frontiers in
NEUROLOGY

MINI REVIEW ARTICLE
published: 17 May 2012
doi: 10.3389/fneur.2012.00082

Cognition in rapid eye movement sleep behavior disorder

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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by excessive muscle activity and undesirable motor events during REM sleep. RBD occurs in approximately 0.5% of the general population, with a higher prevalence in older men. RBD is a frequent feature of dementia with Lewy bodies (DLB), but is only rarely reported in Alzheimer's disease. RBD is also a risk factor for α-synuclein-related diseases, such as DLB, Parkinson's disease (PD), and multiple system atrophy. Therefore, RBD has major implications for the diagnosis and treatment of neurodegenerative disorders and for understanding specific neurodegeneration patterns. Several markers of neurodegeneration have been identified in RBD, including cognitive impairments such as deficits in attention, executive functions, learning capacities, and visuospatial abilities. Approximately 50% of RBD patients present mild cognitive impairment. Moreover, RBD is also associated with cognitive decline in PD.

Keywords: sleep, cognition, elderly, REM sleep behavior disorder, mild cognitive impairment, Parkinson's disease, dementia with Lewy bodies

DESCRIPTION OF RBD

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the presence of undesirable and often violent motor manifestations during REM sleep, such as laughing, shouting, reaching, gesturing, arm flailing, punching, kicking, sitting up, or leaping out of bed (Schenck et al., 1986). These behaviors are generally associated with dream contents: individuals appear to act out their dreams. The violent nature of some dream-enactment behaviors may cause severe injury to individuals with RBD or their bed partners (Schenck et al., 2009). RBD generally affects adults aged 50 years and over, with an estimated prevalence of about 0.5% in the general population (Ohayon et al., 1997). This rate may increase to about 7% in people aged 70 and over (Boot et al., 2012). RBD is predominantly reported in men, at a proportion of around 85% (Bodkin and Schenck, 2009). The reasons for this gender disproportion remain unclear (selection bias or a biological effect).

In normal individuals, muscular activity during REM sleep is suppressed (atonia). In RBD, the mechanisms responsible for atonia are altered, causing abnormally excessive chin or limb electromyographic activity during REM sleep (Montplaisir et al., 2010). This leads to the vigorous behavioral manifestations reported by patients and relatives, which can also be seen on infrared videotape in a sleep laboratory. The RBD diagnosis is confirmed by polysomnographic recording, including analyses of electromyographic activity during REM sleep (American Academy of Sleep Medicine, 2005). Polysomnographic recording has the additional advantage of eliminating other sleep disorders that are confused with RBD, such as somnambulism or moderate to severe sleep apneas. Questionnaires are also available for assessing clinical RBD (Li et al., 2010; Boeve et al., 2011). For treatment of RBD symptoms, clonazepam and melatonin are the two most commonly used pharmacological agents (Gagnon et al., 2006a; Aurora et al., 2010). Changing the sleep environment is also recommended to prevent injuries to the patient and the bed partner. Although the pathophysiology of RBD in humans is still debated, anomalies in the pontomedullary brainstem neural networks responsible for the suppression of muscle tone during REM sleep (i.e., the sublaterodorsal nucleus or coeruleus/subcoeruleus complex) are strongly suspected (Boeve et al., 2007; Luppi et al., 2011).

RBD SUBTYPES

There are different forms of RBD. The acute form is triggered by certain psychotropic drugs (pharmacology-induced RBD), such as antidepressants (Gagnon et al., 2006a). RBD is also strongly associated with certain neurological disorders (symptomatic RBD), including narcolepsy, Machado–Joseph disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, and Guillain–Barre syndrome (Gagnon et al., 2006b; Iranzo et al., 2009). Symptomatic RBD can also be induced by focal lesions (vascular or inflammatory), tumors, or neurodegenerative processes in brainstem regions responsible for normal REM sleep muscle atonia (Gagnon et al., 2006b; Iranzo et al., 2009; Limousin et al., 2009). In fact, RBD is very frequent in synucleinopathies, a class of neurodegenerative diseases characterized by abnormal deposition of α-synuclein proteins. For instance, RBD affects about 33–46% of patients with Parkinson's disease (PD; Gagnon et al., 2002; Sixel-Döring et al., 2011), 75% of patients with dementia with Lewy bodies (DLB; Ferman et al., 2011), and almost 100% of patients with multiple system atrophy (MSA; Vetrugno et al., 2004). Synucleinopathies share a common brainstem neurodegeneration with RBD, which may explain their strong association. On the other hand, RBD is rare in tau-related diseases such as Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia (Gagnon et al., 2006b; Iranzo et al., 2009). RBD is therefore a useful feature to consider for differential diagnosis between DLB and AD. In fact, inclusion of RBD as a core clinical feature improves the DLB diagnosis accuracy (Ferman

