

Temporal Characteristics of Delta Activity During NREM Sleep in Depressed Outpatients and Healthy Adults: Group and Sex Effects

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Study Objectives: The primary aim was to evaluate group and sex differences in delta activity across non-rapid eye movement (NREM) sleep in depressed patients and healthy controls.

Design: Repeated-measures ANOVA contrasted delta power, amplitude and incidence in the first three NREM periods (stages 2,3, and 4) of sleep. The time course of delta activity was evaluated with exponential regressions. Age effects on delta were evaluated with linear regression analysis.

Setting: Two consecutive nights were spent in the laboratory, the first of which served as adaptation.

Patients or Participants: Twenty-two (9 men, 13 women) symptomatic, but unmedicated, outpatients with major depressive disorder (MDD) and 23 healthy controls (15 men, 8 women) participated in the study.

Measurements and Results: Delta power and amplitude showed significant group by sex interactions. Men with MDD showed lower power and amplitude in NREM sleep compared to women with MDD, but did not differ significantly from controls. However, the time course of delta power and amplitude was significantly different in men with MDD, with lower accumulation and slower dissipation across NREM sleep than all other groups. Women with MDD showed no evidence of lower delta power and amplitude or an abnormal time course compared to control women or men. Age had a differential influence on delta activity between the groups, with little age-related change in delta activity in the depressed groups.

Conclusions: It was concluded that slow-wave sleep deficiencies may be characteristic of men, but not women, with MDD. It was also concluded that the influence of age on delta activity varied as a function of both psychiatric status and sex.

Key words: Sleep EEG; depression; delta; sex differences; computer-quantified EEG; period analysis; power spectral analysis

INTRODUCTION

A CONSIDERABLE NUMBER OF STUDIES HAVE INDICATED THAT MAJOR DEPRESSIVE DISORDER (MDD) is characterized by 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. 1). However, a recent meta-analysis has indicated that no single sleep variable reliably differentiates depressed patients from healthy controls.² Moreover, not all studies, particularly more recent work, have shown significant differences between patients and controls.³⁻⁴ Short REM latency (<65 minutes) and/or reduced slow-wave (SW) sleep, for example, are only present in 40%–60% of outpatients with MDD. As suggested recently, it is very likely

that confounds such as age and sex have contributed to discrepant outcomes in sleep studies of MDD, most notably with regard to slow-wave sleep and measures of delta EEG activity (cf. 3-5). This issue is a key focus of the present paper.

Work on REM and SW sleep abnormalities has led to speculation that sleep regulatory processes are disrupted in MDD. Specifically, the regulatory disturbance has been postulated as one of REM disinhibition, due to an imbalance in cholinergic-aminergic neurotransmitters that leads to both the early onset of REM and increased phasic REM activity.⁶ There is fairly strong evidence that MDD is associated with increased cholinergic sensitivity using critical REM induction tests. To date, there is little evidence to refute this theory of sleep disturbance in MDD, although cholinergic sensitivity may not be specific to depression.⁴

Others have suggested that the circadian oscillator that controls temperature, neuroendocrine function, and REM sleep is phase-advanced relative to SW sleep.⁷⁻⁸ More recent evidence indicates that MDD is more likely to be associated with blunted amplitude circadian rhythms,⁹

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although studies rarely evaluate "endogenous" pacemakers in these patients. Using constant routine procedures, Monk et al.¹⁰ failed to show evidence of either phase-advanced or dampened amplitude temperature rhythms in those with MDD.

From a different perspective, Borbély and Wirz-Justice¹¹ have suggested that the reduction in stage 3–4 sleep reported in MDD reflects a deficiency in the homeostatic "Process S"; the failure to accumulate SW sleep pressure during the daytime that results in the early emergence of REM and lower amplitude SW activity in NREM sleep. Considerable data are available for evaluating SW sleep regulation in MDD, aided by increased access to computer algorithms that enhance descriptions of EEG frequency characteristics of sleep. Using power spectral analysis (PSA), based on the fast-Fourier transform, Borbély and colleagues demonstrated lower delta power in nine adult unipolar, unmedicated, depressed patients compared to age- and sex-matched healthy normal controls.¹² This initial finding was confirmed in a group of eight younger patients with MDD (20–30 years old), compared to eight age-matched controls.¹³ Delta power did not, however, differentiate older patients (>50 years) from sex-matched controls in the same age range,¹⁴ and may not be a characteristic of bipolar patients.¹⁵

Kupfer and colleagues have also utilized delta wave-count statistics, based on period amplitude analysis (PAA) to quantify delta activity. In several studies, they have reported lower delta wave counts in patients with MDD compared to controls, but these differences were largely restricted to the first non-rapid eye movement (NREM) period of the night.^{16–18} 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.¹⁹

A more recent study has been unable to replicate either lower delta wave counts or an elevation in delta in the second NREM period in patients with MDD.²⁰ However, the delta wave counts from the Kupfer et al. studies and from Armitage et al.²⁰ both emphasized high-amplitude delta activity (>75 μ V) and as such, may not accurately describe changes in amplitude-independent delta across NREM periods. Perhaps more importantly, van den Hoofdakker and Beersma²¹ have suggested that it is the distribution of delta activity across the night, not the total amplitude or incidence, that differentiates patients with MDD from control subjects.

