Novel EEG Sleep Analysis Toolbox For Drug Discovery

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SUMMARY

Sleep is an essential aspect of individual health and well-being and changes in our body's natural process in response to stimuli, via circadian rhythms, can lead to a variety of health issues. In this study, we developed a MATLAB-based electroencephalogram (EEG) signal analysis toolbox that provides evidence toward the effects of pharmaceutical compounds on sleep in mice through intracranial EEG recordings. EEG data was recorded by previous lab members on a 24/7 video-EEG system and Axoscope software connected to amplifiers. We used this EEG data to measure and characterize EEG signals of sleeping/waking states of mice who were single-housed in their respective cages on a 12-hour light/dark cycle. By applying various signal processing techniques (band power, spectral entropy, RMS, etc.) of each EEG frequency band (delta, theta, alpha, beta, gamma), we were able to evaluate different physiological trends during periods of wakefulness/sleep regarding the upregulation/downregulation of these parameters and how physiological activity leads to electrographic changes during these states. The results gathered can be used by researchers and physicians to analyze the effects of pharmaceutical drugs on sleep. In future applications, this EEG toolbox will provide input data for deep learning and neural networks to characterize sleep/wake states for multiple full-length, comprehensive studies.

INTRODUCTION

Sleep is an essential aspect of individual health and wellbeing and those who suffer from sleep irregularities pertaining to sleep quality, time of sleep, or duration of sleep are more likely to experience medical problems. The body's circadian rhythm, which is a natural process in response to the presence and duration of light over time, can be modulated by pharmaceutical drugs [1]. There are four stages of sleep divided into two categories (non-rapid eye movement (NREM) and rapid eye movement (REM) sleep). In the lightest stage of NREM sleep, the rhythm of the theta (4 - 8 Hz) and alpha (8 - 12 Hz) waves decrease. The second stage of NREM sleep is marked by the expression of short-wave bursts between 11 and 16 Hz called spindles and biphasic waves, lasting less than half a second, called K-complexes [2]. The third stage of NREM sleep, commonly referred to as slow-wave sleep, is characterized by muscle relaxation and the emergence of delta (0 - 4 Hz) waves. Lastly, REM sleep is characterized by low-voltage, higher frequency brain activity, similar to EEG signals of organisms that are awake [3]. Sleep alternates between NREM and REM sleep, with the brain being relatively active during what is typically a dormant period and is important for EEG signal analysis. The goal of this study is to apply EEG feature extraction techniques to provide information on sleep and wake state frequency band regulation to develop and measure the effects of pharmaceutical drugs on sleep.

RESULTS

General Characteristics of Waking and Sleeping EEG Signals

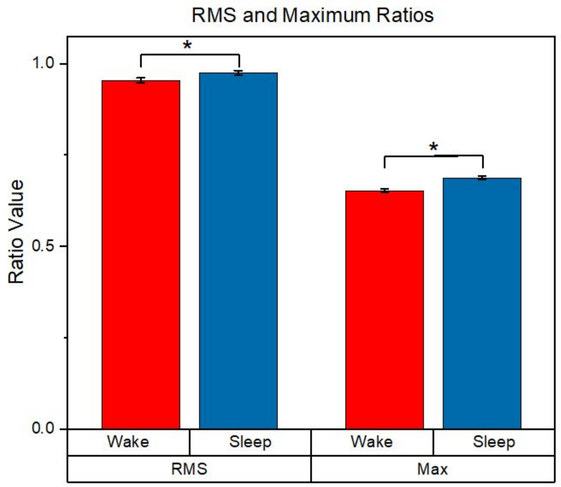

Figure 1: Root Mean Squared and Maximum Amplitude Ratios (per minute): The bar graphs of RMS ratio and maximum amplitude compared to the maximum value of the entire signal for the sleep and wake indicate that the EEG signal of sleeping mice is upregulated in comparison to the the EEG signal of the mice that are awake. The data represents the mean ± SEM. *p < 0.05 (n=30).

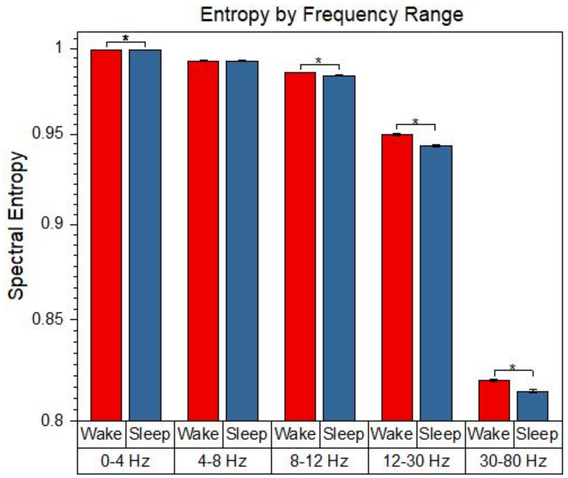

Figure 2: Spectral Entropy (per minute): The bar graphs of the spectral entropy of sleep and wake mice indicates that the volatility of the energy distribution for the wake EEG signals is significantly higher than the sleep EEG signals between 8 - 80 Hz. The data represents the mean ± SEM. *p < 0.05 (n=30).

