Ratti Pietro Luca (Orcid ID: 0000-0002-9941-6721)

Actigraphy enables home screening of REM behavior disorder in Parkinson disease

Flavio Raschellà[1], PhD, Stefano Scafa[2,3,4], MSc, Alessandro Puiatti[4], MSc, Eduardo Martin Moraud[2,3]*, PhD, and Pietro-Luca Ratti[5]*, MD PhD

Affiliations

[1] Onera Health, 5617 BD Eindhoven, The Netherlands

[2] Defitech Centre for Interventional Neurotherapies (.NeuroRestore), Lausanne University Hospital and Ecole Polytechnique Féderale de Lausanne (EPFL), Switzerland

[3] Department of Clinical Neurosciences, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[4] Institute of Digital Technologies for Personalized Healthcare (MedITech), University of Applied Sciences and Arts of Southern Switzerland, Lugano, Switzerland

[5] Neurocenter of Southern Switzerland, Ente Ospedaliero Cantonale, Lugano, Switzerland and Al Centro del Sonno, Venice, Italy

* These authors contributed equally to this work

Correspondence to

Pietro Luca Ratti
Neurocenter of Southern Switzerland
Ente Ospedaliero Cantonale
via Tesserete, 46
CH-6903 Lugano, Switzerland
e-mail: pietroluca.ratti@gmail.com

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SUMMARY FOR SOCIAL MEDIA

Twitter Handles:
@RaschellaFlavio
@EdMoraud

What is the current knowledge on the topic?
The diagnosis of REM sleep behavior disorder remains limited to expensive and cumbersome examinations in clinical settings. Instead, screening in everyday environments is restricted to simple questionnaires. No comprehensive characterization of movement readouts has been performed to enable widespread, thorough screening in home environments.

What question did this study address?
We studied the capacity to identify key movement features of REM sleep behavior disorder using wrist actigraphy only, and to leverage this understanding to develop portable screening tools for home use in patients with Parkinson's disease.

What does this study add to our knowledge?
REM sleep behavior disorder is characterized by well-defined actigraphic movement features that can be used to discriminate patients in home environments.

How might this potentially impact on the practice of neurology?
These results open new perspectives for faster, cheaper, and more regular screening of sleep disorders, both for routine clinical practice and clinical trials.

ABSTRACT

Objectives

REM sleep behavior disorder (RBD) is a potentially harmful, often overlooked sleep disorder affecting up to 70% of Parkinson's disease patients. Current diagnosis relies on nocturnal video-polysomnography, which is an expensive and cumbersome exam requiring specific clinical expertise. Here, we explored the use of wrist actigraphy to enable automatic RBD diagnoses in home settings.

Methods

Twenty-six Parkinson's patients underwent two-week home wrist actigraphy, followed by two in-lab evaluations. Patients were classified as RBD vs. non-RBD based on dream enactment history and video-polysomnography. We comprehensively characterized patients' movement patterns during sleep using actigraphic signals. We then trained machine learning classification algorithms to discriminate patients with or without RBD using the most relevant features. Classification performance was quantified with respect to clinical diagnosis, separately for in-lab and at-home recordings. Performance was further validated in a control group of non-PD patients with other sleep conditions.

Results

To characterize RBD, actigraphic features extracted from both (i) individual movement episodes and (ii) global nocturnal activity were critical. RBD patients were more active overall, and exhibited movements that were shorter, of higher magnitude, and more scattered in time. Using these features, our classification algorithms reached an accuracy of 92.9±8.16% during in-clinic tests. When validated on home recordings in Parkinson's patients, accuracy reached 100% over a two-week window, and was 94.4% in non-PD control patients. Features showed robustness across tests and conditions.

Interpretations

These results open new perspectives for faster, cheaper, and more regular screening of sleep disorders, both for routine clinical practice and clinical trials.

Keywords: REM sleep behavior disorder; Parkinson's disease; Actigraphy; Machine learning; Home screening tool.

INTRODUCTION

REM sleep behavior disorder (RBD) is a sleep disorder affecting up to 70% of patients with Parkinson's disease (PD)[1]. Patients with RBD exhibit movements and dream enactment behaviors during sleep which can be vigorous, sometimes violent and harmful[2]. Diagnosing and treating RBD is of pivotal importance to prevent severe injuries to patients and their bedpartners.

Isolated RBD represents an early stage of PD or other synucleinopathies[3], and can precede for several years more overt clinical manifestations of these disorders[4, 5]. Its early diagnosis offers a unique window to evaluate disease-modifying effects of upcoming treatments[6]. Additionally, PD phenotypes that are associated with RBD tend to be more aggressive and to exhibit more motor complications. They are also more often accompanied by cognitive, behavioral and dysautonomic symptoms[7]. Identifying RBD in PD can thus provide fundamental insights to inform clinical practice, both from a therapeutical and prognostic point of view[8]. RBD associated to synucleinopathies remains overlooked and underrecognized, even among movement disorders specialists. Awareness of RBD both in the general population and healthcare professionals still needs to be increased[6]. RBD diagnosis requires nocturnal video-polysomnography (VPSG)[2], which is a costly, time-consuming exam that is only accessible in specialized centers and can be burdensome for patients. Current screening tools rely on questionnaires or interviews. These approaches are often subjective, and

can either not be available for community-dwelling individuals[9] or require the presence of a bedpartner[10]. In PD patients, their reliability to capture RBD is not well established[11-13].

Although RBD behaviors are known to be more jerky and violent than those observed during wakefulness in patients with PD[14], to our knowledge no objective and systematic characterization has been performed. The lack of objective metrics other than PSG has restricted the development of screening tools for RBD diagnosis in everyday life settings. Home screening would be a mainstay to better understand RBD manifestations and their changes over time, and to assess treatment efficacy during clinical trials and clinical routine[6].

Wrist actigraphy is a promising screening tool for RBD. In a recent study, visual analysis of actigraphic recordings using pattern recognition could distinguish idiopathic RBD from other motor activities during sleep, and to identify subjects with isolated RBD in the general population [15].

