

Sex Differences in Delta and Alpha EEG Activities in Healthy Older Adults

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Study Objectives: To examine sex effects on sleep stages and electroencephalogram (EEG) spectral power in older adults.

Design: Sleep was polygraphically recorded for 2 consecutive nights, and blood was sampled during the last 24 hours.

Setting: The University of Chicago Clinical Research Center.

Participants: Two groups of healthy nonobese older subjects: 10 men (59 \pm 2 years), and 10 postmenopausal women (63 \pm 2 years).

Interventions: N/A.

Measurements and Results: A spectral analysis of the EEG was performed in the delta and alpha bands. There were no sex differences in sleep stages. Blood sampling resulted in reductions of total sleep time, sleep maintenance, slow-wave sleep, and absolute delta activity that were all larger in women than in men. In absolute values, delta and alpha activities in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep were higher in women than in men, but, for delta activity, the sex differences were larger in REM than in NREM sleep. In women, but not in

men, absolute delta activity in REM was decreased during blood sampling and was strongly correlated with absolute delta activity in NREM. Delta activity in REM did not dissipate across the night in either group. When normalized for the activity in REM sleep, the sex difference in delta activity in NREM sleep was reversed, with lower activity in women.

Conclusions: Sex differences in sleep EEG variables are present in older adults. When normalized, delta activity in older women is lower than in older men, which may be more consistent with sex differences in subjective complaints, in fragility of sleep in the presence of environmental disturbances, and in the relationship to growth-hormone release.

Keywords: Aging, sex differences, sleep homeostasis, delta activity, alpha activity.

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INTRODUCTION

ELDERLY INDIVIDUALS FREQUENTLY COMPLAIN OF SLEEP PROBLEMS, REPORTING SHALLOW UNREFRESHING SLEEP, FREQUENT AWAKENINGS DURING THE night, early morning awakenings, and daytime naps.¹⁻⁴ Numerous studies have shown that these age-related changes in subjective sleep quality reflect marked alterations in polysomnographically defined sleep architecture.⁵⁻¹⁵ While the sleep period remains relatively constant across adulthood, significant sleep fragmentation occurs after 50 years of age, resulting in a reduction of total sleep time and thus in a decrease in sleep efficiency.^{7,10,11,13-17} Most studies have observed a marked reduction of slow-wave sleep (SWS) with aging in both men and women.^{8,10,11,13,14,16-19}

In young adulthood, women have more SWS than men, and some studies have indicated that this sex difference persists in later life.^{7,9,13,16,19-27} Electroencephalogram (EEG) spectral power analysis provides a better quantification of sleep depth or sleep intensity than does visual sleep staging. In particular, delta activity (i.e., a measure of the intensity of SWS, quantified by EEG spectral power in the low-frequency range) is the primary marker of the homeostatic regulation of sleep.^{28,29} Dijk and colleagues³⁰

were the first to examine sex differences in EEG spectral power and observed that significantly higher power densities were present over a wide frequency range (0.25-11.0 Hz) in female versus male young volunteers. These differences were of similar magnitude for non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep,³⁰ suggesting that they reflected nonneuronal anatomic differences, such as head size and skull thickness, rather than an impact of sex on homeostatic sleep regulation. A subsequent study using a period-amplitude analysis of EEG activity found no significant sex difference in any sleep stage but detected higher delta power in NREM sleep in young women as compared with young men.³¹ The observation that women have higher spectral power in the low-frequency EEG range was confirmed by Mourtazaev and colleagues across a wide age range (26-101 years).¹⁹ An attempt to control for anatomic differences was proposed by Antonijevec and colleagues, who calculated the ratio of EEG delta power to EEG sigma power in young men and women and showed that, when compared with men, women have a greater decrease in delta activity and a greater increase in sigma activity from the first to the second half of the night.³² Only one study has examined sex differences in the rebound of delta activity after sleep deprivation, and the response was found to be larger in young women than in young men.³³

In a more recent study of 100 subjects aged 20 to 60 years, Carrier and colleagues looked at power spectra over a wide frequency range and showed that women have higher power density than men only in certain frequency ranges (e.g., delta, theta, and low alpha).¹¹ The analysis did not control for menopausal status. The possible role of physical and anatomic factors, such as skull and skin thickness, in these age and sex differences is difficult to ascertain. The fact that these differences were only present for certain EEG frequency ranges supports the hypothesis that the effects of age and sex on EEG activity could involve differences in neuronal activity.

The observation that the homeostatic control of sleep, as in-

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ferred from the amount of delta activity, is more robust in women than in men is not consistent with the fact that women, and, particularly older women, report significantly poorer quality of sleep than men.^{14,34-36} In a recent study, Vitiello and colleagues found significant sex differences in subjective sleep quality as assessed by the Pittsburgh Sleep Quality Index³⁷ in 150 healthy older men and women without sleep complaints.^{37,14} Remarkably, 33% of the women but only 16% of the men had a Pittsburgh Sleep Quality Index score of above 5, the threshold indicative of significant sleep disturbance.

The present study was designed to delineate sex differences in sleep architecture and sleep EEG power spectra. Our analysis focused on the delta and alpha ranges as markers of the synchronization of cortical oscillations in the low- and high-frequency ranges, respectively, that have their origin in distinct neuronal networks and may be dissociated under physiologic conditions.³⁸⁻⁴⁰ Sleep variables were analyzed in the absence and in the presence of a catheter for blood sampling in order to examine possible sex differences in vulnerability to this disturbance.

METHODS

Subjects and Recruitment

A total of 20 healthy fully self-sufficient nonobese older adults participated in the study. The 2 sex groups consisted of 10 men (59 ± 2 years, body mass index [BMI] of 25 ± 0.7 kg/m², mean \pm SEM), and 10 women (63 ± 2 years, 24 ± 0.7 kg/m²).

The volunteers were recruited through ads in local newspapers and flyers posted in the bulletin boards of the University of Chicago Hospitals. Written informed consent was obtained from all subjects.

