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Mapping Sleep using Coupled Biological Oscillations

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Abstract— **Sleep and wake state have different influences on a variety of recordable signals that make up the polysomnogram. Conventional sleep stages are dependent on analysis of electroencephalogram (EEG) waveforms. Non-EEG approaches can provide a different view of sleep. One such example is the electrocardiogram (ECG) derived sleep spectrogram, which computes the coupling and coherence of heart rate variability and respiratory tidal volume influences on the ECG R wave. Novel insights into sleep physiology and pathology are available through this technique.**

I. Introduction

TRADITIONAL approaches to characterize sleep have been dominated by single-physiology methods, dominated by electroencephalogram (EEG) waveforms. Thus, non-rapid eye movement sleep stage N1, N2 and N3, and REM sleep are recognized. However, such characterization has numerous problems, including the age-related loss of stage N3, also called slow-wave sleep, the need for EEG recording, and individual differences-related alterations in the EEG.

Several alternate methods to characterize sleep have been proposed. These include: 1) Measuring motor activation during sleep, typically periodic limb movements. Fragmented sleep can have excessive motor activation, and excessive motor activation can fragment sleep, but PLMs may be entirely absent in sleep apnea patients and other causes of fragmented sleep. 2) Autonomic approaches such as pulse transit time, peripheral arterial tonometry (PAT) and heart-rate based metrics (variability, transient rate kinetics). Periods of vagal dominance are associated with stage N3, but HRV metrics are difficult to use when variability is low, such as in heart failure, diabetes, beta-blocker use, or aging. Moreover, the exact temporal borders of periods of vagal dominance are hard to define. Cyclic variation in heart rate is a useful marker of sleep apnea but not in those with low HFV. The same limitations apply to Pulse Transit Time – it is hard if not impossible to delineate clear periods of "good" vs. "non-good" sleep. PAT characteristic can correlate with conventional slow wave sleep, and may have some utility as a non-EEG marker of sleep quality. 3) Hemodynamic monitoring show that sleep-related blood pressure reductions ("dipping") is a marker of health, and adverse effects of non-dipping have a large volume of supportive data. Dipping does not occur abruptly and thus cannot capture short-term changes. Non-dipping can occur in those with good sleep quality by other measures. 4) Respiration characteristics can identify sleep quality. For example, periods of stable breathing dominate sleep-breathing in health and occur even in those with severe sleep apnea. However, respiratory abnormality is not present in those with sleep fragmentation from other reasons, such as pain, epilepsy, auditory noise. 5) Oxygenation and ventilation tracking is useful only when clearly abnormal as sleep quality markers. 6) Endocrine and metabolic markers, such as cortisol and growth hormone levels, cytokines, inflammatory biomarkers, or glucose disposal during sleep, have not been shown to be practical tools to measure sleep quality.

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II. Effective and Ineffective Sleep

A new concept is proposed, that of "sleep effectiveness". The term effectiveness is used to distinguish it from "efficient" (as the term sleep efficiency has a specific meaning in sleep science) and "fragmented" (as there are numerous opinions, time-scales and definitions of sleep fragmentation). The term "restorative" and "non-restorative" are already used in the literature but definitions are unclear. Effective sleep is conceptualized as a sleep state that allows the normal functions of sleep (for brain and body; a desirable sleep state to be in), and ineffective sleep as a state that does not. An individual can be "efficient and ineffective" as well as "inefficient and effective" if the period of sleep itself is of high quality. The concept is not sleep stage restricted, or graded, but bimodal.

Effective sleep is largely concordant, such that during periods of effective sleep, all components of the sleep system are in a desirable mode, such as stable sleep and breathing, blood pressure dipping, normal oxygenation and ventilation, and absence of EEG arousals. Discordant effectiveness can occur, such as REM sleep hypoventilation, where the quality of REM sleep may be good but gas exchange not.

