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Slow-wave activity in NREM sleep: sex and age effects in depressed outpatients and healthy controls

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Abstract

The amplitude and time course of slow-wave activity (SWA) during NREM sleep were compared in 76 outpatients with depression and 55 healthy control subjects. Lower SWA amplitude was evident in the depressed group, especially among depressed men. For the most part, significant differences between patients and control subjects were restricted to the first NREM period and only in those 20–30 years of age. Significant age-related declines in SWA amplitude were evident in control subjects but not in depressed patients. In addition, sex differences in the depressed group were twice as large as those seen in control subjects. The time course of SWA amplitude, presumed to reflect homeostatic sleep regulation of SWA, was only abnormal in depressed men with lower accumulation and slower dissipation over NREM sleep. Depressed women showed no evidence of an abnormal SWA time course. Furthermore, no sex differences in the time course of SWA were evident in control subjects, and age-related changes in this aspect of regulation were not striking in any group. Thus, the amplitude of SWA showed strong age effects in healthy individuals but not in those with MDD whereas the time course showed very subtle age effects. It was suggested that men, but not women, with MDD show impaired SWA regulation that is evident from 20 to 40 years of age. These findings provide further support that the pathophysiology of depression differs for men and women and suggest that maturational effects on SWA in depression differ from those observed in healthy individuals. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Sleep EEG; Depression; Delta; Sex differences; Computer-quantified EEG; Slow-wave activity; Aging

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1. Introduction

Major depressive disorder (MDD) is associated with a number of sleep disturbances including difficulties initiating and maintaining sleep, increased Stage 1 sleep, an early onset of rapid eye movement (REM) sleep, increased phasic REM activity and a reduction in slow-wave (Stage 3–4) sleep (cf. Reynolds and Kupfer, 1987), although it is debatable whether these abnormalities are unique to MDD (Benca et al., 1992). Nevertheless, the majority of studies do indicate that the timing or distribution of REM and slow-wave sleep stages 3 and 4 are disrupted in symptomatic and unmedicated patients with MDD (Reynolds and Kupfer, 1987; Berger and Riemann, 1993; Armitage, 1995), particularly those studies that include quantitative sleep EEG analyses (Armitage, 1995; Armitage and Hoffmann, 1997; Nofzinger et al., 1999). Disruptions in the timing or distribution of REM and slow-wave (SW) sleep may either reflect disinhibition of REM sleep (McCarley, 1982) or impairment in the homeostatic process 'S', the failure to accumulate SW sleep pressure during the daytime which results in lower slow-wave activity (SWA) in NREM sleep (Borbély and Wirz-Justice, 1982).

Using power spectral analysis (PSA), based on the fast-Fourier transform, Borbély and colleagues demonstrated lower slow-wave activity (SWA) power in NREM sleep in nine adult unipolar, unmedicated, depressed patients compared to age- and sex-matched healthy normal control subjects (Borbély et al., 1984). This initial finding was confirmed in a group of eight younger patients with MDD (20–30 years old), compared to eight age-matched control subjects (Kupfer et al., 1989b). Reduced SWA power may not be a characteristic of bipolar patients (Mendelson et al., 1987).

Kupfer and colleagues have also utilized delta wave-count statistics, based on period amplitude analysis (PAA) to quantify SWA. In several studies, they have reported lower delta wave counts in patients with MDD compared to control subjects, but these differences were largely restricted to the first non-rapid eye movement (NREM) period of the night (Kupfer et al., 1984a,b, 1986). In fact,

Kupfer's group has suggested that delta wave counts in patients with MDD are higher in the second NREM period than in the first, and that this delta ratio is related to the clinical course of illness (Kupfer et al., 1990).

More recent studies have been unable to replicate either lower delta wave counts or an elevation in SWA in the second NREM period in patients with MDD (Armitage et al., 1992a, 2000b). However, the delta wave counts from the Kupfer et al. studies and from Armitage et al. (1992a) both emphasized high-amplitude delta activity ($> 75 \mu\text{V}$) and, as such, may not accurately describe changes in amplitude-independent SWA across NREM periods. Regardless, both of the Armitage et al. studies did demonstrate that the distribution of SWA across successive NREM periods was abnormal in those with MDD.

Although there is a fairly substantial literature on age effects on sleep macroarchitecture, including several comprehensive reviews (Dement et al., 1982; Bliwise, 1993), there are only a few published studies of age effects on sleep microarchitecture (Feinberg et al., 1977, 1984; Dijk et al., 1989b; Landolt et al., 1996). All of these studies demonstrated that the amount of SWA decreases with age, but contrasted 20–30 year olds to late middle age or elderly subjects and were restricted to men. The age effects on the *time course* of SWA, an approximation of process S, were quite small, though still significant (Dijk et al., 1989b; Landolt et al., 1996). One very recent preliminary report (Dijk et al., 1999) confirmed that the accumulation and dissipation of SWA is slower and more shallow in older men but that the effects were reasonably subtle. However, age effects may differ substantially for men and women.

