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Detection of a Sleep Disorder Predicting Parkinson's Disease

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Abstract— **Idiopathic rapid eye-movement (REM) sleep behavior disorder (iRBD) has been found to be a strong early predictor for later development into Parkinson's disease (PD). iRBD is diagnosed by polysomnography but the manual evaluation is laborious, why the aims of this study are to develop supportive methods for detecting iRBD from electroencephalographic (EEG) signals recorded during REM sleep. This method classified subjects from their EEG similarity with the two classes iRBD patients and control subjects. The feature sets used for classifying subjects were based on the relative powers of the EEG signals in different frequency bands. The classification was based on the fast and classical K-means and Bayesian classifiers. With a subject-specific re-scaling of the feature set and the use of a Bayesian classifier the performance reached 90% in both sensitivity and specificity. For the purpose of reducing the feature count, the features were evaluated with the statistical Smith-Satterthwaite test and by using sequential forward selection a well-performing feature subset was found which contained only five features, while attaining a sensitivity and a specificity of both 80 %.**

I. INTRODUCTION

Parkinson's disease (PD) is the 2nd most common neurodegenerative disease after Alzheimer's disease and causes major morbidity, mortality, reduced quality of life for those affected and their families, as well as a major societal burden. A major pathophysiological cause of the disease is progressive development of Lewy Bodies in the brain neuron cytoplasma involving first brain stem and mid brain areas and later basal ganglia and cortical areas. Motor symptoms are clinically present with the involvement of the basal ganglia, but during the period of pre-motor symptoms the involvement of the brain stem and mid brain can cause a number of symptoms including autonomic changes, depression, smell disturbances and sleep disorders; among these iRBD. Due to the long pre-motor period in which the pathophysiological process and degeneration has begun, identifying incipient PD is of great importance - especially if medications slowing the neurodegenerative process becomes available [1] [2].

iRBD has proven to be a promising preclinical marker with 30% to 65% of iRBD patients eventually developing a synucleinopathy [3], [4], [5], [6]. Consequently, diagnosing iRBD carries a possibility for early treatment of PD. Diagnosing RBD is, however, arduous work (the doctor i.e. needs to visually interpret and assess polysomnographic (PSG) signals) which urges for a supportive detection method driven mainly on computer force [7] [8].

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RBD is characterized by a loss of spinal motor inhibition during REM sleep. The patients seem to enact distinct dreams with unpleasant and often violent content (such as being threatened, chased or attacked) and as a result, the patients can be shouting, running, punching etc. during dreaming [8], [9], [10], [11]. Since iRBD manifests itself during dreaming and a main requirement for the diagnosis is alterations during REM sleep, the REM epochs of the EEG signal were chosen as the basis for the classification. The REM epochs involved in this study were extracted using PSG technician scored hypnograms. The workload of this manual scoring could be avoided by automatically detecting the REM sleep using a method proposed by Kempfner et al. which extracts REM sleep from PSG recordings with a mean sensitivity and specificity of 94% and 96%, respectively [12].

Few studies have evaluated the EEG in iRBD patients [13], [14], [15], [16]. They found differences in the EEG signals recorded from iRBD patients as compared to control subjects comparing the absolute power of different frequency bands of the signals. To make the detection method developed in this study more robust to differences in recording equipment, the features used for classification in this study were based on relative powers in different frequency bands.

II. DATA

A. Subjects and Sleep Conditions

This study was based on PSG data from 10 iRBD patients (diagnosed in accordance with [8]) and 10 control subjects. The recordings were made either at the Danish Center for Sleep Medicine (DCSM), Department of Clinical Neurophysiology, Glostrup University Hospital, Denmark, or outpatient with the PSG equipment fitted at the hospital. The control subjects had no diagnosis of Parkinson's disease or sleep disorders and all subjects included took no medicine known to affect sleep. Demographic data for the subjects included are summarized in Table I.