III. Mapping Effective and Ineffective Sleep

The key to quantifying sleep effectiveness is to integrate information from more than one physiological system. An excellent example of ineffective sleep is severe sleep apnea, where (Figure 1) all recorded measures show linked

oscillations every 25-40 seconds (apneas, arousals and an EEG dominated by phasic complexes called Cyclic Alternating Pattern, heart rate accelerations and decelerations, oxygen desaturation, periodic limb movements, blood pressure and muscle sympathetic nerve activity surges). As various physiological systems seem linked during sleep, computing coupled and coherent oscillations may provide a view of sleep unconstrained by the limitations of any single system. For example, heart rate variability-respiration, EEG-blood pressure, respiration-blood pressure and heart rate-blood pressure are all plausible coupled system amenable to computational analysis. The method we have developed uses the electrocardiogram (ECG), from which is extracted autonomic and respiratory influences, both of which are intensely modulated by state (sleep and wake). The resulting "sleep spectrogram" is a map of coupled oscillations during sleep, which yields unique insights into physiological and pathological sleep.

IV. CARDIOPULMONARY COUPLING SLEEP SPECTROGRAMS

The cardiopulmonary coupling technique [1] is based on a continuous electrocardiogram (ECG) signal and employs Fourier-based techniques to analyze 2 features of the signal: (1) the variability of the cardiac interbeat (RR) interval series and (2) the fluctuations in QRS amplitude induced by respiration--the ECG-derived respiration (EDR) signal [1]. These signals have 2 basic patterns: a high frequency component due to physiological sinus arrhythmia that reflects breath-to-breath fluctuations, and a low frequency component that reflects cyclic variation across multiple breaths. Using the Fourier transform, the R-R interval time series and the associated EDR signals are first decomposed into a set of sinusoidal oscillations with specific amplitudes and phases at each frequency. Two factors are considered in evaluating the strength of the coupling between these 2 signals: (1) If, at a given frequency, both signals have relatively large oscillation amplitudes, then it is likely that these 2 signals are coupled with each other. This can be measured by computing the cross-spectral power, i.e., the product of the powers of the two individual signals at a given frequency. (2) If 2 oscillations at a given frequency are synchronized with each other (i.e., they maintain a constant phase relationship), this can be measured by computing the coherence of these signals. We use the product of the coherence and the cross-spectral power to weight these 2 effects in order to quantify the degree of the cardiopulmonary coupling.

Using a single lead ECG, an automated beat detection algorithm is used to detect beats and classify them as either normal or ectopic based on their morphology and timing. In addition, 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 are determined. These fluctuations in the mean cardiac electrical axis (typically between 1 degree and 12 degrees peak-to-peak) correlate with phasic changes in the respiratory cycle. From these amplitude variations, a surrogate ECG derived respiratory signal (EDR) is obtained as previously described. A time series of normal-to-normal sinus (N-N) intervals and the time series of the EDR associated with these N-N intervals are then extracted from the original R-R interval time series. Outliers due to false or missed R-wave detections are removed using a sliding window average filter with a length of 41 data points, where central points lying outside 20% of the window average are rejected. Since Fourier analysis requires evenly sampled data, the resulting N-N interval series and its associated EDR signal are resampled at 2 Hz using cubic spline interpolation. At this sampling rate the Nyquist frequency allows detection of coupling frequencies up to 1 Hz. The cross-spectral power and coherence of these 2 signals are calculated over a 1024 sample (8.5 min) window using the fast Fourier transform applied to the 3 overlapping 512 sample subwindows within the 1024 coherence window. In each sub-window, the DC components and linear trends are removed and the data windowed using the Hanning (cosine) function before calculation of the Fourier transform. The 1024 coherence window is then advanced by 256 samples (2.1 min) and the calculation repeated until the entire N-N interval/EDR series are analyzed.

For each 1024 window, the product of the coherence and cross-spectral power is used to generate a spectrogram of coupling powers at each frequency vs. time. This technique thus generates a moving average of the oscillatory frequencies of the coupling between heart rate and respiration. During sleep, a predominance of power in the low-frequency band is associated with periodic sleep behaviors and periodic respiration during SDB, while a predominance of power in the high-frequency band is associated with physiologic respiratory sinus arrhythmia and deep sleep with stable respiration. To quantify the low and high frequency coupling power distributions, in each 1024 window the coherence and cross power product is used in calculating the ratio of the sum of the 2 maximal coherent cross power peaks in the low-frequency (0.01-0.1 Hz) band to the sum of the 2 maximal peaks in the high-frequency (0.1-0.4 Hz) band.

