



Review article

REM sleep without atonia and the relation with Lewy body disease

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ABSTRACT

REM sleep without atonia (RSWA) is the polysomnographic finding of persistent muscle tone during REM sleep, resulting in paroxysmal phasic or tonic EMG activity. RSWA is essential for the diagnosis of REM sleep behavior disorder (RBD), but can also occur without dream-enacting behavior. Loss of atonia during REM sleep is considered as a biomarker for synucleinopathies. We will give an overview of the pathophysiology of RSWA and will highlight the diagnostic methods for RSWA. We will describe the different etiologies of RSWA and finally we will focus on the role of RSWA as biomarker for Lewy body disease. RSWA severity in isolated RBD patients is a potential predictor for early conversion to Parkinson's disease (PD) or dementia with Lewy bodies. In PD patients, RSWA severity is associated with more severe motor symptoms and disease progression. Future studies are needed to delineate the importance of isolated RSWA as prodromal marker of Lewy body disease.

1. Introduction

Rapid-Eye-Movement (REM) sleep is characterized by low-amplitude and mixed-frequency electro-encephalographic signals with mainly theta waves and some activity in the alpha-frequency band. Polysomnographic (PSG) studies show sharp, irregular and conjugate ocular movements in REM sleep, together with a decrease of muscle tone on EMG (electromyography) measurement [1]. REM sleep without atonia (RSWA) is the PSG finding of persistent muscle tone during REM sleep, resulting in paroxysmal phasic or tonic EMG activity (Fig. 1). RSWA is regarded as a pathological finding; an increasing amount of evidence obtained from animal and human studies suggest a strong link between RSWA and synucleinopathies. Together with dream-enacting behavior (DEB), RSWA is a necessary diagnostic criterion of REM sleep behavior disorder (RBD) [2]. Furthermore, RSWA was recently added as an indicative biomarker in the diagnostic criteria for dementia with Lewy bodies (DLB) [3].

We provide an overview of the pathophysiology and diagnostic criteria of RSWA. Furthermore, we will discuss the different etiologies of loss of muscle atonia during REM sleep. Finally, we will focus on the role of RSWA as a potential biomarker in the spectrum of the synucleinopathies.

2. Pathophysiology of RSWA

A complex neuronal network is involved in the regulation of the sleep-wake cycle [4]. The ascending arousal system, brainstem and hypothalamus play important roles. The cerebral and brainstem regions responsible for normal REM sleep and muscle atonia during this sleep stage are also implicated in RSWA, and have mainly been investigated in animal models, especially in cats and rats [5]. Several nuclei in the pontomedullary brainstem, including the locus coeruleus (LC) and subcoeruleus (LsC) (sublaterodorsal nucleus [SLD] in the rat), the pedunculopontine nucleus (PPN) and the medullary magnocellular reticular formation, have been selectively silenced, resulting in RSWA or RBD [5,6]. These findings suggest that the nuclei involved in REM sleep atonia are primarily located in the pontomedullary brainstem. Glutamatergic projections from the LsC complex activate neurons in the ventro-medial medulla oblongata (ventral part of gigantocellular reticular nucleus in the rat). Glycinergic or GABAergic output from these neurons in the ventral medulla causes an inhibition of spinal motor neurons during REM sleep, which is also modulated by cortical, subcortical, limbic and hypothalamic projections. Therefore, alterations in several neurotransmitter systems, such as GABA, glutamate, serotonin, acetylcholine and noradrenaline, might each separately influence REM

