Original Article

Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram: possible implications for assessing the effectiveness of sleep

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ABSTRACT

Objectives: The physiologic relationship between slow-wave activity (SWA) (0–4 Hz) on the electroencephalogram (EEG) and high-frequency (0.1–0.4 Hz) cardiopulmonary coupling (CPC) derived from electrocardiogram (ECG) sleep spectrograms is not known. Because high-frequency CPC appears to be a biomarker of stable sleep, we tested the hypothesis that that slow-wave EEG power would show a relatively fixed-time relationship to periods of high-frequency CPC. Furthermore, we speculated that this correlation would be independent of conventional nonrapid eye movement (NREM) sleep stages.

Methods: We analyzed selected datasets from an archived polysomnography (PSG) database, the Sleep Heart Health Study I (SHHS-I). We employed the cross-correlation technique to measure the degree of which 2 signals are correlated as a function of a time lag between them. Correlation analyses between high-frequency CPC and delta power (computed both as absolute and normalized values) from 3150 subjects with an apnea-hypopnea index (AHI) of ≤ 5 events per hour of sleep were performed.

Results: The overall correlation (r) between delta power and high-frequency coupling (HFC) power was 0.40 ± 0.18 ($P = .001$). Normalized delta power provided improved correlation relative to absolute delta power. Correlations were somewhat reduced in the second half relative to the first half of the night ($r = 0.45 \pm 0.20$ vs $r = 0.34 \pm 0.23$). Correlations were only affected by age in the eighth decade. There were no sex differences and only small racial or ethnic differences were noted.

Conclusions: These results support a tight temporal relationship between slow wave power, both within and outside conventional slow wave sleep periods, and high frequency cardiopulmonary coupling, an ECG-derived biomarker of “stable” sleep. These findings raise mechanistic questions regarding the cross-system integration of neural and cardiopulmonary control during sleep.

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1. Introduction

The biologic role of periods of nonrapid eye movement (NREM) sleep associated with low delta power is unclear. Restricting such periods has adverse consequences, including sleepiness and metabolic dysregulation similar to total sleep deprivation [1–4]. Delta frequency activity on the surface electroencephalogram (EEG), usually measured between 0.5 and 4 Hz, is considered a biomarker

of homeostatic sleep drive [5]. These slow waves are the scalp surface representation of a highly complex ensemble of oscillatory activity during NREM sleep, including the cortical up and down states that comprise the slow <1 Hz oscillation [6–8]. As a proportion of total EEG power, delta power is the highest during the initial cycles of NREM sleep and decreases across the biologic night, showing rebound effects following sleep deprivation [9,10]. The frequency of occurrence of the <1 Hz slow oscillation is far greater in the first than the final NREM sleep period [11]. However, the biologic worth of stage 2 NREM sleep (N2) may not be fully accounted for by conventional scoring or by absolute delta power profiles. These disparities are especially apparent in individuals

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over the age of 40–50 years, in whom stage 3 NREM sleep (N3) makes up less than 20% of the sleep period [12].

We previously described a complementary approach to characterize sleep based on the interaction of autonomic and respiratory interactions (cardiopulmonary coupling [CPC]), termed the electrocardiogram (ECG)-derived *sleep spectrogram*. [13] Sleep spectrogram analysis reveals that NREM sleep has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of strong high- and low-frequency CPC intensity, respectively. Much of high-frequency CPC occurs during stage N2, especially with the EEG morphology called noncyclic alternating pattern, and is associated with periods of stable breathing; a paucity of phasic EEG transients; and physiologic blood pressure dipping, which are all reduced by sleep apnea and fibromyalgia [14,15].

Cortical slow-wave kinetics can impact autonomic and respiratory function. Slow-oscillation-like activity has been recorded in downstream neural elements (reviewed in [16]), including the hippocampus, cerebellum, thalamus, basal ganglia, and even the locus ceruleus [17]. Increased slow-wave activity (SWA) after sleep deprivation in cats was reported in subcortical structures, such as the hippocampus, amygdala, hypothalamus, nucleus centralis lateralis of the thalamus, septum, caudate nucleus, and the substantia nigra [18]. Thus cortical SWA may directly entrain activities in lower brain centers and networks, plausibly enhancing a state most conducive to the generation of sustained periods of high density slow oscillations. For example, an increased probability of a stable breathing period enabled by the slow oscillation could in turn reduce arousing respiratory afferent stimuli, thus enhancing the likelihood of undisturbed and sustained slow oscillation dense periods.

