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Reduction in delta activity predicted improved negative affect in Major Depressive Disorder

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ABSTRACT

While prior research has demonstrated a paradoxical antidepressant effect of slow-wave disruption (SWD), the specific dimensions of depression affected is still unclear. The current study aimed to extend this research by utilizing a dimensional approach in examining the antidepressant effects of SWD. Of particular interest is the affective dimension, as negative affect in depression is arguably the most salient characteristic of depression. This sample included 16 individuals with depression (10 female) recruited from the community. Participants slept in the lab for three nights (adaptation, baseline night, and SWD) with polysomnography, and completed measures of negative affect and depression severity the following morning. Results show that reduction in delta power was linearly associated with improved negative affect. Comparison of individual change scores revealed that half of the individuals showed improved negative affect, which is comparable to the reported 40–60% antidepressant response rate to sleep deprivation. Results suggest that vulnerability in the sleep homeostatic system may be a contributing individual differences factor in response to slow-wave disruption in depression.

1. Introduction

A large body of research has implicated sleep as an important contributor to affective functioning, especially in mood disorders such as depression (Tsuno et al., 2005). Though sleep is generally positively related to affective functioning (Scott and Judge, 2006; Minkel et al., 2012), sleep deprivation appears to have a paradoxical antidepressant effect in approximately 40–60% of individuals suffering from depression (Pflug and Tölle, 1971; Wu and Bunney, 1990). Consequently, researchers have sought to establish sleep as a viable intervention target for depression.

Though the antidepressant effect of sleep deprivation is notable, it subsides with recovery sleep and is therefore less viable as an intervention due to issues of sustainability and other adverse effects of chronic sleep loss. Subsequently, research has explored the value of selective disruption of slow-wave sleep as a potential mechanism for intervention (Landsness et al., 2011). Previous research has implicated abnormalities in slow-wave sleep as depressogenic (Beersma and Van den Hoofdakker, 1992), and Landsness et al. (2011) successfully demonstrated that disruptions to slow-wave activity in depression resulted in a decrease in symptom severity.

While several studies have indicated that abnormalities in slow-wave sleep are characteristic of those with depression (Beersma and Van den Hoofdakker, 1992; Armitage and Hoffmann, 2001; Goldschmied et al., 2014), the specific relationship between slow-wave abnormalities and the various dimensions in the phenomenology of depression is still unclear. Conceptualizing and understanding depression utilizing a dimensional approach is increasingly important due to the heterogeneity in symptom presentation between individuals. The affective dimension in depression is of particular interest because it is arguably the most salient characteristic of depression, and remains a gateway criterion for a DSM-5 diagnosis of Major Depressive Disorder (i.e. presence of depressed mood for two or more weeks). Depression is also commonly examined by two distinct dimensions comprising of cognitive and somatic symptoms. Prior research has established differential predictive values of these two dimensions in the relationship between sleep disturbance and depression (Aloia et al., 2005).

In order to further extend our knowledge about the role of sleep in depression, the current study builds upon previous research by examining how slow-wave disruption (SWD) during sleep will relate to negative affect, in addition to Somatic and Cognitive–Affective symptoms of depression. It was hypothesized

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that the reduction in delta power from slow-wave disruption will be associated with improvements in negative affect and Cognitive–Affective symptoms of depression.

2. Methods

2.1. Participants

A total of 16 participants (10 females) ages 18 to 50 were recruited as part of a larger study investigating the cognitive and emotional consequences of sleep disturbance in depression. All participants met criteria for MDD, assessed via the Structural Clinical Interview for DSM-IV (SCID; First et al., 2002). Participants were excluded for neurological diseases, current or recent use (<6 months) of any psychotropic and sleep medications (including antidepressants), and co-occurrence of independent sleep disorders. Polysomnography from the first night was also used to screen for independent sleep disorders, such as obstructive sleep apnea and periodic limb movement disorder. Participants were also excluded for lifetime histories of substance dependence, bipolar I or II disorder, psychosis, and eating disorders. Three participants were excluded from analyses involving psychophysiological data due to technological errors and abnormalities in sleep EEG that precluded sleep scoring. Procedures and recruitment for this study were approved by the ethical standards of the Institutional Review Board, with written consent obtained prior to study participation.

2.2. Experimental conditions

Participants in this study completed three nights (adaptation, baseline, slow-wave disruption) with acquisition of polysomnography. A subsample of participants ($N=9$) also completed a fourth condition as part of the larger protocol. The SWD and fourth condition were counterbalanced, and separated with one night of recovery sleep at home. Prior to the first night, participants maintained five nights of a consistent sleep schedule, based on habitual sleep with at least 6 hours in bed. Sleep in the laboratory also matched this sleep schedule. Compliance with the schedule was monitored via sleep diary and actigraphy. Participants refrained from caffeine use after 12 pm, and abstained from alcohol or drug use for the duration of the study.

2.3. Data collection and processing

Sleep EEG was collected on all three laboratory nights on a Vitaport™ III digital data acquisition system. Data were recorded from eight electrodes (F3/4, C3/4, P3/4, O1/2), at the equivalent sensitivity of five (50 μV, 0.5 s calibration), corresponding to a gain of 50,000, with band pass filters set to the equivalent of 0.3 and 30 Hz, respectively. Signals were digitized on-line at 256 Hz (62.5 Hz for electrooculogram and electromyogram). Sleep data were visually scored according to Rechtschaffen and Kales (1968) by research personnel trained to 90% inter-rater reliability. Arousals were defined as any increases in electromyogram that are accompanied by EEG changes. Power spectral analysis was also performed to obtain power (μV^2) in the delta frequency (0.5 to <4 Hz), averaged in 30 s epochs to correspond with stage scores. Delta power was averaged across all electrode sites from all the non-REM periods. Details regarding the quantification of delta activity has been previously described (see Goldschmied et al., 2014).

