Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease


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REM sleep behaviour disorder (RBD) is a parasomnia characterized by the loss of normal skeletal muscle atonia during REM sleep with prominent motor activity accompanying dreaming. The terminology relating to RBD, and mechanisms underlying REM sleep without atonia and RBD based on data in cat and rat are presented. Neuroimaging data from the few published human cases with RBD associated with structural lesions in the brainstem are presented, in which the dorsal midbrain and pons are implicated. Pharmacological manipulations which alter RBD frequency and severity are reviewed, and the data from human neuropathological studies are presented. An anatomic framework and new schema for the pathophysiology of RBD are proposed based on recent data in rat regarding the putative flip-flop switch for REM sleep control. The structure in man analogous to the subcoeruleus region in cat and sublaterodorsal nucleus in rat is proposed as the nucleus (and its associated efferent and afferent pathways) crucial to RBD pathophysiology. The association of RBD with neurological disease (‘secondary RBD’) is presented, with emphasis on RBD associated with neurodegenerative disease, particularly the synucleinopathies. The hypothesized pathophysiology of RBD is presented in relation to the Braak staging system for Parkinson’s disease, in which the topography and temporal sequence of synuclein pathology in the brain could explain the evolution of parkinsonism and/or dementia well after the onset of RBD. These data suggest that many patients with ‘idiopathic’ RBD are actually exhibiting an early clinical manifestation of an evolving neurodegenerative disorder. Such patients may be appropriate for future drug therapies that affect synuclein pathophysiology, in which the development of parkinsonism and/or dementia could be delayed or prevented. We suggest that additional clinicopathological studies be performed in patients with dementia or parkinsonism, with and without RBD, as well as in patients with idiopathic RBD, to further elucidate the pathophysiology and also characterize the clinical and pathophysiological relevance of RBD in neurodegenerative disease. Furthermore, longitudinal studies in patients with idiopathic RBD are warranted to characterize the natural history of such patients and prepare for future therapeutic trials.

Keywords: REM sleep behaviour disorder; parasomnia; dementia with Lewy bodies; Parkinson’s disease; multiple system atrophy; synuclein; synucleinopathy

Abbreviations: AD = Alzheimer’s disease; DLB = dementia with Lewy bodies; EEG = electroencephalographic; EMG = electromyographic; LC = locus coeruleus; LDTN = laterodorsal tegmental nucleus; LPT = lateral pontine tegmentum; MAPT = gene encoding microtubule associated protein tau; MCI = mild cognitive impairment; MCRF = magnocellular reticular formation; MSA = multiple system atrophy; PAF = pure autonomic failure; PD = Parkinson’s disease; PGRN = gene encoding progranulin; PPN = pedunculopontine nucleus; PPND = pallido-ponto-nigral degeneration; PSG = polysomnography;
Introduction

REM sleep behaviour disorder (RBD) is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming (Olson et al., 2000; Schenck and Mahowald, 2002). Herein, we discuss the terminology relating to RBD, and review the known and presumed neural networks involved in REM sleep and RBD pathophysiology based on animal models. We then turn to human RBD and review the pathophysiology of the parasomnia, focusing on pharmacological studies, lesion studies, and neuropathological studies. We propose an anatomic framework for studying the pathophysiology of human RBD. We conclude by discussing the association of RBD and neurodegenerative disease, and elaborate on the overlap of neurodegenerative disease and Parkinson’s disease. Our goals are to heighten awareness of the RBD-neurodegenerative disease association, stimulate further interest in understanding normal REM sleep, and better clarify the clinical and pathophysiological significance of RBD associated with neurodegenerative disease.

Terminology relating to REM sleep behaviour disorder

Some of the terms relating to RBD are confusing, and this terminology warrants clarification. In the absence of any associated neurological disorder, it is termed ‘idiopathic’ RBD. ‘Secondary’ or ‘symptomatic’ RBD refers to the combination of RBD plus another neurological disorder, such as narcolepsy or a neurodegenerative disease.

There are important similarities and differences between REM sleep without atonia, dream enactment behaviour and RBD. REM sleep without atonia (RSWA) refers to the electrophysiologic finding of loss of EMG atonia during REM sleep, which can be measured in animals and humans. Dream enactment behaviour refers to behaviour exhibited during sleep that is interpreted by an observer as ‘acting out dreams’. Dream enactment behaviour is certainly a core feature of RBD, but similar behaviour can also occur in untreated obstructive sleep apnea (Iranzo and Santamaria, 2005), as well as in sleepwalking and sleep terrors in adults, post-traumatic stress disorder, or as an effect of alcohol or drug administration or withdrawal (Schenck et al., 1989; Schenck and Mahowald, 2002). Hence, a history of recurrent dream enactment behaviour could be viewed as representing ‘clinically probable RBD’, and PSG confirmation of RSWA +/- complex motor behaviour during REM sleep in a patient with a history of recurrent dream enactment behaviour could be termed ‘definite RBD’ or ‘PSG-confirmed RBD’.

The recently published 2nd edition of the International Classification of Sleep Disorders requires the following for the clinical diagnosis of RBD (ICSD, 2005):

(i) Presence of RSWA on PSG.

(ii) At least one of the following:

(1) sleep-related, injurious, potentially injurious or disruptive behaviours by history (i.e. dream enactment behaviour) and/or

(2) abnormal REM sleep behaviour documented during polysomnographic monitoring.

(iii) Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.

(iv) The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder.

RSWA is, therefore, an electrophysiologic finding, and is one of the features sought on PSG when evaluating a patient for suspected RBD. Some have applied the term ‘subclinical’ or ‘preclinical’ RBD to patients with RSWA but without associated dream enactment behaviour (Pareja et al., 1996; Kimura et al., 1997). However, RSWA is not synonymous with RBD. While RSWA may represent ‘subclinical’ or ‘preclinical’ RBD in some individuals, there are insufficient longitudinal data in patients with RSWA to prove progression to the clinical syndrome. Thus we will reserve the term RBD for those with both abnormal REM sleep electrophysiology and abnormal REM sleep behaviour. The typical clinical features of RBD are shown in Table 1.