In this study, we comprehensively characterized movement features of RBD from wrist actigraphy signals and extracted those that best discriminate RBD vs. non-RBD PD patients. We then designed and validated a novel, handy, portable screening method for RBD that can be employed at home. We combined actigraphic technology and machine learning algorithms that were optimized in controlled clinical settings and translated to home environments. Finally, the accuracy of our approach was validated at home in non-PD patients with insomnia, either isolated or associated with other sleep disorders, and without history of RBD.

PATIENTS AND METHODS

Study design and population

Ethical considerations

The study was conducted in the framework of the *Awake & Move study*[16, 17]. It was approved by the Ethics committee of the Canton of Ticino, Switzerland (Ref. 2016-00056) and by the ethics committee of the ULSS3 "Serenissima" of Venice, Italy (Ref. EOC.NSI.LS.15.3) and conducted in accordance with the Declaration of Helsinki. Written consent was provided by all participants. Participation in this study was on a voluntary basis and proposed to all patients meeting the eligibility criteria who were attending the outpatient department of the Movement Disorder Unit of the Neurocenter of Southern Switzerland in Lugano, Switzerland. Additional PD patients volunteered to participate after advertisements in the magazine of the Swiss Parkinson's association, and in public conferences organized by the same association.

Non-PD, insomnia patients were consecutively recruited among all referrals to the sleep clinic of one of the co-authors, in Venice, Italy. These patients signed informed consent according to Code of Conduct for the use of health data for educational and scientific publication purposes of Veneto Region, Italy.

Inclusion and exclusion criteria

Eligibility criteria for patients with PD: mild to moderate idiopathic PD (no atypical parkin-sonism)[18] (Hoehn & Yahr stage >1 and ≤3)[19], no cognitive impairment (Mini-Mental State Examination score ≥26/30)[20], no active depression (Beck Depression Inventory score < 14/63)[21], no deep brain stimulation.

Eligibility criteria for non-PD insomnia patients: age ≥18 year-old; presence of a bedpartner; no history of dream enactment behavior, vocalizations while sleeping, nor of sleep-related injuries; no history or clinical signs of neurodegenerative disorders (including PD, parkinsonism, mild cognitive impairment or dementia, narcolepsy); no autonomic dysfunction; having performed a 2-week wrist actigraphy between October 2020 and May 2022 for their clinical workout of insomnia disorder.

Study procedures

Patients' participation and workload

For patients with PD, an initial recruitment visit (Vo) was organized at the hospital by a senior neurologist, expert in sleep medicine and movement disorders, who performed a thorough medical and neurological examination. Evaluations included sleep history and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), with the motor part (III) performed during the "on" phase in patients with motor fluctuations.

In each recruited patient, sleep and wake patterns were profiled by means of continuous actigraphy monitoring, recorded at home over a 2-week period, coupled with an electronic sleep diary. Sleep and wake routines were recorded by means of a proprietary application for tablets, *SleepFit*[22].

At the end of this period, a full in-lab video-polysomnography (VPSG) was performed. The times of "lights-out" and "lights-on" were set for each subject according to their usual bed- and wake-time schedules, mirroring sleep habits of the previous 2 weeks. Habitual hypnotic medications and other psychotropic agents were allowed during the subjects' participation in the study. Alcoholic, caffeinated or other stimulant beverages, as well as tobacco smoking, were not permitted 4 hours prior to bedtime. A second VPSG was performed 7 to 14 days after the first one. Between the first and the second VPSG recordings, the patients were asked to keep their routines and daily medications unchanged.

Non-PD control patients were recruited at the sleep clinic in Venice, Italy. All consecutive subjects coming for clinical examination and meeting the eligibility criteria were contacted for participation in the study. All patients agreed and gave their written, informed consent. Insomnia was defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep and resulting in daytime impairment [2]. Actigraphy was prescribed in all cases when objective estimates of sleep parameters were decisive for clinical decision making [23]. The presence of other co-morbid sleep disorders was systematically investigated by means of standardized history taking and physical examination by an expert sleep physician, according to standard criteria [2]. When sleep disordered breathing was suspected, a home polysomnography or polygraphy was also performed.

Wrist actigraphy

GENEActiv Original wrist actigraph (GENEActiv™, Activinsight Ltd., Kimbolton, Cambridgeshire, UK)[24] was employed during the 2-week home recordings. It was worn on the more affected arm by the patients with PD, and on the non-dominant arm by non-PD patients. It recorded tri-axis arm accelerations (a_x, a_y, a_z) and environmental light. Signals were acquired at 40 Hz sampling frequency, to maximize battery duration. In parallel to the in-lab VPSG recordings, continuous recordings of motor activity were acquired using the same *GENEActiv Original* devices, set to record at a 100-Hz sampling frequency, and worn on both wrists.

Video-polysomnography

VPSG recordings were performed in all the PD patients according to the American Academy of Sleep Medicine standards[25], including scalp electroencephalography, electro-oculogram, surface electro-myogram activity of the chin, bilateral upper limb and lower limb muscles (flexor digitorum superficialis and extensor digitorum brevis, respectively) [26-28], nasal and oral flow, respiratory effort sensors, pulse oximeter and electrocardiogram. Synchronized digital infrared video tracks and ambient sound recordings were also acquired (**Fig. 1**). Visual analysis of PSG recordings were performed by a trained sleep and movement disorder expert (PLR) according to standard criteria [25], taking into account previously published recommendations and suggestions for sleep scoring in PD [2, 29]. VPSG parameters (**Table 2**) for every patient were computed as mean over the two nights.