In our study, we sought to assess the relationship between EEG delta power with CPC to test the hypothesis that slow-wave power fluctuations would positively correlate with high-frequency CPC, thus identifying stage N2 periods that may have potentially similar physiologic characteristics as stage N3. Such a demonstration also would provide evidence of strong cortical effects on cardioautonomic interactions previously described for conventional slow-wave sleep (SWS) and across the entire sleep period.

2. Methods

2.1. Sleep Heart Health Study polysomnogram database

Our study used data from the Sleep Heart Health Study I (SHHS-I), a large database of home-based polysomnography (PSG) [19]. The study was designed to include ~6000 adults at least 40 years of age, each of whom underwent at-home PSG. The study recruited participants from feeder studies in decreasing order of number of participants: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, New York Hypertension Cohorts, and Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study, and the Strong Heart Study. Institutional Review Board approval for data analysis (of de-identified data) was obtained from the Beth Israel Deaconess Medical Center.

The analysis database consisted of 5840 subjects for whom there was adequate data to perform the ECG-derived CPC analysis (5840 of 6441 subjects), 3150 of whom had an apnea-hypopnea index (AHI) of ≤ 5 events per hour of sleep; thus these subjects were the focus of our paper. Data exclusion criteria were excessive ECG signal dropout ($<80\%$ of signal available for analysis and no single ECG signal gap longer than 256 s), atrial fibrillation, ventricular bigeminy, and demand ventricular or biventricular pacing.

2.2. Overview

Cross-correlation is a standard method for estimating the degree to which two signals are correlated as a function of a time

lag between them. To determine the correlations between high-frequency coupling (HFC) and delta power, the ECG and EEG signals were extracted from 5840 EDF (European Data Format) files of the SHHS-I study. CPC analysis was performed on the ECG signal and Fourier analysis of the EEG signal was used to extract delta power. The cross-correlation of these two signals was then calculated, using standard methodology [20] to test for and quantify their time-dependent relationships.

2.3. CPC analysis and sleep spectrograms

The CPC analysis of the ECG signal was performed as previously described in detail [13]. Briefly, heart rate (HR) variability and ECG-derived respiration (EDR) (amplitude variations in the QRS complex due to shifts in the cardiac electrical axis relative to the electrodes during respiration and changes in thoracic impedance as the lungs fill and empty) are extracted from a single channel of ECG. Time series of normal-to-normal sinus (NN) intervals and the time series of the EDR associated with these NN intervals are then extracted from the original R-R (QRS to QRS) interval time series. Outliers due to false or missed R-wave detections are removed using a sliding window average filter with a window of 41 data points and rejection of central points that are lying outside 20% of the window average. The resulting NN interval series and its associated EDR are then resampled using cubic splines at 2 Hz. The cross-spectral power and coherence of these two signals are calculated over a 1024 sample (8.5-min) window using the fast Fourier transform applied to the three overlapping 512 sample subwindows within the 1024 coherence window. The 1024 coherence window is then advanced by 256 samples (2.1 min), and the calculation is repeated until the entire NN interval/EDR series is analyzed. For each 1024 window, the product of the coherence and cross-spectral power is used to calculate the ratio of coherent cross-power in the low-frequency (0.01–0.1 Hz.) bands to that in high-frequency bands (0.1–0.4 Hz.). The logarithm of the high- to low-frequency CPC ratio ($\log [\text{HFC}/\text{low frequency coupling} \{\text{LFC}\}]$) is then computed to yield a continuously varying measure of CPC. The graph of the amplitude of CPC at relevant frequencies (ordinate) vs time (abscissa) provides a sleep spectrogram.

2.4. Delta power

In the SHHS-I, the recording montage was C3/A2 and C4/A1 for EEGs, sampled at 125 Hz. For our analysis, EEG delta power in the 0.3- to 4-Hz band was derived from the C4-A1 EEG signal using a fast Fourier transform applied over a 30-s window, incremented every 15 s. We included the 0.3- to 0.5-Hz band in our analysis to capture some of the <1 Hz slow oscillations, part of which is already filtered by the typical settings (low-frequency filter of 0.3 Hz) used during PSG recordings. As discussed above, the absolute delta power gradually decreases during the night, i.e., leading to relatively lower amplitude for the second half of the night. This trend will distort correlation measurements assume stationarity of signals. Therefore, we also computed the relative delta power, defined as the ratio of power in the delta band to the total EEG power as a normalization procedure to mitigate these artifacts.

