REM Sleep Behaviour Disorder, a narrative review from a technological perspective

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Abstract

Study objectives: Isolated REM sleep behaviour disorder (iRBD) is a parasomnia characterized by dream enactment. It represents a prodromal state of alpha-synucleinopathies, like Parkinson's disease. In recent years, biomarkers of increased risk of phenoconversion from iRBD to overt alpha-synucleinopathies have been identified. Currently, diagnosis and monitoring rely on subjective reports and polysomnography performed in the sleep lab, which is limited in availability and cost intensive. Wearable technologies and computerized algorithms may provide comfortable and cost-efficient means to not only improve the identification of iRBD patients but also to monitor risk factors of phenoconversion. In this work, we review studies using these technologies to identify iRBD or monitor phenoconversion biomarkers.

Methods: A review of articles published until 31st May 2022 using the Medline database was performed. We included only papers in which subjects with RBD were part of the study population. The selected papers were divided into four sessions: actigraphy, gait analysis systems, computerized algorithms, and novel technologies.

Results: 25 articles were included in the review. Actigraphy, wearable accelerometers, pressure mats, smartphones, tablets, and algorithms based on polysomnography signals were used to identify RBD and monitor the phenoconversion. Rest-activity patterns, core body temperature, gait, and sleep parameters were able to identify the different stages of the disease.

Conclusions: These tools may complement current diagnostic systems in the future, providing objective ambulatory data obtained comfortably and inexpensively. Consequently, screening for iRBD and follow-up will be more accessible for the concerned patient cohort.

Keywords: REM sleep behaviour disorder; sleep movement disorders; neurodegenerative diseases; Parkinson's disease; digital biomarkers; wearable sensors; nearable sensors; home monitoring; machine learning.

Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is the most common form of REM-parasomnias. The clinical picture consists of vivid dreaming and enactment of dream content, resulting in injuries to patients and their bed partners [1]. RBD can occur in neurodegenerative diseases, especially α-synucleinopathies like Parkinson's disease (PD), then called secondary RBD [2]. In the absence of arguments for secondary aetiology, RBD is called isolated (isolated RBD, iRBD). The international classification of sleep disorders third edition (ICSD-3) requires the presence of REM sleep without atonia (RSWA) in polysomnography (PSG) for the diagnosis of RBD. The ICSD-3 suggests using the cut-off values for RSWA quantification as proposed by the Sleep Innsbruck Barcelona group (SINBAR) [3]. The same criteria are part of the diagnostic recommendations of the international RBD study group [4].

IRBD has an all-over prevalence of 0.38% [5]. In older subjects (>60 years), it rises to 2%, with 80% of the RBD patients being male [6]. These numbers may be underestimated as most studies were performed without video-PSG. Patients with iRBD are at high risk of converting to overt α-synucleinopathies (6.3% per year, 73.5% after 12 years) [7]. Therefore, iRBD is now considered a prodromal stage of α-synucleinopathies [8]. Other sleep-wake disturbances such as insomnia, restless legs syndrome (RLS), periodic limb movements (PLMS), and sleep apnoea syndrome (SAS) are frequent in α-synucleinopathies [9] [10].

Determination of biomarkers associated with a higher risk of conversion from iRBD to overt α-synucleinopathies will become crucial in the light of potential future disease-modifying neuroprotective therapeutics [11]. Previous studies identified several biomarkers associated with an increased risk of phenoconversion. A large multicentre study by Postuma et al. reports disease progression in several clinical domains (motor function, speech, colour vision and olfaction, cognition, and vegetative functions) [12]. For instance, quantitative motor tests using a Unified Parkinson's Disease Rating Scale (UPDRS-III) score > 4 identified prodromal parkinsonism with 88%

sensitivity and 94% specificity two years before diagnosis [13], even if UPDRS-III > 3 is considered a standard value in the elderly [14]. No individual or combined biomarker is currently validated to predict phenoconversion to overt α-synucleinopathies.

Information on sleep-wake disorders in iRBD patients originates from patients' reports and the observations of partners and caregivers, complemented by clinical examinations and hospital-based objective assessments. Considering that subjective reports are often prone to recall bias, not only in patients with cognitive impairment, the frequent lack of reliable third-party history, and the time-limited assessments by neurologists during single hospital visits, these measures can only provide limited or even inconsistent information.