Clinical classification of patients with vs. without REM sleep behavior disorder

RBD diagnosis was established based on the VPSG recordings from two consecutive nocturnal recordings to improve diagnostic power [30], and the medical history of each patient. The presence or absence of RBD was established according to standard criteria [2]. Concretely, sustained (tonic) and excessive transient (phasic) muscular activity of REM sleep without atonia (RSWA) were defined according to the international scoring rules [25] : sustained muscle activity was defined when the amplitude of chin EMG was greater than its minimum amplitude in NREM sleep for at least 50% of a 30-s epoch. Excessive transient muscular activity was scored on 3-s mini-epochs as a 0.1 to 5-s in duration and fourfold in amplitude increase as the background chin EMG tone in REM sleep. To have a more robust categorization, the presence or absence of RBD in every individual patient was established based on the video-PSG recordings of the two nights for each patient, and considering the recent guidelines from the International RBD Study Group [31] as follows: a) chin and/or bilateral flexor digitorum superficialis EMG showing tonic or phasic activity as defined above during a REM sleep period of 5 minutes or more in at least one of the two VPSGs and no less than a total of 10 minutes in the two VPSGs; b) video/audio recording captured the presence of movements during REM sleep which were not related to an arousal, c) among these REM sleep-related movements **documented by the video recording**, at least one was of a clear-cut "RBD episode", i.e. a complex motor event and/or vocalization that could be interpreted as related to dream enactment; d) **history of complex behaviors presumed to occur during REM sleep based on the clinical history of dream enactment**[2]. "RBD" was defined when all the conditions a), b) and d) were satisfied, i.e. (a+b+c+d) or (a+b+d). Patients were labelled as "No-RBD" if neither the conditions a), c) and d) were met. The patients in whom the above-mentioned conditions showed different combinations were excluded, as a diagnosis of "RBD" vs. "no-RBD" could not be considered clinically reliable in these cases. To perform this classification, all the VPSG recordings where carefully examined by a senior neurologist expert in sleep medicine and movement disorders (PLR), and the audio/video tracks in REM sleep periods were integrally inspected, and all the movements and vocalizations were categorized according to the International RBD Study Group guidelines [31]. This categorization is detailed in Supplementary **Table 1**. If only one VPSG was available, the labelling was established based on that one only. Sleep-related respiratory events and periodic limb movements were scored and accounted for (**Table 2**).

We used the STARD checklist when writing our report [32].

Actigraphic data processing

Pre-processing and features extraction

Tri-axial accelerometer signals were segmented for each night, which was defined as the periods of low illuminance (<200 lux) minus 10 minutes at the beginning and the end. Tri-axial signals during these low-illuminance periods were then combined into a single magnitude vector $||a|| = (a_x{}^2, a_y{}^2, a_z{}^2)^{1/2}$, high-pass filtered ($4^{th}$-order Butterworth, cut-off frequency of 0.1Hz), and used to compute features about movement patterns. These features accounted for both (i) the characteristics of isolated, single movement episodes, as well as (ii) global movement patterns over the course of each night (**Fig. 2A,B**).

Movement episodes were identified through thresholding of the acceleration magnitude (threshold = 1*std). We ensured that this value was never below 0.1. Consecutive episodes that were not spaced by at least 1 second were merged into a unique movement event. Each episode was then parameterized by quantifying its duration (short: ≤2s, medium: >2s & ≤10s, long: >10s), magnitude (low: ≤3*movement threshold, high: >3*movement threshold), elapsed time since the previous event, and time to the next (close/clustered: ≤10s, medium: >10s & ≤60s, far/scattered: >60s).

To capture global movement patterns, we additionally computed the rate of activity, defined as the percentage of activity with magnitudes above the predefined threshold within a sliding window (length = 60 seconds, step = 1ms). This activity rate conveys the overall amount of movement throughout the night.

We then computed a series of statistical metrics for each feature such as mean, standard deviation, skewness or kurtosis.

Overall, twenty-nine features were extracted for each night recording (**Supplementary Table 2** and **Fig. 2B**). To verify the degree of separability (RBD vs no-RBD patients) captured by the extracted features, we further computed principal component (PC) analysis on this 29-dimensional feature representation.

Data were processed using Python v3.8. scikit-learn v0.17.2, and scipy v1.5.2.

Classifier training, testing, and validation

We tested several machine learning classification algorithms (linear discriminant analysis; support vector machine; logistic regression; nearest neighbor; random forest) and compared their performance for discriminating patients with or without RBD.

Prior to model building, a feature selection step was run to reduce the dimensionality of the feature space. Redundant features were first removed if they were not significantly correlated to the subject group (Spearman's, $p>0.05$). Least absolute shrinkage and selection operator (LASSO) regularization was then applied over the retained features: A ranking table was deducted from the subset of features withheld by each LASSO model, computed over 4-fold cross-validation (CV) with 10 repetitions and increasing shrinkage regularization parameter. Features were ranked based on the percentage of times they were selected by a model. Features selected by less than 10% of the models were discarded.

Classifiers were first built (trained and validated) on the data collected during in-lab recordings (RBD N=18, no-RBD N=8), from which we identified the best model type and the subset of features to be used for subsequent home recordings. The ability of models to avoid overfitting was determined using a 4-fold CV with class stratification across folds. CV was repeated 100 times to reduce bias in data splitting. No test set was defined. We then compared models built from data recorded from either the more affected, less affected, or dominant arm, as well as both arms. In 50% of the patients the dominant arm was the more affected arm.

For home recordings of PD patients, classifiers were trained on data from 14 night acquired in six subjects (N=3 RBD and N=3 no-RBD) and validated on all remaining ones (N=20), with 100-time repetition to reduce bias in patient selection. Wrist acceleration signals recorded throughout the entire night were used, regardless of illuminance. Classification performance was evaluated in terms of accuracy, sensitivity, and specificity. For the home recordings, a receiver operating characteristic (ROC) curve was additionally computed to observe classification performance depending on the class probability threshold. We then tested the performance of this approach on a control group of non-PD patients from everyday clinical practice (N = 18), who underwent wrist actigraphy for their routine workout for insomnia disorder [23].

In addition, we also trained and validated the accuracy of the classifiers (4-fold CV with class stratification across folds) when pooling all no-RBD patients together (N=26), regardless of whether they had PD or not. This allowed to evaluate the performance of the decoder even in the presence of larger variance in the no-RBD cohort.