With regard to MDD, there is also evidence to suggest that sleep disturbances become more pronounced with increasing age in MDD. REM latency gets progressively shorter, and both sleep efficiency and slow-wave sleep (%) decrease further (Gillin et al., 1981; Kupfer et al., 1982). Age effects appear to be particularly pronounced in endogenous patients (Reynolds and Kupfer, 1987). The maturational course appears to be earlier than in healthy control subjects, leading to the suggestion that MDD is associated with prema-

ture aging (Reynolds and Kupfer, 1987; Veith and Raskind, 1988). In a large scale study of 302 MDD men and women, Reynolds et al. (1990) demonstrated significant sex main effects for slow-wave sleep and delta wave counts across the whole night and particularly in the first NREM sleep period. Men with MDD had less slow-wave sleep and lower delta counts than women with MDD. Moreover, a NREM period by sex interaction was found, suggesting that the temporal distribution of delta wave counts differed for men and women with MDD. Sex differences in both slow-wave sleep and delta wave counts were also evident in younger patients (20–29 years) with MDD and diminished with increasing age, though not monotonically. Nevertheless, Reynolds et al. concluded that age effects were stronger than sex differences and there was little evidence of a differential maturational time course in men and women with MDD. They also attributed sex differences in delta counts to skull thickness rather than sleep regulatory processes.

In an earlier study by the Pittsburgh group, SWA power did not differentiate older patients (> 50 years) from healthy control subjects (Kupfer et al., 1989a). Comparing relatively young adults (≤ 40), our own group has shown significant group by sex interactions on the time course of SWA in 22 outpatients with MDD and 23 control subjects (Armitage et al., 2000b). Men with MDD had a significantly slower rate of decay with lower predicted SWA power and amplitude parameters from exponential regression analysis than all other groups. Women with MDD, healthy men and healthy women did not differ from each other. In addition, regression analysis indicated that strong age-related changes in SWA amplitude were evident in healthy women. By contrast, men with MDD showed no relationship between SWA amplitude and age with MDD women and healthy men showing only moderate age-related changes. These findings are suggestive of a differential maturational time course for SWA in men and women that is evident relatively early in adult life, regardless of disease. However, there were too few subjects to fully evaluate age effects within groups.

The primary aim of the present study was to

further evaluate group and sex effects on the time course of SWA in a large-scale study of symptomatic, unmedicated depressed patients, contrasted to healthy control subjects. Changes in SWA amplitude and incidence were evaluated across successive NREM periods, to determine whether MDD was characterized by an abnormal distribution of SWA. Group by sex interactions were expected. Secondary aims were to evaluate the maturational effects on SWA by sex and psychiatric status.

2. Methods

2.1. Subjects

Sleep data from participants were selected from our archival database collected under standard conditions over the past 5 years. Inclusion in the study required two consecutive nights of sleep data without recording difficulties or protocol violation. None of the participants were engaged in shiftwork or had independent sleep disorders (e.g. narcolepsy, apnea, bruxism, periodic limb movements) as established by history or polysomnogram. No SWA data from this sample have been reported previously. All participants maintained regular bed- and rise-times based on home diaries collected for 5 days prior to study. This habitual sleep schedule was also followed in the laboratory. Estimated total sleep times were 6.5–7.5 h/night and did not differ between groups ($F < 1$). Furthermore, the amount of prior wakefulness before the laboratory adaptation night was 16.7–17.6 h and did not differ between groups ($F < 1$).

2.2. Depressed outpatients

Seventy-six outpatients (31 men and 45 women) 20–40 years of age (mean 31.7 ± 5.4), who met DSM-III-R criteria for non-psychotic major depression, but who were otherwise physically healthy, participated in the study. Nine men and 28 women were 20–30 years of age. Twenty-two men and 17 women were 30–40 years of age.

Diagnoses were made based on the Structured

Table 1
Clinical and demographic characteristics of outpatients with MDD^a

	Mean	S.D.	Range
No. Men <i>n</i> = 31			
No. Women <i>n</i> = 45			
Age (years)	31.7	5.4	20–40
HRS-D 17-item	21.9	5.2	17–32
Age of onset (years)	22.5	12.2	9–38
No. previous episodes	2.6	2.0	1–7
Length current episode (months)	39.5	32.7	1–120
IDS-C 30-item	40.1	8.2	26–58

^aAbbreviations: MDD, Major Depressive Disorder; HRS-D, Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptoms-Clinician Rated.