Only healthy nonsmoking subjects with regular life habits were included in the study. Shift workers and subjects having traveled across time zones less than 4 weeks prior to the beginning of the study were excluded. All the participants were free of medication, and none of the women were on hormone replacement therapy. Only women who were at least 1 year past menopause and did not suffer from hot flashes were included. None of the subjects consumed more than 2 caffeinated beverages per day on a regular basis. Potential volunteers came as outpatients to the General Clinical Research Center of the University of Chicago to undergo the screening procedures, which included a clinical interview, routine laboratory blood tests, a physical examination, and an oral glucose tolerance test.

Subjects who had diabetes or impaired glucose tolerance were excluded. Selection criteria required that all subjects had a score lower than 5 on the Geriatric Depression Scale Short Form^{41,42} and a score higher than 25 on the Folstein Mini-Mental Status Examination.⁴³ All participants had normal findings on clinical examination, normal results in laboratory tests (including thyroid function tests, biochemistry, complete blood count, and lipid panel) and no history of psychiatric or endocrine illness, sleep disorders, or neurologic disorders.

Experimental Protocol

Starting 1 week before the inpatient study, subjects were requested to maintain regular rest-activity cycles. The bedtime schedule was individually designed for each subject, taking into

account the usual life habits. Compliance was verified by a wrist-activity recording. Subjects were asked to go to bed and to get up at these fixed mutually agreed upon times (± 30 minutes).

The inpatient study spanned 3 days. The subjects were admitted to the General Clinical Research Center at 2:00 PM on day 0 and were discharged on day 3 shortly after 2:00 PM. The first afternoon and night served to habituate the subject to the laboratory environment and procedures. During this first night, electrodes for sleep monitoring were placed on the subject's scalp but no recording took place. On day 1, subjects were allowed to walk around the inpatient area of the General Clinical Research Center, but, on days 2 and 3, when blood was sampled for 24-hour hormone profiles reported in the companion manuscript, they were instructed to remain seated in a comfortable armchair and engage in sedentary activities. Breakfast, lunch, and dinner were served every day at 9:00 AM, 1:00 PM, and 6:00 PM. All meals were of identical nutrient composition (275 kcal, 17% protein, 68% carbohydrates, and 15% fat). Only decaffeinated diet beverages were allowed in addition to water ad libitum. The intensity of the light in the room was less than 300 lux (corresponding to dim indoor light) throughout the periods of wakefulness, while sleep was in total darkness. Naps were not allowed.

Electrodes for polysomnography were placed 1 hour before bedtime, and sleep was recorded during the nights of day 1 and day 2. For all inpatient nights, each subject adhered to the fixed schedule of bedtimes and wake-up times established during the week preceding the study. On day 2 at 12:00 noon, a catheter for blood sampling was placed in the nondominant arm for the measurement of hormone profiles, and blood was collected at 20-minute intervals for 24 hours. Hormone profiles for both sex groups are described in the companion manuscript.⁵⁸

Sleep Recording and Analysis

For both inpatient nights recorded in the laboratory (night of day 1 without catheter for blood sampling; night of day 2 with catheter for blood sampling), polygraphic sleep recordings included EEG, electromyography, and electrooculography. Sensors were placed and equipment was biocalibrated. The recorded EEG signals were Fz, Cz, and Oz. This electrode placement has previously been used in sleep EEG analysis,^{23,19} and no significant difference was reported in comparison to the conventional electrode placement.⁴⁴ The signals were sampled at 50 Hz, and all signals, except electromyography, were filtered through a low-pass filter with a cut-off frequency of 30 Hz. Sleep recordings were scored at 30-second intervals by a board-certified sleep medicine specialist as stages Wake, 1, 2, 3, 4 and REM, according to the criteria of Rechtschaffen and Kales.⁴⁵ Sleep onset was defined as the time corresponding to the first 30-second interval scored 2, 3, 4, or REM, provided the subsequent 30-second interval was not scored wake or stage 1. Morning awakening was defined as the time corresponding to the last 30-second interval scored 2, 3, 4, or REM. The following variables were determined: sleep latency (i.e., time interval separating lights-off from sleep onset), sleep period (i.e., time interval separating sleep onset from morning awakening), total sleep time (i.e., sleep period—total duration of intrasleep awakenings), sleep maintenance (i.e., total sleep time/sleep period time), and the duration of stages Wake, 1, 2, 3, 4, REM, and REM latency.

The EEG signal was submitted to a spectral analysis on the

central EEG lead (Cz-A1) using a software package (PRANA, PhiTools, Strasbourg, France). An automated artifact-detection procedure was applied to each 2-second interval to eliminate ocular, muscular, and movement artifacts, prior to spectral analysis. Recordings were then visually inspected to verify the accuracy of the automated artifact detection, and additional sections of recording that contained artifacts were eliminated. In the first recording night, $7\% \pm 2\%$ of all epochs were removed in women ($4\% \pm 2\%$ in NREM, $2\% \pm 1\%$ in REM) and $5\% \pm 1\%$ in men ($2\% \pm 1\%$ in NREM, $2\% \pm 2\%$ in REM) because of artifacts. In the second recording night, $10\% \pm 3\%$ of all epochs were removed in women ($2\% \pm 1\%$ in NREM, $6\% \pm 5\%$ in REM) and $5\% \pm 1\%$ in men ($0.2\% \pm 0.1\%$ in NREM, $0.4\% \pm 0.2\%$ in REM). The percentages of epochs removed in men were not statistically significantly different from the percentages of epochs removed in women. Then, a fast Fourier transform was computed on consecutive 2-second intervals, resulting in a frequency resolution of 0.5 Hz. A Hanning window was used, which is a signal processing technique that attenuates the contributions of the data from the ends of the epoch, thus minimizing spurious frequencies in the analysis that might arise from the abrupt transition to the analysis epoch.⁴⁶ Power spectra of 15 consecutive 2-second intervals were averaged and matched with the sleep scores. Intervals containing artifacts were considered as missing data to preserve sleep continuity in the analysis. Delta activity was calculated as the absolute spectral power in the frequency band 0.5 to 4 Hz. Alpha activity was calculated as the spectral power in the frequency band 8.5 to 12 Hz. Total power was calculated over the frequency range 0.5 to 12.5 Hz. Relative delta and alpha activities, expressed as a percentage of the total power for each 30-second epoch, were also calculated.

