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Time-varying correlations between delta EEG power and heart rate variability in midlife women: The SWAN Sleep Study

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Abstract

No studies have evaluated the dynamic, time-varying, relationship between delta electroencephalographic (EEG) sleep and high frequency heart rate variability (HF-HRV) in women. Delta EEG and HF-HRV were measured during sleep in 197 midlife women (Mage =52.1, SD =2.2). Delta EEG-HF-HRV correlations in Non-Rapid Eye Movement (NREM) sleep were modeled as whole night averages and as continuous functions of time. The whole-night delta EEG-HF-HRV correlation was positive. Strongest correlations were observed during the first NREM sleep period preceding and following peak delta power. Time-varying correlations between delta EEG-HF-HRV were stronger in participants with sleep-disordered breathing and self-reported insomnia compared to healthy controls. The dynamic interplay between sleep and

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Conflicts of Interest

Clinical Centers: University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.

NIH Program Office: National Institute on Aging, Bethesda, MD – Winifred Rossi 2012 - present; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.

Central Laboratory: University of Michigan, Ann Arbor – Daniel McConnell (Central Ligand Assay Satellite Services).

Coordinating Center: University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.

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autonomic activity can be modeled across the night to examine within- and between-participant differences including individuals with and without sleep disorders.

Keywords

HF-HRV; delta EEG; time-varying correlation; sleep

Introduction

Mounting evidence suggests that sleep is an important determinant of health and functioning, including cardiometabolic disease risk (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Gallicchio & Kalesan, 2009; Loke, Brown, Kwok, Niruban, & Myint, 2012; Schwartz et al., 1999; Sofi et al., 2012). Altered autonomic tone, as measured by decreased heart rate variability (HRV), may represent one pathway through which sleep affects health and functioning (Cappuccio et al., 2011; Gallicchio & Kalesan, 2009; Loke et al., 2012). Alterations in HRV have been observed in sleep apnea and insomnia, which are the two most common sleep disorders seen in primary care settings (Ohayon, 2002; Young, Peppard, & Gottlieb, 2002). Heart rate variability is decreased during both sleep and wakefulness in patients with sleep apnea compared to good sleeper controls across the lifespan (Hilton et al., 2001; Liao et al., 2010; Narkiewicz et al., 1998). Heart rate variability also appears to normalize in conjunction with successful continuous positive airway pressure (CPAP) treatment (Gilman et al., 2008; Karasulu, Epozturk, Sokucu, Dalar, & Altin, 2010). Although the evidence is less conclusive in insomnia, some studies have observed decreased HRV during sleep in patients with insomnia compared to good sleeper controls (Bonnet & Arand, 1998; Israel et al., 2012; Jurysta et al., 2009).

Sleep and HRV are both regulated, in part, by autonomic nervous system activity. Non-rapid eye movement (NREM) sleep is characterized by relatively greater parasympathetic tone, indicated by greater high frequency HRV (HF-HRV), while rapid eye movement (REM) sleep and wakefulness show increased sympathetic nervous system activity (Bonnet & Arand, 1997; Otzenberger, Simon, Gronfier, & Brandenberger, 1997; Somers, Dyken, Mark, & Abboud, 1993). Gradations in HRV are seen within NREM sleep, with lower levels of HF-HRV seen during stage 1 sleep and higher levels seen during stage 3 and 4 “slow-wave” sleep (Bonnet & Arand, 1997; Toscani et al., 1996). Studies that have evaluated cardiac autonomic tone in relation to sleep have often used a “discrete epoch” approach in which spectral analysis of HRV is measured during five- to ten-minute epochs corresponding to specific stages of sleep (e.g., stage N3 sleep, rapid eye movement (REM) sleep). More nuanced methodological approaches, including those that utilize two minute arousal-free discrete epochs, have shown that fluctuations in HRV are attributable to the changing distribution of sleep stages Trinder, Waloszek, Woods & Jordan, 2012; Trinder et al, 2001. These studies have demonstrated that sleep and HRV are correlated in a broad sense; yet converging evidence suggests that sleep and HRV are dynamically coupled over shorter time intervals (Gronfier, Simon, Piquard, Ehrhart, & Brandenberger, 1999a; Otzenberger et al., 1998; Otzenberger et al., 1997) and this relationship is altered in people with sleep

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disturbances such as obstructive sleep apnea (OSA) and insomnia (Jurysta et al., 2006; Jurysta et al., 2009). Taken as a whole, these studies suggest that the relationship between sleep and HRV varies across time as well as among individuals with disturbed sleep. That this relationship is altered in association with disturbed sleep suggests that the dynamics of the EEG-HRV relationship warrant further investigation.

Some studies have used analytical approaches that measure the strength of the linear association between two time series in the frequency domain, suggesting that the time delay between changes in HRV and changes in the EEG that is reliably observed in good sleepers disappears in individuals with sleep apnea or insomnia (Jurysta et al., 2006; Jurysta et al., 2009). While aggregation of data (e.g., discrete epochs, whole night averages) may reveal significant associations between sleep and HF-HRV, this approach may obfuscate more complex EEG-HRV relationships observed within and across non-rapid eye movement (NREM) periods. These complex relationships may be especially important among individuals with primary sleep disorders such as sleep apnea or insomnia (Jurysta et al., 2009). Thus, when evaluating cardiac autonomic activity as a mechanism through which sleep and sleep disturbances affect health and functioning, the analytical approach by which physiological data are examined in relation to one another across the night is an important methodological consideration.

The Present Study

In order to address this methodological consideration, we were interested in understanding if delta EEG power and HF-HRV fluctuate in relation to one another on a moment-to-moment basis, both within and across NREM sleep periods. Specifically, we were interested in modeling correlations between EEG delta power and HF-HRV during NREM sleep as smooth, covariate-adjusted, continuous functions of time, primarily because the dynamics of this relationship might reflect an underlying physiological process critical to the restorative properties of delta EEG power and cardiac parasympathetic activity during sleep. At a more basic level, understanding the time-varying nature of the EEG-HRV relationship will enable researchers to more accurately assess HRV during sleep. A greater understanding of the dynamics of the EEG-HRV relationship provides a more complete picture of the basic physiology of sleep which, despite originating in the brain, is inextricably linked to peripheral physiology (Lugaresi, Provini, & Cortelli, 2001; Silvani, 2008). We chose to focus on NREM delta EEG power as it is a stable and reliable quantitative measure of visually-scored slow-wave sleep, which has been linked with HF-HRV in previous studies (Bonnet & Arand, 1997; Jackman et al., 2012; Toscani et al., 1996; Trinder et al., 2001). Conceptually, delta EEG power and parasympathetic nervous system activity may promote physiological restoration, a putative function on NREM sleep. Although delta power can be detected during REM sleep, its expression during NREM sleep is most closely tied to its role as a marker of sleep homeostasis and sleep depth. To evaluate time-varying associations between HRV and the sleep EEG, we utilized overnight data from a sample of midlife women studied at four sites around the country: Chicago, IL; Detroit, MI; Oakland, CA; and Pittsburgh, PA. The present study addressed the following three aims: (1) To examine whether delta EEG power during NREM sleep and HRV are correlated in midlife women; (2) To examine whether delta EEG power and HRV are correlated on a momentary basis

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and across NREM periods in midlife women; and (3) To examine whether EEG-HRV relationships in midlife women differ as a function of sleep disordered breathing and insomnia.

Method

Participants

A total of 368 women participated in the multi-site Study of Women's Health Across the Nation (SWAN) Sleep Study (Hall et al., 2009; Santoro & Sutton-Tyrrell, 2011). Each study site recruited Caucasian participants and members of one racial/ethnic minority group (African American or Chinese). Eligibility for the SWAN Sleep Study was based primarily on factors known to affect sleep. Specific exclusions were regular overnight shiftwork; current menopausal hormone replacement therapy use; current chemotherapy, radiation, or oral corticosteroid use; and regular consumption of more than 4 alcoholic drinks per day.

A subset (n=197) of the SWAN Sleep Study cohort was used for the current analyses. Of these participants, 19 exhibited symptoms of insomnia without sleep disordered breathing (SDB), 26 exhibited symptoms SDB without insomnia, 6 exhibited both symptoms of insomnia and SDB, and 146 did not exhibit symptoms of insomnia or SDB (see Measures). Participants were not included in the present analyses if quantitative EEG or HRV data were not available due to technical problems with the polysomnography (PSG) recording (n=56); if they were taking medications that affect heart rate variability (e.g., beta blockers, angiotensin-converting-enzyme (ACE) inhibitors) (n=57); if they were missing covariate data (n=19); or were missing too much HRV or EEG data to reliably interpolate HRV and/or EEG profiles (n=39; see Measures). On average, participants not included in the present analyses had higher body mass index (BMI) values, reported more subjective sleep complaints, and had shorter sleep durations, compared to participants who were included in these analyses (p values < 0.01). These groups did not differ in terms of NREM delta EEG power or high frequency HRV during NREM sleep, age, menopausal status, or percent NREM sleep. The study protocol was approved by each site's institutional review board. Participants gave written informed consent and received compensation for participation.