In recent years, technological development has shown promising and reliable results in the use of actigraphy [15], wearable [16], and nearable [17] devices for sleep and motor disorders evaluation. Wearables have been used for several years to monitor biomarkers and validated in many studies [18]. Numerous studies have investigated the use of wearable devices in patients with PD to monitor motor and non-motor symptoms, such as gait, sleep-wake rhythm, and sleep [19]. In contrast, relatively few studies have been conducted with patients in the early stages of α-synucleinopathies like iRBD patients using wearables.

Previous review articles focused on objective and subjective measurements for the workup of suspected RBD [20] biomarkers of phenoconversion [21], with particular emphasis on brain imaging technologies [22]. To our knowledge, this is the first review focusing on novel technological approaches that are becoming very popular for monitoring the disease progression and identifying the RBD population. This review aims to overview studies that applied wearable and nearable technology in patients with RBD defining novel "digital" biomarkers. We will discuss the findings and applied technologies to conclude with an outlook on future functional development to improve the standard of care for patients with iRBD using novel methodologies.

Methods

For this narrative review, the articles were extracted by one author (O.G.) and evaluated by the other authors. A review of articles in English, published until 31st May 2022, using the Medline database, was performed. We used the search term “REM sleep behaviour disorder” to identify articles specific to patients with RBD. We included studies with idiopathic and secondary RBD, PSG-confirmed. The articles should contain an abstract. We included only original articles; case reports and editorials were excluded from the study. We used Web of Science to search for the topic: “REM sleep behaviour disorder” in combination with a second topic such as “actigraphy”, “wearable”, “sensors”, “technology”, “machine learning”, “deep learning”, and “automatic scoring”, or “home-monitoring”. We included only papers in which subjects with RBD were part of the study population. The review is divided into four sections according to the different technological approaches used (actigraphy, gait analysis, computerized algorithms, and novel technologies).

Results

The initial search identified 2040 records about RBD. The number was reduced to 76 by considering “RBD” in combination with the second argument. From this selection, only 25 studies were performed with patients with RBD and therefore have been included in this review. The selected studies differ based on whether they assess patients with isolated RBD or secondary RBD and differ in their purpose. In some cases, we find studies comparing healthy controls with iRBD and patients with neurodegenerative diseases to study phenoconversion. In other cases, authors compare patients with different sleep movement disorders to distinguish iRBD or secondary RBD from the others.

Actigraphy

Actigraphy represents the state-of-the-art for measuring sleep-wake rhythm in sleep medicine. Usually, in sleep clinics, the patient is given an actiwatch to wear at home for one to two weeks. Five studies that used actigraphy with patients with RBD are displayed in Table 1.

Louter et al. used actigraphy to identify RBD in PD patients. 22 patients with PD and no RBD and 23 patients with PD and RBD were included in the study. Using the number of wake bouts at night as a readout, actigraphy could identify patients with RBD with high specificity (95.5%) but low sensitivity (20.1%). The authors suggest that actigraphy might be combined with a sensitive method, such as questionnaires, to diagnose RBD in PD patients [23]. Filardi et al. used a non-parametric analysis of actigraphy to assess nocturnal and diurnal rest-activity features in 19 iRBD patients. These were compared to three control groups with different sleep movement disorders (20 RLS, 19 SAS, and 16 controls*). The relationship between nocturnal and diurnal motor activity intensity (I < O index) can distinguish iRBD from patients with other sleep movement disorders and healthy controls with similar sensitivity and specificity to visual actigraphy analysis performed by sleep experts [24]. However, combined with clinical information (including questionnaires screening for RBD), visual analysis outperformed quantitative analysis in identifying subjects with iRBD and distinguishing iRBD from other motor activities during sleep [25]. Thus, in combination with clinical information and iRBD screening questionnaires, non-parametric actigraphy analysis may significantly improve the accuracy and efficiency of screening and even maybe allow diagnosis of iRBD in the general population.