Although several studies indicate considerable overlap between PSA and PAA in delta frequency bands,^{22–25} it is conceivable that the outcome of the two techniques may differ, particularly in describing delta activity in those with MDD.³ In addition, sex and age may account for a substantial portion of variance in delta activity among healthy

controls²⁶ and in comparison to patients with MDD.^{14,27–28} In general, women tend to show higher delta amplitude than men and may show a decline in delta amplitude later in life than men.²⁹ Sex differences may be even stronger in those with MDD.³⁰

The primary aim of the present study was to evaluate the impact of sex and age on SW sleep disturbances in symptomatic, unmedicated depressed patients, contrasted to healthy controls. Changes in delta amplitude and incidence from PAA and delta power from PSA were evaluated across successive NREM periods, to determine whether MDD was characterized by an abnormal distribution of delta activity. Group by sex interactions were expected. A secondary aim was to describe the time course of changes in delta activity within and across NREM sleep in patients and controls.

METHODS

Subjects

Sleep data from participants were selected from our archival database collected under standard conditions over the past four years. Inclusion in 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 data from this sample have been reported previously. All participants maintained regular bed- and rise-times based on home diaries collected for five days prior to study. This habitual sleep schedule was also followed in the laboratory.

Depressed Outpatients

Twenty-two outpatients (9 men and 13 women) 18–40 years of age (mean 31.4 \pm 6.2 years), who met DSM-III-R criteria for nonpsychotic major depression, but who were otherwise physically healthy, participated in study. The average age in men was 33.7 \pm 5.6 years and 29.8 \pm 6.3 years in women. In addition, other current Axis I disorders, current general medical conditions or substance abuse within 12 months prior to baseline study excluded subjects. Eight women were using implant or oral contraceptives. The remaining five women were studied during the early follicular phase of their menstrual cycles.

Diagnoses were made based on the Structured Clinical Interview for DSM-III-R.³¹ The 17-item Hamilton Rating Scale for Depression (HRS-D)³² 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 two weeks prior to study. Clinical and demographic details of the patient sample are presented in Table 1.

Normal Controls

Although an exact match on age and sex between controls and patients would have been preferable, a trade-off in favor of increased degrees of freedom was made. Criteria for selecting healthy controls closely followed that used for patients with MDD. The final sample of controls consisted of five fewer women and six more men than the depressed sample.

Twenty-three healthy adults (15 men and 8 women) 22–40 years of age (mean 28.4 ± 5.9 years) participated in study. The average age was 27.1 ± 5.5 years in men and 30.9 ± 6.2 years in women. All normal controls (NCs) 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 (nonpatient version). All subjects had HRS-D scores of ≤ 2 at the time of study. Eight women were using oral or implant contraceptives. The ninth woman was studied during the early follicular phase of her menstrual cycle.

Table 1—Clinical and Demographic Characteristics of Outpatients with MDD

	MEAN	S.D.	RANGE
# Men n=9			
# Women n=13			
Age (years)	31.4	6.2	18-40
HRS-D 17-Item	22.8	3.6	17-32
Age of Onset (years)	24.6	11.1	11-37
# Previous Episodes	2.4	1.8	1-6
Length Current Episode(months)	42.4	31.8	1-120
IDS-C 30-Item	39.1	7.9	27-57
RDC			
# Endogenous n=9			
# Probable Endogenous n=6			
# Nonendogenous n=7			

MDD: Major Depressive Disorder
 HRS-D: Hamilton Rating Scale for Depression
 IDS-C: Inventory of Depressive Symptoms - Clinician Rated
 RDC: Research Diagnostic Criteria

PROCEDURES

Each participant spent two 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 in

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 Kohm resistor to minimize nonhomogeneous current flow and potential artifactual hemispheric asymmetries³³ as is standard in our laboratory. EEG was transduced by GRASS™ P511 A/C amplifiers set at a sensitivity of 5 ($50 \mu\text{V}$, 0.5s 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 online at 250 Hz (62.5 Hz for EOG and EMG) through a 16-bit MICROSTAR™ 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 and PSA. Sleep records were scored according to standard criteria³⁴ by research personnel trained at better than 90% 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.

Signal Processing

The PAA algorithm used here has been described in detail elsewhere.^{30,35} For the purposes of this report, only amplitude and incidence (based on a half-wave zero-cross analysis) in the delta band (0.5 to <4 Hz) are 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-second 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.