In order to account for the individual differences in the duration of NREM/REM cycles and to analyze the time course of EEG activity, further analyses were performed, as previously described.¹⁰ Each individual NREM period was subdivided into 50 equal time intervals (i.e., time bins) and each REM period into 20 time bins. NREM/REM cycles were defined according to the criteria of Feinberg and Floyd.⁴⁷

Due to a technical failure, computerized EEG recordings for 1 woman (#35) could only be obtained for the first 3 hours during the first night. Computerized EEG recordings of 1 of the men (#20) exhibited artifacts throughout the first night of recording caused by poor impedance. Therefore, comparisons of delta and alpha activities between men and women were performed without the data of subjects #20 and #35.

Consistent with previous reports,⁴⁸⁻⁵¹ there was a very high within-subject reproducibility of delta and alpha activities from the first to the second night in both men and women. Two men had, however, much lower levels of delta activity during the second night as compared with the first night than the other subjects. The ratio of delta activity during the second night to delta activity in the first night averaged 0.895 ± 0.073 (SD) for the other men, but was only 0.355 and 0.501 for these 2 subjects (i.e., more than 5 SD from the mean, statistical outliers, $P < .0001$). Comparisons of the individual profiles of spectral EEG power for the 2 nights in these 2 outliers confirmed a high degree of concordance in the temporal organization of delta and alpha activities across the 2 nights. The discordance in absolute values was therefore attributed to a difference in amplification parameters. For these 2 subjects, delta and alpha activities during the second night were

extrapolated from the values recorded during the first night using the linear regression equation of night 2 versus night 1 calculated for the remainder of the group.

Statistical Analysis

All group values are expressed as mean \pm SEM. A 2-way analysis of variance (ANOVA) for repeated measures was used to examine sex differences in sleep variables during the 2 nights of recording (i.e., in the absence and in the presence of the catheter for blood sampling). When sex differences were identified, an ANOVA for repeated measures with sleep stage as within-subject factor and sex as between-subject factor was performed to determine whether the impact of sex was different during NREM versus REM sleep. Correlation analyses were used to illustrate sex differences in the relationship between delta (alpha) activity in NREM sleep and delta (alpha) activity in REM sleep. Analysis of variance for repeated measures was used to examine changes in EEG spectral power across sleep cycles. All statistical calculations were performed using the StatViewSE⁺ and SuperAnova software packages for Macintosh (Abacus Concepts Inc., Berkeley, CA).

RESULTS

Sex Differences in Sleep Stages

Table 1 reports the results for sleep variables derived from sleep stage scoring for the 2 nights of recording. There were no significant sex differences for any of the measures, but the interaction sex \times night was significant or close to significance for a number of measures, revealing sex differences in the impact of blood sampling on sleep architecture. Irrespective of sex, the presence of the catheter was associated with increased sleep fragmentation, as reflected by a significant increase in wake and a significant decrease in total sleep time and sleep maintenance. The disturbances introduced by blood sampling tended to be more pronounced in women than in men. Indeed, women had an increase in sleep latency ($+16 \pm 7$ minutes vs -5 ± 3 minutes in men) and a decrease of stage 2 (-52 ± 21 minutes vs $+2 \pm 8$ in men) and tended to have a greater reduction of sleep period time (-26 ± 10 minutes vs $+5 \pm 12$ in men) and of total sleep time (-76 minutes ± 27 vs -21 ± 10 in men). In both sexes, the amount of SWS was reduced during the night of blood sampling. There was no impact of the presence of the catheter on REM sleep.

Sex Differences in EEG Spectral Power in the Delta Range

Figure 1 shows representative profiles of absolute delta and alpha activities for 1 man (left panels) and 1 woman (right panels) during the night without blood sampling.

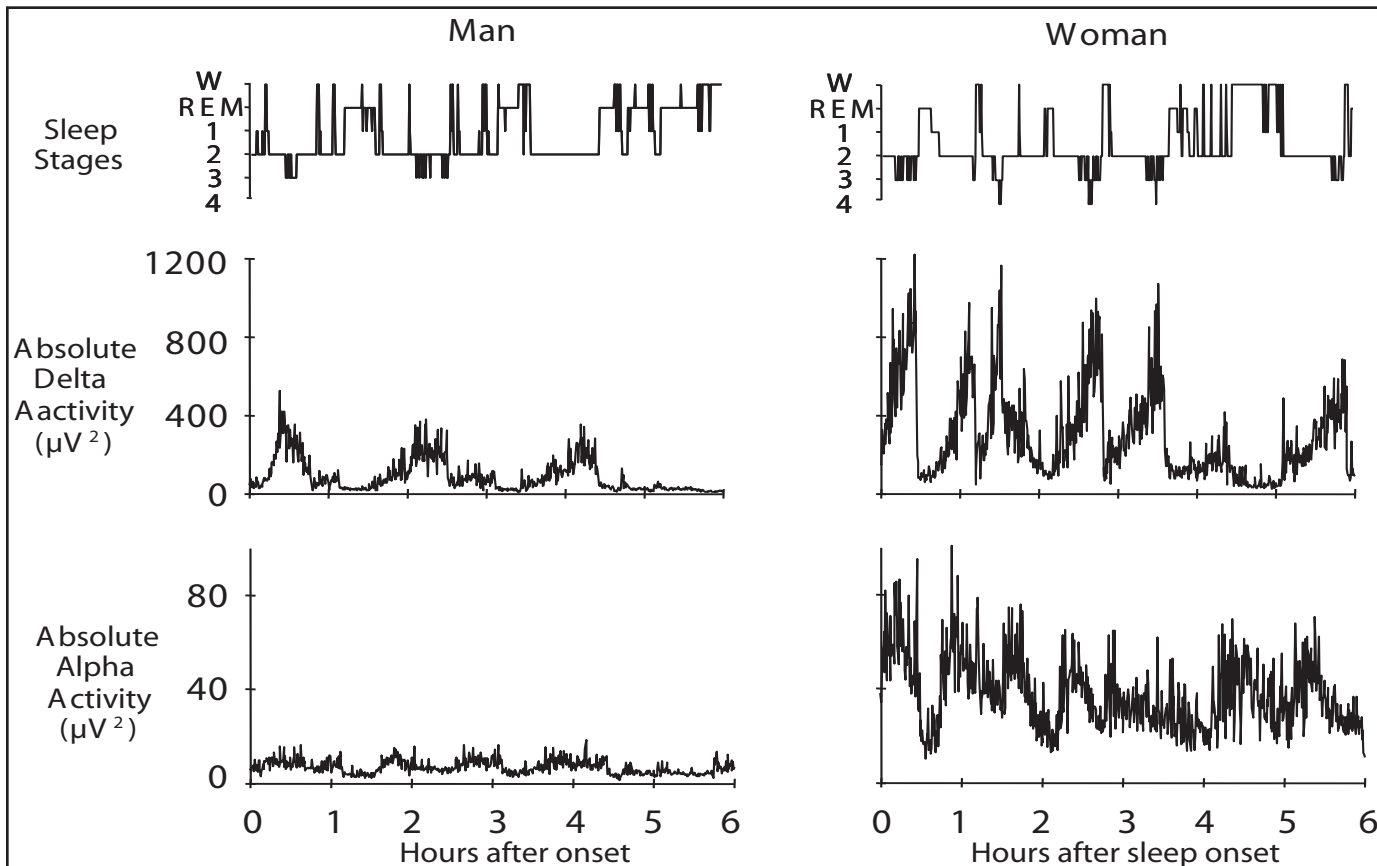
Mean profiles of absolute delta activity for the first 4 NREM/REM sleep cycles during the night without blood sampling are shown for the 2 sex groups in the upper panels of Figure 2. Table 2 summarizes the quantitative estimations of absolute delta activity during NREM and REM sleep for the first 6 hours of sleep (a period during which the majority of subjects were able to maintain sleep) for both nights of recording.