Clinical Interview for DSM-III-R (Spitzer et al., 1986) or DSM-IV (American Psychiatric Association, 1994). The 17-item Hamilton Rating Scale for Depression (HRS-D) (Hamilton, 1960) was used to assess symptom severity. A detailed personal and family history was obtained at the time of clinical interview. All patients were symptomatic at the time of study, and a minimum score of 17 on the HRS-D was required for entry. Patients were also medication-free for a minimum of 2 weeks prior to the study.¹ Other current Axis I disorders, current general medical conditions or substance abuse within 12 months prior to baseline study excluded subjects. Clinical and demographic details of the patient sample are presented in Table 1. None of the clinical measures differed between MDD men and women ($P < 0.17$).

2.3. Normal controls

Fifty-five healthy adults (32 men and 23 women), 20–40 years of age (mean 29.5 ± 5.6), participated in the study. There were 24 men and 14 women in the 20–30 year range and 8 men and 9 women in the 30–40 year range. All normal control subjects (NC) were medically fit and had no personal or family history of Axis I disorders

or substance abuse, based on the Structured Clinical Interview for DSM-III-R (non-patient version). All subjects had HRS-D scores ≤ 2 at the time of study.

Note, that the depressed and control groups did not differ on age nor were there age differences among men and women by analyses of variance. SWA data from eight of the depressed patients and 11 healthy control subjects have been reported previously (Armitage et al., 2000b).

2.4. Procedures

Each participant spent 2 consecutive nights in The University of Texas Southwestern Medical Center Sleep Study Unit. Night 1 served as an adaptation night and as an additional screening for independent sleep disorders unrelated to psychiatric diagnosis including apnea, bruxism and periodic limb movements. A full electrode montage, including leg leads, chest and abdomen respiration bands, and nasal–oral thermistors was used during the first night of the study.

On the subsequent night, the electrode montage included left (C3) and right central (C4) EEG, left and right EOG, recorded from the upper and lower canthi, and a bipolar, chin–cheek EMG. EEG electrodes were referenced to the ear lobes linked together through to a 10 K Ω resistor to minimize non-homogeneous current flow and potential artifactual hemispheric asymmetries (Nunez, 1981) as is standard in our laboratory. EEG was transduced by GRASSTM P511 A/C amplifiers set at a sensitivity of 5 (50 μ V, 0.5 s calibration), corresponding to a gain of 50 000. The half-amp low- and high-bandpass filters were set at 0.3 and 30 Hz, respectively. A 60-Hz notch filter attenuated electrical noise.

Signals were digitized on-line at 250 Hz (62.5 Hz for EOG and EMG) through a 16-bit MICROSTARTM analogue-to-digital (A/D) converter and displayed on a digital polygraph system designed and validated in-house. Raw digitized data were stored on a write-once-read-many (WORM) optical disk for off-line PAA. Sleep records were scored visually according to standard criteria (Rechtschaffen and Kales, 1968) by research personnel trained at better than a 90%

¹4 weeks for monoamine oxidase inhibitors; 6 weeks for fluoxetine.

stage agreement on an epoch-by-epoch basis. All records were inspected visually and epochs containing movement, breathing or muscle artifact, or recording difficulties were excluded from analysis.

2.5. Signal processing

The PAA algorithm used here has been described in detail elsewhere (Hoffmann et al., 1979; Armitage et al., 1992b). For the purposes of this report, only amplitude (based on a half-wave zero cross-analysis) in the delta band (0.5– < 4 Hz) is reported.

The half-wave zero cross-analysis evaluates both negative and positive voltage inflections that cross electrical zero. The algorithm computes the time between successive zero-voltage crossings in each second, thereby determining the frequency of each wave. At the end of each 30 s epoch, the percent of total zero cross-time spent in the delta band is computed. The amplitude measure is derived from the cumulative squared voltage of all points in the delta zero cross-bin.

2.6. Data analysis

The definition of NREM periods closely followed that outlined by Feinberg and Floyd (1979), Dijk et al. (1990a). NREM periods were 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 at least 5 min. Stage 1 sleep epochs were excluded. No minimum REM duration was required for the first or last REM period. SWA amplitude and incidence were summed and then averaged relative to the number of epochs in each NREM period, for each subject. For statistical purposes, only the first three NREM periods were included for analysis, since not all subjects had four or more NREM periods across the night.