The PSA algorithm was taken from Press et al.,³⁶ processing data in two-second epochs. Following their recommendation that PSA be computed where the sample size is an integer power of two, the digitized data values based on 250 Hz were padded with six zeros to produce 512 samples/2s. The PSA generated a vector of data describing power in the delta band (0.5 to <4 Hz). Delta power was then averaged in 30-second epochs to provide identical epoch lengths to the stage-score data and to the PAA.²²

Data Analysis

The definition of NREM periods closely followed that outlined by Dijk et al.³⁷ and Feinberg and Floyd.³⁸ NREM

periods were defined as the succession of stages 2, 3, or 4 of ≥ 15 minute duration and terminated by stage REM or a period of wakefulness of at least five minutes. Stage 1 sleep epochs were excluded. No minimum REM duration was required for the first or last REM period. Delta power from PSA, and delta amplitude and incidence from PAA 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) and sex. All statistical analyses were conducted using SAS[®] routines. Repeated-measures analyses of variance (ANOVAs) were computed, treating NREM period as a three-level repeated measure. Separate ANOVAs were computed on the dependent measures: PSA power, PAA amplitude, and PAA incidence. Interactions were tested first, followed by main effects. When significant group by sex interactions were obtained, least-squares multiple comparisons tested differences between individual means at an experiment-wise $p < .05$, to protect against Type 1 errors.

For analysis of the time course of changes in delta activity across NREM periods, the start point or latency to the first NREM period was used to synchronize subjects within and across groups. Delta power and amplitude measures within a NREM period were expressed relative to delta power in all NREM sleep epochs. Exponential regression equations were fitted to the time course data, using time

since sleep onset is the independent variable. These procedures are similar to those outlined by Borbély's group and our own,^{26,37,39-41} 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 a further evaluation of whether delta homeostasis differed between patients and controls.

With regard to age effects, there was an insufficient number of subjects in each cell to evaluate the three-way group by sex by age interaction as would have been more appropriate statistically. Instead, multiple regressions evaluated age effects on delta power, amplitude and incidence measures using age as a continuous variable.

RESULTS

Sleep Stage Variables

Although not the main focus of the present study, means and standard deviations of select sleep stage variables are included for comparative purposes in Table 2. ANOVAs contrasted group and sex main effects and interactions followed by multiple comparisons. Significant effects are noted in the table. The % SW sleep (stages 3 and 4), % Stage 1, and % Awake showed significant group by sex interactions (F range: 3.5-3.7; $df=3,42$; $p < .02$). Men with MDD had significantly less SW sleep compared to women with MDD and NC men ($p < .007$) by multiple comparison, but did not differ from NC women ($p < .25$). The % Awake was also significantly higher in men with MDD, compared

Table 2—Means and standard deviations (in brackets) 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)

	NCM	MDDM	NCW	MDDW
Sleep Latency ¹ (in min)	15.4 (10.1)	14.3 (7.5)	8.2 (5.8)	17.7 (10.9)
Total Sleep Time (in min)	384.5 (45.3)	402.4 (50.6)	410.3 (37.6)	390.0 (45.0)
REM Latency (in min) ^A	76.5 (33.7)	92.1 (33.1)	72.7 (9.1)	79.3 (28.4)
REM Latency (in min) ^B	75.3 (39.7)	74.0 (25.2)	81.3 (27.2)	76.8 (41.0)
% Stage 1*	14.6 (7.5)	20.9 (3.1)	14.5 (4.8)	13.1 (6.5)
% Stage 2	53.9 (6.5)	48.3 (7.2)	54.9 (4.9)	52.1 (10.9)
% SW Sleep*	9.5 (3.8)	1.2 (1.9)	5.4 (3.6)	9.0 (3.5)
% REM	17.6 (4.4)	19.7 (4.4)	21.4 (3.8)	18.6 (5.3)
% Awake*	4.5 (1.9)	9.1 (5.7)	3.8 (1.9)	6.2 (4.8)
NREM1 Latency ² (in min)	25.9 (18.1)	16.1 (7.8)	37.5 (12.9)	43.1 (31.2)
NREM1 Duration (in min)	75.6 (32.5)	78.1 (27.0)	71.9 (9.5)	71.2 (30.6)
NREM2 Latency ² (in min)	108.9 (17.1)	126.1 (45.3)	202.4 (23.7)	222.5 (80.4)
NREM2 Duration (in min)	75.3 (17.1)	64.7 (28.7)	65.1 (11.3)	70.1 (13.0)
NREM3 Latency ² (in min)	265.7 (35.0)	230.0 (67.0)	393.6 (34.5)	414.5 (75.4)
NREM3 Duration (in min)	64.2 (17.0)	80.6 (15.3)	73.2 (9.4)	83.0 (23.3)

¹Latency in minutes from lights out to persistent sleep, defined as the first 10 minutes of sleep with < 2 minutes of intervening wakefulness.

%expressed relative to total sleep period from sleep onset to morning awakening. REM latency includes awake time and is computed to the first epoch of REM.

