34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Separation of Parkinson's patients in early and mature stages from control subjects using one EOG channel

Julie A.E. Christensen[a,b,c], Rune Frandsen[c], Jacob Kempfner[a,c], Lars Arvastson[b], Soren R. Christensen[b], Poul Jennum[c] and Helge B.D. Sorensen[a]

Abstract— **In this study, polysomnographic left side EOG signals from ten control subjects, ten iRBD patients and ten Parkinson's patients were decomposed in time and frequency using wavelet transformation. A total of 28 features were computed as the means and standard deviations in energy measures from different reconstructed detail subbands across all sleep epochs during a whole night of sleep. A subset of features was chosen based on a cross validated Shrunken Centroids Regularized Discriminant Analysis, where the controls were treated as one group and the patients as another. Classification of the subjects was done by a leave-one-out validation approach using same method, and reached a sensitivity of 95%, a specificity of 70% and an accuracy of 86.7%. It was found that in the optimal subset of features, two hold lower frequencies reflecting the rapid eye movements and two hold higher frequencies reflecting EMG activity. This study demonstrates that both analysis of eye movements during sleep as well as EMG activity measured at the EOG channel hold potential of being biomarkers for Parkinson's disease.**

I. INTRODUCTION

It has been stated that patients suffering from the sleep disorder idiopathic Rapid Eye Movement (REM) Sleep Behavior Disorder (iRBD) are at high risk of developing Parkinson's disease (PD) [1], which makes them essential to analyze in the search for biomarkers of PD. In consequence, many studies focus on sleep data in the search for biomarkers, where polysomnographic (PSG) data have been analysed, including analysis of electromyography (EMG) [2], electroencephalography (EEG) [3] and sleep variables such as sleep latency, sleep time, percentage distribution of sleep stages and sleep efficiency [2].

According to Braak et al., the evolution of PD will involve the basale brain structures to start with (Braak stage I-II), and thereafter progress to the additional brain regions (Braak stage III-IV) [4]. During sleep, eye movements (EMs) are controlled by neurons located in the brain stem structures. In this study, it is therefore hypothesized that patients with iRBD and especially patients with PD will reflect abnorm form of EMs during sleep. To the best knowledge of the authors, no other studies have been focusing on analyzing EMs measured as electrooculography (EOG) during sleep, and for that reason, the study presented here is a pilot study revealing whether EMs hold potential of being a biomarker for PD or not.

The recording of EMs is done by EOG, which is based on a potential difference between the anterior (cornea) and the posterior (retina) point of the eyeball. In that way, the eye acts as a dipole in which the cornea is positive and the retina is negative. By placing electrodes besides each outer canthus, the EMs will be registered as positive potentials by the electrode nearest the cornea and as negative potentials by the electrode nearest the retina. Because of the simultaneously movement of the eyeballs, the EMs registered at the left and right EOG electrode will always appear synchronic and anti-correlated. For clarity, EMs during sleep are in this study defined as holding slow and fast EMs (SEMs and REMs), where the main part of the SEMs lie in the range 0.5-1 Hz and the main part of the REMs lie in the range 1-5 Hz.

II. DATA ACQUISITION

A. Subjects

The patients enrolled in this study were evaluated at the Danish Center for Sleep Medicine at Glostrup Hospital in Denmark. The evaluation of the patients included PSG, multiple sleep latency test and a comprehensive medical history and medication. Patients taking any anti-depressant drug, including hypnotics were excluded, though dopaminergic treatment was continued. Also, the quality of the PSG data was individually evaluated. If too much noise, such as disconnection, was present on the recordings making either the sleep stage scoring or the further analysis unreliable, the subject was excluded. A total of ten PD patients and ten iRBD patients were included in this study. Furthermore, ten age-matched control subjects without history of movement disorder, dream enacting behavior or other former diagnosed sleep disorders were included as controls. Additionally, no medication known to affect sleep was acceptable.