In the ECG-spectrogram output, the 512 second to minute sampling windows increment every 128 s, and thus are a moving average. Our analysis required us to align as closely as possible the simultaneous ebb and flow of ECG-spectrogram power and EEG delta power (Fig. 1). The measures for both absolute delta power and the normalized delta power at consecutive 15-s intervals were averaged over a 512-s window incremented every 128 s to give an average delta power which was time aligned with the HFC ratio. This procedure allowed us to closely match CPC (512 s subwindows incrementing every 128 s) and EEG outputs.

If changes in delta power and changes in the HFC/LFC ratio simultaneously occur, then the maximal cross-correlation between these two signals will occur at zero lag. If changes in delta power precede changes in the coupling ratio, then the maximal correlation between these two signals will occur at a positive lag, equal to the time difference between the corresponding changes in the two signals. Conversely if changes in delta power follow changes in the coupling, then the maximal correlation between these two signals will occur at a negative lag, equal to the time difference between the corresponding changes in the two signals. However, it should be emphasized that mathematical lead lags do not necessarily correspond to physiologic ones, but that a fixed absolute lag strongly supports an interaction between the measured signals.

2.5. Delta power: HFC correlations

The cross-correlations HFC with both the absolute and normalized delta power signals were then calculated for the entire night of sleep for each of the 5840 subjects of the SHHS-I study. The correlations of each subject were then averaged point by point over all subjects and the maximal correlation and the lag at which it occurred were then determined from this overall average cross-correlation. The same analysis also was separately applied to the first and second half of the sleep period for these subjects. To investigate the effects of aging on HFC power and delta power correlations, we further divided the subjects into age groups by decade.

2.6. Statistical methods

For each subject, the value of the cross-correlation occurring at the lag of the maximal average was used to provide a single number per subject, which was then subjected to statistical analysis. Summary measures are given as means and standard deviations. Spearman rho was used to estimate relations of the correlation metric with conventional and spectrographic data. Analysis of variance (ANOVA) was used to assess effects of age categories. Multiple comparisons were made using the Tukey method. Paired *t* tests were used to assess the difference between first and second halves of the sleep period. Multiple regression analysis assessed independent effects of race/ethnicity on the correlation between HFC and conventional stage N3 + N4 sleep. A *P* value of <.05 was considered statistically significant.

Fig. 1. Aligning electroencephalogram (EEG) and electrocardiogram (ECG) analysis windows. Schema for ECG-EEG alignment and analysis.

3. Results

3.1. Database

Selected clinical characteristics of the subjects were as follows: mean age ($\pm$ standard deviation, 60.9 ± 11 y); 63% women; body mass index (27.1 ± 4.5 kg/m²); total sleep time (TST) (366.3 ± 64.4 min); sleep efficiency ($82.7 \pm 10.1\%$); and sleep stages N1, N2, N3 + 4, and REM (%TST) ($5.1 \pm 3.6\%$, $55.6 \pm 11.7\%$, $18.8 \pm 11.8\%$, $20.5 \pm 6.3\%$, respectively). The AHI was 1.8 ± 1.4 events per hour of sleep. The racial/ethnic distribution was 77% white, 8.4% black, 7.6% Native American or Alaskan, 1.8% Asian or Pacific Islander, and 5.3% Hispanic or Mexican American. The Epworth Sleepiness Scale score was 7.3 ± 4.2 . Self-reported medical conditions included diabetes mellitus (8%), myocardial infarction (5%), angina (6%), stroke (2.7%), and hypertension (33.7%).