*Group by sex interaction from ANOVA, $p < .02$

²Time in minutes from sleep onset to the beginning of the NREM (stages 2,3,4) period

^ANo minimum duration criterion, includes awake time

^B3-minute duration criterion, excludes awake time

Table 3—Means and standard deviations (in brackets) of delta power from power spectral analysis (PSA), and delta amplitude and incidence from period amplitude analysis (PAA) collapsed across all NREM (stages 2, 3 and 4) periods for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW)

DELTA MEASURE	NCM	MDDM	NCW	MDDW
PSA Power	330.24 (70.38)	321.26 (48.27)	352.88 (69.92)	443.56 (61.43)
PAA Amplitude	820.58 (188.04)	715.63 (140.87)	858.46 (200.25)	997.26 (204.04)
PAA Incidence	65.98 (6.11)	64.81 (6.89)	65.04 (3.47)	63.92 (7.77)

to all other groups (p range: .003-.001), accompanied by higher % Stage 1 compared to the other groups (p range: .03-.007). Thus, MDD men showed more disturbed sleep than the other groups. Interestingly, they did not show shorter REM latency. No group or sex main effects were evident for REM latency, regardless of whether it was computed including or excluding intervening awake time or a three-minute minimum duration criterion.

The latencies to, and durations of, the first three NREM periods were also compared across groups. Although some differences were noted as seen in Table 2, the repeated-measures interaction between NREM period and group, sex, or group by sex failed to reach significance for durations or for latencies ($F < 1$). As a result, no univariate analyses of the individual NREM periods were computed. None of the remaining sleep-stage measures showed significant main effects or interactions.

Delta Power: Group and Sex Effects

A significant overall group by sex interaction was obtained in delta power derived from PSA ($F = 9.53$; $df = 3, 41$; $p < .0001$). In addition, there was a significant overall sex main effect ($F = 12.16$; $df = 1, 42$; $p < .0012$), whereas the overall group main effect approached significance ($F = 3.26$; $df = 1, 42$; $p < .0783$). The means and standard deviations for all delta measures, collapsed across NREM periods, are shown in Table 3. Higher overall delta power was evident in women in both the NC and MDD groups than that observed in men. Surprisingly, women in the MDD group had higher delta power than all other groups. Men with MDD, on the other hand, showed lower delta power than all other groups, accounting for the significant overall group by sex interaction. Multiple comparisons indicated that women with MDD showed significantly higher delta power than all other groups (p range: .008-.0001). None of the other individual mean differences approached significance (p range: .74-.31).

Group by sex interactions were also evident in each of the first three NREM periods from the univariate ANOVAs (NREM1 [$F = 6.03$; $df = 3, 41$; $p < .0017$], NREM2 [$F = 8.00$; $df = 3, 41$; $p < .0003$], NREM3 [$F = 5.81$; $df = 3, 41$; $p < .0021$]). These effects are illustrated in Figure 1. Note that all groups showed a decrease in delta power over successive NREM periods. Women with MDD had higher delta power

than all other groups in each NREM period, confirmed by multiple comparison (p range: .03-.0001). Although men with MDD had lower delta power in the first two NREM periods than either men or women in the NC group, they did not differ significantly by multiple comparison (p range: 0.19-0.71).

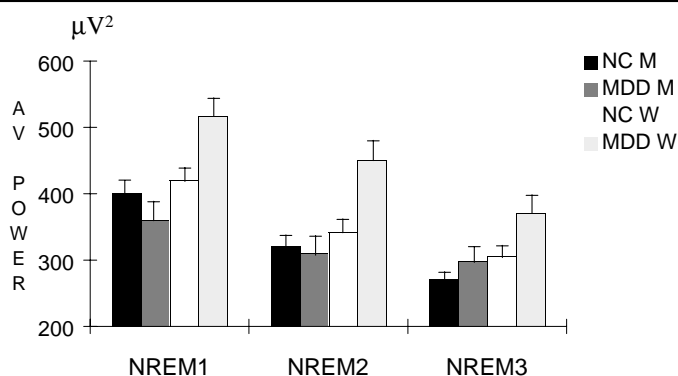


Figure 1—Average delta power from PSA in the first three NREM (Stages 2, 3, 4) periods for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW). Standard deviations are represented as error bars.

Delta Amplitude: Group and Sex Effects

A significant overall group by sex interaction ($F = 4.34$; $df = 3, 41$; $p < .01$) and an overall sex effect ($F = 33.36$; $df = 1, 42$; $p < .0001$) were also evident in the delta amplitude measures, derived from PAA. The means and standard deviations for each group are shown in Table 2, collapsed across NREM periods. As seen in the delta power measures from PSA, women with MDD show the highest delta amplitude, whereas men with MDD show the lowest, accounting for the significant interaction. Multiple comparisons indicated that delta amplitude in women with MDD was significantly higher than men in the NC and MDD groups ($p < .02$, .001; respectively), but not in comparison to NC women ($p < .10$). Although women in the NC group showed 4.6% higher amplitude delta than NC men and 19.9% higher than men in the MDD group, these differences did not reach statistical significance ($p < .65$, .19; respectively).