et al., 2011). Finally, RBD can appear alone ("idiopathic" RBD or iRBD) without any associated condition (Gagnon et al., 2006b; Iranzo et al., 2009). However, the term "idiopathic" is subject to challenge because iRBD may be a risk factor for synucleinopathies (Fantini et al., 2005; Ferini-Strambi, 2011).

"IDIOPATHIC" RBD AS A RISK FACTOR FOR SYNUCLEINOPATHIES

Three longitudinal studies performed in a sleep disorders center found that RBD is a significant risk factor for developing synucleinopathies. Schenck et al. (1996) reported in 29 iRBD patients that 38% had parkinsonism 3.7 years after RBD diagnosis. Another study in 44 iRBD patients found that 36% developed a synucleinopathy 5.1 years following RBD diagnosis (Iranzo et al., 2006). Of the converted patients, 56% developed PD, 38% DLB, and one patient developed MSA. Four additional patients with iRBD met the criteria for mild cognitive impairment (MCI) at follow-up. In 2009, our group published the follow-up results on a large cohort of 93 patients with iRBD: 28% developed a neurodegenerative disease 4.8 years following RBD diagnosis (Postuma et al., 2009a). Of the diseased patients, 54% developed PD, 42% DLB, and one patient developed MSA. Using a life table (survival) analysis, the risk for developing a synucleinopathy in iRBD patients was estimated at 18% after 5 years, 41% after 10 years, and 52% after 12 years (Postuma et al., 2009a).

In the only population-based study to date, Boot et al. (2012) followed 651 cognitively intact participants, including 44 individuals with baseline clinical iRBD. After a median of 3.8 years, only 2% of iRBD patients developed PD, whereas 32% met MCI criteria. Although the conversion rate was far lower than in previous clinical studies, the iRBD patients had a 2.2-fold increased risk of developing MCI or PD over non-RBD patients. A potential explanation for the link between RBD symptoms and the development of synucleinopathies comes from studies on the pathological progression of synucleinopathies (Braak et al., 2003; Halliday et al., 2011). In the first stages, before clinical motor symptoms appear, Lewy bodies and Lewy neuritis can be found in brainstem areas involved in RBD pathophysiology. The gradual progression of the neurodegeneration to more rostral brain structures would subsequently cause symptoms characteristic of synucleinopathies. This may explain why RBD is an early symptom in certain patients with synucleinopathies. These results show the importance of performing neurological and neuropsychological assessments to detect early signs of a synucleinopathy or MCI in iRBD patients, particularly for those referred to a sleep disorders center.

MARKERS OF NEURODEGENERATION IN "IDIOPATHIC" RBD

Several markers of synucleinopathies have been identified in iRBD. Recent studies have reported that the severity of the loss of REM sleep muscle atonia (Postuma et al., 2010), olfaction and color vision impairments (Postuma et al., 2011a), substantia nigra hyperechogenicity, and decreased striatal dopamine transporters uptake (Iranzo et al., 2010a) can predict the development of synucleinopathies in iRBD (Postuma et al., 2011b). Other studies have found cognitive (Ferini-Strambi et al., 2004; Gagnon et al., 2009), subtle motor (Postuma et al., 2009b), waking EEG (Fantini et al., 2003), autonomic (Miyamoto et al., 2006; Postuma et al., 2009b), and functional and structural neuroimaging (Unger et al., 2010; Hanyu et al., 2011; Scherfler et al., 2011; Vendette et al., 2011) anomalies in iRBD, similar to those reported in synucleinopathies (Gagnon et al., 2006b; Postuma et al., 2011b).

