http://dx.doi.org/10.5665/sleep.1398

Evaluation of the Association of Menopausal Status with Delta and Beta EEG Activity during Sleep

Ian G. Campbell, PhD[1]; Joyce T. Bromberger, PhD[2,3]; Daniel J. Buysse, MD[3]; Martica H. Hall, PhD[3]; Kimberly A. Hardin, MD[4]; Howard M. Kravitz, DO, MPH[5]; Karen A. Matthews, PhD[2,3]; Marianne O'Neill Rasor, MA[6]; Jessica Utts, PhD[7]; Ellen Gold, PhD[6]

[1]Department of Psychiatry and Behavioral Sciences, University of California, Davis; [2]Department of Epidemiology, University of Pittsburgh, Pittsburgh PA; [3]Department of Psychiatry, University of Pittsburgh, Pittsburgh PA; [4]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, University of California Davis; [5]Department of Psychiatry and Department of Preventive Medicine, Rush University Medical Center, Chicago IL; [6]Division of Epidemiology, Department of Public Health Sciences, University of California, Davis; [7]Department of Statistics, University of California, Irvine

Study Objectives: Women report increasing sleep difficulties during menopause, but polysomnographic measures do not detect sleep disturbances. We examined whether two spectral analysis sleep measures, delta and beta power, were related to menopausal status.

Design: The Study of Women's Health Across the Nation (SWAN) Sleep Study compared cross-sectionally spectral sleep measures in women in different stages of menopause.

Setting: Sleep EEG was recorded in the participants' homes with ambulatory recorders.

Participants: A multi-ethnic cohort of premenopausal and early perimenopausal (n = 189), late perimenopausal (n = 73), and postmenopausal (n = 59) women.

Measurements: EEG power in the delta and beta frequency bands was calculated for all night NREM and all night REM sleep. Physical, medical, psychological, and socioeconomic data were collected from questionnaires and diaries.

Results: Beta EEG power in NREM and REM sleep in late perimenopausal and postmenopausal women exceeded that in pre- and early perimenopausal women. Neither all night delta power nor the trend in delta power across the night differed by menopausal status. In a multivariate model that controlled for the physical, demographic, behavioral, psychological, and health-related changes that accompany menopause, beta power in both NREM and REM sleep EEG was significantly related to menopausal status. The frequency of hot flashes explained part but not all of the relation of beta power to menopausal status.

Conclusions: Elevated beta EEG power in late perimenopausal and postmenopausal women provides an objective measure of disturbed sleep quality in these women. Elevated beta EEG activity suggests that arousal level during sleep is higher in these women.

Keywords: FFT, spectral analysis, menopause, midlife women

Citation: Campbell IG; Bromberger JT; Buysse DJ; Hall MH; Hardin KA; Kravitz HM; Matthews KA; Rasor MO; Utts J; Gold E. Evaluation of the association of menopausal status with delta and beta EEG activity during sleep. *SLEEP* 2011;34(11):1561-1568.

INTRODUCTION

The menopausal transition is characterized by a number of hormonal and symptomatic changes. Circulating estradiol levels decline while follicle stimulating hormone levels increase.[1] Most women experience vasomotor symptoms including hot flashes/flushes and night sweats,[2-4] and some experience an increase in mood-related symptoms[4-6] during the menopausal transition.

Subjective reports of sleep difficulties also increase during this time of physiologic and symptom-related changes.[7-9] Prevalence of sleep disturbances range from 16% to 42% in premenopausal women and 35% to 60% in postmenopausal women.[8] Both self-reported difficulty falling asleep and difficulty staying asleep increase with progression through the menopausal transition.[7,9] This increase in subjective sleep difficulties is independently related to the menopausal transition and persists even after age and other covariates are controlled.[7,10]

However, these subjective sleep disturbances have not been reflected in objective sleep measures. The first polysomnography (PSG) studies of menopausal women found that sleep stage percentages and latencies were similar in women in different stages of menopausal.[11] In the Wisconsin Sleep Cohort study of 589 women, total sleep time, adjusted for age and other covariates, was actually longer in postmenopausal than in premenopausal women.[12] Furthermore, the percentage of deep sleep (stages 3 and 4) was higher in postmenopausal women.[12] Young et al. also measured subjective sleep quality and found that ratings of how often sleep was satisfactory were worse in the same postmenopausal women who had PSG indicators of longer and deeper sleep.[12] In the Study of Women's Health Across the Nation (SWAN) Sleep Study, more rapid increase in follicle stimulating hormone (FSH) was significantly associated with higher visually scored deep sleep percentage and longer total sleep time, but less favorable self-reported sleep quality.[13]

Spectral analysis of the electroencephalogram (EEG) can provide additional information about sleep, beyond measures derived from visually scored PSG. The slow wave EEG that characterizes NREM sleep reflects the homeostatic processes of sleep.[14,15] Delta (0.5-4 Hz) EEG power is highest at the start of the night when the need for recuperation is greatest and decreases across the night as this need is met. Delta EEG activity is increased in NREM sleep following sleep deprivation[16] and is decreased in the night following a daytime nap.[17] The high frequency components of the EEG are associated with cognition during waking, and beta (16-32 Hz) EEG power reflects

Submitted for publication January, 2011
Submitted in final revised form May, 2011
Accepted for publication June, 2011
Address correspondence to: Ian G. Campbell, PhD, UC Davis Sleep Lab, 1712 Picasso Ave, Suite B, Davis, CA 95618; Tel: (530) 752-7216; Fax: (530) 757-5729; E-mail: igcampbell@ucdavis.edu

arousal level during sleep.[18] Beta EEG power is higher in the lighter parts of NREM sleep and higher in REM sleep compared to NREM sleep.[19] Furthermore, elevated beta power is found in some insomniacs and may indicate a higher arousal level related to reports of less satisfactory sleep.[18,20-23]

Although PSG has not detected substantial differences in sleep by menopausal status, spectral analysis of the EEG may provide objective sleep measures that change across the menopausal transition. Delta EEG power may reveal differences in homeostatic sleep regulation, and beta EEG power may indicate differences in arousal levels during sleep. Thus, the purpose of the current cross-sectional study was to determine whether delta and beta EEG power were related to menopausal status in a multi-ethnic cohort of midlife women. The analyses adjusted for possible confounding effects of age as well as physical, medical, psychological, and socioeconomic covariates.

