Examining the effects of sleep delay on depressed males and females and healthy controls

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SUMMARY

Individuals with major depressive disorder typically exhibit sleep electroencephalograpy abnormalities which have been shown to vary by sex. Recent research has shown that depressed males display deficits in slow wave sleep and delta electroencephalograph (EEG) activity that are not apparent in depressed females. This may suggest that males and females with depression vary with respect to their homeostatic regulation of sleep. Utilizing archival data, the present study examined the effects of a 3-h sleep delay, which represents a mild sleep challenge, on slow wave activity in healthy controls and individuals with depression. All participants slept in the laboratory for three sequential nights. On the third night in the laboratory, the participants' bedtime was delayed by 3 h. Slow wave activity was calculated utilizing power spectral analysis and compared across groups. Following the sleep delay, males with depression exhibited the lowest slow wave activity compared to all other groups. These results may suggest that males with depression are at a greater risk for homeostatic dysregulation than females, and may require specialized intervention.

INTRODUCTION

Sleep disturbance is one of the central symptoms reported by most individuals with major depressive disorder (MDD; Mendlewicz, 2009). Years of research looking at differences in sleep between healthy subjects and those diagnosed with MDD have greatly increased our understanding of the qualitative difference in sleep in those with MDD. With regard to the most common differences in visually scored sleep variables, research has shown consistently that individuals with MDD have more proportionate time awake, a measure of sleep efficiency, shorter time to enter REM sleep (REM latency), greater amount of REM sleep, increased amounts of rapid eye movements (REM density) and decreases in slow wave sleep compared to healthy controls. Understanding these qualitative differences has been an essential first step; however, newer methodology, including quantitative electroencephalograph (EEG) analysis, may allow us to assess more clearly the differences in sleep regulation in MDD. Borbély and Wirz-Justice (1982) suggested that the sleep disturbances occurring in individuals with MDD, including delayed sleep onset and difficulty maintaining sleep, were a result of a reduced drive for sleep (process S). This model also suggests that those with MDD would present reduced slow wave sleep during the first portion of the night, when slow wave activity is typically at its highest. Kupfer *et al.* (1986) demonstrated that there was indeed a reduction in slow wave EEG activity in NREM sleep (SWA) in those with MDD; however, they also noted that there was only a very small relationship between time awake and reduced delta activity in those with MDD. Utilizing quantitative EEG analyses, Armitage *et al.* (1992, 1995, 1997, 2000a,b) have also shown that individuals with MDD exhibit an abnormal distribution of SWA across the night. These findings suggest that those with MDD exhibit greater dysfunction than originally theorized with respect to physiological functioning, including homeostatic regulation.

Research into the function of SWA has shown that SWA increases proportionately to the amount of prior wakefulness and dissipates rapidly over NREM sleep time (Borbély, 1981). Moreover, how quickly SWA asymptotes after sleep onset is presumed to reflect the basic sleep drive, whereas SWA dissipation has been taken as a proxy for neuronal recovery function. In order to explore SWA regulation and its relationship to homeostatic functioning it is necessary to utilize a sleep manipulation, such as sleep deprivation, to challenge the system. A 3-h sleep delay, as described in Armitage *et al.* (2007, 2012), has been utilized successfully

to study SWA response in MDD, as it results in similar increases in SWA in the first NREM period as other sleep manipulations, indicative of the increase in the homeostatic sleep response (Armitage and Hoffmann, 2001; Dijk, 1991). This procedure also allows total sleep time to be held constant, in addition to allowing recovery sleep to occur during the same night. Thus far, the evidence supports both reduced sleep drive and impaired recovery in individuals with MDD. However, none of these studies took into account that sex differences may modify the results.

The incidence of MDD is two times greater in females than males, and as a result, there has been much research into the sex differences in MDD. Somatic symptoms, including complaints of fatigue and insomnia, have been found to be twice as high in females as in males, in both lifetime and 12-month estimates of MDD (Silverstein *et al*., 2013). There are also substantial sex differences in the neurobiology of MDD between sexes, including the findings that there is a hyper-response in the HPA axis in females with MDD, and that females respond differently to antidepressants revealing a difference in the pharmacokinetics and dynamics of the female brain and metabolic system (Armitage, 2007). Additionally, while waking EEG asymmetry has typically been found in frontal regions in samples including female participants, Knott *et al.* (2001) found evidence of such asymmetry over both frontal and other regions in a solely male sample of depressed patients. They interpreted these findings to suggest that depression in males affects unique brain areas than those affected in females. Less research, however, has been conducted into the sex differences in MDD in sleep. Armitage *et al.* (2000a) have noted that the sex differences in individuals with MDD are twice as large as those in healthy controls.

