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Decreased sleep spindle density in patients with idiopathic REM sleep behavior disorder and patients with Parkinson's disease

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HIGHLIGHTS

- During non-REM sleep, the sleep spindle density is reduced in idiopathic REM sleep behavior disorder (iRBD) and Parkinson's disease (PD) patients, inducing sleep spindles as a potentially PD biomarker.
- This study raises questions on how to validate abnormal sleep spindels in patients with neurodegenerative diseases.
- The introduced new method for automatic sleep spindle detection showed acceptable performance when validated on middle-aged subjects.

ABSTRACT

Objective: To determine whether sleep spindles (SS) are potentially a biomarker for Parkinson's disease (PD).
Methods: Fifteen PD patients with REM sleep behavior disorder (PD + RBD), 15 PD patients without RBD (PD − RBD), 15 idiopathic RBD (iRBD) patients and 15 age-matched controls underwent polysomnography (PSG). SS were scored in an extract of data from control subjects. An automatic SS detector using a Matching Pursuit (MP) algorithm and a Support Vector Machine (SVM) was developed and applied to the PSG recordings. The SS densities in N1, N2, N3, all NREM combined and REM sleep were obtained and evaluated across the groups.
Results: The SS detector achieved a sensitivity of 84.7% and a specificity of 84.5%. At a significance level of $\alpha = 1\%$, the iRBD and PD + RBD patients had a significantly lower SS density than the control group in N2, N3 and all NREM stages combined. At a significance level of $\alpha = 5\%$, PD − RBD had a significantly lower SS density in N2 and all NREM stages combined.
Conclusions: The lower SS density suggests involvement in pre-thalamic fibers involved in SS generation. SS density is a potential early PD biomarker.
Significance: It is likely that an automatic SS detector could be a supportive diagnostic tool in the evaluation of iRBD and PD patients.

1. Introduction

Sleep spindles (SSS) and K-complexes are EEG hallmarks of non-REM (NREM) sleep. SS are generated by a complex interaction between thalamic, limbic and cortical areas and are probably involved in sleep maintenance and memory consolidation (Caporro et al., 2012). These structures are sensitive to involvement in neurodegenerative disorders and it has recently been suggested that changes in SS have the potential to be biomarkers of neurodegenerative disease (NDD) (Ktonas et al., 2009), through the reduced SS activity in patients with Parkinson's disease (PD) (Puca et al., 1973; Myslobodsky et al., 1982; Comella et al., 1993). REM sleep behavior disorder (RBD) is closely associated with PD and is a marker of later

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development of synucleinopathies (Postuma and Montplaisir, 2009; Kempfner et al., 2010). We hypothesize that SS activity is progressively reduced in RBD and PD patients, which would be consistent with the progressive nature of these disorders. SS activity has not previously been evaluated in idiopathic RBD (iRBD). It has been suggested that these patients have a higher risk of developing PD (Schenck et al., 1996), and that this patient group therefore offers an opportunity for detecting early markers of PD before the onset of clinical disease.

Manual scoring of SS is a tedious and time-consuming task. It requires sleep experts and the degree of agreement among experts has been reported as being relatively low: 70 ± 8% (Zygierewicz et al., 1999). Therefore, an automatic SS detector would be valuable for standardizing the SS scores. If SS are potential biomarkers of PD, it could also be a supportive diagnostic tool.

The aims of the study were twofold: firstly, to develop an automatic SS detector based on Matching Pursuit (MP) for feature extraction and a Support Vector Machine (SVM) for classification; secondly, to measure the SS densities found automatically in normal controls, patients with iRBD and PD patients with or without RBD.

2. 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 polysomnography (PSG) and with a multiple sleep latency test (MSLT). Patients taking any benzodiazepines, antipsychotic or anti-depressant drug, including hypnotics, were excluded, though dopaminergic treatments were continued. A total of 15 PD patients without RBD (PD − RBD), 15 PD patients with RBD (PD + RBD) and 15 iRBD patients were included. Fifteen age-matched control subjects with no history of movement disorder, dream-enacting behavior or other previously diagnosed sleep disorders were included. Patients using any type of medication known to affect sleep were also excluded.

The demographic data for the three patient groups and the control group are summarized in Table 1.