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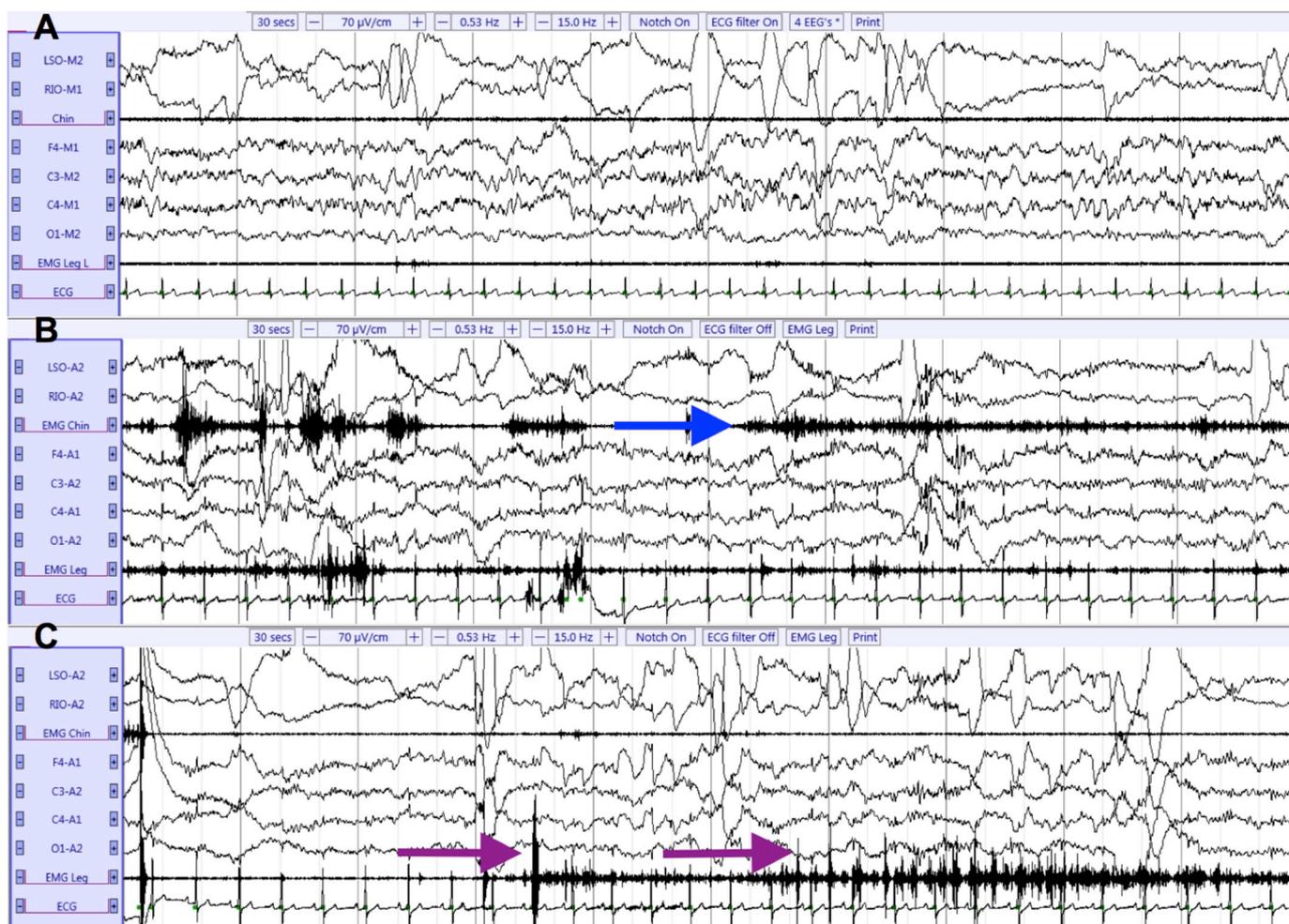


Fig. 1. REM sleep without atonia on polysomnography. Polysomnographic study, showing a 30-second epoch with 2 electrooculography (EOG) channels (LSO and RIO), a chin electromyography (EMG) channel, 4 electroencephalography (EEG) channels, a leg EMG channel (covering both tibialis anterior muscles) and an electrocardiography (ECG) channel. Fig. 1A shows normal REM sleep with typical Rapid-Eye-Movements on both EOG channels and muscle atonia on both EMG channels. Fig. 1B shows REM sleep without atonia with tonic activity on the chin EMG channel (blue arrow) and Fig. 1C shows REM sleep without atonia with phasic (purple arrows) superimposed on tonic activity on the leg EMG channel. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sleep and REM sleep atonia [6,7]. It is thus conceivable that RSWA and RBD can be caused by different mechanisms within these complex neuronal pathways. In humans, several case studies confirmed that focal structural pontomedullary and limbic lesions cause RSWA and RBD [8]. Furthermore, diffusion tensor magnetic resonance imaging (DTI-MRI) studies have confirmed microstructural changes in the pons in isolated RBD patients [9,10]. Moreover, neuromelanin-sensitive MRI studies showed integrity changes in the LC/LsC complex in isolated RBD patients, with a negative correlation between RSWA severity and LC/LsC signal intensity, suggesting a relevant role of these structures in RSWA pathogenesis in humans as well [11,12]. The high prevalence of RSWA and RBD in Lewy body disorders might be explained by the Braak hypothesis [13]. Intra-neuronal alpha-synuclein aggregation and Lewy body formation follow a caudal to rostral trajectory, ascending from the lower brainstem, over the mesencephalon to the cerebral cortex. Since the pontomedullary nuclei are affected prior to the degeneration of nigrostriatal projections and cerebral cortex, RBD often precedes deterioration of motor and cognitive functions [14]. A post-mortem study confirmed the presence of Lewy body pathology in the LsC, PPN and gigantocellular reticular nucleus in PD and DLB patients with RBD [15]. In some PD patients the progression of Lewy body pathology, however, will follow anatomical routes, which are different from those described in the Braak model [16]. These findings might

explain the heterogeneity in RBD symptoms between patients and the absence of RSWA or RBD in some patients.