The low and high-frequency coupling regimes has only weak correlation with standard sleep staging but did follow cyclic alternating pattern (CAP) scoring, where low-frequency coupling is associated with CAP and high-frequency coupling with non-CAP. It was also determined that the ratio of the sum of the 2 maximal peaks in the very low frequency (0-0.01Hz) to the combined power of the 2 maximal peaks in each of the low- and high-frequency bands could be used to estimate wake/REM periods where a predominance of power in the very low-frequency band is associated with wake/REM periods. For each of the 3 sleep states of non-CAP, CAP, and combined wake/REM, separate receiver-operator curves were calculated over a range of power thresholds, and the thresholds giving the maximum combined sensitivities and specificities for that state were selected as optimal for the detection of that state. Using these thresholds, sleep demonstrating predominantly non-CAP, CAP, and wake/REM states could be identified.

Analysis of the PhysioNet Sleep Apnea Database using the cardiopulmonary coupling technique indicated that elevated power in the low frequency coupling region coincided with periods of scored apnea/hypopnea. Sensitivities and specificities for minute-by-minute apnea/hypopnea detection were calculated for a range of low frequency coupling powers and low/high coupling ratios. Receiver operator curves were then calculated and the thresholds giving the maximum combined sensitivity and specificity for apnea/hypopnea detection was selected as optimal. These detection thresholds required that the minimum low frequency power be greater than 0.05 normalized units and that the low to high frequency ratio be >30 to define periods of probable apnea/hypopnea, which we term elevated LFC (e-LFC).

Some spectrograms from the PhysioNet Sleep Apnea Database demonstrated periods of near-constant frequency spectral peaks in the e-LFC region that was reminiscent of the oscillations of heart rate variability seen in Cheyne-Stokes respiration in heart failure patients, which has a relatively constant cycle length. To explore this phenomenon further, we applied the algorithm to the PhysioNet Congestive Heart Failure Database, with the expectation that the database would provide more prolonged episodes with central periodic oscillations. Since the period of central apnea can be as slow as 120 seconds or longer we use the frequency band between 0.006 and 0.1 Hz to define narrow spectral band e-LFC (putative central sleep apnea, periodic breathing, or complex sleep apnea). We required (1) a minimum power in this band of 0.3 normalized units and (2) that the coupling frequency of each pair of consecutive measurements remains within 0.0059 Hz of each other over 5 consecutive sampling windows (totaling 16.9 continuous minutes). Periods of e-LFC not meeting these criteria were defined as broad spectral band e-LFC (putative obstructive sleep apnea). The amounts of broad and narrow spectral band coupling in e-LFC bands are again expressed as the percentage of windows detected in relation to the total sleep period. Thus, the narrow spectral band e-LFC identifies periods with oscillations that have a single dominant coupling frequency, suggesting central sleep apnea or periodic breathing. The broad spectral band e-LFC identifies periods with oscillations that have variable coupling frequencies, suggesting an alternate process, which we posit is dominance of anatomic upper airway obstructive processes. As it takes 16.9 min of continuous narrow-band cardiopulmonary coupling to reach the detection threshold, we estimated that this would be approximately equal to an averaged central apnea index of 5/h of sleep, assuming 6 h of sleep and a periodic breathing cycle length of approximately 35 sec. Thus the cardiopulmonary coupling technique can be used to detect apnea/hypopnea and differentiate these into obstructive vs. central. In essence, chemoreflex effects on sleep breathing can be mapped and quantified.

TABLE I
CARDIOPULMONARY COUPLING VARIABLES

Designation	Frequency (Hz)	Clinical / pathological correlate
HFC	0.1-0.4	Stable / effective sleep
LFC	0.01-0.1	Unstable / ineffective sleep
VLFC	0.001-0.01	Wake/REM/sleep-wake transitions
e-LFC	0.01-0.1	Subcomponent of LFC associates with fragmented sleep and sleep apnea

HFC: high, LFC: low, VLFC: very low, frequency coupling

V. RESULTS OF SLEEP SPECTROGRAM ANALYSIS IN INDIVIDUAL SUBJECTS AND LARGE DATABASES

The method is a non-linear approach to amplify the spectral peaks. If one signal is weak, e.g., the HRV can be reduced with age, beta-blockers, sleep apnea or congestive heart failure, the EDR component is sufficient. Similarly, the EDR can be noisy but when computed with the HRV in this analysis, the dominant frequencies come through cleanly.

