35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

SLEEP phenomena as an early biomarker for Parkinsonism

Jacob Kempfner [a,d], Poul Jennum [b,c,d], Miki Nikolic [c], Julie A. E. Christensen [a] and Helge B. D. Sorensen

Abstract— **Idiopathic Rapid-Eye-Movement (REM) sleep Behavior Disorder (iRBD) is one of the most potential biomarkers for Parkinson's Disease (PD) and some atypical PD (AP). It is characterized by REM sleep with abnormal high surface EMG (sEMG) activity. Some twitching during REM sleep is normal, but no one has defined what normal is, and no well-defined methodology for measuring muscle activity in REM sleep exists. The purpose of this study is to investigate the possibility of detecting abnormal high muscle activity during REM sleep in subjects diagnosed with iRBD. This has been achieved by considering the abnormal high muscle activity during REM sleep in iRBD subjects as an outlier detection problem, while exploiting that iRBD muscle activity is more grouped. It was possible to correctly discriminate all iRBD subjects from healthy elderly control subjects and subjects diagnosed with periodic limb movement (PLM) disorder. However, not all PD subjects were classified as having abnormal muscle activity, which is assumed to support the fact that not all PD subjects develop RBD.**

I. INTRODUCTION

The pathology of PD and AP is complex and not completely understood [1]. The motor symptoms (tremor, rigidity, akinesia, postural instability) of PD results from the loss of dopamine-generating neurons located in the brain parts called substantia nigra. When the motor symptoms are prominent, and the diagnosis is set, the brain is seriously affected. Recent research shows that there are some earlier symptoms, which can be simply described as abnormal high muscle activity during REM sleep [2]. The medical term for this phenomenon is REM sleep behavior disorder (RBD), and is characterized by REM sleep without atonia (RSWA) and, consequently, increased muscle tone and burst activity of the submental or limb sEMG [2]. RBD without current signs of PD/AP, or any other diseases, is designated as idiopathic RBD (iRBD). Idiopathic RBD is most likely one of the earliest signs of PD/AP. In long-term prospective studies the percentage of subjects with iRBD, who will eventually develop PD or AP, ranges from 40% to 65% after average 10-15 years [3], [4]. Correct detection of iRBD is therefore essential, especially if treatment becomes available. However, some muscle activity during REM sleep is normal, but no one has defined what normal is, and no accepted methodology exists for measuring abnormal high muscle activity in REM sleep. Investigation of RSWA has been studied for some years using different approaches. Mostly, this has been done manually, with few semi-automatic exceptions [5–11]. There is no conventional standard for labeling muscle activity during REM sleep, but one manual method is widely used in the literature [12]. This manual scoring method, however, is time consuming and can be interpreted differently. Therefore, new automatic quantification methods of muscle activity during REM sleep is required. This study is an improved version of our previous work [13], which includes enhanced features and an improved quantification scheme.

[a] Department of Electrical Engineering, Technical University of Denmark, Kgs. Lyngby, Denmark.
[b] Danish Center for Sleep Medicine, Glostrup University Hospital, Denmark.
[c] Department of Clinical Neurophysiology, Glostrup University Hospital, Denmark.
[d] Center for Healthy Ageing, University of Copenhagen, Copenhagen, Denmark.

II. DATA

A. Subjects and demographics

A total of forty-eight subjects from the Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Glostrup University Hospital, Denmark, were enrolled in this study. They were divided into four groups according to their diagnosis. The demographics of the four groups are summarized in Table 1. Subjects with periodic limb movements disorder (PLM) are experiencing twitching or jerking movements that occur as frequently as every 20 to 40 seconds during NREM sleep, which, in a suppressed form, may continue into REM sleep. The consequences of this must therefore be investigated, since PLM should not be confused with iRBD.

Table 1: Demographics

Diagnose	Nº (♀, ♂)	Age μ ± σ (min, max, median) *years* [A]
Control	12 (8, 4)	57.5 ± 9.2 (45, 73, 54)
PLM	12 (6, 6)	58.7 ± 11.6 (43, 75, 59)
iRBD	12 (2, 10)	62.2 ± 7.3 (51, 76, 62)
PD	12 (3, 9)	64.5 ± 6.4 (52, 74, 64)

[A] μ and σ corresponds to the mean and standard deviation.

B. Data acquisition

All involved subjects underwent one full night polysomnography in accordance with the international standard [14]. This corresponds to approximately seven to eight hours of sleep per subject when using data from light-off to light-on (total recording time). A total of three sEMG

channels were used to detect RSWA, corresponding to the submentalis (CHIN) and the left and right anterior tibialis (TIBL, TIBR). All recordings were visually inspected by specialists to ensure their quality. The sampling frequency of the analyzed sleep data was 256 Hz.