Statistical analysis

Differences in population demographics and VPSG parameters were analyzed using the Mann-Whitney U Test, except categorical differences which were investigated using a Chi-squared ($\chi 2$) test. The contribution of individual features to help discriminate between RBD and no-RBD patients was evaluated by relating each feature score to the corresponding patient label. Significance was analyzed using linear mixed-effects models, with individuals as random effects (to control for repeated measurements per subject). Homoscedasticity was apparent for all models. Comparisons in performance between machine learning models were evaluated using the Mann-Whitney U Test; all

results were corrected for multiple comparisons by means of Tukey-Kramer's correction. All data are reported as mean values ± standard deviation (SD). Stars *,**,*** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively.

RESULTS

Patients' population

Twenty-seven PD patients were enrolled in the study. 18 patients were labelled as RBD and eight as no-RDB. One subject was excluded since one of their VPSG recordings was lost, and during the remaining one, the EMG showed REM sleep without atonia, but neither RBD episodes were observed at the audio/video recording, nor history of dream enactment was reported. **Supplementary Table 1** reports each patient's labelling (RBD vs. no-RBD) and the classification procedure. Twelve patients were diagnosed as RBD according to the above-mentioned criteria and meeting (a+b+c+d) conditions, and 6 satisfying (a+b+d) conditions. Demographic and clinical characteristics of PD patients are reported in **Table 1**. **Table 2** reports the video-polysomnographic parameters. PD patients in the two groups did not differ in terms of respiratory disturbance, periodic limb movements in sleep, or sleep fragmentation.

Eighteen subjects with insomnia disorder were recruited as non-PD controls. Their demographic and clinical characteristics are summarized in **Table 1**. Four of them were suspected to have comorbid sleep disordered breathing, which was confirmed by polysomnography (N=2 patients) or polygraphy (N=2). Apnea-Hypopnea Index (AHI) was 27.3 ± 22.5 SD. None of the two patients undergoing polysomnography showed RSWA. Five patients were diagnosed with comorbid circadian rhythm sleep/wake disorder, and two with restless legs syndrome.

Clinical validation of RBDAct methodology

Extraction of features describing RBD movements and behaviors

We first computed mathematical features that captured nocturnal movement patterns from the acceleration signals. We specifically aimed to account for both (i) the characteristics of single, isolated movement episodes, and (ii) global movement patterns over the course of each night. Overall, twenty-nine features were extracted, for each night **(Fig. 3A** and **Supplementary Table 2**). These were then matched with the corresponding clinical label (RBD vs no-RBD) provided by the clinical expert for training the algorithms.

To verify the capacity of the identified features to capture key differences between RBD and no-RBD patients, we projected the computed 29-dimensional parameterization into a low-dimensional space using PC analysis (**Fig. 3A**). The first 3 PCs explained 79.7% of the overall variance (PC1: 51.3%, PC2: 14.9%; PC3: 13.5%), and highlighted clear differences in space between the two groups. PC1 specifically segregated patients based on the characteristics of movement episodes, based on their duration and magnitude. A closer analysis of the factor loadings of PC1 emphasized that RBD patients exhibited predominantly short, yet high-magnitude movement episodes that were scattered throughout the night, as reflected by the lower mean activity rate and lower percentage of clustered movements (**Fig. 3B**). Additionally, overall nocturnal activity was higher in RBD than no-RBD patients.

We then identified the most meaningful features for classification. A feature selection step was run to extract the ones that maximized the separability between groups. All selected features (N=12) exhibited (i) a high correlation to the patient group (> 10%), (ii) a high occurrence in LASSO regression (> 10%), and (iii) low inter-feature correlation (**Fig. 3C**). As anticipated by the PC analysis, this set of features confirmed that group separability was based on the amount of motor activity throughout the entire night, as well as episode duration and magnitude.

In-lab RBDAct classification performance

To automatically discriminate RBD patients using the selected features, we compared the performance of different classification algorithms. All algorithms consistently yielded a high prediction accuracy (mean performance 89.6%), based on the actigraphic recordings acquired during the two nights spent by the patient at the sleep lab. The best performance was achieved by a support vector machine (SVM) model (92.9 ± 8.16% accuracy, 94.9 ± 7.4% sensitivity, 92.7 ± 13.8% specificity; **Fig. 3D**). This model was then retained as the most suitable algorithm to subsequently test home recordings.

We additionally explored if sensor placement had an impact on the features' ability to capture RBD patterns. We compared the performance of models when the wrist actigraph was worn on the (i) more affected side, (ii) less affected side, (iii) dominant side or (iv) both arms. We only considered patients who exhibited asymmetric motor deficits and wore actigraphic sensors on both arms (N=16 RDB, N=5 no-RBD). Maximum performance was systematically obtained using classifiers that were built on data from the more affected arm, as compared to using the dominant or less affected arm (**Fig. 4**). Placing sensors on both wrists did not improve classification performance.

RBDAct performance in home environments

We then tested RBDAct at home. All the patients wore the actigraph during the whole duration of the study (adherence = 100%).

We run our SVM algorithm using the selected features on a 2-week home recording set (**Fig. 5A**). We computed the classification accuracy for each individual night (**Fig. 5B**) and derived a diagnosis from the 2-week probability average to account for daily variability in spontaneous occurrence of RBD movements that would affect classification outcome (**Fig. 5C**). Setting a classification threshold between 0.5 and 0.6 revealed an accuracy of 100% after 7 nights. Progressively increasing the number of nights from 7 to 14, accuracy remained stable between 96 and 100%

We then tested this decoder in the control group of non-PD patients with insomnia disorder. Our results confirmed that 17 out of the 18 patients were correctly classified based on the 14-night average probability (mean probability p = 0.21 +/- 0.1 SD) (**Fig 5C**). Only one participant had an average probability of 0.71 (>0.5) and was thus incorrectly classified as "RBD".