2.2. Polysomnograph recordings

Polysomnograph (PSG) data were collected in this study. All controls underwent at least one night of PSG recording as outpatients, and all patients underwent at least one night of PSG recording either as outpatients or in hospital in accordance with the AASM standard (Iber et al., 2007). Two or more PSG routines were performed if and only if the prior recording(s) did not meet the technical needs required to make an assessment of acceptable quality. When manually scoring the SS, only the F3-A2, C3-A2 and O1-A2 EEG derivations were visible for the SS scorer, and for 13 control subject a number of randomly selected sleep epochs, each of a duration of 30 s, were chosen for SS scoring. The selection of sleep epochs was carried out by the SS scorer, who aimed at selecting approximately 30 sleep epochs containing one or more visible SS randomly distributed across the sleep cycles. It was ensured that every SS within a chosen sleep epoch was marked. Filter conditions were as stated in the AASM standard, and the AASM standard SS definition was used, whereby SS have frequencies in the range 11–16 Hz, last for 0.5–3 s and have no amplitude criteria. The left EEG derivations were chosen as these are known to exhibit an overall higher spindle density (Bódizs et al., 2009). In order to reproduce realistic conditions, sleep epochs with moderate noise contamination were allowed and no artifacts were removed manually. The scoring yielded a total of 375 sleep epochs with 882 manually scored SS. The distribution of the chosen sleep epochs across the different sleep stages is seen in Table 2. All the scored SS within these sleep epochs were confirmed by an expert.

The raw sleep data, hypnograms and sleep events were extracted from Somnologica Studio (V5.1, Embla, Broomfield, CO 80021, USA) or Nervus (V5.5, Cephalon DK, Nørresundby, Denmark), using the built-in export data tool. For further analysis, the data were imported into MATLAB (R2010b, MathWorks, Inc., Natick, MA, USA).

2.3. Development of SS detector

The steps in the method for developing the automatic detector are shown in Fig. 1. Firstly, appropriate features were extracted from the C3-A2 and F3-A2 EEG derivations. These are variables that represent characteristics of the classes and may therefore reflect differences between them. These were sent through a classifier that determines the class ('SS' or 'background EEG') to which the data segment belongs.

2.3.1. Feature extraction

Before feature extraction, the polysomnograph C3-A2 and F3-A2 EEG derivations were band pass-filtered from 2 to 35 Hz. The lower cutoff frequency at 2 Hz was chosen to avoid the influence of the high-energy contents at the very low frequencies, and the cutoff at 35 Hz was chosen to reflect the AASM standard.

In this study, the Matching Pursuit (MP) method (Mallat and Zhang, 1993) was chosen for feature extraction in the classification of SS. In the MP signal processing algorithm a given signal is represented by a weighted sum of known basic waveforms, known as Gabor atoms, $g_\gamma(t)$, which in continuous time are expressed as:

$$g_\gamma(t) = K(\gamma)e^{-\pi\left(\frac{t-u}{s}\right)^2}\cos(\omega(t-u)+\phi) \quad (1)$$

Table 1
Demographic data for the control and the patient groups.

Patient group	Frequency	Male/female frequency	Age (years)	BMI (kg/m^2)	Sleep efficiency (%)	Bed times (min)
Controls	15	6/9	58.3 ± 9.5	23.2 ± 2.8	88.9 ± 8.4	480 ± 47.5
iRBD	15	12/3	60.1 ± 7.4	24.4 ± 3.1	85.6 ± 8.3	489 ± 95.3
PD − RBD	15	8/7	61.9 ± 6.1	24.7 ± 2.2	82.8 ± 7.9	443 ± 67.2
PD + RBD	15	11/4	62.4 ± 5.2	26.0 ± 3.2	85.4 ± 9.7	445 ± 71.8

Table 2
The distribution of the different sleep stages within the four groups evaluated and for use in the development of the SS detector.

Sleep stage	For use in the development of SS detector	Controls	iRBD	PD − RBD	PD + RBD
Wake (%)	0 (0)	1606 (11)	2220 (15)	2387 (18)	1889 (14)
REM (%)	4 (1)	2710 (19)	2893 (20)	1808 (13)	1761 (13)
N1 (%)	13 (4)	1205 (8)	1238 (8)	1191 (9)	1623 (12)
N2 (%)	330 (88)	6491 (45)	5909 (40)	5817 (44)	5957 (45)
N3 (%)	28 (7)	2388 (17)	2423 (17)	2097 (16)	2128 (16)
Sum (%)	375 (100)	14400 (100)	14683 (100)	13300 (100)	13358 (100)