

# Rapid Eye Movements Sleep Behavior Disorder

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Sleep parasomnias have drawn the interest of sleep experts because they represent a valuable window to directly monitor dream activity and sleep mentation associated with nocturnal events. Indeed, parasomnias and their manifestations are helpful in investigating dream activity and features, overcoming methodological limits that affect dream study. Specifically, REM sleep Behavior Disorder (RBD) is a parasomnia characterized by enacted dream episodes during Rapid Eye Movements (REM) sleep, caused by the loss of physiological atonia. Patients suffering from RBD report a peculiar oneiric activity associated with motor episodes characterized by high Dream Recall Frequency (DRF) and vivid dreams. Additionally, isolated RBD (iRBD) represents a prodromal stage of neurodegeneration preceding the development of  $\alpha$ -synucleinopathies.

parasomnias

REM sleep behavior disorder

dream recall frequency

dream contents

oneiric activity

## 1. Introduction

Sleep parasomnias are described in the third edition of the International Classification of Sleep Disorders (ICSD-3) <sup>[1]</sup> as sleep disorders involving unusual motor and vocal behaviors accompanied by emotional or sensory perceptions and associated with dream mentation. These episodes appear during transition periods between sleep and wake or are concomitant to specific sleep stages. Hence, parasomnias can be classified into Non-Rapid Eye Movement (NREM) (i.e., confusional arousals, Sleep Walking (SW), Sleep Terrors (ST), and sleep-related eating disorder) and Rapid-Eye Movement (REM) related (i.e., REM sleep Behavior Disorder (RBD), recurrent isolated sleep paralysis, nightmare disorder, and sleep-related hallucinations) <sup>[1]</sup>.

REM and NREM parasomnias have drawn the interest of sleep experts not only on the clinical characteristics reported by the patients but also because these conditions represent a precious window to directly monitor dream activity and sleep mentation associated with nocturnal events. Indeed, an intrinsic issue of dream study concerns their inaccessible nature: dream contents are not directly accessible, and knowledge on oneiric activity is collected through retrospective recall <sup>[2]</sup>. As a consequence, the retrospective nature of dream collection leads to several methodological problems due to distortions and omissions in the recall caused by memory reprocessing <sup>[3]</sup>.

## 2. How RBD Patients Dream?

From the first observation and description [4], RBD drew the attention of sleep experts for its unique characteristics of dream-enactment during REM sleep.

Motor behaviors observed in this parasomnia appear to act out dream contents and settings, as demonstrated by the correspondence between the features of dream recall and the observed behaviors. Moreover, dream contents reported have recurrent elements and similar characteristics among patients. The analysis of dream contents highlighted recurrent unpleasant dreams and nightmares reported by RBD patients [5][6]. Specifically, the main themes collected in the dream recall were attacks by people or animals [6][7][8], violence [5][9][10], and fright [5] (for detailed dream report examples, see Leclair-Visonneau et al. [11]). Interestingly, these violent and aggressive oneiric themes are not due to and do not match personality features. Indeed, RBD patients did not show hostile and violent traits during wakefulness; on the contrary, they appeared quiet and calm [12][13][14]. Moreover, dream assessment proved that the more dreams with aggression, misfortune, and negative emotions occurred, the more the patients had lower traits of hostility, anger, and less tendency to be aggressive [12].

Another key feature of this REM parasomnia is the prevalence of the disorder in the male population [15][16], reporting more severe symptoms and nocturnal behavioral episodes in men than women with RBD [17][18]. However, studies that explored gender differences in oneiric activity revealed the absence of significant differences between males and females in dreams and nightmares recall rates [8][19][20], vividness [21], and contents [20][21].

Moreover, elevated dream and nightmare recall frequency (from 98.6% to 75%) was reported in RBDs [5][8][19][22][23]. In 63% of dream reports, the recall was associated with behavioral episodes [7], and higher DRF was found in RBD patients causing injuries than in RBDs in which injury did not occur, although no between-groups differences were reported in the dream contents [24]. However, this peculiar framework of oneiric activity observed in RBD, characterized by high DRF and violent dream contents, has not always been confirmed by studies that examined the effect of treatment on RBD symptoms and studies that compared patients with HCs.