TABLE I
DEMOGRAPHICS

	Age ($\mu \pm \sigma$)	No. of subjects (♀,♂)
Controls	59.8 ± 8.4	10 (5,5)
iRBD	59.0 ± 14.1	10 (2,8)

B. Recordings

The PSG recordings were performed by PSG technicians in accordance with the AASM sleep scoring standard (from 2004)[7]. The PSG signals used in this study were retrieved

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from six EEG electrodes placed at F3, F4, C3, C4, O1 and O2 with reference to the far mastoid (electrode mounting were in accordance with the AASM manual [7]). The signal quality was evaluated by visual inspection and only signals relatively uncorrupted by noise were selected for further analysis. The sampling frequency of the analysed sleep data was 256 Hz and signal processing was performed in MATLAB (R2011a, 32-bit, The MathWorks, Natick, MA, USA). Table II contains the amount of REM sleep epochs analysed:

TABLE II
REM SLEEP EPOCHS USED IN STUDY

	No. of epochs in total	Epochs per subject ($\mu \pm \sigma$)
Controls	2000	200 ± 50.1
iRBD	1832	183.2 ± 79.9

III. METHODS

The features used for classification were derived from manually extracted REM sleep epochs of the EEG signals of 30 second duration and consisted of the relative powers in various frequency bands. These were then used to train and test both a Bayesian and a K-means classifier. The classification of all REM sleep epochs in a PSG recording further lead to the classification of a subject as either iRBD patient or control subject. A subject-specific re-scaling of the features was performed to improve the performance of the classification. To reduce the feature count, the features of highest class separability were determined using sequential forward selection. Five subsets of all features were then assessed through classification performance. In this study the classification performance was evaluated with sensitivity and specificity.

A. Feature Extraction

Absolute powers have previously been used to detect EEG differences of iRBD patients, as seen in studies [13], [14], [15], [16]. Since EEG signals are often heavily noised due to movements of eyes and contractions of facial muscles, a large-amplitude noise can be present in all relevant frequencies. Therefore, it was decided to use the relative power in each frequency band compared to the total power in the area of interest, 0.75-32 Hz. The low cut-off frequency was chosen to attenuate the high amplitude noise that often is present close to DC. Five linear-phase, FIR band-pass filters were created, all with an order of 1296, transition bands of 0.5 Hz, and an attenuation of at least -80 dB in the stop band. The frequency bands can be seen in Table III. The signals were filtered leading to a total of 30 features (five frequency bands from each of six electrodes).

Eventually, to increase the performance of the classification of the subjects, a subject specific re-scaling of the features was carried out according to equation (1),

$$x_{new,i,j} = \frac{x_{old,i,j} - x_{min,i,j}}{x_{max,i,j} - x_{min,i,j}}, \tag{1}$$

TABLE III
FREQUENCY BANDS USED

Band	Low-Cut	High-Cut
δ	0.75	4
θ	4	8
α	8	13
$\beta 1$	13	22
$\beta 2$	22	32

where x_{max} and x_{min} were chosen as the 1st and 99th percentiles of all REM epochs of the subject, i is the subject the REM epochs originated from, and j is the element in the feature vector. The classification was performed with both the original and the re-scaled features.

B. Feature Selection

After feature extraction a Smith-Satterthwaite test was performed to investigate if any of the features (the relative power in different frequency bands) had significantly different group means in the two groups, iRBD patients and control subjects. The test is based on equation (2),

$$t' = \frac{(\overline{X} - \overline{Y}) - \delta}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}} \tag{2}$$

The features were further analysed by the Fisher's Discriminant Ratio (FDR) which is a class separability measure for each feature given by the difference in group means divided by the sum of variances of the two groups. The feature displaying the highest FDR was used as initiator in the feature selection process. The order of features used was determined by sequential forward selection as described by [17], where the class separability of the first selected feature and every other feature is assessed, and the combination with the best performance measure is kept. This process continues until the desired amount of features is reached. The measure for class separability used was J_3 which can compare combinations of a fixed number of features and is given by,

$$J_3 = trace(S_w^{-1} S_m), \tag{3}$$

where S_w^{-1} is the within-class scatter matrix and S_m is the mixture-class scatter matrix, given as the sum of the within-class scatter matrix and the between-class scatter matrix [18].

This suboptimal sequential forward selection was used to lighten the computational load from testing all combinations.