3. Diagnosis of RSWA

RSWA is diagnosed with a video-PSG and is characterized by a loss of normal atonia during REM sleep, leading to an increase in phasic or tonic muscle activity in surface EMG recordings. The surface electrodes are placed at the mentalis or submentalis muscle (for detection of tonic or phasic RSWA, Fig. 1B), and bilateral tibialis anterior muscles (for detection of phasic RSWA, Fig. 1C) [1]. Recent studies, however, suggest the use of upper limb muscles (especially m. flexor digitorum superficialis) rather than tibialis anterior muscles in order to increase the specificity of RSWA diagnosis [17,18]. Classically, visual scoring of each epoch for RSWA was performed, but more recently alternative methods have been developed for both visual and automatic scoring of RSWA (Table 1).

The first method, referred to as the Montreal method, was published by Lapierre and Montplaisir in 1992 and validated in 2010 [19,20]. RSWA is measured using only chin EMG, with visual scoring. A 20-second epoch is defined as tonic RSWA if the chin EMG amplitude is more than twice of the background EMG amplitude; or more than 10 μ V and lasting at least 50% of the epoch. Phasic activity is scored in 2-

Table 1
The different methods for diagnosis of REM sleep without atonia (RSWA)

Method	EMG Muscles	Scoring method	RSWA definition	Cut-off for RBD
Montreal criteria [19,20]	Chin	Visual	<i>Tonic RSWA</i> : chin amplitude \geq twice the background EMG or $\geq 10\mu\text{V}$ for $> 50\%$ of 20-second epoch. <i>Phasic RSWA</i> : transient muscle activity, lasting 0.1–1.0 seconds and ≥ 4 times the amplitude of background amplitude in 2 second mini epochs.	Tonic activity in 30% of the REM epochs. Phasic activity in 15% of the mini-epochs.
SINBAR criteria [17,18,22]	Chin	Visual or automatic	<i>Tonic RSWA</i> : chin amplitude \geq twice the background EMG or $\geq 10\mu\text{V}$ for $\geq 50\%$ of 30-second epoch (measured in chin EMG). <i>Phasic RSWA</i> : transient muscle activity, lasting 0.1–5 seconds and with amplitude \geq twice the background EMG (or \geq twice the tonic amplitude when superimposed on tonic activity) in 3-second mini-epoch (measured in chin and M. flexor digitorum superficialis EMG).	Any activity in 27% of REM 30-second epochs Any activity in 32% of REM 3-second mini-epochs.
McCarter and coworkers[27,28]	M. flexor digitorum superficialis Chin	Visual or automatic	<i>Any RSWA</i> : either tonic activity, phasic activity or a combination of both in 3-second mini-epoch (measured in chin EMG). <i>Tonic RSWA</i> : chin amplitude \geq twice the background EMG or $\geq 10\mu\text{V}$ for $\geq 50\%$ (measured in chin and M. tibialis anterior EMG).	Any activity in 43,4% of 3 second-mini epochs.
AASM criteria [1]	M. tibialis anterior Chin	Visual	<i>Phasic RSWA</i> : - transient muscle activity, lasting 0.1–1.4.9 seconds and with amplitude ≥ 4 times the background EMG (or \geq twice the tonic EMG when superimposed) in ≥ 5 of 3 second mini epochs within epoch (measured in chin and M. tibialis anterior EMG) - each phasic muscle burst during REM sleep is directly measured, for each muscle, resulting in an average phasic muscle burst duration. <i>Any RSWA</i> : either tonic activity, phasic activity or a combination of both (5–15 seconds) in 3-second mini-epoch (measured in chin and M. tibialis anterior EMG).	Chin phasic muscle burst duration of 0.65 seconds. AT phasic muscle burst duration of 0.79 seconds. No cut off defined
Blwise and coworkers [30,31]	M. tibialis anterior Chin	Visual or automatic	<i>Phasic RSWA</i> : transient muscle activity, lasting 0.1–5 seconds and with amplitude ≥ 4 times the background EMG in ≥ 5 of 3-second mini-epochs within a 30-second epoch. <i>Phasic activity/phasic EMG metric (PEM)</i> : bursts of EMG activity ≥ 100 milliseconds, with an amplitude ≥ 4 times the background EMG in the presleep baseline. PEMs were scored in 2,5-second mini-epochs.	No cut off defined
REM sleep atonia index (RAI) [23]	M.brachioradialis Chin	Automatic	1 second mini REM epoch is categorized into 1 of 20 categories, based on average EMG amplitude in μV . RAI = (amplitude $\leq 1\mu\text{V}$)/(100-(1 μV < amplitude $\leq 2\mu\text{V}$)). An algorithm calculates the variance of the chin EMG signal during all 3-s mini-epochs, with an upper limit for normal EMG background activity defined as four times the 5 th percentile of the variance observed during all NREM epochs.	Index of 0.8
STREAM [21]	Chin	Automatic	<i>Short muscle activity index (SMI)</i> , < 0.5 s) and <i>long muscle activity index (LMI)</i> , > 0.5 s) with an amplitude \geq twice the amplitude of baseline EMG activity in REM (after smoothing the amplitude curve) as an index per hour of REM sleep.	15% of total REM sleep
Mayer and coworkers [32]	Chin	Automatic	<i>Short muscle activity index (SMI)</i> , < 0.5 s) and <i>long muscle activity index (LMI)</i> , > 0.5 s) with an amplitude \geq twice the amplitude of baseline EMG activity in REM (after smoothing the amplitude curve) as an index per hour of REM sleep.	Chin: 90.1/43.1 M. tibialis anterior: 323.0/133.5
	M. tibialis anterior			
	M. flexor digitorum superficialis			M. flexor digitorum superficialis 124.3/50.1 (SMI/LMI in number/h REM)