Absolute delta activity was higher in women than in men, irrespective of sleep stage. The interaction terms revealed sex differences in the impact of blood sampling during both NREM and REM sleep (Table 2). During NREM sleep, delta activity was

Table 1—Impact of Sex and Blood Sampling on Sleep Variables in 10 Men and 9 Women

Sleep Variable	Night with blood sampling		Night without blood sampling		ANOVA P level		
	Men	Women	Men	Women	Sex	Blood Sampling	Interaction
Sleep latency, min	12±3	13±7	7±2	29±14	.2674	.1314	.0159
Sleep period, min	431±15	449±15	436±15	423±17	.8932	.2077	.0643
Total sleep time, min	380±13	407±10	359±14	331±28	.9895	.0026	.0631
Sleep maintenance, %	88±2	91±2	83±3	78±6	.7948	.0137	.3288
Sleep stage amount, min							
Wake	74±10	62±11	96±11	136±31	.4942	.0048	.0989
1	49±10	34±8	36±3	37±7	.3988	.4171	.2009
2	235±15	268±7	237±12	216±19	.7341	.0313	.0243
3	24±4	27±4	19±4	18±4	.7892	.0002	.1415
4	3±1	3±1	1±1	1±1	.9550	.0027	.5401
SWS	27±5	30±5	20±5	19±4	.8338	.0001	.1922
REM	68±6	75±6	66±7	59±9	.9892	.1351	.2683
REM latency, min	67±10	77±9	75±24	76±14	.7240	.8017	.7576

Data are presented as mean ± SEM unless otherwise indicated. ANOVA refers to analysis of variance; SWS, slow-wave sleep; REM, rapid eye movement sleep.

**Figure 1**—Representative profiles of delta and alpha activities for a 51-year-old-man and a 65-year-old woman for the night without blood sampling.

decreased by blood sampling in both sex groups, but more so in women than in men. During REM sleep, delta activity in men was not affected by blood sampling, whereas a significant decrease occurred in women (sex-specific paired comparisons; REM sleep: $P = .5615$ in men, $P = .0116$ in women).

The mean values reported in Table 2 suggest that the sex difference in absolute delta activity tended to be smaller during NREM sleep than during REM sleep. Therefore, we examined the impact of sex on delta activity in NREM versus REM sleep by an ANOVA for repeated measures with delta activity as dependent variable, sleep stage as within-subject factor (i.e., NREM versus

REM), and sex as between-subject factor. For the night without blood sampling, both stage ($P = .0003$) and sex ($P = .005$) were, as expected, significant main effects, but the interaction stage \times sex was also highly significant ($P = .0189$). Similar findings were obtained for the night with blood sampling. Figure 3 illustrates the marked sex difference in the relationship of EEG characteristics during NREM sleep versus REM sleep. In men, there was no correlation between delta activity in NREM and delta activity in REM on either night (night 1: $r = 0.0727$, $P = .8531$; night 2: $r = 0.059$, $P = .8803$). In contrast, in women, delta activity in NREM was strongly correlated with delta activity in REM (night 1: r

