Clinical Neurophysiology 127 (2016) 1403–1409

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Bradysomnia in Parkinson's disease

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ARTICLE INFO

Article history:
Accepted 25 August 2015
Available online 2 September 2015

Keywords:
Sleep
Parkinson's disease
State space model
EEG
Spectral analysis

HIGHLIGHTS

- State space analysis enables quantitative assessment of the dynamics of sleep–wake behavior.
- Dynamical aspects of sleep/wake behavior are significantly impaired in Parkinson's patients.
- We suggest *Bradysomnia* as a novel potential biomarker for Parkinson's disease.

ABSTRACT

Objective: Polysomnography studies in Parkinson's disease (PD) patients show altered sleep microstructure with decreased level of arousability, indicating impaired sleep–wake dynamics in PD. The aim of this study was to investigate dynamical aspects of sleep EEG in PD as compared to healthy controls.
Methods: In this retrospective, controlled study, we applied a previously established mathematical model of sleep EEG analysis (state space model) to PD patients and age- and gender-matched healthy volunteers ($N = 64$). Dynamical aspects of sleep were quantified by measuring the spectral variability of the sleep EEG (by means of state space velocity).
Results: State space analysis revealed preserved global sleep–wake architecture in PD patients, but the velocity of sleep stage transitions was significantly reduced as compared to healthy controls. Correlation analysis revealed a strong association of state space velocity with arousal scores and daily dopamine agonist intake.
Conclusions: Quantitative analysis of spectral sleep EEG variability (state space velocity) revealed reduced sleep–wake dynamics in PD patients as compared to control subjects.
Significance: We propose state space velocity as an objective and quantitative measure for altered sleep microstructure and as a potential biomarker of sleep alterations in PD, not accessible by conventional sleep analysis.

1. Introduction

Sleep–wake disturbances are common in patients with Parkinson's disease (PD). During the disease course, the majority of PD patients are at some point affected by sleep disorders (Factor et al., 1990; Tandberg et al., 1998; Kumar et al., 2002; Garcia-Borreguero et al., 2003) or excessive daytime sleepiness (Comella, 2007).

Clinical studies in PD patients reveal disturbed global sleep architecture with a high degree of sleep fragmentation and quantitative reduction of REM sleep as compared to healthy controls (Emser et al., 1988; Wetter et al., 2000). Fragmented sleep architecture in PD is often multifactorial, e.g. related to pain, mood disorders, obstructive apnea, nycturia, or nocturnal akinesia. On the other hand, polysomnographic case–control studies assessing arousals in response to respiratory and motor events suggest a *decreased* level of arousability in PD patients (Brunner et al., 2002; Diederich et al., 2005; Peeraully et al., 2012). Also, when controlled for sleep-related breathing disorders, we showed recently that arousability in response to respiratory events is significantly decreased in PD patients (Sommerauer et al., 2015).

Spectral analysis of sleep EEG in PD patients also shows alterations of sleep microstructure, including slowing in the occipital and tempo-occipital regions (Soikkeli et al., 1991; Primavera and Novello, 1992), reduction in delta frequency power and an increase

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http://dx.doi.org/10.1016/j.clinph.2015.08.012
1388-2457/

in the low gamma frequency band in NREM sleep (Brunner et al., 2002). The latter study in *de novo* PD patients revealed that dopaminergic treatment normalizes the disturbed spectral distribution, indicating a direct pathophysiological link between the sleep EEG and the dopamine-depleted state in PD. In this line, administration of the dopamine agonist apomorphine induces a significant increase in slow-wave activity (i.e. delta power) and normalizes the spectral properties of REM sleep EEG in PD patients (Cianchetti et al., 1980).

The altered sleep EEG in PD with reduced sleep characteristics such as sleep spindles or K-complexes (Comella et al., 1993) and the reduction of muscle atonia during REM sleep are challenging to analyze using classical sleep scoring rules, which were established for healthy sleep (Bliwise et al., 2000; Iber et al., 2007). Therefore, a direct comparison between healthy controls (with normal sleep EEG pattern) and PD patients (with altered sleep microstructure) is prone to a biased sleep analysis by conventional sleep scoring. To address these difficulties, we recently adapted a quantitative sleep EEG analysis (state space model) for human sleep (Gervasoni et al., 2004; Diniz Behn et al., 2010; Imbach et al., 2012). In contrast to conventional (i.e. manual) sleep EEG analysis, this model accomplishes an objective and quantitative spectral analysis of the sleep EEG independent from manual scoring. Using this model, the sleep EEG can be represented as a trajectory in a 2-dimensional space and classical sleep stages are found to build clusters (Supplementary video). Thus, this approach enables assessment of the dynamics of sleep–wake behavior. For example, in a previous study, we showed that velocity in state space can be interpreted as a measure for sleep state instability and therefore the dynamic properties of sleep EEG can be scaled by the absolute velocity in state space (Imbach et al., 2012). Simply put, individuals with high sleep EEG variability, have *higher* state space velocity (i.e. more unstable sleep), whereas a stable sleep EEG pattern is linked to a *slower* state space velocity.