With respect to the regulation of SWA in MDD, Reynolds *et al.* (1990) demonstrated that males with MDD had lower delta wave counts during the first NREM period, and across the night, compared to females who exhibited significantly higher delta activity. Additionally, utilizing a subset of participants from the present sample (n = 30), Armitage (2007) noted that males with MDD demonstrate an impaired time–course for delta activity, including slower dissipation, as indicated by a slower rate of decay from exponential regression analyses during the course of the night. In contrast, Armitage *et al.* (2000a) also demonstrated that females with MDD do not show impaired homeostatic regulation of SWA, but rather show more poorly synchronized sleep EEG rhythms and increased fast frequency EEG at baseline than males with MDD (2001; 1995) which, they suggest, is indicative of more global EEG frequency dysregulation (2007) and more dynamic organization of sleep microarchitecture (2010). Taken together, these findings suggest that MDD does not statically affect males and females, especially with respect to sleep, and perhaps other physiological regulatory mechanisms. Whereas females may display more generalized EEG dysregulation, the slower dissipation of SWA exhibited by males with MDD reflects a dysfunctional recovery process and may thus suggest that general homeostatic functioning of males is more impaired than females.

In addition, very recent research has looked into the topography of SWA in both individuals with MDD and healthy controls using high-density EEG (Plante *et al*., 2012). Results of this work revealed that SWA was higher in females with MDD compared to age-matched healthy controls, found most significantly in the bilateral prefrontal regions during the first NREM period. Alternatively, they did not find any differences in SWA in males with depression compared to healthy males. These findings further substantiate the claim that there are sex-specific impairments in MDD, and may also suggest that females with MDD have developed mechanisms with regard to SWA regulation, specifically, to compensate for certain disease-related dysfunction.

The purpose of the current study was to confirm sex differences in SWA, in MDD compared to healthy controls, and extend the work to include assessments of the accumulation, dissipation and topography of SWA in response to a mild sleep challenge. We predicted that men with MDD would show a blunted response to the challenge, whereas women with MDD would more resemble their healthy counterparts.

METHODS

Participants

Sleep data were selected from our archival database of participants collected over the past 10 years from the Sleep and Chronophysiology laboratory at the University of Texas Southwestern Medical Center at Dallas (UTSW) and the University of Michigan (UM), under the same conditions. Participants were self-referred and responded to advertisements in the community, and habitually slept between 6 and 8 h per night. Inclusion criteria for the study required 2 consecutive nights of recording without any difficulties or deviations from protocol. 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. All participants were unmedicated, other than non-steroidal anti-inflammatory drugs, prior to sleep study for 4 weeks or more. 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 included 40 men and 40 women, between the ages of 20 and 41 years, diagnosed with MDD. All diagnoses were based on the Structured Clinical Interview for DSM-III-R and IV (SCID; non-patient version, Spitzer *et al*., 1997). Participants met criteria for non-psychotic MDD, but no other current Axis I disorders, substance abuse or substance

dependence (American Psychological Association, 1994) within 12 months prior to baseline study. The 17-item Hamilton Rating Scale for Depression (HRS-D; Hamilton, 1960) was used to assess symptom severity. Those with MDD were mild-to-moderately depressed (HRS-D mean score 21.8 ± 4.0), had an adult age of onset (mean age of onset 21.3 ± 8.3), and had experienced two prior episodes of depression (mean number of episodes 2.1 ± 1.4). Polysomnographic data were incomplete as a result of recording difficulties for three participants, and thus the final sample included 40 men and 37 women (mean age 29.49 ± 6.6).

Healthy controls

The healthy control (HC) group consisted of eighty healthy adults, 20–48 years of age (40 men and 40 women; mean age 29.3 ± 6.0). The HCs also underwent SCID to confirm the absence of personal or family history of psychopathology. All healthy controls subjects had Hamilton Rating Scale for Depression scores ≤2.