Procedure

Ambulatory PSG sleep studies were conducted in participants' homes on the first three nights of the SWAN Sleep Study protocol as previously described (Hall et al., 2009). Study staff visited participants in their homes on each sleep study night to apply and calibrate PSG study monitors. Pursuant to American Academy of Sleep Medicine guidelines for overnight PSG (Iber, Ancoli-Israel, Chesson, & Quan, 2007), channels included bilateral central referential EEG (C3 and C4, referenced to A1 + A2), bilateral electro-oculograms (EOG), submentalis electromyogram (EMG), a modified V2 lead electrocardiogram (EKG), and inductance plethysmograpghy abdominal and thoracic belts. The first night of data collection was used to collect additional data (nasal pressure monitoring, oral-nasal thermistors, fingertip oximetry and bilateral anterior tibialis EMG) to assess sleep disordered breathing and periodic leg movements. Participants slept at their habitual sleep times. Upon awakening in the morning, participants turned off the PSG monitor and removed the study

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equipment. Participants' apnea-hypopnea index (AHI), assessed by PSG on the first night of the sleep study, was used to quantify sleep disordered breathing (SDB). Covariates included study site (Chicago, Detroit area, Oakland, and Pittsburgh) as well as the following sociodemographic, physiological, and behavioral factors known to affect sleep and/or heart rate variability: age, race, BMI, menopausal status, vasomotor symptoms, use of medications that affect sleep, caffeine intake, and AHI. Diary data collected concurrently with PSG was used to identify women who reported nocturnal vasomotor symptoms (cold sweats, hot flashes or flushes, night sweats) on the sleep night used in these analyses.

A single night of data was used to compute power spectral analysis of the EEG and HRV for each participant given the high short-term temporal stability of whole night measures of EEG delta power and HF-HRV (Israel et al., 2012b). EEG and HRV data used in the present study were selected from Night 2, when available (n=178) or Night 3 (n=19). As previously noted, EEG power and HRV are highly stable across consecutive nights (Israel et al., 2012b). PSG records were visually scored in 20-second epochs (Rechtschaffen & Kales, 1968). Fast Fourier Transform (FFT) was employed to derive EEG power spectral estimates in 4-second epochs and HRV power spectral estimates in 2-minute epochs. EEG and HRV epochs occurring during NREM sleep were then temporally aligned across the entire sleep period. The bins selected for analysis of EEG and HRV data were consecutive 4-second intervals, corresponding to the non-overlapping spectral estimates of delta EEG power generated by FFT. Missing data were handled in a "paired" fashion; when 4-second bins of EEG data were missing values (e.g., as a result of artifacts, Stage 1 or Wake epochs), the corresponding 4-second bins of HRV data were also considered missing values. Only a portion of an entire 2-minute HRV measurement was discarded, unless the concurrent EEG data were missing for the entire 2-minute interval. Similarly, if a 2-minute epoch of HRV data was a missing value, the simultaneous bins of EEG data were treated as missing values. In our analyses, n=39 potential participants (16.5% of the sample not excluded for all other aforementioned reasons) were not included in the present study due substantial amounts of missing data.

Measures

Demographic and Psychological Measures

Demographics: Age was determined by self-report and participants self-identified their race/ethnicity as African American, Caucasian, or Chinese. Body mass index (BMI) was calculated from Core SWAN measurement of participants' height and weight, and menopausal status (premenopausal/early perimenopausal, late perimenopausal, postmenopausal) was defined by bleeding patterns pursuant to World Health Organization guidelines (World Health Organization Scientific Group, 1996). Diary data were also used to identify the use of medications that affect sleep including hypnotics and sedatives, antihistamines, antidepressants, anxiolytics, opioids, and antiepileptics. Use of medications that affect sleep was dichotomized as "yes" or "no" and treated as a binary covariate in analyses. In addition, diary data collected concurrently with PSG was used to quantify caffeine intake. The average number of caffeinated beverages per PSG day was calculated for each participant and included as a continuous covariate in analyses.

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Insomnia symptoms: The self-report Insomnia Symptom Questionnaire (ISQ), a 13 item self-report instrument, was used to identify participants meeting criteria for insomnia based on the American Psychiatric Association's fourth edition of the Diagnostic Statistical Manual (DSM-IV) criteria for insomnia and the American Academy of Sleep Medicine's (AASM) Research Diagnostic Criteria (RDS) (American Psychiatric, 2000; Edinger et al., 2004). The ISQ retrospectively queried participants' chronic sleep disturbances, such as difficulties initiating or maintaining sleep, or experiencing un-refreshing sleep at least 3 nights per week over the past month or longer (Okun et al., 2010). In the present sample, 19 participants met criteria for insomnia and 6 met criteria for insomnia in combination with clinically-significant sleep disordered breathing as defined by an AHI of ≥15.

Physiological Measures

Electroencephalogram (EEG): Signals were acquired with Vitaport-3 (TEMEC VP3) ambulatory monitors and digitized for off-line scoring (Vasko, Jr. et al., 1997). The EEG data were acquired at a sampling rate of 256 Hz with a low pass filter set at 0.3 Hz and a high pass filter at 100 Hz. Visual sleep stage scoring was based on Rechtschaffen and Kales criteria and scored in 20-second epochs (Rechtschaffen & Kales, 1968) as data were collected prior to the updated American Academy of Sleep Medicine manual (Iber et al., 2007). Scorers were trained PSG technologists with established reliability (interclass correlation coefficients above 0.90 for wake, NREM and REM). Sleep scoring was used to identify waking, NREM (stages 1, 2, 3 or 4) and REM sleep epochs. A REM period was defined as the elapsed time between the first epoch of REM sleep and the epoch of REM sleep which is followed by 30 consecutive minutes of NREM sleep or wakefulness, and a REM period consists of at least 3 minutes of REM sleep. A NREM period was defined as the elapsed time between sleep onset and the beginning of the first REM period, the elapsed time between 2 subsequent REM periods or elapsed time between the last REM period and the end of the PSG recording (Kravitz et al., 2011). An automated artifact rejection program was then run to remove any epochs containing EMG artifacts from the EEG record (epochs with artifact accounted for fewer than 5 minutes of NREM sleep, on average). Fast Fourier Transform (FFT) was used to generate power spectral analysis of the EEG in each 4-second epoch of NREM sleep (Brunner et al., 1996). In the present report, we focus on absolute power in the delta (0.5-4 Hz) band as a marker of sleep depth and homeostatic sleep drive (Fuller, Gooley, & Saper, 2006). The present report is focused on delta power during NREM sleep, including stages 2, 3 and 4 of NREM sleep. Delta EEG power is a quantitative measure of visually-scored slow-wave sleep and both are behaviorally described as "deep sleep" due to decreased awareness of external cues and difficulties orienting to the environment upon awakening from slow-wave sleep (Rechtschaffen, Hauri, & Zeitlin, 1966). Stage 1 was not used in the analyses as it is characterized by a more wake-like EEG profile and is often difficult to reliably differentiate from wakefulness.

Electrocardiogram (EKG): EKG signals were collected throughout sleep at a sampling rate of 1024 Hz using a 2-lead electrode placement (European Task Force Society of Cardiology & the North American Society of Pacing & Electrophysiology, 1996). A commercially-available software package was used to detect and mark R waves in successive 2-minute epochs, which provides sufficient data to reliably quantify the low and

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high frequency components of HRV (Mindware Heart Rate Variability Scoring Module, Mindware Technologies Ltd., Gahanna, OH). An automated artifact detection algorithm and accompanying visual inspection were used to identify and manually remove suspected artifacts. The time series of interbeat intervals (IBIs) was used to quantify the variability between R-R intervals, or heart rate variability. Fast Fourier Transform was used to derive HRV power spectral estimates for each 2-minute epoch of NREM sleep. Power was integrated in the low-frequency band (LF: 0.04 to 0.15 Hz) and the high-frequency band (HF; 0.15 to 4.0 Hz). The European Task Force Guidelines (European Task Force Society of Cardiology & the North American Society of Pacing & Electrophysiology, 1996) as well as more recent reviews (Thayer, Hansen, & Johnsen, 2010) note that 2 minutes are sufficient for the accurate estimation of both LF and HF. The HRV variable considered in this study was normalized high-frequency HRV power (HFnu-HRV), defined as the ratio of HFHRV over the sum of LF-HFV and HF-HRV. HF-HRV data were normalized to minimize between-participant differences in absolute HRV power that are unrelated to cardiac parasympathetic tone (European Task Force Society of Cardiology & the North American Society of Pacing & Electrophysiology, 1996; Todd et al., 2007).