We also verified the classification performance when pooling together all "no-RBD" patients in a single group (regardless of whether they were patients with PD or non-PD with other sleep disorders). Results were consistent with our previous observations: only 3 patients out of 44 were incorrectly classified based on the 14-night average probability, all of them belonging to the "no-RBD" group (2 PD patients, and 1 control). (Fig 5E)

DISCUSSION

We developed a novel screening tool, termed RBDAct, to automatically identify RBD at home in patients with mild to moderate PD. We first identified features that characterized differences in nocturnal movements and behaviors in RBD vs. no-RBD patients from actigraphic recordings. We then trained various machine learning classification algorithms using in-lab actigraphic data acquired in parallel to VPSG. Classification proved to be highly accurate (92.9 ± 8.16%). Finally, we tested the performance of the best algorithm on a 14-night actigraphic home recording. This out-of-lab validation reached an accuracy of 100% across patients. When tested in an independent validation cohort of patients with other sleep conditions, 17 out of 18 patients were correctly classified based on the 14-night average. Only one participant had an average probability of 0.71 (>0.5) and was thus incorrectly classified as "RBD".

Actigraphic features robustly capture RBD movements and behaviors

RBDAct relied exclusively on accelerometer signals to detect movements and behaviors characteristic of RBD. These have been reported to be qualitatively different from the movements during wakefulness, and particularly during arousals and awakenings. RBD movements were reported to be faster, more abrupt, jerky, and violent, both when observed in VPSG or by patients' bedpartners [14]. These observations provided the ground for using acceleration as a marker of RBD among the full range of nocturnal movements. Our automated approach confirms these differences from an objective, quantitative standpoint.

Both global night activity patterns, and isolated movement episodes were found to be critical to discriminate between RBD and no-RBD patients, regardless of the analytical methodology employed (i.e. PCA or feature selection algorithms). Features related to global night activity underscored that RBD patients were more active overall, which is in line with VPSG observations [30, 33, 34], and that they exhibited movements that were scattered in time over the course of the night. Instead, patients without RBD moved less frequently and, if they did, their movements were long-lasting and clustered in concise periods of the night. Features related to isolated movement episodes showed that RBD patients exhibit predominantly short, high-magnitude movements compared to no-RBD patients.

From a clinical standpoint, RBD movements and behaviors are expected to cluster intermittently, in correspondence to REM sleep periods. Sleep destructuring in PD [35, 36], with REM sleep exhibiting a non-nychthemeral distribution, **or the presence of 'covert REM sleep'** [37] might explain why RBD movements detected by means of actigraphy were found to be spread over the course of the night. **RBD is as a hallmark of a phenotype of PD that induces a more profound neurodegeneration encompassing the brainstem, where sleep is regulated [38, 39]. As such, on top of motor dysregulation during REM sleep, patients with RBD may exhibit motor dysregulation also encompassing NREM sleep.**

Regardless of cross-patient differences, all tested classification algorithms systematically achieved high performances, confirming the robustness of the identified features to capture key aspects of RBD.-Similar performance was achieved during home recordings, both in patients with PD and in control patients with other sleep conditions (insomnia, circadian rhythm sleep/wake disorder, sleep disordered breathing, and restless legs syndrome), emphasizing the stability of the procedure on multiple observations from the same subject and across symptomatic manifestations.

Relevance of the number and location of actigraphic sensors

Maximal classification performance was achieved on average when the sensor was placed on the more affected arm, as compared to the less affected side or the dominant side. This observation suggested that abnormal movements of RBD may be more pronounced on the most affected hemibody. While this may not apply to all individual patients, our experience suggests that the most appropriate *a-priori* placement should be on the most affected arm.

Using two sensors (one per wrist) did not improve the ability to discriminate between RBD vs. no-RBD patients. In some cases, it even worsened prediction accuracy. This suggests that movements of the less affected arm are "less abnormal", thus reducing the separability between RBD and no-RBD measurements. These observations have compelling practical implications: the ability to restrict recordings to one arm simplifies the setup, increasing comfort and decreasing cost. It certainly accounts for the 100% adherence achieved during home recordings.

Relevance of the number of nocturnal recordings

Combining measurements from multiple nights proved to be essential to ensure an accurate identification of RBD. In this study, information from VPSG recordings from two nights was necessary to confirm or rule out RBD diagnosis, in a few patients.

An average accuracy of 100% was reached after 7 consecutive nights of actigraphic home recordings. It remained stable between 96-100% when accounting for subsequent nights. Based on these results, we recommend that at least one week of actigraphy data be collected to maximize diagnostic accuracy.

Limitations and future improvements

Considering the relatively small cohort of patients included in this study, the generalization of our approach for widespread clinical use requires further validations. Our algorithms were trained only on patients with RBD that was secondary to mild or moderate PD. They were then tested in the same patients (home recordings) and in a control group of non-PD patients with insomnia, either isolated or associated to sleep disordered breathing, restless legs syndrome or circadian rhythm sleep/wake disorder. We did not include neither patients with RBD secondary to disorders other than PD, nor patients with isolated RBD.

Similarly, RBDAct did not account for sleep stages in the classification pipeline. Performance may improve by including information about REM and NREM periods. It may be necessary to account for sleep fragmentation and disruption in PD and for the fact that RBD movements may not be exclusively restricted to REM phases, but may also appear at NREM/REM transitions during "covert REM sleep" [37] or during "undifferentiated" sleep[36]. RBDAct is biased towards identifying patients with RBD characterized by phasic loss of muscle atonia, as only phasic activity can be detected by accelerometers. This is nevertheless more clinically meaningful than tonic RSWA in patient management, to prevent consequences such as injuries to patients or bedpartners. The small size and limited representativeness of the control group implies that RBDAct may indeed lead to false positives. This applies in particular to the capacity to discriminate RBD movements from other sleep-related movements and behaviors, such as RBD-like movements observed on respiratory arousals [40] or in other parasomnias, restless legs syndrome or sleep-related seizures, for which this methodology still need to be appropriately tested and fine-tuned. Considering that RBDAct is meant to provide a first screening step to guide further in-depth clinical evaluations, such as second-level VPSG, our methodology is optimized to ensure that false negatives are prevented, even at the expense of some false positives.

