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Altered slow wave activity in major depressive disorder with hypersomnia: a high density EEG pilot study

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Abstract

Hypersomnolence in major depressive disorder (MDD) plays an important role in the natural history of the disorder, but the basis of hypersomnia in MDD is poorly understood. Slow wave activity (SWA) has been associated with sleep homeostasis, as well as sleep restoration and maintenance, and may be altered in MDD. Therefore, we conducted a post-hoc study that utilized high density electroencephalography (hdEEG) to test the hypothesis that MDD subjects with hypersomnia (HYS+) would have decreased SWA relative to age and sex-matched MDD subjects without hypersomnia (HYS-) and healthy controls ($n=7$ for each group). After correcting for multiple comparisons using statistical non-parametric mapping, HYS+ subjects demonstrated significantly reduced parieto-occipital all-night SWA relative to HYS- subjects. Our results suggest hypersomnolence may be associated with topographic reductions in SWA in MDD. Further research using adequately powered prospective design is indicated to confirm these findings.

Keywords

sleep; depression; spectral analysis

1. Introduction

Sleep disturbance commonly occurs in major depressive disorder (MDD) and plays an important role in the natural history of the disorder. Diagnostic criteria for sleep-related complaints associated with MDD include either insomnia, broadly defined as difficulty initiating or maintaining sleep despite adequate opportunity, or hypersomnia, defined as excessive sleepiness or increased total sleep time (American Psychiatric, 2000). Self-report of insomnia and hypersomnia occurs in roughly eighty and thirty percent of MDD patients, respectively (Armitage, 2007; Kaplan et al., 2009). Although a sizeable literature has examined the role of insomnia in MDD (Baglioni et al., 2011), relatively little research has examined the role of hypersomnia in the disorder. Since hypersomnia increases the risk of incident depression (Breslau et al., 1996; Roberts et al., 2000), is a highly treatment-resistant symptom (Worthington et al., 1995; Zimmerman et al., 2005), increases the risk of

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depressive relapse (Kaplan et al., 2009; Kaplan et al., 2011), and increases the risk of suicide (Goldstein et al., 2008), further research regarding the epidemiology and pathophysiology of hypersomnia in MDD is a crucial, yet neglected area in mood disorders research.

Polysomnography has been widely employed to study sleep in MDD, demonstrating alterations in sleep continuity, rapid eye movement (REM) sleep, and slow wave sleep (SWS) (Benca et al., 1992; Steiger and Kimura, 2010). Slow wave activity (SWA), the power density of low frequency delta activity during sleep, more accurately reflects slow oscillations than traditional sleep staging, and has been established as a marker of sleep homeostasis that is also associated with sleep restoration, maintenance, and quality (Borbély, 1982; Achermann et al., 1993; Dijk 2009). Several investigations have examined SWA in depression; however, findings have not been consistent across studies, with decreases (Borbély et al., 1984; Hoffman et al., 2000), increases (Schwartz et al., 2001), and non-significance (Mendelson et al., 1987; Armitage et al., 1992) reported, with differential effects of age and sex (Armitage et al., 2000a; Armitage et al., 2000b; Armitage et al., 2001). Notably, spectral analysis in prior studies was limited to central EEG derivations, and none examined SWA in the context of clinical sleep disturbance.

Therefore, the primary aim of this study was to examine SWA in MDD segregated into subtypes based on the presence or absence of hypersomnia. This study utilized high density electroencephalography (hdEEG), which yields superior spatial resolution compared to standard montages when examining SWA topography. Because reductions in SWS/SWA have been described in other central nervous system disorders associated with hypersomnolence, including idiopathic hypersomnia (Sforza et al., 2000) and paramedian thalamic stroke (Bassetti et al., 1996; Fonseca et al., 2011), we hypothesized that MDD subjects with hypersomnia would demonstrate decrements in all-night SWA relative to controls and MDD subjects without hypersomnia.