Statistical Analyses—Descriptive statistics were used to characterize the sample and evaluate the distribution of delta EEG power and HF-HRV. Absolute delta EEG power was natural-log-transformed and normalized HF-HRV power was square-root-transformed in order to produce approximately normally-distributed values. Smoothing spline methods were used for the nonparametric estimation of time-varying correlations between delta EEG power and HF-HRV during each NREM period. Analyses were limited to the first 3 NREM periods due to the limited amount of data available for subsequent sleep cycles. Analyses were conducted in relative time as opposed to absolute (clock) time in order to compensate for inter-individual differences in the length of individual NREM periods, based on the approach used by Achermann and colleagues (Achermann, Dijk, Brunner, & Borbely, 1993). First, each participant's NREM “clock” was standardized to values between t = -1 and t = +1. Next, the time at which the maximum in delta EEG power occurred was detected for each participant, and this time was designated as t = 0. Finally, each participant's HRV and EEG data were then linearly interpolated and re-sampled on the new time scale, giving the same number of relative time points per participant (n=582) within each NREM period. Conceptually, EEG and HRV data were time-aligned and correlations were computed for evenly-spaced intervals within each NREM period. We evaluated these correlations within each NREM period (i.e., from beginning of each NREM period to peak delta power and from peak delta power to the end of the NREM period) and across NREM periods (i.e., NREM-1 compared to NREM-2, NREM-1 compared to NREM-3, and NREM-2 compared to NREM-3). These analyses were conducted in the sample as a whole and then repeated in individuals with symptoms of sleep apnea and individuals with symptoms of insomnia, compared to those without apnea or insomnia.

To carry out the first set of analyses, whole-night correlations were computed using within-participant averages of NREM delta EEG power and NREM HF-HRV. In order to estimate the correlation between delta EEG power and HF-HRV as a smooth function of time within a given NREM period, correlations were computed at each relative time interval while

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adjusting for covariates including study site, age, race, BMI, menopausal status, vasomotor symptoms, use of medications that affect sleep, caffeine intake, and AHI. These correlations were then transformed using Fisher's Correlation Transformation, which produces approximately normally-distributed values. Cubic smoothing splines were used to obtain estimates of the time varying correlation on Fisher's transformed scale by minimizing penalized sum-of-squares with smoothing parameters selected through generalized cross-validation (Chong Gu, 2002). Point-wise 95% Gaussian bootstrap confidence intervals were computed for the time-varying Fisher's transformed correlation from 250 random bootstrapped samples. The estimated curve and confidence intervals were transformed back to the original correlation scale, providing a denoised, covariate-adjusted temporal correlation function and 95% confidence intervals. This method allowed us to investigate how the covariate-adjusted correlation between delta EEG power and HF-HRV evolves over time within each NREM period.

The second set of analyses evaluated whether the time-varying correlations between delta EEG power and HF-HRV differ significantly across NREM periods. The difference in estimated Fisher-transformed correlations between each pair of NREM periods was computed at each relative time interval, and 95% Gaussian bootstrap confidence intervals of this difference were obtained. In these models, 95% confidence intervals on the Fisher-transformed scale that do not include zero represent a significant difference between NREM periods on the original correlation scale.

The final set of analyses examined the effects of sleep apnea and insomnia symptoms on the dynamic coupling of delta EEG power and HF-HRV during NREM sleep. Three sub-groups of our sample of 197 midlife women were constructed: a clinically significant SDB group, a self-reported insomnia group, and a non-disorder control group. Participants with an AHI ≥ 15 were included in the clinically significant SDB group (n=32), and participants meeting criteria for insomnia based on the self-report Insomnia Symptom Questionnaire (ISQ) were included in the insomnia group (n=25). Participants with an AHI < 15 and who did not meet the ISQ insomnia criteria comprised the non-disorder control group (n=146). We first calculated the time-varying correlation between delta EEG power and HF-HRV during each NREM period separately for each of the three groups using the same approach described above. For each sleep disorder, the difference in estimated Fisher-transformed correlations between the disorder-present group and the control group were then computed at each relative time point, and 95% Gaussian bootstrap confidence intervals were obtained. In these models, 95% confidence intervals on the Fisher-transformed scale that do not include zero represent a significant difference between the disorder-present group and the control group on the original correlation scale. With the exception of AHI and insomnia (present/absent), covariates in the sleep disorder-stratified models were similar to those used for all participants combined.

Results

The majority of participants were pre-or early-perimenopausal when studied and more than a third reported vasomotor symptoms coincident with their sleep study (see Table 1). Mean AHI for the entire sample was 9.5, + 14.5 and over 20% reported taking medications that

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affect sleep including antihistamines, hypnotics and sedatives, antidepressants, or anxiolytics. Other sleep parameters such as sleep quality and PSG-assessed sleep duration, continuity and architecture in this sample have been previously reported (Hall et al., 2009). Neither the sleep apnea nor insomnia groups significantly differed from the control group in terms of whole-night mean delta EEG power or mean HF-HRV ($p>0.33$ for all comparisons).

How are Whole-Night Delta EEG Power and HF-HRV During NREM Sleep Correlated in Midlife Women?

Whole-night averages for NREM delta EEG power were significantly correlated with HF-HRV in the sample as a whole. Higher mean HF-HRV values during NREM sleep were associated with higher mean delta EEG power during NREM sleep ($r=0.24$, $p<0.001$).

How are Delta EEG Power and HF-HRV Correlated over Time within NREM Periods?

The time-varying correlations between delta EEG power and HF-HRV during the first three NREM periods, for all participants combined, are displayed in Figure 1. Time 0 (t=0) corresponds to each participant's peak delta power, and each NREM period is divided into relative time preceding and following peak delta power. As shown in Figure 1, the correlation profile for the delta EEG power and HF-HRV relationship during NREM-1 is bimodal; the correlation increases from zero at sleep onset to a local maximum of $r = +0.29$ with 95% CI (0.20, 0.38). The correlation then decreases in magnitude until the peak of EEG delta power, $t = 0$, at which point the correlation is no longer significant. Following t=0, the correlation between these two physiological parameters increases to $r = +0.35$ with 95% CI (0.25, 0.43) and remains significant and positive until the end of the first NREM period, when the correlation approaches zero. During NREM-1, the correlation is significantly positive for 86% of the time before the peak in delta power (t=0) and 90.8% of the time after peak delta power.

During NREM-2, the time-varying correlation between delta EEG power and HF-HRV also has two peaks; the correlation rises to a maximum value $r = +0.22$ with 95% CI (0.12, 0.31) and subsequently decreases to zero when the maximum in delta EEG power occurs. After $t = 0$, the correlation increases to $r = +0.17$ with 95% CI (0.06, 0.26) and decreases back to zero by the end of NREM-2. The amount of time during which the correlation is significantly positive decreased from NREM-1 to NREM-2; significant results were observed for 52.3% of time before t=0, and 71.4% of time following t=0. Qualitatively, the NREM-2 correlation function crudely follows the same pattern as the first NREM period, but the overall magnitude of the correlation function is lower. In addition, the peaks in the correlation function during NREM-2 are much broader compared to NREM-1, and the drop in correlation near $t = 0$ is much sharper. During the third NREM period, the time-varying correlation between delta EEG power and HF-HRV drops dramatically. The correlation function during NREM-3 is unimodal and only significant for 11% of the time before t=0 and 46.2% of the time after t=0, reaching a maximum of $r = +0.15$ with 95% CI (0.07, 0.23) following the peak in delta EEG power.

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How are Delta EEG Power and HF-HRV Dynamically Coupled across NREM Periods?

The previous analyses suggest that EEG-HRV coupling may differ as a function of NREM period. Differences in time-varying correlations across NREM periods were computed to quantitatively examine changes in the dynamic coupling of delta EEG power and HF-HRV across NREM periods in the sample as a whole (see Figures 2a – c). The time-varying correlation between these two physiological parameters differs significantly during NREM-1 compared to NREM-2 and NREM-3. The 95% confidence intervals do not include zero for 18.6% of time before peak delta power and 37.4% of time following peak delta power when comparing NREM-1 and NREM-2, and for 22.4% of time before t=0 and 81.1% of time after t=0 when comparing NREM-1 and NREM-3. This difference is most noticeable when comparing the first and third NREM periods, as evidenced by a significant decrease in the magnitude of the time-varying correlation between delta EEG power and HF-HRV during NREM-3 compared to NREM-1 (Fig. 2b). There were few significant differences in the dynamic coupling of delta EEG power and HF-HRV during NREM-2 compared to NREM-3 (Fig. 2c). In summary, correlations between delta EEG power and HF-HRV significantly differ across NREM periods, with the largest correlations seen during NREM-1 compared to subsequent NREM periods.

Does the Relationship between Delta EEG Power and HF-HRV Differ as a Function of Sleep Apnea?