Finally, not all non-PD control patients with insomnia disorder systematically underwent a full VPSG. This might have resulted in the inclusion of false negatives. Nevertheless, the selection bias remains very limited considering the low prevalence of RBD in the general population.

CONCLUSION

RBDAct is an innovative technological solution to automatically detect RBD in PD patients. Considering the simplicity of manipulation and affordable price of actigraphy, our approach paves the way for widespread screening of large numbers of patients in ecological environments, both for clinical and research purposes.

Replacing in-lab VPSG with home recordings holds important implications for patients exhibiting severe motor difficulties or dementia, for whom in-lab VPSG can be complex and bothersome. Its potential may also be meaningful for patients who do not have a bed partner. In research, RBDAct would eventually permit large-scale screening and profiling of PD patients during clinical trials. There is a potential for rapid deployment within commercially available technologies, with the advantage of being an automated procedure that is simple to interpret.

Further studies are needed to evaluate the applicability of our methodology. The first step will be to train and test it in larger, well-profiled cohorts of patients with RBD, such as patients with isolated RBD, RBD secondary to other synucleinopathies, to narcolepsy, or acute, non-degenerative RBD. This methodology should then be tested in other patients with sleep disorders, for discriminating RBD from other sleep-related behaviors, such as NREM parasomnia,

nocturnal epilepsy, arousals from phasic respiratory events. Finally, broader applicability needs to be evaluated in a large cohort of subjects from the general population.

Future directions will also include leveraging RBDAct to assess the variability of RBD-related movements and behaviors over time, within and across patients. This would allow our methodology to become a quantitative marker of abnormal sleep-related movements. It could then be employed to adapt symptomatic treatments, or to monitor the progression of RBD and its response to neuro-protective or disease-modifying medications.

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Author contributions

PLR, FR, AP, and EMM contributed to the conception and design of the study; PLR, FR, and SS contributed to the acquisition and analysis of data; PLR, FR, EMM, AP and SS contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors have no potential conflicts of interest to report.

Onera Health had no role in funding neither in providing direct or indirect support of any kind. FR worked in this project outside his paid working time by Onera Health, and without employing resources from his employer. No intellectual property, commercial interest or use of the algorithms will be exploited by the company. Onera health did not have any access to the data, nor did they contribute to the preparation of the manuscript.

No entity with which the authors are affiliated will have direct or indirect benefits from this study.

Data availability

Data are available with a granted proposal upon reasonable request.

FIGURES AND CAPTIONS

Figure 1 | Experimental setup for in-lab recordings and study design. Video-polysomnography (VPSG) was recorded concurrently to actigraphy (1). All VPSG signals were displayed (2a) and processed by a clinical expert (3a) to perform RBD diagnosis following a standard manual approach (4). In parallel, actigraphic signals (2b) were processed using machine learning algorithms (3b) to generate an automatic diagnosis of RBD. The study timeline displays the chronological series of recordings performed for each patient, which combined both home and in-clinic evaluations.

Figure 2 | Data processing methodology and feature extraction. a, The sleeping period was derived using a light sensor (top), aligned with movement wrist actigraphy recordings (bottom). The night period considered for analyses is shadowed in grey. **b,** Features of nocturnal behavior were extracted from single movement episodes (top), which characterized behavior at well-defined isolated times throughout the night, and global movement patterns (bottom).

Figure 3 | Features capturing RBD movements and behaviors. a, Representation of each patient in a low-dimensional feature space (principal components PC1 to PC3). RBD patients indicated in red, and no-RBD patients in cyan. The contribution of each individual feature highlights the movement and behaviors that are most meaningful along PC1. Features outlined in green correspond to those shown in panel b. **b,** Barplots showing group-level differences between RBD and no-RBD patients in gait features identified in a. **c,** A feature selection algorithm identified the most discriminant features between groups using Spearman's correlation and LASSO regression. **d,** Classification accuracy for the five machine learning algorithms implemented and confusion matrix for the better performing one (SVM). LDA: linear discriminant analysis; SVM: support vector machine; LR: logistic regression; NN: nearest neighbor; RF: random forest.

Figure 4 | Comparison of classification performance depending on actigraphy sensor position. All algorithms systematically achieved better accuracies when sensors were worn on the most affected side. LDA: linear discriminant analysis; SVM: support vector machine; LR: logistic regression; NN: nearest neighbor; RF: random forest.

Figure 5 | Classification performance during home recordings. **a,** Heatmap of classification probabilities per patient and night (left), and mean probability over the 14-night period aligned to the corresponding clinical diagnosis (right). Probability values range from 0 (cyan, no-RBD) to 1 (red, RBD). **b,** ROC curve to identify the classification threshold (between 0 and 1) that best discriminates RBD vs no-RBD patients across the 14 night period. A threshold of 0.5 was identified as providing the best results. **c,** Changes in classification accuracy when accounting for multiple consecutive nights. Using 7 nights or more lead to performances above 96.15% across patients (threshold = 0.5). d, Same representation as in (a) when testing the previous decoder in N=18 control patients (non-PD, insomnia disorder). e, Pie charts and cross-validation accuracy when pooling together all no-RBD participants together (N=26), regardless of whether they had PD or not.

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Table 1 | Patient's demographic and clinical characteristics.