Table 1 describes the most frequently used methods for RSWA diagnosis on polysomnographic electromyography. Abbreviations: SINBAR criteria = Sleep INnsbruck BARcelona criteria. EMG = electromyography. AASM = American Academy of Sleep Medicine. RAI = REM sleep atonia index. mV = millivolt. STREAM: Supra-Threshold REM Activity Metric.

second mini-epochs (within a 20-second epoch) and defined as a burst of EMG amplitude as least 4 times as high as the background EMG amplitude, lasting 0.1–10 s. The percentage of phasic RSWA is calculated by dividing the number of RSWA positive 2-second mini-epochs by the number of total artifact free REM time. A cut-off score for RBD of tonic activity in 30% of the REM epochs or phasic activity in 15% of the mini-epochs is used. An automatic scoring method in line with the Montreal method, called the Supra-Threshold REM Activity Metric (STREAM), has been developed by Burns and coworkers [21]. It only uses scoring in 30/3-second epochs rather than 20/2-second epochs and a computer algorithm calculates the variance of the chin EMG signal during all 3-second mini-epochs, in which an upper limit for normal EMG background activity is defined as four times the 5th percentile of the variance observed during all NREM epochs. The cut-off score for RBD is defined as 15% of total REM sleep positive for RSWA.

The SINBAR (Sleep INnsbruck BARcelona) method is frequently used for visual scoring of RSWA and is further enhanced and elaborated from the Montreal method [17,18]. The SINBAR criteria include RSWA measurement in the chin muscle in 30-second epochs in combination with phasic RSWA in the extremities, which are scored in 3-second mini-epochs. Different muscle combinations have been compared, with the highest specificity and sensitivity for measuring phasic RSWA activity in the bilateral m. flexor digitorum superficialis (FDS) [17]. Besides scoring of tonic or phasic RSWA, this method allows to score an additional category of RSWA, namely “any RSWA”. This category is defined as either tonic, phasic activity, or a combination of both in a 3-second mini-epoch. The amount of RSWA can be calculated in 30-second epochs (positive for phasic and/or “any” RSWA when at least 50% of the mini-epochs within an epoch show RSWA) or 3-second mini-epochs. For a diagnosis of RBD, according to the International Classification of Sleep Disorders (ICSD)-3 criteria [2], at least 27% of total REM sleep should be scored as RSWA using m. mentalis and bilateral FDS in 30-second epochs (and 32% in 3-second mini-epochs) [17]. Recently, an automatic scoring method based on the SINBAR criteria has been developed [22].

A third scoring method involves automatic calculation and generates the REM sleep atonia index (RAI) [23]. The RAI is restricted to the analysis of the chin muscle tone. It subdivides each 1-second mini-epoch into 20 categories, based on average EMG amplitude, with an amplitude of $\leq 1 \mu\text{V}$ in category 1 (normal atonia), an amplitude between 1 and $2 \mu\text{V}$ in category 2 etc. An index is calculated [$\text{RAI} = (\text{amplitude} \leq 1\mu\text{V}) / (100 - (1\mu\text{V} < \text{amplitude} \leq 2\mu\text{V}))$] that expresses the proportion of normal atonia during REM sleep. A RSWA cut-off value of 0.8 is used for RBD, with a value between 0.8 and 0.9 being considered as borderline RSWA, and a value above 0.9 as normal. The RAI has been validated by several independent studies with slightly different cut-off scores [24–27].

McCarter and coworkers [27,28] developed a visual scoring method based on the SINBAR criteria with RSWA scoring in the m. submental and bilateral m. tibialis anterior. Tonic and “any” activity was scored in the m. tibialis anterior as well as in the m. submental, with a cut-off score of “any” activity in 43,4% (measured in 3-second mini-epochs). In addition, each phasic muscle burst was calculated separately, resulting in an overall average phasic burst duration per muscle. In combination with “any” activity, average phasic burst duration improved sensitivity and specificity for RBD diagnosis. This method has been validated in OSA patients as well. Recently, a semi-automatic scoring algorithm was developed for this method [29].