For this study, we applied the state space model to quantitatively assess sleep state dynamics in PD patients and healthy volunteers. In light of the above-mentioned studies that showed diminished arousability in PD patients and altered sleep microstructure, we hypothesize that sleep dynamics as quantified by the state space model is reduced in PD patients. In analogy to *bradykinesia* as the principal motor symptom in PD and *bradyphrenia* reflecting slowness of thought in a subset of PD patients, we ask the question: Do PD patients suffer from *bradysomnia*?

2. Methods

2.1. Subjects

In this case–control study, we retrospectively included 70 PD patients who were assessed for sleep–wake disturbances by whole night video-polysomnography between 2004 and 2009 in our clinic for sleep disorders. Indication for polysomnography was based on clinical grounds. No selection was done regarding PD type, disease duration, motor symptoms or medical treatment upon diagnosis. Sleep assessment was performed without change of the dopaminergic medication. As a control group, we included 70 healthy volunteers without history of sleep disturbances and who did not take any psychoactive medication. PD patients and control subjects were one-to-one matched for age, sex, body mass index (BMI) and apnea–hypopnea index (AHI) (Table 1). Six patients and six control subjects had to be eliminated from the analysis because of severe EEG artifacts or incomplete EEG signal. The clinical characterization of PD patients was performed as introduced before (Baumann et al., 2014). We rated motor symptoms according to the motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS III) in off condition in all patients. This work was approved by the local ethical board and all patients provided informed consent for study participation.

Table 1
Matching variables, sleep parameters and PD characteristics.

	PD	Controls	*p*-Value
Matching variables			
Age [y]	64.3 ± 8.9	63.5 ± 11.1	0.65
Sex [m/f]	26/42	22/42	0.8
BMI [kg/m^2]	25.3 ± 4.4	25.1 ± 3.8	0.74
Hypopnea index	4.6 ± 5	4.4 ± 4	0.84
Sleep parameters			
ESS	9.5 ± 4.6	7.1 ± 6.4	**0.02**
Total sleep time [min]	335 ± 81	336 ± 77	0.95
Sleep efficiency [%]	76.1 ± 18.1	78.4 ± 15.4	0.43
Wake [%]	22.4 ± 15.2	21.6 ± 15.4	0.76
NREM1 [%]	13.8 ± 7.2	12.4 ± 6.3	0.24
NREM2 [%]	12.7 ± 8.5	13.8 ± 7.9	0.42
SWS [%]	38.2 ± 9.7	37.2 ± 9.7	0.59
REM [%]	12.8 ± 9.3	14.9 ± 8.3	0.19
Arousal index	9.1 ± 7.1	18.6 ± 21.5	<0.005
Patients characteristics			
PD type [A,T,E]	45/13/6	◆	◆
Disease duration [y]	8.6 ± 7.0	◆	◆
Full UPDRS-III score	21.9 ± 8.4	◆	◆
LED (L-Dopa) [mg/d]	426 ± 322	◆	◆
LED (DA) [mg/d]	193 ± 189	◆	◆

BMI: body mass index, ESS: Epworth sleepiness scale, NREM: non-REM sleep, SWS: slow wave sleep (NREM 3), PD type: A: acinetic-rigid, T: tremor predominant, E: equivalent type (Baumann et al., 2014), UPDRS: Unified Parkinson Disease Rating Scale, LED: daily L-Dopa equivalent dose. *P*-Values are given for two-sided *t*-tests or χ^2-tests (categorical data). Bold values indicate statistical significance at 0.05 level.

2.2. Data analysis and model based approach

We performed a model-based sleep EEG analysis (state space model) in all subjects. This approach was introduced in rodents (Gervasoni et al., 2004; Diniz Behn et al., 2010), and we have recently adapted this model for human sleep: a detailed explanation of the methodological aspects and the mathematical description can be found in our previous work (Imbach et al., 2012). Briefly, in state space EEG analysis, the spectral information of each epoch is projected into a 2-dimensional plane by calculating two different frequency ratios of previously determined frequency bands for consecutive epochs. Thus, each EEG epoch can be represented as a single point in the corresponding 2-dimensional state space and a whole night polysomnography is described as a scatterplot with clusters representing the different sleep behavioral states (Imbach et al., 2012). Accordingly, transitions between and within sleep states result in trajectories in the state space.

For the current study, we applied the state space model on the sleep EEG data of all patients and healthy volunteers. Importantly, the previously developed model for normal healthy sleep was not modified or optimized for the current data set. Also, by using the model-based approach for automated sleep scoring, we were able to perform the EEG analysis without any information about manual sleep scoring. Thus, despite the retrospective study design, the data analysis was performed by analyzing raw sleep EEG data traces in a blinded and unbiased way.

In detail, we performed the EEG analysis as follows: We recorded sleep EEG channels (F3, F4, C3, C4, O1, O2, referenced to linked bilateral auricular electrodes). The raw data traces were then subdivided into 5 s epochs and a fast Fourier transformation (FFT) was applied on each 5-s epoch after multiplication by a Hann window to address the problem of edge discontinuities. Next, we determined the frequency ratios as derived from the fixed frequency bands (Imbach et al., 2012) for each epoch (frequency band parameters: Ratio1 =