The last two studies in Table 1 used actigraphy to monitor sleep-wake rhythm as a putative biomarker of neurodegenerative disease progression. In a cross-sectional study, Liguori et al. compared 27 iRBD patients with 19 healthy controls for two weeks. They found a desynchronized rest-activity cycle (as represented by a lower relative amplitude) and significantly increased time in bed and sleep latency while sleep efficiency was reduced in iRBD patients [26]. Feng et al. compared

the rest-activity pattern of 44 secondary RBD patients with overt α-synucleinopathies (PD, DLB, MSA), 88 iRBD, and 44 controls for one week. In line with the previous results from [24] and [26], significant increases in probable napping behaviours, activity fragmentation, and physical inactivity during active periods from controls to iRBD to α-synucleinopathies were found in actigraphy recordings. The 88 patients with iRBD were longitudinally followed and monitored for two years. Within two years, 22 had converted to overt alpha-synucleinopathies. Comparing baseline actigraphy analysis of these converters to the 66 non-converts showed more probable napping features and, even after adjusting for napping, significantly less activity during the day [27]. This result suggests that increased daytime napping and decreased daytime activity may present a biomarker of disease progression and higher phenoconversion risk.

Gait Analysis

Gait disturbances are considered a significant daytime biomarker of phenoconversion [11]. Table 2 summarizes five studies that have used different techniques to monitor gait parameters in iRBD and secondary RBD patients.

All studies in Table 2 have identified specific gait parameters as biomarkers of neurodegeneration as a common outcome. Decreased gait velocity and cadence and increased stride variability in iRBD patients compared to healthy controls have been reported by monitoring gait in a free-condition environment using a tri-axial accelerometer [28]. However, gait analysis comparing 24 iRBD patients and 14 healthy controls with Zeno pressure sensor walkway did not find differences in step length and velocity. In contrast, iRBD patients showed greater gait asymmetry during fast-paced walking, and in the dual-task walking condition, step width variability was increased [29]. Deficits in dual-task gait have been reproduced in a later study by the same group in a paradigm using a foot pedal system with concomitant functional brain magnetic resonance imaging (MRI). Dual task-gait deficits

were associated with impaired cortico-striatal connectivity [30]. Finally, Ma et al. investigated subclinical gait changes as a prodromal symptom of PD in 31 iRBD using six wearable devices containing gyroscopes and accelerometers placed on the chest, wrists, ankles, and abdomen. They identified decreased trunk motion and increased step time before turning as prodromal symptoms of PD [31].

Interestingly, an earlier study conducted in 2010 by Benninger et al. on 26 patients with mild-to-moderate PD (13 with polysomnography confirmed and 13 with excluded RBD) and 20 age-matched healthy controls found no association of the presence of RBD with prevalence or severity of gait disturbances or postural impairment. Gait assessment on a treadmill and static and dynamic posturography was performed. Moreover, RBD was not associated with any particular motor phenotype [32]. This indicates that gait disturbances and RBD arise from the degeneration of different neuronal networks that may degenerate to various degrees independently. Thus, gait disturbances emerging in iRBD patients may indeed point toward disease progression due to the spreading of α-synuclein pathology. Further longitudinal studies are needed to investigate the emergence of gait disturbances in iRBD patients and evaluate their potential as biomarkers for phenoconversion. The availability of well-tolerated and comfortable wearable devices to evaluate gait will facilitate such investigations.

Computerized Algorithms

A new frontier of digital research in medical science is automated signal processing algorithms to understand patients' behaviours. In Table 3, we report eight studies that applied this technological approach to the gold standard of sleep evaluation, the PSG. Through the automated analysis of electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (ECG), and electrocardiogram (EOG), these studies identify not only RBD episodes but also new biomarkers for

neurodegeneration in α-synucleinopathies. Earlier studies by Christensen et al. reported that patients with RBD (patient number, n=30), either isolated or in the context of PD, had decreased sleep spindle density (SSD) compared to healthy controls (n=15) and PD patients not suffering from RBD (n=15), suggesting that SSD may be a biomarker for the presence of RBD [33]. Ruffini et al. used a deep learning approach with EEG spectrograms to train a neural network to classify patients with iRBD (n=121) compared to healthy controls (n=91). Fourteen of these patients with iRBD developed PD after two to four years. The algorithm classified iRBD, which converted to PD with 80% accuracy [34]. Research performed by Cooray et al. aims at developing algorithms to identify RBD based on a minimum set of signals that wearable devices can obtain at the patient's home. They developed an algorithm to detect iRBD in a fully automated analysis of PSG signals (EEG, EOG, and EMG), performed with an accuracy of 92% [35]. Their latest study demonstrated the algorithm's functionality without the cumbersome EEG [36].

