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Effects of slow-wave activity on mood disturbance in major depressive disorder

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Original Article

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Abstract

Background. Studies have demonstrated that decreases in slow-wave activity (SWA) predict decreases in depressive symptoms in those with major depressive disorder (MDD), suggesting that there may be a link between SWA and mood. The aim of the present study was to determine if the consequent change in SWA regulation following a mild homeostatic sleep challenge would predict mood disturbance.

Methods. Thirty-seven depressed and fifty-nine healthy adults spent three consecutive nights in the sleep laboratory. On the third night, bedtime was delayed by 3 h, as this procedure has been shown to provoke SWA. The Profile of Mood States questionnaire was administered on the morning following the baseline and sleep delay nights to measure mood disturbance.

Results. Results revealed that following sleep delay, a lower delta sleep ratio, indicative of inadequate dissipation of SWA from the first to the second non-rapid eye movement period, predicted increased mood disturbance in only those with MDD.

Conclusions. These data demonstrate that in the first half of the night, individuals with MDD who have less SWA dissipation as a consequence of impaired SWA regulation have greater mood disturbance, and may suggest that appropriate homeostatic regulation of sleep is an important factor in the disorder.

Introduction

Sleep disturbances are frequently observed among psychiatric disorders (Baglioni *et al.*, 2016). In major depressive disorder (MDD) specifically, sleep disturbance has been shown to be an independent risk factor for the development and maintenance of the disorder (Swanson *et al.*, 2010). Moreover, individuals with MDD tend to exhibit differences in visually scored electroencephalographic (EEG) measures of sleep compared with healthy controls (HCs), such as longer sleep onset latency, increased rapid eye movement (REM) density, and decreased REM latency (Swanson *et al.*, 2010). Analysis of the microarchitecture of sleep, which uses quantitative EEG to describe the underlying frequency structure, has also demonstrated significant differences between healthy individuals and those with MDD. For example, at baseline, those with MDD show increased fast frequency EEG and lower slow-wave activity (SWA) amplitude than healthy individuals, especially in the first non-REM (NREM) period (Armitage *et al.*, 2000*b*).

That SWA impairment which has been associated with MDD is notable, as SWA has been implicated in the homeostatic regulation of neuroplasticity (Tononi and Cirelli, 2003), and there is evidence to suggest that neuroplasticity is impaired in MDD (Pittenger and Duman, 2008). For example, decreases in neural plasticity, which refers to changes in the number of synapses or the remodeling of dendrites, have been evidenced by reduced grey matter volume in those with MDD (Drevets *et al.*, 1997). Several studies have also indicated that key components in regulating synaptic plasticity, the process through which synapses are weakened or strengthened, is likewise reduced in MDD (Gorgulu and Caliyurt, 2009). Moreover, Player *et al.* (2013) and Kuhn *et al.* (2016*b*) demonstrated that those with MDD exhibited an attenuated response *v.* HCs following a brain stimulation paradigm designed to increase the excitability of the motor cortex, providing further evidence for decreased neuroplasticity in MDD. Taken together, this body of research suggests that neuroplasticity, and more specifically synaptic plasticity, is impaired in MDD. Because SWA has been implicated in the homeostatic regulation of synaptic plasticity in the cortex, it is possible that abnormalities in SWA are associated with these impairments. Furthermore, since enhanced synaptic plasticity in brain areas implicated in mood has been suggested to be the basis of the antidepressant effects of ketamine (Duncan *et al.*, 2013), it is reasonable to suggest that if

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abnormalities in SWA are associated with impaired synaptic plasticity, these abnormalities may also be associated with mood dysregulation in MDD.

