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Research paper

Differential spectrum approach to uncovering the electroencephalographic signatures of the opponent driving forces for sleep and wake underlying alternations of sleep and wake states

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ABSTRACT

The opponent model of sleep-wake regulation postulated two opposing drives for sleep and wake. Simple measurement of slow wave activity does not allow their separation in the electroencephalographic (EEG) signal. However, we previously showed that scores on the 1st and 2nd principal components of variation in the EEG power spectrum can serve as markers of the opposing sleep and wake drives, respectively. The major purpose of the present report was to confirm and extend methodology for measurement of these drives by applying a new approach aimed on uncovering differences in their EEG signatures. A set of new single EEG measures was calculated in analysis of the waking and sleep EEG signals recorded in experimental studies of night sleep, multiple naps and sleep deprivation with, in total, 62 participants. Most measures summarized differences between a pair of the EEG spectra representing two distinct sleep-wake sub-states. Analysis of these differences between spectra revealed only two typical patterns that were interpreted as the spectral EEG signatures of the sleep and wake drives. The calculated single measures were subjected to principal component analysis. It yielded two largest principal components representing these opposing drives. Time courses of scores on these two principal components of variation in the calculated single measures closely resembled time courses of scores on two principal components of variation in the EEG power spectrum. It was concluded that such methodology can facilitate quantitative evaluations and model-based simulations of the opponent regulatory processes underlying normal and abnormal alternations of sleep and wake states.

1. Introduction

Since publication of the seminal two-process model postulating two basic processes of sleep-wake regulation, homeostatic and circadian [3,5], the indexes of electroencephalographic (EEG) slow-wave activity have been considered the “gold standards” for quantification of one of these two processes, the homeostatic process (or, in other terms, the sleep drive or sleep homeostasis). For instance, these indexes were implicated into description, prediction and simulation of time courses of payment of sleep debt during Non-Rapid-Eyes Movement (NREM) sleep after its accumulation during preceding wakefulness [1,7,8]. However, an indicator of another basic regulatory process, the circadian process, was not expected to be identified in analysis of the EEG signal. A slightly different conceptualization of the sleep-wake regulation known as the opponent model [6,9] interprets the two basic regulatory processes as the competing drives for sleep and wake. However, again, analysis of the EEG signals was not expected to provide an indicator of the opposing wake drive associated in this model with the same circadian process.

Since the EEG power spectrum can reflect summation of simultaneous influences of the opponent sleep-wake regulatory processes, scoring of its orthogonal and uncorrelated principal components can help in separating the brain signatures of these two opposing processes [12]. It was found that score on the 2nd principal component exhibits unidirectional changes during transition from alertness sub-state of wakefulness state to the deepest sub-state of sleep state known as slow wave sleep or stage 3 of NREM sleep (N3). In contrast, the 1st principal component score was found to be low during wakefulness and stage 1 sleep to start to build up rapidly only after entering into well-established NREM sleep, i.e., during stages 2 and 3. Such time courses of these scores allowed the suggestion that the 1st and 2nd principal components

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of the EEG spectrum can represent the opposing drives for sleep and wake, respectively [13].

In terms of principal component structure of the EEG power spectrum, slow wave activity seems to represent the combining effect of the 1st and 2nd principal components. Therefore, the indexes of this activity cannot be interpreted as pure measures of either sleep or wake drive [14]. Moreover, only when slow wave activity is measured during sleep it can inform about these drives whereas its measurements in the waking EEG signal can say nothing about them. For instance, increased propensity to enter into NREM sleep is often termed “accumulation of sleep pressure”, but indexes of slow wave activity are useless for direct measurement of such accumulation, i.e., until occurrence of this entering. We earlier demonstrated that, in contrast, the time course of score on the 2nd principal component obtained in analysis of the waking EEG signal can reliably inform about the processes underlying alternations between sub-states of wakefulness state [19]. Finally, data on slow wave activity and data on the 1st principal component score disagree on possibility of involvement of stage 1 (N1) in the process of sleep debt payment Putilov, 2015a, Putilov, 2016.

Unfortunately, it is hard to compare accuracy of any possible EEG indicators of the sleep drive. Nobody can yet conclude *a priory* whether a suggested indicator actually reflects the governing forces underlying the sleep-wake cyclicity, because it is unknown how to measure such forces. For instance, the development of the two-process model was stimulated by the observations of strong correlation between duration of preceding wakefulness and intensity of slow wave activity after initiation of sleep episode [4]. However, the underlying sleep drive has not been identified so far. Therefore, there is a need for development of the EEG markers of the sleep-wake regulating processes that, instead of being correlational in their nature, can more directly reveal the signatures of the wake and sleep drives in the EEG signal.