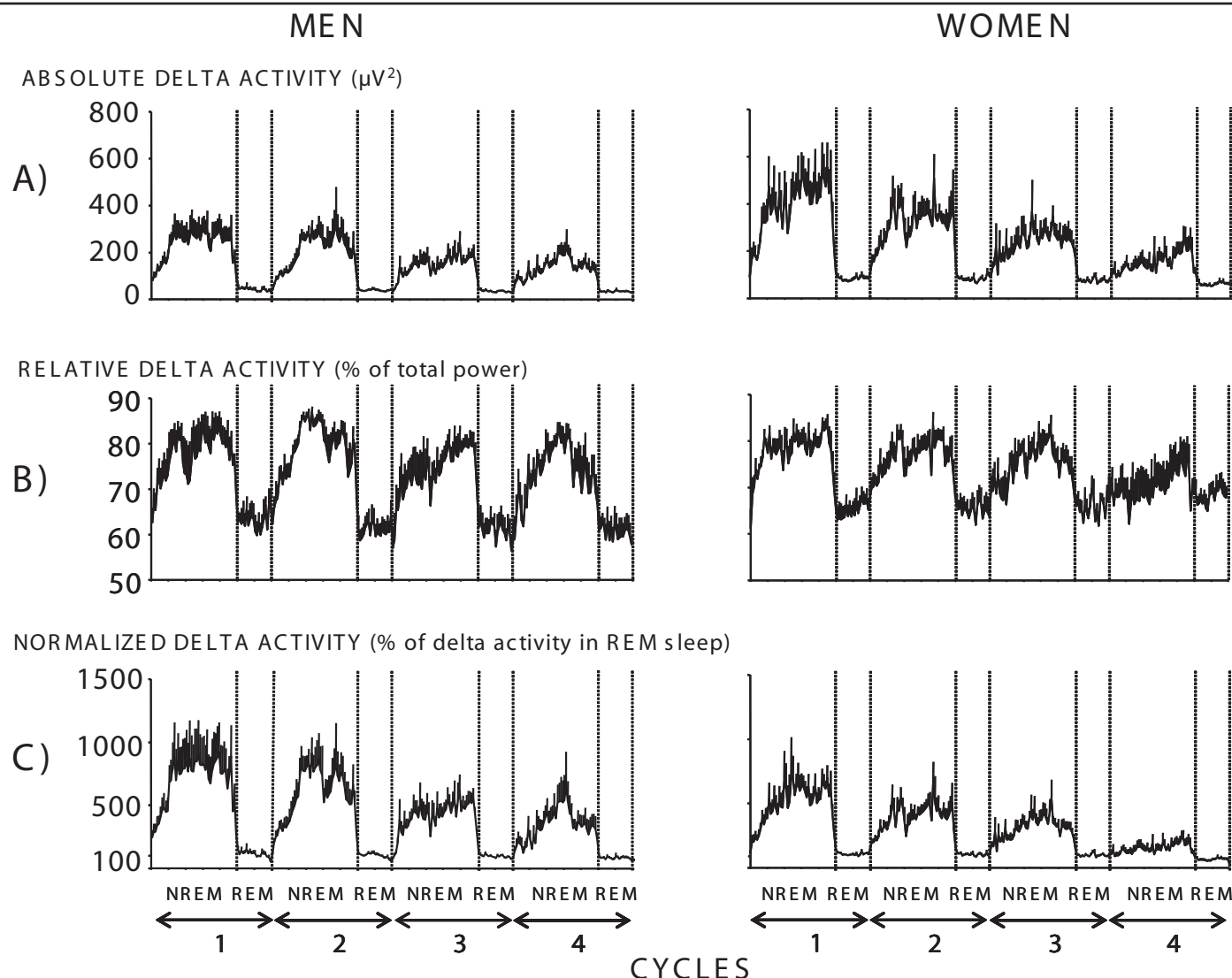


Figure 2—(A) Mean profiles of absolute delta activity in men (left panel) and women (right panel) for the first 4 non-rapid eye movement (NREM)/rapid eye movement (REM) sleep cycles for the night without blood sampling. (B) Mean profiles of relative delta activity in men (left panel) and women (right panel) for the first 4 cycles of NREM/REM sleep for the night without blood sampling. (C) Mean profiles of delta activity in men (left panel) and women (right panel) for the first 4 NREM/REM sleep cycles for the night without blood sampling when, in each epoch and for each subject, delta activity is expressed as a percentage of the mean delta activity in REM sleep. Dashed vertical lines delimit REM sleep episodes.

Table 2—Impact of Sex and Blood Sampling on Absolute Delta and Alpha Activities and Total Power in 9 Men and 9 Women

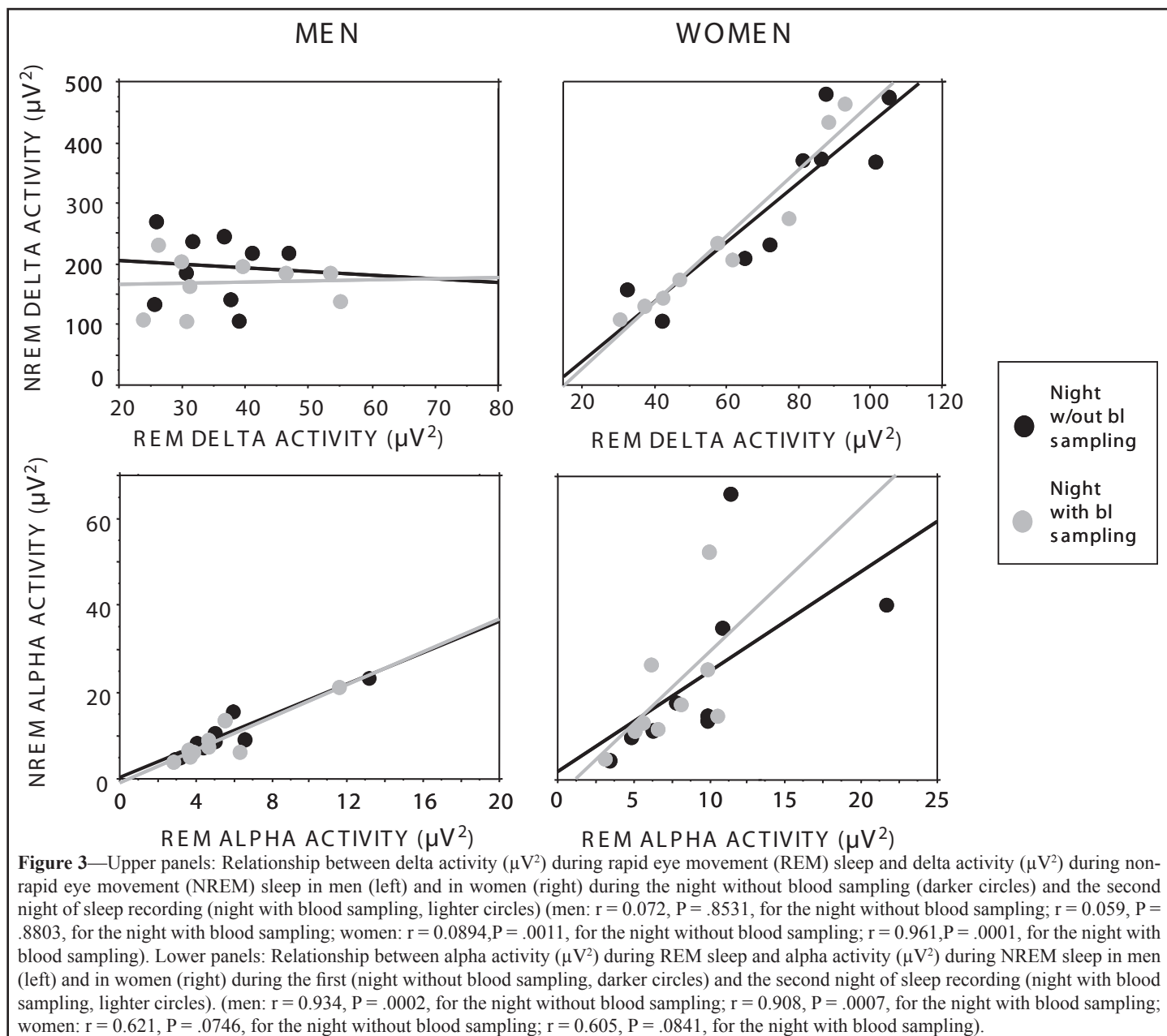
	Night without blood sampling		Night with blood sampling		Sex	ANOVA P level	
	Men	Women	Men	Women		Blood Sampling	Interaction
Delta, μV^2							
NREM	195±19	309±45	172±15	242±43	.0649	.0004	.0450
REM	35±2	75±8	37±4	60±8	.0015	.0259	.0041
Alpha, μV^2							
NREM	10±2	24±7	9±2	20±5	.0559	.0281	.2434
REM	6±1	10±2	5±1	7±1	.0541	.1420	.2922
Total power, μV^2							
NREM	235±24	385±56	209±20	307±50	.0431	.0005	.0465
REM	56±3	113±13	57±5	90±12	.0018	.0207	.0157