Whole-night averages for NREM delta EEG power were not significantly correlated with HF-HRV in participants with clinically significant SDB (n=32), defined as an AHI of ≥ 15 (r=0.27, p=0.13). The whole-night correlation for non-disorder controls (n=146) was significantly positive (r=0.23, p=0.005); however, the difference in whole-night correlation between the SDB group and the control group was not significant (p=0.83). Figure 3 shows the time-varying correlations between delta EEG power and HF-HRV in the control group, and Figure 4 shows the time-varying correlations in the clinically significant SDB group. Compared to controls, the correlation function for participants with sleep apnea is stronger and higher in magnitude for virtually the entire first NREM period, reaching a maximum of r=+0.62 with 95% CI (0.46, 0.73) near t=−0.5. Between-group comparisons revealed a statistically significant effect of sleep apnea on the coupling of delta EEG power and HF-HRV during NREM-1. Compared to controls, participants with clinically significant SDB evinced a significantly stronger time-varying correlation for 35.2% of the time before t = 0 and for 8.8% of the time after t = 0 during the first NREM period (Fig. 5a).

During NREM-2, the correlation function appears higher for participants with sleep apnea compared to controls, although formal comparisons did not reveal significant group differences (data not shown). Significant group differences were observed for 21.5% of the time before t=0 during NREM-3 (Fig. 5b), with stronger correlations between delta EEG power and HF-HRV in participants with clinically significant SDB compared to non-SDB controls.

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Does the Relationship between Delta EEG Power and HF-HRV Differ as a Function of Insomnia?

Whole-night averages for NREM delta EEG power were not significantly correlated with HF-HRV in participants with self-reported insomnia (n=25) (r = 0.24, p=0.26). As previously stated, the whole-night correlation for non-disorder controls (n=146) was significantly positive (r=0.23, p=0.005). Similar to the SDB case, the whole-night correlation did not significantly differ between the insomnia group and the control group (p=0.98). Figure 6 shows the time-varying correlations in participants with self-reported symptoms of insomnia. The correlation function during the first NREM period reaches a maximum of r = +0.62 with 95% CI (0.35, 0.79) before t=0 and a maximum of r = +0.78 with 95% CI (0.65, 0.87) after t=0 in the insomnia group, while the correlation function for controls attains maximum values r = +0.26 and r = +0.32 before and after t=0, respectively. The between-group difference in mean Fisher-transformed correlation functions during NREM-1 is shown in Figure 7a. This formal comparison reveals that delta EEG power and HF-HRV are more strongly coupled in participants with self-reported insomnia compared to non-insomnia controls. During NREM-1, group differences are significant for 39.0% of the time before t=0 and for 56.3% of the time after t=0.

The correlations among delta EEG power and HF-HRV remains noticeably stronger for the insomnia group compared to controls during NREM-2. The correlation function reaches a maximum of r = 0.60 with 95% CI (0.38, 0.77) before t=0 and a maximum of r = +0.49 with 95% CI (0.19, 0.70) after t=0 in the self-reported insomnia group. In contrast, the maximum correlation attained in non-insomnia controls is r = +0.22. Between-group comparisons revealed a statistically significant effect of self-reported insomnia on the correlation between delta EEG power and HF-HRV during the second NREM period. As shown in Figure 7b, the dynamic coupling of these two physiological parameters is higher in participants with self-reported insomnia compared to controls for 41.3% of the time before peak delta power and for 12.6% of time after peak delta power. Self-reported insomnia was unrelated to the time-varying relationship between delta EEG power and HF-HRV during NREM-3 (data not shown).

Discussion

The dynamic relationship between sleep and cardiac autonomic tone may reflect an underlying physiological process critical to the restorative properties of delta EEG power. The present study is the largest and most comprehensive assessment of the dynamic relationship between delta EEG power and heart rate variability conducted to date. Moreover, participants were all midlife women, who are at increased risk for sleep disturbances and cardiometabolic disease in association with the menopausal transition (Barrett-Connor, 2013; Dancey, Hanly, Soong, Lee, & Hoffstein, 2001; Guidozzi, 2013; Szmuilowicz, Stuenkel, & Seely, 2009). Our major finding is that, while whole-night correlations among delta EEG power and HF-HRV were strongly and positively correlated in midlife women, the dynamics of this relationship varied within and across NREM sleep periods. Additionally, the dynamics of this relationship differed as a function of sleep-disordered breathing and insomnia.

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Within individual NREM periods, delta EEG power and HF-HRV had similar profiles when viewed in relative time, with HF-HRV power rising and then falling in conjunction with peak delta power. When examined in relation to one another and on a moment-to-moment basis, the time-varying correlation between delta EEG power and HF-HRV had a bi-modal profile, with significant peaks in the strength of these positive correlations both preceding and following peak delta power. Not only did the dynamics of this relationship differ within individual NREM periods, the time-varying correlations between delta EEG power and HF-HRV were weaker in the second and third, compared to the first NREM period. Consistent with our results, converging evidence suggests that the relationship between sleep and HRV is highly dynamic (Otzenberger et al., 1998; Otzenberger et al., 1997; Yang, Lai, Lai, & Kuo, 2002). In a small but well-controlled study of eight healthy young males, Gronfier and colleagues demonstrated that HRV-derived indices of cardiac sympathovagal activity varied significantly within individual NREM periods (Gronfier, Simon, Piquard, Ehrhart, & Brandenberger, 1999b). Using spectral coherence analysis, Jurysta and colleagues reported that alterations in HRV-derived indices of cardiac parasympathetic activity virtually paralleled changes in EEG delta power in adult men, with changes in HRV temporally preceding changes in the EEG (Jurysta et al., 2003; Jurysta et al., 2005). Taken as a whole, these data suggest that delta EEG power and cardiac parasympathetic activity during NREM sleep are positively and dynamically coupled.

Consistent with previous reports, whole-night correlations between delta EEG power and HF-HRV did not differ as a function of clinically significant sleep disordered breathing or self-reported insomnia (Jurysta et al., 2006; Jurysta et al., 2009) although in the present study this may be due to the limited number of participants in each of these groups. Similar to the studies of Jurysta and colleagues, between-group differences in the EEG--HRV relationship only became evident when the data were evaluated in a time-varying fashion (Jurysta et al., 2006; Jurysta et al., 2009). Jurysta and colleagues' reported a loss of coherence between delta EEG power and HF-HRV in patients with sleep apnea or insomnia, while we found that the time-varying correlations between delta EEG power and HF-HRV were stronger in participants with versus those without clinically significant SDB or self-reported insomnia in two out of three NREM periods. Although the sleep disorders findings reported by Jurysta and colleagues appear to differ from ours, each study measured a different aspect of the EEG-HRV relationship. Coherency measures the strength of the linear association between two time series in the frequency domain, while temporal correlation measures the strength of the linear association as a function of time. The coherency results suggest that the time delay between changes in HRV and changes in the EEG observed in good sleepers is not evident in individuals with sleep apnea or insomnia (Jurysta et al., 2006; Jurysta et al., 2009). Our results suggest that the moment-to-moment relationship between HRV and EEG delta power is stronger in individuals with sleep apnea and self-reported insomnia compared to good sleepers, perhaps due to the loss in time delay between changes in HF-HRV and delta EEG power. Together, these approaches provide a more complete picture of sleep and nocturnal physiology among adults with clinically significant sleep disturbances or disorders. Our data indicate that EEG delta power and HF-HRV are most strongly coupled at the beginning of the night, prior to and following peak delta power within individual NREM periods, and in association with clinically-significant sleep-

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disordered breathing and with self-reported symptoms of insomnia. The present results are relevant to our basic understanding of nocturnal physiology as well as the role of sleep in health and functioning. Previous studies have shown that the profile of slow wave sleep (SWS), an index of delta power assessed via visual scoring, across NREM periods coincides with growth hormone (GH) secretion, with increased temporal association of GH and SWS during the first compared to subsequent NREM periods (Van Cauter et al., 1997; Van Cauter & Plat, 1996). Our study demonstrates that a similar profile is observed for delta EEG power and HF-HRV.

Temporal changes across NREM periods in delta EEG power and HF-HRV have been well documented. Delta EEG power, a marker of homeostatic sleep drive during sleep, dissipates across successive NREM periods,(Borbely, 1982) whereas HF-HRV, a marker of parasympathetic activity, increases across successive NREM periods (Hall et al., 2004). The time-varying correlations between delta EEG power and HF-HRV power observed in our analyses were largest in the first NREM period and smaller in the second and third NREM periods. In this sense, the dynamic coupling of EEG-HRV followed a time course more similar to delta EEG than HF-HRV, suggesting that the relationship may be more strongly driven by the former (and, perhaps, by homeostatic sleep factors) than the latter. However, we cannot exclude the alternate possibility that EEG-HRV relationships may primarily follow a circadian time course. Homeostatic and/or circadian regulation of the dynamic coupling of EEG-HRV could be further investigated using experimental paradigms such as sleep deprivation, constant routines, or forced desynchrony.