Research, including that from our group, has demonstrated that males with MDD exhibit abnormalities in the regulation of SWA (Armitage *et al.*, 2000*a*; Goldschmied *et al.*, 2014); however, it is unclear whether abnormalities in the regulation of SWA are also associated with mood disturbance. To this end, and in order to assess the relationship between the regulation of SWA and mood in MDD, it is necessary to probe the homeostatic system with a sleep challenge paradigm where the response in SWA can be assessed (Armitage, 2007). Our group has demonstrated that a sleep delay challenge paradigm, which extends prior wakefulness by 3 h, provokes a homeostatic response in SWA in healthy individuals, such that SWA significantly increases, particularly in the first NREM period (Armitage, 2007; Armitage *et al.*, 2012). These findings are consistent with sleep deprivation studies in healthy individuals that have demonstrated that total sleep deprivation increases SWA during recovery sleep in an exceedingly predictable manner (Borbely, 2001). This sleep delay paradigm may provide an opportunity to examine the association of the homeostatic regulation of SWA on mood.

The occurrence of SWA, however, is not evenly distributed across the night as evidenced by the use of non-linear functions to model SWA across NREM periods (Armitage *et al.*, 2000*a*). Furthermore, studies have shown that the most significant differences in sleep EEG between HC and those with MDD occur during the first two NREM periods, and that these differences highlight the importance of the distribution of SWA in the first half of the night (Kupfer *et al.*, 1990; Lee *et al.*, 1993; Antonijevic *et al.*, 2000). The delta sleep ratio (DSR), the ratio of the amount of SWA in the first NREM period relative to the second NREM period, is a metric that has been used to examine the distribution of SWA, and has been shown to predict clinical outcomes in MDD (Kupfer *et al.*, 1990; Thase *et al.*, 1998; Nissen *et al.*, 2001; Lotrich and Germain, 2015). Lower DSR values, indicative of less dissipation of SWA from the first to the second NREM period, have been associated with higher risk of relapse (Kupfer *et al.*, 1990) and less favorable therapeutic outcomes (Thase *et al.*, 1998), which may suggest that the regulation of SWA is an important factor in MDD.

In addition to the impairments in SWA regulation, there is also evidence that the amount of SWA is associated with mood. Two recent studies demonstrated that reducing SWA in those with MDD could improve mood. Utilizing a real-time paradigm in which auditory tones were administered to individuals when slow waves were visually detected during NREM sleep, Landsness *et al.* (2011) demonstrated that a 37% decrease in SWA, without decreasing total sleep time, resulted in a 10% decrease in depressive symptoms in those with MDD. Additionally, a more recent study by Cheng *et al.* (2015) showed that reduced SWA predicted an improvement in negative mood in those with MDD. Taken together, these results demonstrate that there is a relationship between the amount of SWA and mood in MDD and suggests that the presence of SWA may contribute to mood disturbance.

The aim of the present study was to determine if impaired SWA regulation in the first half of the night (NREM periods 1–2) predicts mood disturbance in a sample of depressed and healthy adults following a 3-h sleep delay challenge. Given preliminary evidence that there is a relationship between the amount of SWA and mood in MDD, and that low DSR has been associated with worse functioning, we hypothesize that for those with MDD, a lower DSR (i.e. less dissipation of SWA from the first to the second NREM period), will be associated with a worsening of mood, or increased mood disturbance on the Profile of Mood States – Short Form (POMS-SF) in the morning following sleep delay.

Methods

Participants

Participants, between the ages of 20 and 40, were recruited from the Sleep and Chronophysiology laboratory at the University of Texas Southwestern Medical Center (UTSW; $n = 79$) and at the University of Michigan (UM; $n = 17$), under the same conditions. Participants reported sleeping habitually between 6 and 8 h per night, with a bedtime between 10 and 12 am, did not have any significant previous or concurrent general medical illness, significant head injury, seizure, or unconsciousness for more than 5 min, and were unmedicated for 4 weeks or more. Females were not pregnant or lactating. As determined by medical history or polysomnogram, participants were free of sleep disorders including narcolepsy, sleep apnea, bruxism, or periodic limb movements, and were not engaged in shiftwork. In total, 178 participants were recruited, of which 110 individuals, who met inclusion criteria for the study including a week of sleep diary to confirm bed and rise time and two consecutive nights of polysomnographic recording without any difficulties or deviations from the protocol, were included. From these 110, an additional 14 participants were excluded due to missing behavioral data (see POMS below). All subjects provided written informed consent, and the protocol was approved by the Institutional Review Boards at UTSW and UM.