Data are presented as mean \pm SEM unless otherwise indicated. NREM refers to non-rapid eye movement sleep: stages 2, 3 and 4; REM, rapid eye movement sleep.

= 0.8943, $P = .0011$; night 2: $r = 0.961$, $P = .0001$). Similar sex differences were found for the relationship between total power (which is dominated by power in the delta range) in NREM sleep and total power in REM sleep (women: $r = 0.9254$, $P = .0003$;

men: $r = 0.3839$, $P = .3078$).

The profiles shown in the upper panels of Figure 2 also suggest that absolute delta activity during REM periods remained relatively constant across sleep cycles, in contrast to the marked



dissipation of delta activity across successive cycles of NREM sleep. This was confirmed by ANOVA with cycle number as within-subject factor and sex as between-subjects factor. During NREM sleep, the main significant effects for delta activity were cycle number ($P = .0006$) and, as expected, sex ($P = .0178$), but the interaction sex \times cycle number was not significant ($P = .3591$), revealing that the rate of decrease of delta activity across successive sleep cycles was similar in both sexes. In contrast, the same analysis for delta activity during REM sleep confirmed the main effect of sex ($P = .0004$) but showed no significant decrease of activity across cycles ($P = .2880$) in either sex (interaction: $P = .9773$).

The lack of dissipation of delta activity during REM sleep in both sexes is consistent with the fact that neuronal mechanisms that are responsible for the synchronization of thalamocortical oscillations in the low-frequency range are normally suppressed during REM sleep. The present analysis revealed 2 important sex differences in nondissipated delta activity during REM sleep. First, delta activity during REM sleep was affected by blood sampling

in women but not in men. Second, a robust relationship between delta activity in NREM sleep and delta activity in REM sleep was evident in women but not in men (Figure 3). Taken together, these observations suggest that, in women but not in men, common factors that appear unrelated to homeostatic sleep pressure influence absolute delta activity (and, consequently total EEG power) during NREM and REM sleep.

A commonly used procedure to control for differences in total EEG spectral power is to examine relative spectral power obtained by dividing, in each epoch, absolute spectral power by total power. The middle panels of Figure 2 illustrate these profiles of relative delta activity in both sexes for the night without blood sampling. The normalization for total power masks the decrease of delta activity across consecutive sleep cycles (cycle number: $P = .1959$; sex: $P = .6830$). Sex differences in relative delta activity are not significant in either NREM sleep or in REM sleep (Table 3). The amplitude of the NREM/REM cycle of relative delta activity (middle panels of Figure 2) appears dampened in women as compared with men, but the difference is not significant ($P =$

Table 3—Impact of Sex on Absolute, Relative, and Normalized EEG Delta and Alpha Activities in the Night Without Blood Sampling

	Men	Women	t test
Delta Activity			
Absolute, μV^2			
NREM	195.3 \pm 18.9	308.5 \pm 45.3	.035
REM	34.9 \pm 2.4	74.6 \pm 8.2	.0003
Relative, %			
NREM	79.1 \pm 1.4	76.5 \pm 1.9	.2897
REM	61.4 \pm 2.4	65.7 \pm 1.9	.1881
Normalized, %			
NREM	590 \pm 80	410 \pm 30	.0439
Alpha Activity			
Absolute, μV^2			
NREM	10.3 \pm 2.0	23.8 \pm 6.6	.0671
REM	5.6 \pm 1.0	9.5 \pm 1.8	.0719
Relative, %			
NREM	5.5 \pm 0.7	6.9 \pm 1.1	.2857
REM	10.2 \pm 1.7	8.7 \pm 1.3	.4948
Normalized, %			
NREM/REM	180 \pm 10	240 \pm 50	.1276

Data are presented as mean \pm SEM unless otherwise indicated.

NREM refers to non-rapid eye movement sleep: stages 2, 3 and 4; REM, rapid eye movement sleep.

.5179).