The American Academy of Sleep Medicine (AASM) manual criteria for RSWA [1] are based on visual scoring and define tonic RSWA as a 30-second epoch of REM sleep with at least 50% of the duration of the epoch having a chin muscle EMG amplitude greater than the minimal amplitude demonstrated in non-REM sleep. The AASM manual defines phasic RSWA as a 30-second epoch of REM sleep, divided in 3-second mini-epochs, with at least 50% of the mini-epochs containing bursts of transient muscle activity, lasting between 0,1 and 5 s and being at least

4 times as high in amplitude as the background EMG amplitude.

Some of the other methods for RSWA scoring include the phasic EMG metric (PEM), which is visually or automatically scored and reflects phasic activity in 2,5-second epochs [30,31]. The short muscle activity index (SMI) and long muscle activity index (LMI) [32] are both automatically scored and reflect phasic (SMI) and tonic (LMI) activity calculated in number/hour of REM sleep rather than in epochs.

The above-mentioned methods all have RSWA measurement on the chin EMG in common. However, differences between these methods can be found in additional EMG recording in the extremities, visual versus automatic scoring and subtle variations in the definition of phasic and tonic RSWA activity. Until now, there is no consensus regarding the best scoring method for RSWA. A comparative study of three scoring methods (Montreal, SINBAR and automatic RAI method) showed a similar diagnostic performance (sensitivity ranging from 94.6 to 100%; specificity ranging from 88 to 100%) for the Montreal and SINBAR methods with a slightly lower specificity for the RAI (72%) [25]. Since visual scoring methods are time-consuming, automatic scoring is a faster alternative that can be replicated more easily in clinical practice and some studies suggest automatic scoring as the first line method for detection of RSWA, with additional visual inspection in doubtful cases. A recent study that compared several methods for automatic scoring was not able to show the superiority of a particular automatic method and concluded that all automatic methods need further improvement before their introduction as diagnostic tools without visual correction [26]. Future research efforts should focus on harmonization of RSWA scoring methods to build a consensus definition for RSWA. Furthermore, all cut-off values for pathological RSWA are based on RSWA with concomitant RBD. A cut-off score for pathological RSWA without DEB still needs to be defined [33].

Several studies investigated RSWA night-to-night variability in isolated RBD and Parkinson's disease (PD) patients. A low night-to-night variability of chin RSWA has been consistently reported, with a higher variability of phasic RSWA measured for the tibialis anterior muscles [34–36]. These findings suggest that a one-night PSG should be sufficient for diagnosing RSWA. In the context of RBD, tonic RSWA seems a stable biomarker, whereas DEB can be fluctuating between nights [36].

4. Etiologies of RSWA

The different etiologies of RSWA are summarized in Table 2. RSWA was most extensively studied in the context of isolated RBD and PD, which will be further discussed in sections 6 and 7. Isolated RBD was

Table 2

The different etiologies of REM sleep without atonia (RSWA).

Synucleinopathies (common):
- Isolated REM sleep behavior disorder
- Parkinson's disease
- Dementia with Lewy bodies
- Multiple system atrophy
- Pure autonomic failure
Tauopathies (rare):
- Alzheimer's disease
- Progressive supranuclear palsy
- Corticobasal degeneration
- Frontotemporal dementia
Brainstem lesions
Autoimmune disorders:
- Narcolepsy (common)
- Anti-IgLON5 auto-immunity syndrome (common)
- Voltage-gated potassium channel antibody-associated encephalitis (anti-LGI1 and Caspr2 encephalitis) (rare)
- Anti-Ma2 encephalitis (rare)
- Guillan-Barré syndrome (rare)
Medications:
- Antidepressants (common)
- Beta-blockers (rare)

until recently termed idiopathic RBD. Since a majority of these patients will develop Lewy body pathology, the term “isolated” (RBD without motor or cognitive symptoms) is now more frequently used by sleep experts. In addition to PD, isolated RBD can also frequently precede other synucleinopathies: multiple system atrophy (MSA) and DLB. The prevalence of RSWA in both the cerebellar and parkinsonian variant of MSA seems to be higher than in PD patients [37–39]. PSG studies in DLB patients show evidence for the presence of RSWA in 46–71% of the patients [40–42]. Moreover, RSWA was recently added as an indicative biomarker in the diagnostic criteria for DLB [3]. RSWA can contribute to the differentiation of DLB from other forms of dementia, such as Alzheimer's disease and vascular dementia. However, RSWA has also been reported in a minority of Alzheimer's disease patients [40,43] and in tauopathies (progressive supranuclear palsy and corticobasal degeneration) [44–48]. Pathological confirmation is not available in most of these cases, which opens a possibility for the presence of a dual pathology, including alpha-synuclein-specific neurodegeneration.

RSWA has not only been reported in the context of neurodegenerative brain diseases. Brainstem lesions, ranging from ischemic or hemorrhagic strokes, inflammatory lesions, demyelinating plaques to brainstem tumors, have been described to cause RSWA [8]. These conditions can most often be diagnosed by MR imaging and require prompt and adequate treatment. RSWA has been identified in particular neuro-inflammatory syndromes, such as IgLON5 autoimmunity syndrome [49], voltage-gated potassium channel antibody-associated encephalitis (covering anti-LGI1 and Caspr2 encephalitis) [50] and Guillain-Barré syndrome [51].