METHODS

Data for this study were collected from participants in the SWAN (Study of Women's Health Across the Nation) Sleep Study. Between 2003 and 2005, data were collected at 4 sites: University of Pittsburgh, Rush University Medical Center, University of Michigan, and University of California, Davis. The Sleep Study was an ancillary study of the larger core longitudinal cohort SWAN study of 3302 women enrolled at 7 sites (the 4 above plus UCLA, University of Medicine and Dentistry of New Jersey, and Massachusetts General Hospital.)

Participants

The 370 participants in the SWAN Sleep Study were recruited from 1561 women enrolled in the SWAN core study at the 4 participating sites at the time of their fifth, sixth, or seventh annual SWAN core visit. Exclusion criteria for the Sleep Study included having had a hysterectomy or bilateral oophorectomy, use of menopausal hormone therapy, ongoing cancer treatment, current oral corticosteroid use, regular consumption of > 4 alcoholic drinks/day, noncompliance with Core SWAN procedures (missed > 50% of annual visits, refused annual visit blood draw), and regular night shift work. At the time of the Sleep Study recordings, women were between 48 and 59 years of age.

Study Design

Subjective and objective sleep data were collected using questionnaires, daily diaries, actigraphy, and PSG as previously described in detail.[7,13,24] For women who were still menstruating, the Sleep Study protocol began within 7 days of the onset of a menstrual period and continued for the entire menstrual cycle or 35 days, whichever came first. Diary and actigraphy data were collected for the duration of the entire protocol. For 3 consecutive nights at the beginning of the protocol, PSG data were recorded at the participant's home with a Vitaport 3 PSG recorder (Temec; Kerkade, Netherlands). On all 3 nights, the PSG montage included EEG recorded at C3 and C4 referred to linked mastoids, bilateral electrooculogram (EOG), and bipolar submental electromyogram (EMG). Night 1 included additional parameters to evaluate sleep disordered breathing and periodic leg movements. Oral-nasal temperature probes evaluated airflow; impedance plethysmography measured chest and abdominal effort; fingertip oximetry measured oxygen saturation; and bilateral anterior tibialis EMG measured leg movements. To eliminate possible first-night effects, only EEG data from nights 2 and 3 were used for this set of analyses. Of the 370 participants in the Sleep Study 338 women had usable quantitative EEG data on at least one night. For the 224 participants with usable EEG data on both nights 2 and 3, the two nights of data were averaged. For the other 114 participants, a single night of data was used. Data from 17 participants were excluded because they began hormone use after being enrolled in the study, resulting in a sleep analysis dataset with 321 women. For multivariate analyses, additional exclusions were made for those lacking sleep diary data (n = 22), resulting in a multivariate model dataset with 299 participants.

EEG Recording and FFT Analysis

The Vitaport 3 digitized the EEG at 256 Hz. Low frequency hardware filters were set at 0.3 Hz, and high frequency hardware filters were set at 70 Hz. No additional software filters were applied. The digitized data were decimated to 128 Hz and then analyzed with fast Fourier transform with the following parameters: 4-sec Hanning tapered windows with no overlap, i.e., 5 windows per 20-sec epoch. Each 20-sec epoch was visually scored according to Rechtschaffen and Kales[25] criteria. Artifacts were identified by computer using the methods of Brunner et al.[26]; 4-sec windows containing artifacts identified by this algorithm were eliminated from the analysis. Epochs scored as awake or movement time were not included in the analysis. EEG artifacts due to eye movements during REM sleep were not specifically identified. Power was averaged separately across all artifact-free epochs of NREM and REM sleep for the delta (0.5-4 Hz) band and the beta (16-32 Hz) band. This average power measure is independent of sleep stage duration. Additionally for delta, power was calculated for each NREM period so that the delta trend across the night could be analyzed.

Polysomnography (PSG) Measures

Based on the visual scoring of each 20-sec epoch, the following PSG measures were determined for each night of usable EEG recording: total sleep time, stage 1 as a percent of total sleep time, stage 2 %, slow wave sleep (stage 3 and stage 4) %, stage REM %. In addition, the hypopnea index (AHI) was determined by the number of apneas and hypopneas on night 1.

Menopausal Status

Menopausal status was defined using bleeding criteria and was determined at the annual core SWAN exam closest to the time of the Sleep Study protocol. Women having regular menstrual bleeding in the prior three months with no change in regularity were classified as premenopausal (n = 16). Women who had menstruated in the previous 3 months but reported having irregular menstrual cycles were classified as early perimenopausal (n = 173). Women who had menstruated in the preceding 12 months but not in the preceding 3 months were classified as late perimenopausal (n = 73), and women with ≥ 12 months of amenorrhea were classified as postmenopausal (n = 59). Because of the inherent variability in cycles during the early perimenopausal period and because we only asked women's menopausal status annually, some misclassification

of premenopausal status could have occurred. Therefore, premenopausal and early perimenopausal status categories were combined for purposes of the present analyses.

