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Circadian Variation of Scalp EEG: A Novel Measure Based on Wavelet Packet Transform and Differential Entropy

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Abstract— **We propose a novel entropy-based measure to quantify the circadian variations of scalp electroencephalogram (EEG) by analyzing waking epochs of nap opportunities under an ultradian sleep-wake cycle (USW) protocol. To compute this circadian measure for a nap opportunity, each waking epoch (∼1 sec) is decomposed using wavelet packet transform and the relative energy for the desired frequency band (here, 10–12 Hz) is calculated. Then, in a bootstrapping procedure, a shape statistic (skewness or kurtosis) of the relative energy distribution, after each resampling, is computed. Finally, the probability density function of this statistic is estimated, and the corresponding differential entropy is considered as the circadian measure. This measure was evaluated using EEG recordings from 4 healthy subjects during a 72-h USW procedure. According to the results, the proposed measure showed a significant circadian variation both for individual and group data, with peak values occurring near the core body temperature minimum. The performance of the entropy-based measure was also compared with that of two other measures, namely mean energy logarithm and mean energy ratio, revealing the superiority of this measure.**

I. Introduction

Circadian rhythms are endogenous 24-h oscillations observed in various physiological, hormonal and behavioral processes in humans, and are driven by an endogenous central circadian pacemaker that is located in the suprachiasmatic nucleus of the hypothalamus. Under controlled conditions, several processes including core body temperature, melatonin secretion, and cortisol levels can be used to reliably assess circadian phase [1].

Circadian variations of the electroencephalogram (EEG) signal, the most utilized tool in brain function analysis, have been studied for both sleep and waking states in humans [2]–[6]. Using a forced desynchrony protocol in 7 healthy subjects, Dijk *et al*. reported the EEG signal recorded during rapid and non-rapid eye movement sleep varied across circadian phases [2]. Using a 37-h to 42-h constant routine procedure in 19 healthy subjects, Aeschbach *et al*. [3] observed a circadian variation in the EEG power spectral density for the frequency ranges of 4.25–8 Hz and 10.25–13 Hz. The circadian variation in different frequency bands of the EEG was also assessed during wakefulness by Cajochen *et al*. in 7 men during a forced desynchrony procedure [5]. Prior studies used Fourier analysis of the EEG.

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This paper presents a novel entropy-based measure to quantify scalp EEG variations at different circadian phases. Data were collected under an ultradian sleep-wake cycle (USW) protocol, separating the effects of sleep-wake dependent and circadian changes. The relative energy of EEG waking epochs (for 10–12 Hz) for each nap opportunity is calculated by wavelet analysis, and the differential entropy of a shape statistic distribution, resulting from a bootstrapping procedure, is computed. The ultimate objective of this research is to develop a reliable non-invasive circadian marker based on EEG analysis. Section II describes the data and protocol used in this study and provides computation details of the proposed assessment of circadian phase. In Section III, the results of assessment of this novel measure are presented and compared with those of two other wavelet-based measures. Results are presented for individual and group data (as opposed to previous studies, only reporting circadian rhythms for the study group).

II. Materials and Methods

A. Data and Protocol

Four healthy subjects were recruited to participate in this study following ethics approval and informed consent (two women and two men; mean age ± SD: 28.1 ± 5.2 years). Exclusion criteria included any medical conditions, night shift work, excessive tobacco or alcohol use, and illicit drug use. Women were not on oral contraceptives, had regular menstrual cycles and were studied during the follicular phase of their menstrual cycle. All subjects maintained a regular sleep-wake cycle for at least 3 weeks prior to admission, according to their habitual sleep-wake schedule. Their compliance was verified by daily phone calls to the laboratory, a sleep-wake log, and actigraphic monitoring during the week before admission.