Subset analysis

In addition to our *a priori* hypotheses, a secondary analysis examining topographical changes resulting from sleep delay was included. Only participants with complete data for electrode sites F3, F4, C3, C4, P3, P4, O3 and O4 were included from our original sample (n = 92).

Procedures

For 5 days prior to study, participants kept an 11:00–06:00 hours sleep schedule, verified by sleep diary and actigraphy. Participants spent three consecutive nights in the sleep laboratory, utilizing the same sleep schedule for the first two nights. 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 on the third night, the SWA regulation challenge. Total available sleep time was held constant at 7 h on all nights. Subjects refrained from napping, using alcohol and drugs, and limited caffeine use to one cup before noon for the 24 h before the study, confirmed by diary and random urine screening.

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 electro-oculography (EOG) and a bipolar electromyography (EMG). The reference electrode was comprised of linked earlobes passed through a 10 K resistor to minimize possible artefacts. All impedances remained below 2 k, and EEG was monitored throughout the sleep delay period to verify that subjects did not fall asleep.

Sleep EEG

One hundred and twenty-seven subjects were collected on a GRASS™ P511 amplifier-based paperless polygraph, described in detail elsewhere (Armitage *et al*., 2002). Data from the remaining 30 subjects were collected on a Vitaport™ III digital data acquisition system, described in detail in Armitage *et al*., 2012. Data systems were cross-validated, simultaneously recording and analysing data from 10 subjects.

EEG data were quantified at the equivalent of a sensitivity of 5 (50 μV, 0.5 s calibration), a gain of 50 000, filters set at 0.3 and 30 Hz, respectively, and a filter to attenuate electrical noise.

Research personnel scored sleep records visually 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 or muscle artefact or recording difficulties were omitted from further analysis.

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 Hanning window taper to reduce overlap between adjacent frequencies. The PSA generates power in all five frequencies, but the analysis for the present paper was restricted to the delta activity expressed as μV^2.

Delta power was averaged in 30-s epochs to provide identical epoch lengths to the stage-score data and sorted by NREM period for each subject on each night in the laboratory. The 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 periods. Delta power was summed and then averaged relative to the number of epochs in each NREM period, for each subject, referred to henceforth as slow wave activity (SWA). For statistical purposes, only the first three NREM periods were included for analysis, as not all subjects had four or more NREM periods across the night.

In addition to the raw SWA power, the latency to each NREM period and duration of each NREM period on each night were computed and contrasted across groups. Further, in order to normalize the data, a %SWA measure was included, expressing SWA on the delay night to SWA on the baseline night, controlling for any potential individual differences in power values between and within groups.

Data analysis

All data were coded for sex (male, female), group (HC, MDD), EEG system (Grass, Vitaport) and age (below and including 30 years of age, above 30 years) and entered into SAS™ for statistical analysis. One four-way, split-plot factorial,

repeated-measures analysis of variance (ANOVA) was computed on SWA amplitude measures, using age and EEG system as statistical covariates. The NREM period was treated as a three-level within-subjects variable. Univariate statistics for each NREM period are only reported if a main effect or interaction was obtained. Least-squares multiple comparisons tested differences between individual means at an experiment-wise $P < 0.05$, to protect against type 1 errors. In each group, exponential regression analysis was also conducted to evaluate the accumulation and dissipation of SWA over the night, (Armitage *et al.*, 2000b).

For all analyses, the group × sex interaction was tested first, followed by simpler effects as appropriate statistically.

RESULTS

Healthy control participants

The sleep delay manipulation had a significant impact on some PSG measures within the healthy control group. Table 1 displays means and standard deviations of key PSG variables.

Table 2 displays the means and standard deviations of latency, duration and SWA power, for each group and sex, during baseline and delay nights in each NREM period. There were no significant main effects or interactions with respect to the latencies to each of the NREM periods, or the durations of each NREM period for the HC or MDD. Therefore, no further analyses were performed on these measures.

As expected, the key dependent variable,%SWA, indicated that SWA was higher following sleep delay than following baseline sleep, and was significantly different among males and females, group × sex ($F_{3,151} = 4.65$, $P < 0.005$). Fig. 1 illustrates the SWA on the delay night expressed as a percentage of baseline sleep in each group.