3.2. Correlations between delta power and ECG-derived HFC

Minimal correlations were separated by 89.6 min in absolute delta power and 91.7 min in normalized delta power, in agreement with the previously observed 90 min rapid eye movement (REM)/NREM sleep-state cycling. Maximal cross-correlations between HFC and EEG delta power showed statistically significant correlations between these two signals ($P < .0001$) (Fig. 2). Significant correlations were obtained, with a mean *r* (correlation) value of 0.40 ± 0.18 for the entire database across the whole night. Correlations of HFC with normalized delta power were significantly greater than the correlations with absolute delta power (0.40 ± 0.18 vs 0.34 ± 0.19 ; paired *t* test, $P < .001$). The values for the first and second half of the night for normalized correlations were 0.45 ± 0.20 and 0.34 ± 0.23 , respectively; these differences were significant (first vs second half) (paired *t* test; $P < .001$).

No statistically significant sex differences were noted between men and women for the whole night (0.41 ± 0.17 vs 0.40 ± 0.18 ; *t* test, $P = .09$) or the first half of the night (0.45 ± 0.121 vs 0.45 ± 0.20 ; *t* test, $P = .40$). The correlation for the second half of the night was statistically higher for men (0.35 ± 0.22 vs 0.33 ± 0.23 ; *t* test, $P = .002$), though the absolute difference was small (Fig. 3).

3.3. Relation to conventional PSG

Correlations between the relative delta power HFC correlation measures with ECG-spectrographic measures and standard EEG-PSG measures generally were low (Table 1). The Spearman rho was 0.17 for HFC and 0.23 with stage N2 + N4; these results were the highest correlations. In this dataset, HFC and stage N3 + N4 was significantly correlated (Spearman rho 0.14; $P < .001$).

3.4. Age and gender effects

There were 48, 452, 1032, 857, 620, and 140 subjects in the age groups of <40, 41–49, 50–59, 60–69, 70–79, and >80 years, respectively. The delta power HFC correlations were relatively well maintained across decades, demonstrating only a small reduction (ANOVA $F_{[5,3143]}$, 4.54; $P < .001$), being 0.44 ± 0.18 , 0.41 ± 0.17 , 0.40 ± 0.18 , 0.41 ± 0.18 , 0.39 ± 0.18 , and 0.35 ± 0.20 , respectively. After correcting for multiple comparisons, the only statistically significant differences were between the group of subjects aged >80 years and all other groups. In a multiple regression analysis, age differences remained significant after adjusting for % NREM stage N3 + N4 sleep. During the first half of the sleep period, only the group of subjects aged >80 years showed significant reductions in relation to other age groups (0.51 ± 0.19 , 0.46 ± 0.19 , 0.46 ± 0.20 ,

Fig. 2. Correlations of delta (electroencephalogram [EEG] 0–4 Hz) power and high-frequency coupling (HFC) power. Delta power 0–4 Hz and cardiopulmonary coupling (CPC) and their cross-correlations for a representative subject in the Sleep Heart Health Study database. From the top: absolute delta power 0–4 Hz (μV^2) (A). Note the higher absolute delta power in the first half of the night compared to the second half. The 0- to 4-Hz delta power normalized to total EEG power (B). Note that the relative delta power in the first and second halves of the night are of relatively equal maximal magnitude. The logarithm of the ratio of high-frequency to low-frequency CPC (C). Note the correspondence between delta power fluctuations and the CPC ratios. The CPC sleep spectrogram (D). The cross-correlation between absolute and normalized delta power and HFC in this subject was $r = 0.61$ and $r = 0.75$, respectively.

0.46 ± 0.20 , 0.43 ± 0.21 , and 0.37 ± 0.24 , respectively). During the second half of the sleep period, there were no statistically significant reductions with age (0.35 ± 0.24 , 0.32 ± 0.22 , 0.33 ± 0.23 , 0.35 ± 0.23 , 0.34 ± 0.23 , and 0.33 ± 0.24 , respectively) (Table 2).

No sex differences were noted (men vs women [correlation], 0.46 ± 0.13 vs 0.46 ± 0.12 [$P = .3$]). On the other hand, SWS (stage N3 + N4% TST) was 14 ± 10.8 vs 21.8 ± 11.5 , and HFC (proportion of sampling windows for the sleep period) was 0.44 ± 0.21 vs 0.54 ± 0.21 ; both results were higher in women.