Data were then coded for group (MDD or NC), sex and age (20–30 years, 30–40 years), all between-group variables. All statistical analyses were conducted using SASTM routines. One four-way factorial, repeated-measures analysis of variance (ANOVA) was computed on SWA ampli-

tude (1-within 3-between variables). The NREM period was treated as a three-level within-subjects variable. Univariate statistics for each NREM period are only reported if the four-way NREM period by group by sex by age interaction or the overall group by sex by age effect was significant (Howell, 1982; Stevens, 1986). Least-squares multiple comparisons tested differences between individual means at an experiment-wise $P < 0.05$, to protect against Type 1 errors.

For analysis of the time course of changes in SWA across NREM periods, the start point or latency to the first NREM period was used to synchronize subjects within and across groups. SWA amplitude measures within a NREM period were expressed relative to total SWA amplitude in all NREM sleep epochs. Exponential equations were fitted to the time course data, using time since sleep onset (excluding intervening awake time) as the independent variable. These procedures are similar to those outlined by Dijk's and Borbély's groups and our own (Dijk et al., 1989a, 1990a,b; Armitage and Roffwarg 1992; Armitage et al., 2000a,b; Aeschbach and Borbély 1993), although we excluded epochs of Stage 1 sleep from the time course analysis due to the high amounts of Stage 1 sleep in MDD men. The time course analysis permitted an evaluation of whether the accumulation and dissipation of SWA (i.e. homeostatic regulation) differed between patients and control subjects.

Age effects on SWA were further evaluated with linear regression analysis, computed separately by sex and group and treating age as a continuous variable. These analyses tested the hypothesis of differential age effects in men and women and in depressed patients vs. control subjects.

3. Results

3.1. Sleep macroarchitecture

To facilitate comparison to published reports that include only sleep macroarchitecture (based on visual sleep-stage scoring), the following variables were derived: time in bed; total sleep period

Table 2

Means and standard deviations (in parentheses) of select sleep stage variables and NREM period characteristics for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW) collapsed across age

Variable	MDDM (<i>n</i> = 31)	MDDW (<i>n</i> = 45)	NCM (<i>n</i> = 32)	NCW (<i>n</i> = 23)
Time in bed	440.2 (4.8)	441.6 (3.4)	439.5 (3.7)	440.8 (4.2)
Total sleep period	422.2 (53.2)	423.6 (50.0)	420.4 (45.9)	430.3 (40.8)
Sleep latency ^a	13.9 (4.3)	20.0 (16.0)	15.4 (11.4)	9.8 (9.0)
REM latency ^b	76.8 (24.6)	77.9 (28.0)	74.8 (41.4)	72.4 (12.9)
% Stage 1*	18.2 (5.3)	12.1 (5.8)	14.8 (6.6)	13.3 (5.6)
% Stage 2	52.4 (8.5)	56.1 (8.5)	54.7 (8.2)	56.0 (6.1)
% SW (3 + 4)*	2.5 (3.1)	7.6 (6.6)	5.8 (6.9)	7.5 (5.5)
% REM	18.2 (5.9)	18.8 (4.8)	17.5 (4.5)	21.2 (3.5)
% Awake*	8.0 (7.2)	4.9 (3.6)	5.4 (4.0)	3.7 (1.7)
SW min in NREM1*	6.3 (9.8)	16.5 (15.5)	13.8 (15.3)	17.3 (17.0)

^a Latency in minutes from lights out to persistent sleep, defined as the first 10 min of sleep with < 2 min of intervening wakefulness. (%) expressed relative to total sleep period from sleep onset to morning awakening.

^b No minimum duration criterion. REM latency includes awake time and is computed to the first epoch of REM.

* Group by sex by age interaction, $P < 0.05$.

(TSP); sleep latency; REM latency; and the percentage of TSP spent in each sleep stage. See Armitage et al. (1994) for computational detail. The minutes of slow-wave sleep in the first NREM period were also computed. A straight between-group three-way MANOVA tested sex by group by age interactions. Two-way interactions or main effects were only tested if the three-way interaction was not significant, following standard principles (Howell, 1982; Stevens, 1986). Multiple comparison tested individual mean differences.

3.2. Sleep stage variables

Although not the main focus of the present study, means and standard deviations of select sleep stage variables are included for illustrative purposes in Table 2. For ease of presentation, the data are shown by group and sex collapsed across age.

MANOVA revealed a significant overall group by sex by age interaction ($F_{7,123} = 2.3$, $P < 0.04$). As can be seen in Table 2, men with MDD had the most disturbed sleep compared to all other groups, with less SW sleep (%), fewer SW minutes in the first NREM period, more Stage 1 and more awake time confirmed by multiple comparison (P range: 0.003–0.04). None of the other

sleep macroarchitectural variables showed significant effects.