2. Methods

2.1 Subjects

All subjects were right-handed, free of psychotropic medications for 6 months, and drawn post-hoc from larger studies of sleep homeostasis in neuropsychiatric disorders, conducted at the University of Wisconsin-Madison. MDD was diagnosed via the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) (First et al., 2002a). Healthy comparison subjects were evaluated with the non-patient SCID (First et al., 2002b) to rule out current or past psychiatric disorders. All MDD subjects were unipolar, and had no history of psychosis, significant medical or neurological condition, or active drug/alcohol dependence. Global depression severity was evaluated with the clinician-administered Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). In addition, subjects were administered either the Beck Depression Inventory, version II (BDI II) (Beck et al., 1996) or the Inventory of Depressive Symptomatology (IDS-C₃₀) (Rush et al., 2000). Hypersomnia was defined as either subjective report of >10 hours of sleep per day in a 24 hour period (IDS-C₃₀, Item #4) or “sleeping a lot more than usual” (BDI-II, Item #16), as these items have demonstrated the most favorable balance of sensitivity/specificity for inter-episode hypersomnia, as well as predictive value for subsequent depression among standard psychometric measures (Kaplan et al., 2011). Comparison subjects [MDD subjects without hypersomnia (HYS–) and healthy controls (HC)] were selected to be age and sex-matched to MDD subjects with hypersomnia (HYS+).

All subjects provided informed consent and were instructed to maintain regular sleep-wake schedules, avoid napping, and to limit the use of caffeinated or alcoholic beverages during the study. Adherence was monitored using sleep-diaries and wrist-worn actigraphy

(Actiwatch, Mini-Mitter, Bend, OR). This study was approved by the Institutional Review Board of the University of Wisconsin-Madison.

2.2 hdEEG Polysomnography

All subjects underwent in-laboratory hdEEG polysomnography (PSG) that utilized 256-channel hdEEG (Electrical Geodesics Inc., Eugene, OR) including standard monitoring with electrooculogram (EOG), sub-mental and tibial electromyogram (EMG), electrocardiogram (ECG), respiratory inductance plethysmography, pulse oximetry, and a position sensor. After set-up, subjects slept undisturbed in the laboratory beginning within one hour of their usual bedtime. The following morning, participants were woken after at least 7 hours of sleep. Sleep hdEEG recordings were collected with vertex-referencing, using NetStation software (Electrical Geodesics Inc., Eugene, OR) and DC amplifiers with 200Hz analog low-pass filters. To optimize signal-to-noise, hdEEG processing and analyses were restricted to the 185 channels overlaying the scalp (Goncharova et al., 2003). Subjects with clinically significant sleep-disordered breathing (apnea-hypopnea index > 10/hr) or sleep-related movement disorders (periodic limb movement-arousal index > 10/hr) were excluded. Sleep staging was performed in 30-second epochs according to standard criteria (Iber et al., 2007) using 6 bipolar mastoid-referenced channels (F3, F4, C3, C4, O1, and O2), sub-mental EMG, and EOG with Alice® Sleepware (Philips Respironics, Murrysville, PA).

2.3 Spectral Analysis

All-night hdEEG recordings were sampled at 500 Hz, first-order high-pass filtered (Kaiser type, 0.6 Hz), downsampled to 128 Hz, band-pass filtered (2-way least-squares FIR, 1–40 Hz), and average-referenced. Semi-automatic artifact rejection was conducted to remove epochs with high-frequency noise or interrupted contact with the scalp for the majority of the recording, and visual inspection was performed to remove channels with noise across all frequencies. Spectral analysis was performed for each channel in consecutive 6-second epochs (Welch's averaged modified periodogram with a Hamming window) for all epochs of NREM sleep. SWA was defined as power density in 1–2Hz range.

2.4 Statistics

Polysomnographic variables and global SWA averaged across all scalp electrodes were compared using ANOVA with post-hoc *t* tests (2-tailed) with Bonferroni correction for multiple comparisons. Given the exploratory nature of the study, post-hoc *t*-tests were performed for any variable with corresponding $p < 0.10$ from overall ANOVA. Topographic differences in all-night SWA between groups were examined using channel-by-channel 2-tailed, unpaired *t* tests. Because of the relatively small sample size, all-night SWA was considered to be the primary outcome measure of interest to limit sampling bias of EEG data, with exploratory analyses of differences of SWA by sleep cycle. To correct for multiple comparisons of topographical hdEEG data, statistical non-parametric mapping with suprathreshold cluster tests (STCT) was utilized (Nichols et al., 2002). Statistical analyses were performed using MATLAB (The MathWorks Inc., Natick, MA) and STATISTICA (StatSoft Inc., Tulsa, OK).