MDD participants

Sleep delay also had a significant impact on PSG measures within the MDD group.

Similar to the HC, SWA was also significantly higher following sleep delay in MDD females, group × sex ($F_{3,151} = 8.90$, $P < 0.001$). MDD males, in contrast, showed less SWA after sleep delay during the first three NREM periods, as indicated by a significant NREM period × sex × group interaction ($F_{9,453} = 3.91$, $P < 0.001$). In addition to the raw SWA power measures, males with MDD also showed a blunted SWA response to sleep delay compared to all other groups with regard to %SWA, sex × group, ($F_{3,151} = 4.65$, $P < 0.005$).

Analyses on asymptotic SWA confirmed that MDD males have a lower baseline accumulation of SWA during the night than both MDD females and HC females, falling outside the 95% confidence interval. The sleep delay manipulation, however, did not appear to significantly affect asymptotic SWA or rate of decay for either the raw or %SWA measures, for all groups, as evidenced by all values falling within the confidence intervals of the baseline SWA. Table 3 illustrates the means and confidence intervals of the factors, the rates of decay and asymptotes of the exponential regression equations that were calculated to demonstrate the differences in SWA during the course of the night.

Secondary analysis

In order to examine the effects of sleep delay on the topography of SWA distribution, a subset of the original

Table 1 Means and standard deviations of polysomnographic variables, by group and sex

	HCM		*HCF*		*MDDM*		*MDDF*	
	Baseline	*Delay*	*Baseline*	*Delay*	*Baseline*	*Delay*	*Baseline*	*Delay*
Total sleep period (min)†	409.2 (10.5)	395.1 (41.6)	407.2 (12.8)	400.6 (49.0)	422.2 (44.4)	413.1 (38.8)	408.0 (24.8)	415.9 (24.4)
Sleep latency (min)*†	7.0 (5.8)	4.5 (3.5)	7.7 (6.4)	4.0 (3.9)	10.4 (13.1)	8.3 (8.1)	18.6 (19.0)	8.6 (12.4)
Sleep efficiency (%)†	95.3 (2.0)	94.0 (4.6)	95.2 (2.9)	95.7 (3.3)	91.4 (8.5)	92.0 (5.6)	91.5 (6.3)	93.4 (5.9)
Awake and movement (%)†	2.9 (2.1)	3.6 (2.6)	2.7 (1.9)	2.7 (2.5)	5.6 (6.5)	5.8 (5.0)	4.2 (4.8)	4.5 (5.1)
% Stage 1*†	6.3 (6.1)	6.8 (5.8)	6.1 (5.1)	5.6 (4.4)	11.9 (8.0)	12.9 (9.2)	6.7 (6.2)	9.1 (8.6)
% Stage 2*†	57.2 (7.9)	54.6 (5.9)	54.8 (7.8)	51.9 (8.2)	53.4 (8.3)	54.1 (8.3)	51.7 (7.4)	50.5 (6.6)
% SWS†	10.1 (8.7)	10.7 (8.6)	13.1 (8.7)	13.5 (9.0)	7.5 (8.0)	7.5 (8.6)	14.7 (8.6)	14.1 (8.6)
%REM†	23.5 (5.7)	24.3 (7.9)	23.2 (5.4)	25.8 (6.3)	21.7 (5.9)	19.5 (7.6)	22.8 (7.0)	21.7 (8.6)
REM latency†	78.5 (26.5)	69.1 (26.3)	72.2 (24.6)	64.4 (28.0)	78.5 (27.5)	98.5 (76.9)	77.6 (38.0)	91.6 (67.1)
Minute SWS in 1st NREM†	22.6 (19.9)	19.5 (18.4)	28.2 (18.9)	25.8 (19.1)	15.3 (17.2)	15.1 (20.8)	28.2 (18.8)	29.1 (18.2)

HCM, healthy controls male; HCF, healthy controls female; MDDM, major depressive disorder male; MDDF, major depressive disorder female SWS, slow wave sleep; REM, rapid eye movement; NREM, non-REM.
*Denotes significant sleep delay main effect.
†Denotes significant group main effect.