Individuals with MDD

The sample includes 37 adults, diagnosed with MDD. All diagnoses were based on the Structured Clinical Interview for DSM-III-R or IV. Participants met criteria for non-psychotic MDD, but no other current Axis I disorders or substance abuse within 12 months prior to baseline study. Participants were not currently undergoing antidepressant therapy or counseling, and had no significant suicidal ideation (as judged clinically), or previous suicide attempt. The 21-item Beck Depression Inventory-II (BDI; Beck *et al.*, 1996) was used to assess symptom severity.

Healthy controls

The HC group consisted of 59 healthy adults. SCID confirmed the absence of current or past personal or family history of psychopathology.

Procedures

For 5 days prior to study, participants kept an 11 pm to 6 am sleep schedule, as verified by sleep diary and actigraphy[1]. Participants

[1]As this was a sleep delay challenge study, it was necessary to fix total sleep time across participants. Since there is individual variation in sleep time, we specifically recruited those who slept 6–8 h, habitually. Selecting a 7 h bedtime guarantees that none of our participants will have a sleep opportunity that differs for more than 1 h from their habitual sleep schedule.

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then spent 3 consecutive nights in the sleep laboratory. The first night served as an adaptation to the laboratory environment and screening for independent sleep disorders, while the second served as the baseline. Bedtime and rise time were delayed by 3 h during the sleep delay challenge on night 3. Total available sleep time was held constant at 7 h for adults on all nights. The POMS-SF was administered in the morning after the baseline sleep night and in the morning after the sleep delay night. Subjects refrained from napping, using alcohol and drugs, and limited caffeine use to one caffeinated beverage for 5 days before study, confirmed by sleep diary and urine screening.

Profile of Mood States – Short Form

The POMS-SF (Shacham, 1983) is a measure consisting of 30 adjectives describing feelings designed to assess transient, fluctuating subjective mood states, and has been used extensively to measure state mood changes during sleep manipulations (Dinges *et al.*, 1997; Scott *et al.*, 2006). Utilizing a five-point scale, participants select the degree to which each adjective describes their present mood. The POMS-SF produces a total mood disturbance (TMD) score defined as the sum of five POMS subscale scores (depression, tension, anger, confusion, and fatigue) minus the sixth subscale score (vigor). TMD can thus be viewed as a proxy for general negative mood. TMD has been shown to be reliable and valid indicator of affective state. POMS-SF data were not available from 14 individuals with complete sleep data (HC: $n = 9$; MDD: $n = 5$), and as such, these individuals were not included in the present analyses.

Sleep EEG

Standard laboratory procedures were followed (Armitage *et al.*, 2012). On the first overnight in the laboratory, leg leads, chest and abdomen respiration bands, and nasal–oral thermistors were used in addition to a full EEG montage. On each successive night, the montage included C3, C4, F3, F4, P3, P4, O1, and O2 EEG, left and right electrooculography (EOG), and a bipolar electromyography (EMG). The reference electrode was comprised of linked earlobes passed through a 10 KΩ resistor to minimize possible artifacts. All EEG impedances remained below 2 kΩ, and EEG was monitored throughout the sleep delay period to verify that subjects did not fall asleep. Research personnel visually scored sleep records following standard criteria (Rechtschaffen and Kales, 1968), after training to a ⩾90% agreement on an epoch-by-epoch basis. Thereafter, any epochs that contained movement, breathing muscle artifact, or recording difficulties were omitted from further analysis. In general, artifact rejection resulted in the exclusion of <5% of epochs.

Data from UTSW ($N = 79$) were collected on a GRASS™ P511 amplifier-based paperless polygraph, while data from the UM laboratory ($N = 17$) were collected on a Vitaport™ (The Netherlands) III digital data acquisition system. EEG was recorded at the equivalent sensitivity of 5 (50 μV, 0.5 s calibration), corresponding to a gain of 50 000. For the GRASS system, halfamp low- and high-bandpass filters were set at 0 ± 3 and 30 Hz, respectively. A 60 Hz notch filter attenuated electrical noise. For the Vitaport™ III system, filter settings were set at 0.3 and 70 Hz for EEG and 30 and 100 Hz for EOG. All signals were digitized at 256 Hz and displayed digitally during acquisition[2].