We also cannot exclude the possibility that some third regulatory process or system governs time-varying EEG-HRV correlations. It is likely that the associations between EEG and HRV are regulated by overlapping structures and circuits within the central nervous system. For instance, the ventromedial prefrontal cortex is involved in regulation of both vagal activity and delta EEG power (Dang-Vu et al., 2010; Thayer & Lane, 2000). Certainly, more research is needed to evaluate the additive and synergistic effects of delta EEG power and cardiac autonomic activity in relation to the restorative properties of delta-EEG power. A greater understanding of the dynamics of the sleep-HRV relationship is especially important in the context of sleep apnea and insomnia, as both have been linked to cardiometabolic disease risk putatively due, in part, to alterations in autonomic tone (Grandner & Perlis, 2013; Mezick, Hall, & Matthews, 2011; Schuster, Tabba, & Sahota, 2006).

The results of the current study have significant methodological implications for the measurement of HRV during sleep and in relation to health and functioning. Correlations between EEG delta power and HF-HRV during NREM sleep were modeled as smooth, covariate-adjusted, continuous functions of time. This approach provides a correlation estimate with confidence limits at any given time point within a NREM sleep cycle and has several advantages over the “discrete epoch” approach used in many studies of HRV during sleep. Prior studies have measured HRV during discrete five- to ten-minute epochs corresponding to specific stages of sleep (e.g., stages N1-N3 of NREM sleep, REM sleep). A significant limitation of this discrete epoch approach is that HRV epochs corresponding to a specific stage of sleep for a given group(s) of participants may not sampled from the same point in time either within sleep cycles or across the night as a whole. For example, a two-

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minute epoch of HRV during stage N2 sleep may be sampled from the beginning of a NREM sleep period for one participant, but later in the NREM period, or in an entirely different NREM period, for another participant. Sampling differences may be especially problematic when comparing healthy, good sleeper controls to participants with sleep, psychiatric, or medical disorders that fragment or alter the architecture of sleep and circadian rhythms. Future studies employing the discrete epoch approach may benefit from our findings; more accurate results may be obtained if HRV is measured in different individuals at similar points during NREM sleep, particularly when the study goal is to compare different groups of individuals. Furthermore, if the study goal is to quantify differences in HRV between good and poor sleepers, our results may provide direction as to when the measurements should be taken.

Ultimately, these methodological issues are important for evaluating cardiac autonomic activity as a mechanism through which sleep and sleep disturbances affect health and functioning.

Study Limitations and Strengths

The present results should be considered in relation to several limitations. Results cannot be generalized to younger and older adults given marked age effects on both the amount and profile of SWS and changes in HRV across the lifespan (Brandenberger et al., 2003; Jurysta et al., 2009; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Although Jurysta and colleagues did not observe age effects on the coherence of EEG delta power and HRV in men, there is some evidence that the temporal relationship between sleep and other physiological parameters such as growth hormone is weaker in women compared to men and changes over the course of the menopausal transition (Jurysta et al., 2003; Kalleinen et al., 2012; Schuessler et al., 2005). A second limitation of the present study is that differences in sampling frames used for spectral estimates of EEG power and HRV may have blunted our ability to detect the dynamic coupling of these two physiological parameters. Alternative power spectral estimation techniques, such as sliding-window Fast Fourier Transforms, may improve the detection of dynamic coupling between delta EEG power and HF-HRV. The use of time-frequency analysis such as the short-term Fourier transform, where shorter spectral estimates of the HRV data are possible, may be especially useful for the analysis of the dynamic coupling of sleep and cardiac autonomic activity (Cohen & Cohen, 1983).

In addition, sleep disordered breathing was assessed on PSG Night 1, but not on Nights 2 or 3 from which the HRV and EEG data for the current analyses were selected. We believe that our findings would be similar in participants with insomnia and in good sleeper controls, as delta EEG power and HF-HRV exhibit high short-term stability in these participant groups (Israel et al., 2012). The short-term stability of delta EEG power and HF-HRV in participants with clinically significant SDB, however, remains unknown; low short-term stability could potentially result in residual confounding of our results. Finally, although the insomnia group was defined by a validated self-report questionnaire, diagnostic interviews were not used to confirm presence, or absence, of primary insomnia, which may have introduced noise into the data. These study limitations are offset by several notable strengths. Most previous studies of the dynamic coupling of delta EEG power and HRV

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have been conducted in small samples of adult males, with some notable exceptions (Brandenberger, Ehrhart, & Buchheit, 2005; Yang et al., 2002). Our results suggest that delta EEG power and HRV are, similarly, coupled in a large sample of midlife women. We were also able to demonstrate that the time-varying association between delta EEG power and HF-HRV is robust to adjustment for age, race, BMI, menopausal status, vasomotor symptoms, caffeine intake and use of medications that affect sleep. The treatment of correlations as continuous functions of time provided novel information about the dynamic relationship between delta EEG power, as a measure of sleep depth, and cardiac parasympathetic activity within and across NREM periods.

Conclusions and Directions for Future Research

In conclusion, the present study revealed robust whole-night and time-varying correlations between delta EEG power and HF-HRV during NREM sleep in midlife women. Not only did the EEG-HRV relationship vary within and between NREM periods, the relationship was strongest in participants with, compared to those without, clinically significant sleep disturbances. Our results shed light on the EEG-HRV relationship in midlife women, which may play a critical role in cardiometabolic disease risk in association with the menopausal transition. Future studies should consider utilizing cross-correlational analyses to examine time-lagged relationships between HF-HRV and delta EEG power within sleep periods, as prior cross-correlational analyses have shown positive time-lagged associations between whole-night HRV and variations in EEG mean frequency, suggesting that changes in heart rate variability preceded variations in sleep EEG activity (Otzenberger et al., 1997; Otzenberger et al., 1998). Future research should test the utility of using time-varying associations between HF-HRV and EEG as predictors of both cross-sectional and longitudinal cardiometabolic outcomes (e.g. hypertension, metabolic syndrome) important for health and well-being in both men and women.

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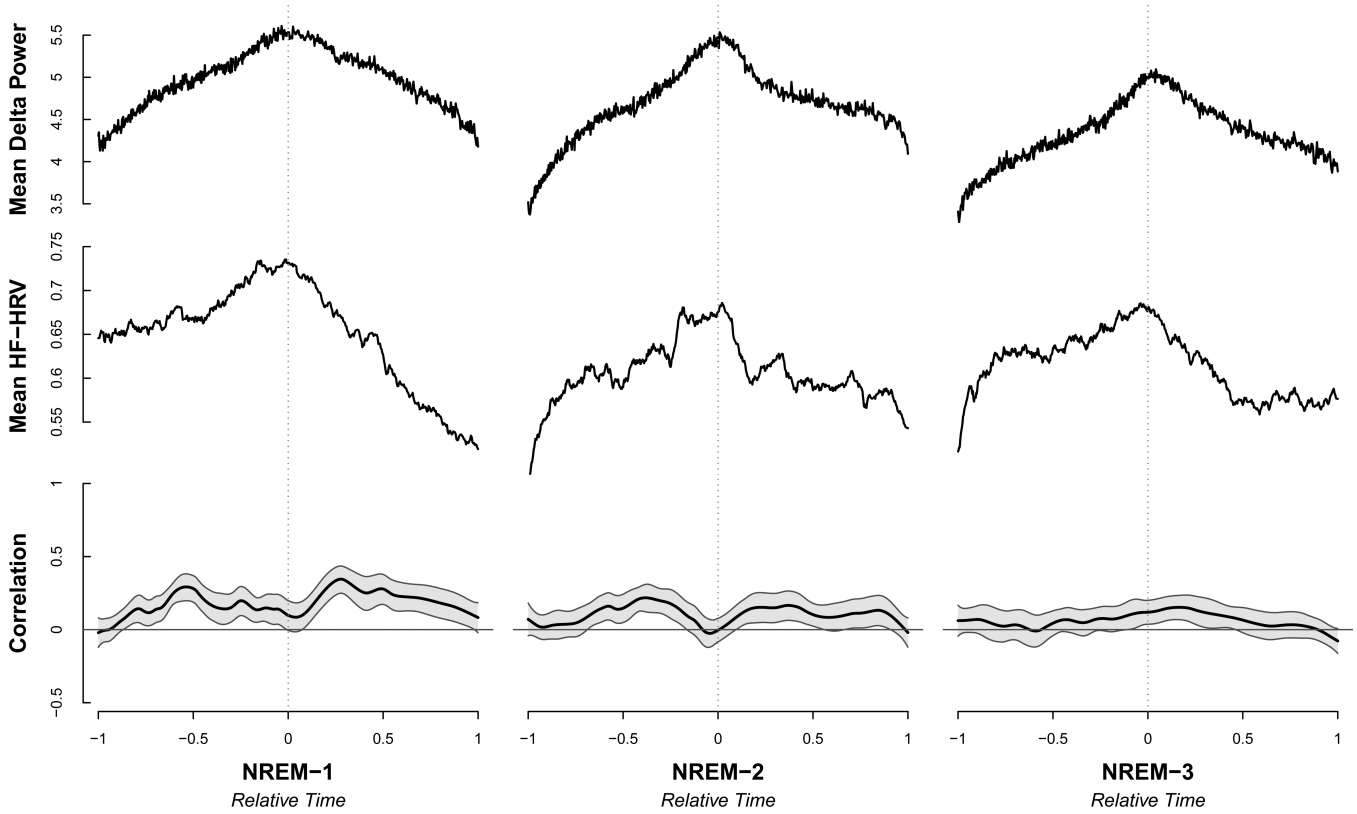

Figure 1.