COGNITIVE DECLINE IN RBD

POOR COGNITIVE PERFORMANCE IN "IDIOPATHIC" RBD

Increasing evidence shows that iRBD patients perform poorly on neuropsychological tests (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). However, results vary across studies depending on which cognitive domain is impaired (**Table 1**). Population heterogeneity, small sample size, and the use of different cognitive tasks with variable sensitivity to detect deficits and variable specificity to a cognitive domain may explain these discrepancies. In general, attention, executive functions, episodic verbal memory (mainly free recall capacities), and non-verbal learning are the most affected domains in iRBD (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). Additionally, some studies reported in iRBD anomalies in visuospatial/visuoperceptive abilities (Ferini-Strambi et al., 2004; Iranzo et al., 2010b; Marques et al., 2010; Fantini et al., 2011), but this remains controversial (Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009). In fact, the presence of visuospatial (or non-verbal learning) impairment appears to be related to the extent of cognitive decline in iRBD patients (Iranzo et al., 2006; Molano et al., 2010; Fantini et al., 2011), as reported in RBD-associated neurodegenerative diseases such as PD or DLB (Ferman et al., 2002; Gagnon et al., 2009). On the other hand, language and praxis appear to be well preserved in iRBD, although these functions have received little research attention.

Table 1 | Controlled studies on cognitive performance in "idiopathic" rapid eye movement sleep behavior disorder.

Cognitive domains	Terzaghi et al. (2008)	Massicotte-Marquez et al. (2008)[a]	Gagnon et al. (2009)[a]	Marques et al. (2010)	Ferini-Strambi et al. (2004)[b]	Fantini et al. (2011)[b]
Attention/executive functions	Yes	Yes	Yes	Yes	Yes	No
Verbal episodic memory	Yes	Yes	Yes	Yes	Yes	Yes
Non-verbal memory	Yes	–	–	–	Yes	Yes
Visuospatial abilities	No	No	No	Yes	Yes	Yes

[a,b] *Share common participants; Yes = patients show poorer performance than controls ($p < 0.05$); No = similar performance between patients and controls.*

Box 1 | Case report.

Mister X is a 62-year-old man referred to a memory clinic for cognitive assessment. He complains about his reduced abilities to concentrate and recall information. The scan is normal. No vascular risk factors or major psychiatric symptoms are found. The neuropsychological exam shows mild deficits in cognitive tests assessing attention and episodic verbal memory (affected free recall capacities with preserved recognition). Daily life activities are reported as satisfactorily accomplished. Based on this clinical profile, Mister X meets the criteria for mild cognitive impairment. When questioned about his sleep, he reports the presence of violent behaviors associated with vivid dreams. His wife confirms this and reports that she sleeps in a separate bed to avoid potential injury. Mister X is referred to a sleep disorders center to confirm a diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD). The polysomnographic recording shows excessive chin muscle tone during REM sleep with no other anomalies. When these results are combined with the reports of dream-enactment behaviors, Mister X meets the RBD diagnosis criteria. Unfortunately, subsequent assessments at the memory clinic reveal cognitive decline, particularly in executive functions and visuospatial abilities. In addition, at the last visit, the patient reports a significant impact of the cognitive impairment on his daily life activities and shows signs of parkinsonism. The diagnosis of probable dementia with Lewy bodies is confirmed.