In comparisons of individual groups, the largest differences were between MDD men and women, regardless of age group (P range: 0.0001–0.005). By contrast, NC men and women did not differ from each other, regardless of age (P range: 0.27–0.63). However, in differentiating MDD men from NC men, significant effects were restricted to those of 20–30 years of age (P range: 0.01–0.04). No group differences were evident in 30–40-year-old men (P range: 0.60–0.90). Thus, men with MDD continued to show more disturbed sleep than either MDD or NC women across age groups, but differences from NC men were restricted to those under 30. This, coupled with larger sex differences in the MDD group, accounts for the significant sex by group by age interaction from MANOVA.

3.3. Sleep microarchitecture

3.3.1. SWA amplitude

The repeated-measures ANOVA of SWA amplitude revealed a significant overall group by sex by age interaction ($F_{7,123} = 4.5$, $P < 0.0002$), a NREM period main effect ($F_{2,246} = 97.1$, $P < 0.0001$), and a four-way NREM period interaction

Table 3

Means and standard deviations (in parentheses) of SWA amplitude collapsed across all NREM (Stages 2, 3 and 4) sleep for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW) in each age group

	MDDM		MDDW		NCM		NCW	
	20–30	30–40	20–30	30–40	20–30	30–40	20–30	30–40
SWA measure	<i>n</i> = 9	<i>n</i> = 22	<i>n</i> = 28	<i>n</i> = 17	<i>n</i> = 24	<i>n</i> = 8	<i>n</i> = 14	<i>n</i> = 9
Amplitude	762.9 (147.9)	719.5 (176.8)	922.3 (257.4)	824.5 (189.5)	891.5 (199.5)	734.9 (230.1)	1047.0 (199.2)	801.7 (140.1)

with group, sex and age ($F_{14,246} = 2.0, P < 0.02$). The means and standard deviations of SWA amplitude are shown in Table 3 collapsed across NREM periods, to illustrate the overall between-group effect. Here it can be seen that men with MDD have lower overall SWA amplitude than any other group, regardless of age. However, women showed higher amplitude than men regardless of group or age. Again, the age-related

changes in SWA amplitude were stronger in the NC than in the MDD group.

Fig. 1 illustrates the four-way group by sex by age by NREM period interaction. Note that between-group differences were most pronounced in younger subjects and particularly in the first NREM period. Multiple comparisons revealed that men with MDD, 20–30 years of age, had significantly lower SWA amplitude than NC men

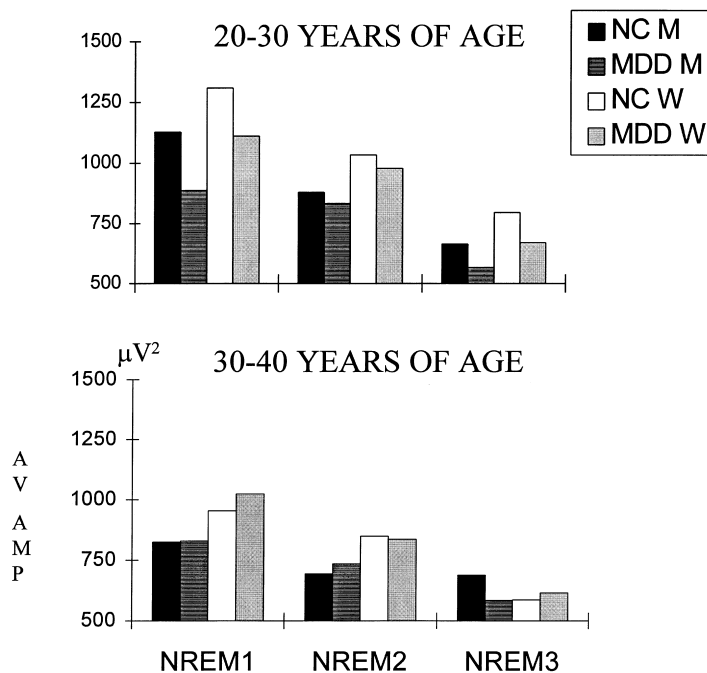


Fig. 1. Average SWA amplitude in the first three NREM (Stages 2, 3, 4) periods for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW) in those 20–30 years of age (top) and those 30–40 years of age (bottom).

($P < 0.03$), NC women ($P < 0.0005$) and MDD women ($P < 0.04$) in the same age group. Younger NC women also had higher SWA amplitude than all other groups ($P < 0.04$). Among 30–40-year-olds, MDD men also had significantly lower delta amplitude than MDD women ($P < 0.04$). None of the other multiple comparisons reached significance in the 30–40-year-olds, although MDD women had marginally higher amplitude than NC men ($P < 0.09$).