Characteristic	PD RBD (N=18)	PD no-RBD (N=8)	Difference p-value[1]	Non-PD controls (N=18)
Age (year)	69.9±8.2	63.8±13.9	0.29	52.7±15.3
Sex (M/F)	15/3	4/4	0.07[2]	12/6
Headedness (score)	74.2±34.9	80.6±39.7	0.29	N/A
More affected side (right/left/symmetrical)	7/9/2	4/2/2	0.43	N/A
MDS-UPDRS total score	50.9±23.1	46.6±15.4	0.59	N/A
part I	8.8±5.1	10.2±4.8	0.48	N/A
part II	9.7±6.2	10.1±4.3	0.65	N/A
part III (on)	29.8±14	25.6±12.7	0.54	N/A
part IV	2.6±2.8	0.6±1.2	0.07	N/A
Hoehn & Yahr stage	2.0±0.4	1.9±0.4	0.44	N/A
Disease duration (year)	7.4±5.9	4.9±4.9	0.26	N/A
Presence of motor fluctuations (yes/no)	1/17	1/7	0.53[2]	N/A
Presence of dyskinesias (yes/no)	10/8	2/6	0.14[2]	N/A
Medications				
levodopa daily equivalent dose (mg)	589.7±275.6	655.3±338.8	0.78	0
benzodiazepines (yes/no)	5/13	1/7	0.39[2]	5/13
Z-drugs (yes/no)	0/16	0/7		2/16
melatonin (yes/no)	0/16	0/16		3/15
antidepressants (yes/no)	7/11	2/6	0.93[2]	2/16
antipsychotics (yes/no)	1/15	0/7		1/17
Cumulative illness rating scale - revised (score)	12.9±3.6	21.0±3.6	0.62	5.6±4.5
Cumulative illness rating scale - musculoskeletal (score)	0.9±0.8	1.4±1.1	0.25	0.3±0.6
Parkinson's disease sleep scale (score)	11.8±7.7	14.5±9.8	0.43	N/A
Pittsburgh sleep quality index (score)	5.7±2.7	6.0±2.1	0.75	N/A
Epworth sleepiness scale (score)	6/12	4/4	0.42[2]	N/A

Legend

Clinical scores taken as the average per subject over the entire study. Data are reported as mean ± SD or proportions. [1]Mann-Whitney U Test; [2]Chi-squared test.

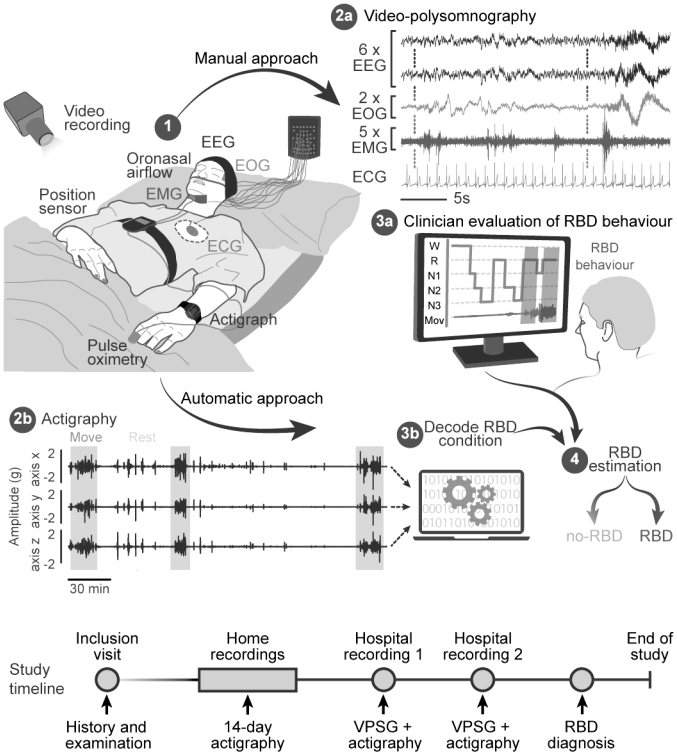
N/A: Information not applicable or not available.

Table 2 | Video-polysomnographic parameters.

Characteristic	**PD RBD (N=16)**	**PD no-RBD (N=7)**	**Difference p-value[1]**
Total sleep time (min)	297.5±69.3	316.0±66.0	0.56
Sleep efficiency (%)	79.7±7.1	75.8±14.5	0.80
Sleep latency (min)	12.0±8.2	9.5±8.2	0.52
REM sleep latency (min)	177.5±61.8	201.7±132.0	0.74
Stage N1 (min)	55.1±27.0	70.5±31.6	0.29
Stage N2 (min)	159.2±48.9	177.2±67.4	0.27
Stage N3 (min)	60.8±23.0	37.0±16.7	0.02*
REM (min)	22.5±17.0	25.6±14.9	0.56
Wake after sleep onset (min)	59.5±24.1	94.3±66.5	0.19
Arousal index	35.6±25.3	41.8±19.6	0.15
Sleep Fragmentation index	33.9±11.4	43.1±12.9	0.09
Apnea-Hypopnea index	18.1±14.2	16.2±18.9	0.70
Apnea-Hypopnea index in REM sleep	23.2±19.1	8.5±16.9	0.03*
Respiratory disturbance index	30.2±26.7	33.8±25.9	0.81
Periodic limb movement in sleep index	10.5±22.4	0.9±1.5	0.71

Legend

Video-polysomnographic parameters taken as the average per subject over the entire study. Data are reported as mean ± SD. [1]Mann-Whitney U Test; *$P < 0.05$.



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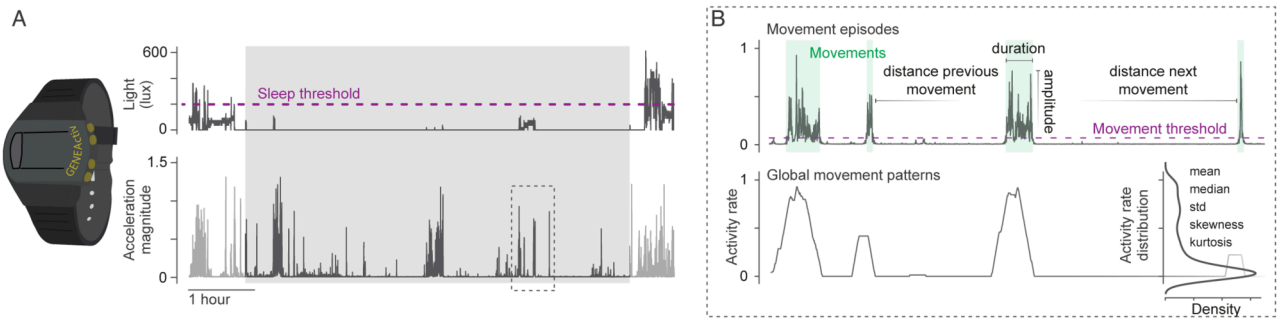