Table 2 Means and standard deviations of latency to SWA, duration of SWA and raw SWA power by group and sex

	HCM		*HCF*		*MDDM*		*MDDF*	
	Baseline	*Delay*	*Baseline*	*Delay*	*Baseline*	*Delay*	*Baseline*	*Delay*
NREM 1								
Latency (min)	12.6 (9.7)	36.9 (64.5)	10.1 (6.6)	33.1 (63.8)	12.0 (7.7)	42.6 (66.0)	11.9 (9.5)	47.2 (74.1)
Duration (min)	70.5 (24.1)	61.2 (13.7)	67.2 (20.5)	58.6 (16.5)	64.4 (24.9)	76.7 (38.1)	63.9 (22.3)	68.0 (26.1)
SWA power (μV2)	*524.6 (110.7)*	**543.0 (141.4)**	*574 (129)*	**595.1 (140.2)**	*471.5 (119.2)*	**451.9(100.5)**	*552.8 (111.8)*	**574.6 (119)**
NREM 2								
Latency (min)	100.5 (27.7)	117.8 (69.4)	97.4 (27.5)	112 (68.1)	94.7 (40.5)	141.6 (77.9)	90.4 (25.4)	133.7 (73.9)
Duration (min)	69.8 (17.4)	64.3 (19.5)	66.8 (16.2)	66.8 (18.5)	66.7 (25.2)	64.6 (20.5)	72.2 (21.6)	76.6 (23.5)
SWA power (μV2)	*425.8 (97.5)*	**444.8 (118.3)**	*451.1 (117.9)*	**470.9 (116.2)**	*401.2 (91.9)*	**358.9 (80.7)**	*472.9 (99.4)*	**463.1 (117)**
NREM 3								
Latency (min)	204.5 (49.7)	215.8 (74.8)	191.3 (36.1)	206.2 (70.7)	188.6 (66.4)	230.7 (84.1)	192.6 (46.4)	245.1 (83.8)
Duration (min)	66.5 (22.4)	56 (30.7)	66.0 (19.8)	54.3 (12.7)	65.4 (19.5)	57.1 (22.7)	67.4 (24.7)	62.3 (19.4)
SWA power (μV2)	359.3 (73.2)	**360.5 (85.4)**	370.8 (69.4)	**382.9 (86.5)**	331.9 (60.7)	**310.3 (79.9)**	364.4 (85.3)	**357.6 (86.9)**
NREM 4								
Latency (min)	297.3 (49.8)	310.1 (83.9)	289.6 (42.6)	296.1 (73.6)	290.8 (72.7)	322.6 (84.6)	293.1 (44.6)	344.1 (96.1)
Duration (min)	51.4 (20)	51.6 (25)	49.2 (15.9)	49.4 (10.9)	49.0 (17.3)	45.0 (17.0)	57.7 (16.2)	52.0 (15.7)
SWA power (μV2)	*311.4 (83.8)*	343.5 (103.1)	*322.6 (69.6)*	355.1 (80.4)	*292.5 (52.8)*	291.3 (69.9)	*331.1 (64.0)*	325.5 (77.9)

SWA, slow wave activity; HCM, healthy controls male; HCF, healthy controls female; MDDM, major depressive disorder male; MDDF, major depressive disorder female.
Latencies defined as minutes from sleep onset to the beginning of each non-rapid eye movement (NREM) sleep period.
Italic type denotes significant group effect at baseline; bold type denotes significant group effect after delay.

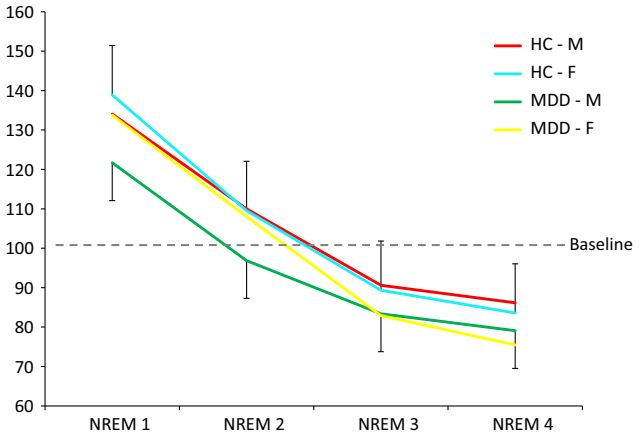

Figure 1. Percentage of slow wave activity (SWA) response to sleep delay relative to baseline night by non-rapid eye movement (NREM) sleep period, by group and sex.

participants with complete data for electrode sites F3, F4, C3, C4, P3, P4, O3 and O4 was included for analysis of electrode sites and hemispheric asymmetry (n = 92).