Current concepts on REM sleep, RSWA and RBD based on animal studies

The states of being in the existence of most animals occur in three states: wakefulness, non-REM (NREM) sleep and REM sleep. Essentially all animal species have some or all elements of REM sleep, which very likely represents some constitutive survival-based need since animals deprived of REM sleep die (Kushida et al., 1989); however, the precise benefit of sleep and particularly REM sleep in unknown. The loss of skeletal muscle tone, which is one of the hallmarks of REM sleep, can be measured electrophysiologically via surface electromyographic (EMG) leads over skeletal muscles.

Much of our knowledge of the neural substrates of REM

sleep is based on animal studies over the past 40 years,
primarily involving the cat and rat. Paradoxical sleep in animals is the state analogous to REM sleep in humans.

**Studies in cat**

Studies in cat suggested that there are two motor systems involved in normal REM sleep: one for generating muscle atonia and one for suppressing locomotor activity. Figure 1 incorporates data and concepts derived from multiple groups of investigators (Jouvet and Delorme, 1965; Hendricks et al., 1982; Lai and Siegel, 1988, 1990; Shouse and Siegel, 1992; Lai and Siegel, 1997a, b; Morrison, 1998; Rye, 1998).

In this schema, the absence of motor activity in normal REM sleep occurs via active inhibition of spinal motoneurons (shown in the network on the right in Fig. 1) plus reduced drive within locomotor generators (shown on the left in Fig. 1). While phasic oculomotor and locomotor activity such as REM and brief and low amplitude muscle twitches occur as normal phenomena in REM sleep, more elaborate motoric activity is directly or indirectly suppressed (Mahowald and Schenck, 2000).

The final common pathway of spinal motor neuron inhibition was inferred to be via the medullary magnocellular reticular formation (MCRF); this inhibitory nucleus is known to suppress anterior horn cell activity via projections of the ventrolateral reticulospinal tract (VLST). Several pontine nuclei are known to influence the REM and non-REM sleep circuits, including the noradrenergic locus coeruleus (LC) and the cholinergic nuclei, pedunculopontine nucleus (PPN) and laterodorsal tegmental nucleus (LDTN). In addition, forebrain structures have been tied into these circuits: substantia nigra, hypothalamus, thalamus, basal forebrain and frontal cortex. However, the precise interactions of these nuclei, and their roles in normal REM sleep have been unclear.

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**Table 1** Typical clinical features of REM sleep behaviour disorder

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Male gender predilection</td>
<td>Mean onset age 50–65 years (range childhood—80 years)</td>
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<tr>
<td>Vocalizations, swearing, screaming</td>
<td>Motor activity varies from simple limb jerks to complex motor behaviour, with injuries to patient or bedpartner</td>
</tr>
<tr>
<td>Dreams often involve chases or attacks by animals or humans</td>
<td>Exhibited behaviours mirror dream content</td>
</tr>
<tr>
<td>Behaviors tend to occur in latter half of the sleep period</td>
<td>When associated with neurodegenerative disease, RBD often precedes dementia and/or parkinsonism by years or decades</td>
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**Fig. 1** Control of REM sleep based on the study of cat. See text for details. Excitatory projections represented by encircled plus sign, inhibitory projections represented by encircled minus sign, with the size of these symbols representing the relative effect of each projection on the synapsing nuclei. Normally populated nuclei are represented by coloured circles or ovals. EMG = electromyographic, REM = rapid eye movement. Adapted from Boeve *et al.* (2003b). Reprinted with permission from Human Press, Inc.
The brainstem regions that have classically been considered in RBD pathophysiology based on lesion studies in cat include the MCRF, locus coeruleus/subcoeruleus complex, PPN, LDTN and possibly substantia nigra (SN) (Fig. 2) (Jouvet and Delorme, 1965; Hendricks et al., 1982; Lai and Siegel, 1988, 1990; Shouse and Siegel, 1992; Lai and Siegel, 1997a, b; Morrison, 1998; Rye, 1998). Although these studies have identified components of REM sleep circuits, the primary sites and interactions have been debated. Lesions in the MCRF release the tonic inhibition on spinal motoneurons, leading to RSWA, but these lesions also destroyed fibres of passage. Lesions in the coeruleus/subcoeruleus complex cause RSWA, and the site and size of the lesion determines whether simple or complex behaviours are exhibited (Hendricks et al., 1982). There is also debate whether lesions in the PPN cause REM sleep without atonia (Rye, 1997, 1998; Morrison, 1998). The substantia nigra has been proposed as a component of this REM sleep system, but there is a paucity of direct evidence to implicate this nucleus. Similarly, no convincing examples of RSWA nor RBD that have resulted from diencephalic or telencephalic lesions have been reported to date. Most evidence now suggests populations of neurons that are considered ‘REM-on’ cells in the subcoeruleus region are central to REM sleep and the associated EMG atonia (Siegel, 2006).

**Studies in rat**

The principle nuclei mediating REM sleep and the interactions with other brainstem and forebrain nuclei has recently been clarified via elegant work in rat (Fig. 3). The sublaterodorsal (SLD) nucleus identified by Boissard et al., which is equivalent to the subcoeruleus or peri-locus coeruleus in the cat, is the major structure responsible for REM sleep (Boissard et al., 2002, 2003). More recent work has led to the concept of a putative on/off switch for control of REM sleep (Lu et al., 2006). The proposed nuclei and pathways involved in REM sleep control are based on lesioning, anterograde tracing, and c-Fos protein expression in the rat. While homologous structures in humans have yet to be precisely defined, this new and more complex schema allows many hypotheses to be tested.

In this model, the ventrolateral part of the periaqueductal grey matter (vPAG) and the lateral pontine tegmentum (LPT) represent the REM-off region; i.e. these nuclei turn off REM sleep. Lesions of these nuclei increase the amount of REM sleep. This region is regulated by multiple afferents. It is inhibited by GABAergic and galanin-ergic projections from the forebrain ventrolateral preoptic nucleus (eVLPO) plus the cholinergic projections from the PPN/LDTN. The vPAG and LPT REM-off neurons are activated by...
projections from the noradrenergic LC, serotonergic raphe nucleus (RN) and importantly, by hypocretinergic pathways from the lateral hypothalamus. Of clinical relevance, narcolepsy is characterized by inappropriate intrusions of REM sleep and severe reductions of brain hypocretin; this could be explained by loss of this hypocretin projection, thereby tipping the balance in favor of REM-on firing.