Considering age-related changes in each group, 20–30-year-olds had significantly lower SWA amplitude than those 30–40 years of age among NC women ($P < 0.0003$) and men ($P < 0.007$), but not in those with MDD ($P < 0.30$). Thus, age effects were significantly stronger in the control group as seen in Fig. 1. These age effects were attenuated in the second and third NREM periods, with no significant differences by multiple comparison, accounting for the four-way interaction.

To more completely evaluate age-related changes in SWA, linear regression analyses were computed separately for group and sex. SWA in the first NREM period was regressed on age as a continuous variable. Normal control women showed the strongest age-related changes with a slope of -34.6 ($P < 0.0003$). Normal men showed a significant but smaller age-related decline in SWA amplitude with a slope of -28.2 ($P < 0.002$). Neither depressed group showed significant age effects. Depressed women had a slope of -9.8 ($P < 0.19$) whereas men with MDD showed a slope of -2.9 ($P < 0.74$). Note, however, that SWA amplitude in NREM1 was equivalently *low* in both MDD men in the 20–30- and 30–40-year groups. By contrast, SWA amplitude was equivalently *high* in both younger and older women with MDD.

3.4. Time course of SWA

The time course of SWA amplitude throughout NREM sleep was quantified separately for women and for men, comparing those with and without MDD. To depict the time course, data were synchronized at sleep onset and SWA was expressed as a percentage of total NREM amplitude for each subject. Values were then averaged in each

group. The time course of SWA is shown for women in both groups in Fig. 2 (left). Note that the initial accumulation of SWA amplitude was very similar between depressed and control women, regardless of age. The decay of SWA over NREM sleep time was also similar. The time course of SWA amplitude for men in both groups is shown in Fig. 2 (right). Although the SWA decay in younger NC men was similar to that obtained in younger MDD and NC women, men with MDD showed a distinctly flatter time course. The initial SWA (%) was lower and the shape of the decline over time more shallow. What is more, age effects on the SWA time course appeared to be minimal in women.

Exponential functions were computed from individual subject data in each group, using the model $y = bxe^{c \times \text{time}}$, where b is the predicted SWA (%) value at time = 0, c is the exponential change, and time is the minutes of NREM sleep since sleep onset (Armitage and Roffwarg, 1992). Note that a negative value of c indicates a decay over NREM time.

The resultant exponential regression parameters are shown in Table 4, and confirm that the time course of SWA was abnormal in men with MDD, but not women. Depressed men under 30 showed a SWA (%) value that was outside the 95% confidence intervals of NC and MDD women and NC men in the same age group ($P < 0.05$). The rate of decay was significantly lower in the MDD men compared to all other groups in the same age range and was slower. The regression parameters did not differ among NC men, NC women and MDD women in the 20–30-year age group.

Older depressed men also showed significantly lower predicted SWA (%) and a slower decay than both NC and MDD women ($P < 0.05$), and fell just on the edge of the 95% confidence interval for NC men over 30 ($P < 0.06$). These findings are consistent with impaired SWA regulation in men with MDD, but not women. Note also that normal control men showed some evidence of impaired SWA regulation with age since both the SWA (%) and decay parameters differed in those under and over 30 ($P < 0.05$).