Results revealed that SWA distribution differed depending on the NREM period, NREM period × hemisphere × electrode site ($F_{9,792}$ = 4.49, P < 0.005). Delta activity was higher in the right hemisphere in the first three NREM periods, but equally high in the left and right hemispheres in the fourth NREM period. A similar pattern emerges where SWA appears to be highest in the frontal electrodes and lowest in the occipital electrodes in the first NREM period, suggesting that SWA is concentrated fronto-centrally and spreads anteroposteriorly. Nevertheless, the delta activity difference between electrode sites decreased across the four NREM periods.

SWA activity was greater in the right than the left hemisphere in the fourth NREM period in all participants except females with depression, NREM period × hemisphere × sex × group interaction ($F_{9,264}$ = 2.38, P < 0.05). Additionally, the difference in SWA between groups decreases across NREM period. With respect to group and sex, the difference in SWA between the left and right hemispheres was greater in males than in females, and greater in healthy participants than those with depression.

Analyses were also conducted on the relative SWA measures. A significant NREM period × electrode site interaction was obtained ($F_{9,792}$ = 22.70, P < 0.001), with the highest SWA in the frontal electrode site during the first NREM period, but in the occipital site during the fourth NREM period.

DISCUSSION

Following a mild sleep challenge, males with MDD showed impaired regulation of SWA, displaying both a blunted response in the first NREM period and slower dissipation of SWA across the night in response to the sleep delay. The sex

Table 3 Exponential regression parameters and 95% confidence intervals (CI) on (a) baseline and delay nights, (b) %SWA, by group and sex

	Baseline				*Delay*			
	SWA	*95% CI*	*Decay*	*95% CI*	*SWA*	*95% CI*	*Decay*	*95% CI*
(a)								
HCM	581.8	486.3 to 677.3	−70.6	−105.5 to −35.8	593.7	436.0 to 751.4	−68.3	−125.9 to −10.7
HCF	*638.2*	498.8 to 777.6	−83.4	−134.4 to −32.5	653.0	472.1 to 833.9	−80.8	−146.9 to −14.8
MDDM	525.9	463.4 to 588.3	−60.7	−83.5 to −37.8	485.7	347.1 to 624.3	−53.1	−103.7 to −2.5
MDDF	*623.7*	501.0 to 746.4	−77.4	−122.2 to −32.5	643.4	485.2 to 801.6	−85.3	−143.1 to −27.5
	%SWA	*95% CI*	*Decay*	*95% CI*				
(b)								
HCM	146.0	108.4 to 183.5	−16.3	−30.0 to −2.6				
HCF	151.9	107.7 to 196.1	−18.6	−34.8 to −2.5				
MDDM	130.6	92.2 to 168.9	−14.1	−28.1 to −0.1				
MDDF	150.0	113.2 to 186.9	−20.0	−33.5 to −6.5				

HCM, healthy controls male; HCF, healthy controls female; MDDM, major depressive disorder male; MDDF, major depressive disorder female; SWA, slow wave activity; CI, confidence interval.
Italic type denotes significant group difference; bold type denotes significant delay effect within group.

differences found were also much greater than that of the healthy individuals, but were apparent only after being amplified by the sleep challenge. These results may demonstrate that males with MDD are at increased risk for more generalized homeostatic dysregulation than females and may require specialized intervention.

Research has suggested that SWA, particularly that from the first part of the night, is a reflection of neuronal recovery, as it is associated directly with the amount of time spent awake prior to sleep (Dijk *et al.*, 1990; Tononi and Cirelli, 2003). In keeping with this viewpoint, therefore, the results suggest that males with MDD, but not females, may show impaired neuronal recovery during sleep. Tononi and Cirelli (2003) further suggest that the amount of slow wave activity may be correlated directly with the amount of synaptic potentiation, described as the 'LTP-like changes in synaptic strength' that occurs during prior wakefulness, which would ultimately balance the input on cortical neurons through a series of depolarizations and hyperpolarizations during sleep, throughout the brain. Therefore, our findings may reflect impairment in the ability to down-regulate the cortical circuits during sleep, which are strengthened throughout wake, in males with MDD.