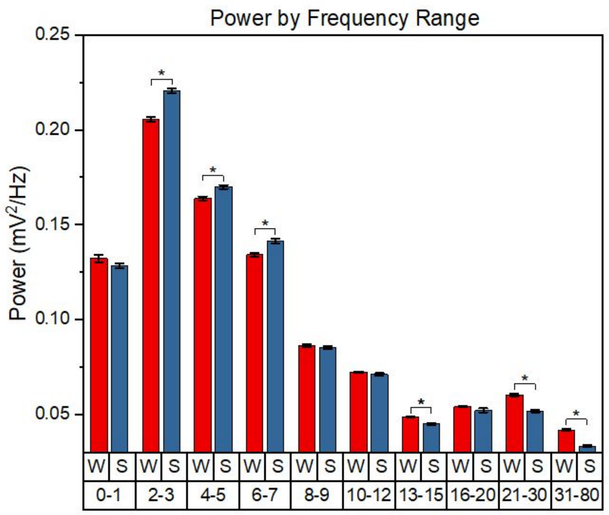

Figure 3: Power Spectral Density (per minute): The bar graphs of the power spectral density represent the average power, per minute, of the delta, theta, alpha, beta, and gamma brain waves, normalized by the total power of all frequency bands evaluated (0 - 80 Hz) between the sleeping and wake mice. Frequency-specific changes in the EEG signals show the transient increase and decrease of band power relative to a baseline. The data represents the mean ± SEM. *p < 0.05 (n=30).

Feature		Wake (Mean ± SEM)	Sleep (Mean ± SEM)
Ratio	RMS	0.954374 ± 0.007356	0.975104 ± 0.005889
	Max	0.652471 ± 0.005486	0.687762 ± 0.005041
Band Power	0 - 1 Hz	0.132319 ± 0.001889	0.128608 ± 0.001227
	2 - 3 Hz	0.205425 ± 0.001115	0.220399 ± 0.001341
	4 - 5 Hz	0.163889 ± 0.000979	0.169925 ± 0.001008
	6 - 7 Hz	0.134236 ± 0.000988	0.141428 ± 0.001151
	8 - 9 Hz	0.086239 ± 0.00067	0.08445 ± 0.000728
	10 - 12 Hz	0.072323 ± 0.000359	0.071267 ± 0.000641
	13 - 15 Hz	0.048651 ± 0.000307	0.045124 ± 0.000294
	16 - 20 Hz	0.054345 ± 0.000461	0.05236 ± 0.001013
	21 - 30 Hz	0.060512 ± 0.000719	0.05199 ± 0.00068
	31 - 80 Hz	0.042061 ± 0.00058	0.033451 ± 0.000472
Entropy	0 - 4 Hz	0.998837 ± 5.435E-05	0.998974 ± 4.23E-05
	4 - 8 Hz	0.99261 ± 0.000187	0.992641 ± 0.000127
	8 - 12 Hz	0.98586 ± 0.000158	0.983987 ± 0.000153
	12 - 30 Hz	0.949986 ± 0.000638	0.943533 ± 0.000665
	30 - 80 Hz	0.819841 ± 0.000746	0.814495 ± 0.000775

Table 1: Feature Extraction Technique Values for Sleep & Wake EEG Signals: The chart quantifies the mean ± SEM values of the extracted features to demonstrate the up-regulation and down-regulation between the sleeping mice and mice that are awake.

METHODS

Using data from a four month animal model collected by members of our lab, where wild-type mice were surgically implanted with an electrode in their hippocampus to record continuous brain activity via EEG and video to monitor their behavior, mice were characterized into sleep states and wake states. To characterize sleep and waking periods, 30 EEG samples of sleep and 30 samples of wakefulness were recorded, along with the corresponding video recordings for verification purposes. Waking periods were chosen based on activity or small movements from the animal indicative of cleaning, eating, or nest-making along with bursts of activity occurring above the animal's baseline. Sleeping periods were chosen by a combination of evaluating EEG recordings for relatively slow-wave activity and video recordings for a lack of significant movement. From here, the corresponding EEG file was split into one-minute segments for the duration of the time period. These segments were then analyzed to provide granular measurements of normalized bandpower and spectral entropy , as well as the ratio of the segment's maximum and RMS to the entire signal's maximum to evaluate general activity. To normalize the bandpower and entropy values, each bandpower segment was divided by the total bandpower for the signal (Figure 3). The same normalization was done to the entropy values (Figure 2). The maximum value of the segment was found by finding the highest amplitude within the segment of sleep or wake and this same process was used to find the maximum value of the entire EEG signal (Figure 1). After these calculations, two-tailed t-tests, mean values, and SEM values were all computed in Microsoft Excel to quantify the significance of which signals were being up-regulated and down-regulated, followed by corrections for multiple tests (Table 1).

RESULTS

- The power spectral density of the lower frequencies (2-7 Hz) are upregulated while the higher frequencies (13-80 Hz) are downregulated in sleep when compared to wake which illustrates how power processing methods can be used to quantify sleep/wake states.
- The spectral entropy of the higher frequencies (13-80 Hz) are up-regulated in waking mice when compared to sleeping mice, which illustrates how potential for signal variability can be used to characterize sleep/wake states.
- The data obtained by these processing methods will be used in a deep learning algorithm, to characterize sleep/wake states across multiple full-length, comprehensive studies.

*All results of this small pilot study are tentative. A larger sample size will be used to reinforce these findings.

REFERENCES

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