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Original Article

The diagnostic value of power spectra analysis of the sleep electroencephalography in narcoleptic patients

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ABSTRACT

Objective: Manifestations of narcolepsy with cataplexy (NC) include disturbed nocturnal sleep – hereunder sleep–wake instability, decreased latency to rapid eye movement (REM) sleep, and dissociated REM sleep events. In this study, we characterized the electroencephalography (EEG) of various sleep stages in NC versus controls.

Methods: EEG power spectral density (PSD) was computed in 136 NC patients and 510 sex- and age-matched controls. Features reflecting differences in PSD curves were computed. A Lasso-regularized regression model was used to find an optimal feature subset, which was validated on 19 NC patients and 708 non-NC patients from a sleep clinic. Reproducible features were analyzed using receiver operating characteristic (ROC) curves.

Results: Thirteen features were selected based on the training dataset. Three were applicable in the validation dataset, indicating that NC patients show (1) increased alpha power in REM sleep, (2) decreased sigma power in wakefulness, and (3) decreased delta power in stage N1 versus wakefulness. Sensitivity of these features ranged from 4% to 10% with specificity around 98%, and it did not vary substantially with and without treatment.

Conclusions: EEG spectral analysis of REM sleep, wake, and differences between N1 and wakefulness contain diagnostic features of NC. These traits may represent sleepiness and dissociated REM sleep in patients with NC. However, the features are not sufficient for differentiating NC from controls, and further analysis is needed to completely evaluate the diagnostic potential of these features.

1. Introduction

Narcolepsy with cataplexy (NC) is a neurological sleep disorder found in approximately one in 3000 individuals. It is characterized by sleep–wake instability, rapid eye movement (REM) sleep abnormalities, and cataplexy. The pathophysiology of the disorder is a selective destruction of hypocretin/orexin neurons in the hypothalamus [1–3], resulting in low or undetectable levels of hypocretin-1 in the cerebrospinal fluid (CSF) [4,5]. The loss of hypocretin neurons is thought to be of autoimmune origin [6], although this is not yet fully established.

Hypocretin neurons play a central role in the regulation of sleep–wake transitions [7–9] and in the stabilization of the REM and non-REM (NREM) sleep states. REM sleep is a physiological state that includes loss of consciousness, fast electroencephalographic (EEG)

Abbreviations: AASM, American Academy of Sleep Medicine; AUC, area under the receiver operating characteristic curve; NC, narcolepsy with cataplexy; CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; LASSO, Lasso-regularized logistic regression model; MSLT, multiple sleep latency test; PSD, power spectral density; PSG, polysomnography; R&K, Rechtschaffen & Kales; REM, rapid eye movement sleep; REMs, rapid eye movements; ROC, receiver operating characteristics; SEM, standard error of the mean; SOREMP, sleep onset to REM sleep period of ≤15 min.

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activation with dreaming, muscle atonia, phasic events such as REMs and muscle twitches, elevated arousal threshold, and other features (erection, temperature dysregulation, cardiovascular changes). Narcoleptic patients have been shown to have many clinical symptoms linked to abnormal REM sleep, including sleep paralysis, hypnagogic hallucinations, and REM sleep behavior disorder [10]. In addition, abnormal distribution of REM sleep [11], increased density of REMs, and abnormal EEG frequency during REM sleep are found during nocturnal sleep polysomnography (PSG) [11]. Finally, nocturnal sleep fragmentation and increased NREM sleep stage 1 (N1) amounts [12–14] are typical PSG findings. None of these PSG findings are used in the diagnosis of narcolepsy.

Studies in both animals and humans have shown that rapid transitions from wake to REM sleep is a diagnostic hallmark of narcolepsy [7,15]. On the basis of this finding, rapid onsets into REM sleep (latency from sleep onset to REM sleep [SOREMP] of ≤15 min) during nocturnal PSG and during daytime napping (measured by the Multiple Sleep Latency Test [MSLT]) are used to diagnose narcolepsy [15,16]. Whereas a SOREMP at night is highly specific (99%), it is only modestly sensitive (~45%); thus, many patients are missed out [15]. It has the advantage, however, of being theoretically feasibly assessed using home recordings, and its evaluation is required before the MSLT to exclude sleep deprivation. By contrast, a positive MSLT (mean sleep latency [MSL] of ≤8 min as well as the presence of ≥2 SOREMPs) is both sensitive (90–95%) and specific (95%), but time consuming and expensive.

Considering that the distribution of REM sleep itself is also abnormal in NC, we postulated that the frequency distribution of the sleep EEG power spectra may be consistently changed in NC patients, and that this could be used as a diagnostic feature during nocturnal PSGs. Such abnormality has been shown in hypocretin knockout mice compared with wild-type mice [17] as well as in narcoleptic patients, notably during sleep paralysis and cataplexy [11]. In this study, we aimed at quantifying the diagnostic value of power spectra density (PSD) features extracted from the EEG in all sleep stages. In particular, we were seeking to identify features with high specificity (>95%) that could be added to a nocturnal SOREMP to raise sensitivity without lowering specificity. Our ultimate goal was to be able to identify NC patients using features extracted from a nocturnal PSG alone, avoiding the need for a subsequent time-consuming MSLT.