On the one hand, researchers can affirm that specific dream contents, characterized by violent and aggressive themes, are typical of RBD. Moreover, longitudinal studies showed that melatonin and clonazepam assumptions suspended frightening, violent dreams [25][26][27], and nightmares [27] during treatment. In the same line, compared to HCs, dreams in RBDs were characterized by a prevalence of violent and aggressive themes, also involving animal or people attacks [12][22][28][29][30], with a high incidence of negative emotions and nightmare distress [12][28]. Moreover, using the RBD Questionnaire (RBDQ) [31], patients showed higher scores in Factor 1 (which considers the dreams and nightmares frequency and the emotional, violent, and aggressive contents) than HCs [30][31][32][33][34]. This evidence has been explained in two ways. The first hypothesis regards the biological and evolutionistic role of dreaming in simulating dangers and threats that have to do with ancestral human fears to “prepare” the subject to rehearse threat perception and its avoidance during wakefulness [35]. The second hypothesis to explain aggressive features in the RBDs’ dream reports could be to account for cognitive dysfunctions due to impairments observed in the frontal cortex [36]. Thus, these results suggest that violent nightmares and dreams in RBD may have clinical importance in predicting the possible onset of neurodegeneration. Indeed, the aggressive dream contents reported by PD patients is suggestive to be related to frontal cognitive dysfunction [37]. In addition, the

violent and aggressive dream contents experienced by RBDs could be also explained by the lack of inhibition due to frontal cortex dysfunctions, leading to archaic defense behaviors acted out in dreams [36]. However, findings that may help to clarify this relationship will be reported and discussed in the next paragraph.

On the other hand, studies reported the absence of more vivid dreams in RBDs [29], no higher DRF [28][29][38], and no differences in dream contents [29][39] when comparing RBDs to HCs and when comparing pre and post treatment [40][41]. Contrasting results between studies in RBDs can be explained by methodological limits that affect results. Indeed, retrospective studies assessing oneiric activity in the past and during the entire patient's life reported high rates of dreams and nightmare recall [5][7][8][19][22][24]. Retrospective methodology to collect dreams leads to the so-called "recall bias", which is the predisposition of patients suffering from RBD to recall more frequently vivid dreams with violent and frightening contents accompanied by motor behaviors [42].

Concluding, although literature findings confirm a predisposition of RBDs to report oneiric activity characterized by violent content, findings in dream frequency are not sufficient and are not solid enough to conclude a clear increase of DRF in RBDs. Researchers recommend employing prospective experimental designs to collect dreams in future studies exploring dreaming in RBDs.

### 3. Dreaming in RBD: A Window into Neurodegenerative Mechanisms?

The intrinsic features of dream activity in iRBD patients described in the previous paragraph focus researchers' attention on identifying potential markers able to predict the phenoconversion of parasomnia into  $\alpha$ -synucleinopathies years before signs of neurodegeneration emerge [43]. Indeed, iRBD and PD conditions share similar dream features, such as a high prevalence of dreams with violent and distressing contents, and nightmares [44]. In this view, establishing a relationship between oneiric activity in iRBD and neuropathological mechanisms could allow early detection of neurodegeneration processes and make it possible to understand neural mechanisms underlying the generation and recall of dreams.

Researchers' literature analysis reported 6 studies investigating dreaming in RBDs compared to PDs [14][45][46][47][48][49] and one study that compared dreaming between RBDs and DLBs [50].

These studies described high rates (from 50% to 70%) of DRF [48][49][50] and more vivid dreams [45][46][49] in RBD conditions in comorbidity with  $\alpha$ -synucleinopathies (i.e., PD and DLB) than RBD without signs of neurodegeneration.

To clarify the association between dream-related features and neurodegenerative mechanisms that seem to underlie the RBD pathophysiology, interesting findings are those that consider specific RBD symptoms as RSWA. Results showed that in RBD the higher percentage of phasic muscle activity during REM sleep was related to more elements with natural disasters in dream recall. On the other hand, RBDs that showed higher tonic muscle activity percentage during REM sleep were less prone to recall dreams [22]. RSWA is one of the key criteria to diagnose

RBD syndrome [1] and authors suggest it may reflect a progressive damage to the brainstem [51]. Tonic and phasic EMG activities during REM sleep have different neural mechanisms. Specifically, phasic EMG activity is regulated by locomotor nuclei in the ventromedial medulla, structure impaired yet in the early stages of PD [52]. On the other hand, increasing tonic muscle activity, depending on REM-on neurons of the sublaterodorsal tegmental nucleus, seems to be strictly associated with the phenoconversion to PD [53]. However, evidence from this entry is not enough to confirm a strong relationship between dreams and RSWA features.