The REM-on region has reciprocal interactions with the REM-off area and these structures are mutually inhibitory. The REM-on region is represented by the sublaterodorsal nucleus and the precoeruleus (PC) region. Studies in rat indicate that the SLD contains glutamatergic neurons that project to the medulla and the spinal cord, where they contact inhibitory interneurons that hyperpolarize anterior horn motor neurons during REM sleep. This occurs via glutamatergic projections from the SLD to ventral horn glycinergic and GABAergic interneurons; these inhibit the spinal cord motor neurons, resulting in atonia during REM sleep. There are projections from the SLD to MCRF which may be active during REM sleep, but they are not required for the generation of EMG atonia during REM sleep. It also appears that the theta electroencephalographic (EEG) activity characteristic of REM sleep occur via precoeruleus glutamatergic projections to the medial septum, which activates the hippocampi and other structures.

Considering the recently reported lesioning studies in the rat, in which the REM sleep-on region, REM sleep-off region, REM sleep muscle atonia region and REM sleep theta EEG activity promoter region were identified (Lu et al., 2006), the following model is proposed for REM sleep without atonia in rat (Fig. 4). Lesions to the SLD nucleus leads to disinhibition of spinal motoneurons, resulting in increased EMG tone during REM sleep (Lu et al., 2006). Lesions of MCRF neurons, sparing fibres of passage, failed to alter EMG atonia in REM sleep (Lu et al., 2006); thus, prior lesioning studies implicating the MCRF in REM sleep atonia may have inadvertently disrupted the descending SLD projections, which accounted for the findings.

Current concepts on RSWA and RBD based on human studies
Insights into the pathophysiology of RSWA and RBD in humans can be appreciated by considering drug effects, radiographic lesion studies and neuropathological studies.

Insights from pharmacotherapy in humans
No randomized, double-blind, placebo-controlled study has ever been reported for any drug treatment for RBD. Yet, numerous medications have been tried over the past...
20 years to reduce the frequency and severity of RBD, with clonazepam being the most successful agent (Schenck and Mahowald, 1990, 2002; Olson et al., 2000), and melatonin also showing efficacy alone or in combination with clonazepam (Kunz and Bes, 1999; Boeve et al., 2003a) (Table 2). Interestingly, clonazapam has little effect on EMG tone in REM sleep on PSG despite near complete suppression of clinical RBD; whereas partial restoration of normal EMG atonia during REM sleep has been observed in RBD patients treated with melatonin (Takeuchi et al., 2001). Thus, these two agents may affect different aspects of the pathophysiological circuitry of RBD. Levodopa (Tan et al., 1996; Rye, 1998; Yamouchi et al., 2003) and pramipexole (Fantini et al., 2003a) reduce the clinical manifestations of RBD, but may do this via suppression of REM sleep. Other drugs with inconsistent effects include carbamazepine (Bamford, 1993),

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**Table 2** Drugs that significantly alter the frequency and/or severity of REM sleep behaviour disorder (RBD)

<table>
<thead>
<tr>
<th>Agents that tend to decrease the frequency and/or severity of RBD</th>
<th>Agents that tend to increase the frequency and/or severity of RBD</th>
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<tbody>
<tr>
<td>Clonazepam</td>
<td>Donepezil</td>
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<tr>
<td>Melatonin</td>
<td>Galantamine</td>
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<tr>
<td>Levodopa</td>
<td>Triazolam</td>
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<tr>
<td>Pramipexole</td>
<td>Clozapine</td>
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<tr>
<td>Carbamazepine</td>
<td>Quetiapine</td>
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<tr>
<td>Tricyclic antidepressants (particularly amitriptyline)</td>
<td>Selective serotonin and norepinephrine reuptake inhibitors (particularly venlafaxine and mirtazapine)</td>
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<tr>
<td>Chocolate</td>
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**Fig. 4** Pathophysiology of REM sleep without atonia based on studies in rat. See text for details. Excitatory projections represented by encircled plus sign, inhibitory projections represented by encircled minus sign, with the size of these symbols representing the relative effect of each projection on the synapsing nuclei. Nuclei are represented by circles or ovals, with solid coloured circles and ovals reflecting those with normal populations of neurons, and speckled circles and ovals reflecting those with significantly reduced populations of neurons. A cross sign reflects ablation of a nucleus. The relative tonic influences of each projection are represented by line thickness, with thicker lines depicting stronger influences, thinner lines depicting weaker influences, and dashed and dotted lines depicting weak influences due to damage to neurons in the respective nuclei. The REM-off region is represented by the vlPAG and LPT in red, and the REM-on region is represented by the PC and SLD in green. The SLD projects to spinal interneurons (‘direct route’, denoted by the dotted line from SLD to spinal interneurons) and represents the final common pathway that causes active inhibition of skeletal muscle activity in REM sleep. The ‘indirect route’, denoted by the dashed line from SLD to the MCRF to the spinal interneurons, may also contribute to EMG atonia. However, lesions in structures which project to and from the MCRF, and lesioning the MCRF itself, are not considered critical in altering EMG atonia during REM sleep in animal models.
donepezil (Ringman and Simmons, 2000) and quetiapine (Boeve et al., 2001a, 2004). Many other drugs, such as benzodiazepines (other than clonazepam), tricyclic antidepressants and antiepileptic agents, have been tried with generally poor response.

There is growing evidence implicating the newer generation antidepressant agents, particularly venlafaxine and mirtazapine (Husain et al., 2001; Schenck and Mahowald, 2002; Onofrj et al., 2003b; Winkelman and James, 2004), are frequent precipitators or aggravators of RBD. Chocolate (Vorona and Ware, 2002) and caffeine (Stolz and Aldrich, 1991) consumed in excess have also been implicated with RBD.

Any theory on RBD pathophysiology must explain these positive and negative responses to various therapies, but no adequate hypothesis has been suggested as yet that adequately takes these factors into account. It appears that a complex interplay of noradrenergic, serotonergic, cholinergic and other neurochemical systems are involved in RBD pathogenesis.