The functioning of SWA in males with MDD may also be more generally reflective of a sleep regulatory failure. We found that the patterns in dissipation of SWA during the course of the night were different between groups, which may suggest that males with MDD are not able to maintain more basic homeostatic functioning and recover sufficiently from a sleep challenge, in addition to having a reduced drive for sleep. If individuals with MDD are not able to maintain sleep homeostasis, it may also follow that other homeostatic systems may also be unable to regulate. Of particular interest are the metabolic abnormalities that have recently been noted in MDD. Germain *et al.* (2007) indicated that, compared to healthy subjects, individuals with MDD showed increased cerebral metabolic activity in limbic regions, while showing decreased metabolic activity in frontal and parietal regions. Additionally, their research has also found that subjects with MDD demonstrated a higher level of metabolic activity in several brain regions when transitioning from wakefulness to NREM sleep than did healthy subjects (Germain *et al.*, 2004). They have pointed to these findings to suggest that thalamocortical dysfunction may be central to MDD. The results found here, with respect to the disturbance of SWA, could indeed be demonstrative of a problem in the generation of thalamocortical activity, or may indicate that thalamocortical activity is generated, but does not propagate throughout the entirety of the brain. Topographical analyses of SWA across different brain regions may be able to tease apart these distinct problems.

The S-deficiency hypothesis, posited by Borbély (1982), suggests that those with MDD exhibit an impaired homeostatic drive for sleep, and as such should demonstrate a reduced SWA response to challenge. Furthermore, Gillin and colleagues (1981) have also suggested that, in this way, the sleep patterns in MDD may parallel typical ageing, as SWA has been shown to decrease in healthy older individuals. Frey *et al.* (2012) investigated this theory by comparing the response to a sleep challenge in both healthy older and depressed young females. Their results revealed that young depressed females exhibited increased SWA in response to sleep deprivation compared to either young healthy or older healthy females, analogous to the results found in the present study. They thus determined that the functioning of SWA in females with MDD did not reflect premature ageing. Conversely, our results demonstrate that males with MDD show an attenuated SWA response to a sleep challenge that might

be expected of older healthy males. In this way, the premature ageing hypothesis in MDD may hold true only for males.

Additionally, the impaired regulation of SWA in males with MDD found currently may also reflect a larger, unrecognized deficit, such as sleep-disordered breathing. Deldin and colleagues (2006) have identified a significant relationship between sleep-disordered breathing and major depressive disorder. The authors (Deldin *et al*., 2006) found that certain sleep-related breathing variables, such as average overnight oxygen saturation, predict membership accurately in a healthy control group versus MDD. Moreover, in a more recent study, they found that those with MDD displayed higher rates of respiratory events than healthy controls, despite not reaching threshold for clinically significant sleep apnea (Cheng *et al*., 2013). Taken together, these studies illustrate the importance of further understanding the relationship between major depression and sleep-disordered breathing and the potential physiological consequences which may include impaired SWA. As the prevalence of SDB is two times greater in males than females, our finding of impaired regulation of SWA in only males with MDD may further suggest that sleep-disordered breathing may be playing a role.

Previous research in healthy male subjects has found that SWA is highest in the frontal regions compared to temporal and parietal regions, and have their highest amplitude during early sleep, or NREM periods 1 and 2 compared to late sleep, or NREM periods 3 and 4 (Riedner *et al*., 2007). Additionally, Ferrara *et al.* (2002) also found that, during a recovery night of sleep following selective slow wave sleep deprivation, the left hemisphere showed greater SWA power than the right hemisphere, which they suggest indicates that the left hemisphere has a greater sleep need following sleep deprivation. With respect to female subjects, Birchler-Pedross *et al.* (2011) found that females with MDD exhibited higher low-frequency EEG activity than healthy controls during night sleep and daytime naps, which they suggested could mean that females exhibit a generally higher homeostatic sleep pressure. Our results indicated that SWA was generally highest in the right hemisphere, regardless of the sleep delay, but was sex-, group- and NREM period-dependent. Contrary to previous findings (Plante *et al*., 2012), our results did not indicate any group or sex effects for electrode sites, including any significant differences for females with and without MDD, in the frontal site during the first NREM period, at baseline or following the sleep delay challenge.