Cesari et al. developed an algorithm to differentiate patients with different sleep movement disorders based on the analysis of the EMG signals. The algorithm distinguished iRBD patients (n=29) from patients with PLMD (n=36) with an accuracy of 70.8%. It performed best when both REM and NREM phases were considered, and movements caused by apnoea or awakening were not removed [37]. In a subsequent study, EEG and EOG signals were used for automatic macro (30s-epoch)- and micro (5s-epoch)-sleep stage scoring in a population of patients with PD, divided into three groups: 26 patients with secondary RBD, 54 patients without RBD, and 27 patients with REM behavioural events (RBE). RBE are defined as minor motor behaviours and vocalizations with a seemingly purposeful component occurring in REM sleep, but RSWA cut-off criteria for RBD diagnosis are not met. RBE have been proposed as prodromal RBD in PD patients. They found that micro-sleep instability may be a biomarker for the presence of RBD and progression from RBE to RBD in PD patients [38]. This finding is in line with an earlier study by Christensen et al. with an unsupervised, data-driven machine learning approach that identified a decrease in NREM3 duration and the inability to maintain the NREM and REM phases as potential early predictors of PD [39]. Finally,

Dijkstra et al. found that increased total, tonic, chin RSWA, and supine sleep position, extracted from the PSG report, are prodromal biomarkers of neurodegeneration, identified in PD patients (n=30) before the onset of parkinsonism and irrespective of the presence of RBD [40].

In conclusion, automated PSG computerized algorithm-based analysis can identify RBD with high accuracy, approaching visual analysis by sleep experts. Furthermore, several biomarkers of phenoconversion have been identified using PSG-derived data.

Novel Technologies

In Table 4, we report eight studies to summarize the approaches with the newest technologies used in recent years with RBD patients.

Lee et al. applied machine learning methods to diffusion tensor imaging (DTI) data. DTI is an MRI technique that uses anisotropic diffusion to estimate the central nervous system's axonal organization. The classifier, known as Support Vector Machine (SVM), using conventional DTI measures such as fractional anisotropy, mean, axial, and radial diffusivity, classified 20 iRBD patients from 20 healthy controls with an accuracy of 87.5% [41]. Waser et al. analysed the images of a 3D video camera (Microsoft Kinect v2 sensor) to distinguish iRBD (n=40) from patients with different sleep movement disorders (n=64). They found that minor leg jerks discriminated with the highest accuracy (90.4%) iRBD from other patients [42].

Several studies used smartphone-based technology to investigate speech and other physiological features as biomarkers for neurodegeneration. Postural tremor, rest tremor, and voice discriminated best between iRBD patients (n=104), PD patients (n=334), and controls (n=84) [43]. The capability of smartphone-based speech analysis to discriminate iRBD patients from PD patients and controls (n = 112 iRBD, 335 PD, and 92 controls, respectively) was confirmed by another study from the same group [44] as well as by the work of a different team [45]. Both studies yielded comparable results

based on the analysis of smartphone-recorded speech. IRBD patients could be discriminated from healthy controls with sensitivity and specificity of 60 – 70%. It did not matter if the patients performed a specific speech task [44] or if the spontaneous speech was analysed [45]. In the latter study, the duration of pause intervals and rate of speech timing was sufficiently sensitive to separate the groups significantly. These studies suggest that voice abnormalities may be considered a putative digital neurodegeneration biomarker.