The results from the exponential regression

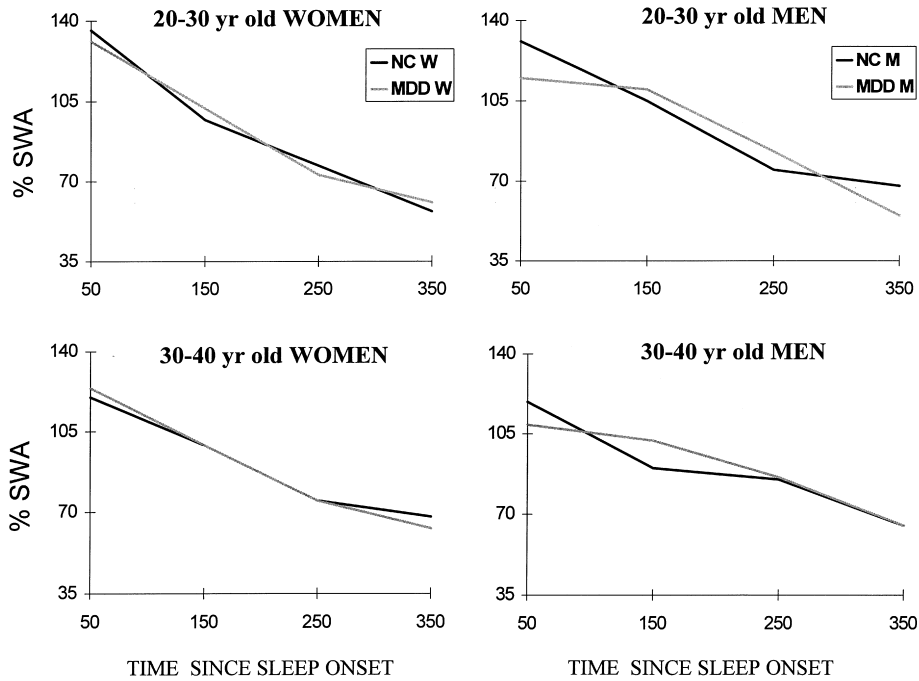


Fig. 2. The average time course of SWA amplitude expressed as a percentage of total NREM (Stages 2, 3, 4) amplitude in depressed women (MDDW) and normal control women (NCW) 20–30 years of age (top left) and 30–40 years of age (bottom left), depressed men (MDDM) and normal control men (NCM) 20–30 years of age (top right) and 30–40 years of age (bottom right).

Table 4

Exponential regression parameters from the time course of % SWA amplitude expressed as % of total NREM amplitude by group, sex and age^a

Group	Parameter	Estimate	Asymptotic S.E.	95% Confidence interval	
				Lower	Upper
NCW	b	130.9	4.5	121.8	140.0
20–30	c	–0.0013	0.0002	–0.0017	–0.0010
NCW	b	128.1	6.9	119.5	142.7
30–40	c	–0.0011	0.0002	–0.0016	–0.0009
MDDW	b	132.1	4.8	122.5	141.7
20–30	c	–0.0013	0.0002	–0.0016	–0.0010
MDDW	b	131.4	4.9	121.5	141.3
30–40	c	–0.0012	0.0002	–0.0015	–0.0009
NCM	b	133.2	3.71	125.9	140.5
20–30	c	–0.0013	0.000	–0.0016	–0.0011
NCM	b	124.7	4.8	114.7	134.8
30–40	c	–0.0011	0.0002	–0.0014	–0.0007
MDDM	b	119.1	4.1	111.0	121.3
20–30	c	–0.0008	0.0001	–0.0011	–0.0005
MDDM	b	115.5	7.4	100.2	130.8
30–40	c	–0.0008	0.0003	–0.0015	–0.0001

^a Model $y = bxe^{cx \text{ time}}$; b = predicted % SWA at time = 0; c , exponential decay; and time, minutes since sleep onset.

analyses also differ dramatically from the age regressions on SWA amplitude in the first NREM period. Normal control women showed the most dramatic age-related declines in SWA amplitude but with very little change in the time course and regulation of SWA. The regression analysis on age in normal men indicated a less dramatic decline in SWA amplitude in the first NREM period, but the time course was different in younger and older men.

By contrast, SWA regulation was equivalently impaired in younger and older depressed men, and age did not significantly influence SWA amplitude in the first NREM period. Depressed women showed neither evidence of SWA impairment nor age-related changes in either the time course or the amplitude within the first NREM period. Furthermore, SWA incidence also indicated greater age effects in healthy adults than in those with MDD.

4. Discussion

The major finding of this study was that men with MDD showed lower SWA amplitude and an abnormal time course of SWA across the night in comparison to healthy men and women and to depressed women. By contrast, no evidence of impaired SWA regulation was evident in depressed women, although SWA amplitude in the first NREM period was lower than in younger NC women. The analysis of the time course of SWA strongly suggested that depressed men show abnormalities in the accumulation and dissipation of SWA across NREM sleep in comparison to both control groups and to depressed women. Men with MDD showed lower amplitude parameters from exponential regression parameters and a significantly slower rate of decay than all other groups. By contrast, the time course of SWA in depressed women virtually mirrored that of control women, regardless of age. Traditional visual stage-scoring indicated that depressed men also had reduced high-amplitude delta activity (lower SW (%) sleep) compared to control men or women to depressed women.