An important cause of RSWA and RBD in young patients is narcolepsy. In narcolepsy type 1 patients, selective loss of hypocretin-producing neurons in the lateral hypothalamus will cause typical symptoms, including cataplexy, excessive daytime sleepiness, sleep paralysis, hallucinations, sleep-onset REM periods and fragmented nocturnal sleep [2]. The decrease in hypocretinergic tone will not only lead to instability in the regulation of the sleep-wake system, but also to an impaired regulation of REM sleep motor tone [52,53].

Several medications have been reported to induce RSWA. Antidepressant medications, especially selective serotonin re-uptake inhibitors, are strongly associated with RSWA with or without DEB [54,55]. The causality of this association is still unclear [56]. In some patients, discontinuation of antidepressant drugs led to the disappearance of RSWA [57,58]. In other RBD patients however, persistence of RSWA was observed [59,60]. During longitudinal follow-up, patients receiving antidepressants showed a lower frequency of phenoconversion to an overt neurodegenerative disease, yet equivalent neurodegenerative marker frequency, suggesting that antidepressants may be associated with the diagnosis of an otherwise covert synucleinopathy earlier in the disease course, rather than causing a purely pharmacological effect. Whether this is also true in patients with PSG-confirmed RSWA (without DEB) is still unknown and longitudinal studies are required to confirm this hypothesis. An acute presentation of RBD, following the use of beta-blockers was also reported [61].

The first line treatment for RBD is clonazepam or melatonin [62]. Both medications decrease the DEB. Several studies, however, reported no effect of clonazepam on REM muscle tone [63–65], suggesting that clonazepam is not interfering with the RSWA neuronal circuits. Therefore, RSWA may be useful as progression marker of neurodegeneration in RBD patients, even under clonazepam treatment. In contrast, melatonin administration is associated with a decrease of RSWA in RBD patients [66,67]. The effect of dopaminergic drugs on RSWA is rather inconsistent. Some studies showed an increase in RSWA in PD patients [68,69], while others reported no difference in RSWA percentage or effect on RSWA [70,71] or even an inverse correlation between RSWA severity and levodopa equivalent daily dose in PD patients [72].

5. Pseudo RSWA and pseudo RBD

Several co-morbidities can mimic RSWA and RBD. These concomitant disorders should be taken into account during PSG interpretation. Severe obstructive sleep apnea (OSA) can resemble DEB and has been termed “pseudo RBD”, with several case reports also showing (pseudo) RSWA [73–75]. Respiratory arousals (during resumption of breathing after an apnea) and snoring artifacts are sometimes difficult to differentiate from RSWA. Therefore, a follow-up PSG with continuous positive airway pressure (CPAP) therapy is recommended to confirm RSWA diagnosis in OSA patients. Furthermore, an experienced PSG interpreter should exclude increased muscle tone in the context of respiratory events, when performing RSWA analysis. Another frequent co-morbidity is severe periodic limb movement disorder (PLMD), in which the limb movements sometimes show EMG activity similar to RSWA [76]. The limb movements can also be vigorous, resembling DEB. Periodic aspect of these movements can help to differentiate them from RBD, as well as EMG recording of the m. flexor digitorum superficialis rather than the m. tibialis anterior for RSWA measurement.

Besides OSA and PLMD, nocturnal motor behaviors mimicking DEB can occur in the context of nocturnal epilepsy, other parasomnias (such as confusional arousals, sleepwalking, sleep-related eating disorder, sleep terrors, nightmare disorder, sleep-related hallucinations and sleep talking), other sleep-related movement disorders (such as fragmentary myoclonus) and delirium [2]. A detailed history, combined with a history from the bed partner and PSG findings can usually differentiate between RBD and these disorders. Since PSG can be time consuming, expensive and not always available, RBD is sometimes diagnosed on history of DEB alone or with RBD questionnaires [6]. In the case of RBD as symptom in patients with established synucleinopathies this approach seems reasonable, considering the high frequency of RBD in synucleinopathies [77]. In the case of RBD as diagnostic criterion for a synucleinopathy this may lead to a false positive diagnosis; PSG confirmation of RSWA is therefore recommended [6,33,42,77]. The ICSD-3 criteria require a PSG confirmation of RSWA as well for the diagnosis of definite RBD [2]. The recently updated diagnostic criteria for dementia with Lewy bodies, however, include RBD symptoms without PSG confirmation of RSWA as a core clinical feature [3]. Validation studies are necessary to confirm the contribution of RBD symptoms (without PSG confirmation) in the differential diagnosis of dementia.

