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Data-driven modeling of sleep EEG and EOG reveals characteristics indicative of pre-Parkinson's and Parkinson's disease

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HIGHLIGHTS

- A data-driven topic modeling approach characterizing sleep EEG and EOG is proposed.
- The approach showed potential for evaluating patients with neurodegeneration.
- The number of topics linked with REM and N3 could be an early PD biomarker.
- The ability to maintain NREM and REM sleep could be an early PD biomarker.
- Patients were classified with 91.4% sensitivity and 68.8% specificity.

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ABSTRACT

Background: Manual scoring of sleep relies on identifying certain characteristics in polysomnograph (PSG) signals. However, these characteristics are disrupted in patients with neurodegenerative diseases.
New method: This study evaluates sleep using a topic modeling and unsupervised learning approach to identify sleep topics directly from electroencephalography (EEG) and electrooculography (EOG). PSG data from control subjects were used to develop an EOG and an EEG topic model. The models were applied to PSG data from 23 control subjects, 25 patients with periodic leg movements (PLMs), 31 patients with idiopathic REM sleep behavior disorder (iRBD) and 36 patients with Parkinson's disease (PD). The data were divided into training and validation datasets and features reflecting EEG and EOG characteristics based on topics were computed. The most discriminative feature subset for separating iRBD/PD and PLM/controls was estimated using a Lasso-regularized regression model.
Results: The features with highest discriminability were the number and stability of EEG topics linked to REM and N3, respectively. Validation of the model indicated a sensitivity of 91.4% and a specificity of 68.8% when classifying iRBD/PD patients.
Comparison with existing method: The topics showed visual accordance with the manually scored sleep stages, and the features revealed sleep characteristics containing information indicative of neurodegeneration.
Conclusions: This study suggests that the amount of N3 and the ability to maintain NREM and REM sleep have potential as early PD biomarkers. Data-driven analysis of sleep may contribute to the evaluation of neurodegenerative patients.

1. Introduction

Patients suffering from the sleep disorder idiopathic rapid eye-movement sleep behavior disorder (iRBD) have been observed to be at high risk of developing Parkinson's disease (PD) (Iranzo et al.,

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2006; Schenck et al., 2013, 1996). These longitudinal studies indicate that after a period of approximately 13 years 45% of the patients initially diagnosed with iRBD develop PD or another neurological disorder. Sixteen years after an iRBD diagnosis the incidence rate is 81%. This indicates long latencies from the reported onset of iRBD to the appearance of detectable neurodegeneration. Braak et al. (2003) described the evolution of PD as initially involving the brain stem, then pursuing an ascending course to additional brain areas including the cortex. During this process, there is symptom progression that can potentially be detected in features that are expressed electrophysiologically during sleep. It follows that investigating polysomnograph (PSG) data either manually or automatically may be useful for developing specific and objective markers for PD diagnosis (Christensen et al., 2014; Latreille et al., 2011; Postuma et al., 2010a). According to the American Academy of Sleep Medicine (AASM) Staging Manual from 2007, sleep annotation is done by manually assigning periods of 30 s to either wakefulness (W), rapid eye movement (REM) sleep stage or one of three non-REM sleep stages (N1–N3). Manual scoring relies on identifying certain characteristics in the electrophysiological PSG signals, including the various EEG frequency bands (delta, theta, alpha, beta), EEG microsleep events, such as sleep spindles and K-complexes, and EOG events, such as rapid and slow eye movements (REMs and SEMs, respectively) (Iber et al., 2007). The duration of microsleep events is typically 0.5–3.0 s (Iber et al., 2007).

Reported sleep EEG changes in patients with PD and other neurodegenerative diseases (NDDs) include changed patterns and/or reduced numbers of several sleep-specific phenomena such as sleep spindles (Christensen et al., 2014), changed slow wave characteristics (Latreille et al., 2011) and frequency-slowing (Rodrigues Brazète et al., 2013) relative to age-matched control subjects. As eye movements (EMs) are controlled by neurons located in the brain stem, midbrain areas and frontal areas (Carpenter, 2000), it is believed that patients suffering from an NDD can show affected EMs. Several studies have reported impairment of the oculomotor function in patients with PD (Corin et al., 1972; Mosimann et al., 2005). The oculomotor abnormalities include limitation or absence of gaze in various planes, inadequate convergence and impairment in reflexive saccades during wakefulness. Few studies have investigated PSG EOG in patients with iRBD or PD during sleep, and these reported abnormalities in the outlook and the nightly distribution of rapid and slow EMs (Christensen et al., 2013, 2012).