**Insights from lesion studies**

To our knowledge, there are five cases of RBD associated with lesions in the brainstem. Kimura et al. reported on a 75-year-old woman who had PSG-verified RBD associated with a presumably ischaemic lesion in the left upper pons (Fig. 5, Kimura et al. case) (Kimura et al., 2000). A 25-year-old patient with relapsing–remitting multiple sclerosis (MS) had several hyperintensities in cerebral and pontine white matter (imaging studies not shown in this report) (Plazzi and Montagna, 2002). We also recently evaluated a 51-year-old female patient with MS who developed RBD, verified by PSG, suddenly after experiencing an MS exacerbation which was associated with a new demyelinating lesion in the dorsal pontine tegmentum (Fig. 5, Tippmann-Peikert et al. case) (Tippmann-Peikert et al., 2006a). A 32-year-old patient who underwent a second surgical procedure for a tegmental ponto-mesencephalic cavernoma developed RBD (Fig. 5, Provini et al. case) (Provini et al., 2004). Additionally, a 59-year-old male with a 6-year history of essentially nightly RBD was found to have a brainstem neurinoma, and dream enactment behaviour disappeared after resection of the tumor (not shown in Fig. 5) (Zambelis et al., 2002). Based on the imaging findings in these reports, these cases indicate that lesions within or near the mesencephalic and pontine tegmentum can be associated with human RBD. Nevertheless, the specific nuclei, projections and neurochemical systems involved in human RBD pathophysiology are not adequately characterized. Clearly, neuroimaging of patients with acute onset RBD may further enhance our understanding of the neuroanatomic systems involved in RBD.

**Insights from neuropathological studies**

Additional insights have been gained by the neuropathological study of patients with idiopathic or secondary RBD. Only one case of PSG-proven idiopathic RBD that has undergone neuropathological examination has been reported, and ‘incidental Lewy body disease (LBD)’ was identified in this patient (Uchiyama et al., 1995). The distribution of

![Published cases with RBD associated with brainstem lesions shown as approximate lesions on human brainstem templates](http://brain.oxfordjournals.org/)

**Fig. 5** Published cases with RBD associated with brainstem lesions shown as approximate lesions on human brainstem templates. Letters represent cross-sectional views through the brainstem, with A corresponding to the pontomesencephalic junction, B to the upper/mid pons, C to lower/mid pons and D just rostral to the pontomesencephalic junction. The approximate locations of the lesions based on the magnetic resonance imaging (MRI) data associated with the three published cases are shown.
Lewy bodies in this case would now be classified as brainstem-predominant Lewy body disease (LBD) or PD stage 3 (McKeith et al., 1996, 2005; Braak et al., 2003). Due to the severe neuronal loss and gliosis in the substantia nigra (SN) and coeruleus/subcoeruleus complex in their case, the authors postulated that degeneration of brainstem monoaminergic neurons explained RBD (Uchiyama et al., 1995). However, the focus was on monoaminergic nuclei in this case and it is unclear whether other brainstem nuclei were carefully examined.

We have recently encountered another patient with a 15-year history of idiopathic RBD and no associated neurological symptoms, who died (at age 72 years); neuropathological examination revealed brainstem-predominant Lewy body disease, yet only mild degeneration of the SN, LC and raphe nuclei was present (Boeve et al., 2007). These findings therefore argue against degeneration of the monoaminergic SN and LC being the primary cause of idiopathic RBD.

We have also performed PSG in six affected and five genealogically at risk family members of the pallido-pontonigral degeneration (PPND) kindred, who have the N279K mutation in the microtubule associated protein tau (MAPT) (Boeve et al., 2006). None of the subjects had any history of dream enactment behaviour. Nine of the eleven members attained sufficient REM sleep on PSG, and the electrophysiologic features of RSWA and behavioural manifestations of RBD were absent in all subjects. Neuropathological examination in four affected individuals revealed marked nigral degeneration in three along with mild degenerative changes in the locus coeruleus, pontine gray and pontine tegmentum. These findings also argue against nigral degeneration being sufficient to cause RBD.

Two other studies have reported neuronal quantification in RBD patients. In one case of RBD associated with combined Lewy body with Alzheimer’s disease pathology, marked neuronal loss within the locus coeruleus but higher density of cholinergic mesopontine neurons were found (Schneck et al., 1996b, 1997). One interpretation of these data is that the increase in cholinergic neurons and possible disinhibition of these neurons by the reduced number of locus coeruleus neurons led to increased REM sleep drive and RBD (Schneck et al., 1996b). In the other analysis, four patients with multiple system atrophy (MSA) were studied—these four cases had depletion of the cholinergic neurons in the pedunculopontine nucleus/laterodorsal tegmental nucleus as well as neurome lanin-containing locus coeruleus neurons (Benarroch and Schmeichel, 2002). Depletion of cholinergic neurons in the pedunculopontine nucleus/laterodorsal tegmental nucleus neurons was thought to possibly underlie RBD in these patients (Benarroch and Schmeichel, 2002) and could conceivably explain the occasional benefit of cholinesterase inhibitors, such as donepezil, in RBD (Ringman and Simmons, 2000) and the presence of RBD in some patients with PSP (Arnulf et al., 2005). However, the recent experimental evidence discussed above (Lu et al., 2006) indicates that cholinergic mechanisms may have a modulatory role in REM-related phenomena rather than a primary role in RSWA. The disparate findings in the pedunculopontine nucleus/laterodorsal tegmental nucleus in the two studies noted above suggest alterations in the pedunculopontine nucleus/laterodorsal tegmental nucleus nuclei do not fully account for RBD pathogenesis. It should be noted that the LC is silent during REM sleep (Gervasoni et al., 2000; Lu et al., 2002) and hence this nucleus, per se, should not be directly responsible for RBD.

**Proposed anatomic substrate for REM sleep control in humans**

If we extrapolate the findings on REM sleep control in the rat model to humans, one could propose a similar network of nuclei and projections as depicted in Fig. 4, with the locations of specific nuclei in the human brainstem as shown in Fig. 6. There may be species-specific differences in REM sleep control (Siegel, 2006), and thus further analyses in humans will be necessary to determine how similar REM sleep control and dyscontrol is between humans and animal models, particularly with respect to the structure(s) in humans analogous to the subcoeruleus in cat and sublaterodorsal nucleus in rat.