Significant group by sex interactions were also evident in the first ($F = 2.97$; $df = 3, 41$; $p < .05$) and second ($F = 4.19$; $df = 3, 41$; $p < .01$) NREM periods, but not the third ($F = 1.17$;

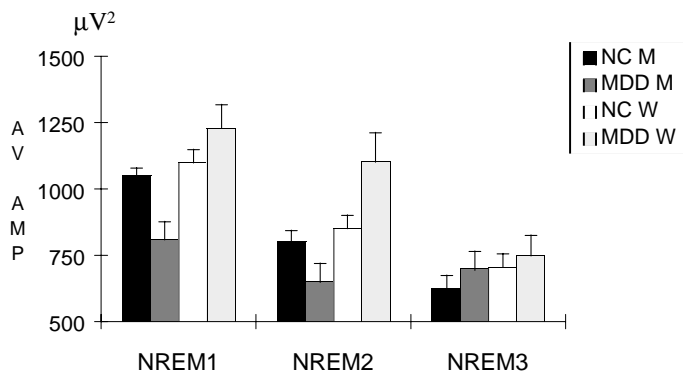


Figure 2—Average delta amplitude from PAA in the first three NREM (Stages 2, 3, 4) periods for normal control men (NCM), depressed men (MDDM), normal control women (NCW) and depressed women (MDDW). Standard deviations are represented as error bars.

df=3,41; $p<.34$). These effects are shown in Figure 2. Multiple comparisons of means in the first NREM period revealed that women with MDD had significantly higher delta amplitude than MDD men ($p<.005$), but did not differ from men or women in the control group ($p<.17, .26$;

respectively). Although men with MDD showed lowest amplitude delta activity, they did not differ significantly from NC men or women, by multiple comparisons ($p<.08, .11$; respectively).

With regard to the second NREM period, MDD women showed significantly higher delta amplitude than NC or MDD men ($p<.001, .02$; respectively), but did not differ from NC women ($p<.10$). See Figure 2. None of the remaining multiple comparisons reached significance.

Delta Incidence: Group and Sex Effects

The means and standard deviations for delta incidence, collapsed across NREM periods are also shown in Table 2. Repeated-measures ANOVA failed to reveal overall group or sex main effects or interactions ($F<1$). Thus, no further analyses were conducted.

Time Course of Delta in NREM Sleep

Due to the significant group by sex interactions obtained from ANOVA, the time course evaluations were conducted separately for women and for men, comparing those with