An USW procedure, illustrated in Fig. 1, was adopted in this study. The USW procedure provides the opportunity to quantify the circadian variation of physiological parameters while minimizing the confounding effect of sleep deprivation. It allows the occurrence of sleep and waking at a variety of circadian phases [7]–[9]. For this study, each subject stayed in a time isolation suite for 5 consecutive days. The experiment started with an 8-h baseline sleep episode on the evening of Day 1 at the subject's habitual bedtime, determined based on his/her prior 3-week sleep-wake log. Then, the subject underwent a 72-h USW procedure upon awakening, consisting of 60-min wake episodes in very dim light (<10 lux) alternating with 60-min nap opportunities in total darkness (<0.3 lux). Throughout the USW procedure,

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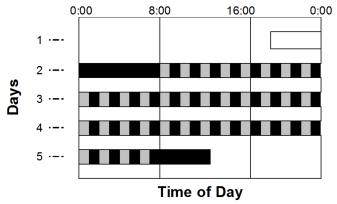

Fig. 1. The ultradian sleep-wake cycle (USW) procedure. Following an 8-h baseline sleep episode (Days 1–2), subjects started a 72-h USW procedure (Days 2–5). White bars refer to waking episodes in ∼150 lux, while grey bars represent waking episodes in very dim light (<10 lux) and black bars show nap opportunities in total darkness (<0.3 lux).

the subject remained in a semi-recumbent position in bed with low activity levels, while meals were replaced by balanced iso-caloric snacks administered during each wake episode. The USW procedure was followed by an *ad-libitum* nap episode on Day 5 to conclude the experiment.

Throughout the experiment, core body temperature (CBT) and polysomnographic (PSG) recordings were done, including the scalp EEG, electromyogram (EMG), and electrooculogram (EOG). The CBT was recorded every 15 sec using a thermistor (Steri-Probe, Cincinnati Sub-Zero Products Inc., Cincinnati, OH, USA), inserted 10 cm into the rectum and connected to an in-house data acquisition system. An ad-hoc program was used to compensate for probe slips and malfunctions by excluding data points lying outside the range of 36°C to 38°C or data showing a rate of change greater than 0.2°C/min. Before discarding any data, they were visually inspected; then, the CBT values were averaged into 1-min bins for further analysis. The CBT minimum for each subject was determined using a dual-harmonic regression model.

The EEG was continuously recorded according to the international 10–20 system [10] and sampled at 250 Hz using the Harmonie system (Natus Medical Inc., Montreal, Canada). PSG recordings were visually scored using 30-sec sleep epochs, according to the standard criteria [11]. Epochs belonging to the waking state of the nap opportunities (narrow black bars in Fig. 1) were used to quantify the variation of EEG at different circadian phases. The circadian variation of EEG was assessed by analyzing activities in the frequency range of 10–12 Hz (i.e., upper α-band), in agreement with previous studies reporting circadian rhythms of EEG during wakefulness, e.g. [3]. For this purpose, we chose the occipito-parietal montages of O_1–P_z and O_2–P_z at which the α-band activity is more prominent during relaxed state with eyes closed. EEG recordings were segmented into non-overlapping epochs of 1.024 sec. That is, the length of each epoch was 256 samples (based on the sampling frequency of 250 Hz), suitable for analysis by wavelet transform which requires the given signal has a length that is a power of two to be properly analyzed [12].

B. Wavelet Analysis

In this work, the circadian variation of the EEG signal is analyzed based on the epoch relative energy calculated using the wavelet packet transform (WPT), as a suitable analytical tool for analysis of transient and non-stationary time series [12]. Using bounded basis functions, the wavelet transform is able to locate the patterns of interest, including those with short duration that are not usually captured by the Fourier transform. As a generalization of the discrete wavelet transform, the WPT provides a greater range of possibilities for signal analysis by offering the dyadic decomposition procedure in both lower and higher frequencies [12]. Each EEG epoch from the waking state of a given nap opportunity is decomposed using WPT, and the coefficients at the last decomposition level (maximum frequency resolution) are used to compute the energy. Here, Daubechies-6 wavelet (i.e., filter length of 12) is employed based on the reported performance of Daubechies wavelets in EEG analysis [13], [14]. Let $\{c_i\}$ be the wavelet coefficients corresponding to a desired frequency band F at the last decomposition level, and $i = 1, \ldots, N$ (where N is the total number of coefficients corresponding to F). Then, the energy of the signal for F is calculated as $E = \sum_{i=1}^{N} c_i^2$.