III. Method

A. Preprocessing of the sEMG data

The sEMG may contain artifacts such as baseline drift, powerline noise, electrocardiography (ECG) crosstalk, or even respirational artifacts in CHIN. These were reduced by the use of a fourth-order Butterworth (BW) bandpass filter according to [15]. The chosen cutoff frequencies (3dB) were 30 Hz and 65 Hz, respectively [16]. The lowest amplifier anti-aliasing filter cutoff frequency in our data was 70 Hz. The power-line noise was reduced by using a fourth-order BW notch filter with the cutoff frequencies (3 dB) 48 Hz and 52 Hz, respectively [15]. The sEMG activity was described by two envelope curves, a baseline and an activity envelope curve. This is also addressed in section *C*. In this study the envelope curves are obtained by smooting the full-wave-rectified preprocessed sEMG signals with a normalized Blackman window according to [15]. The normalized Blackman window is defined as:

$$w(m) = \frac{1}{\tau}\left(0.42 - 0.5\cos\left(\frac{2\pi m}{\mathrm{M}-1}\right) + 0.08\cos\left(\frac{4\pi m}{\mathrm{M}-1}\right)\right) \quad (1)$$

where $0 \le m \le \mathrm{M}-1$ and τ is given by:

$$\tau = \sum_{m=0}^{\mathrm{M}-1} 0.42 - 0.5\cos\left(\frac{2\pi m}{\mathrm{M}-1}\right) + 0.08\cos\left(\frac{4\pi m}{\mathrm{M}-1}\right) \quad (2)$$

The Blackman window durations were $\mathrm{M_b} = 1280$ points for the baseline envelope and $\mathrm{M_a} = 128$ points for the activity envelope, respectively.

B. Partition of the preprocessed sEMG data

The envelope curves, from a given subject, were then partitioned into mini-epochs with a fixed duration of 3-seconds. One robust feature, which could characterize muscle activity, was extracted from each individual mini-epoch using a sliding window as illustrated in Fig. 1.

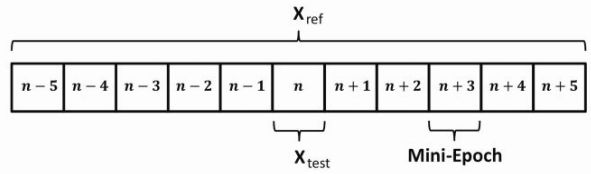

Fig. 1: Sliding window. The reference window consists of 31 mini-epochs, while the center test window consists of one mini-epoch. The step size is one mini-epoch [13].

C. Feature extraction of the envelope curves

For diagnosis of iRBD it was recommended by [17] that any type of sEMG activity, whether it consists of sustain or burst activity or a combination of both should be used to quantify the muscle activity. Therefore, a simple relative sEMG feature has been designed. The sEMG must be analyzed relatively, and should not be compared between muscles or subjets directly. Therefore, the activity window (Fig. 1) was relatively compared to the baseline window by following relationship:

$$\rho(n) = \frac{1}{\mathrm{M}} \frac{\sum_{m=0}^{M-1} \mathrm{x_{test}}(n,m)}{\min\ \mathrm{x_{ref}}(n)} \quad (3)$$

where n amd m is the mini-epoch index and test window sample index respectively, while $\mathrm{x_{test}}$ and $\mathrm{x_{ref}}$ are the envelope curves of the activity and baseline window. The feature computed by (3) compares relatively the mean of the activity envelope ($\mathrm{x_{test}}$) with the minimum of the baseline envelope ($\mathrm{x_{ref}}$). In [13] only one envelope curve with duration of 128 points was used. A baseline envelope ($\mathrm{x_{ref}}$) with a longer duration, 1280 points in this case, reduces the risk of getting unexpected low values in the denominator in (3). A total of three features were extracted from each subject, which corresponds to one feature from each of the three sEMG channels (CHIN, TIBL and TIBR).

D. Outlier detection

The objective of the outlier detector, the one-class support vector machine (OC-SVM) is this case, was to classify the feature samples computed by (3) into two classes, an inlier class or an outlier class. The inlier class is assumed to contain the normal REM sleep mini-epochs (with atonia), while the outlier class is assumed to contain the abnormal REM sleep mini-epochs (RSWA). The REM sleep features were selected from the manual scored hypnogram, which was scored by sleep a specialist. An example of outlier detection is illustrated in Fig. 2.