**Proposed pathophysiology of human RBD**

Based on the available animal and human lesion and pathological data as well as the known brainstem structures in humans, a schematic representation underlying RBD in humans is proposed in Fig. 7. This schema is clearly a work in progress, with other pertinent structures and neurochemical systems perhaps not yet identified, or not yet known to contribute to REM sleep physiology. We hypothesize that the structures and networks are similar to the animal models, with the SLD or analogous nucleus with projections to spinal interneurons (‘direct route’, denoted by the dotted line from SLD to spinal interneurons in Fig. 7) being the final common pathway that causes active inhibition of skeletal muscle activity in REM sleep. The ‘indirect route’ (denoted by the dashed line from SLD to spinal interneurons in Fig. 7) can also contribute, with SLD lesioning causing reduced excitation of the MCRF, thereby causing a net reduced inhibition of spinal motoneurons (either directly or via spinal interneurons). It remains to be seen if lesioning or degeneration of the MCRF is sufficient to cause RBD in humans.

The locomotor generators, which are presumed to project to the spinal motoneurons either directly or indirectly via other brainstem nuclei, have yet to be identified and characterized. The neuronal circuitry for this process is poorly understood, and supratentorial influences on both the locomotor generators and the muscle atonia system are likely. One might expect a variety of stimuli could alter locomotor drive and/or muscle atonia, such as other primary sleep disorders (e.g. obstructive sleep apnea), neurodegeneration,
structural lesions in the brainstem, medications, illicit drugs, head trauma, etc.

If the brainstem lesions associated with RBD as shown in Fig. 5 are superimposed on the proposed nuclei involved in REM sleep control as shown on Fig. 6, one can see that two of the lesions involve the region expected to represent the SLD (Fig. 8). Since the caudal extent of the lesion in the instructive case reported by Provini et al. (2004) cannot be surmised based on the reported MRI, it is not known if the proposed SLD region is necessarily involved in every instance of RBD associated with a brainstem lesion. It also remains to be seen if lesions that either affect the REM-off region or projections to and from the REM-on region are sufficient to cause RBD in humans.

Increased phasic locomotor drive and/or loss of REM sleep atonia has been suggested as the likely mechanism for the clinical expression of human RBD (Mahowald and Schenck, 2000). As noted earlier, some patients have PSG evidence of RSWA but have never exhibited dream enactment behaviour. One could propose that lesions to, degeneration of, or pharmacological manipulations of the SLD or MCRF would be sufficient to cause RSWA but insufficient to cause dream enactment behaviour. One could also posit that processes that activate the locomotor generators may overcome the tonic inhibition of the SLD or MCRF on spinal motoneurons, potentially leading to occasional dream enactment behaviour. This could explain why patients with moderate to severe obstructive sleep apnea, who have increased REM sleep drive due to the sleep fragmentation inherent to untreated obstructive sleep apnea, exhibit features indistinguishable from RBD, except that EMG atonia in REM sleep is typically normal on PSG (Iranzo and Santamaria, 2005). Administration or discontinuation of drugs could cause similar effects.

RBD is a dream disorder almost as much as a REM motor disorder (Fantini et al., 2005), and the tendency for the dream content to involve an aggressive, attacking or chasing theme is well-known but poorly understood (Olson et al., 2000; Schenck and Mahowald, 2002; Fantini et al., 2005). RBD is often considered to reflect an individual ‘acting out one’s dream’, implying that the dream content dictates the vocalizations and motor behaviours that are exhibited. Yet another explanation involves the concept of ‘dreaming around one’s actions’. In other words, the loss of EMG atonia and increased locomotor drive could lead to limb movements, and the dream content could evolve secondarily around what is exhibited. We have heard many patients describe dreams that seemed to emanate from physical stimuli occurring at the time. Examples include patients who describe dreams about being in an earthquake if they are sleeping in a car while traveling on a bumpy road, and the potentially dangerous experience of dreaming that a person is grabbing and attacking them when in fact their spouse is grabbing the patients’ arms in an attempt to
suppress the fighting behaviour during a dream; the latter can lead to injuries to the bedpartner. These two phenomena of ‘acting out one’s dreams’ and ‘dreaming around one’s actions’ are not mutually exclusive, and could be working in concert.

In those with pervasive RBD, it is likely that sufficient locomotor drive is necessary in the setting of RSWA to result in clinical RBD on a nightly basis. Yet, we have observed many patients with RBD, whether ‘idiopathic’ or associated with a neurological disorder, who report that their nightmares and dream enactment behaviour tend to cluster. That is, such patients may experience RBD features many times over several nights or weeks, alternating with periods of weeks or months when no nightmares or episodes of dream enactment behaviour occur. Few are ever able to describe any consistent pattern of food or beverage ingestion, change in sleeping, change in exercise, emotional stressors or drugs that adequately explains this clustering effect. We do not have a clear explanation for this phenomenon, but clustering is well-known in other neurological disorders, such as cluster and migraine headaches as well as seizures, and perhaps a similar mechanism could result in RBD clustering.

Clinical and pathophysiological relevance of RSWA and RBD associated with human neurodegenerative disease

The REM sleep behaviour disorder—neurological disorder association

RBD has been reported in association with many aetiological categories of neurological disorders (i.e. secondary RBD), including vascular lesions, tumours, demyelinating disease (examples of these are described earlier), autoimmune/inflammatory disorders and neurodegenerative disorders (described later). Within the autoimmune/inflammatory
disorder spectrum, RBD is often associated with narcolepsy (Schenck and Mahowald, 1992; Nightingale et al., 2005) and more recently has been reported with limbic encephalitis associated with voltage-gated potassium channel antibodies (Iranzo et al., 2006a). These disorders may reflect autoimmune/inflammatory processes affecting the structures and pathways involved in RBD pathophysiology as shown in Fig. 7. Quantitative neuropathological studies in brainstem nuclei of autopsied patients with narcolepsy and limbic encephalitis associated with voltage-gated potassium channel antibodies, with and without RBD, could help delineate the key nuclei involved in human RBD.