Delta EEG power, HF-HRV, and time-varying correlation for NREM-1, NREM-2 and NREM-3 in the full sample (n=197). Data appear in relative time as opposed to absolute (clock) time in order to account for inter-individual differences in NREM period length. On the relative time scale, t=0 designates the time at which the maximum in delta EEG power occurs for all participants, represented in the figure by dotted vertical lines. The top row displays the mean delta EEG power profile (natural-log-transformed) as a function of relative time. The middle row displays the mean normalized HF-HRV profile (square-root-transformed) as a function of relative time. The bottom row reveals the time-varying correlation between delta EEG power and HF-HRV; solid lines represent the estimated time-varying correlation functions, and the shaded areas represent point-wise 95% confidence intervals for the correlation functions. A correlation is deemed statistically significant if its 95% confidence interval does not include zero.

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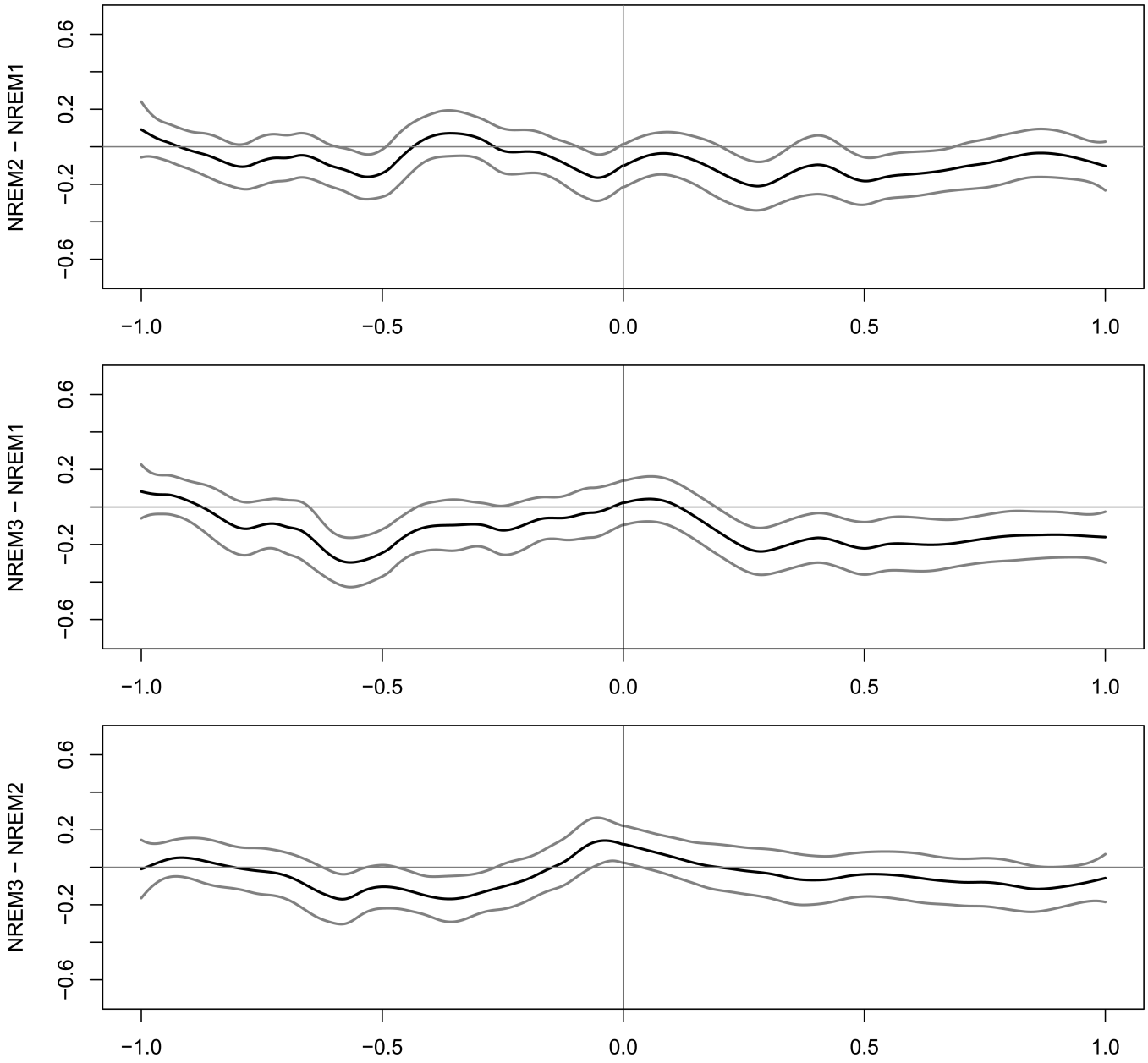

Figure 2.

Comparison of time-varying correlations between delta EEG power and HF-HRV across different NREM cycles in the full sample. In each figure, the middle curve represents the estimated correlation difference between two NREM periods on the Fisher-transformed scale, and the upper and lower curves represent point-wise 95% confidence limits for the correlation difference. 95% confidence intervals on the Fisher-transformed scale that do not include zero represent a significant difference in correlation between NREM periods on the original correlation scale. The figures shown compare (a) NREM2 – NREM1, (b) NREM3 – NREM1, and (c) NREM3 – NREM2.

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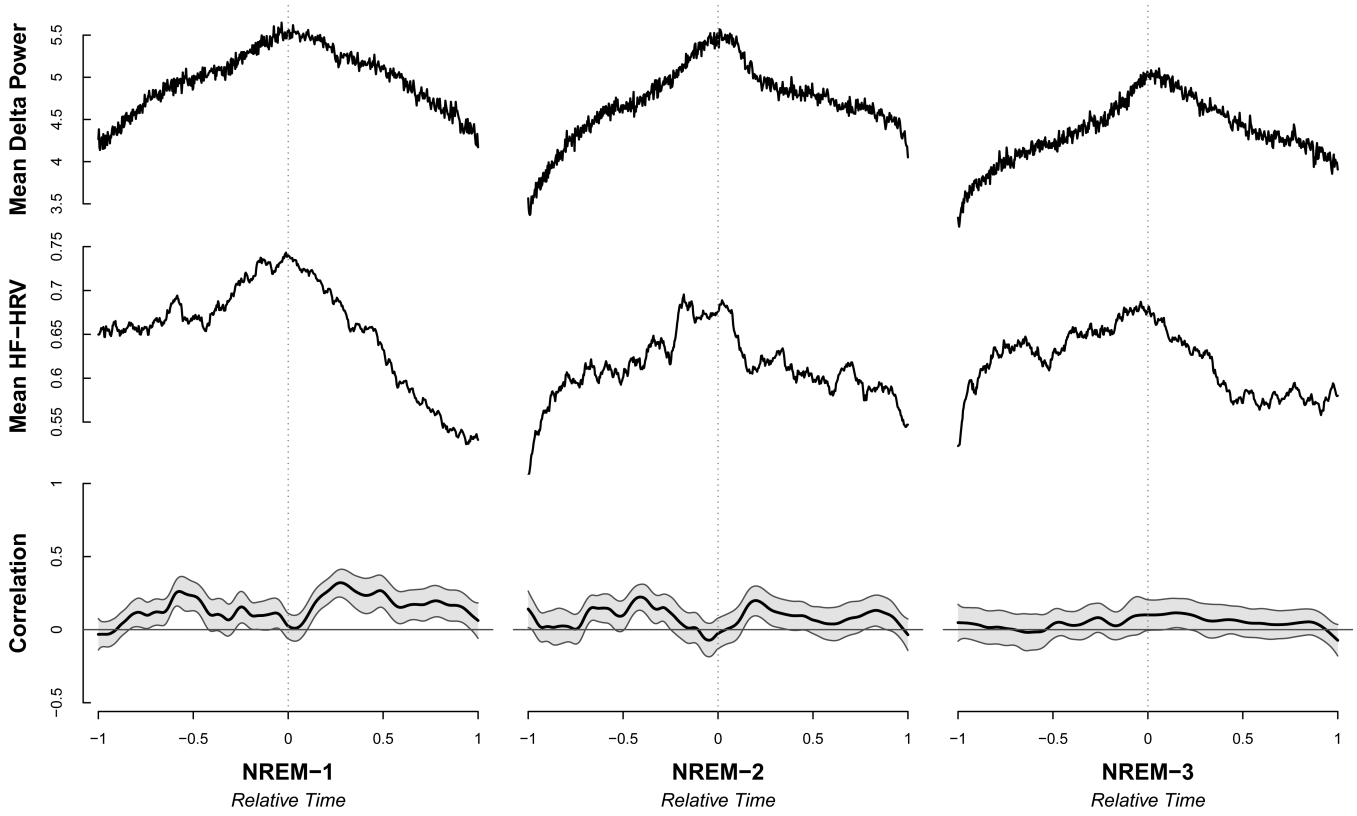

Figure 3.

