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Altered overnight modulation of spontaneous waking EEG reflects altered sleep homeostasis in major depressive disorder: a high-density EEG investigation

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Abstract

Background—Prior investigations have suggested sleep homeostasis is altered in major depressive disorder (MDD). Low frequency activity (LFA) in the electroencephalogram during waking has been correlated with sleep slow wave activity (SWA), suggesting that waking LFA reflects sleep homeostasis in healthy individuals. This study investigated whether the overnight change in waking LFA and its relationship with sleep SWA are altered in MDD.

Methods—256-channel high-density electroencephalography (hdEEG) recordings during waking (pre- and post-sleep) and during sleep were collected in 14 unmedicated, unipolar MDD subjects (9 women) and age- and sex-matched healthy controls (HC).

Results—Waking LFA (3.25–.25 Hz) declined significantly overnight in the HC group, but not in the group of MDD subjects. Overnight decline of waking LFA correlated with sleep SWA in frontal brain regions in HC, but a comparable relationship was not found in MDD.

Limitations—This study is not able to definitely segregate overnight changes in the waking EEG that may occur due to homeostatic and/or circadian factors.

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Contributors

Dr. Plante designed the study, managed literature searches and analyses, and wrote the first draft of the manuscript. Mr. Goldstein performed statistical analyses, hdEEG processing and analysis, design of figures/tables, and contributed to study design and writing the manuscript. Dr. Landsness contributed to the study design, evaluation of participants, management of hdEEG processing and analyses, and writing the article. Mr. Wanger, and Mr. Guokas performed statistical analyses and hdEEG processing, and contributed to the writing of the manuscript. Dr. Riedner contributed to analysis and interpretation of the data and writing the manuscript. Dr. Tononi contributed to the study design, data analysis and interpretation, and to writing the article. Dr. Benca contributed by being the principal investigator, contributing to the study design, participating in data analysis and interpretation, and writing the article. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

Dr. Plante has owned stock in Pfizer, and has received honoraria from Oakstone Medical Publishing, the American Academy of Sleep Medicine, Kishwaukee Community Hospital, and royalties from Cambridge University Press. Dr. Tononi has consulted for Sanofi-Aventis and Takeda, and he is currently the David P. White Chair in Sleep Medicine at the University of Wisconsin–Madison, endowed by Phillips Respironics. Dr. Tononi has also received unrelated research support from Phillips Respironics. Dr. Benca has consulted for Merck and Sanofi-Aventis. All other authors declare they have no conflicts of interest.

Conclusions—MDD involves altered overnight modulation of waking low frequency EEG activity that may reflect altered sleep homeostasis in the disorder. Future research is required to determine the functional significance and clinical implications of these findings.

Keywords

major depressive disorder; high-density EEG; waking EEG

1. Introduction

Sleep and major depressive disorder (MDD) are intricately related. Sleep disturbance is a core feature of MDD cross-sectionally, as a diagnostic criterion for the disorder (American Psychiatric Association, 2000), and longitudinally, as a risk factor for both incident depression (Baglioni, et al, 2011) and depressive relapse after remission (Dombrowski, et al, 2007; Karp, et al, 2004; Paykel, et al, 1995). In addition, polysomnographic abnormalities of sleep continuity, rapid eye movement (REM) sleep, and slow wave sleep (SWS) are robust, but non-specific, biological markers in MDD (Benca, et al, 1992; Steiger and Kimura, 2010). Finally, experimental manipulation using sleep deprivation (total, partial, and REM/SWS-selective) transiently alleviates depressive symptoms, although the mechanisms underlying these effects remain unknown (Landsness, et al, 2011; Vogel, et al, 1975; Wirz-Justice and Van den Hoofdakker, 1999; Wu and Bunney, 1990).