The REM sleep behaviour disorder—neurodegenerative disease association

Numerous cases of RBD have been reported in association with clinically diagnosed Parkinson’s disease (Schenck et al., 1986; Silber and Ahlskog, 1992; Silber et al., 1993; Tan et al., 1996; Sforza et al., 1997; Comella et al., 1998; Kunz and Bes, 1999; Rye et al., 1999; Arnulf et al., 2000; Olson et al., 2000; Gagnon et al., 2002; Onofrj et al., 2002, 2003a, b; Eisensehr et al., 2003; Fantini et al., 2003a; Iranzo et al., 2005; Ozekmekci et al., 2005; Pacchetti et al., 2005; Scaglione et al., 2005; Hanoglu et al., 2006; Iranzo et al., 2006b; Sinforniani et al., 2006), dementia with Lewy bodies (Boeve et al., 1998, 2001b, 2003a, b, c; Ferman et al., 1999; Ferman et al., 2002; Massironi et al., 2003; Ferman et al., 2004, 2006; Iranzo et al., 2006b), multiple system atrophy (Coccagna et al., 1985; Quera Salva and Guilleminault, 1986; Schenck et al., 1986, 1987; Wright et al., 1990; Manni et al., 1993; Tison et al., 1995; Plazzi et al., 1997; Sforza et al., 1997; Tachibana et al., 1997; Olson et al., 2000; Tachibana and Oka, 2004; Iranzo et al., 2005, 2006b). Pure autonomic failure has also been reported (Sforza et al., 1997; Weyer et al., 2006). RBD was identified in several members of a kindred with a parkin mutation (Kumru et al., 2004), and Lewy body disease pathology has been reported in a different large kindred with parkin mutations (Pramstaller et al., 2005). The association of RBD with PD, DLB, MSA, PAF and other disorders with Lewy body pathology is therefore clearly established. In fact, RBD is now considered a suggestive feature in the clinical diagnostic criteria for DLB (McKeith et al., 2005).

RBD has been reported in two cases of clinically suspected sporadic PSP (Sforza et al., 1997; Olson et al., 2000) and in 2/15 (13%) of a group of PSP subjects (Arnulf et al., 2005). Spinocerebellar atrophy—type 3 (SCA-3) has also been reported associated with dream enactment behaviour (although few have had PSG confirmation) (Friedman, 2002; Fukutake et al., 2002). One case of RBD with amyotrophic lateral sclerosis has also been identified (Sforza et al., 1997). RSWA has been reported in a single case of sporadic CBD (Kimura et al., 1997), but this patient did not have clinical RBD features. There are no published reports of RBD associated with Pick’s disease, frontotemporal dementia, progressive nonfluent aphasia syndrome, semantic dementia, progressive subcortical gliosis, argyrophilic grain disease or dementia lacking distinctive histopathology.
(Boeve et al., 2001b), and no evidence of RSWA or RBD was found in a recent study of 11 members of the pallido-pontonigral degeneration kindred (Boeve et al., 2006). One case of clinically diagnosed Alzheimer’s disease was associated with RBD (Schneck et al., 1996b), but neuropathological analysis identified both Alzheimer’s disease and Lewy body disease (Schneck et al., 1997). We (Boeve et al., unpublished data) and others (Gagnon et al., 2006a, b) have observed sparse cases of RBD associated with clinically probable AD, but until neuropathological examinations are completed on such cases, it remains to be seen if RBD occurs in pure AD.

The REM sleep behaviour disorder—synucleinopathy association

Recent immunocytochemical analyses have revealed that Parkinson’s disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and pure autonomic failure (PAF) share the similarity of α-synuclein positive intracellular inclusions (Spillantini et al., 1998; Dickson et al., 1999; Arai et al., 2000), and these disorders are now considered collectively as the ‘synucleinopathies’. Most other neurodegenerative and prion disorders can be classified as ‘tauopathies’, ‘prionopathies’ and ‘polyglutamine triplet repeat disorders’ (Hardy, 1999; Hardy and Gwinn-Hardy, 1999), with the very recent addition of ‘hypo-progranulinopathies’ representing frontotemporal dementia and/or parkinsonism associated with mutations in progranulin (PGRN) and frontotemporal degeneration with ubiquitin-positive inclusions pathology (Baker et al., 2006). Several reports over the past few years have led to the appreciation that RBD is frequently associated with the synucleinopathies and less frequently with the non-synucleinopathy neurodegenerative disorders (Boeve et al., 2001b, 2003a, b, c; Ozekmekci et al., 2005; Stiasny-Kolster et al., 2005; Gagnon et al., 2006b; Iranzo et al., 2006b).

Our clinicopathological experience at Mayo Clinic of RBD associated with dementia and/or parkinsonism, updated from our prior report (Boeve et al., 2003c), is shown in Table 3. These cases represent patients who satisfy all of these criteria: (i) have been diagnosed with probable or definite RBD based on a history of recurrent dream enactment behaviour +/- PSG confirmation; (ii) have experienced parkinsonism and/or dementia and have been clinically diagnosed with Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, Parkinson’s disease (with or without dementia), multiple system atrophy, frontotemporal dementia, primary progressive aphasia/progressive non-fluent aphasia syndrome/semantic dementia, corticobasal syndrome, posterior cortical atrophy or progressive supranuclear palsy based on established criteria; and (iii) have undergone autopsy and been neuropathologically diagnosed with Alzheimer’s disease, Lewy body disease, vascular dementia, multiple system atrophy, Pick’s disease, frontotemporal lobar degeneration with or without ubiquitin-positive inclusions, frontotemporal dementia and parkinsonism due to a mutation in microtubule associated protein tau, corticobasal degeneration, argyrophilic grain disease or progressive supranuclear palsy based on established criteria. As can be seen, 35/36 (97%) of such cases have had an underlying synucleinopathy. Over this same time period, well over 300 cases with a non-synucleinopathy disorder verified neuropathologically had no history of dream enactment behaviour. Therefore, the clinical and pathological literature suggests that when associated with a neurodegenerative disorder, RBD often (but not always) reflects an underlying synucleinopathy (Boeve et al., 2001b, 2003b, c; 2004; Stiasny-Kolster et al., 2005; Boeve and Saper, 2006; Gagnon et al., 2006b; Iranzo et al., 2006b; Postuma et al., 2006).