3.5. Race/ethnicity effects

Small but statistically significant effects of race were seen ($F_{[4,3139]}$, 4.98; $P = .001$). Race differences were persistent after adjusting for age and total HFC ($F_{[3,3138]}$, 48.4; $P < .001$) or stage N3 + N4 ($F_{[3,3064]}$, 47.4; $P < .001$). The highest correlations between high-frequency CPC and normalized delta power were seen in Asian/Pacific Islanders (0.45 ± 0.18 , 0.51 ± 0.19 , and 0.38 ± 0.25) for whole night, first half, and second halves, respectively. Pairwise testing using the Tukey honestly significant difference method to correct for multiple comparisons showed that black subjects and Native American/Alaskan subjects had reduced full-night delta HFC correlations relative to white subjects. There were no statistically significant racial differences during the second half of the night, though the whole-night and first-half relationships were identical.

Racial differences in HFC ($F_{[4,3139]}$, 17.1; $P < .001$) and SWS ($F_{[4,3139]}$, 26.4; $P < .001$) were seen (Table 3). Pairwise testing showed that black subjects had significantly higher and white subjects had significantly lower HFC than other groups. However, SWS

Fig. 3. Cross-correlation between normalized delta power and the logarithm of the high-frequency to low-frequency cardiopulmonary coupling (CPC) ratio for 3150 subjects of the Sleep Heart Health Study with an apnea-hypopnea index < 5 (gray shading shows the standard deviation of the mean). Note that the maximal average cross-correlation of 0.401 occurs at a lag of -4.267 min, indicating that fluctuations in the CPC coupling ratio precede fluctuations in delta power by a median of approximately 4 min. Also note that the minimal correlations that occur when delta power and the CPC ratio are maximally out of phase at an interval of 91.7 min, consistent with the well-known 90-min period of rapid eye movement and nonrapid eye movement sleep cycling.

was significantly lower in black subjects and highest in white subjects.

Table 1

Relationship between the correlation of all-night delta power high-frequency coupling to polysomnographic and electrocardiogram-spectrographic variables.

Variable	Spearman rho (P value)
High-frequency coupling	0.17 (<.001)
Low-frequency coupling	−0.12 (<.001)
TST	−0.01 (.80)
Sleep efficiency	0.08 (.01)
Stage 1 sleep% TST	−0.04 (.03)
Stage 3 + 4% TST	0.23 (<.001)
Stage REM sleep% TST	−0.02 (.20)
Arousal index	−0.06 (.002)
Apnea-hypopnea index	0.01 (.56)
Respiratory disturbance index	−0.03 (.10)

Abbreviations: TST, total sleep time; REM, rapid eye movement.

3.6. Effects of associated medical conditions

There were no significant delta sleep CPC correlation differences between subjects with and without self-reported diabetes mellitus, ischemic heart disease, stroke, hypertension, chronic obstructive pulmonary disease, or specific medications (e.g., benzodiazepines, antidepressant agents). Body mass index did not modify the correlation metric. Although our analysis focused on subjects without sleep apnea using an AHI threshold of 5 events per hour of sleep, the differences between those individuals who had greater degrees of sleep apnea (categories of <5, 5–15, >15 and <30, and >30 events per hour of sleep), though significant ($F_{[3,5836]}$, 25.56; $P < .001$), were small except in the >30 events per hour of sleep category (0.40 ± 0.18 , 0.41 ± 0.18 , 0.41 ± 0.19 , and 0.31 ± 0.24 , respectively). A further analysis of the effects of the arousal index as a marker of sleep fragmentation in general used thresholds of ≤ 20 , 20 to 40, and >40 events per hour of sleep (3607, 1824, and 256 subjects, respectively; 153 with missing values). We used the entire SHHS-I dataset for this analysis, as those with the highest arousal index also had sleep apnea. The whole night normalized delta power HFC power correlation across arousal groups was 0.41 ± 0.18 , 0.39 ± 0.19 , and 0.30 ± 0.21 , respectively (ANOVA: $F_{[2,5687]}$, 56.48; $P < .001$). These differences were significant following Tukey multiple comparisons correction, but only the differences between the highest and mild to moderate categories were likely to be biologically relevant.