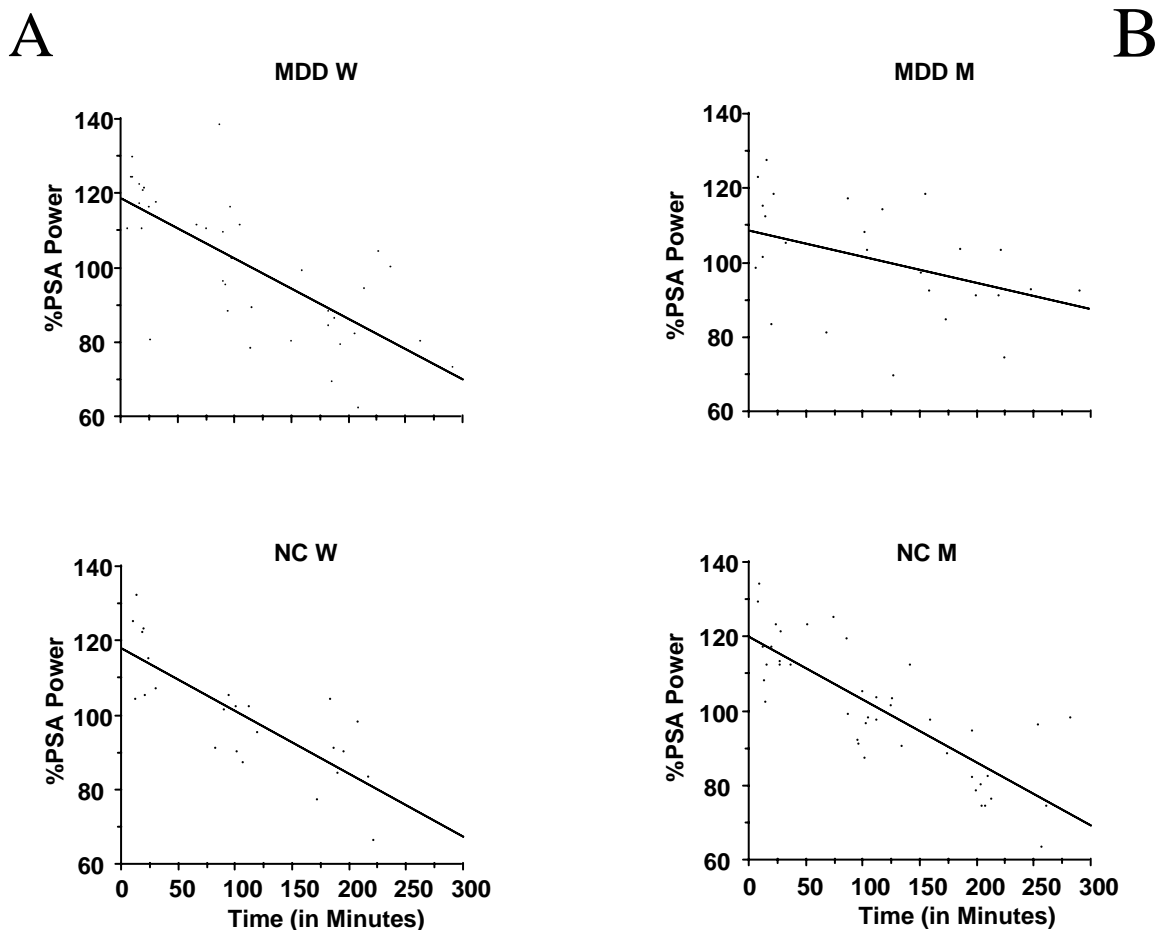


Figure 3—The time course in minutes of delta power expressed as a percentage of all NREM (stage 2, 3, 4) power for depressed women (MDDW), shown top left A, normal control women (NCW), bottom left A, depressed men (MDDM), top right B, and normal control men (NCM) bottom right B.

and without MDD. The time course of delta power is shown for women in both groups in Figure 3A (left). Delta power in the first 25–30 minutes of NREM sleep exceeded 100% of NREM delta power and dissipated over the course of NREM sleep. By minute 150–200, the majority of data points fell below 90% of NREM power. The time course was strikingly similar for control and depressed women. Exponential functions were fitted to data from each group, using the model $y = b \times e^{-c \times \text{time}}$, where b is the expected delta power value at time = 0, c is the exponential change or decay, and time is the minutes of NREM sleep since sleep onset.³⁹ For MDD women, the expected delta power (b) was 119.99 with a asymptotic standard error of 3.82 (95% confidence interval 112.3-127.7) and a rate of decay of $-.0017 \pm .0003$. For NC women, the expected delta power was 119.00 ± 3.71 (95% confidence interval 111.30-126.70) and a $-.0017 \pm .0003$ rate of decay. The R^2 for the exponential function, reflecting goodness of fit was only marginally higher in NC women ($R^2=.63$) compared to women with MDD ($R^2=.52$).

The time course of delta power for men in both groups is shown in Figure 3B (right). Although the rate of decay in NC men was similar to that obtained in both MDD and NC women, men with MDD showed a distinctly different time course. The exponential functions for NC men provided an expected delta power of 122.77 ± 3.88 (95% confidence interval 114.88-130.67) and a $-.0018 \pm .0002$ rate of decay. For MDD men, the expected delta power was 109.42 ± 4.37 (95% confidence interval 100.42-118.41) and a rate of decay of $-.0007 \pm .0003$. The exponential equation for men with MDD produced an $R^2=.21$, well below that observed in any other group. The goodness of fit in NC men was more similar to both groups of women, producing an $R^2=.66$. Men with MDD differed dramatically in the dissipation of % delta across NREM sleep compared to all other groups, as seen in Figure 3. Student's t -tests indicated a significantly slower rate of decay (c) and lower expected delta power estimates in MDD men compared to all three other groups (p range: .03-.001). The exponential parameter estimates did not differ significantly among MDD or NC women and NC men.

The time course analysis of delta amplitude from PAA mirrored the findings for delta power, with only very minimal differences in parameter estimates and goodness of fit in all groups. Therefore, these data are not shown. Again, men with MDD showed a slower rate of decay across

NREM sleep and lower delta amplitude parameter estimates compared to all other groups (p range: .032 - .001).

Age Effects

Although an ANOVA of group by sex interactions on age (treated as a dependent variable) was not statistically significant ($F=2.4; df=3,40; p<.11$), MDD men were significantly older than men in the NC group by multiple comparison ($p<.02$). The MDD men did not show significantly lower delta power and amplitude than the control groups, but did show an abnormal time course. This raises the possibility that age may contribute to between-group differences in delta activity.

Multiple regressions were used to further clarify the potential influence of age on the observed group by sex interactions. Regressions were computed on the entire sample and separately for each group. The resultant R^2 values and associated probabilities for delta power, amplitude and incidence in the first NREM period are shown in Table 4. Note that only NC women showed a strong age influence, with decreases in delta power, amplitude and incidence with increasing age. Women in the MDD group and men in the NC group showed only moderate correlations between delta power, amplitude and age, whereas MDD men showed no relationship between any of the delta measures and age. These results strongly suggest that there are differential age effects on delta activity in depressed patients and healthy controls that are sex dependent.

Regression analysis of age on delta power and amplitude collapsed across NREM periods also revealed significant differences between groups, indicating that the differential influence of age is not restricted to the first NREM period. Thus, neither higher delta power and amplitude in depressed women nor an abnormal time course of delta in depressed men can be explained by age differences in the sample. As confirmation, we recomputed ANOVAs and exponential regressions on an age-matched subset of subjects restricted to 26–40 years of age ($n=33$). Higher delta power and amplitude were still evident in MDD women compared to all other groups ($p<.005$) and men with MDD continued to show lower than expected delta power and amplitude estimates with a slower rate of decay than all other groups ($p<.01$).