Motor function abnormalities have been associated with an increased risk of phenoconversion [12]. Two recent studies published by Cochen De Cock et al. [46] and R. Krupička et al. [47] investigated finger tapping as a biomarker of neurodegeneration. Both included patients with iRBD, PD, and healthy controls. The first study used a tablet application to identify temporal distortions in the production and perception of rhythmic events in 21 patients with iRBD as early markers of phenoconversion. They found that iRBD and PD patients revealed impaired spontaneous rhythm production and poor rhythm perception compared to the 38 controls [46]. The second study explored whether finger tapping abnormalities, assessed with a 3D motion capture system, are already present in iRBD patients (n = 40) and found decreased finger tapping amplitude and velocity compared to healthy controls (n = 25), probably reflecting prodromal bradykinesia in iRBD patients [47].

Impairment of body temperature regulation has been described in PD patients [48]. Raupach et al. asked patients suffering from iRBD, PD with and without RBD, or dementia with Lewy bodies (DLB) (n = 52) and healthy controls (n = 10) to take an ingestible pill that transmits temperature data to monitor core body temperature (CBT) during the night. They found that CBT amplitude is significantly reduced in iRBD patients but not in PD patients without RBD [49]. These findings indicate a dysregulation of the circadian system and circadian thermoregulatory and, thus, their role as a potential early biomarker for iRBD and the ongoing neurodegenerative process.

Discussion

This paper reviewed studies conducted with wearable, contactless technologies, and computerized PSG signal analysis algorithms in RBD patients. These technologies were selected for their potential usefulness in assessing different aspects of the disorder.

Actigraphy, which contains an accelerometer and a light sensor, is critical for monitoring the disturbances that characterize RBD in a free-condition environment. While the accelerometer can measure gait dysfunction during the day and movements to potentially identify RBD occurrence at night, the light sensor can be used in combination with the accelerometer to monitor sleep-wake rhythm alterations. The inconsistency of primary gait parameters found across the reviewed studies can be partly attributed to the different methods of gait detection and to the intrinsic difficulties in recognizing the transition phase from iRBD to over alpha-synucleinopathies. The different expertise of the various centers may further contribute to the observed differences.

Considering the in-lab standard clinical assessment of the PSG, the development of computerized algorithms applied to PSG signals allows quantifying the RSWA, provides biomarkers that may not be accessible to visual analysis, improves diagnosis, and monitors disease progression. In the future, these algorithms can be adapted to signals generated by wearable devices, enabling the diagnosis of RBD and monitoring of phenoconversion biomarkers under real-world conditions.

Besides studies focusing on computerized algorithms, most of the other techniques mentioned in this review focus on detecting motor impairments as biomarkers of phenoconversion. However, since about half of iRBD patients phenoconvert to DLB, the development of screening tests for cognitive impairment focusing on attentional and executive performance will be important in the future. New technologies, such as smartphone and tablet apps, can bridge and supplement it, allowing the assessment of cognitive states. For example, personalized smartphone and tablet apps could monitor the cognitive level of patients longitudinally at risk of phenoconversion.

The studies selected for this review used the technologies mainly for two purposes: first, to identify RBD and discriminate it from other sleep movement disorders, and second, to identify and monitor biomarkers for phenoconversion in manifest alpha-synucleinopathies. According to these studies, I<O index (sensitivity of 63.2%, specificity of 89.1%) and wake bouts (specificity of 20.1%, sensitivity of 95.5%), both obtained by actigraphy, micro-sleep instability (sensitivity and specificity over 75%), obtained from EEG, and leg jerks (sensitivity of 97.5%, specificity of 85.9%), obtained from 3D camera recordings, were most accurate in identifying patients suffering from RBD. Further studies are needed to refine and simplify the analytic frameworks, to obtain high identification accuracy with lower patient burden and maximum cost efficiency. In addition to the already-known biomarkers of phenoconversion, many diagnostic features mentioned above may serve as digital biomarkers for an increased risk of neurodegeneration. Sleep spindle density (sensitivity of 84.7% and specificity of 84.5%); step time before turning (sensitivity of 39.7%, specificity of 82.8%); and gait velocity (sensitivity of 66.7, specificity of 60%) were markers that could discriminate the different stages of the disease. Figure 1 provides a schematic summary of the markers described in this literature review.