C. Classification

The classification was performed with all 30 features, but also with subsets of these. In the classification process, the feature vectors (each representing a REM epoch) were sectioned into two clusters - a cluster for control subjects and a cluster for iRBD patients. Subsequently, the REM epoch classification was used for classifying subjects. The classification of REM epochs was done using two different hard-clustering classifiers. The first, a classifier based on Bayes? formula [18], is a probabilistic, supervised method,

that creates a second-order decision line between clusters and assigns REM epochs to the cluster it is most probable to origin from. Bayes' formula is stated as in equation 4,

$$P(C_i \mid \mathbf{x}) = \frac{P(C_i) \cdot p(\mathbf{x} \mid C_i)}{p(\mathbf{x})}, \tag{4}$$

where P($C_i \mid$ x) is the a posteriori probability that an observed sample x comes from C_i, P(C_i) is the a priori probability of class C_i, p(x $\mid$ C_i) is the likelihood function of C_i and p(x) is the point distribution function of x, regardless of class.

The training of the second classifier was based on K-means clustering which is an unsupervised method. It creates K centroids (in this case two) and assigns all data points to the centroid they are closest to according to the minimum distance [18], hence making a cluster around each centroid. It then relocates the centroids to the weighted center of all points belonging to that cluster and iterates, assigning all data points to the closest centroid once again. This continues until the centroids no longer moves significantly. The classifier determined which cluster to assign to which group (iRBD or control) depending on the fractions of feature vectors in the clusters originating from either of the groups. When testing the classifier on the REM epochs of a test subject, feature vectors (representing the REM epochs) are assigned to the class with the nearest centroid following the principle of a minimum distance classifier.

In the subject classification a test subject was categorized as control if more than half of the classified REM epochs belonged to the cluster labelled as control, or as iRBD if the opposite was the case. This was done with both the normalized and the re-normalized features. Classification was assessed with several performance measures are calculated, including the sensitivity and the specificity.

D. Cross-validation

The classification followed a leave-one-subject-out cross-validation method where the models were trained on the REM epochs of all subjects but one and the REM epochs of the last subject were used for testing. In that way the fraction of REM epochs from each person assigned to either group can be determined, and the subject will be labelled control or iRBD patient depending on where the highest fraction of REM epochs are.

IV. Results and Reflections

In this section, the results of the statistical analyses and classification is presented. The feature sets consisting of the relative powers in the five frequency bands will be denoted normalized before re-scaling, and re-normalized afterwards.

A. Statistical analysis

The results from the Smith-Satterthwaite test on the normalized data is shown in Table IV. With a 97.5 % confidence two of all features showed significant difference between iRBD and control group means, and with 90 % confidence four features were significantly different. This indicates that the used EEG measures of the iRBD patients do not vary much from that of the control subjects. The significant differences found occurred in higher frequency bands, and in all four features the control subjects had higher mean values of the relative powers, indicating a relative EEG slowing in patients with iRBD.

TABLE IV
Significant results from Smith-Satterthwaite test for difference in relative powers and their significance levels.

Channel & Band	O1-A2 β1	C3-A2 β1	C4-A1 β1	O1-A2 β2
Significance	0.005	0.025	0.10	0.10
Highest mean	Healthy	Healthy	Healthy	Healthy

B. Classification

The results of all attempts to classify subjects with the Bayesian classifier with various amounts of features is shown in Fig. 1. Generally, the Bayesian classifier provided well performing results. The most prominent was the classification with all 30 features and re-normalized data, which reached a sensitivity and specificity of 90 %. It is worth noticing that by use of five normalized features, the classifier was able to attain 80 % in sensitivity and specificity. This is a valuable result if the aim is to reduce the amount of features, the computational load, or the complexity of the method. Another interesting observation is that the five features which attained the good classification all origin from the O1-A2 and F3-A2 signals, both located in the left hemisphere of the brain.