Covariates

The core SWAN study collected information about a wide range of demographic, behavioral, psychological, physical, and health measures. These data provided the opportunity to control statistically for a wide range of covariates and confounding factors when examining the relation between EEG power and menopausal status. Age was calculated as time from birth to the beginning of the sleep protocol. The physical, sociodemographic, behavioral, psychological, and health-related measures relevant to the current analyses were collected at the annual core SWAN exam closest to the time of the sleep study protocol. Body mass index (BMI) was calculated as measured weight (kg) divided by height (m) squared. Self-assessed health was ascertained from standard questions,[27] as was information about cigarette use.[28] As an indicator of financial strain, participants responded to a question about how hard it was to pay for basics and also indicated their total annual household income. Quality of life was assessed by the SF-36.[29] Participants responded to questions about stress related to work, money problems, and the responsibility of caring for others. Participants provided information about how frequently they felt lonely, sad, bothered, or restless. Participants also responded to standard questions about their social support[30] and provided information about current medication use, race/ethnicity and marital status. Of the 321 participants with usable EEG data, 50 were Chinese, 119 were black or African American, and 152 were Caucasian. The clinical site was also included as a covariate. However, race/ethnicity and clinical site were confounded because the 3 races were not represented at all sites. Therefore, race/ethnicity and site were combined into a race/ethnicity-site variable comprising 8 groups.

For the duration of the sleep study protocol, participants completed a daily diary in the morning and at bedtime, in which they provided information about menopausal symptoms, mood, and medication usage. They reported the number and severity of hot flashes and sweating during the day and at night. For the analyses below, we used the ratings of daytime hot flashes because participants may not have recalled all symptoms that occurred during the night. They also reported alcohol and caffeine use, smoking, prescription drug use, and daytime nap duration. On day 4 of the sleep study protocol, participants completed the Pittsburgh Sleep Quality Index (PSQI).[31] At the time of the Sleep Study, participants also completed the Inventory of Depressive Symptomology (IDS).[32] IDS questions related to sleep quality were not included in the IDS score because sleep quality was measured separately with the PSQI. If a variable was measured at the SWAN exam and recorded in the diary, the diary measure was used for analysis because it was recorded closer in time to the EEG recording.

Statistical Analyses

We examined the distributions of the outcome variables (NREM delta power, NREM beta power, REM delta power, and REM beta power) to determine if transformations were needed to meet statistical assumptions, and all outcomes were log transformed as a result. (Henceforth the term "EEG power" in the discussion of the analyses refers to the log-transformed EEG power values, even when not explicitly denoted as such, unless stated otherwise.) One-way ANOVAs (with menopausal status as the independent variable and log EEG power as the dependent variable) were used to test whether delta and/or beta EEG power differed across menopausal status groups. NREM delta power, NREM beta power, REM delta power, and REM beta power were evaluated separately, setting statistical significance at $\alpha = 0.01$. Potential covariates for the relation of EEG power to menopausal status were identified by evaluating whether EEG power was related to various sociodemographic, physical, health, and sleep diary measures. One-way ANOVA (for categorical variables) or regression (for continuous variables) was used in these potential covariate determinations.

To evaluate the independence of the relation of menopausal status to EEG power, a multiple regression model was fit using menopausal status and all covariates that were marginally related to EEG power ($P < 0.20$) as independent variables. We also included other covariates that previous studies have found may be related to delta or beta EEG activity or arousal level, including age, caffeine use, daytime nap duration, AHI, and the IDS measure of depression. Covariates that did not reach $P < 0.20$ in this initial multiple regression model, were determined to contribute little to the model and were removed from the final model. Two-way ANOVA and analysis of covariance were used to evaluate independently whether individual covariates affected the relation between EEG power and menopausal status.

We also statistically tested whether the decline in delta power across the night differed by menopausal status. We used data only from women ($n = 267$) who completed ≥ 4 sleep cycles in the night of EEG recording. Delta power in each NREM period was expressed as a percent of average delta power in the first 4 NREM periods. We initially used nonlinear mixed effect analysis to fit a declining exponential function to delta power in each NREM period.[33,34] However, both linear and cubic functions fit the delta decline better than did a declining exponential. Therefore, further evaluations of menopausal status effects on the delta decline were made with SAS proc mixed using either a linear or cubic function with status as a grouping factor.

We also evaluated if beta EEG power provided an objective measure of the sleep difficulties reported by these women. We determined if subjective sleep quality, as measured with the PSQI, was related to menopausal status and to log beta EEG power (for NREM and REM sleep). The relation between subjective sleep quality and menopausal status was evaluated with ANOVA, and the relation between log beta EEG power and subjective sleep quality was evaluated with regression.

RESULTS

Polysomnography Measures

None of the polysomnography measures differed by menopausal status (Table 1). Average total sleep time was very similar in the 3 status groups. Neither the REM sleep percentage nor the percentages of the stages of NREM sleep showed any status-related differences.

Unadjusted Relation of Beta and Delta EEG Power to Menopausal Status

For both NREM and REM sleep, mean log beta EEG power differed significantly by menopausal status (Table 1). In NREM sleep, mean log beta power was significantly lower in the pre- and early perimenopausal group than in the late perimenopausal and the postmenopausal groups. Mean log NREM beta power did not differ significantly between late perimenopausal and postmenopausal women. A similar relation between menopausal status and beta EEG power was found for REM sleep EEG. Again, mean log beta power in late perimenopausal women and postmenopausal women exceeded that for pre- and early perimenopausal women, and mean log beta power did not differ significantly between the late perimenopausal and postmenopausal groups.