Finally, for patients with cognitive and motor impairments, long-term use of wearables for more than 2-3 days is difficult [50]. For this reason, the use of nearable devices such as pressure sensors mattresses [51], passive infrared sensors [52], and radars [53] represents a promising approach to obtaining an objective estimate of motor activity, circadian rhythm, and sleep parameters without disturbing the patient in their daily life and maybe evaluated further in the future. However, a critical aspect to consider for monitoring sleep disturbances in a free-condition environment is the presence of bedpartners. In particular, for contactless technologies, it is essential to identify the patients and distinguish them from the bedpartners before calculating sleep and movement parameters that have the potential to become digital markers.

In conclusion, wearable technology and novel analysis methods hold the potential to enable screening for RBD and monitoring of phenoconversion biomarkers in an accurate, efficient, and cost-effective way. RBD diagnosis and the phenoconversion risk assessment may reach maximum accuracy if combined with several technologies and analysis methods. Future studies are needed to determine the optimal combination of sensors, signal analysis methods, and biomarkers [54]. Wearable technology may support such longitudinal study designs by posing a minimal burden on the patients and enabling continuous monitoring of objective features at the patient's home.

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Figure Caption

Figure 1: Identification markers are used to discriminate RBD from other sleep movement disorders. Neurodegeneration markers are associated with a high risk of phenoconversion. A) Actigraphy. B) Wearable accelerometers and pressure walking mattresses. C) Computerized algorithms like automatic scoring and machine and deep learning approaches. D) Smartphones, tablets, 3D cameras, DTI, and ingestible capsule sensors.

Table 1: Actigraphy in patients with RBD

Authors	Study	Aims	Subjects	Type of sensors	Duration	Main Findings
Louter et al. 2014 [23]	Actigraphy as a diagnostic aid for RBD in PD	To compare actigraphy outcomes in PD patients with and without RBD.	22 PD - RBD 23 PD + RBD	Actiwatch AW4, Cambridge Neurotechnology Ltd, UK	8 nights	PD patients with RBD showed a significantly higher number of wake bouts compared to patients without RBD.
Filardi et al. 2020 [24]	Objective rest-activity cycle analysis by actigraphy identifies iRBD	To explore whether rest-activity measures can distinguish iRBD from patients with other movement sleep disorders and controls.	19 iRBD 20 RLS 19 SAS 16 Controls*	MicroMini Motionlogger - Ambulatory Monitoring, NY	2 weeks	Nocturnal and diurnal motor activity intensity index (I < O index**) distinguished iRBD patients from those with other pathological motor activity during sleep and controls with 89.1% specificity.
Stefani et al. 2018 [25]	Screening for iRBD: usefulness of actigraphy	To evaluate the utility of actigraphy in identifying patients with iRBD.	20 iRBD 20 RLS 20 SAS 10 RLS + SAS 20 Controls*	MicroMini Motionlogger - Ambulatory Monitoring, NY	2 weeks	Visual actigraphy analysis can identify subjects with iRBD and distinguish iRBD from other motor activities during sleep.
Liguori et al. 2020 [26]	Sleep–wake cycle dysregulation in iRBD	To evaluate the sleep–wake rhythm in patients with iRBD compared with healthy age-matched controls.	27 iRBD 19 HC	Actiwatch 2 - Philips Respironics	14 days	IRBD showed reduced relative amplitude and alteration of both sleep and wake compared with controls.
Feng et al. 2020 [27]	Rest-activity pattern alterations in iRBD	To investigate the differences in rest-activity patterns measured with actigraphy across different stages of α-synucleinopathies.	44 αSyn 44 non-RBD 88 iRBD 22 convertors 66 non-convertors	Actiwatch Spectrum Plus - Philips Respironics	7 days 2 years follow-up	Significant increases in probable napping behaviours, activity fragmentation, and physical inactivity during active periods across non-RBD and iRBD, to α-synucleinopathies. Convertors had significantly more probable napping features.

* Controls are intended for individuals with suspected sleep disturbance admitted to the sleep clinics but diagnosed with no sleep disturbances.