The findings of the present report are not in-

consistent with the suggestion of Borbély and colleagues that a SW sleep deficiency and impaired homeostatic regulation of SWA are characteristic of depression (Borbély and Wirz-Justice, 1982; Borbély, 1987), with the caveat that the effect appears to be *sex-dependent*. There was, however, little evidence that REM sleep was phase-advanced relative to SW sleep in depression as suggested by Wehr and colleagues (Wehr et al., 1979; Wehr and Wirz-Justice, 1982; Wehr and Goodwin, 1983). Neither REM latency nor the durations of the first NREM period account for the SWA differences obtained between MDD men and NC men nor can the sex differences within the depressed group be accounted for by the phase theory. In addition, the results of this study cannot be explained on the basis of differences in prior wakefulness or sleep on the adaptation night in the laboratory, as noted in the subject section of this report. Rather, the outcome described here appears to reflect both disease-dependent and sex-dependent effects on SWA. Taken together, this further strengthens the interpretation that men with depression have impaired homeostatic regulation of SW sleep. To fully confirm the hypothesis, however, it would be necessary to systematically manipulate SWA by extending prior wakefulness or to examine SWA recovery in response to sleep deprivation. We would hypothesize that men with MDD would show a smaller SWA response to sleep deprivation than all other groups.

With regard to sex differences, the magnitude of the effect in healthy control subjects was considerably smaller than in some previous reports. Dijk et al. found 50% higher SWA power in healthy women with higher expected SWA parameters from the time course analysis, compared to men (Dijk et al., 1989a). By contrast, Ehlers and Kupfer (1997) have noted sex differences in SWA in healthy adults only after the age of 30. In the present study, 20–30-year-old healthy women showed approximately 14% higher SWA amplitude than healthy men overall, and in the first NREM period. Healthy women 30–40 years of age did not differ from men nor did either younger or older women differ from men in SWA regulation. Several other studies in our lab have

also shown small sex differences in SWA in young healthy control subjects (Armitage and Roffwarg, 1992; Armitage and Hoffmann, 1997; Armitage et al., 2000b). The present findings also indicated that age-related changes in SWA amplitude differed from NC men and women. However, a recent preliminary study demonstrated similar age-related declines in SWA amplitude in healthy men and women in comparisons of 20–40-year-olds with those over 50 (Carrier et al., 1999). Clearly, additional work is necessary to determine whether healthy women show a differential maturational time course from men. Regardless, these maturational effects clearly differ from those in patients with MDD. In fact, neither depressed men nor women showed a strong relationship between age and SWA measures, a finding that is provocative in light of the relatively young sample (20–40 years of age). Men with MDD showed SWA impairment in the 20–30 and 30–40 years of age groups, whereas no evidence of SWA impairment was found in women with MDD in either age group. This also raises the possibility that equivalent SWA impairment may also be evident in males with early onset MDD. If this suggestion is correct, SWA abnormalities should also be present in adolescent males with depression and perhaps even in younger males with MDD. Preliminary evidence supports this view (Armitage et al., 2000a). Adolescent females with MDD, however, also showed lower SWA amplitude than healthy control subjects, but the depressed adolescent females were only 20–25% higher than the 20–40-year-old women with MDD in the present study. Therefore, it appears that depressed females show an initial decrease in SWA at adolescence with little additional decline in the middle years. The maturational time course in depressed males appears quite different, with more substantial loss of SWA by the early twenties. Although previous work has also suggested that depression is associated with premature aging (Reynolds and Kupfer, 1987; Veith and Raskind, 1988), the present study indicated that more than just accelerated aging is evident in men with MDD since the time course of SWA in MDD men under 30 was abnormal in comparison to both younger and older NC men and was also

abnormal in MDD men over 30. If just premature aging were evident, the between-group differences in the regulation of SWA would not have been evident in older men.

Differential age effects do, nonetheless, appear to influence between-group discrimination. Thus, distinguishing between depression-related and age-related influence may become increasingly more difficult in middle to later life as suggested previously (Reynolds et al., 1990), particularly if studies focus on the amount of SWA rather than its distribution or time course. With regard to women, neither the amount nor the time course of SWA is likely to differ in early to mid adulthood. Regardless, the sex differences in the depressed group are consistent with previous reports (Reynolds et al., 1990; Armitage et al., 1995) and continue to demonstrate that sex differences in depression are more striking than those observed in healthy adults (Dijk et al., 1989a; Armitage et al., 1995, 2000b; Armitage and Hoffmann, 1997; Ehlers and Kupfer, 1997). These findings provide very strong support for the hypothesis that the pathophysiology of depression differs for men and women.

In summary, depressed men, but not women, showed an abnormal time course of SWA amplitude in NREM sleep, compared to healthy control subjects. The accumulation and dissipation of SWA across NREM was significantly flatter and slower in men with MDD than in all other groups. Women with MDD showed little evidence of SWA impairment. Age also appeared to differentially influence SWA activity between men and women in both depressed and control groups. Particularly in the first NREM period, age effects on SWA amplitude appeared to be both disease- and sex-dependent. Researchers should be sensitive to the possibility that the influence of age on SWA activity may not be constant across groups.

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