An alternative analysis to control for sex differences in nondissipated delta activity in REM sleep is to express, for each subject, delta activity in NREM sleep as a percentage of the mean delta activity in REM sleep. This procedure has been previously used for rodent sleep data.^{52,53} The lower panels of Figure 2 illustrate the resulting mean profiles of “normalized” delta activity in men and women. The sex difference is now reversed, with men showing more “normalized” delta activity than women in NREM sleep (Table 3). An ANOVA for repeated measures examining sex differences across cycles reveals a significant dissipation of normalized delta activity across the night ($P = .0022$) that occurs at a similar rate in men and women (interaction term: $P = .7823$).

Sex Differences in EEG Spectral Power in the Alpha Range

Mean profiles of absolute alpha activities for the 2 sex groups for the first 4 NREM/REM sleep cycles during the night of recording without blood sampling are shown in Figure 4 (upper panels).

The overall levels of absolute alpha activity tended to be elevated in women, as compared with men, during both NREM sleep and REM sleep (Table 2). Unexpectedly, blood sampling resulted in a statistically significant decrease of absolute alpha activity during NREM sleep, but not REM sleep, in both men and women. In contrast to delta activity, sex differences in absolute alpha activity were of similar magnitude in NREM and in REM sleep.

Alpha activity during NREM sleep decreased significantly with successive sleep cycles in women but not in men (cycle number: $P = .0213$; interaction cycle number \times sex: $P = .0111$). During REM sleep, alpha activity remained constant across successive sleep cycles in both men and women (cycle number: $P = .1789$; interaction cycle number \times sex: $P = .8325$).

Similar to delta activity, alpha activity was lower in REM sleep, as compared with NREM sleep, and was not subject to dissipation. Alpha activity in NREM sleep was correlated with alpha activity in REM sleep in both sexes (Figure 3).

The middle panels of Figure 4 illustrate the mean profiles of relative alpha activity for both sexes. There are no significant sex differences in relative alpha activity (Table 3). In contrast to absolute alpha activity, relative alpha activity did not decrease significantly across the night in either NREM or REM sleep (cycle number: $P = .2043$ and $P = .7621$, respectively).

The lower panels of Figure 4 show the mean profiles of alpha activity normalized for alpha activity in REM sleep. Normalized alpha activity tended to be higher in women than in men, but the difference was not significant (Table 3). The sex difference in patterns of normalized alpha activity in NREM sleep across sleep cycles is clearly evident (Figure 4; cycle number: $P = .0091$; interaction: $P = .0170$). Across successive sleep cycles, alpha activity in NREM sleep paralleled delta activity in NREM sleep in women but not in men.

DISCUSSION

The present study examined sex differences in sleep EEG variables in healthy, fully self-sufficient older men and postmenopausal women who did not take any medication and who considered themselves as good sleepers. Two consecutive nights were recorded, 1 without and 1 with blood sampling. Our findings regarding sex differences in sleep stages, absolute EEG power in the delta range, and the impact of the sampling catheter, were largely consistent with those of previous well-documented studies.^{11,19,27,32,54} In our study, sleep-stage distribution was similar in both sex groups, but women had higher delta activity than men and suffered more-severe sleep disturbances related to the presence of the catheter. In agreement with previous results in both young and older adults, there were no sex differences in visually scored SWS, but absolute delta activity was larger in women than in men.^{11,30} In addition, our study showed that women tended to have higher levels of absolute alpha activity during NREM sleep than men, extending previous observations in adults 20 to 60 years old¹¹ to an older sample controlled for menopausal status.

Our detailed analysis of EEG delta and alpha activities during NREM and REM sleep also revealed a number of important sex differences that had not been recognized in previous studies. In our older volunteers, women had more absolute delta activity than men both during NREM and during REM sleep. However, the sex difference was larger during REM sleep than during NREM sleep. This latter observation is in contrast to a previous report in young adults that showed sex differences of similar magnitude for REM and NREM sleep.³⁰ In both sexes, delta activity decreased across the night during NREM sleep but not during REM sleep. Normally, during REM sleep, the mechanisms responsible for the synchronization of thalamocortical neuronal firing in the low-frequency range are quiescent, and therefore absolute EEG spectral power in the delta range should reflect nonspecific “background activity,” consistent with the fact that the Fourier transform of any signal sampled at discrete intervals cannot yield zero amplitudes in any frequency range. Our observations in men are consistent with this interpretation of delta activity in REM as “background activity” because delta activity in REM was not affected by the perturbation introduced by blood sampling and was unrelated to