** I < O index is a 24-h measure that expresses the relation- ship between nocturnal and diurnal motor activity intensity

Table 2: Gait monitoring of patients with RBD

Authors	Study	Aims	Subjects	Type of sensors	Task	Main Findings
Del Din et al. 2019 [28]	Continuous real-world gait monitoring in iRBD	To investigate if real-world gait monitoring with wearables can detect early gait changes and discriminate individuals with iRBD from controls.	63 iRBD 34 Controls	Tri-axial accelerometer. (Axivity AX3, York, UK)	Walk in a real-world environment for 7 days with an accelerometer placed at the lower back.	Reduced gait velocity, variability, and rhythm.
Martens et al. 2019 [29]	Subtle gait and balance impairments occur in iRBD	To characterize gait and balance impairments in iRBD.	24 iRBD 14 HC	Pressure Mattress Zeno Walkway (Protokinetics, Havertown, PA)	1. Self-speed walking 2. Fast-speed walking 3.-5. Dual-task gait conditions	Significant differences between the two groups in fast-speed walking and dual-task gait conditions.
Martens et al. 2020 [30]	The neural signature of impaired dual tasking in iRBD	To determine the neural signature of dual-tasking deficits in iRBD using a validated gait paradigm.	24 iRBD 17 HC	MRI + VR** + Foot pedals Pressure Mattress Zeno Walkway (Protokinetics, Havertown, PA)	MRI scans as performing a dual-task VR gait paradigm using foot pedals. Single- and dual-task walking	Evidence of dual-task gait deficits such as greater mean step time in iRBD.
Ma et al. 2021 [31]	Detection of motor dysfunction with wearable sensors in iRBD	To investigate subclinical gait changes in iRBD as prodromal symptoms of PD.	31 iRBD 20 HC	6 wearable gyroscopes and accelerometers (APDM; Mobility Lab, Portland, OR, USA).	1. Self-speed walking 2. Fast-speed walking 3. Dual-task gait conditions	Decreased trunk motion and increased step time before turning may be possible prodromal symptoms of PD.

**Virtual reality (VR).

Table 3: Computerized algorithms for patients with RBD

Authors	Study	Aims	Subjects	Signals	Main Findings
Christensen et al. 2014 [33]	Decreased sleep spindle density in patients with iRBD and patients with PD	To determine whether SSD is a potential biomarker for PD.	15 PD + RBD 15 PD – RBD 15 iRBD 15 HC	PSG	IRBD and PD + RBD patients had a significantly lower SSD than the control group in N2, N3, and all NREM stages combined.
Ruffini et al. 2019 [34]	Deep Learning with EEG spectrograms in RBD	To classify subjects as PD or HC using a neural network trained with EEG spectrograms.	121 iRBD 91 HC 14 PD 13 DLB	EEG	Classification accuracy of 80% (±1%) in HC vs. PD-conversion. AUC* of 87% ((±1%).
Cooray et al. 2019 [35]	Detection of RBD by automated PSG analysis	To propose a fully automated framework for sleep staging and iRBD identification.	53 iRBD 53 HC	EEG EOG EMG	This study validates a tractable, fully automated, and sensitive pipeline for RBD identification that could be translated to wearable take-home technology.
Cooray et al. 2021 [36]	Proof of concept: Screening for RBD with a minimal set of sensors	To propose a fully automated framework for sleep staging and iRBD identification without cumbersome EEG.	50 iRBD 50 HC	ECG EOG EMG	The EOG and EMG combination provided the optimal minimalist, fully automated performance for sleep staging and an RBD detection with an accuracy of 90%
Cesari et al. 2019 [37]	Validation of a new data-driven automated algorithm for muscular activity detection in RBD	To validate a data-driven method for muscular activity detection to classify iRBD patients.	27 HC 29 iRBD 36 PLMD	EMG	71% accuracy in distinguishing HC, RBD, and PLMD patients. RBD patients can be better identified when both REM and NREM muscular activities are considered.
Cesari et al. 2021 [38]	A data-driven system to identify RBD and to predict its progression from the prodromal stage in PD	To investigate EEG, EOG, and micro-sleep abnormalities associated with RBD and RBE in PD.	54 PD - RBD 26 PD + RBD 27 PD +	EEG EOG	5-second epochs sleep instability could be a biomarker for RBD identification and conversion from RBE to definite RBD in PD.