Sleep and wakefulness are regulated by the interaction of a homeostatic sleep-wake dependent process and a circadian pacemaker (Borbely, 1982; Dijk, 2009). According to the two-process model, homeostatic sleep propensity (process S) builds during wakefulness, and dissipates during sleep (Borbely, 1982). Slow wave activity (SWA) during non-REM (NREM) sleep is a widely accepted marker of homeostatic process S that declines during NREM sleep independent of circadian phase, and is increased during recovery sleep following sleep deprivation (Dijk, 2009). In addition to SWA during NREM sleep, several studies have suggested that increases in low frequency EEG power during waking may also be a marker of homeostatic function. Multiple investigations in human and animal models have demonstrated waking EEG power increases in various low-frequency bands (~1–8Hz) over the course of sleep deprivation (Aeschbach, et al, 1997; Aeschbach, et al, 1999; Cajochen, et al, 1995; Cajochen, et al, 1999b; Cajochen, et al, 2002; Dumont, et al, 1999; Finelli, et al, 2000; Hung, et al, 2013; Leemburg, et al, 2010; Tinguely, et al, 2006; Vyazovskiy and Tobler, 2005). Additionally, increases in both waking low frequency activity (LFA) and SWA in NREM sleep are predominantly observed in frontal brain regions, suggesting a topographical susceptibility to homeostatic processes across the cortex (Cajochen, et al, 1999a; Cajochen, et al, 2002; Finelli, et al, 2000; Tinguely, et al, 2006; Werth, et al, 1997). Finally, prior studies have demonstrated that the overnight decline of spontaneous waking delta activity (1–4Hz) correlates with nocturnal SWA (Hulse, et al, 2011), and that the subsequent rise in SWA in response to sleep deprivation correlates with increases in theta activity (~5–8 Hz) during the preceding period of wakefulness (Finelli, et al, 2000; Vyazovskiy and Tobler, 2005).

Several hypotheses have been proposed to explain these clinical and experimental observations in MDD, including decrements (Borbely and Wirz-Justice, 1982) or increases (Beersma and van den Hoofdakker, 1992) in sleep homeostatic processes as potential mechanisms for depression. Prior investigations have examined homeostatic function in MDD using SWA during sleep (reviewed in (Armitage, 2007)) however, very few investigations have examined homeostatic function in MDD using waking EEG power. Two studies that examined theta activity over the course of sleep deprivation in seasonal affective disorder (SAD) demonstrated a progressive increase in waking low frequency power in

healthy subjects, which was attenuated (Cajochen, et al, 2000) or absent (Danilenko and Putilov, 2005) in SAD, suggesting altered homeostatic mechanisms in this depressive subtype. Birchler-Pedross and colleagues recently demonstrated increased LFA in MDD women relative to controls in response to extended wakefulness, with frontal LFA correlating with depression severity (Birchler-Pedross, et al, 2011). The current study sought to further examine homeostatic function in MDD using high-density EEG (hdEEG) prior to, during, and after a night of sleep. Our primary hypothesis was that the overnight change in waking LFA would be impaired in MDD subjects, suggestive of altered homeostatic function in the disorder.

2. Methods

2.1. Participants

Fourteen right-handed subjects with MDD (9 women) were drawn from a larger study of sleep homeostasis in depression. Subjects were included if samples of waking EEG recordings that were obtained prior to and following their sleep recordings were available for analysis. Diagnosis of MDD was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First, et al, 2002b). All subjects were experiencing a depressive episode at the time of the study, and did not meet criteria for a lifetime history of bipolar or psychotic disorders. MDD subjects were administered the 17-item Hamilton Rating scale for depression (Hamilton, 1960). Age and sex-matched healthy controls (HC) without personal history of current or past psychiatric disorders or family history of mood disorders were evaluated with the non-patient SCID (First, et al, 2002a). All subjects were free of psychotropic medications 6 months prior to enrollment.

All subjects provided informed consent and were instructed to maintain regular sleep-wake schedules, avoid napping, and to limit the use of caffeinated and alcoholic beverages for the duration of the study. Adherence was monitored using sleep-logs and actigraphy (Actiwatch, Mini-Mitter, Bend, OR). This study was approved by the Institutional Review Board of the University of Wisconsin-Madison.

2.2. Study design

All participants underwent in-laboratory polysomnography (PSG) prior to their experimental night, which served to acclimate participants to the laboratory environment and to rule out evidence of primary sleep disorders. PSG included electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), bilateral tibial EMG, respiratory inductance plethysmography, pulse oximetry, and a position sensor. Subjects with evidence of clinically significant sleep disordered breathing (apnea-hypopnea index >10/hr) or sleep-related movement disorder (periodic limb movement arousal index >10/hr) during overnight PSG were excluded.