High frequency coupling is reduced and low frequency coupling increased in states of fragmented sleep, including depression, fibromyalgia, sleep apnea, and heart failure. Sleep spectrogram biomarkers are heritable, and are associated with hypertension and stroke [2-4]. High frequency coupling increased are seen in the sleep following sleep deprivation, during positive pressure titration, following sleep restriction, and with the use of benzodiazepines.

EEG power in the 0.5 to 4 Hz is used as a marker of homeostatic sleep drive. While high frequency coupling occurs in both stage N2 and N3, there is a relationship with relative delta power. The ebb and flow of sleep homeostatic drive across the night is thus reflected in simultaneous changes in cardiopulmonary coupling.

Blood pressure decreases during the sleep period; this phenomenon of “dipping” is considered a sign of autonomic health. Dipping occurs only during sustained periods of high frequency coupling, providing an ECG-spectrogram biomerker of a desirable cardiovascular regulatory state.

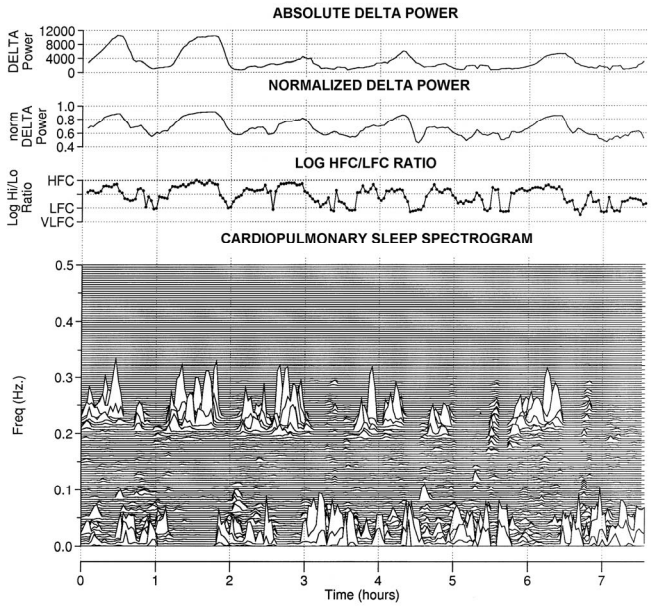

Fig. 1. ECG-derived sleep effectiveness. From top: 1) Absolute delta power 0-4 Hz (arbitrary units). Note the higher absolute Delta power in the first half of the night compared to the second half. 2) 0-4 Hz delta power normalized to total EEG power. Note that the first vs. second half of night differences are reduced. 3) The logarithm of the ratio of high frequency to low frequency cardiopulmonary coupling. Note the correspondence between delta power fluctuations and the CPC coupling ratios. 4) The cardiopulmonary coupling sleep spectrogram. Note the high correlation (r=0.84 in this example) between HFC power and normalized delta power, across the entire night.

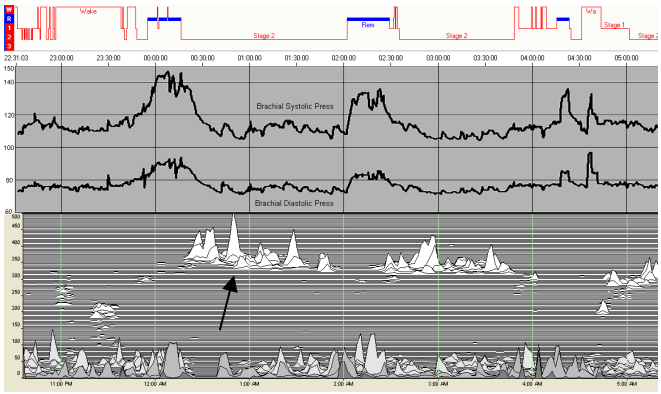

Fig. 2. Blood pressure and sleep effectiveness. From top: conventional stages (REM sleep in blue), intra-arterial systolic and diastolic blood pressure, and the sleep spectrogram. Note that dipping occurs in association with high frequency coupling (arrow) even thought conventional sleep is stage N2. Thus, the ECG-spectrogram provides improved detection of a sleep state with desirable hemodynamic features.

VI. Conclusion

Mapping coupled oscillations provide new insights into sleep physiology and pathology. The ease of acquiring the ECG allows the ECG-spectrogram to provide repeatable dynamic markers of state.

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