Stage shifts during sleep and the transition from sleep to wakefulness are controlled by switching mechanisms regulated by several neurons mainly located in the brainstem and midbrain areas (Saper et al., 2001, 2010; Schwartz and Roth, 2008). Proposed models describe the transitions between sleep and wakefulness, and those between REM and NREM as flip-flop switches. These switches are mutually dependent and determine the wake-sleep cyclic rhythm (Lu et al., 2006). The sleep–wake flip-flop switch involves the ascending arousal pathway and the sleep-promoting pathway. The ascending arousal pathway involves a branch of cholinergic neurons, which fire rapidly during wakefulness and REM sleep. Further, the ascending pathway involves a branch of noradrenergic, serotoninergic, dopaminergic and histaminergic neurons, which fire rapidly during wakefulness, less rapidly during NREM sleep and almost cease firing during REM sleep (Saper et al., 2010; Schwartz and Roth, 2008). The neurons of the sleep-promoting pathway inhibit the circuits of the ascending arousal system, and the mutually inhibitory relationship can generate rapid transitions between waking and sleeping states. The REM–NREM flip-flop switch involves two mutually inhibitory populations of GABAergic neurons located in the upper pons, which enables it to generate rapid transitions between REM and NREM sleep states. A malfunction or destruction of any of the loops involved in the two flip-flop switches might be observed in the sleep architecture as either unstructured transitions and/or abnormal amount of time spent in the individual stages. This study investigates whether the neurodegeneration present in iRBD and PD patients affects these mechanisms to a degree that can be revealed by analyzing EEG and EOG. The putative changes in the appearance of the EEG or EOG are linked to the ascending cortical branch of neurons active during REM sleep. It has been shown that the normal descending inhibition of the skeleton muscles in iRBD patients during REM sleep is affected by neurodegeneration (Kempfner et al., 2010; Postuma et al., 2010b). The electromyograph (EMG) activity in these patients is enhanced, which suggests that a neurodegenerative process occurs in the region of the brain stem generating REM atonia (Brown et al., 2012). By not including EMG features, this study focus on the characteristics affected by the ascending cortical parts of the sleep–wake and the REM–NREM sleep switches.

The aim of this study was to evaluate the diagnostic value of features reflecting sleep characteristics such as the stability, fragmentation and distribution of sleep stages in patients with iRBD or PD. To solve the well-known problems with the manual scoring of sleep, we characterized sleep using a data-driven approach based on certain clues from either EEG or EOG. By addressing sleep analysis with a topic modeling approach, we did not attempt to match the manually scored sleep stages. We set out to identify topics in the EEG and EOG and thereby capture latent diversities between subjects with and without neurodegeneration. Data from control subjects were used to develop models defining EEG or EOG topics. To analyze how well the EEG and EOG sleep structures from NDD patients fell into the standard topics, the models were applied to PSG data from additional control subjects, patients with a motor disturbance but not an NDD (periodic leg movements (PLMs)), iRBD patients and PD patients. By extracting features reflecting characteristics of the EEG and EOG topic patterns, this study attempted to reveal sleep characteristics indicative of early and mature neurodegeneration in PD patients.

2. Materials and methods

2.1. Subjects

Subjects were recruited from patients evaluated at the Danish Center for Sleep Medicine (DCSM) in the Department of Clinical Neurophysiology, Glostrup University Hospital. All patient evaluations included a comprehensive medical and medication history. All patients were assessed by PSG and with a multiple sleep latency test (MSLT). Patients treated with medication known to affect sleep stages (antidepressants, antipsychotics, hypnotics) were excluded, although dopaminergic treatments were continued. A total of 36 PD, 31 iRBD and 25 PLM patients were included. The iRBD patients included expressed dream enactment coinciding with REM sleep without atonia (RSWA), manifested as sustained muscle activity in the chin EMG and/or excessive transient muscle activity in either the chin or limb EMG. They were diagnosed with idiopathic RBD since the disease could not be linked to the presence of narcolepsy, neurodegenerative, cerebrovascular, or other neurological disorders or other factors such as specific drugs or psychological state. The PLM patients included did not show any signs of neurodegeneration or RSWA. No PSG findings or NDD-related symptoms were reported for the PLM group, and they were considered as solely PLM patients. Henceforth, the term ‘PLM patients’ refers to patients suffering solely from PLMs. Thirty-three age-matched control subjects with no history of movement disorder, dream-enacting behavior or other previously diagnosed sleep disorders were included.

The data were split into three groups: one for developing the topic models (10 control subjects), another for training a statistical model for classifying NDD patients (16 subjects from each group),