The frequency of RBD is ~33–60% in PD patients (Comella et al., 1998; Gagnon et al., 2002), 50–80% in DLB patients (Boeve et al., 2004) and 80–95% of MSA patients (Plazzi et al., 1997; Tachibana et al., 1997), but these frequencies are based on convenience samples of patients with these disorders evaluated at specialized centres. The true frequency of RSWA and RBD in the various neurodegenerative disorders will require PSGs to be performed in a population-based manner in all subjects with a neurodegenerative disease (or at least by a random sampling method) regardless of a history of dream enactment behaviour or not, and then all study participants will then require neuropathological examination. Due to the rarity of some neurodegenerative disorders, problem of identifying or sampling appropriate subjects, expense required to examine subjects and perform PSGs, infrastructure needed to secure autopsies and surely other issues, determining the true frequency of RSWA and RBD in the various neurodegenerative disorders will indeed be challenging.

Among the non-synucleinopathy disorders associated with RBD (e.g. PSP, SCA-3 and AD), patients have tended to have RBD evolve in concert with or after the onset of parkinsonism, whereas RBD typically begins years before the onset of cognitive and motor features of PD, DLB, MSA and PAF. Hence, RBD preceding the motor and cognitive features of a neurodegenerative disorder may be particularly specific for synucleinopathies.

<table>
<thead>
<tr>
<th>Pathological diagnoses</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy body disease</td>
<td>31</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>4</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
</tr>
</tbody>
</table>

aTwelve of the LBD cases also met criteria for intermediate or high likelihood of Alzheimer’s disease.
bCoexisting vascular and Alzheimer pathology was present.
The one patient we followed longitudinally with the corticobasal syndrome who had a long history of dream enactment behaviour was ultimately found to have mixed Lewy body disease/Alzheimer’s disease pathology, again exemplifying the need to perform neuropathological examination in patients with probable or definite RBD. This is the only patient with the corticobasal syndrome among over 50 patients evaluated at our institution with this clinical diagnosis over the past 10 years who had a history suggesting RBD. Despite evaluating over 200 patients with clinically diagnosed progressive supranuclear palsy also over the past 10 years, and pathologically characterizing well over 400 PSP brains as part of the Society for Progressive Supranuclear Palsy Brain Bank (D.W. Dickson et al., unpublished data), a history of recurrent dream enactment behaviour in clinically and/or pathologically diagnosed PSP is extremely uncommon in our experience. Our experience and the literature published to date clearly indicates that RBD is more frequent in the synucleinopathies than in the non-synucleinopathies, which suggests that despite the presence of parkinsonism as well as pathologically verified nigral degeneration in most synucleinopathies, tauopathies and other neurodegenerative disorders, there are likely other abnormalities in the brainstem that are different between the synucleinopathy and non-synucleinopathy disorders that explain the differential expression of RBD.

The tendency of RBD to occur frequently in the synucleinopathies and rarely in the tauopathies and other neurodegenerative disorders supports the concept of selective vulnerability occurring in key brainstem neuronal networks in the synucleinopathies, and such neuronal networks are likely to be less dysfunctional or normal in the tauopathies and other neurodegenerative disorders (Boeve et al., 2001b, 2003b, c, 2004; Boeve and Saper, 2006; Gagnon et al., 2006b; Iranzo et al., 2006b). PD, DLB, MSA, the other few non-synucleinopathy disorders associated with RBD and the rare RBD cases with structural brainstem lesions may provide particular insights into RBD pathophysiology by demonstrating which neuronal networks are dysfunctional compared to the multitude of disorders and cases that are not associated with RBD. Comparing the neuropathological findings (especially if neuronal quantification of key brainstem structures can be performed) in the rare cases of RBD associated with non-synucleinopathy disorders to the more common cases of non-synucleinopathy disorders not associated with RBD may be particularly enlightening.

**Overlap of brainstem nuclei degeneration in Parkinson’s disease and REM sleep behaviour disorder**

Any theory on RBD pathogenesis must be consistent with the high frequency of the disorder in the synucleinopathies and the tendency for RBD to precede parkinsonism and/or dementia. A recently proposed staging system for the neuropathological characterization of PD may be particularly pertinent to these issues (Boeve et al., 2003c, 2004; Braak et al., 2003, 2004; Stiasny-Kolster et al., 2005; Gagnon et al., 2006b; Iranzo et al., 2006b; Postuma et al., 2006). This staging system posits a temporal sequence of synuclein pathology in the brain beginning in the medulla and eventually ascending to more rostral structures (Braak et al., 2003, 2004). Dysfunction in the SLD (Stage 2) could lead to RSWA and RBD, and more specifically, prominent degeneration in the SLD could be the critical nucleus involved. This temporal sequence of pathology could explain why RBD precedes parkinsonism (Stages 3 and 4) and dementia (Stages 4–6) in many patients with Lewy body pathology. Recent studies provide further support for this staging system as it relates to RBD (Stiasny-Kolster et al., 2005; Postuma et al., 2006). Yet, if this staging scheme is accurate, why do a significant minority of patients with PD +/− dementia and DLB never exhibit dream enactment behaviour, and why do some DLB patients never exhibit parkinsonism? One explanation is that RBD may not be expressed until sufficient degeneration in the relevant nuclei has occurred, and parkinsonism may not be expressed until sufficient degeneration (typically thought to be at least 80% neuronal loss) in the substantia nigra has taken place. Yet, most cases that come to autopsy have had parkinsonism and/or dementia for many years, in which severe and end-stage pathology is found at autopsy. Hence, further characterization of the temporal and topographical course of degenerative changes in patients with early neurodegenerative disease in the synucleinopathies and non-synucleinopathies, with and without RBD, is needed. Analyses in patients with idiopathic RBD (Boeve et al., 2007), and/or only mild cognitive and motor features, may be most enlightening as the degenerative changes may be more mild and selective, and thus more revealing.