3. Results

Participant characteristics and polysomnographic data are presented in Table 1. Each group consisted of age and sex-matched subjects (4/7 female). Three HYS+ subjects and 1 HYS– subject met criteria for atypical depression. No MDD subjects were characterized as having a seasonal pattern to their illness. Depression severity as measured by HRSD was not significantly different between HYS+ and HYS– MDD groups ($t = 0.89$, $p = 0.39$). One-way ANOVA demonstrated an effect of sleep onset latency ($F_{2,18} = 4.17$, $p = 0.03$), whereby

HYS+ subjects had significantly increased sleep onset latency compared to healthy controls ($p = 0.04$). Otherwise, no significant differences in polysomnographic variables between groups were observed.

All-night global SWA (average of 185 channels) was not significantly different among groups (Table 1). There was no significant correlation between depression severity, as measured by the HRSD-17, and global SWA among depressed subjects ($r = -0.08$, $p = 0.78$). To explore global SWA across the night, a 3 (group) $\times$ 3 (NREM cycle) mixed model ANOVA was utilized. A main effect was observed for NREM cycle ($F_{2,26} = 19.56$, $p < 0.0001$); however, no significant main effect of group ($F_{2,13} = 1.45$, $p = 0.27$), nor group $\times$ cycle interaction ($F_{4,26} = 1.26$, $p = 0.31$) was observed. Post-hoc analysis demonstrated typical decline of global SWA for all subjects from NREM1 to NREM2 ($p = 0.002$) and NREM3 ($p < 0.0001$).

Topographic analyses revealed significant decreases in parieto-occipital all-night SWA for HYS+ relative to both HYS- and controls (Figure 1). Additionally, all-night SWA was decreased right-frontally in HYS+ compared to HYS-. HYS- demonstrated bilateral frontal increases in all-night SWA relative to HC. However, only left parieto-occipital decreases in all-night SWA in HYS+ relative to HYS- remained significant after correcting for multiple comparisons with statistical non-parametric mapping (Figure 1). Exploratory analyses demonstrated similar, but attenuated topographic findings for an expanded SWA frequency range (1–4.5Hz) and across NREM cycles (data not shown).

4. Discussion

This study demonstrates parieto-occipital decreases in all-night SWA in MDD subjects with hypersomnia. These findings are important in the context of mood and sleep disorders research because they suggest SWA is differentially regulated within sleep-related subtypes of MDD, and that the clinical sleep complaint of hypersomnolence may be a marker of decreased SWA in the disorder.

The literature examining SWA in MDD has been inconsistent, with decreased (Borbély, et al., 1984; Hoffman et al., 2000), increased (Schwartz et al., 2001), and equivalent (Mendelson et al., 1987; Armitage et al. 1992) SWA demonstrated in depressed relative to control subjects. As a result, conflicting hypotheses regarding the role of slow waves in depression have been posited. On one hand, the S-deficiency hypothesis, which suggests MDD is related to deficient build-up of sleep homeostatic processes during wakefulness with subsequent reductions in SWA during sleep (Borbély and Wirz-Justice 1982; Borbély 1987), is supported by studies that demonstrate reduced SWA in MDD. However, studies that demonstrate increases in SWA in depressed subjects support the notion that slow waves may in fact be depressogenic, and it is the acute reduction of SWA that is associated with antidepressant response (Beermsma et al., 1992; Landsness et al., 2011). Given the results of this study, it is noteworthy that prior studies have not accounted for type of sleep disturbance in their study design, and thus, although speculative, it is possible that inconsistencies in the literature may be in part related to failure to account for heterogeneous sleep disturbances among subjects. Moreover, the decrements in SWA observed in hypersomnolent MDD subjects in this study suggest that the S-deficiency hypothesis may potentially be more applicable to this subset of depressives than those without hypersomnolence.

Slow waves play an important role in sleep restoration and maintenance, and as such play a role in several pathologic states associated with hypersomnolence (Dijk, 2009). Decrements in SWS/SWA in central nervous system disorders such as idiopathic hypersomnia and

hypersomnolence secondary to paramedian thalamic stroke have been described (Sorfza et al., 2000; Bassetti et al., 1996; Fonseca et al., 2011). Additionally, selective slow wave deprivation increases daytime sleepiness as measured by the multiple sleep latency test (MSLT), the most commonly used objective measure to quantify daytime somnolence (Dijk et al., 2006). Notably, prior studies that have utilized the MSLT have found this test is unable to distinguish hypersomnolent mood disordered subjects from healthy controls (Vgontzas et al., 2000; Billiard et al., 1994; Dolenc et al., 1996; Nofzinger et al., 1991). However, decreased SWS in hypersomnolence associated with chronic dysthymia has been reported (Dolenc et al., 1996), which is congruent with the results of the present study, and suggests that decrements in slow waves during sleep may be related to the subjective report of hypersomnolence in mood disorders.