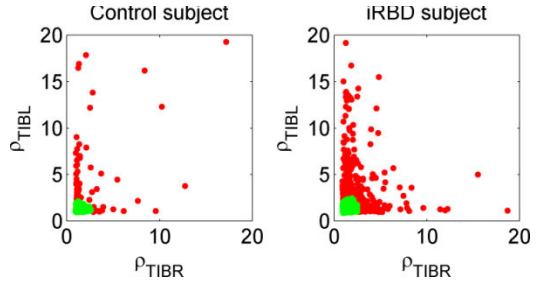

Fig. 2: Scatterplot of the outlier detection using the TIBL and TIBR. The left plot corresponds to a healthy control subject, while the right plot shows an iRBD subject. The green dots are detected inliers, whereas red dots are outliers. It can be seen that the activity in the iRBD subject is higher than the healthy control, due to the amount of red dots.

1) The one-class support vector machine

The original support vector machine (BC-SVM) is a relatively new supervised-learning algorithm, originally introduced by [18], [19], and widely used in the litterature. The one-class support vector machine (OC-SVM) is an unsupervised extension of the BC-SVM learning algorithm

[20], [21]. The OC-SVM has successfully been applied in different fields, which includes fraud detection, text document classification and medical diagnosis. In contrast to the original SVM, which finds the discriminative boundary between two classes, the OC-SVM finds the smallest possible boundary that encloses most of the target data. This may be obtained in the absence of any anti-target data (only one class). The OC-SVM algorithm creates a function, which takes the value +1 in a small region enclosesing most of the data points and -1 elsewhere. This is illustrated in Fig. 2. Assuming a set of training vectors is available $\mathbf{x}_i \in \mathbb{R}, i = 1, \dots, \mathrm{N}$, in this case features computed by (3), the OC-SVM solves the optimization problem:

$$\min_{\mathbf{w},\rho,\xi} \ \frac{1}{2}\|\mathbf{w}\|^2 + \frac{1}{\nu N}\sum_{i=1}^{N}\xi_i - \rho \qquad (4)$$

subject to

$$(\mathbf{w}\cdot\phi(\mathbf{x}_i)) \geq \rho - \xi_i \qquad (5)$$

and

$$\xi_i \geq 0, \qquad i = 1, \dots, N \qquad (6)$$

Where $\mathbf{w}$ and ρ are the weights and offset respectively, both of which have to be learned from the data. The ξ_i is the slack variable, which specifies the amount of misplacement contributed by each data point. To avoid overfitting the parameter $\nu \in (0,1]$ is introduced which characterizes the fraction of outliers, or in other words, the proportion of data points for which the OC-SVM output takes the value -1. The Radial Basic Function was used as kernel in this study, which maps the feature vector $\mathbf{x}$ into an inner product space , such that the dot product in this feature space can be computed by evaluating the kernel given by:

$$K(\mathbf{x}_i, \mathbf{x}_k) = \phi(\mathbf{x}_i)\cdot\phi(\mathbf{x}_k) = \exp(-\gamma\|\mathbf{x}_i - \mathbf{x}_k\|^2) \qquad (7)$$

A freely available MATLAB implementation of the used OC-SVM classifier (LIBSVM) was used [22], [23].

2) Validation of algorithm

All the adjustable OC-SVM parameters were found by a simple grid-search approach, in combination with the leave-one-out cross validation scheme. It is assumed that healthy controls have fewer muscle activations during REM sleep compared to iRBD subjects (Fig. 2). Therefore, inspired from [24], the OC-SVM classifier was trained using *only* healthy controls. The REM sleep features from the healthy controls was selected from the manual scored hypnogram. The feature samples from a given subject may be correlated. For that reason a fold consists of whole subjects. A single fold (one healthy control) was held out for validation, while the remaining 11 folds (11 healthy controls) were used for training. The trained OC-SVM was then applied on the healthy control that was left out and one random selected iRBD, PLM and PD subject. This procedure was repeated 12 times in total, each time leaving a different healthy control out as validation subject, which was matched to a different iRBD, PLM and PD subject each time.