On the experimental night, participants arrived at the laboratory between 19:00 and 21:00 and were outfitted with 256-channel hdEEG net (Electrical Geodesics Inc., Eugene, OR, USA). Pre-sleep (PM) waking hdEEG recordings were obtained approximately one hour prior to lights out. Subjects then slept undisturbed in the laboratory for the remainder of the night and sleep hdEEG recordings were collected. The following morning, participants were awoken after at least 7 hours of recording time. Subsequent post-sleep (AM) waking EEG recordings were collected at least 30 minutes after awakening to minimize effects of sleep inertia (Tassi and Muzet, 2000). To quantify level of alertness, participants completed a psychomotor vigilance task (PVT) immediately prior to each waking EEG recording and mean reaction time was computed for analysis (Dinges, et al, 1997). All waking and sleep

hdEEG recordings were collected with vertex referencing, using NetStation software (Electrical Geodesics Eugene, OR).

2.3. Waking EEG

During waking hdEEG data collection, subjects were comfortably seated and instructed to relax with their eyes open, fixating for 2 minutes on a target 2 meters away. EEG data were processed offline in NetStation (Electrical Geodesics) and MATLAB (Mathworks, Natick, MA), including the MATLAB plugin EEGLAB (Delorme and Makeig, 2004), as previously described (Hulse, et al, 2011). HdEEG signals were sampled at 500Hz, and data were filtered with a 0.6 Hz first order highpass filter, followed by a 59 Hz lowpass FIR Kaiser filter with stopband attenuation of 60dB and the rolloff set to 0.3 Hz. Channels were rejected using an automatic outlier detection tool (using amplitude threshold criteria) and verified by visual inspection of the data. Rejected channels were subsequently interpolated via spherical splines. Independent Component Analysis in EEGLAB was used to identify characteristic eye, muscle and cardiac artifacts for removal (Jung, et al, 2000; Makeig, et al, 1997). Any residual artifacts were excluded by visual inspection. All artifact-free segments were average-referenced and power spectra were calculated for 4-sec epochs (Welch's averaged modified periodogram with a Hamming window), resulting in a frequency resolution of 0.25 Hz. Frequency bins below 1 Hz were excluded from data analysis because of their sensitivity to low-frequency artifacts. Similarly, spectral data were analyzed up to 25 Hz to minimize influence of high-frequency artifacts.

2.4. Sleep EEG

HdEEG signals were sampled at 500 Hz, first-order high-pass filtered in NetStation (0.1Hz), downsampled to 128 Hz, band-pass filtered (2-way least-squares FIR, 1–40 Hz) in MATLAB, and average-referenced to the average scalp voltage computed in all channels. Semi-automatic artifact rejection was conducted to remove channels with high-frequency noise or interrupted contact with the scalp. To maintain congruence between spectral analysis and traditional sleep staging based on 30 second epochs, spectral analysis of NREM sleep was performed for each channel in consecutive 6-second epochs (Welch's averaged modified periodogram with a Hamming window), resulting in a frequency resolution of 0.17 Hz, consistent with prior studies from our laboratory ((Goldstein, et al, 2012; Landsness, et al, 2011; Plante, et al, 2012). To normalize SWA for tests of association with overnight change in waking LFA, for every channel and each artifact-free NREM epoch, the power of each frequency bin was divided by the total power for all bins of that channel, similar to prior investigations that have demonstrated an association between overnight change in waking LFA and sleep SWA (Hulse, et al, 2011). Sleep staging was performed by a registered polysomnographic technologist in 30-second epochs according to standard criteria (Iber, et al, 2007) using Alice® Sleepware (Philips Respironics, Murrysville, PA) based on 6 EEG channels at approximate 10–20 locations (F3, F4, C3, C4, O1, and O2) re-referenced to the mastoids, sub-mental EMG and EOG.