Power spectral analysis (PSA) was performed on the EEG data in 2-s blocks using an algorithm based on a fast Fourier transform (512 samples for each 2 s). The sampling rate was set to 256 Hz, with a Hamming window taper to reduce overlap between adjacent frequencies. The PSA generates power in all five frequency bands, but analyses for the present study were restricted to the delta activity (0.5–3.9 Hz) expressed as μV^2. Delta power was averaged in 30-s epochs to provide identical epoch lengths to the stage-score data. Both raw EEG and power spectral data were inspected epoch-by-epoch for evidence of movement artifact. Epochs with high amplitude artifact were excluded from all EEG analyses. Only data from C3 electrodes are reported here. Data were then sorted by NREM period for each subject on each night in the laboratory. NREM period was defined as the succession of stages 2, 3, or 4 of ⩾15-min duration and terminated by stage REM or a period of wakefulness of ⩾5 min. Stage 1 sleep epochs were excluded. No minimum REM duration was required for the first or last REM period. Delta power was summed and then averaged relative to the number of epochs in each NREM period, for each subject, henceforth referred to as SWA.

In addition to the raw SWA power, percentage of SWA was included (BL-Normalized SWA), expressing SWA in each NREM period on the delay night relative to total SWA on the baseline night, in order to normalize power and control for any potential individual differences across subjects, consistent with previous studies (Armitage *et al.*, 2012). EEG analyses were focused exclusively on the central leads as SWA is known to be frontocentrally distributed. For statistical purposes, only the first four NREM periods were included for analysis, since not all subjects had more than four NREM periods across the night. DSR was operationalized as the baseline-normalized delta power from the first NREM period divided by the second NREM period. A higher DSR represents more dissipation of delta activity from the first to the second NREM period.

Data analysis

All data were first coded for group (HC, MDD). One-way analysis of variance (ANOVA) was computed for each demographic variable to examine any differences between groups. Repeated-measures ANOVA was computed for each macroarchitectural and microarchitectural variable, with group (HC, MDD) as the between-subjects variable and condition (baseline, post-sleep delay challenge) as the within-subjects variable. Univariate statistics for each variable are only reported if a main effect or interaction was obtained. Post-hoc analyses were computed using one-way ANOVA or paired *t* tests, where appropriate. The χ^2 was used to detect differences in the proportion of responders *v.* non-responders.

[2]Data systems were cross-validated using two procedures. First, a sine-wave generator was utilized for simultaneous signal recording on the two data acquisition systems, and then subjected to power spectral analysis to confirm that spectral profiles were identical. Second, whole night EEG data from 10 subjects were simultaneously acquired and analyzed to confirm that power values of each system fell within the 95% confidence interval. In the present study, SWA across the night at baseline, $F_{(1,94)} = 1.808$, $p > 0.05$, and following sleep delay, $F_{(1,94)} = 2.328$, $p > 0.05$, in addition to SWA during NREM1, $F_{(1,94)} = 1.787$, $p > 0.05$, NREM2, $F_{(1,94)} = 0.378$, $p > 0.05$, NREM3, $F_{(1,94)} = 0.003$, $p > 0.05$, and NREM4, $F_{(1,94)} = 0.281$, $p > 0.05$, were compared and did not differ between data systems.