The present analysis focusses on exploration of possibility to obtain such a marker by calculation of a single measure that summarizes the differences in the EEG spectra calculated for two distinct sub-states of the continuum of sleep-wake states and sub-states. The idea is to quantify the results of pairwise comparison of power spectra. Such comparison was previously performed for spectra of alertness vs. sleepiness sub-state of wakefulness state [14] and for spectra with higher vs. lower intensity of the sleep-debt payment process [15]. The present analysis extends these comparisons to spectra reflecting higher vs. lower level of homeostatic sleep pressure, representing one vs. another conventional stage of sleep-waking, obtained around initiation vs. termination of all-night sleep, etc. This approach includes *a priory* suggestion that such a differential spectrum can measure a distance between two levels of underlying sleep-wake regulatory processes, and, therefore, this can help in evaluating accuracy of measures that were previously suggested on a role of the EEG indicators of these processes, e.g., scores on the largest principal components of the EEG power spectrum. Consequently, the present analysis was performed to provide evidence for possibility of application of the suggested differential spectrum approach for confirmation and further extension of the findings linking the opposing sleep and wake drives to two scores on the 1st and 2nd principal components of the EEG power spectrum.

The first tested hypothesis was that any single measure summarizing differences between a pair of the EEG power spectra resembles either score on the 1st or score on the 2nd principal component of the EEG spectrum. Therefore, only two general forms of such a differential spectrum can be uncovered. One of them reveals the EEG signature of the sleep drive and another reveals the signature of the wake drive. The second tested hypothesis was that principal component analysis applied to the set of such single measures yields the 1st and 2nd principal components representing the sleep or wake drive, respectively. Such conclusion can be made from the result showing that there are several single measures that load on the 1st component along with score on the 1st principal component of the EEG spectrum, and the remaining single measures load on the 2nd component along with score on the 2nd principal component of the EEG spectrum. The third tested hypothesis was that, due to the existence of just two such patterns of loadings, time courses of scores on the two principal components of variation in the calculated single measures closely resemble time courses of scores on two principal components of variation in the EEG power spectrum. If these three hypotheses are supported by the present results, they, in overall, can open a possibility to implicate this new methodology into separation of the EEG markers of the sleep and wake drives. Moreover, since the differential spectrum approach differ from the earlier proposed methodology of scoring principal components of the EEG spectrum, it offers novel EEG markers of the opposing processes of sleep-wake regulation for quantitative evaluations and model-based simulations of the mechanisms underlying normal and abnormal alternations of sleep and wake states and sub-states.

2. Material and methods

The EEG datasets collected in several experimental studies with normally slept and sleep deprived unmedicated participants were analyzed in the present report. Earlier the primary analysis of these datasets revealed the major characteristics of the time courses of principal component scores that were briefly described in Introduction [12,19,17]. The experiments were performed in accordance with principles and practices of studies involving human subjects and followed the ethical standards laid down in the Declaration of Helsinki. The Ethics Committee of the Institute of Molecular Biology and Biophysics approved the experimental protocols. Informed written consent was signed by each of participants.

2.1. Participants

In total, there were four experimental studies. In two of them, a response to two-day sleep deprivation was evaluated in young and old adults, and, in two other, the multiple nap protocol was applied in the study of women of different age and young men. Participants of two identical sleep deprivation experiments were 15 young adults aged between 19 and 26 years (7 were males) and 15 older adults aged between 45 and 66 years (5 males). Details on participants, protocols, and methods were earlier reported in [18]. Fourteen female participants with ages from 17 to 55 years (mean ± standard deviation = 35.4 ± 11.0 years) and 18 young adults with ages ranged from 18 to 22 years participated in two multiple nap experiments. Details on these participants, protocols, and methods were earlier reported in [12]. Participants selected for each of the studies denied a history of sleep disorders and serious health problems as well as involvement in either shift work or *trans*-meridian flights during the preceding month.

2.2. Protocol and recording of the EEG signals in sleep deprivation experiments

Participants of sleep deprivation experiments were admitted to a research unit of the institute on Friday evening. The EEG recordings started at 19:00 h to be continued with 2-h interval until Sunday evening (19:00 h). Participation in the experiment can be terminated when a participant felt irresistible desire to sleep during one of the intervals between these 25 EEG recording sessions. The EEG was recorded for 7 min with the eyes open (2 min) and then with the eyes closed (5 min). Only spectra on eyes