MCI IN "IDIOPATHIC" RBD

Mild cognitive impairment is known to be an intermediate state between normal cognitive functioning and dementia (Gauthier et al., 2006). MCI can be diagnosed according to the following criteria: (1) subjective cognitive complaint by the patient or a relative, (2) cognitive decline on neuropsychological testing compared to age- and education-equivalent individuals, and (3) preserved daily life activities (Gagnon et al., 2009; Albert et al., 2011). MCI can be subdivided into different subtypes according to the number (single-domain vs. multiple-domain) and nature (amnestic vs. non-amnestic) of the cognitive domains impaired (Petersen and Morris, 2005). MCI is a risk factor for dementia such as AD, DLB, or vascular dementia (Gauthier et al., 2006). However, the progression of MCI is also highly variable. Some MCI patients remain with mild cognitive deficits for many years whereas a substantial proportion return to normal cognitive functioning (Ganguli et al., 2004; Gauthier et al., 2006; Fischer et al., 2007). Moreover, several factors may disrupt cognition in elderly individuals, including psychiatric symptoms, medication side effects, respiratory conditions (sleep apneas, chronic obstructive pulmonary disease), and vascular diseases. Consequently, clinicians and researchers should be careful not to directly link MCI to the future development of a neurodegenerative disease or to consider MCI as part of a neurodegenerative disease.

Mild cognitive impairment is a frequent feature of iRBD (Iranzo et al., 2006; Gagnon et al., 2009; Molano et al., 2010). In iRBD patients referred to a sleep disorders center, MCI frequency was estimated at up to 50% compared to 8% in healthy subjects (Gagnon et al., 2009). The main MCI subtype reported was non-amnestic MCI single-domain with predominant attention and executive dysfunctions. No study to date has systematically followed a large cohort of iRBD patients with MCI to determine the risk of developing dementia. However, Molano et al. (2010) followed seven iRBD patients for many years. All patients met MCI criteria and subsequently developed Lewy body disease, which was confirmed by autopsy. This suggests that iRBD patients with MCI are at higher risk for developing DLB.

COGNITIVE DECLINE IN PD ASSOCIATED WITH RBD

A substantial proportion of PD patients have cognitive impairment, and more than 50% will develop dementia during the course of PD (Aarsland and Kurz, 2010). As mentioned above, RBD is also a frequent feature of PD (Gagnon et al., 2002; Sixel-Döring et al., 2011). RBD in PD patients has been associated with cognitive impairment (Sinforiani et al., 2006; Vendette et al., 2007; Gagnon et al., 2009; Naismith et al., 2011), waking EEG slowing (Gagnon et al., 2004), a predominance of akinetic-rigid signs (Postuma et al., 2008), symmetric disease (Bliwise et al., 2010), visual hallucinations (Pacchetti et al., 2005), and autonomic dysfunction (Postuma et al., 2009b, 2011c). Our team found a higher risk of having MCI in PD with concomitant RBD: MCI was present in 73% of PD patients with RBD compared to 11% of PD patients without RBD and 8% of healthy controls (Gagnon et al., 2009). Moreover, we recently conducted a prospective follow-up study in a cohort of PD patients to assess whether the presence of polysomnographic-confirmed RBD at baseline predicted the future development of dementia according to neurological and neuropsychological assessments (Postuma et al., 2012). The sample comprised 42 PD patients without dementia, including 27 with RBD and 15 without RBD. Over a mean 4-year follow-up, 48% of PD patients with RBD developed dementia, whereas none of PD patients without RBD converted to dementia. Although these results remain to be confirmed in a larger cohort of PD patients, they suggest that the presence of RBD in PD could indicate a more devastating and wide-spread neurodegenerative disease compared to PD patients without RBD symptoms (Postuma et al., 2012).

CONCLUSION

Box 1 summarizes a case report of an individual referred to a memory clinic for cognitive decline and subsequently diagnosed with RBD. This case shows the importance of identifying RBD in patients with cognitive impairment. A better understanding of this sleep disorder would enable a deeper grasp of the underlying pathophysiology and diagnosis of synucleinopathies, and would contribute to the development of neuroprotective treatments.

ACKNOWLEDGMENTS

The authors thank Dr. Jacques Montplaisir and Dr. Ronald Postuma for their contribution to the research program on cognition in REM sleep behavior disorder and Parkinson's disease. Our research is supported by the Canadian Institutes of Health Research and the Fonds de recherche du Québec – Santé.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 January 2012; accepted: 25 April 2012; published online: 17 May 2012.

Citation: Gagnon JF, Bertrand JA and Génier Marchand D (2012) Cognition in rapid eye movement sleep behavior disorder. Front. Neur. ***3****:82. doi: 10.3389/fneur.2012.00082*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.