3.7. Delta power lags

The maximal correlations between CPC and EEG delta power showed a consistent lag between these two signals, with fluctuations (increases) in HFC power preceding the fluctuations (increases) in absolute delta power by a median value of −6.40 min; the negative value signifies that delta power lagged HFC power and normalized delta power by a median of −4.27 min. The 25th and 75th percentile boundaries were −6.40 and −2.13 min, respectively, for normalized delta power. The mean lag for normalized

delta power was −1.25 min (95% confidence intervals, −3.01 to 0.52; and 90% confidence intervals, −2.7 to 0.23 min). Lags for normalized and non-normalized data and related summary measures are given in Table 4, including the first and second half of the night. When correcting for multiple comparisons using the Tukey test, only the means of the non-normalized entire night and first half of the night were significantly different. Using a *t* test and a null hypothesis of zero lag, all lags were statistically significant (except the whole night non-normalized lag) as follows: whole non-normalized, whole normalized, and first half non-normalized, first half normalized, second half non-normalized, and second half non-normalized ($P = .99$, $P < .001$, $P = .02$, $P = .01$, $P < .001$, and $P = .001$, respectively).

4. Discussion

The key findings of our study were (1) delta power measured from the surface EEG correlates with ECG-derived CPC high-frequency power, further supporting a link between cortical EEG electrical activity and brain stem-related cardiorespiratory functions; (2) normalized delta power provided improved correlation compared to correlations based on absolute delta power; (3) there was a consistent lag (median of approximately 4 min) between the start of the high-frequency power increase in relation to delta power increase; (4) correlations were reduced but still highly significant in the second half of the night relative to the first half; (5) age effects appeared to be small, with correlations only being reduced in the group of subjects aged >80 years; and (6) arousals tended to reduce the strength of the correlations.

The correlation between delta power and high-frequency CPC is consistent with strong top-down modulation of autonomic and cardiorespiratory activity during the former. Delta power is positively correlated with high-frequency HR variability, and power fluctuations of delta power across the night are associated with temporally linked HR variability power changes [21–24]. High-frequency HR variability related to respiratory sinus arrhythmia is a marker of a vagal-dominant state. Our results are consistent with these findings and with a complex dynamic integration of autonomic, cortical, and peripheral interactions.

The apparently paradoxical 4-min lag between the onset of high-frequency power and increases in delta power increases was unexpected but has several potential explanations. First, the lag could be an artifact of the filtering properties of the skull. Second, directly recorded thalamic spindles can appear before simultaneously cortical surface recordings, such that the lag could reflect a subcortical-thalamic sleep generation process that then entrains the cortex, followed in turn by increasing cortical influences on thalamic and downstream processes as sleep progresses [25–27]. If EEG signals were collected at strategically placed depth recordings in humans or experimental animals, this hypothesis could then be directly tested. Of note, one such recent report has described a similar lag in cortical vs thalamic sleep-like activity [28].

Table 2

Delta power: high-frequency coupling correlations and age.

Age group, mean (range) in y	n	Stage 3 + 4	HFC (%)	Full-night delta-HFC correlation	First-half delta-HFC correlation	Second-half delta-HFC correlation
40 ± 0.2 (39–40)	48	19.4 ± 9.7	53 ± 15.2	0.44 ± 0.18	0.51 ± 0.19	0.35 ± 0.24
45.3 ± 2.5 (41–49)	452	18.1 ± 10.2	51.3 ± 21.4	0.41 ± 0.17	0.46 ± 0.19	0.32 ± 0.22
54.9 ± 2.8 (50–59)	1032	19 ± 11.3	51.4 ± 21.5	0.40 ± 0.18	0.46 ± 0.20	0.33 ± 0.23
64.3 ± 3 (60–69)	857	19.1 ± 12.6	51.3 ± 21.9	0.41 ± 0.18	0.46 ± 0.20	0.35 ± 0.22
74 ± 2.6 (70–79)	620	19.1 ± 12.6	47.7 ± 22.7	0.39 ± 0.18	0.43 ± 0.21	0.34 ± 0.23
83 ± 3.2 (80–98)	141	18.2 ± 12.8	46.9 ± 23.6	0.35 ± 0.20	0.37 ± 0.24	0.33 ± 0.24

Abbreviations: n, number of subjects; HFC, high-frequency coupling; y, years.

Table 3
Race and ethnicity effects.