Unlike beta EEG, log delta power did not differ significantly by menopausal status for either NREM or REM sleep EEG (Table 1). Nor did the across the night decline in delta power differ by menopausal status. When the decline in delta power across NREM periods was fit with a linear function neither the intercept, i.e. the delta power at the start of the night ($P = 0.89$), nor the slope, i.e., the rate of delta decline across the night ($P = 0.83$) differed by menopausal status. Similarly when the decline was fit by a cubic function, none of the cubic parameters differed significantly ($P > 0.30$ for all) by menopausal status.

Further analyses explored potential explanations for the menopausal status effects on beta EEG. Because delta EEG did not differ by menopausal status, no further delta EEG results are presented.

Table 1—Comparisons by menopausal status of polysomnography measures and log power in all night NREM and REM EEG. Averages and one-way ANOVA results.

	Average			ANOVA Results	
	Pre and Early (n = 189)	Late Peri (n = 73)	Post (n = 59)	$F_{2,318}$	P value
Stage 1 (%)	7.0	7.6	7.4	0.34	0.71
Stage 2 (%)	64.5	63.5	66.0	1.77	0.17
Slow wave sleep (%)	3.6	3.9	2.8	1.12	0.33
Stage REM (%)	24.9	25.1	23.8	1.11	0.33
Total sleep time (min)	386	380	388	0.34	0.71
Log NREM delta power (μV^2)	2.18	2.20	2.22	1.14	0.32
Log REM delta power (μV^2)	1.57	1.61	1.59	1.32	0.27
Log NREM beta power (μV^2)	0.483[a]	0.555[b]	0.551[b]	6.34	0.0020
Log REM beta power (μV^2)	0.532[a]	0.632[b]	0.633[b]	8.27	0.0003

[a,b]Means sharing a common superscript (or lacking a superscript) do not differ significantly at $\alpha < 0.05$ (Tukey multiple comparison).

Table 2—Significance (P level) of the relation between log beta (16-32 Hz) power and potential covariates

	NREM	REM	Direction
Hot flash frequency	0.0081	0.0087	+
Overall health	0.028	0.031	-
SSRI use	0.039	0.41	+
BMI	0.045	0.098	+
Blood pressure medicine in past 2 weeks	0.072	0.17	+
Caffeinated drinks per day	0.095	0.027	+
How upset by increased workload	0.10	0.27	+
Race/ethnicity-site	0.13	0.54	N/A
How hard to provide basics	0.14	0.34	+
Quality of life	0.16	0.16	±
Body pain	0.18	0.069	+
Social support	0.18	0.29	±
Nap duration	0.19	0.84	+
IDS (without sleep questions)	0.35	0.60	+
Log AHI	0.70	0.52	+
Age	0.85	0.22	+

Results are from ANOVA for class variables and from regression for continuous variables entered one at a time. The "Direction" column indicates whether beta power is positively or negatively related to the covariate.

Potential Covariates for the Relation of Beta Power to Menopausal Status

Variables that showed a possibly significant ($P < 0.2$ for either NREM or REM) relation to beta power in one-way ANOVA or regression were considered potential covariates (Table 2). For NREM sleep EEG, log beta power was most significantly related to hot flash frequency, overall health, SSRI use on the day of EEG recording, and BMI. For REM sleep EEG, log beta power was most significantly related to hot flash frequency, overall health, and caffeinated beverage consumption. Log beta power was not significantly related to age, AHI, nap duration, or depression score on the IDS. (Analysis of the beta EEG power relation to additional variables is shown in Supplemental Table S1). If a variable was closely related to another variable, it was not included in further analyses, even if the variable met the $P < 0.2$ criterion. For example, we did not include both hot flash frequency and hot flash severity.

Adjusted Relation of Beta Power to Menopausal Status

Results of the multiple regression modeling (Table 3) indicated that simultaneously controlling for the effects of 7 covariates attenuated the relation of beta power to menopausal status. For both NREM and REM sleep, the relation of log beta power to menopausal status was no longer significant ($P = 0.17$ for NREM, $P = 0.06$ for REM). Subsequent bivariate analysis with 2-way ANOVA or ANCOVA determined independently for

each of the covariates if controlling for that covariate attenuated the relation of beta power to menopausal status (Supplemental Tables S2 and S3). Only controlling for hot flash frequency attenuated this relation to a noticeable degree. When controlling for the variance related to hot flash frequency, the significance of the relation of log beta power to menopausal status was P = 0.030 for NREM and P = 0.0045 for REM (attenuated from the P = 0.0020 and P = 0.0003 found in the one-way analysis). After adjusting for each of the other covariates independently in separate bivariate analyses, the relation of log beta power to menopausal status remained statistically significant at P < 0.005. Thus, for each of these covariates, the two-way ANOVA or ANCOVA showed significant relations of menopausal status to log beta power with significance levels similar to those seen with the one-way ANOVA analysis of menopausal status. In a different multiple regression model (Table 3) that included all covariates except hot flash frequency, log beta power was significantly related to menopausal status, but the significance was attenuated to P = 0.014 for NREM and P = 0.0043 for REM. Thus, even when controlling for the physical, demographic, behavioral, psychological, and health-related changes that accompany menopause, log beta power in both NREM and REM sleep EEG was related to menopausal status.