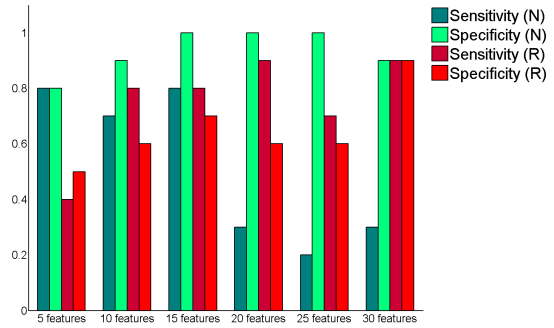

Fig. 1. Results of performance measures from the Bayesian classifier. Green bars are from normalized data, red bars are from re-normalized data.

The same classifications were performed for the unsupervised K-means classifier, displayed in Fig 2, to investigate the performance of a simpler method. Despite attempting different percentiles for re-normalization and various amounts of features, no good classifications occurred. The best classification was by use of 20 normalized features which attained a sensitivity and specificity of 50 % and 80 %, respectively. This indicates that the K-means classifier is not sufficiently advanced for achieving a proper classification of the data used in this study.

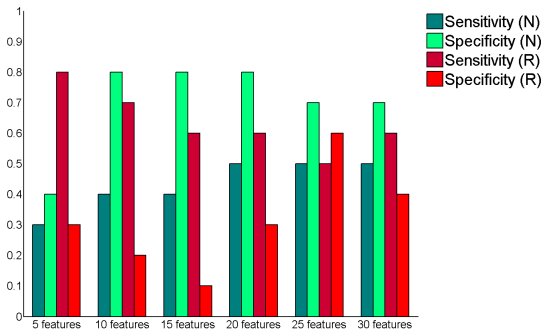

Fig. 2. Results of performance measures from the K-means classifier. Green bars are from normalized data, red bars are from re-normalized data.

V. Discussion

The Smith-Satterthwaite test showed that two features had different iRBD and control group means on a 2.5% significance level. Both features reflect power in the frequency band 13-22 Hz in which both EEG and EMG activity can be present according to the AASM standard. Since the diagnosis of iRBD is based on loss of atonia during REM sleep, the EMG activity during REM sleep could be considerably increased in iRBD patients. Therefore, it could be discussed whether the significant differences found at O1-A2 and C3-A2 can be caused or at least influenced by the higher amount of EMG activity present. Generally, the increased possibility of measuring EMG activity on iRBD patients during REM sleep, could contribute favourably to the classification.

Other factors possibly affect the clustering and hence the final classification: The credibility of the hypnogram manually scored by the PSG technician is lowered when dealing with patients having a sleep diagnosis. This means that the hypnogram of an iRBD patient is more likely to have true non-REM epochs erroneously scored as REM epochs entailing an unintentional inclusion of non-REM epochs in the iRBD class data. Furthermore, the PSG recordings of the control subjects were recorded outpatient whereas the iRBD patients were recorded inpatient. This could imply differences in the EEG signals caused by recording conditions rather than brain activity.

Another issue is the electrode-scalp connection. The impedance is solely measured at the initiation of the recording and thus there is no guarantee that the impedance is kept constant during the whole night of sleep. Variations in impedance would induce erroneous signal changes. Finally, only a visual inspection for artifacts has been performed; If these issues could be minimized or completely removed it would increase the credibility of the results.

In order to generalize the results obtained in this study more subjects should be included in the analyses in future works. Also a randomization of the recording conditions for iRBD patients and controls should be performed as well as better treatment of the noise, e.g. using the multivariate PSG recordings for adaptive noise cancellation. It could be interesting to examine other features and classification methods. Possibly ICA and wavelet derived features could improve the sensitivity of the detection method.

VI. Conclusion

A promising, simple approach for detecting iRBD from EEG signals during REM sleep has been developed. Using 30 features the Bayes' classifier reached 90 % in both sensitivity and specificity when classifying subjects. The statistical analysis showed alterations in the 13-22 Hz frequency band of iRBD patients in the left hemisphere. From the sequential forward selection a subset of five features were found that reached a relatively high classification performance of 80 % in both sensitivity and specificity which demonstrates potential of the approach. It is thus concluded that the EEG patterns of iRBD patients and control subjects during REM sleep provide a basis for detecting iRBD and the method developed in this study shows promising results while keeping the computational load low.

References are important to the reader; therefore, each citation must be complete and correct. If at all possible, references should be commonly available publications.

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