2.5. Statistics

Clinical, polysomnographic, PVT, and spectral measures between groups were compared using unpaired t-tests. Changes in overnight spectral power and PVT values from PM to AM within groups were compared using paired t-tests. To increase the signal-to-noise ratio, all hdEEG analyses were restricted to 185 channels overlying the scalp (Goncharova, et al, 2003). Global sleep and waking power was defined as the average of these 185 channels. To limit spurious findings due to multiple comparisons, overnight changes in global waking power spectra were considered significant if t-values corresponded to $p < 0.05$ for greater than 3 contiguous 0.25Hz bins. Linear correlation was used to assess the relationship between the overnight change in waking EEG activity and normalized SWA (1–4.5Hz)

during sleep. To limit spurious correlations due to outliers, correlations were restricted to data ± 2.5 standard deviations from the mean. Because prior reports have found significant correlations between waking low frequency activity and sleep SWA using all-night data (Hulse, et al, 2011), as well as specifically in the first NREM period (NREM1) (Finelli, et al, 2000), correlations with both all-night and NREM1 SWA were evaluated. Statistical non-parametric mapping with suprathreshold cluster testing was utilized to correct for multiple comparisons of topographic data (within and between group t-tests and channel-by-channel linear correlations) in MATLAB using a t-value threshold equivalent to an $\alpha < 0.05$ for the uncorrected comparisons (Nichols and Holmes, 2002). All other comparisons and correlations were conducted in Statistica 6.0 software package (StatSoft, Tulsa, OK) and MATLAB (The MathWorks, Inc., Natick, MA).

3. Results

3.1. Clinical and Polysomnographic (PSG) Variables

MDD and HC subjects were young adults (MDD: 22.4 ± 2.8 , range 19–27 years; HC: 22.1 ± 2.3 , range 18–28 years) (Table 1). Depression severity was mild to moderate (HRSD-17 score 16.2 ± 5.3 , range 8–25) among MDD participants. MDD subjects demonstrated a greater percentage of REM sleep relative to controls (25.8% vs. 19.4%; $p=0.01$) consistent with prior literature (Benca, et al, 1992). Otherwise, there were no significant differences between groups on standard PSG measures or global SWA.

3.2. Waking EEG activity

HC subjects demonstrated an overnight decline in global waking power in both a low frequency activity (LFA) range (3.25–6.25Hz) and a broad beta range (11.75–21.5Hz) (Figure 1). MDD subjects, however, did not demonstrate a significant global overnight decline in waking LFA power, and had an attenuated overnight decline in beta power (14.75–15.75Hz)(Figure 1). There were no significant differences in global waking power between MDD and HC for any frequency band at either the PM or AM time point (data not shown).

Topographic analysis of waking EEG power demonstrated that the overnight decline in LFA (3.25–6.25 Hz) among controls was most prominent in bilateral frontal and left parietooccipital channels, whereas pre-to-post sleep decline in beta activity (11.75–21.5Hz) occurred globally across the scalp (Figure 2). Conversely, there were no significant topographic changes in overnight LFA among MDD subjects (Figure 2). Moreover, the overnight topographic decline in beta activity was attenuated in MDD subjects, such that it was localized to centroparietal regions (Figure 2). Although visual inspection suggested potentially increased LFA among HC relative to MDD at the PM timepoint, between group topographic comparisons of waking power demonstrated no statistically significant differences in waking LFA or beta activity between HC and MDD subjects at either PM or AM timepoint (Figure 2).

There were no significant differences in PVT mean reaction time observed between PM and AM for either group, nor between groups at either time point ((MDD: PM 300.4 ± 47.5 msec, AM 303.5 ± 57.3 msec; HC: PM 290.2 ± 21.8 msec, AM 295.2 ± 27.6 msec; $p=0.44-0.75$), suggesting waking EEG results were not confounded by levels of vigilance.

3.3. Relationship between overnight change in low frequency waking EEG activity and sleep slow wave activity

Among HC, the overnight change in global LF did not significantly correlate with either all-night SWA ($r=-0.21$, $p=0.51$) or SWA from NREM1 ($r=-0.41$, $p=0.17$). Topographically,

however, HC demonstrated a significant negative correlation with overnight change in LFA and SWA in frontal channels, whereby greater sleep SWA (both all-night and NREM1) correlated with a greater decline in waking LFA (Figure 3). Conversely, MDD subjects did not demonstrate either significant global (all-night; $r=0.44$, $p=0.11$; NREM1: $r=0.25$, $p=0.39$) or topographic (Figure 3) correlations between overnight change in waking LFA and sleep SWA.