Table 3—Multiple regression model type III P-values for associations of each variable to log beta EEG power, with and without hot flash frequency (HFF) in the model

	NREM		REM	
Independent Variable	+HFF P value	−HFF P value	+HFF P value	−HFF P value
Menopausal status	0.17	0.014	0.060	0.0043
Hot flash frequency	0.026		0.059	
Overall health	0.0033	0.0092	0.031	0.040
Drug SSRI (n = 48)	0.19	0.16	0.092	0.10
Caffeinated drinks	0.29	0.43	0.029	0.050
Race/ethnicity-site	0.29	0.35	0.81	0.81
How hard to provide	0.30	0.34	0.53	0.57
Quality of life	0.0080	0.026	0.022	0.050

Type III P values are the significance of adding the independent variable after all the other variables have been added to the model.

Hot Flash Symptoms

Further exploring the relation of beta power to hot flashes showed that for both NREM and REM sleep, log beta power was higher in women reporting hot flashes than in women who did not. Women were separated into 3 groups based on the number of hot flashes reported per day (0, 0.1-1, and 1.1-9 hot flashes/day). Beta power did not differ between the last 2 groups, but both of these groups had significantly higher beta power than women who did not report any hot flashes. Ratings of other types or characteristics of vasomotor symptoms, such as the number and severity of sweats and the severity of hot flashes were not as consistently related to log beta power. For example, women who reported having cold sweats did not have significantly higher mean log beta power in REM sleep (P = 0.27) or NREM sleep (P = 0.38) than women who did not have cold sweats. Chi square analysis showed that hot flash frequency was strongly related (P < 0.0001) to menopausal status. Although including hot flash frequency in a bivariate analysis (Tables S2 and S3) attenuated the relation of beta power to menopausal status, beta power remained significantly related to menopausal status even with hot flash frequency controlled. Thus, hot flash frequency explained part but not all of the relation between beta power and menopausal status.

Subjective Sleep Quality

The global score on the subjective sleep quality measure, PSQI, differed significantly ($F_{2,307}$ = 4.53, P = 0.011) by menopausal status. The mean (± SE) global score was lower in pre- and early perimenopausal women (5.28 ± 0.22) than in late perimenopausal (6.25 ± 0.45) and postmenopausal (6.57 ± 0.47) women. A lower score indicates better subjectively assessed sleep quality. The PSQI score was related to log beta EEG power in both NREM (r = 0.14, P = 0.010) and REM (r = 0.11, P = 0.048) sleep with the general trend being an increase in beta power with increasing PSQI score.

Other EEG Frequencies

Our original hypotheses regarded only beta and delta EEG. However, the strong relation between menopausal status and beta power raises the question whether menopausal differences were limited to beta. We, therefore, conducted post hoc analyses of theta (4-8 Hz), alpha (8-12 Hz), and sigma (12-15 Hz) power. In both NREM and REM sleep, neither theta (P = 0.56 and P = 0.46, respectively) nor alpha (P = 0.41 and P = 0.27, respectively) power differed by menopausal status. Sigma power in NREM sleep EEG was significantly (P = 0.017) lower in premenopausal and earlier menopausal women than in late peri- and postmenopausal women, but sigma did not differ (P = 0.10) by menopausal status in REM sleep.

DISCUSSION

Unlike traditional visually scored PSG measures, beta EEG power changed across the menopausal transition. Beta EEG was significantly higher in late perimenopausal and postmenopausal women, even with age and other covariates controlled. Beta power was also related to hot flash frequency, and this relation explained part, but not all, of the relation between beta EEG and menopausal status. Delta EEG activity during NREM sleep reflects the intensity of a recuperative process that reverses the effects of waking on the brain.[14,15,35] Cross-sectional studies have shown that delta EEG activity decreases with age across adulthood.[36-39] The current study is the first to examine whether midlife changes in delta EEG power occur in women and can be explained by the menopausal transition. The current study of over 300 women found that delta power did not change significantly with menopausal status. Nor did the delta trend across consecutive NREM periods of the night differ by menopausal status. These findings indicate that the recuperation represented by delta EEG is not affected by the menopausal transition.

Beta EEG power, indicative of arousal, on the other hand, was elevated in both NREM sleep and REM sleep in late peri-

menopausal and postmenopausal women. This increased beta power was associated with menopause itself and not a result of covariates as the relation of increasing beta power in the later stages of the menopausal transition was unaffected by controlling for covariates. Obviously, women age as they progress through menopause, and beta EEG activity increases with age.[36] Therefore, EEG changes related to aging must be considered when evaluating menopausal differences in beta power. Beta EEG power was unrelated to age in the narrow age range of this cohort of women, and the significance of the relation between menopausal status and beta EEG power was not altered by including age as a factor in a two-way ANOVA or a multiple regression model. Similarly, physical and mental health, or medication related to these characteristics, might have been related to the EEG changes, but, again, the significance of the menopausal relation to beta power persisted when these health-related variables were controlled.

The elevated beta EEG power in late perimenopausal and postmenopausal women suggests that the arousal level during sleep is higher in these women. This elevated arousal level may explain the more frequent complaints of sleep difficulties in late perimenopausal and postmenopausal women.[7-9] Beta is also elevated in individuals with primary insomnia, particularly in women, and in association with symptoms of stress.[18,20-23] It has been proposed that this hyperarousal during sleep may be related to insomniacs ruminating and failure to shut down cognitive process during sleep.[18] Our study did not include a specific question about dwelling on problems while trying to sleep. The study did include measures of financial hardship, workload, troubles at work, and other stresses, but the increase in beta power associated with later stages of the menopausal transition was independent of the relation of these stressors to beta power. The multiple regression model identified covariates to which beta power was significantly related even when menopausal status was controlled. Thus, other factors, particularly overall health status and quality of life contribute to the arousal level reflected by beta EEG activity, and the elevated beta in late perimenopausal and postmenopausal women may be a combination of multiple factors that raise the arousal level.