Although reductions in SWA are not specific to hypersomnia associated with MDD, the topography of SWA in other disorders of hypersomnolence has not been studied. Thus, it is plausible that different topographic patterns of SWA may segregate disorders associated with hypersomnia, but this is currently highly speculative. Future studies that apply hdEEG to other disorders of excessive sleepiness would help clarify whether regional alterations in SWA can distinguish disorders of hypersomnolence from one another.

Despite the lack of directly comparable studies that examine MDD segregated by clinical sleep disturbance or that utilize hdEEG, the primary finding of this investigation is consistent with literature that has examined atypical depression (AD), a subtype of depression that is frequently (although not exclusively) associated with hypersomnia (Stewart et al., 2007; American Psychiatric Association, 2000). 99mTc-HMPAO SPECT studies have demonstrated increased perfusion in AD relative to melancholic depressives in extended networks involving brain frontal, temporal, and parietal areas including regions linked to motor and sensorimotor functions and to the association cortices (Pagani et al., 2007; Fountoulakis et al., 2004). Additionally, AD subjects have a reversed pattern of visual evoked potentials relative to those with melancholia, suggesting differential physiologies in the occipital cortex (Fotiou et al., 2003). Finally, AD is not associated with reductions in occipital γ -aminobutyric acid, which is found in undifferentiated and melancholic MDD (Sanacora et al., 2004). Notably, however, these studies of AD must be interpreted with caution in the context of this investigation since none examined SWA, most did not report rates of hypersomnolence in AD cohorts, and the majority of subjects in the current study did not meet criteria for AD.

There are strengths and limitations of this study that merit discussion. Primary strengths include age and sex-matching of subjects, lack of confounding psychotropic medications, and the use of hdEEG for spectral analyses allowing for high-resolution topographic analysis of SWA. Limitations include a retrospective design in which subjects were drawn post-hoc from larger studies on SWA in neuropsychiatric disorders. As a result, not every subject completed the same psychometric scales to quantify hypersomnolence. Subjects did not have an adaptation night in the sleep laboratory, which may have affected results, if groups were differentially affected by first-night effects. Also, subjects were not allowed to sleep ad libitum, and thus their sleep in the laboratory may be shorter than their usual night of sleep, particularly for subjects with hypersomnia. However, it is noteworthy that prior studies of hypersomnolent mood disordered subjects have similarly demonstrated total sleep times that are not prolonged compared to healthy subjects when evaluated with polysomnography, despite subjective report of increased total sleep time, suggesting a discrepancy between subjective and objective sleep time in these patients (Kaplan and Harvey, 2009). Moreover, because the majority of SWA occurs in the first portion of the night, even if subjects had slept longer in the morning if allowed, it is unlikely that doing so would have increased SWA appreciably. It is additionally possible that hypersomnolent

MDD subjects may have had brief occult naps/microsleeps that were not evident with sleep logs/actigraphy on the day of their study that may have artificially decreased SWA (Werth et al., 1996). Subjects were young adults, and thus, results may not be applicable to middle-aged or older subjects with MDD, as it has been suggested alterations in SWA in MDD are more apparent in younger cohorts, and there are a number of structural and functional changes that occur during adolescence continue into young adulthood (Armitage, 2007; Paus et al., 2008). Severity of MDD was mild to moderate, and thus results may not be broadly applicable to more severely depressed patients. Also, given the pilot nature of this study, sample size may have resulted in inadequate power to detect differences in SWA between groups, particularly in regions in which significant differences did not remain after controlling for multiple comparisons.

There are also limitations of spectral analysis performed that affect interpretation of this study. Analysis of SWA was limited to SWA averaged across the night and for individual sleep cycles. The exponential decay of SWA was not analyzed due to small sample size, and thus, future studies with a larger number of subjects are required to examine this variable. Additionally, analysis was limited to NREM sleep, and thus alterations in REM sleep, such as increased REM density (Benca et al., 1992; Steiger and Kimura, 2010), and their relationship to hypersomnolence in MDD is unknown. Furthermore, other physiologic alterations that have been connected with hypersomnolence such as depletion of catecholamines were not considered, and their effects on hypersomnolence in MDD remain unclear (Meyers et al., 2010). In addition, the subjective severity of co-morbid insomnia was not rigorously evaluated with standardized instruments in any group, and despite similar polysomnographic measures of sleep latency and continuity between hypersomnolent and non-hypersomnolent depressives, this unmeasured co-variate may have potentially affected findings. Finally, due to the cross-sectional design of this investigation, it is not clear if alterations in SWA reflect a state or trait-marker for hypersomnolence in MDD (Hatzinger et al., 2004).