3.4. Additional exploratory analyses

Two additional analyses were performed to substantiate the absence of a relationship between overnight change in waking LFA and sleep SWA among MDD participants. First, since prior literature has suggested patients with MDD can have a shift of SWA such that it occurs predominantly in the second NREM period (NREM2)(Kupfer, et al, 1990), the relationship between overnight change in LFA (3.25–6.25Hz) and SWA from NREM2 among MDD participants was examined; however, no significant global ($r=-0.13$, $p=0.67$) or topographic (data not shown) correlations between these variables were observed.

Moreover, because prior investigations have demonstrated correlations between sleep SWA and waking EEG activity across variable waking low frequency bands from 1–8Hz, the use of a defined LFA range (3.25–6.25 Hz) that was derived from globally significant decreases from PM to AM in the current HC group could have inadvertently missed pertinent topographic correlations among MDD subjects. Therefore, to minimize the chance of type II error, we conducted a secondary topographic analysis to explore correlations of SWA with the overnight change in waking power across the entire frequency range from 1–8 Hz (Supplementary Figure 1). In this analysis, for every channel in which there was a significant correlation ($p<0.05$) between SWA and one 0.25Hz bin of waking power within the range of 1–8Hz, the channel was denoted along with the direction of the correlation (a negative correlation corresponding to greater sleep SWA associated with a greater overnight decline of waking power). To further liberalize the analysis to mitigate any reasonable chance of failing to find a significant association with overnight decline in waking LFA and sleep SWA among MDD, these data were uncorrected for multiple comparisons (e.g. statistical non-parametric mapping with suprathreshold cluster testing was not applied). Using this exploratory analysis, large topographic negative correlations between the overnight decline in waking power and SWA were observed among HC subjects, most prominently in bilateral frontal and parietal regions, both utilizing all-night and NREM1 SWA (Supplemental Figure 1). However, even using this liberal *post hoc* analysis, there were no negative correlations between SWA and overnight change in waking EEG activity among MDD subjects observed anywhere on the scalp, and the dispersed correlations observed in frontal, parietal, and occipital regions were exclusively in the opposite (positive) direction from those observed in HC (Supplementary Figure 1).

We also examined the relationships between overnight change in waking beta activity and sleep SWA, as well as associations with depression severity and nocturnal REM sleep percentage with waking EEG power on an exploratory basis. There were no significant correlations (global or topographic) between overnight change in waking beta activity (11.75–21.5Hz) and sleep SWA (all-night and NREM1) for either HC or MDD groups. There were also no significant correlations (global or topographic) between overnight change in LFA (3.25–6.25Hz) or beta activity and nocturnal REM sleep percentage. Among MDD subjects, there were no significant correlations (global or topographic) for LFA or beta activity (overnight change, or PM/AM spectral power) and HRSD score.

4. Discussion

Our findings demonstrate an overnight decline in waking EEG low frequency activity (LFA) in healthy controls (HC), but not in an age and sex-matched group of subjects with unipolar major depressive disorder (MDD). Moreover, this overnight decline in LFA in HC subjects correlated with increased frontal slow wave activity (SWA) during sleep, however, there was no such corresponding correlation among MDD subjects. In addition, HC subjects demonstrated an overnight decline in waking EEG beta power across the entire scalp, which was restricted to a smaller cortical area in MDD subjects. Strengths of this investigation include lack of confounding psychotropic medications and the use of hdEEG for spectral analysis, which allowed for topographic analyses of the data.

These results are consistent with prior investigations that have demonstrated the overnight change in waking EEG LFA after a night of sleep may reflect sleep homeostasis in healthy subjects (Hulse, et al, 2011). Moreover, these results are congruent with recent work from our laboratory that has demonstrated the pre- to post-sleep decline in waking auditory evoked potential (AEP) amplitude correlates with sleep SWA in HC, but not in MDD subjects (Goldstein, et al, 2012). Taken together, these data suggest absence of overnight changes in both waking EEG LFA and AEP amplitude may reflect abnormal sleep homeostatic mechanisms in MDD.