2.4. Slow-wave disruption (SWD)

The SWD protocol was adapted from previous research (Ferrara et al., 1998), where delta waves were visually detected, and interrupted by using tones delivered via audiometric earphones (E-A-RTone 3A Insert Earphones). A 1000 Hz tone of 1 s duration was delivered at detection of delta activity, with each tone increasing by 5 dB every 15 s until a response was observed. The delivery of tones maximized disruption in slow-waves without waking the subject. Participants were not informed of the specific research questions or hypotheses related to this protocol. A change score of slow-wave activity (EEG power in the delta band) between baseline and SWD conditions was calculated and used in subsequent analysis as a measure of the proportion of reduction in delta activity.

2.5. Negative affect and depression

Negative affect was measured after sleep in all conditions using the Visual Analog Scale (VAS). The VAS asked "How negative do you feel right now?", and was anchored with "Not at all" and "Extremely". The Visual Analog Scale is commonly used across multiple domains of psychological functioning, and has been validated as a measure for global affect (Monk, 1989). Change scores were calculated for negative affect by subtracting scores following baseline night from those following interruption night.

Depression symptom severity was also measured via the BDI-II (Beck et al., 1996). Cognitive–Affective and Somatic subscales (Beck et al., 1996) were also examined to compare the cognitive versus somatic dimensions of depression. The Somatic subscale included items for loss of energy, tiredness or fatigue, changes in sleeping, changes in appetite, and concentration difficulties. The remaining items on the BDI-II were included on the Cognitive–Affective subscale. Change scores (SWD – Baseline) were calculated for both subscales.

2.6. Analyses

In order to test the effect of SWD on affect, a linear regression was conducted with change in VAS negative affect as the outcome variable, and the decrease of slow-wave activity as the predictor. Change in arousal, REM and stage 2 sleep, and order of conditions were entered as covariates to control for the non-slow wave changes that also occurred during the SWD condition. Regressions were also similarly conducted for change in the Cognitive–Affective and Somatic subscales of the BDI-II. Individual change scores were also examined based on the previous finding that only a subset of depressed individuals respond to sleep deprivation.

3. Results

Individuals in this sample exhibited a mean BDI-II score of 23 (S.D.$=6.50$), indicating moderate severity of depression symptoms. Baseline sleep indicated a normal sleep onset latency and sleep efficiency. To examine the effectiveness of the SWD manipulation, polysomnographic variables were compared between the baseline and SWD conditions via paired-sample *t*-tests. The SWD resulted in a significant reduction of both slow-wave sleep (stages 3 and 4) and delta power (see Table 1). Results also confirmed that sleep duration was not significantly impacted by the SWD, though the manipulation did result in increased number of arousals. The predominant response to the SWD appears to be increased stage 2 sleep, with a small increase in rapid eye-movement (REM) sleep.

Results from the linear regression indicated that even after controlling for covariates, reduction in delta activity significantly predicted decreased negative affect following SWD, $\beta=0.576$, $t(12)=2.332$, $p<0.05$ (see Fig. 1 for scatter plot). No significant effects of arousal, REM, stage 2, or order were detected in the model. As change in visually scored slow-wave sleep was also detected, a post-hoc regression was conducted with change in VAS negative affect as the outcome variable, and change in slow-wave sleep as the predictor. The same covariates previously used were also entered into the model. Results revealed that change in slow-wave sleep was not a significant predictor of change in negative affect.

Results also indicated that change in the Cognitive–Affective subscale was marginally predicted by reduction in delta activity, $\beta=0.507$, $t(12)=1.899$, $p<0.1$, even after controlling for changes in arousal, stage 2, REM sleep, and order. The standardized-beta indicates a large effect size, suggesting that statistical significance

Table 1
BSL, baseline; SWD, slow-wave disruption; TST, total sleep time; SOL, sleep onset latenct; SE, sleep efficiency; AR, number of arousals during sleep; SWS, slow-wave sleep; REM, stage REM; REM-L, latency to REM.

Variables	BSL M (SEM)	SWD M (SEM)	*T*-test *t*	*p*-Value
TST (min)	410.07 (10.49)	400.23 (9.71)	1.01	ns
SOL (min)	10.19 (6.79)	15.57 (13.93)	−1.47	ns
SE (%)	94.53 (2.31)	90.65 (5.75)	3.30	<0.01
AR (#)	12.87 (1.48)	18.6 (2.17)	−2.46	<0.05
Stage 1 (%)	4.05 (0.76)	4.9 (1.06)	−1.501	ns
Stage 2 (%)	51.89 (1.85)	58.53 (3)	−3.27	<0.01
SWS (Stages 3&4) (%)	16.08 (1.99)	8.97 (2.4)	4.48	<0.001
REM (%)	24.91 (1.23)	21.66 (2.03)	2.32	<0.05
REM-L ($_{min}$)	68.93 (9.44)	100.33 (18.97)	−1.49	ns
Delta Power (μV^2)	445.37 (34.23)	398 (31.04)	3.48	<0.01