Race	n	Stage 3 + 4% TST	HFC% sleep period	Full-night delta-HFC correlation	First-half delta-HFC correlation	Second-half delta-HFC correlation
White	2428	19.9 ± 11.8	48.9 ± 21.7	0.41 ± 0.17	0.46 ± 0.20	0.34 ± 0.23
Black	265	16.1 ± 11.5	60 ± 20.9	0.36 ± 0.21	0.39 ± 0.24	0.31 ± 0.25
Native American/Alaskan	239	12.4 ± 10.6	53.4 ± 22.6	0.37 ± 0.19	0.42 ± 0.20	0.32 ± 0.23
Asian/Pacific Islander	52	19.3 ± 10.5	50.4 ± 20.3	0.45 ± 0.18	0.51 ± 0.19	0.38 ± 0.25
Hispanic/Mexican American	165	18.2 ± 10.4	54.2 ± 21	0.41 ± 0.16	0.47 ± 0.17	0.31 ± 0.23

Abbreviation: n, number of subjects; HFC, high-frequency coupling; TST, total sleep time.

Table 4
High-frequency coupling: delta power lags.

	Non-normalized: entire sleep period	Non-normalized: first half of sleep period	Non-normalized: second half of sleep period	Normalized: entire sleep period	Normalized: first half of sleep period	Normalized: second half of sleep period
Mean ± SE	0.01 ± 1.16	−4.01 ± 0.58	−1.62 ± 0.72	−1.25 ± 0.90	−2.50 ± 0.50	−1.69 ± 0.62
Median, 25th and 75th percentiles	−6.40 (−8.53, −2.13)	−4.27 (−8.53, −2.13)	−6.40 (−14.93, 2.13)	−4.27 (−6.4, −2.13)	−2.13 (−6.4, −2.13)	−4.27 (−10.67, 0)

Abbreviation: SE, standard error.

Values given in units of minutes. The temporal resolution (steps) of the electrocardiogram spectrogram is 2.13 min; therefore, the median and percentile values are multiples of that value.

Correlations were slightly reduced in the second half of the night. Although speculative, this result is consistent with the dynamics of intracortical SWA that recently have been described in relation to the cortical <1 Hz slow oscillations and associated up and down states [11]. One postulated function of sleep is synaptic downscaling [29–31], which would lead to reduced strength of cortical synapses in the second relative to the first half of the night. This effect has been shown by both modeling and by using dense EEG array methods [29–31] and is reminiscent of our correlation results.

There remains an important degree of unexplained variability in the correlation of delta power and HFC power. Although the ebb and flow of SWS is smooth, periods of HFC dominance are relatively abrupt in onset. The ECG-spectrogram necessarily is a moving average, using sampling windows of several minutes. Thus short-term EEG power fluctuations may not be accompanied by discernible changes in HFC power. Intracortical interactions and network activity over shorter and longer distances are required for generation of slow-wave power and the <1 Hz slow oscillation; the network behavior of cortical-subcortical vs higher center-brain stem interactions may be different, with lags and phase differences which are not yet known. Individual differences in slow-wave power also may add to variability of the measured correlations. Arousals also seem to disrupt the relationship of delta power and HFC, further contributing to variability.

The racial differences noted are small and most likely are not of clinical significance. However, HFC was increased in the SHHS black subjects as shown in Table 3, though conventional SWS is known to be reduced in black individuals [32]. The effect of age was small and was only seen in the oldest subjects; the clinical significance of this finding is not clear. Some of our findings may be explained by considering sleep in the dimension of effectiveness, in which effective sleep is restorative and spans both conventional SWS and periods of stage N2. The link we demonstrated between slow-wave power and ECG-derived HFC suggests that periods of stage N2 may have biologic characteristics and functions of stage N3, especially when absolute delta power is lower (e.g., as with aging).

Our analysis has important limitations. The method does not apply to REM sleep. The inability to differentiate between the contribution of standard delta power and the <1-Hz NREM sleep slow oscillation in our analysis is an important limitation and should be a target for further analysis in appropriate datasets with less restrictive filtering. The sampling windows of EEG power, which

can vary from less than 1 to 30 s in sleep EEG analysis, and CPC estimates (8.5 min) are different requiring interpolation and smoothing of EEG activity. The effects of drugs that increase SWS or alcohol that alter the proportion of waves of different frequencies are unknown. Artifacts may obscure the EEG or induce slow frequencies.

In summary, we described findings that support links between electrocortical activity with autonomic-respiratory interactions. The ECG-spectrogram, which shows ECG-derived high-frequency CPC for which stable breathing periods are required, may reflect an important component of integrated brain stem output associated with cortical delta power and NREM sleep slow oscillation dynamics.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2013.10.002>.

