep were acquired using high-density EEG (256 electrode nets; Electrical Geodesics, Eugene, OR). Specifications for sampling and filtering of the hdEEG signal, as well as for artifact rejection and spectral analysis, have been previously described (Landsness et al., 2009). To increase the signal-to-noise ratio, hdEEG processing and analysis were restricted to the 185 channels overlaying the scalp, removing channels around the cheeks, ears, and neck that are susceptible to artifacts (Goncharova et al., 2003). For sleep scoring, 6 bipolar mastoid-referenced channels (F3, F4, C3, C4, O1, O2) were extracted from the high-density montage. Sleep stages and arousals were visually scored by a registered polysomnographic technologist in 30-second epochs according to standard criteria (Iber et al., 2007). Evaluations of mood were obtained in the evening before and after SWD treatment via a modified version of the self-rated Inventory of Depressive Symptomatology (see Section 2.4 "Modified IDS Scale") (Rush et al., 1996). We evaluated a subset ($n = 6$) of participants with a modified version of the researcher-administered 17-item Hamilton Rating Scale for Depression (HRSD-13; 4 questions about appetite/weight and insomnia removed) (Hamilton, 1960; Hernandez et al., 2000; Smith et al., 2009). The researcher administering the HRSD-13 was blind to the treatment condition and thus unaware of the expected amelioration of depressive symptoms following SWD. To measure changes in vigilance for all participants, data from the Psychomotor Vigilance Task (PVT) (Dinges et al., 1997), VAS for alertness and sleepiness (Folstein and Luria, 1973), and Stanford Sleepiness Scale (SSS) (Herscovitch and Broughton, 1981) were collected in the evening and following morning of each overnight visit.

2.4. Modified IDS Scale

Rush and colleagues found that the self-rated 16-item version of the IDS (QIDS-SR_{16}) yielded strong psychometric properties and correlated well with longer self-rated scales in assessing change in depressive symptomatology (Rush et al., 2003, 2005). Because the current study evaluated the overnight change in depressive symptomatology, it was important to implement a scale that could assess such an acute change in scale ratings. In a similar fashion as previous SD studies with the HRSD-13 (Hernandez et al., 2000; Smith et al., 1999, 2009), we modified the QIDS-SR_{16} by removing questions about sleep and weight (Smith et al., 1999) and adding items from the full-length version of the IDS (IDS-SR_{30}) about irritability, anxiety, response of mood to good events, view of future, and general capacity for enjoyment. Participants were instructed to rate each item according to how they felt since the last rating. The modified IDS self-rated scale (mIDS-SR) showed sufficient internal reliability as measured by Cronbach's alpha for the two time points (Pre-SWD: $\alpha = .731$; Post-SWD: $\alpha = .774$) and was therefore used as the primary outcome measure.

2.5. SWD intervention

SWD was performed with a technique similar to previous studies (Dijk and Beersma, 1989; Ferrara et al., 1999; Aeschbach et al., 2008; Tasali et al., 2008; Landsness et al., 2009). While the participant was asleep in a sound-attenuated room, the hdEEG recording was remotely monitored in real-time. Each time a slow wave (.5–4.5 Hz; > 75 μV) was visually detected, an auditory tone (500–2000 Hz; 40–110 DB; 1–2 s) was delivered through a loudspeaker placed next to the participant's bed using LabView (National Instruments, Austin, TX). The type and incidence of tones played were tailored to each participant to suppress slow waves without arousing the subject.

For 2 participants, a greater all-night average SWA value was observed in the SWD night relative to the baseline night (1 due to a technical failure and 1 due to difficulty in inhibiting slow waves with the tones). These participants, for whom the SWD intervention was not successful, were excluded from the analysis, and the results from the remaining 15 participants are reported.

2.6. Statistical analysis

To examine changes in mood and vigilance, we directly compared the evening pre-treatment (Pre-SWD) and post-treatment (Post-SWD) scores using 2-tailed, paired *t*-tests, controlling for possible