3) Post processing of the OC-SVM output

Each 30-second epoch consist of 10 mini-epochs. The voting principple was used to classify each epoch into normal or abnormal, denoted $\mathrm{Epoch}_{\mathrm{norm}}$ and $\mathrm{Epoch}_{\mathrm{abnorm}}$, respectively. If six or more mini-epochs in each epoch was classified as an outlier, then the whole epoch was labeled as abnormal. This will label most of the PLM epochs as normal, since they usually only have few outlier mini-epochs in each epoch continuously during the night, which may continue into REM sleep. However, iRBD ourlier mini-epochs are assumed more grouped, and will therefore be classified as abnormal. The number of abnormal epochs with respect to the total number of REM sleep epochs in each subject was used as a quantitative muscle score for that subject. The muscle score as a percentage is given by:

$$\mathrm{S} = \frac{\#\mathrm{Epoch}_{\mathrm{abnorm}}}{\#\mathrm{Epoch}_{\mathrm{abnorm}} + \#\mathrm{Epoch}_{\mathrm{norm}}} \cdot 100 \qquad (8)$$

Misclassification of PLM subjects was a minor issue in our previous study [13], where the total amount of mini-epochs that was classified as outliers during REM sleep in percentage was used as muscle score (S). A local voting principple as abovementioned solved that issue. Nevertheless, four muscle scores ($S_{control}$, S_{iRBD}, S_{PLM}, S_{PD}) from the 12 validations were computed, corresponding to a total of 48 score values. The performance of the algorithm was measured by the area under the receiver operating characteristic (ROC) curve (AUC), where the iRBD scores were labeled as the positive group, while the controls and PLM scores were labeled as the negative group [25]. The PD subjects were not included in the optimization process. The reason is discussed below. The parameter combimation with the highest AUC was then chosen. The muscle scores are shown in Fig. 3.

IV. Results and Discussion

Periodic limb movements (PLMs) normally appears in NREM sleep, and may continue, in a suppresed form, in REM sleep. The method was therefore tested on subjects diagnosed with PLM disorder. Additionally, the algorithm was also tested on PD subjects, but they were not included in the parameter optimization process, since not all PD subjects develop RBD, and the hypnogram inter-score agreement of PD subjects is low [26]. All the sEMG channels were preprocessed to reduce the number of outliers that were not associated with muscle activity. However, the applied pre-processing step can not guarantee that all detected outliers are associated with musle activity, but the "mis-classification" is at least systematic. All the controls, PLM and iRBD subjects were classified correctly when using a threshold of 5.5% ($\mathrm{AUC} = 1.00,\ \nu = 0.19,\ \gamma = 2^{-7}$).

However, 9/12 of the PD subjects were classified as having RBD. This supports that not all PD subjects develop RBD.

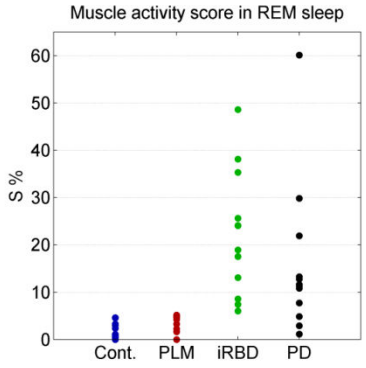

Fig. 3: The muscle activity score of the four classes. Blue, red and green corresponds to healthy controls, PLM and iRBD subjects, while black corresponds to PD.

V. Conclusion

Detection of abnormal high muscle activity during REM sleep can be considered as an outlier detection problem and that iRBD muscle activity is more grouped compared to PLM activity, which consist of short lasting muscle bursts that are more periodic. It was possible to separate all PLM subjects and healthy controls from iRBD subjects using the proposed method. Furthermore, 9/12 of the enrolled PD subjects were classified as having abnormal high muscle activity during REM sleep, which is assumed to support the fact that not all PD subjects develop RBD. Other sleep disorders, such as apnea, may also have increased muscle activity during REM sleep, and should be tested in future work.

References

[1] A. Abbott, "Neuroscience: while you were sleeping," *Nature*, vol. 437, no. 7063, pp. 1220–1222, 2005.

[2] American Academy of Sleep Medicine, *International classification of sleep disorders: diagnostic and coding manual*, 2nd ed. Westchester, Illinois: AASM, 2005, pp. 148–152.

[3] 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.

[4] R. Postuma, J. Gagnon, and J. Montplaisir, "REM sleep behavior disorder: from dreams to neurodegeneration," *Neurobiol Dis*, vol. 46, no. 3, pp. 553–558, 2012.

[5] J. Burns, F. Consens, R. Little, K. Angell, S. Gilman, and R. Chervin, "EMG variance during polysomnography as an assessment for REM sleep behavior disorder," *Sleep*, vol. 30, no. 12, pp. 265–271, 2007.

[6] G. Mayer, K. Kesper, T. Ploch, S. Canisius, T. Penzel, W. Oertel, and K. Stiasny-Kolster, "Quantification of tonic and phasic muscle activity in REM sleep behavior disorder," *J Clin Neurophysiol*, vol. 25, no. 1, pp. 48–55, 2008.

[7] M. Shokrollahi, S. Krishnan, D. Jewell, and B. Murray, "Analysis of the electromyogram of rapid eye movement sleep using wavelet techniques," in *Conf Proc IEEE Eng Med Biol Soc 2009*, 2009, pp. 2659–2662.