Considering the energies of 10–12 Hz and 0.5–12 Hz for the kth EEG epoch as E_k^d and E_k^T respectively, we define the *relative energy* measure (used to quantify EEG variations) as

$$\mathcal{E}_k = \frac{E_k^d}{E_k^T} \, . \tag{1}$$

C. Entropy–Based Circadian Measure

Once the relative energy measure is calculated for all waking epochs of a nap opportunity, the resulting set of $\{\mathcal{E}_k\}$ ($k = 1, \ldots, K$, where K is the total number of waking epochs) is used to quantify the waking EEG variations in the desired frequency band (here, upper α-band) for this nap opportunity. Considering $\{\mathcal{E}_k\}$ as a set of values observed for the given EEG period, we may quantify this EEG segment based on the changes seen in the distribution of the observation set when it is resampled with replacement (i.e., bootstrapping procedure [15]). For this purpose, the skewness (as a measure of "asymmetry") or kurtosis (as a measure of "peakedness") [16] of the observation set distribution is calculated after each resampling. Let δ_m be a statistic (skewness or kurtosis) calculated based on the mth resampling of $\{\mathcal{E}_k\}$ (here, $m = 1, \ldots, 1000$) , then the *circadian measure* ($\mathcal{C}$) describing the variations of EEG for the waking state of the given nap opportunity is defined as the differential entropy [17] of the continuous variable δ

$$\mathcal{C} = -\int_{-\infty}^{\infty} \hat{p}(\delta) \ln \hat{p}(\delta) \, d\delta \, , \tag{2}$$

where $\hat{p}(\delta)$ is the probability density function (PDF) of the variable δ, estimated using the kernel density estimation [18], as a nonparametric approach. Given M data points $\{\delta_1, \ldots, \delta_M\}$ of an unknown distribution, $p(\delta)$, the PDF estimator with kernel $\mathbb{K}(\cdot)$ is defined as $\hat{p}(\delta) = \frac{1}{Mw} \sum_{m=1}^{M} \mathbb{K}\left(\frac{\delta - \delta_m}{w}\right)$, where w is the window width (also called smoothing parameter). In this work, a standard Gaussian kernel is used and the window width is estimated by $w = \hat{\sigma}\left(\frac{4}{3M}\right)^{1/5}$, where $\hat{\sigma}$ is the estimated standard deviation of data [18].

TABLE I

DIFFERENT MEASURES FOR IDENTIFYING THE CIRCADIAN VARIATION OF SCALP EEG USING INDIVIDUAL AND GROUP DATA, UNDER THE USW PROTOCOL.

Measure	Channel O_1–P_z					Channel O_2–P_z				
	Subj. 1	Subj. 2	Subj. 3	Subj. 4	All	Subj. 1	Subj. 2	Subj. 3	Subj. 4	All
MEL	0.52 (1e-4)	0.02 (0.73)	0.35 (1e-3)	0.55 (2e-5)	0.19 (<1e-12)	0.55 (5e-5)	0.12 (0.13)	0.39 (3e-4)	0.49 (2e-5)	0.23 (<1e-12)
MER	0.49 (2e-4)	0.53 (5e-6)	0.48 (3e-5)	0.24 (1e-2)	0.41 (<1e-12)	0.41 (1e-3)	0.39 (3e-4)	0.35 (1e-3)	0.28 (6e-3)	0.31 (<1e-12)
$\mathcal{C}$ **(Skew.)**	0.68 (5e-7)	0.73 (6e-10)	0.46 (6e-5)	0.37 (6e-4)	0.53 (<1e-12)	0.66 (2e-6)	0.58 (1e-6)	0.38 (4e-4)	0.37 (5e-4)	0.47 (<1e-12)
$\mathcal{C}$ **(Kurt.)**	0.63 (4e-6)	0.67 (2e-8)	0.52 (8e-6)	0.31 (2e-3)	0.51 (<1e-12)	0.60 (1e-5)	0.41 (2e-4)	0.40 (2e-4)	0.35 (9e-4)	0.42 (<1e-12)

MEL: mean energy logarithm; MER: mean energy ratio; Skew.: skewness; Kurt.: kurtosis

R^2 (p–value) are reported for each case (see Section III-A for details). p–values are given in parentheses.