The significant relationship between hot flash frequency and beta power may provide some insight into the elevated arousal level in late peri- and postmenopausal women. Women who reported hot flashes had significantly higher beta power than women who did not, and inclusion of this covariate attenuated the significance of the relation of menopausal status to beta power. Multiple studies have shown that hot flash frequency is negatively associated with subjective sleep quality but unrelated to PSG measured objective sleep quality.[12,40,41] Beta EEG power provides an objective measure that is related not only to menopausal status but also to the frequency of the most frequent menopausal vasomotor symptom, hot flashes. Evaluations of objective measures of hot flashes during the night have indicated that hot flashes are often associated with awakenings, especially in the first half of the night.[40] Our hot flash measure was a subjective rating of the number of hot flashes during the day; therefore, we cannot determine if elevated beta activity was directly related to the occurrence of nighttime hot flashes.

In the bivariate analysis, hot flash frequency only partially attenuated the relation of menopausal status to beta power. In addition to the quality of life and overall health factors mentioned above, hormonal changes in the levels of FSH and estrogen might further explain the relation between menopausal status and beta power. A rapid rate of change in FSH is associated with longer total sleep time but less satisfactory subjective ratings of sleep quality.[13] Baseline estradiol is modestly and negatively associated with sleep quality.[13] Future analyses of the SWAN dataset will explore whether hormonal changes may also be related to changes in beta EEG power.

The post hoc analysis of other frequency bands showed that menopausal related differences were limited to higher frequency bands. Increases in beta power are often accompanied by decreases in low frequency power; however, our finding is not unique. Some insomnia studies have found effects limited to the beta band.[18] Other than beta, sigma during NREM sleep was the only frequency band showing differences by menopausal status. Without further detailed analysis, we cannot determine if the sigma increase in late perimenopausal and post menopausal women is an increase in the spindle activity that dominates this band[42] or a nonspecific elevation of high frequency activity that spreads beyond the beta band to include sigma EEG during NREM sleep.

Our study had a number of significant strengths and a few limitations of note. The strengths included the large sample size, which permitted sufficient statistical power to detect meaningful differences in spectral measures of sleep in relation to the stages of the menopausal transition, while simultaneously adjusting for known and detected confounding factors. The study also was able to examine the contribution of reported hot flashes and of the menopausal transition. In addition, the multi-ethnic, non–clinic-based nature of our study sample enhanced the generalizability of our findings. Furthermore, our sleep outcomes were objectively measured without knowledge (and thus potentially biased observational influence) of the menopausal status or symptom reporting of the women. A limitation of the study is that nearly one-third of the women had only one usable night of EEG data. However, beta power from 1 night of EEG recording correlates fairly well ($r = 0.80$) with 5-night averages of beta power.[43] In all women the night of EEG analyzed was not the first night of EEG recording and was, thus, not influenced by the new experience of the sleep assessment equipment. Because we did not eliminate epochs containing artifacts related to eye movements, we cannot firmly conclude that delta EEG during REM sleep did not differ across menopausal status groups. However, we have no a priori reason to believe that eye movements would differ across the menopausal transition. Additional limitations include the cross-sectional design, which inhibited our ability to assess the temporal relation of the sleep measures to progression through the menopausal transition. Also, while the study sample was multi-ethnic, race/ethnicity and site were confounded.

The finding that beta EEG is elevated in late perimenopausal and postmenopausal women while polysomnography measures show no difference provides the first objective measure of disturbed sleep quality in these women and adds some justification to their subjective reports of impaired sleep. As other studies have previously demonstrated, we found that subjective sleep quality decreased across the progression of the menopausal transition. PSQI ratings have been shown to be poorly related

to objective polysomnographic measures of sleep quality in older subjects particularly women.[44,45] We found that the objective EEG measure, beta power, was significantly related to the subjective measure, PSQI. However, we note that, in this group of women between 48 and 59 years of age, the correlation between beta power and PSQI scores was week, with beta explaining less than 2% of the variance in PSQI scores. The inability of the polysomnogram to detect sleep differences related to menopausal status may point less to differences between objective and subjective sleep measures but instead to visually scored sleep staging being a relatively insensitive objective measure. We are not dismissing traditional PSG and sleep staging as tools in evaluating sleep disturbances. For instance, traditional PSG measures of sleep efficiency are related to primary sleep disorders in menopausal women.[40] We agree that failure to address problems such as sleep apnea will provide inadequate treatment for menopausal women complaining of sleep disturbances. However, the underlying cause of subjective reports of impaired sleep in menopausal women may be related to a change in arousal levels. Treating this change in arousal level may provide menopausal women with relief from sleep problems.