B. Polysomnographic recordings

All controls underwent at least one night of PSG recorded outpatient, and all patients underwent at least one night of PSG recorded either outpatient or in-hospital. For the outpatient recordings, the PSG equipment was fitted at the clinic. The PSG recordings were performed in accordance with the sleep scoring standard stated in 2004 by the American Academy of Sleep Medicine (AASM) [5]. The EOG

Corresponding author: Julie AEC: jaec@elektro.dtu.dk
Contact information: HBDS: hbs@elektro.dtu.dk
RF: RFRA0011@regionh.dk, JK: jkem@elektro.dtu.dk
LA: larv@lundbeck.com, SRC: srac@lundbeck.com,
and PJ: poje@glo.regionh.dk
[a]DTU Electrical Eng., Ørsteds Plads, bldg. 349, DK-2800 Kgs. Lyngby
[b]H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby
[c]Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Center for Healthy Aging, Faculty of Health Sciences, University of Copenhagen, Glostrup Hospital, DK-2600 Glostrup

978-1-4577-1787-1/12/$26.00 ©2012 IEEE

electrodes were placed one cm out and up (left) or down (right) from the outer canthus with reference to the mastoids.

The sleep staging of all subjects were performed by experienced PSG technicians in accordance with the AASM standard [5] staging every epoch of 30 seconds of PSG data into either REM sleep, three stages of non-REM sleep (N1, N2 or N3) or wake (W) resulting in a hypnogram of same length as the entire recording. The total number of scored epochs between lights off and lights on is seen in Table I.

TABLE I

TOTAL NO. OF EPOCHS BETWEEN LIGHTS OFF AND LIGHTS ON.

Stage	Controls	iRBD	PD
Wake (%)	1173 (12)	1881 (18)	1882 (19)
REM (%)	2000 (21)	1731 (16)	1531 (15)
N1 (%)	678 (7)	1081 (10)	1275 (13)
N2 (%)	4443 (46)	4881 (46)	4073 (42)
N3 (%)	1347 (14)	1114 (10)	1084 (11)
Sum (Σ%)	9641 (100)	10688 (100)	9827 (100)

The raw sleep data, hypnograms and sleep events were extracted from Nervus (V5.7, Cephalon DK, Nørresundby, Denmark) using the build-in export data tool. For further analysis, the data were imported to MATLAB (R2012a, The MathWorks, Natick, MA, USA). The analyzed data had a sampling frequency of 256 Hz.

III. METHODOLOGY

A schematic illustration of the signal processing in this study is seen in Fig. 1. For feature extraction, the wavelet decomposition technique was used, and the Shrunken Centroids Regularized Discriminant Analysis (SCRDA) method was used to choose a subset of features and classify the subjects [6]. The wavelet decomposition technique was chosen as we preferred a good resolution at lower frequencies compared to higher frequencies, as the lower frequency ranges are the ones reflecting EMs during sleep. Other feature extraction techniques such as Principal Component Analysis (PCA) or Singular Value Decomposition (SVD) could have been tried, but as this is a preliminary study, we preferred to use a method in which the features are easily interpreted. The SCRDA was chosen as it is designed for classification problems where the number of features is larger or nearly the same as the number of samples. Additionaly, it is suitable for feature elimination purposes, which enabled us to choose the optimal subset of features. Below follows a more detailed description of the steps seen in Fig. 1.