			RBE		
Christensen et al. 2014 [39]	Data-driven modelling of sleep EEG and EOG reveals characteristics indicative of pre-PD and PD	To identify sleep features with an unsupervised learning approach from EEG and EOG signals.	23 HC 25 PLMS 31 iRBD 36 PD	EEG EOG	The duration of N3 and the ability to maintain NREM and REM sleep have potential as early PD biomarkers.
Dijkstra et al. 2021 [40]	REM sleep without atonia and nocturnal body position in pre-diagnostic PD	To characterize polysomnographic alterations in PD and pre-diagnostic PD.	13 iRBD 30 PD 30 HC	PSG	Increased total, tonic, chin RSWA, and nocturnal supine body position are prodromal PD biomarkers.

*AUC = area under the curve

Table 4: Novel technologies for patients with RBD

Authors	Study	Aims	Subjects	Type of sensors	Monitoring	Main Findings
Lee et al. 2021 [41]	Application of machine learning analysis based on diffusion tensor imaging to identify RBD	To evaluate the feasibility of machine learning analysis using DTI parameters to identify patients with iRBD	20 iRBD 20 HC	DTI	1 image In clinic	SVM classifier based on conventional DTI measures revealed an accuracy of 87.5% and an AUC of 0.9 to identify iRBD.
Waser et al. 2020 [42]	Automated 3D video analysis of lower limb movements during REM sleep: a new diagnostic tool for iRBD	To evaluate automated 3D video analysis of leg movements during REM to differentiate iRBD from other sleep movement disorders.	40 iRBD 11 SA 4 PLMS 44 SA + PLMS 5 RLS	Microsoft Kinect v2 sensor (Microsoft Corporation)	1 night In clinic	Minor leg jerks discriminated iRBD from other sleep movement disorders with an accuracy of 90%.
Arora et al. 2018 [43]	Smartphone motor testing to distinguish iRBD, controls, and PD	To identify motor features to distinguish individuals with iRBD from controls and PD using a customized smartphone application.	334 PD 104 iRBD 84 Controls	Smartphone	7 tasks 7 days In clinic At home	Postural tremor, rest tremor, and voice were the most discriminatory tasks overall, whereas the reaction time was the least discriminatory.
Arora et al. 2021 [44]	Smartphone speech testing for symptom assessment in RBD and PD	To investigate smartphone speech testing to distinguish iRBD from controls and PD.	92 Controls 112 iRBD 335 PD	Smartphone	1 task 4 times/day 7 days In clinic At home	Speech as a putative digital biomarker for PD and RBD.
Rusz et al. 2018 [45]	Smartphone allows capture of speech abnormalities associated with high risk of developing PD	To find speech features representing the key aspects of hypokinetic dysarthria in the early stages of PD.	50 iRBD 30 de-novo PD 30 HC	Smartphone	3 tasks In clinic	Duration of pause intervals and rate of speech timing extracted from the spontaneous speech was sufficiently sensitive to significantly separate groups.
Cochen De Cock et al. 2020 [46]	Rhythm disturbances as a potential early marker of PD in iRBD	To identify timing distortions in production and perception of rhythmic events as early markers of PD.	21 iRBD 38 PD 38 HC	Tablet	15-20 min In clinic	IRBD and PD revealed impaired spontaneous rhythm production and poor rhythm perception compared to controls.
Krupička et al. 2020 [47]	Instrumental analysis of finger tapping reveals a novel early biomarker of parkinsonism in iRBD	To explore whether finger-tapping abnormalities, evaluated with a 3D motion capture system, are already	40 RBD 25 de-novo PD 25 HC	3D motion capture system (V120: Trio, Optitrack)	1 clinical assessment	Decreased finger tapping amplitude and velocity compared to healthy controls.

		present in RBD patients.				
Raupach et al. 2019 [49]	Assessing the role of nocturnal core body temperature dysregulation as a biomarker of neurodegeneration	To investigate nocturnal CBT changes in patients with iRBD, which may prove to be an early objective biomarker for α-synucleinopathies.	15 iRBD 31 PD 6 DLB 10 HC	CBT ingestible capsule sensor (VitalSense, Phillips Respironics)	1 night In clinic	Reduced nocturnal CBT amplitude in iRBD, PD+RBD, and DLB, not in PD-RBD. Significant negative correlation between the amplitude of the CBT and self-reported RBD.

Figure 1