[8] M. Shokrollahi, S. Krishnan, D. Jewell, and B. Murray, "Autoregressive and cepstral analysis of electromyogram in rapid movement sleep," in *WC IFMBE Proceedings 2009*, 2009, vol. 25, no. 4, pp. 1580–1583.

[9] M. Shokrollahi, S. Krishnan, D. Kumar, and S. Arjunan, "Chin EMG analysis for REM sleep behavior disorders," in *Biosignals and Biorobotics Conference*, 2012, pp. 1–4.

[10] J. Fairley, G. Georgoulas, and G. Vachtsevanos, "Sequential feature selection methods for Parkinsonian human sleep analysis," in *Conf on Control and Automation, 2009. MED '09. 17th Mediterranean*, 2009, pp. 1468–1473.

[11] J. Fairley, G. Georgoulas, C. Stylios, G. Vachtsevanos, D. Rye, and D. Bliwise, "Phasic Electromyographic Metric detection based on wavelet analysis," in *Control & Automation*, 2011, pp. 497–502.

[12] O. Lapierre and J. Montplaisir, "Polysomnographic features of REM sleep behavior disorder: development of a scoring method," *Neurology*, vol. 42, no. 7, pp. 1371–1374, 1992.

[13] J. Kempfner, G. Sorensen, M. Nikolic, R. Frandsen, H. Sorensen, and P. Jennum, "REM Sleep Behavior Disorder as an Outlier Detection Problem," *Accepted in Journal of Clinical Neurophysiology*.

[14] C. Iber, S. Ancoli-Israel, A. Chesson, and S. Quan, *The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification*, 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.

[15] F. Gustafsson, "Determining the initial states in forward-backward filtering," *IEEE Transactions on Signal Processing*, vol. 44, no. 4, pp. 988–992, 1996.

[16] J. Drake and J. Challaghan, "Elimination of electrocardiogram contamination from electromyogram signals: An evaluation of currently used removal techniques," *J Electromyogr Kinesiol.*, vol. 16, no. 2, pp. 175–187, 2006.

[17] B. Frauscher, A. Iranzo, C. Gaig, V. Gschliesser, M. Guaita, V. Raffelseder, L. Ehrmann, N. Sola, M. Salamero, E. Tolosa, W. Poewe, J. Santamaria, and B. Högl, "Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder," *Sleep*, vol. 35, no. 6, pp. 835–847, 2012.

[18] B. Boser, M. Guyon, and V. Vapnik, "A training algorithm for optimal margin classifiers," in *Proceedings of the 5th Annual ACM Workshop on Computational Learning Theory 1992*, 1992, pp. 144–152.

[19] C. Cortes and V. Vapnik, "Support-vector network," *Machine Learning*, vol. 20, pp. 273–297, 1995.

[20] B. Schölkopf, J. Platt, J. Shawe-Taylor, A. Smola, and R. Williamson, "Estimating the support of a high-dimensional distribution," *Journal Neural Computation*, vol. 13, no. 7, pp. 1443 – 1471, 2001.

[21] J. Shawe-Taylor and N. Cristianini, *Kernel methods for pattern analysis*. Cambridge University Press, 2004.

[22] C. Chang and C. Lin, "LIBSVM : A library for support vector machines," *ACM Transactions on Intelligent Systems and Technology*, vol. 2, no. 3, 2011.

[23] C. Hsu, C. Chang, and C. Lin, "A practical guide to support vector classification," 2010. [Online]. Available: http://www.csie.ntu.edu.tw/~cjlin/.

[24] J. Mourão-Miranda, D. Hardoon, T. Hahn, A. Marquand, S. Williams, J. Shawe-Taylor, and M. Brammer, "Patient classification as an outlier detection problem: an application of the one-class support vector machine," *Neuroimage*, vol. 58, no. 3, pp. 793–804, 2011.

[25] G. Forman and M. Scholz, "Apples-to-apples in cross-validation studies: pitfalls in classifier performance measurement," *ACM SIGKDD Explorations Newsletter*, vol. 12, no. 1, pp. 49–57, 2010.

[26] H. Danker-Hopfe, D. Kunz, G. Gruber, G. Klösch, J. Lorenzo, S. Himanen, B. Kemp, T. Penzel, J. Röschke, H. Dorn, A. Schlögl, E. Trenker, and G. Dorffner, "Interrater reliability between scorers from eight European sleep laboratories in subjects with different sleep disorders," *J Sleep Res*, vol. 13, no. 1, pp. 63–9, 2004.