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Regression analysis was then used to assess if having more sustained SWA, as indicated by lower DSR, predicted increased mood disturbance. Repeated measures of mood were modeled via a marginal regression, which is similar to a linear mixed-effects model approach without the need to specify random effects (Lindstrom and Bates, 1990). This approach was selected because it confers significant advantages beyond a repeated-measures ANOVA and is more parsimonious compared with a linear mixed-effect model. First, the marginal regression can model change across time as a linear variable, which preserves statistical power because it reduces the degrees of freedom. Similar to the linear mixed-effects approach, the marginal regression also does not require the assumption of sphericity. Finally, the marginal regression is also more robust in handling of missing data without resorting to listwise deletion. The model specified TMD scores from the POMS-SF questionnaire as the dependent variable. Independent variables included time (baseline, sleep delay), group (MDD, HC), DSR, the interaction of time × group × DSR, and all lower order interactions. As prior research has indicated that the ability to generate SWA is impaired in depression, we also tested SWA response to the sleep delay challenge as a moderator. Individuals were categorized as a responder if SWA following the sleep delay challenge was higher compared with baseline and a non-responder if SWA was the same or lower compared with baseline. Age, sex, and laboratory (University of Texas Southwestern Medical Center, University of Michigan) were also tested as covariates, and were removed from the final model due to non-significance. All continuous variables were standardized for comparison of effect sizes between predictors.

If the hypotheses are supported, the model would indicate that changes in TMD vary as a function of the DSR, and that this relationship will differ between depressed and healthy individuals, as indicated by a significant time × group × DSR interaction.

Results

Baseline variables: participant characteristics

Demographic and mood variables (Table 1) were compared between the HC group and participants with MDD. As expected, the MDD group had higher levels of depression as measured by the BDI $F_{(1,92)} = 439.51$, $p < 0.01$, but did not differ from HC in age or percentage of number of females.

Macroarchitectural variables

Polysomnographic variables were likewise examined at baseline and following sleep delay (Table 2). As compared with HC, those with MDD had less stage 2 sleep at baseline, $F_{(1,95)} = 278.53$, $p < 0.05$. No other group differences emerged. Following the sleep delay, the HC group exhibited shorter sleep onset latency, $t_{(58)} = 4.09$, $p < 0.01$, less stage 2 sleep, $t_{(58)} = 3.82$, $p < 0.01$, more REM sleep, $t_{(58)} = -2.28$, $p < 0.05$, and shorter REM latency than at baseline, $t_{(58)} = 2.29$, $p < 0.05$, while the MDD group exhibited shorter sleep onset latency, $t_{(36)} = 2.60$, $p < 0.01$, and shorter REM latency, $t_{(36)} = 3.48$, $p < 0.01$.

Table 1. Demographic variables, by group and condition

	HC	MDD
N (No. female)	59 (32)	37 (21)
Age (s.d.)	29.03 (5.77)	27.65 (6.30)
Beck depression inventory score (s.d.)	0.72 (1.44)[a]	25.23 (8.74)[a]

Means, standard deviations (within parenthesis) and ANOVA results.
[a]Indicates group difference.

Sleep delay challenge manipulation check: microarchitectural variables

SWA variables were then analyzed to examine the effectiveness of the sleep delay in evoking a slow-wave response (Table 3). The HC group exhibited more SWA during baseline and following sleep delay than those in the MDD group, $F_{(1,92)} = 9.371$, $p < 0.01$. Collapsed across groups, SWA was higher following sleep delay than baseline, $F_{(1,92)} = 4.558$, $p = 0.035$. However, as indicated by a significant condition × group interaction, $F_{(1,92)} = 4.364$, $p = 0.039$, the sleep delay did not result in increased delta power across the night in both groups. Post-hoc analyses revealed that following delay, the MDD group did not show increased delta across the night, or in any NREM period. However, as expected, the HC group exhibited significantly more average delta power across the night following the sleep delay, $t_{(58)} = -3.51$, $p < 0.01$, and during the first, $t_{(58)} = -2.02$, $p < 0.05$, and fourth NREM periods, $t_{(58)} = -3.12$, $p < 0.01$, specifically. With regard to response to the sleep delay challenge, in the HC group, 33.9% of individuals were considered responders, and 66.1% were considered non-responders. In the MDD group, 37.8% were considered responders, while 62.2% were considered non-responders. No group differences were detected in SWA response.