There are various factors that may contribute to the absence of an overnight decline in waking LFA and/or the lack of correlation of this measure with SWA during sleep among MDD subjects. MDD is a heterogeneous disorder (Krishnan and Nestler, 2010), and thus it is certainly plausible that uncontrolled covariates and/or unrecognized subgroups may be responsible for the findings of this investigation. One possible factor that could mediate our findings is gender, since significant sex-related effects on sleep SWA in MDD have been described, with increases in SWA among depressed women and decreases in SWA among depressed men, relative both to each other and to healthy comparison subjects (Armitage, et al, 2000a; Armitage, et al, 2000b; Armitage, 2007; Frey, et al, 2012a; Frey, et al, 2012b; Plante, et al, 2012). In addition, women with MDD have demonstrated an enhanced homeostatic response in sleep deprivation paradigms, evidenced by increased SWA during recovery sleep and waking low frequency activity, particularly in frontal EEG derivations (Armitage, 2007; Birchler-Pedross, et al, 2011; Frey, et al, 2012a; Frey, et al, 2012b). Taken together, these data suggest that MDD women may live with or tolerate an elevated level of homeostatic sleep pressure relative to men. However, because this study is underpowered to examine the role of sex on overnight changes in waking EEG in MDD, future studies that employ adequately powered designs to explore sex-related differences in overnight change in waking LFA in MDD are indicated.

Our experimental design was cross-sectional, and thus we are not able to determine whether absence of overnight changes in waking EEG observed in MDD are a state or trait process. The lack of a correlation between waking EEG power and depression severity may support the notion that alterations in these measures are a trait marker in MDD, however, it is also plausible that our MDD subjects did not have sufficient variability in HRSD scores (e.g. most had relatively moderate depression), to detect a correlation. In addition, correlations of waking frontal low frequency activity with depression severity have been observed in studies that have utilized extended wakefulness paradigms (Birchler-Pedross, et al, 2011), and thus the dynamics of the waking EEG, either across the day or during extended wakefulness, may be a more fruitful correlate with depressive symptoms than overnight changes in waking LFA, as evaluated in this study. In this context, it is notable that recent investigations have demonstrated local, experience-dependent changes in waking theta activity during prolonged wakefulness that correlate with similar local changes in sleep

SWA in healthy subjects, suggesting sleep is locally regulated by the amount of experience-dependent plasticity during wakefulness (Hung, et al, 2013). Interventions that rapidly alleviate depressive symptoms in MDD, such as sleep deprivation and ketamine, result in changes that reflect increases in synaptic strength, including increased slow wave amplitude and slope, as well as increased brain-derived neurotrophic factor (Duncan, et al, 2012; Gorgulu and Caliyurt, 2009; Kavalali and Monteggia, 2012). Given the findings of this study, further research is warranted to clarify how alterations in local, experience-dependent waking LFA may reflect specific sleep-related alterations in synaptic plasticity in MDD.

5. Limitations

A primary limitation of our study is an inability to definitively segregate overnight changes in the waking EEG that may occur due to homeostatic and/or circadian factors. Prior investigations that have utilized extended wakefulness paradigms have demonstrated that increases in waking EEG activity in the 1–8Hz range reflect both the duration of time awake (i.e., homeostatic influence) and circadian modulation (Aeschbach, et al, 1997). However, low frequency activity in frontal derivations appears to be more strongly determined by homeostatic processes than in parieto-occipital regions (Cajochen, et al, 1999b; Cajochen, et al, 2002), suggesting relative contributions of circadian and homeostatic factors on the EEG vary across the cortex. Our finding of significant correlations between overnight change in LFA and sleep SWA in frontal regions among HC supports the notion that frontal waking LFA is more strongly related to homeostatic than circadian factors. In addition, both HC and MDD participants maintained regular sleep-wake patterns prior to the study, and both groups had similar total sleep times and latency to sleep onset in the laboratory, making it less likely that one group was significantly phase advanced or delayed relative to the other. However, since both homeostatic factors and circadian rhythms have been hypothesized to be aberrant in MDD (Borbely, 1987; Germain and Kupfer, 2008), further research that utilizes sleep deprivation and/or constant routine/forced desynchrony protocols are indicated to explore further the influence of these factors on overnight changes in waking EEG in MDD.