Our results also demonstrated that while SWA power was significantly different among groups, the latencies to each NREM period, or durations of each NREM period, were not. This suggests that enhanced SWA power is neither a result of significantly shorter latency to SWA nor due to prolonged duration of SWA in the first NREM period. Additionally, it has also been suggested that SWA and sleep latency may both be indices of sleep drive. Consistent with this view, we found that males with MDD had both lower SWA power and longer sleep latency in the first NREM period. However, while females with MDD exhibited higher SWA power following the sleep delay, they did not display shorter sleep latency. These results suggest that latency to SWA is not a proxy for SWA power.

The results of this study, however, are not unique to those individuals with MDD. Recent findings from our laboratory (Armitage *et al*., 2012) showed that males with alcohol dependence (AD) had similarities to males with MDD, with regard to impaired homeostatic regulation of SWA. Males with AD demonstrated impaired generation of SWA following a challenge, in addition to the impaired speed of recovery of SWA during the course of the night. Females with AD, however, did not show this pattern, similar to the females with MDD in the current study. These findings, in addition to those found in the current study, suggest that the pathophysiology of MDD and other diseases are sex-dependent, and may shed light on the process of neuronal recovery. The clinical course of MDD has been shown to be affected by gender, with more disturbed sleep found in males with an earlier age of onset of MDD and in females with more lifetime episodes (Swanson *et al*., 2010). Taken together, these data suggest that clinicians and researchers should be sensitive to the possibility that the influence of gender on sleep, specifically, and depression, more generally, may not be consistent across groups.

Our present findings should be interpreted in light of several limitations. In order to mimic the effects of total sleep deprivation while minimizing the time before recovery sleep, the present study utilized a 3-h sleep delay. As expected, our healthy control groups showed a response to the sleep delay in the predicted direction, exhibiting an increase in the percentage of SWA in the first NREM period. Males with MDD, also as predicted, exhibited a smaller response to the challenge compared to the other groups. This finding may point to the fact that males with MDD exhibit a blunted response to the challenge, as we have interpreted, or it could indicate that the homeostat of these individuals may be broken. It is possible that the 3-h sleep delay procedure is not strong enough to evoke a response, and that the system of the males with MDD only respond to a much larger threat in order to preserve resources. In order to tease apart these differences, future studies interested in exploring the homeostatic response in SWA may want to utilize full-night sleep deprivation.

Our results are also somewhat at odds with an earlier study from our laboratory (Armitage *et al*., 2007), which showed that females with MDD had a greater response than healthy females to the sleep delay challenge. This difference, however, may be a result of clinical differences in the current sample, as the females with MDD reported a fewer number of lifetime episodes and a later age of onset than in our previous study. Although females with MDD did not demonstrate the same patterns as males with MDD with regard to SWA, previous studies have indicated that the disease still seems to have a substantial impact on the sleep system of females, such as biological rhythm abnormalities and dysregulation in the organization of sleep EEG (Armitage, 2007).

Additionally, although we were cognizant about our recruitment process, the generalizability of the sample is limited by our stringent inclusion criteria. We were interested in exploring the effects of sleep delay on a depressed sample, and as such we excluded any individuals who exhibited diagnostic criteria for any other Axis I disorder according to the Structured Clinical Interview for the DSM. Although this provided a relatively clean sample, research has shown that many individuals with MDD also have other comorbid Axis I disorders (Kessler *et al.*, 1996), and therefore may limit how our results apply to the general population of those with MDD.

In summary, this study utilized a 3-h sleep delay in order to evoke a SWA response in a sample of healthy controls and individuals with depression. Results revealed that males with MDD exhibit impaired regulation of SWA, with decreased accumulation of delta in the first NREM period, in addition to a slower rate of decay across NREM periods compared to healthy controls and females with MDD.

AUTHOR CONTRIBUTIONS

JRG completed the majority of data analyses and writing of manuscript; PC provided statistical and technical support for data analyses; RA is Director of UM Sleep and Chronophysiology Laboratory where the data were collected; PJD provided data analyses support and all edits of the manuscript.

CONFLICTS OF INTEREST

JG, PC and PD report no conflicts of interest. RA was previously a consultant for Eisai, Inc.

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