6. RSWA in Parkinson's disease

Parkinson's disease (PD) is the most prevalent synucleinopathy and is a movement disorder, characterized by an asymmetric hypokinetic-rigid syndrome and resting tremor [78]. According to the Braak hypothesis, several nuclei within the lower brainstem already show Lewy body pathology in the prodromal disease stages and for this reason many patients will develop RBD before the onset of motor symptoms [13,79]. Consequently, PD patients show more frequently RSWA on PSG compared to control subjects [71,80]. RSWA was identified in 40–75% of PD patients [71,81–83]. RBD was present in 50–58% of PD patients with RSWA, while RSWA without DEB was observed in the remaining patients. These observations suggest that RSWA is an independent feature of PD and not always related to DEB [68]. Furthermore, studies consistently reported a positive correlation between RSWA severity, disease duration and severity of PD symptoms [70,84].

Regarding motor symptoms, several studies have consistently reported more severe Hoehn-and-Yahr (HY) stages in PD patients with more prominent RSWA [68,70,71]. A positive correlation was observed between both phasic and tonic RSWA activity and motor severity, using the HY stage and Unified Parkinson's Disease Rating Scale (UPDRS) motor score. Other studies have demonstrated a higher percentage of (especially tonic) RSWA in PD patients with freezing of gait [85], with a positive correlation between RSWA severity and severity of freezing problems [86]. Interestingly, a higher percentage of RSWA was

observed in PD patients with motor fluctuations compared to patients without motor fluctuations [70].

Non-motor symptoms are highly prevalent across all PD disease stages and can include depression, autonomic dysfunction, excessive daytime sleepiness or cognitive dysfunction [87]. Only few studies have investigated the relation between RSWA and non-motor symptoms [68,84,86]. Heart rate variability, as a marker for autonomic dysfunction, showed a positive correlation with both phasic and tonic RSWA [88]. Montreal Cognitive Assessment (MoCA) scores were lower in patients with more severe RSWA [84]. In a similar study, a negative correlation between RSWA severity and cognitive function was noted [68].

Regarding the potential role of RSWA as a marker for disease progression, promising data have already been obtained. Motor progression, as measured by the UPDRS motor score was assessed in 3 groups of PD patients: patients with normal REM sleep atonia, RSWA patients without DEB and RBD patients [81]. Disease duration, levodopa equivalent daily dose and UPDRS motor score at baseline were similar in the three groups. After a follow-up duration of 2.5 ± 1.5 years, significant deterioration in UPDRS motor scores was observed in RBD patients. An intermediate but significant deterioration was seen in PD patients with RSWA, while almost no deterioration was observed in patients with normal muscle atonia during REM sleep. The progression of cognitive symptoms was evaluated in three similar groups of PD patients [89]. A twofold increase in the occurrence rate of dementia was seen in the RBD group when compared with the normal REM sleep group after a follow-up duration of 1.8 ± 0.9 years. The RSWA group showed a non-significant and mild increase in the occurrence of dementia, suggesting that clinical RBD rather than RSWA was a predictor of cognitive decline in this short-term follow-up study of PD patients.

In summary, these observations confirm the presence of RSWA, even without the context of RBD, in a majority of PD patients. Higher percentages of RSWA are associated with longer disease duration, more severe motor symptoms and disease progression. A similar relation between RSWA and non-motor symptoms can possibly be observed, but further research is needed concerning this topic.

7. RSWA in isolated REM sleep behavior disorder

Both RSWA and DEB are observed in isolated RBD, usually together with vivid and violent dreams [2]. This well-defined REM sleep parasomnia is regarded as an important prodromal symptom of Lewy body disease. Up to 91% of the isolated RBD patients will develop PD, DLB or MSA within 15 years after onset of RBD [14]. Isolated RBD is associated with other prodromal PD symptoms, such as depression, hyposmia and autonomic dysfunction [90]. Furthermore, biomarkers for nigrostriatal degeneration, such as abnormal 123-I-*I*-ioflupane single-photon emission computerized tomography (SPECT) and substantia nigra hyperchogenicity in midbrain ultrasound studies are frequently observed in isolated RBD patients [91,92].

RSWA severity increases over time in isolated RBD patients, possibly reflecting the ongoing neurodegenerative process in the lower brainstem [93]. RSWA severity generally correlates well with DEB severity [70], however, both phenomena are not always equally present in each isolated RBD patient. Interestingly, RSWA severity can vary between patients with similar disease duration, reflecting possible subtypes within isolated RBD [94].