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This study is dedicated to the memory of the late Joseph E. Mietus.

References

- [1] Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117–26.
- [2] Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 2004;89:2119–26.
- [3] Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;3:519–28.
- [4] Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA* 2008;105:1044–9.
- [5] Achermann P. The two-process model of sleep regulation revisited. *Aviat Space Environ Med* 2004;75:A37–43.
- [6] Chauvette S, Volgushev M, Timofeev I. Origin of active states in local neocortical networks during slow sleep oscillation. *Cereb Cortex* 2010;20:2660–74.
- [7] Menicucci D, Piarulli A, Debarnot U, d'Ascanio P, Landi A, Gemignani A. Functional structure of spontaneous sleep slow oscillation activity in humans. *PloS one* 2009;4:e7601.
- [8] Steriade M, Amzica F. Slow sleep oscillation, rhythmic K-complexes, and their paroxysmal developments. *J Sleep Res* 1998;7(Suppl. 1):S30–5.
- [9] 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.
- [10] Cajochen C, Foy R, Dijk DJ. Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Res Online* 1999;2:65–9.
- [11] Vyazovskiy VV, Olcese U, Lazimy YM, Faraguna U, Esser SK, Williams JC, et al. Cortical firing and sleep homeostasis. *Neuron* 2009;63:865–78.
- [12] Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med* 2009;10(Suppl. 1):S7–S11.
- [13] Thomas RJ, Mietus JE, Peng CK, Goldberger AL. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. *Sleep* 2005;28:1151–61.
- [14] Thomas RJ, Mietus JE, Peng CK, Goldberger AL, Crofford LJ, Chervin RD. Impaired sleep quality in fibromyalgia: detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Med* 2010;11:497–8.
- [15] Thomas RJ, Weiss MD, Mietus JE, Peng CK, Goldberger AL, Gottlieb DJ. Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling. *Sleep* 2009;32:897–904.
- [16] Vyazovskiy VV, Harris KD. Sleep and the single neuron: the role of global slow oscillations in individual cell rest. *Nat Rev Neurosci* 2013;14:443–51.
- [17] Eschenko O, Magri C, Panzeri S, Sara SJ. Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb Cortex* 2012;22:426–35.
- [18] Lancel M, van Riezen H, Glatt A. Enhanced slow-wave activity within NREM sleep in the cortical and subcortical EEG of the cat after sleep deprivation. *Sleep* 1992;15:102–18.
- [19] Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997;20:1077–85.
- [20] Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical recipes: the art of scientific computing. 3rd ed. Cambridge, UK: Cambridge University Press; 2007.
- [21] Ako M, Kawara T, Uchida S, Miyazaki S, Nishihara K, Mukai J, et al. Correlation between electroencephalography and heart rate variability during sleep. *Psychiatry Clin Neurosci* 2003;57:59–65.
- [22] Brandenberger G, Ehrhart J, Piquard F, Simon C. Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep. *Clin Neurophysiol* 2001;112:992–6.
- [23] Yang CC, Lai CW, Lai HY, Kuo TB. Relationship between electroencephalogram slow-wave magnitude and heart rate variability during sleep in humans. *Neurosci Lett* 2002;329:213–6.
- [24] Yang CC, Shaw FZ, Lai CJ, Lai CW, Kuo TB. Relationship between electroencephalogram slow-wave magnitude and heart rate variability during sleep in rats. *Neurosci Lett* 2003;336:21–4.
- [25] Steriade M. The corticothalamic system in sleep. *Front Biosci* 2003;8:d878–99.
- [26] Steriade M. Grouping of brain rhythms in corticothalamic systems. *Neuroscience* 2006;137:1087–106.
- [27] Steriade M, Amzica F. Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Res Online* 1998;1:1–10.
- [28] Magnin M, Rey M, Bastuji H, Guillemand P, Manguiere F, Garcia-Larrea L. Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans [published online ahead of print February 8, 2010]. *Proc Natl Acad Sci USA* 2010;107:3829–33.
- [29] Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep* 2007;30:1617–30.
- [30] Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep* 2007;30:1643–57.
- [31] Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G. Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. *Sleep* 2007;30:1631–42.
- [32] Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* 2004;164:406–18.