The circadian measure $\mathcal{C}$ shows high values when the distribution of the relative energy measure changes noticeably by resampling, resulting in values of the statistic δ that are more scattered (high entropy). In contrast, when the EEG manifests more homogeneous patterns in the frequency band of interest, the distribution of $\{\mathcal{E}_k\}$ preserves its approximate shape through the resampling procedure, and consequently the resulting statistic δ is more condensed (low entropy).

D. Other Measures

To better evaluate the performance of the proposed entropy-based circadian measure, we defined two other measures of EEG variations, namely *mean energy logarithm* (MEL) and *mean energy ratio* (MER), and computed them for EEG recordings from the four subjects. Results have been compared with those of the entropy-based measure (see Section III). The MEL is simply defined for the waking state of a nap opportunity as $\frac{1}{K}\sum_{k=1}^{K}\ln E_k^d$, where E_k^d is the energy of 10–12 Hz for the $k$the epoch (calculated using the WPT) and K is the total number of EEG waking epochs. The MER, on the other hand, is defined as $\frac{1}{K}\sum_{k=1}^{K}\mathcal{E}_k$ for the waking state, where $\mathcal{E}_k$ is calculated by (1).

III. RESULTS

The performance of the proposed entropy-based measure $\mathcal{C}$ in describing the EEG circadian variation was assessed by applying it to the waking state of the nap opportunities of the four healthy subjects (introduced in Section II-A), using both skewness and kurtosis statistics. The performance of this measure was also compared with that of MEL and MER measures in this study.

A. Evaluation Approach

To quantitatively evaluate the performance of a given measure for identifying the EEG circadian patterns for each subject, we fit a sinusoidal curve with a period of 24 h to the values of the measure calculated at each nap opportunity for that subject. That is, considering y_{ik} as the value of the given measure at kth time point for the ith subject, the measure is modeled as $y_{ik} = a_0^i + a_1^i\cos(2\pi\tau_{ik}/24) + a_2^i\sin(2\pi\tau_{ik}/24) + \epsilon_{ik}$; where τ_{ik} refers to the time (in hours), $\{a_l^i\}_{l=0}^2$ are the regression coefficients, and ϵ_{ik} is the regression error (residual). The goodness–of–fit for each subject is then determined by calculating the "coefficient of determination", R^2. Moreover, the F-statistic is computed to test whether the amplitude of the fitted curve is significantly different from zero, and the corresponding p-value is reported.

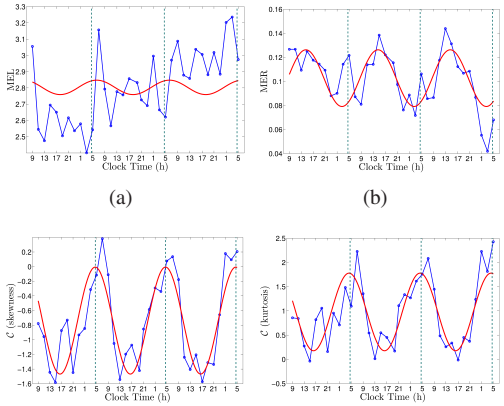

Fig. 2. Different EEG-based measures calculated for the waking state of nap opportunities of Subject 2 (channel O_1–P_z): (a) mean energy logarithm (MEL), (b) mean energy ratio (MER), (c) entropy-based measure $\mathcal{C}$ (skewness), and (d) entropy-based measure $\mathcal{C}$ (kurtosis). The x-axis shows the clock time, where the CBT minimum occurs at 04:46 h (vertical dashed lines).

To investigate the performance of the measure on the group data, the set of values obtained for each subject is first standardized (dividing by its standard deviation after removing the mean) to reduce the inter-subject variability. Next, the values from different subjects are aligned relative to each subject's CBT minimum (the common CBT minimum time is considered as 06:00 h). A mixed-effect regression model is then used to fit a sinusoidal curve to the standardized measure values from all subjects together. For each case, the R^2 and p-value are calculated to evaluate the performance of the measure.

B. Assessment Results

The results of the quantitative assessment (i.e., R^2 and p-values, illustrated in Section III-A) of different measures in describing circadian patterns in both occipito-parietal EEG channels (O_1–P_z and O_2–P_z) for all subjects are presented in Table I. The entropy-based measure $\mathcal{C}$ shows significant circadian patterns in all cases using both skewness and kurtosis statistics, where its overall performance is noticeably superior to MEL and MER measures.