A. Feature extraction

For feature extraction, only the left side EOG signal (EOGL) was used. Before the feature extraction, the 50 Hz powerline noise was removed by a FIR equiripple notch filter with cutoff frequencies at 49 Hz and 51 Hz, respectively. The hypnogram and the EOGL signal were evaluated in all sleep stages (both REM and non-REM) in between lights off and lights on. Each sleep epoch was decomposed using the

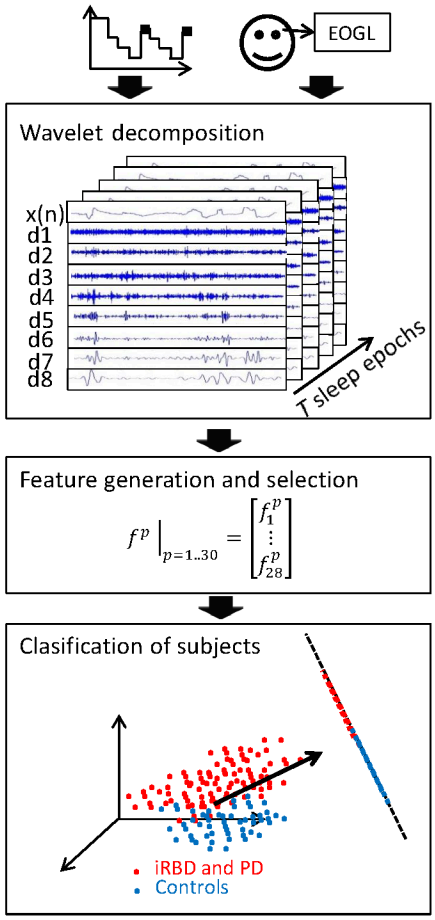

Fig. 1. A schematical view of the methodology of this study. Each sleep epoch between lights off and lights on was extracted from the left side EOG signal and decomposed using wavelet decomposition. The energy percentages and the common logarithm of the summed absolute signal values of the reconstructed detail subbands d2-d8 were computed. The mean and standard deviation of these across all sleep epochs composed the feature vectors. An optimal subset of features were found and the subjects were classfied by use of the Shrunken Centroids Regularized Discriminant Analysis (SCRDA) method.

Discrete Wavelet Transform (DWT). In DWT, an input signal $x(n)$ is passed through a series of filters, which split the signal equally into its high- and low frequency components denoted as detail (D) and approximation (A) components, respectively [7]. After filtering, the components contain redundancies and therefore a downsampling by a factor of two is applied. The decomposition of each sleep epoch was carried out to level eight using a Daubechies 4 (db4) as the mother wavelet. The mother wavelet can be described as the structure which is used to analyze the input signal by comparing it with different scaled and shifted mother wavelets [7]. The choice of the db4 was based on other studies analyzing EOG, [8] [9], as well as a wish to have a rather smooth basisfunction.

Following the wavelet decomposition, the energy percentages and the common logarithm of the summed absolute signal values of the reconstructed detail subbands d2-d8 were computed, yielding 14 values for each sleep epoch.

A single feature vector for each subject was computed by taking the mean and standard deviation of the values across every sleep epoch, thereby yielding f^p holding 28 feature values describing subject p

$$f^p = \begin{bmatrix} \left[f^p_{\mu(\%E)}\right]_{d2}^{d8} \\ \left[f^p_{\sigma(\%E)}\right]_{d2}^{d8} \\ \left[f^p_{\mu(\log_{10}E)}\right]_{d2}^{d8} \\ \left[f^p_{\sigma(\log_{10}E)}\right]_{d2}^{d8} \end{bmatrix} \quad \text{where} \quad \left[f^p_E\right]_{d2}^{d8} = \begin{bmatrix} f_{E_{d2}} \\ \vdots \\ f_{E_{d8}} \end{bmatrix}, \quad (1)$$

where $\%E_{dx}$ and $\log_{10}E_{dx}$ indicate the energy percentage and the common logarithm of the summed absolute signal values of the reconstructed detail subband dx, respectively. The σ and μ indicate the mean and standard deviation across all sleep epochs, respectively. These measures were computed in trying to reflect the hypothesis that the patients have low amplitude EMs during long periods of the night compared to the controls who have concentrated periods with pronaunced EMs.