2. Materials and methods

2.1. Subjects and recordings

Two PSG datasets similar to those described in Andlauer et al. [15] were used. The first was considered a training dataset, the second a validation dataset. In these samples, NC was clinically defined as narcolepsy with clear cataplexy and human leukocyte antigen (HLA)-DQB1*06:02, forward in this study referred to as NC patients.

In the training dataset, PSGs from 136 NC patients were gathered from the Stanford Sleep Clinic as well as from two sodium oxybate drug trials (baseline sleep studies) conducted by Jazz Pharmaceuticals [18,19]. In these trials, patients were not treated with sodium oxybate, but antidepressants and centrally acting stimulants were allowed if used at a stable dose. A total of 39% and 79% of the patients in these trials were treated with antidepressants and stimulants, respectively. Patients were age- and sex-matched with controls obtained from volunteers drawn from the Wisconsin Sleep Cohort, an ongoing longitudinal population-based study of sleep patterns in the general population [20]. A stratified random sample of employed adults aged 30–60 years in south Wisconsin was recruited for a nocturnal PSG at baseline. These subjects are randomly selected, and they have not been screened for sleep disorders, and as such a significant portion has sleep-disordered breathing [15], periodic leg movements during sleep [21], parasomnias, depression, etc. Only four subjects were excluded as they have been suggested to possibly have narcolepsy in a prior study [22]. A case/control ratio of four was used giving a total of 510 control subjects in the training dataset. Antidepressants such as serotonin-specific reuptake inhibitors were taken by approximately 22%, and stimulants, mostly methylphenidate, were taken by <2% of the control subjects. This was considered acceptable as doses were stable, and as we explored separately medication effects on our results. As with patients, non-narcolepsy controls were allowed to take usual medications such as over-the-counter antihistamine and pain relievers.

As we aimed to find features that can help identify narcoleptic patients in a clinical setting, the validation dataset included subjects referred to and evaluated at a sleep clinic, the Stanford Sleep Clinic. As such, these subjects are more enriched in sleep pathologies than the other sample, notably sleep-disordered breathing. This dataset included a total of 727 patients, whereof 19 were diagnosed as NC patients (untreated when tested) and 708 were non-narcoleptic patients diagnosed with sleep disorders other than narcolepsy, most notably sleep apnea. The sample has been described elsewhere [15,21], and all evaluation included a comprehensive medical and medication history, nocturnal PSG, and, for narcolepsy cases, a PSG-MSLT. As the validation is a clinical sample, it is unbalanced in the number of cases versus controls, and it is not matched in age or gender. The demographics for the training and validation dataset can be seen in Table 1.

Data used in this study were heterogeneous and collected over a long historical period using Rechtschaffen & Kales (R&K) [25] or American Academy of Sleep Medicine (AASM) [24] criteria. For consistency, stage S4 was replaced as N3 for recordings scored using the older R&K criteria. We realize that the use of two sets of rules could have affected our results. The rules do, however, mostly differ in the transitions to and from N1, and as we have excluded epochs before and after any sleep stage transition, these methodological differences are unlikely to have affected the results. Optimally, spectra could be extracted from automatically scored hypnograms to limit differences in scoring – both across the two standards and also across sites and scorers. This would, however, introduce new challenges as no automatic scoring method has proven to be valid in narcoleptic patients.

2.2. Cleaning of EEG

Fig. 1 illustrates the overall methodology of this study. To ensure minimum contamination by artifacts of the PSD spectra for each sleep stage, a set of successive cleaning procedures was followed starting with the removal of signal surrounding sleep transitions as well as signal contaminated with electromyography (EMG) artifacts.

Sleep stage transitions were identified using the manually scored hypnogram as epochs going from any stage (N1, N2, N3, REM, or W) to another. EEG in epochs neighboring stage transitions was excluded from the analysis to minimize “mixed” stage 30-s epochs.

The entire EEG recorded at the C3–A2 derivation was passed through a muscle artifact detector described in detail by Brunner et al [26]. This detector is a widely used method, and it compares high-frequency activity in each 4-s window with the activity level in a local 3-min window surrounding the 4-s window. If the value in the 4-s window exceeded the local background activity by a factor of four, it was flagged as artifact and removed.

The PSGs of NC patients in the training dataset were recorded with different sampling frequencies with some older recordings being sampled with a sampling frequency of 100 Hz, a frequency below newest standards. Power spectra were thus analyzed up to 35 Hz for all, which is reliable according to Nyquist Theorem [27]. Due to