Fig. 2 depicts the values of different measures along with the fitted sinusoidal curves (in red) for channel O_1–P_z of Subject 2. As can be seen, while the measure $\mathcal{C}$ (based on both statistics) shows a clear circadian rhythm, the MEL measure barely reveals any circadian patterns. Since the MEL measure is based on the absolute energy in the frequency band of 10–12 Hz, the depressed performance of MEL measure can be explained by generally weak α activities seen

in this subject's EEG. Choosing the relative energy measure (MER), on the other hand, improves the identification of the circadian patterns, as shown in Fig. 2 (b). Fig. 3 presents the values of different measures (blue '$\circ$') from all subjects together for channel O_1–P_z (after standardization), overlaid with the average ($\pm$ SD) over all subjects. The red sinusoidal curve, in each case, presents the best fit obtained using the mixed-effect regression model (Section III-A).

IV. Discussion and Conclusion

In this paper, a new method for analyzing the circadian variation of the EEG (upper α-band) in the occipito-parietal regions was presented. The scalp EEG recordings of four healthy subjects, who underwent a 72-h USW procedure, were processed using different wavelet-based measures, namely MEL, MER and $\mathcal{C}$ (based on skewness and kurtosis statistics). The proposed measure $\mathcal{C}$ quantifies the signal variations based on the changes in the shape of the relative energy distribution, resulting from a bootstrapping procedure. Analyzing the waking state of the nap opportunities, this novel entropy-based measure revealed clear and significant circadian patterns in the EEG signal (using both statistics) for each individual subject as well as for the group. In comparison, the MEL and MER measures, in general, showed noticeably weaker circadian variations. Although a measure may disclose significant circadian rhythms on a population of subjects (e.g. MEL), it may fail to show such rhythms for every individual.

The maximum of $\mathcal{C}$ always occurred close to the nadir of the CBT cycle (within 2 h from CBT minimum), indicating the occurrence of inhomogeneous upper-α activities near the CBT minimum. Considering the noticeable circadian rhythm seen in this measure, the current study clearly shows the potential of such a measure to be used as a non-invasive marker of circadian phase. The average time for computing measure $\mathcal{C}$ was $\sim$22 sec[1], which is low enough for real-time implementation of the proposed method considering that the measure is updated for each nap opportunity (here, every 2 h). More studies need to be performed to better investigate the capability of this measure as well as the reliability of each of the statistics used (skewness and kurtosis). We will, in the near future, apply this measure to scalp EEG recordings from a larger group of subjects and will analyze other brain regions and other frequency bands.

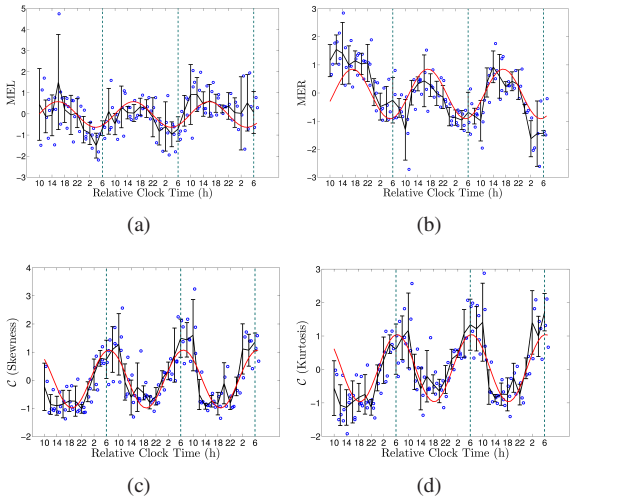

Fig. 3. Different EEG-based measures calculated for the waking state of nap opportunities of all subjects (channel O_1–P_z), after standardization. The group average ($\pm$ SD) values (in black) and individual data points (blue '$\circ$') are shown along with the fitted sinusoidal curve (in red): (a) mean energy logarithm (MEL), (b) mean energy ratio (MER), (c) entropy-based measure $\mathcal{C}$ (skewness), and (d) entropy-based measure $\mathcal{C}$ (kurtosis). Time axis is scaled with respect to the time of the CBT minimum, which is assigned a relative clock time of 06:00 h (vertical dashed lines).

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