B. Feature evaluation and selection

The 30 subjects included in this study were each represented by a feature vector of 28 feature values. To avoid overfitting, feature evaluation was therefore needed to appropriately choose a subset of features. This was done by use of the SCRDA method, which generalizes the idea of the Nearest Shrunken Centroids (NSC) into the classical discriminant analysis [6]. In the standard Linear Discriminant Analysis (LDA), G populations are assumed to have a multivariate normal distribution and they are described by mean vectors μ_g $(g = 1,...,G)$ and a common covariance matrix Σ, [6]. An observation $x_{g,i}$ is classified to a population g which minimizes $(x_{g,i}-\mu_g)^T\Sigma^{-1}(x_{g,i}-\mu_g)$, which under the multivariate normal assumptions is the same as chosing the population that maximizes the likelihood of the observation. When including the prior probabilities π_g of each population, the choice of population can be stated based on the posterior probability rather than the likelihood, and because of the assumption of common covariance matrix, the criteria in LDA can be summarized to,

$$\begin{aligned} x_{g,i} \in \text{population}\left(g = \text{argmax}_{g'} d_{g'}(x_{g,i})\right) \quad \text{where} \\ d_g(x) = x^T\Sigma^{-1}\mu_g - \frac{1}{2}\mu_g^T\Sigma^{-1}\mu_g + \log(\pi_g). \end{aligned} \quad (2)$$

The discriminant function, $d_g(x)$, is used in a sample version, $\hat{d}_g(x) = x^T\hat{\Sigma}^{-1}\hat{\mu}_g - \frac{1}{2}\hat{\mu}_g^T\hat{\Sigma}^{-1}\hat{\mu}_g + \log\pi_g$ with $\hat{\mu}_g = \frac{1}{n_g}\sum_{i=1}^{n_g} x_{g,i}$ and $\hat{\Sigma} = \frac{1}{n}\left(X-\overline{X}\right)\left(X-\overline{X}\right)^T$. Here, X is a $p\times n$ matrix holding the observations columnwise, $\overline{X}$ is a $p\times n$ matrix holding the observation mean vectors columnwise and n_g is the number of samples in population g. The sample covariance matrix calculated in this way is badly estimated (or even singular) in the cases where the number of samples is small compared to the number of features. To overcome this issue, different forms of regularizations can be done in the estimation of the covariance matrix, and in SCRDA, the covariance matrix is regularized by use of parameter α, $0 \le \alpha \le 1$ as in equation 3,

$$\widetilde{\Sigma} = \alpha\hat{\Sigma} + (1-\alpha)\hat{D} \;\text{ with }\; \hat{D} = \text{diag}(\hat{\Sigma}) \quad (3)$$

In SCRDA, a threshold forces the group centroids of a particular feature towards zero [6]. In this way, features will be eliminated, and an optimal subset of features can be found. The idea is incorporated by substituting the centroids $\hat{\mu}_g$ by the shrunken centroids $\widetilde{\mu}_g$ found by,

$$\widetilde{\mu} = \text{sgn}(\widetilde{\Sigma}^{-1}\hat{\mu})\left(|\widetilde{\Sigma}^{-1}\hat{\mu}| - \Delta\right)_+. \quad (4)$$

Conclusively, the criteria in the SCRDA method both stabilizes the covariance matrix and eliminates non-contributing features and can be stated as,

$$\begin{aligned} x_{g,i} \in \text{population}\left(g = \text{argmax}_{g'} \widetilde{d}_{g'}(x_{g,i})\right) \quad \text{where} \\ \widetilde{d}_g(x) = x^T\widetilde{\Sigma}^{-1}\widetilde{\mu}_g - \frac{1}{2}\widetilde{\mu}_g^T\widetilde{\Sigma}^{-1}\widetilde{\mu}_g + \log(\pi_g). \end{aligned} \quad (5)$$

Each subject was classified by a leave-one-out approach, where the optimal value for the threshold Δ and the regularizing parameter α was found by a 10-fold crossvalidation on the training set consisting of 29 subjects. The final values of Δ and α were found as the mean across the 30 runs. The mean values for Δ and α indirectly give the optimal subset of features across the 30 runs.