Response to the sleep delay challenge

Regression analysis was then used to test if the pattern of SWA following the sleep delay challenge significantly predicted mood disturbance. Model fit was confirmed using a likelihood ratio statistic, which indicated that the full model performed significantly better than an intercept-only model, $\chi^2(8) = 112.88$, $p < 0.0001$. SWA response was tested as a moderator of the interaction of interest (time × group × DSR interaction), and was not significant ($p = 0.65$), and thus was retained in the final model as a covariate where it was marginally significant ($p = 0.08$). Age, sex, and laboratory were also tested as covariates, and were removed from the final model due to non-significance.

Results revealed a significant three-way time × group × DSR interaction, $F_{(1183)} = 2.44$, $p < 0.05$, indicating that the relationship between mood disturbance and the DSR response to the sleep delay challenge differed between HC and MDD groups. Further examination of the marginal effects indicated that depressed individuals showed less mood disturbance if they exhibited a higher DSR (i.e. more dissipation), $\beta = -0.18$, $p < 0.001$ (Fig. 1). In contrast, the HC group did not show a significant relationship between DSR and mood disturbance following the sleep delay challenge, $\beta = -0.02$, $p = 0.64$. With the exception of a main effect of group, indicating higher mood disturbance in depressed individuals, $\beta = 1.71$, <0.001, no other main effects or interactions were detected.

Discussion

The present study demonstrated that among individuals with MDD, a lower DSR was predictive of increased mood disturbance after a sleep delay challenge paradigm, consistent with our initial

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Table 2. Means and standard deviations of polysomnographic variables, by group and condition

	HC ($n = 59$)		MDD ($n = 37$)	
	Baseline	Delay	Baseline	Delay
Time in bed (min)	416.04 (7.90)	413.22 (20.95)	418.20 (5.82)	410.50 (27.51)
Sleep efficiency (%)	95.15 (2.51)	94.90 (4.26)	93.82 (4.97)	95.25 (3.25)
Sleep latency (min)	7.56 (6.21)	4.15 (3.02)[a]	12.51(18.50)	4.57 (4.19)[a]
% Stage 1	6.35 (5.31)	6.46 (5.44)	5.35 (5.28)	6.05 (5.66)
% Stage 2	56.19 (7.66)[b]	53.10 (7.55)[a]	52.69 (8.16)[b]	50.58 (7.61)
% Slow-wave sleep	11.32 (9.01)	11.90 (9.13)	13.76 (8.31)	13.82 (9.19)
Awake and movement (%)	2.83 (1.96)	3.17 (2.57)	3.16 (3.05)	3.29 (2.72)
REM (%)	23.32 (5.82)	25.37 (7.10)[a]	25.04 (6.38)	26.26 (5.59)
REM latency (min)	75.95 (24.50)	68.38 (29.54)[a]	79.93 (40.76)	57.73 (23.71)[a]

[a]Denotes significant, within-group condition difference.
[b]Denotes significant group difference.

Table 3. Means and standard deviations of slow-wave activity, by group and condition

	HC ($n = 59$)		MDD ($n = 37$)	
	Baseline	Delay	Baseline	Delay
Average delta (μV^2) across the night	427.34 (81.01)	450.48 (91.98)[a]	392.39 (62.35)	393.19 (77.51)
Delta (μV^2) in first NREM	569.52 (119.86)	593.70 (136.21)[a]	510.42 (113.76)	507.31 (113.54)
Delta (μV^2) in second NREM	449.37 (112.12)	472.25 (126.10)	422.65 (102.00)	421.19 (105.88)
Delta (μV^2) in third NREM	368.97 (69.93)	377.23 (78.08)	336.35 (60.48)	336.54 (78.41)
Delta (μV^2) in fourth NREM	321.49 (78.59)	358.74 (83.54)[a]	300.14 (56.05)	307.74 (75.38)

[a]Indicates significant within-group condition difference.

hypotheses. In this way, lower DSR represents inadequate dissipation of SWA from the first to second NREM period. These findings suggest that mood disturbance in depressed individuals may be associated with an impairment in sleep homeostasis, and highlight the importance of appropriate homeostatic regulation of SWA to emotional functioning. Studies have shown that the exponential decay of SWA throughout sleep, typically with a prompt decrease from the first to the second NREM period, is indicative of healthy dissipation. That dysregulated slow-wave dissipation has consequences for emotional functioning in MDD has been demonstrated previously: individuals who have a low DSR have a higher chance of relapse (Kupfer *et al.*, 1990), and are more likely to develop MDD as a result of interferon treatment (Lotrich and Germain, 2015). Taken together, these findings suggest that impaired homeostatic regulation of SWA is associated with emotional dysregulation in MDD.