Moreover, a single study [46] retrospectively explored changes in RBDs converted in PD, reporting higher nightmares frequency after the onset of PD symptoms. However, a paper [14] investigating DRF through sleep diaries compiled for one month showed lower rates of dreams reported in PDs with and without RBD (<2 dreams per month) and no significant differences in DRF between the two groups. In the same direction, no between-group differences are revealed in the dream contents reported by iRBDs and RBDs with PD symptoms. Specifically, the absence of significant differences was found in vividness and intense emotional contents such as threat, aggression, or negativity [14][46]. Also in this case, these findings may be explained by the “recall bias” occurring when dreams are collected retrospectively. Indeed, studies reporting the absence of group differences in DRF and contents between RBD patients with and without PD adopted prospective designs (i.e., daily dream logs for one month [14] and systematic laboratory awakenings protocol [46]). Undoubtedly, these procedures reduce recall bias. These findings are consistent with the work by D’Agostino et al. [39] illustrated in the previous paragraph, which compared dream contents in RBDs and HCs employing immediate free recall through 3 weeks of daily dream diaries.

Overall, although the theory proposed is fascinating, the state of the art does not confirm the predictive value of dream features as markers able to track the neurodegenerative process in RBD.

## 4. Dream Features in RBD and NREM Parasomnias or Other Sleep Disorders

RBD nocturnal episodes appear as abnormal motor and vocal behaviors (i.e., punching, falling out of bed, and shouting) often associated with peculiar dream mentation [54]. These behavioral manifestations may also occur in other sleep disorders (e.g., OSA) and other NREM parasomnias (e.g., SW and ST). In severe OSA conditions, quite common among older adults, the respiratory effort and/or breathing resumption associated with sleep arousals lead to motor and vocal behaviors both during REM and NREM sleep [55]. In clinical settings, it is common to perform a differential diagnosis between RBD and OSA, based on the RSWA as a key feature for the RBD diagnosis [1].

Regarding SW and ST, these NREM parasomnias show complex, unaware, and aggressive or harmful motor and vocal behaviors, which might be mistaken for RBD episodes. However, SW/ST behaviors occur mostly during the first half of the night and always during Slow Wave Sleep (SWS) [1]. Consequently, the vPSG is the gold standard for a differential diagnosis between RBD and other sleep disorders.

Moreover, since the importance of operating a rapid and effective differential diagnosis to address different treatments and to indicate different prognoses, clinical information may also be useful. In this vein, the associated dream mentation features to the behavioral episodes may be suitable in terms of clinical implication to differentiate RBD from sleep disorders that mimic RBD symptoms.

In the literature, two studies [56][57] compared dreaming between RBD and OSA patients, and three studies [13][29][38] explored dreaming in RBDs and SWs or STs.

However, these works indicate in RBDs a prevalence of unpleasant and complex dreams [13][29][56][57], specifically containing attacks and violent contents [13][56]. However, this evidence refers to all retrospective dream collection. Indeed, when dream recall was performed immediately after the awakening in the sleep laboratory, these findings were completely reversed, showing in SWs/STs more complex and long dream reports, without significant difference in violent and unpleasant dreams [13].

One particular case regards sleep disorders due to trauma or severe anxiety states, such as PTSD. Despite PTSD not being considered a sleep disorder by the ICD-3 [4], sleep-related symptoms are common. Specifically, PTSD patients report sleep disturbances, hyperarousal, and sleep movements. Furthermore, intrusive thoughts and images are key features of the PTSD diagnosis, which occur as nightmares during the night [58]. As in RBD, an increased phasic and tonic electromyography (EMG) activity during REM sleep can be observed also in PTSD [59][60][61], caused by similar neuroanatomic abnormalities in both syndromes. Indeed, one of the hypotheses advanced points to a loss of neurons in the locus coeruleus in patients with RBD and with PTSD [62]. Despite RBD and PTSD sharing such clinical similarities, only one study in literature [63] described dream content between these two conditions. Although the authors provided only a descriptive overview not performing any statistical analysis, nevertheless the findings reported seem relevant. Indeed, 100% of PTSDs with and without RBD recalled dreams containing frightening emotions and unpleasant dreams related to past trauma; on the other hand, RBD patients without PTSD symptoms reported lower rates of frightening dreams (67%) and dreams related to trauma (42%). Conversely, pleasant dreams were reported in 17% of RBDs and never reported by PTSDs (with and without RBD).

This preliminary evidence suggests that nightmares are a PTSD hallmark, beyond the presence of RBD symptoms. However, further works investigating the relationship between nightmare occurrence and EMG activity in these two disorders would be interesting in order to consider similar neuropathological mechanisms underlying RBD and PTSD.

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