Table 4—Regression R^2 and probabilities (in brackets) of age on delta measures in the first NREM period by group and sex

MEASURE	NCM	NCW	MDDM	MDDW
Power	.29 (.06)	.62 (.04)	.05 (.59)	.23 (.11)
Amplitude	.18 (.14)	.76 (.01)	.00 (.802)	.24 (.10)
Incidence	.00 (.95)	.79 (.004)	.00 (.93)	.23 (.10)

Exploratory Analyses

A number of exploratory analyses were also undertaken in an effort to further understand and integrate the group by sex interactions with existing theory and data on delta activity in depression. Previous work has suggested that the level of delta power and amplitude are dependent upon the amount of prior wakefulness.⁴⁰ Since sleep/wake diaries were collected for five days prior to study, data were available to evaluate whether the amount of prior wakefulness influenced between-group differences in delta measures. All subjects estimated total sleep time between 6.5–7.5 hours on each of the prior five nights and means did not differ between groups ($F < 1$). Comparing the duration of wakefulness immediately preceding the adaptation night in the laboratory, no group or sex main effects or interactions were evident ($F < 1$). Most relevant to the interpretation of the findings reported in the present study, women with MDD had the shortest amount of prior wakefulness (16.8 ± 2.1 hours) but yet showed highest delta power and amplitude. Control men showed the longest duration (17.9 ± 1.5 hours), with NC women (17.0 ± 1.3) and MDD men (17.1 ± 2.4) in the middle. Moreover, sleep characteristics on the adaptation night did not suggest that women with depression had more disrupted sleep as might be expected. In fact, men in the depressed group showed the longest sleep latency, lowest sleep efficiency, and more intermittent wakefulness on the adaptation night, but showed the lowest delta power and amplitude overall and in the first NREM period.

Of additional theoretical and interpretive interest was the relationship between REM latency and delta activity. Although there were no significant between-group differences on REM latency, this variable could still differentially influence delta power and amplitude between groups. Since men with MDD had the lowest delta power and amplitude, it might be expected that they would show shortest REM latency. Pearson's correlation coefficients were computed among the key variables to evaluate this possibility. None of the correlations exceeded $\pm .20$ and did not show evidence of between-group differences. In fact, REM latency accounted for less than 5% of the variance in delta power and amplitude. Even restricting the analysis to the 15 subjects (6 NC, 9 MDD) who showed short (< 65 min) REM latency did not improve the relationship with delta measures, producing correlations that were smaller than $\pm .13$.

DISCUSSION

The major finding of this study was that depressed men showed evidence of delta abnormalities in NREM sleep, with an abnormal time course of delta amplitude and power in comparison to both control groups and to depressed women. Men with MDD showed lower delta power and

amplitude from exponential regression parameters and a significantly slower rate of decay than all other groups. In essence, there was a lower accumulation of delta with little decay over NREM sleep time. Traditional visual stage-scoring indicated that depressed men also had reduced high-amplitude delta activity (lower % SW sleep) compared to control men or depressed women, but not relative to normal control women. By contrast, depressed women showed no evidence of lower delta power or amplitude in NREM sleep, nor did they show an altered time course in comparison to normal control women.

The findings of the present report are not inconsistent with the suggestion of Borbély and colleagues that a SW sleep deficiency is characteristic of depression,^{11,45} but add the caveat that it appears to be sex-dependent. There is, however, little evidence that REM sleep is phase-advanced relative to SW sleep in depression as suggested by Wehr and colleagues,^{7-8,44} since REM latency and the first NREM period duration do not appear to relate to delta measures. The phase-advance theory would predict that those individuals with the shortest REM latency would be most likely to show lower delta power or amplitude and a short first NREM period duration. However, men with MDD showed the longest REM latency but lowest delta power and amplitude and the longest duration first NREM period compared to all other groups, although these differences were not always statistically significant. Moreover, REM latency did not correlate strongly with delta measures overall or those obtained from the first NREM period. This finding was somewhat surprising since most theories of sleep disturbance in depression share the implicit assumption that REM latency and SW activity have a reciprocal relationship.⁴³ In fact, the outcome of this study suggests that the amount or amplitude of delta activity bears little relationship to REM latency in either healthy controls or depressed patients. 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. Rather, the outcome described here appears to reflect both disease-dependent and sex-dependent effects on SW activity.

As discussed in the introduction, studies have provided inconsistent results with regard to delta differences between healthy controls and depressed patients. Some studies have shown significantly lower delta amplitude and incidence in patients with MDD,^{12-13,18-19} although perhaps not in bipolar patients.¹⁵ In the present study, delta power and amplitude did show evidence of group main effects, but they were substantially smaller than the group by sex interactions. Delta incidence was not lower in those with MDD, nor did it show a systematic change across successive NREM periods. Thus, we cannot confirm Kupfer et al.'s findings of lower delta wave counts in depression.¹⁶⁻¹⁹ However, Kupfer's group focuses on high-amplitude delta waves ($> 75 \mu V$), perhaps accounting for the discrepancies

in findings. Nevertheless, our earlier report,²⁰ based on high-amplitude delta waves also failed to reveal abnormal delta incidence and ratios in those with MDD.