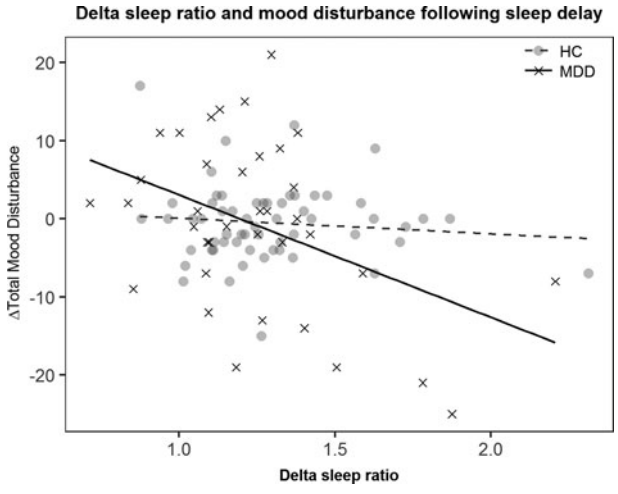

Fig. 1. Change in total mood disturbance (sleep delay minus baseline) following sleep delay is significantly associated with δ sleep ratio in the MDD group, but not the HC group. Predicted values of the model are superimposed upon sample observations. HC, healthy control; MDD, major depressive disorder.

Importantly, our data also indicate that impaired dissipation is associated with mood disturbance regardless of the initial response to the sleep delay challenge. This underscores the distinction of the two homeostatic processes of SWA: initial accumulation of SWA and subsequent dissipation of SWA, and highlights that dissipation is important in the context of emotional functioning. Tononi and Cirelli (2003) have also postulated that the accumulation and dissipation of SWA are representative of two distinctive phenomena. First, they posit that initial SWA is a marker of net cortical synaptic strength, the level of postsynaptic response resulting from presynaptic activity. Supporting this hypothesis, Liu *et al.* (2010) measured changes in miniature excitatory postsynaptic current (mEPSC) frequency and amplitude in the frontal brain areas of rodents and demonstrated that these measures increased following

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sleep deprivation, providing direct evidence of increases in synaptic strength with continued wakefulness. Second, they suggest that dissipation of SWA is a marker of the functional downscaling of synaptic strength that takes place during sleep. They contend that downscaling of synaptic strength is a vitally important homeostatic mechanism that prevents an oversaturation of synaptic strength that might otherwise lead to neuronal firing instability (Tononi and Cirelli, 2003). Because our results indicate that mood disturbance in MDD is associated with impaired dissipation, this may suggest that there is an impairment in the homeostatic mechanism that modulates synaptic strength in MDD, and that the severity of this impairment is associated with the severity of mood disturbance.

The idea that the modulation of synaptic strength is associated with mood in MDD has been suggested recently. Wolf *et al.* (2016) have posited that there exists 'a window of optimal associative synaptic plasticity' that those with MDD fail to reach during a day of typical wakefulness, suggesting that those with MDD exhibit deficient daytime levels of synaptic strength. According to their model, during sleep deprivation, prolonged wakefulness increases synaptic strength creating a favorable window for associative synaptic plasticity, or the inducibility of long-term potentiation, that previously did not exist. This model may explain a potential mechanism of the antidepressant effect of sleep deprivation (Wirz-Justice *et al.*, 1999; Gillin *et al.*, 2001), and is in line with pharmacological models that suggest that the rapid antidepressant effects of ketamine in MDD result from an increase in synaptic strength (Duncan *et al.*, 2013).