ACKNOWLEDGMENTS

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). Funding for the SWAN Sleep Study is from the National Institute on Aging (Grants AG019360, AG019361, AG019362, AG019363). Sleep data were processed with the support of RR024153. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. Work for this study was performed at University of California, Davis, Rush University Medical Center, University of Pittsburgh and University of Michigan.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Buysse serves as a consultant for Actelion, Arena, Cephalon, Eli Lily, GlaxoSmithKline, Merck, Neurocrine, Neurogen, Pfizer, Purdue Pharma, L.P., Respironics, Sanofi-Aventis, Sepracor, Servier, Somnus Therapeutics, Stress Eraser, Takeda and Transcept Pharmaceuticals, Inc. He is an investigator on an investigator–initiated study sponsored by Sepracor and has helped to produce CME materials and has given paid CME lectures indirectly supported by industry sponsors. Dr. Hardin has lectured at engagements sponsored by Respironics, the Academy of Clinical Dentistry, and Sleep Diagnostics. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Randolph JF Jr, Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88:1516-22.
2. Freeman EW, Sherif K. Prevalence of hot flushes and night sweats around the world: a systematic review. Climacteric 2007;10:197-214.
3. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006;96:1226-35.
4. Woods NF, Smith-Dijulio K, Percival DB, Tao EY, Taylor HJ, Mitchell ES. Symptoms during the menopausal transition and early postmenopause and their relation to endocrine levels over time: observations from the Seattle Midlife Women's Health Study. J Womens Health 2007;16:667-77.
5. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord 2007;103:267-72.
6. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S. Symptoms in the menopausal transition: hormone and behavioral correlates. Obstet Gynecol 2008;111:127-36.
7. Kravitz HM, Zhao X, Bromberger JT, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep 2008;31:979-90.
8. NIH. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 2005;142:1003-13.
9. Woods NF, Mitchell ES. Sleep symptoms during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Sleep 2010;33:539-49.
10. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause 2003;10:19-28.
11. Shaver J, Giblin E, Lentz M, Lee K. Sleep patterns and stability in perimenopausal women. Sleep 1988;11:556-61.
12. Young T, Rabago D, Zgierska A, Austin D, Finn L. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. Sleep 2003;26:667-72.
13. Sowers MF, Zheng H, Kravitz HM, et al. Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh Sleep Quality Index. Sleep 2008;31:1339-49.
14. Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195-204.
15. Feinberg I. Changes in sleep cycle patterns with age. J Psychiatr Res 1974;10:283-306.
16. Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D. Sleep-deprivation: effect on sleep stages and EEG power density in man. Electroencephalogr Clin Neurophysiol 1981;51:483-93.
17. Feinberg I, March JD, Floyd TC, Jimison R, Bossom-Demitrack L, Katz PH. Homeostatic changes during post-nap sleep maintain baseline levels of delta EEG. Electroencephalogr Clin Neurophysiol 1985;61:134-7.
18. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 2001;24:110-7.
19. Uchida S, Maloney T, Feinberg I. Beta (20-28 Hz) and delta (0.3-3 Hz) EEGs oscillate reciprocally across NREM and REM sleep. Sleep 1992;15:352-8.
20. Buysse DJ, Germain A, Hall ML, et al. EEG spectral analysis in primary insomnia: NREM period effects and sex differences. Sleep 2008;31:1673-82.
21. Hall M, Thayer JF, Germain A, et al. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. Behav Sleep Med 2007;5:178-93.
22. Krystal AD, Edinger JD, Wohlgemuth WK, Marsh GR. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. Sleep 2002;25:630-40.
23. Merica H, Blois R, Gaillard J-M. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neurosci 1998;10:1826-34.
24. Hall MH, Matthews KA, Kravitz HM, et al. Race and financial strain are independent correlates of sleep in midlife women: the SWAN sleep study. Sleep 2009;32:73-82.
25. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Washington, DC: Public Health Services, U.S. Government Printing Office, 1968.
26. Brunner DP, Vasko RC, Detka CS, Monahan JP, Reynolds CF III, Kupfer DJ. Muscle artifacts in the sleep EEG: automated detection and effect on all-night EEG power spectra. J Sleep Res 1996;5:155-64.

27. Centers for Disease Control and Prevention NCfHS. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. Vital Health Stat 1 1994:1-407.
28. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 1978;118:1-120.
29. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
30. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32:705-14.
31. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
32. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573-83.
33. Achermann P, Dijk D-J, Brunner DP, Borbély AA. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. Brain Res Bull 1993;31:97-113.
34. Daan S, Beersma DGM, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 1984;246:R161-R78.
35. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 2003;62:143-50.
36. Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old). Psychophysiology 2001;38:232-42.
37. Dijk D-J, Beersma DG, van den Hoofdakker RH. All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. Neurobiol Aging 1989;10:677-82.
38. Ehlers CL, Kupfer DJ. Effects of age on delta and REM sleep parameters. Electroencephalogr Clin Neurophysiol 1989;72:118-25.
39. Feinberg I, Hibi S, Carlson VR. Changes in EEG amplitude during sleep with age. In: Nandy K, Sherwin I, eds. The aging brain and senile dementia. New York: Plenum Press, 1977:85-98.
40. Freedman RR, Roehrs TA. Sleep disturbance in menopause. Menopause 2007;14:826-9.
41. Polo-Kantola P, Erkkola R, Irjala K, Helenius H, Pullinen S, Polo O. Climacteric symptoms and sleep quality. Obstet Gynecol 1999;94:219-24.
42. Dijk DJ, Hayes B, Czeisler CA. Dynamics of electroencephalographic sleep spindles and slow wave activity in men: effect of sleep deprivation. Brain Res 1993;626:190-9.
43. Tan X, Campbell IG, Palagini L, Feinberg I. High internight reliability of computer-measured NREM delta, sigma and beta: biological implications. Biol Psychiatry 2000;48:1010-9.
44. Buysse DJ, Reynolds CF 3rd, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991;14:331-8.
45. Vitiello MV, Larsen LH, Moe KE. Age-related sleep change: Gender and estrogen effects on the subjective-objective sleep quality relationships of healthy, noncomplaining older men and women. J Psychosom Res 2004;56:503-10.