In conclusion, we have demonstrated that healthy young adult subjects exhibit a significant overnight decline in waking low frequency EEG activity that correlates with frontal slow wave activity during sleep. A comparable relationship, however, was not found in MDD subjects of similar age and sex. These preliminary findings suggest that altered overnight modulation of waking low frequency EEG activity in MDD may reflect altered sleep homeostasis in the disorder. Further research is indicated to explore the dynamics of waking LFA in MDD, as well as the functional significance and clinical implications of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The NIMH had no further role in the study design, data collection, analysis and interpretation of the data, and the decision to submit the paper for publication.

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Figure 1.

Overnight decline in EEG waking power (eyes open) from PM to AM for A) Group average of spectral power at each timepoint for HC and B) MDD subjects. Global power derived as the average of 185 channels overlaying the scalp. Lower panel denotes significant 0.25Hz bins with $p < 0.05$ after paired t-test.

Figure 2.

Topographic waking EEG A) low frequency activity (LFA; 3.25–6.25Hz) and B) beta activity (11.75–21.5Hz) for HC and MDD subjects (units: $\mu V^2/Hz$). Horizontal columns denote topographic comparisons within group for overnight PM to AM change in HC and MDD subjects, using channel-by-channel paired t-test. Vertical columns denote channel-by-channel unpaired t-tests for between group comparisons. T-values for paired and unpaired tests plotted at each corresponding channel. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test.

Figure 3.

Correlation between overnight change in waking LFA (3.25–6.25 Hz) and sleep slow wave activity (SWA) in HC and MDD subjects. A) Topographic correlations of change in waking LFA with all-night (AN) and NREM1 SWA. White dots denote significant channels after statistical non-parametric mapping with suprathreshold cluster test. Note the frontal correlation between overnight change in waking LFA and sleep SWA among HC subjects and lack of an association among MDD participants. Red circle denotes channel Fp1. B) Representative scatterplot and correlation from an individual frontal channel (Fp1) using all-night SWA data. Closed black squares denote HC; open green circles indicate MDD subjects. Note significant correlation among HC but not MDD (HC: $r = -0.56$; $p = 0.04$; MDD: $r = 0.14$; $p = 0.63$). Similar significant correlations for HC occurred at both Fp1 and Fp2, examining both AN and NREM1 SWA, however, there were no significant correlations among MDD (data not shown).

Table 1

Demographic, clinical, and polysomnographic data

	HC	MDD	p*
	(N=14)	(N=14)	
Sex (male/female)	5/9	5/9	-
Age (years)	22.1 (2.3)	22.4 (2.8)	0.77
HRSD-17	-	16.2 (5.3)	-
TST (min)	427.3 (29.6)	411.0 (54.9)	0.34
WASO (min)	22.2 (18.2)	24.5 (22.6)	0.76
AI (#/hr)	9.2 (4.3)	11.0 (4.5)	0.30
SE (%)	92.0 (6.6)	90.5 (6.9)	0.56
SOL (min)	16.6 (18.7)	18.1 (12.6)	0.80
N1 (%)	5.9 (3.4)	6.6 (4.4)	0.65
N2 (%)	56.6 (7.3)	50.9 (9.6)	0.09
N3 (%)	18.1 (5.3)	16.7 (9.8)	0.64
SWA ($\mu V^2/Hz$)	28.5 (19.1)	24.2 (12.5)	0.49
REM (%)	19.4 (7.0)	25.8 (5.2)	0.01
REML (min)	83.0 (34.5)	72.7 (39.2)	0.47

MDD, major depressive disorder; HC, healthy control; HRSD-17, Hamilton Rating Scale for Depression (17-item); TST, total sleep time; WASO, wake after sleep onset; AI, arousal index; SE, sleep efficiency (TST/time in bed); SOL, sleep onset latency; N1/2/3, NREM stage 1/2/3 (% of TST); REM, stage REM (% of TST); REML, REM latency (time from sleep onset to first REM sleep epoch); SWA, global slow wave activity (EEG power in 1 – 4.5 Hz range average 185 channels); Values are displayed as mean (standard deviation).

* p-value derived using 2-tailed, independent samples t-tests. Significant items marked in bold.