Delta EEG power, HF-HRV, and time-varying correlation for NREM-1, NREM-2 and NREM-3 in the control group of participants without clinically significant SDB or self-reported Insomnia (n=146). See Figure 1 legend for details.

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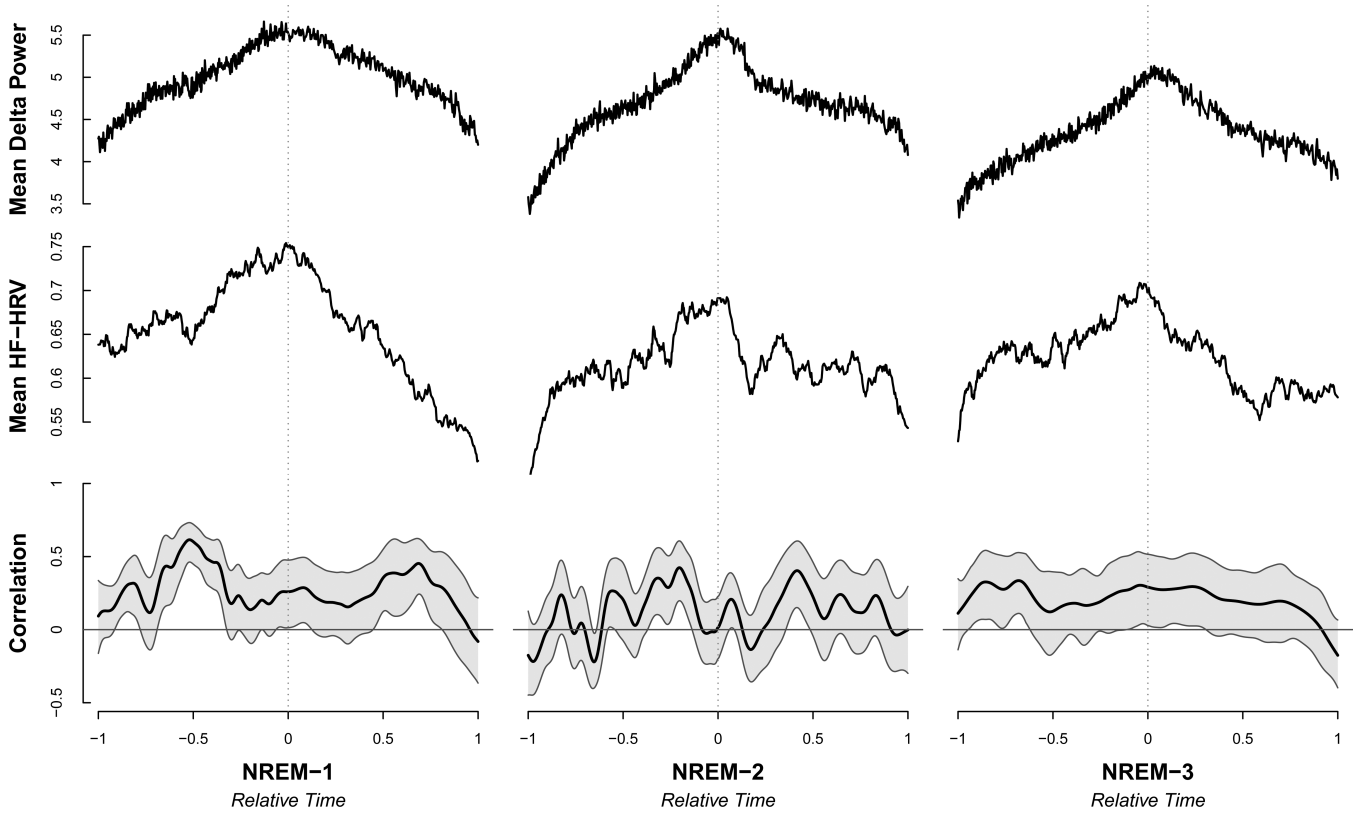

Figure 4.

Delta EEG power, HF-HRV, and time-varying correlation for NREM-1, NREM-2 and NREM-3 in the group of participants with clinically significant SDB (AHI > 15) (n=32). See Figure 1 legend for details.

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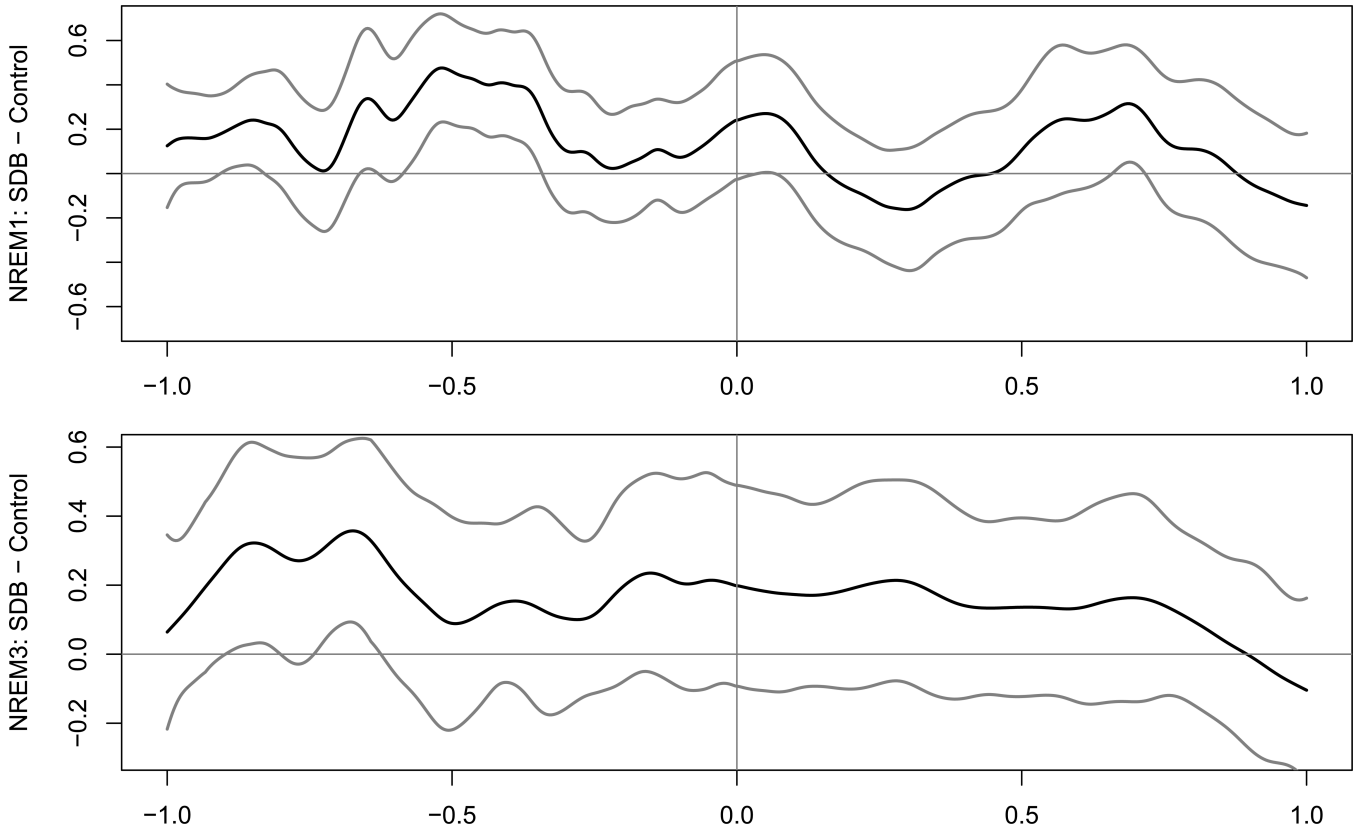

Figure 5.

Between-group comparison (SDB – Controls) of time-varying correlations between delta EEG power and HF-HRV for (a) NREM-1 and (b) NREM-3. In each figure, the middle curve represents the estimated difference in correlation between participants with clinically significant SDB and control participants on the Fisher-transformed scale, and the upper and lower curves represent point-wise 95% confidence limits for the correlation difference. 95% confidence intervals on the Fisher-transformed scale that do not include zero represent a significant difference in correlation between participants with clinically-significant SDB and control participants on the original correlation scale.