IV. RESULTS AND DISCUSSION

In Table II is seen the optimal subset of features found by the mean values for Δ and α across the 30 runs.

TABLE II

THE OPTIMAL SUBSET OF FEATURES FOUND BY THE SCRDA METHOD, WHERE THE PARAMETERS Δ AND α WERE FOUND AS THE MEAN ACROSS THE 30 RUNS IN THE LEAVE-ONE-OUT APPROACH. WITHIN EACH RUN, THE PARAMETERS WERE FOUND BY A 10-FOLD CROSS VALIDATION.

Original feature no.	Frequency range [Hz]	Description of feature
1	32-64	Mean of the logarithmic "energy" in d2
2	16-32	Mean of the logarithmic "energy" in d3
20	1-2	Mean of the percentage energy in d7
27	1-2	Std of the percentage energy in d7

It is seen that the optimal subset of features includes one feature derived from the reconstructed detail subband d2, one from d3 and two from d7. These reconstructed detail subbands hold frequencies in the range 32-64 Hz, 16-32 Hz and 1-2 Hz, respectively. Using the REM frequency range definition of 1-5 Hz as stated in [10], two of the four included features found in this study reflect REMs. According to the AASM standard, EOG signals should be evaluated in the frequency range 0.3-35 Hz and EMG signals in the frequency range 10-100 Hz when scoring sleep data [5]. Based on this, it can be stated that EOG activity free of EMG activity includes frequencies below 10 Hz. Feature number 2 could therefore hold a portion of EM activity, but could also hold

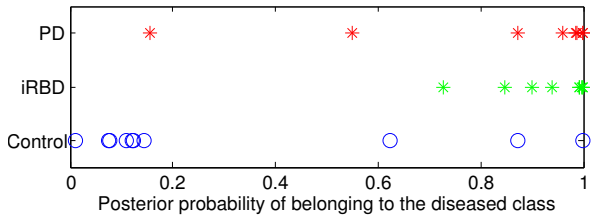

Fig. 2. The posterior probabilities of belonging to the diseased class. These were calculated for each subject during the leave-one-out classification. The diseased class holds the stars indicating iRBD (green) and PD (red) patients, and the control class holds the circles indicating control subjects. It is seen that by choosing the class with the highest posterior probability, three control subjects are misclassified as diseased and one PD patient is misclassified as control.

EMG activity, which must be considered more likely because of the higher frequency content. Feature number 1, on the other hand, must be concluded to hold much more EMG activity than EOG activity.

In the AASM standard, EEG signals should be evaluated in the frequency range 0.3-35 Hz, which is the same as the EOG signals [5]. In generel, EEG signals have less prominant amplitudes than EOG, and do therefore not appear in the EOG signals. During sleep, although, some EEG events such as distinct K-complexes and sleep spindles, are likely to appear in the EOG signals. During N3 sleep, EEG appears as slow wave activity (SWA), which is waves of frequencies 0.5-2 Hz and peak-to-peak amplitudes of above 75 μV [5]. SWA is mainly measured over the frontal regions, and is thereby very likely to appear in the EOG channels. It is not thoroughly evaluated how much of such EEG artifacts appears in the EOGL signal analyzed in this study. It is thereby neither evaluated in which degree such artifacts would affact the results obtained. It is though presumed, that the SWA is the main EEG artifact, that could have an impact on the results, and it is seen in Table I, that the amount of N3 sleep included in this study is more or less the same for each group.

Assuming that the EOG signals are anti-correlated during EMs, the presence of EEG artifacts may be reduced by analyzing a correlation measure between the two EOG signals. It should also be emphasized that the influence of other artifacts, such as baseline drift, has to be adressed in future work.