The relation between RSWA severity and disease progression is a relevant research topic in the era of upcoming disease-modifying therapies and was studied in isolated RBD patients. Mentalis muscle RSWA severity (both tonic and phasic activity) showed a negative correlation with striatal tracer uptake on 123-I-*I*-ioflupane SPECT [72], suggesting that nigrostriatal degeneration is more prominent in isolated RBD patients with severe RSWA, which might reflect early conversion to PD, DLB or MSA in this subgroup of RBD patients. In a longitudinal study of 56 isolated RBD patients, 26 patients developed a

synucleinopathy (PD in 12 patients, DLB in 13 patients and MSA in 1 patient) after mean follow-up of 6.7 years [94]. In this study, increased baseline tonic RSWA was identified as a predictor for the development of PD, but not of DLB or MSA. Fernandez-Arcos and coworkers investigated 85 isolated RBD patients with a longitudinal design, of which 49 converted: 15 patients to PD, 19 patients to DLB and 13 patients to mild cognitive impairment (MCI) [95]. Again, increased baseline tonic RSWA was a predictor of conversion to PD instead of DLB and MCI. Two more recent longitudinal studies, a multicenter study of 1130 isolated RBD patients (RSWA data available in 382 patients) with a mean follow-up duration of 4.5 years [96], and a single center study of 216 isolated RBD patients with a mean follow-up duration of 5.0 years [97], however, confirmed increased RSWA as a predictor for early conversion to both PD and DLB. The inconsistency in these results might be due to the larger sample sizes in the latter studies.

8. Isolated RSWA: a prodromal synucleinopathy biomarker?

In about 5% of the patients undergoing a PSG for clinical purposes, RSWA without clear etiological explanation was observed (no DEB, no clinical signs of PD/DLB/MSA, none of the co-morbidities described in section 4) [98]. Epidemiological studies in healthy subjects from the general population have shown percentages of RSWA frequency ranging from 5 to 25% [99,100]. Whether this RSWA is an incidental finding as part of normal variance (“incidental RSWA”) or a pathological finding (“isolated RSWA”: RSWA without DEB, parkinsonism or cognitive deterioration, also termed subclinical RBD or prodromal RBD) is still unknown. In this review, we will further use the term isolated RSWA. Isolated RSWA levels are greatest in older men, mirroring the biology underlying RBD and synucleinopathy [101]. Since RSWA severity in isolated RBD and PD patients increases over time, isolated RSWA is hypothesized to be part of the prodromal phase of Lewy body disease [33].

Stefani and coworkers have investigated isolated RSWA patients in a longitudinal design [102]. They included 14 isolated RSWA subjects with a mean follow-up duration of 8.6 ± 0.9 years. In the majority of the subjects RSWA severity increased over the duration of the study: 1 subject (7.3% of the study population) converted to RBD during this longitudinal study. None of the subjects developed obvious parkinsonian symptoms during the follow-up period. At least one biomarker, suggestive of ongoing neurodegeneration, however, was detected in 74% of the study population: mild cognitive impairment, hyposmia, substantia nigra hyperchogenicity or decreased color vision. Additional biomarkers of prodromal PD (abnormal heart rate variability and decreased striatal 123-I-*I*-ioflupane uptake) have also been identified in isolated RSWA patients [92,103]. Again, in isolated RSWA subjects RSWA severity correlated negatively with striatal 123-I-*I*-ioflupane SPECT uptake [92]. However, in several other isolated RSWA case descriptions inconsistent results regarding prodromal biomarkers were reported [104,105]. Antidepressant use was documented in the majority of these cases, which might have triggered the loss of REM sleep atonia.

These findings are in line with the hypothesis of isolated RSWA as a prodromal PD biomarker. Longitudinal studies with larger sample sizes and longer follow-up duration are needed to confirm this hypothesis. These studies are warranted, since isolated RSWA patients might suffer from other prodromal PD symptoms. RSWA could therefore serve as a biomarker for patient selection in future clinical trials with neuroprotective therapies [33]. On the other hand, a subpopulation of isolated RSWA patients might not be predisposed to develop Lewy body disease and further characterization of these patients would also be relevant for clinical practice.

9. Conclusions and future directions

In conclusion, RSWA is the PSG finding of increased tonic or phasic

EMG activity during REM sleep. RSWA is essential for the diagnosis of RBD, but also occurs without DEB. Several diseases and medications are associated with RSWA. In the context of synucleinopathies, RSWA severity increases over time, probably reflecting ongoing neurodegeneration. Tonic RSWA severity is a predictor of early conversion to PD and DLB in isolated RBD patients, while in PD patients it seems to be associated with more severe motor symptoms and motor progression. Future studies should focus on the development of a more standardized method for RSWA scoring and validated cut-off scores to differentiate between physiological and pathological RSWA. Furthermore, the clinical relevance of isolated RSWA as prodromal marker of Lewy body disease should be further investigated in large prospective studies with long follow-up duration. Isolated RSWA as biomarker might provide a time-window for disease modification before the clinical manifestation of PD/DLB/MSA symptoms.

Ethical compliance statement

The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Declarations of interest

The authors have no competing interests to declare.

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Author roles

FD, IDV and DC have contributed to the conception and design of the manuscript. KvdB, BdB and NR contributed equally in drafting the first version of the article. FD and DC drafted the final version of the article. IDV, MV and PC critically revised the article. All authors gave final approval.

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