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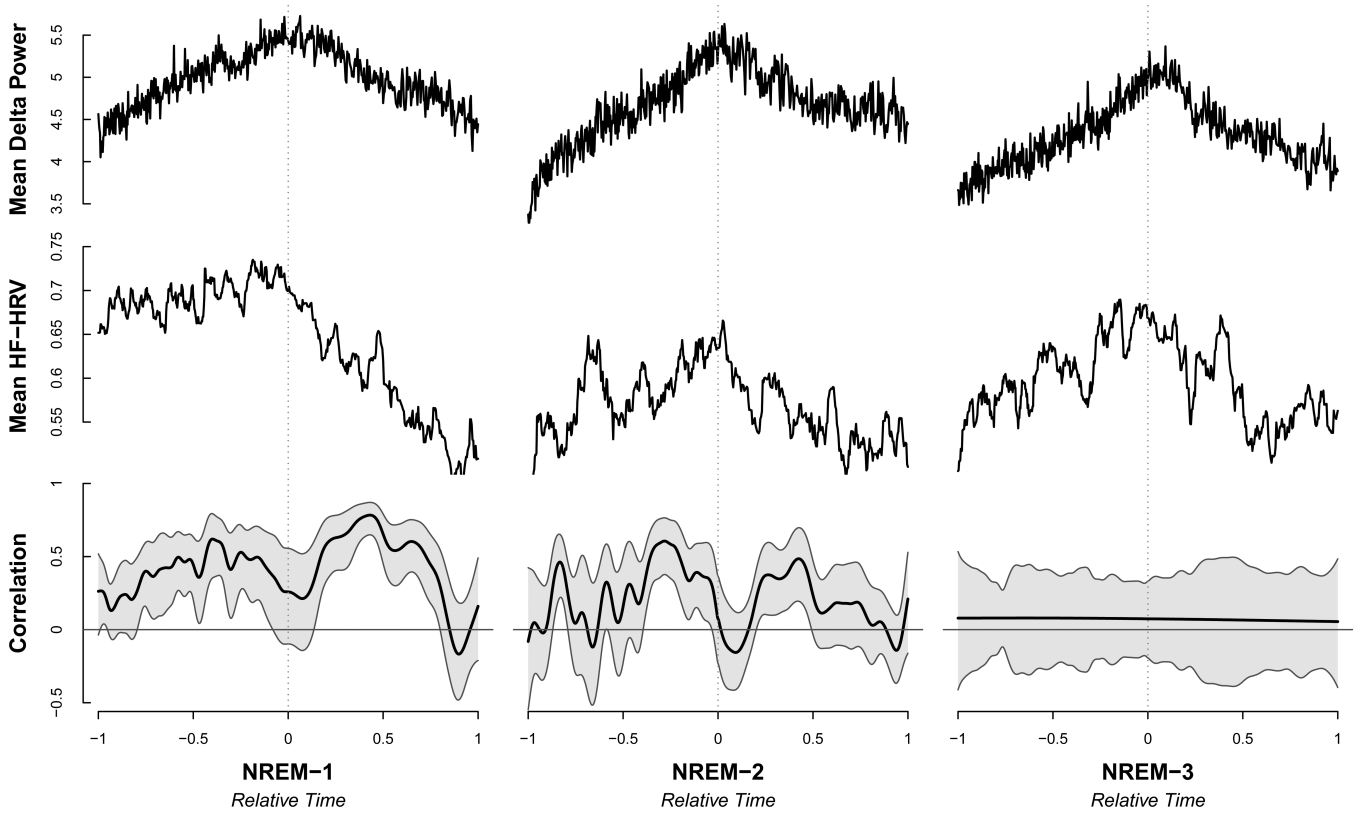

Figure 6.

Delta EEG power, HF-HRV, and time-varying correlation for NREM-1, NREM-2 and NREM-3 for participants with self-reported insomnia (n=25). See Figure 1 legend for details.

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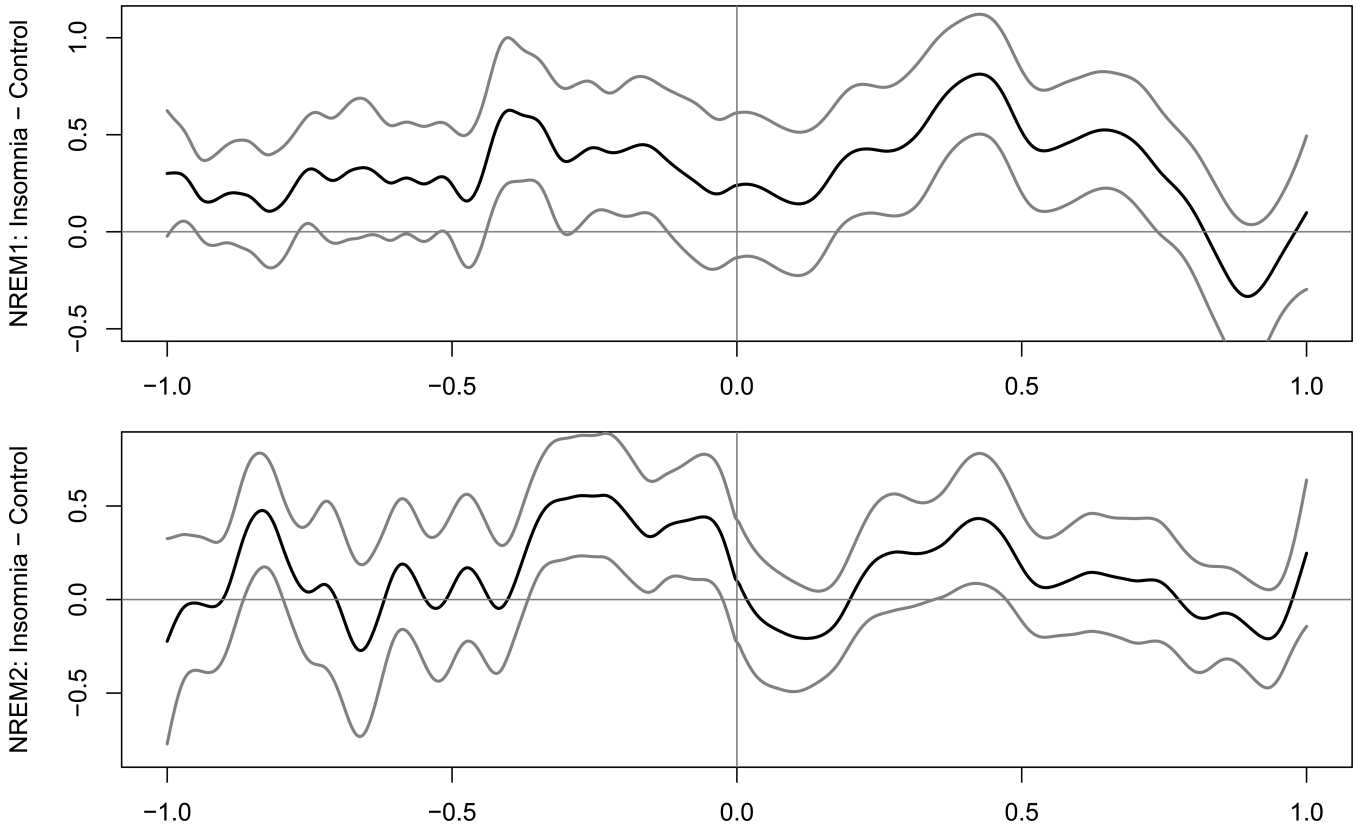

Figure 7.

Between-group comparison (Insomnia – Controls) of time-varying correlations between delta EEG power and HF-HRV for (a) NREM-1 and (b) NREM-2. In each figure, the middle curve represents the estimated difference in correlation between participants with self-reported insomnia and control participants on the Fisher-transformed scale, and the upper and lower curves represent point-wise 95% confidence limits for the correlation difference. 95% confidence intervals on the Fisher-transformed scale that do not include zero represent a significant difference between participants with self-reported insomnia and control participants on the original correlation scale.

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Table 1

Sample Characteristics

	Mean (standard deviation)	Number (percent)
Age, years	52.1 (2.1)	
Body Mass Index (BMI)	28.6 (7.1)	
Race		
African American		60 (30.5%)
Caucasian		98 (49.7%)
Chinese		39 (19.8%)
Menopausal Status		
Pre- or early-menopausal		141 (71.6%)
Peri-menopausal		37 (18.8%)
Post-menopausal		19 (9.6%)
Nocturnal Vasomotor Symptoms (VMS)		
None		129 (65.5%)
≥ 1		68 (34.5%)
Apnea-Hypopnea Index (AHI)	9.5 (14.5)	
Taking Medications That Affect Sleep		43 (21.8%)
Average # of Caffeinated Beverages per day	1.51 (1.41)	