In Fig. 2 is seen the posterior probability of belonging to the diseased class. The posterior probabilities were calculated for each subject during the leave-one-out classification by use of the discriminant function in equation 5. The blue circles indicate the ten control subjects, the green stars indicate the ten iRBD patients and the red stars indicate the ten PD patients. When interpreting the result, it should be kept in mind that the iRBD and PD patients were treated as one class, i.e. the subset of features were found based on separation of controls and patients and not based on separation of controls, iRBD and PD patients.

Following the criteria in the SCRDA method stated in equation 5, it is seen from Fig. 2 that three control subjects are misclassified as diseased and one PD patient is misclassified as control. The classification approach in this study therefore obtain a sensitivity of 95%, a specificity of 70% and an accuracy of 86.7%.

It should be emphasized, that the four features presented in Table II was found by the mean values of the parameters Δ and α across the 30 runs in the leave-one-out classification. This means, that the included features for classifying each subject may vary as a consequence of the different parameter values in each run. Therefore, the classification results represented in Fig. 2 are not all obtained by use of the four features presented in Table II, as these reflect the overall best subset. During the simulations, though, it was noticed that feature 1 and 27 were represented in each of the 30 runs, indicating that these two features might be the most discriminative ones. This should, however, be evaluated more thoroughly in future work. Also, the patient group should be separated into iRBD and PD patients and it should be investigated which features would be selected in the three class case.

V. CONCLUSIONS

Selection of features holding different frequency bands yielded that the optimal subset of features include two features reflecting REMs and two features reflecting EMG activity. It is thus concluded, that EMs during sleep as well as EMG activity measured at one EOG channel hold information, which can be used to classify iRBD and PD patients. Allthough more research is needed, this study demonstrates that analysis of EMs during sleep and EMG activity during sleep both hold potential of being biomarkers for PD.

REFERENCES

[1] C. Schenck, S. Bundlie, and M. Mahowald, "Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder," *Neurology*, vol. 46, no. 2, pp. 388–393, 1996.

[2] R. B. Postuma, J. F. Gagnon, S. Rompré, and J. Y. Montplaisir, "Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease.," *Neurology*, vol. 74, pp. 239–244, Jan. 2010.

[3] V. Latreille, J. Carrier, J. Montplaisir, M. Lafortune, and J.-F. Gagnon, "Non-rapid eye movement sleep characteristics in idiopathic REM sleep behavior disorder.," *Journal of the Neurological Sciences*, vol. 310, pp. 159–162, June 2011.

[4] H. Braak, K. D. Tredici, U. Rüb, R. A. de Vos, E. N. H. J. Steur, and E. Braak, "Staging of brain pathology related to sporadic Parkinson's disease," *Neurobiology of Aging*, vol. 24, pp. 197–211, Apr. 2003.

[5] C. Iber, *The AASM Manual for the Scoring of Sleep and Associated Events*. American Academy of Sleep Medicine, 2007.

[6] Y. Guo, T. Hastie, and R. Tibshirani, "Regularized linear discriminant analysis and its application in microarrays," *Biostatistics*, vol. 8, no. 1, pp. 86–100, 2007.

[7] P. M. Bentley and J. T. E. McDonnell, "Wavelet transforms : an introduction," *Electronics & Communication Engineering Journal*, vol. 6, no. 4, pp. 175–186, 1994.

[8] J.-X. Ma, L.-C. Shi, and B.-L. Lu, "Vigilance estimation by using electrooculographic features.," in *32nd Annual International Conference of the IEEE EMBS*, pp. 6591–6594, Jan. 2010.

[9] A. Bulling, J. A. Ward, H. Gellersen, and G. Tröster, "Eye Movement Analysis for Activity Recognition Using Electrooculography," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, vol. 33, no. 4, pp. 741–753, 2011.

[10] R. Agarwal, T. Takeuchi, S. Laroche, and J. Gotman, "Detection of rapid-eye movements in sleep studies.," *IEEE Transactions on Bio-Medical Engineering*, vol. 52, pp. 1390–1396, Aug. 2005.