With regard to sex differences, the magnitude of the effect in healthy controls was considerably smaller than that reported previously. Dijk et al.²⁶ found 50% higher delta power in healthy women with a different time course from men. By contrast, Ehlers and Kupfer²⁹ have noted sex differences in delta activity in healthy adults only after the age of 30. In the present study, healthy women showed only marginally higher delta power and amplitude than healthy men and did not differ in the time course of delta activity. Since the healthy women in this study were on average more than eight years older than those in the Dijk et al. study,³⁷ but the men were only 3.6 years older, it is entirely possible that we have underestimated the sex differences in delta activity in healthy controls. However, the secondary age-restricted analyses of the time course also failed to confirm sex differences in NCs who are 26–40 years of age. Taken together, these results suggest that sex differences in delta activity in healthy adults are likely to decline with increasing age. This may not be the case with depressed patients.

Unfortunately, there were too few subjects in each age group in the present study to determine if delta power and amplitude differed between young MDD and NC men, or to determine if the strength of the sex differences in the depressed group was evident across ages. The use of age as a statistical covariate would not have helped resolve the issue since differential age effects were evident between groups, and hence violated the assumptions of analysis of covariance.⁴⁸ Using age as a covariate would have undercompensated for the age effects in NC women and overcompensated in MDD men. In the age-restricted analyses, however, men with MDD continued to show an abnormal delta time course, although the power and amplitude within a NREM period did not differentiate them statistically from NC men. Women with MDD showed higher delta power and amplitude than all other groups but did not differ in time course from controls as found in the full sample. Moreover, a preliminary report of older (>40 years of age) depressed patients confirms that sex differences in MDD are also evident in older patients, again demonstrating significantly higher delta power and amplitude in MDD women than in men.⁴⁶ Taken together with the present study, it appears that sex differences in MDD do indeed persist throughout the life cycle.

The regression analyses revealed differential age effects on delta between men and women in both the control and depressed groups. In fact, depressed men showed no relationship between age and delta measures, a finding that is provocative in light of the relatively young sample (18–40 years of age). This raises the possibility that the expected age-related decline in delta occurs earlier in depressed men

than in healthy controls and depressed women. If this suggestion is correct, delta abnormalities should also be present in adolescent males with depression and perhaps even in younger males with MDD. To our knowledge, no study has evaluated delta activity during sleep in early onset depression. Regardless, the sex differences in the depressed group are consistent with previous reports^{27–28} and continue to demonstrate that sex differences in depression are more striking than those observed in healthy adults.^{26–27,29,46}

It is also particularly interesting that depressed women showed highest delta power and amplitude yet have also been reported to show more fast-frequency activity during sleep than depressed men.^{27,47} A concomitant increase in fast-frequency EEG with no subsequent decrease in delta does not fit the view that depression is associated with hyperarousal, *per se*. Rather, in depressed women, these paradoxical findings are more suggestive of dysregulation in the organization of arousal and activation in the brain during sleep.⁵ We have reported previously that depressed women show lower temporal coherence in ultradian (90 min) rhythms during sleep and are more likely to show variable phase relationships between EEG rhythms during sleep.^{3,5,47} Coupled with the findings reported here, it appears that the pathophysiology of depression differs for men and women. Unfortunately, there are too few studies of sex differences in depression to speculate on the mechanisms underlying the preservation of delta activity and SW sleep regulation in depressed women. Further, it remains to be demonstrated whether the sex differences in depression (or in normal controls) reflect divergent sleep regulatory processes, maturational or anatomical differences between men and women.²⁶ Such evidence could be obtained in sleep deprivation studies and direct manipulation of the amount of prior wakefulness.

On a final note, there has been considerable debate about the comparability of PSA and PAA in quantifying sleep EEG.^{22–25} The results from PSA power and PAA amplitude in the present study were equivalent with regard to group and sex effects and the influence of age. Further, although the delta amplitude values were higher relative to delta power, the distribution across NREM periods and the time course of delta was very similar between the two techniques within and between groups. We take this as further evidence for the comparability of PSA and PAA in quantifying the power or amplitude of delta activity. Clearly, however, delta incidence does not always covary with delta power and amplitude.

In summary, depressed men, but not women with MDD, showed an abnormal time course in delta power and amplitude in NREM sleep, compared to healthy controls. The dissipation of delta activity across NREM sleep did not differ among healthy men and women and depressed women but was significantly slower and flatter in men with MDD.

Women with MDD were not characterized by low delta power or amplitude. Age also appeared to differentially influence delta activity between men and women in both depressed and control groups. These findings provide further evidence that the pathophysiology of MDD differs between men and women and strongly suggests that sleep studies should evaluate sex differences statistically in this population. Researchers should be sensitive to the possibility that influence of age on delta activity may not be consistent across groups.

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