It has long been appreciated that sleep and MDD are intimately linked; however, previous hypotheses have not been able to fully explain all aspects of sleep alterations in depression, likely in part due to heterogeneity of the disorder (Tsuno et al., 2005; Krishnan et al., 2010). This investigation suggests that presence or absence of hypersomnolence in MDD may be a useful clinical marker associated with alterations in slow wave activity in the disorder. Further adequately powered prospective research that more rigorously examines the role of clinical sleep disturbance in MDD may potentially help develop more comprehensive theoretical models for the disorder, as well as more targeted therapeutic modalities.

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Figure 1. Topographical comparison of all-night SWA (EEG power in 1–2Hz range) between groups. White dots represent channels with significant group differences following statistical non-parametric mapping with a suprathreshold test.

Table 1

Demographic, clinical, and polysomnographic data

	HYS+ (N = 7)	HYS- (N = 7)	CON (N = 7)	Overall ANOVA		<i>t</i> tests*		
				df	F	p	1 vs. 2 3	2 vs. 3
Sex (m/f)	3/4	3/4	3/4	--	--	--	--	--
Age (years)	22.43 (2.1)	21.29 (2.3)	22.00 (1.3)	2,18	0.63	0.55		
HRSD-17	17.57 (5.1)	15.00 (5.7)	--	--	--	--	0.39	--
TST (min)	376.29 (74.1)	346.43 (36.3)	395.07 (47.0)	2,18	1.40	0.27		
WASO (min)	48.36 (31.7)	72.57 (50.7)	35.79 (27.0)	2,18	1.71	0.21		
AI (#/hr.)	10.27 (5.4)	10.94 (6.3)	5.03 (2.8)	2,18	2.88	0.08	1.00	0.13
SE (%)	82.80 (10.2)	80.36 (10.7)	89.71 (7.6)	2,18	1.80	0.19		
SOL (min)	29.79 (20.1)	14.00 (10.9)	8.86 (8.8)	2,18	4.17	0.03	0.15	1.00
N1 (%)	9.77 (3.9)	16.84 (11.8)	6.81 (3.5)	2,18	3.37	0.06	0.28	1.00
N1 (min)	36.71 (18.6)	56.50 (35.2)	25.86 (10.8)	2,18	2.98	0.08	0.41	1.00
N2 (%)	59.34 (9.3)	51.30 (6.6)	59.89 (7.0)	2,18	2.70	0.09	0.20	1.00
N2 (min)	224.43 (59.1)	178.36 (30.8)	236.64 (35.4)	2,18	3.48	0.05	0.19	1.00
N3 (%)	13.07 (6.2)	19.10 (6.1)	17.29 (6.6)	2,18	1.70	0.21		
N3 (min)	47.07 (19.4)	66.86 (24.5)	67.50 (24.7)	2,18	1.78	0.20		
REML (min)	165.71 (93.3)	133.57 (100.4)	116.93 (37.0)	2,18	0.64	0.54		
REM (min)	68.21 (34.4)	44.93 (30.3)	65.50 (29.7)	2,18	1.14	0.34		
REM (%)	17.81 (7.1)	12.76 (8.1)	16.01 (5.9)	2,18	0.92	0.42		
SWA (1-2Hz)	28.85 (13.0)	51.95 (28.1)	33.53 (10.2)	2,18	2.96	0.08	0.10	1.00
								0.25

HYS+, depressed with hypersomnia; HYS-, depressed without hypersomnia; HC, healthy control; HRSD-17, Hamilton Rating Scale for Depression (17-item); TST, total sleep time; WASO, wake (time) after sleep onset; AI, arousal index; SE, sleep efficiency; SOL, sleep onset latency; N1/2/3, NREM stage 1/2/3 (min. and % of TST); SWA, slow wave activity (average EEG power in 1–2 Hz range); REML, REM latency; REM, stage REM (% of TST)

Values are displayed as group mean (standard deviation).
*
p-value for post-hoc *t* tests with Bonferroni correction