Table S1—Significance (P level) of the relation between log beta (16-32 Hz) power and each potential covariate

	NREM	REM
Demographic		
Age	0.85	0.22
Marital status	0.83	0.93
Recording site	0.043	0.16
Race/ethnicity	0.083	0.71
Race/ethnicity-site	0.13	0.54
Income (family total)	0.53	0.32
How hard to provide basics	0.14	0.34
Physical and Mental Health		
BMI	0.045	0.098
Overall health	0.028	0.031
Log AHI	0.70	0.52
Smoker	0.68	0.41
SSRI use	0.039	0.41
Benzodiazepine use	0.58	0.47
Tricyclic antidepressant use	0.12	0.26
β-Blocker use	0.17	0.45
Narcotic use	0.44	0.96
BP meds in past 2 wks	0.072	0.17
CES-D	0.54	0.38
IDS (Sleep questions removed)	0.35	0.60
Mood and Well-being		
Quality of life	0.16	0.16
Social support	0.18	0.29
Upset by troubles at work	0.19	0.63
Upset about job loss	0.84	0.92
Upset by increased workload	0.10	0.27
Upset by money problems	0.30	0.29
Upset by responsibility of caring for others	0.74	0.44
Upset by serious illness	0.77	0.027
How often bothered	0.78	0.96
How often have the blues	0.58	0.30
How often sad	0.076	0.14
How often depressed	0.32	0.12
Mood and Well-being (cont.)		
How often lonely	0.53	0.20
How often have crying spells	0.33	0.23
Unable to control things	0.60	0.82
Difficulties piling up	0.43	0.21
Perceived stress	0.41	0.47
Body pain	0.18	0.069
Bedtime Diary		
Alcoholic drinks per day	0.27	0.73
Caffeinated drinks per day	0.095	0.027
Number of cigarettes per day	0.89	0.90
Nap duration	0.19	0.84
Number of minutes exercised	0.24	0.34
Number of times felt fatigued	0.54	0.076
Severity of fatigue	0.48	0.24
Number of times had cold sweats	0.38	0.27
Number of times had hot flashes	0.0081	0.0087
Severity of hot flashes	0.10	0.13
Number of times had cramps	0.84	0.83
Severity of cramps	0.59	0.83
Waking Diary		
Feel rested	1.0	0.85
Feel blue	0.87	0.22
Feel anxious	0.74	0.54
Number of times had cold sweats	0.31	0.84
Number of times had hot flashes	0.087	0.12
Severity of hot flashes	0.12	0.32
Number of times had night sweats	0.63	0.57
Severity of night sweats	0.98	0.24
Number of times had cramps	0.94	0.88
Severity of cramps	0.19	0.40
Number of times worried	0.31	0.43
Severity of worries	0.44	0.46

Results are from ANOVA for class variables and from regression for continuous variables.

Table S2—Results of univariate and bivariate analysis of NREM log beta EEG power relations to potential covariates

	Univariate	Multivariate	
	P value	Covariate P value	Status P value
Hot flash frequency	0.0081	0.12	0.030
Overall health	0.028	0.043	0.0033
SSRI use	0.039	0.050	0.0025
BMI	0.045	0.053	0.0029
BP meds in past 2 wks	0.072	0.14	0.0034
Caffeinated drinks per day	0.095	0.20	0.0086
Upset by workload	0.10	0.21	0.0089
Race/ethnicity-site	0.13	0.12	0.0018
How hard to provide basics	0.14	0.12	0.0013
Quality of life	0.16	0.15	0.0019
Body pain	0.18	0.052	0.0023
Social support	0.18	0.14	0.0016
Nap duration	0.19	0.30	0.0049
IDS	0.35	0.48	0.0029
Log AHI	0.70	0.71	0.0026
Age	0.85	0.38	0.0021

Univariate analysis examined the relation of beta to each covariate alone. Bivariate analysis examined the relation of beta to menopausal status with each covariate controlled and to each covariate with menopausal status controlled. Comparing "Status P" to the one-way ANOVA status P-value of 0.0020 for NREM shows that the only measureable change in these P-values came from adding "hot flash frequency."

Table S3—Results of univariate and bivariate analysis of REM log beta EEG power relations to potential covariates

	Univariate	Multivariate	
	P value	Covariate P value	Status P value
Hot flash frequency	0.0087	0.099	0.0045
Overall health	0.031	0.075	0.00088
SSRI use	0.41	0.30	0.00026
BMI	0.098	0.15	0.0006
BP meds in past 2 wks	0.17	0.31	0.00050
Caffeinated drinks per day	0.027	0.075	0.0013
Upset by workload	0.27	0.48	0.00066
Race/ethnicity-site	0.54	0.47	0.00028
How hard to provide basics	0.34	0.30	0.00031
Quality of life	0.16	0.13	0.00028
Body pain	0.069	0.068	0.0006
Social support	0.29	0.20	0.00022
Nap duration	0.84	0.87	0.0004
IDS	0.60	0.41	0.0004
Log AHI	0.52	0.78	0.0002
Age	0.22	0.97	0.0007

Univariate analysis examined the relation of beta to each covariate alone. Bivariate analysis examined the relation of beta to menopausal status with each covariate controlled and to each covariate with menopausal status controlled. Comparing "Status P" to the one-way ANOVA status P-value of 0.0003 for REM shows that the only measureable change in these P-values came from adding "hot flash frequency."