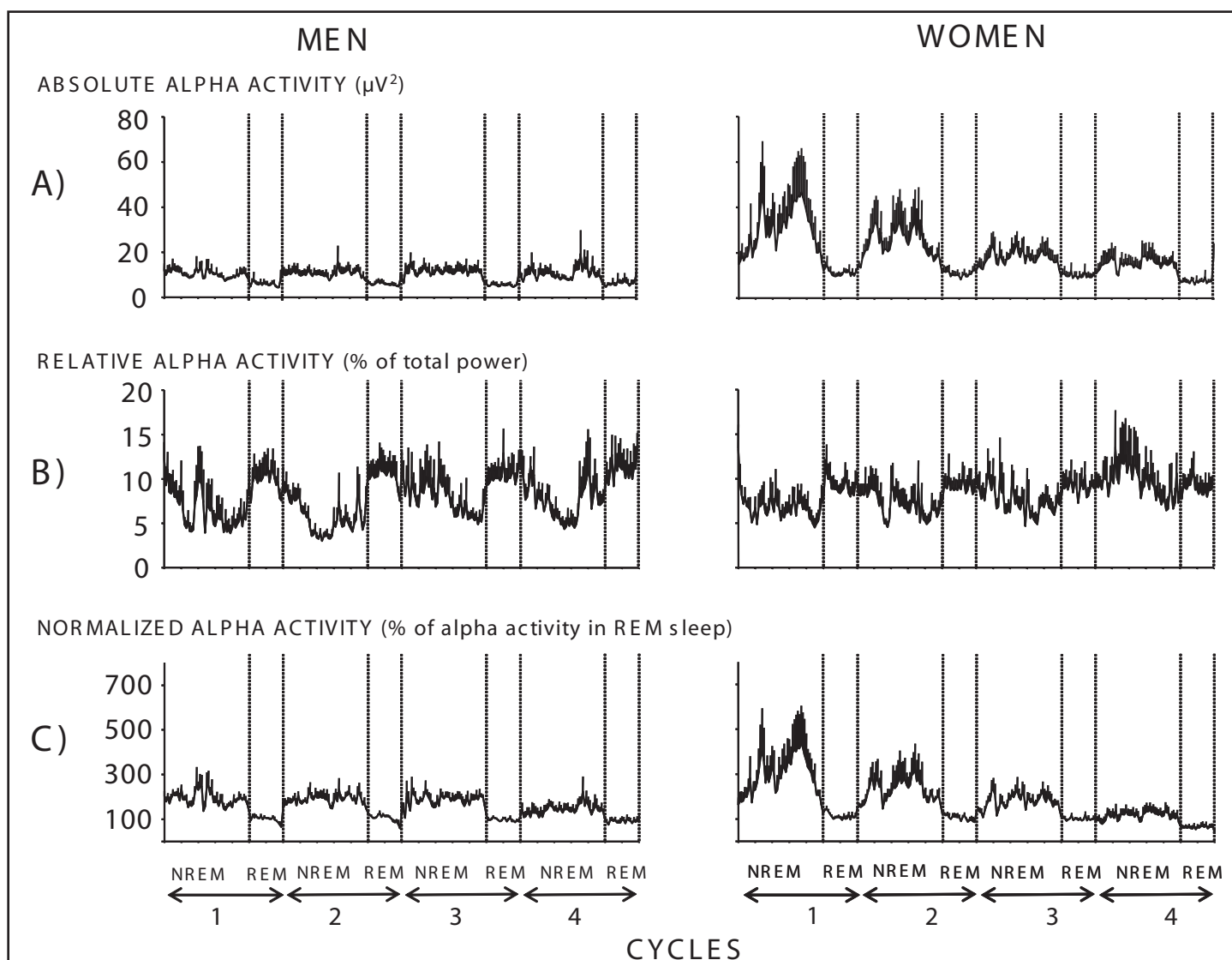


Figure 4—(A) Mean profiles of absolute alpha activity in men (left panel) and women (right panel) for the first 4 non-rapid eye movement (NREM)/rapid eye movement (REM) sleep cycles for the night without blood sampling. (B) Mean profiles of relative alpha activity in men (left panel) and women (right panel) for the first 4 cycles of NREM/REM sleep in the first night of recording (without blood sampling). (C) Mean profiles of alpha activity in men (left panel) and women (right panel) for the first 4 NREM/REM sleep cycles in the first night of recording when, in each epoch and for each subject, alpha activity is expressed as a percentage of the mean alpha activity in REM sleep. Dashed vertical lines delimit REM sleep episodes.

the levels of delta activity in NREM sleep. Therefore, in men, individual differences in delta activity during REM sleep are likely to reflect physical characteristics rather than differences in neuronal electrical activity. In women, however, delta activity in REM sleep was decreased by blood sampling and was highly correlated with delta activity in NREM sleep and, thus, cannot be interpreted as only dependent on physical parameters, such as head size and skull thickness. One possible explanation of our observations is that in women, in contrast to men, the mechanisms generating SWS are not fully suppressed during REM sleep. Irrespective of its origin, the contribution of this constant delta activity across successive REM periods needs to be controlled for when evaluating differences in the dissipation of NREM delta activity across different conditions or subject populations.

We thus normalized delta activity in NREM sleep for delta activity in REM sleep, as previously proposed in rodent sleep studies.^{52,53} This novel analysis of spectral power in the human sleep EEG revealed that sex differences in delta activity, the primary marker of the strength of the homeostatic process, could in fact be

in the direction opposite to that postulated so far.^{11,19,27,30} Indeed, when delta activity in NREM sleep was normalized for delta activity in REM sleep, men had nearly 50% more delta activity in NREM sleep than women.

Analyses of alpha activity in NREM and REM sleep in both sex groups also revealed an important sex difference, which is that, in women but not in men, absolute alpha activity in NREM sleep decreased across successive sleep cycles, paralleling delta activity. The similarity of the patterns of delta and alpha activities across successive NREM periods in women but not in men is suggestive of a sex difference in the shape of the delta waves. Absolute alpha activity in REM sleep remained constant across successive sleep cycles in both sex groups, and its apparent decrease during blood sampling did not reach statistical significance (Table 2).

The combination of higher levels of normalized delta activity and lower levels of normalized alpha activity resulted in a ratio of normalized delta to alpha activity 2- to 3-fold higher in men than in women. This dramatic sex difference in quality of NREM sleep

in older adults is in the direction opposite to that suggested by previous analyses but reconciles sex differences in EEG measures with differences in subjective sleep complaints and, as shown in the companion manuscript, in nocturnal growth-hormone release. An association between alpha-delta patterns during NREM sleep and unrefreshing sleep has been previously observed in various subject populations.⁵⁵

The finding that women may have lower delta activity but higher alpha activity than men is indeed consistent with the fact that women have more subjective sleep complaints than men.^{1,14,34,35,56,57} In the present study, we were able to verify that sleep disturbances introduced by the presence of the catheter were more pronounced in women than in men, an observation that would seem somewhat contradictory with a higher absolute delta activity in women than in men, but more consistent with their lower amount of normalized delta activity and lower delta-to-alpha ratio.

In conclusion, this study suggests the presence of major sex differences in sleep variables in a small sample of healthy older adults carefully controlled for menopausal status and medication use. A novel analysis of delta and alpha activities in NREM and REM sleep suggests that, contrary to current beliefs, the quality of NREM sleep may be better preserved in older men than in older women. While the normalization of EEG power in NREM sleep for EEG power in REM sleep used in the present study is clearly in need of further validation, the findings from this analysis would reconcile sex differences in the sleep EEG with sex differences in subjective complaints, in the fragility of sleep in the presence of environmental disturbances, and in the relationship to hormonal release.

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