With the recent appreciation of secondary RBD associated with neurodegenerative disease, particularly the synucleinopathies, there is increasing interest in better understanding RBD pathogenesis (Abbott, 2005). One reflection of the growing interest in the RBD-neurodegenerative disease association can be found in the National Sleep Disorders Research Plan from the National Center on Sleep Disorders Research from the United States, in which it was recommended that investigators ‘better define the pathophysiology and neuroanatomic substrates of primary parasomnias in human and animal studies’ and ‘establish a brain bank for RBD and other parasomnias’ (2003). The structures of interest in the human brain are shown in Figs 9–11. Some testable hypotheses to confirm or refute that the subcoeruleus/sublatertodorsal nucleus and/or magnocellular reticular formation are central to RBD pathophysiology in humans include (i) in patients with idiopathic RBD and in those with RBD associated with neurodegenerative disease, significant neuronal loss will be
present in the subcoeruleus/sublaterodorsal nucleus and/or magnocellular reticular formation and (ii) in subjects with normal EMG atonia during REM sleep as documented by PSG, normal populations of neurons will exist in the subcoeruleus/sublaterodorsal nucleus and magnocellular reticular formation.

‘Idiopathic’ REM sleep behaviour disorder—a harbinger of neurodegenerative disease

As noted earlier, RBD tends to precede the onset of parkinsonism or dementia in patients with MSA, PD and DLB by years or decades (Wright et al., 1990; Silber and Ahlskog, 1992; Tison et al., 1995; Tan et al., 1996;
Schenck et al., 1996a, 2003, 1997; Turner et al., 1997; Boeve et al., 1998, 2001b, 2003c; Ferman et al., 1999; Olson et al., 2000; Turner et al., 2000; Schenck and Mahowald, 2002, 2004. Almost 40% of patients with idiopathic RBD in one series were subsequently found to have developed a parkinsonian disorder (Schenck et al., 1996a), and with continued longitudinal follow-up, over 65% of the original cohort has developed parkinsonism and/or dementia (Schenck et al., 2003). In another series of idiopathic RBD followed over a mean period of 11 years, 23 subjects have been re-contacted, with three being diagnosed with DLB, one with PD, one with dementia (not otherwise specified) and another 10 subjects have developed neurological symptoms highly suggestive of parkinsonism and/or dementia (total 15/23 = 65%) (Tippmann-Peikert et al., 2006b). Symptoms of RBD preceded dementia and/or parkinsonism in 67% of another series (Boeve et al., 2003c). Recent studies have demonstrated changes on electroencephalography (Fantini et al., 2003b; Massicotte-Marquez et al., 2005), single photon emission computed tomography (Eisensehr et al., 2000, 2003; Mazza et al., 2006), neuropsychological testing (Ferini-Strambi et al., 2004), smell testing (Stiasny-Kolster et al., 2005), colour discrimination (Postuma et al., 2006), cardiac autonomic activity (Ferini-Strambi et al., 1996) and more subtle abnormalities on measures of autonomic, motor and gait functioning (Postuma et al., 2006), also suggesting that a more widespread multisystem neurological disorder is present. In a recent study comparing 17 cognitively normal patients with histories of dream enactment behaviour to 17 controls, the patients with dream enactment behaviour had reduced cerebral metabolic rate for glucose in regions preferentially affected in patients with dementia with Lewy bodies, suggesting that dream enactment behaviour may be a possible risk factor for the development of DLB (Caselli et al., 2006). Therefore, several lines of evidence suggest that many cases of ‘idiopathic’ RBD may not be truly idiopathic, leading some to suggest the term ‘cryptogenic’ rather than ‘idiopathic’ (Ferini-Strambi et al., 2004). Rather, such cases may represent an early clinical manifestation of an evolving neurodegenerative disease, which in many cases may be a synucleinopathy. The presence of RBD may therefore be particularly relevant early in the course of a neurodegenerative disease when intervention may be most critical.

**Future directions**

As we have noted previously (Boeve et al., 2003c, 2004; Boeve, 2004; Boeve and Saper, 2006), RBD is analogous to the syndrome of mild cognitive impairment (MCI). MCI is considered by many to represent the earliest clinical manifestation of an evolving dementing illness, which is usually Alzheimer’s disease (Petersen et al., 1999, 2001a, 2006; Petersen, 2000; Jicha et al., 2006). MCI has gained significant attention of late, and clinicians are now encouraged to identify and monitor patients with MCI (Petersen et al., 2001b). Approximately 80% of those who meet the criteria for amnestic MCI will have Alzheimer’s disease within 6 years (Petersen et al., 1995, 1999). Several treatment trials are either just completed or currently in progress to potentially delay the progression of patients from MCI to Alzheimer’s disease, with one recent trial demonstrating delayed conversion from MCI to Alzheimer’s disease with donepezil (Petersen et al., 2005). A similar line of reasoning could apply to those with ‘idiopathic’ RBD, particularly once agents that may positively affect synuclein-based pathophysiology are developed—these therapies could potentially delay or prevent the development of cognitive impairment or parkinsonism. The lengthy time period between the onset of RBD and onset of parkinsonism and/or dementia, in which most studies have shown the duration can range from 5 to 40 years, suggests that the early window of opportunity for intervention may be even more potentially beneficial in delaying or preventing the motor and cognitive features (Boeve and Saper, 2006). In the absence of such treatments at present, longitudinal investigations into the
natural history of ‘idiopathic’ RBD are critical to prepare for future treatment trials (Boeve and Saper, 2006).

Decades of work on dopamine physiology, substantia nigra degeneration and the oxidative stress hypothesis have led to symptomatic therapies for PD, but complications of such therapies clearly occur. The cholinesterase inhibitors can improve cognition and neuropsychiatric features in patients with DBL and PD with dementia, but the cognitive decline ultimately progresses. No truly promising treatments for synucleinopathies have been developed to date, due in part to the prolonged focus on the motor aspects of PD (Ahlskog, 2005), and on the cognitive and neuropsychiatric aspects of DBL, in the waking state. It is to be hoped that this review will stimulate further work between sleep and neurodegenerative disease investigators to understand normal and abnormal sleep—particularly REM sleep behaviour disorder—which may provide insights into preventative or disease-altering approaches for therapy of synucleinopathies.

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RBD in neurodegenerative disease


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