Research within the past year has demonstrated that sleep reduces synaptic strength in rodents (de Vivo *et al.*, 2017; Diering *et al.*, 2017). However, because the ability to measure synaptic strength in humans is limited (Kuhn *et al.*, 2016*a*), we are unable to confirm that inadequate dissipation of SWA is a reflection of an impairment in the modulatory activity of synaptic strength. Tononi and Cirelli (2012) also acknowledge that the role of SWA in synaptic downscaling presently remains hypothetical. Future studies could address this by utilizing multi-modal assessment of indirect measures of synaptic strength, such as cortical evoked responses, and waking EEG θ activity (Kuhn *et al.*, 2016*a*).

These results should be interpreted in light of limitations. First, as this was a study of the homeostatic response to sleep delay, total sleep time was required to be kept constant. Participants were allotted a 7-h sleep opportunity, reflecting the current recommendation for the amount of sleep for adults (Watson *et al.*, 2015). Additionally, inclusion criteria required all participants to have a habitual sleep time between 6 and 8 h, which would limit the maximum adjustment to study bedtime to only 1 h. However, there is still a possibility that some participants were sleep deprived during the study protocol, which could impact mood measures. Future studies may consider only including participants who have a habitual sleep schedule that exactly mirrors study parameters. Relatedly, limiting the sample to depressed individuals without sleep disorders, and with a consistent sleep pattern, limits the generalizability.

Second, mood effects were measured by the POMS SF. Although the POMS SF has been shown to be a good alternative to the full length POMS (Curran *et al.*, 1995), and has been used extensively to measure state mood changes during sleep manipulations (Dinges *et al.*, 1997; Scott *et al.*, 2006), it would be useful to incorporate additional mood measures including visual analog scales, which have been shown to have high degrees of sensitivity (McCormack *et al.*, 1988).

Third, whereas SWA significantly increased in HC, SWA in the MDD group as a whole did not change following sleep delay. Previous work has demonstrated that individuals with MDD do not respond to sleep challenges as robustly as HC (Armitage, 2007). However, those in the MDD group did exhibit shorter sleep and REM latency following the sleep delay, suggesting that the challenge did have an effect on sleep, but not SWA specifically. Future studies could address this by utilizing a total sleep deprivation paradigm to examine whether SWA can be increased in MDD.

Lastly, our results may be limited by our study parameters. Our study methods focus solely on cortical areas assessed with EEG, which may function differently than other cortical areas and subcortical structures. For example, using learning tasks as proxy measures of synaptic plasticity, Nissen *et al.* (2010) demonstrated that individuals with MDD showed evidence of decreased synaptic plasticity in the dorsal executive network, while having increased synaptic plasticity in the ventral emotional network. This may indicate that our results may be specific to certain areas of cortex and highlight the limitations of using EEG data to make inferences about whole brain processes. It is also possible that there could be circadian effects on both sleep and mood in MDD that may interact with slow-wave dissipation. Future studies should combine other methodology with EEG, in addition to utilizing protocols designed to examine circadian influence.

In summary, this study examined the amount and pattern of SWA following a 3 h sleep delay challenge, and found that a lower DSR, representative of inadequate dissipation of SWA from the first to the second NREM period, was predictive of mood disturbance in individuals with MDD. These results may suggest that there is an impairment in the homeostatic mechanism that modulates synaptic strength in MDD, and that the severity of this impairment is associated with the severity of mood disturbance. Developing an understanding of the relationship between sleep, synaptic strength, and mood regulation in MDD is of great importance as it is essential to developing novel treatments and identifying the pathophysiology of the disorder.

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Conflict of interest. Dr Cheng disclosed consulting fees from NeuroTrials Research from September 2016 to December 2016, for research unrelated to results presented in this study. Dr Cheng was not a consultant when the data were collected or during the initial analysis. Dr Armitage disclosed consulting fees from the University of Ottawa, Institute of Mental Health Research from May 2013 to March 2015. Dr Armitage was not a consultant when the data were collected or during the initial analysis. Drs Goldschmied, Hoffmann, Boland, and Deldin reported no biomedical financial interests or potential conflicts of interest.

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