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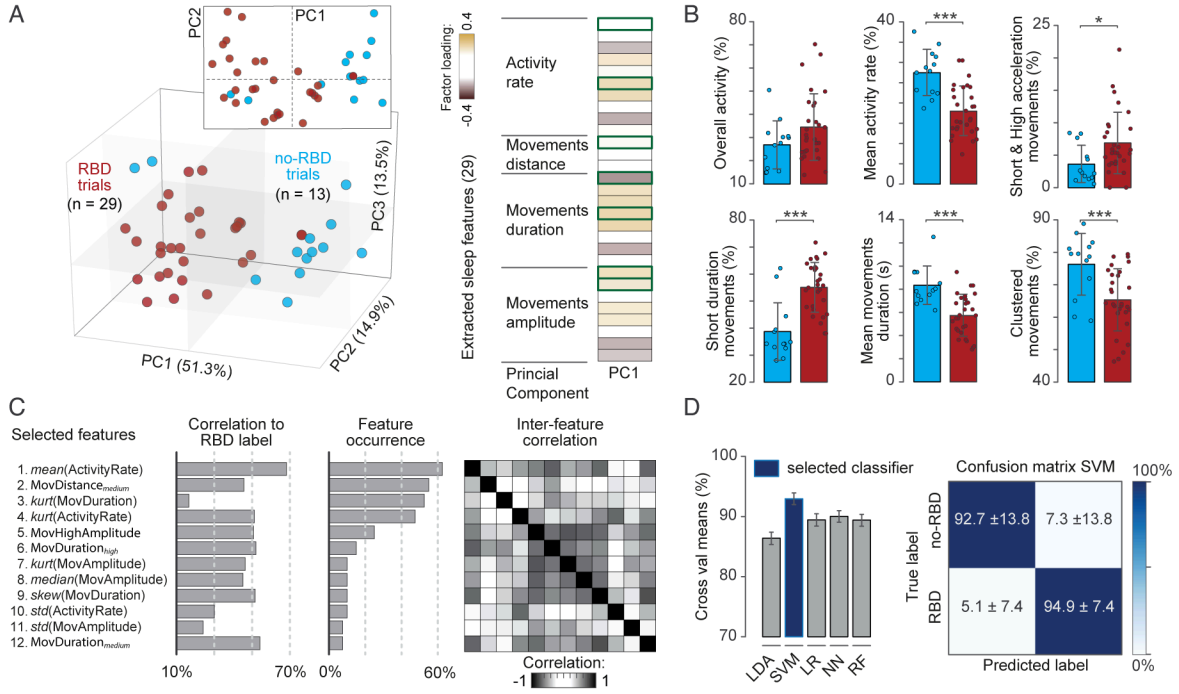

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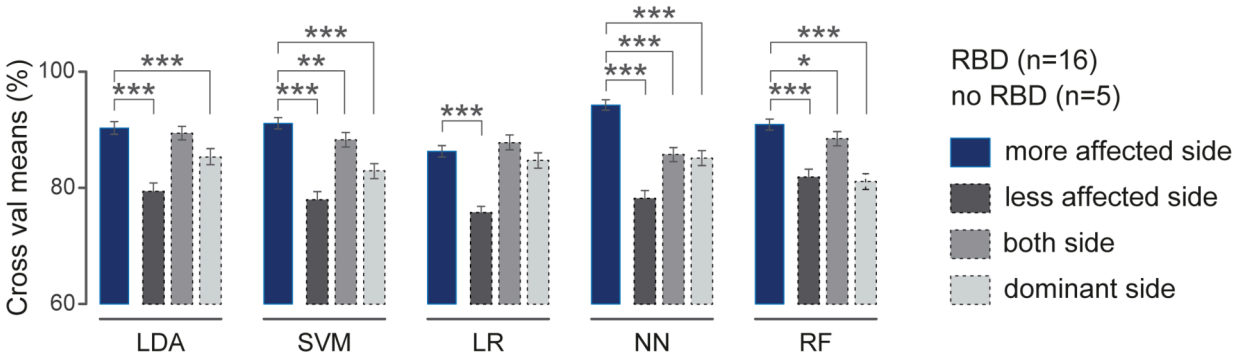

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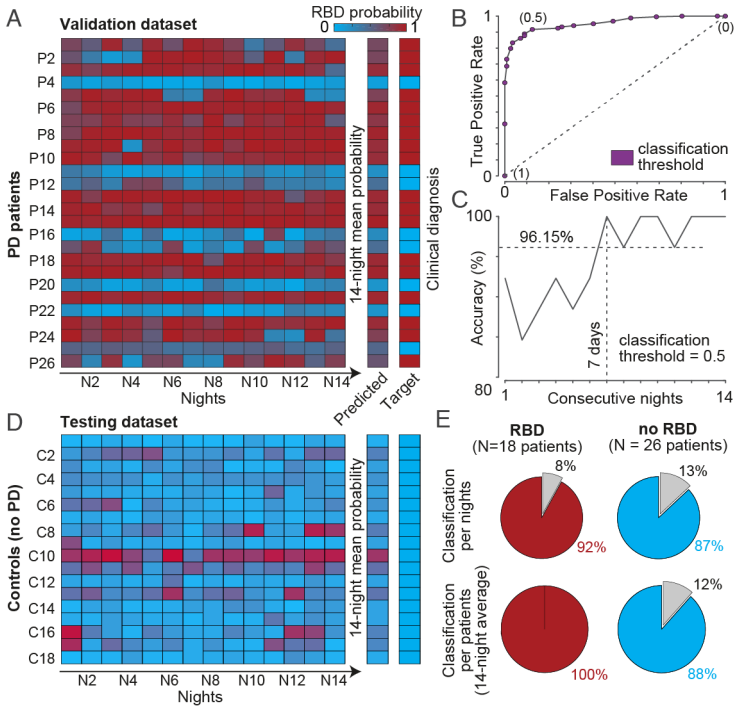

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