

Impact of rapid eye movement sleep behavior disorder and autonomic disorders on Parkinson's disease: a review

Impacto do transtorno comportamental do sono REM e doenças autonômicas na doença de Parkinson: uma revisão

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ABSTRACT

Parkinson's disease (PD) has heterogeneous clinical manifestations and prognoses. It is accompanied by a group of motor and non-motor symptoms ranging from independence to total disability, limiting work and personal care activities. Currently, disease subtype markers for informing prognosis remain elusive. However, some studies have reported an association between rapid eye movement (REM) sleep behavior disorder (RBD) and faster motor and non-motor symptom progression, including autonomic dysfunction and cognitive decline. Moreover, since autonomic dysfunction has been described in idiopathic forms of RBD, and they share some central regulatory pathways, it remains unclear whether they have a primary association or if they are more severe in patients with PD and RBD, and thus are a disease subtype marker. This article aimed at critically reviewing the literature on the controversies about the prevalence of RBD in PD, the higher incidence of PD non-motor symptoms associated with RBD, the evidence of faster motor worsening in parkinsonian patients with this parasomnia, and the main pathophysiological hypotheses that support these findings.

Keywords: Parkinson Disease; REM Sleep Behavior Disorder; Autonomic Nervous System Diseases; Pathology; Epidemiology.

RESUMO

A doença de Parkinson (DP) apresenta variadas manifestações clínicas e distintos prognósticos. É caracterizada por um conjunto de sintomas motores e não motores que podem variar desde um quadro de independência até a completa incapacidade laborativa e de cuidados pessoais. Até o momento, não está claro quais seriam os marcadores de subtipos da doença que poderiam alertar para formas de prognóstico. Porém existem alguns estudos que mostram que a presença do transtorno comportamental do sono REM pode estar associada à progressão mais rápida dos sintomas motores e não motores, como disfunção autonômica e declínio cognitivo. Questiona-se ainda se a disautonomia está primariamente associada ao transtorno do sono REM, já que são relatadas nas formas idiopáticas deste transtorno de sono e compartilham alguns núcleos reguladores centrais. Ou se são mais graves nos pacientes com diagnóstico de DP e transtorno comportamental do sono REM, marcando assim um subtipo da doença. Esta revisão teve como objetivo revisar criticamente os principais estudos publicados envolvendo as controvérsias sobre a prevalência do transtorno comportamental do sono REM na DP, a maior incidência de sintomas não motores da DP associados ao transtorno do sono REM, as evidências de piora motora mais rápida nos pacientes parkinsonianos que apresentam este transtorno do sono e as principais hipóteses fisiopatológicas que justificam esses achados.

Palavras-chave: Doença de Parkinson; Transtorno do Comportamento do Sono REM; Doenças do Sistema Nervoso Autônomo; Patologia; Epidemiologia.

INTRODUCTION



Parkinson's disease (PD) has heterogeneous clinical manifestations and prognoses. It is classified based on the clinical presentation of motor symptoms and is often categorized as either tremor or non-tremor dominant subtypes. The latter

is characterized by predominant akinesia/rigidity, gait disturbance, or postural instability. These clinical presentations impact the prognosis and could contribute towards the better elucidation of PD mechanisms¹.

Several studies have addressed the presence and prevalence of non-motor symptoms in PD and their association

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with motor disease subtypes and prognosis. These studies could provide a better understanding of the disease subtypes, severity markers, and associated risk factors. Among the non-motor symptoms, rapid eye movement (REM) sleep behavior disorder (RBD) and autonomic dysfunction indicate a more severe and disabling form of the disease^{2,3,4,5}. It remains unclear whether RBD is a PD subtype marker and whether it is associated with a higher prevalence of other non-motor symptoms, including cognitive decline and autonomic dysfunction. The latter could be primarily associated with RBD or more prevalent and severe in patients with PD and RBD^{6,7}.

This review aimed to assess the impact of RBD on PD, the controversies about its prevalence, other non-motor symptoms that seem to be associated with RBD, especially autonomic dysfunctions, thus defining a PD subtype, and the pathophysiological hypotheses that support these findings.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

PD patients with different etiologies have a high prevalence of sleep disorders (>70%). They include nighttime sleep disorders and daytime sleepiness, with the most common being insomnia, RBD, and restless legs syndrome⁸.

RBD is characterized by behaviors resulting from acting out dreams involving complex non-stereotyped movements, such as light gestures, punches, kicks, and even violent movements, potentially leading to injury of the patient as well as their bed partner⁹.

According to the International Classification of Sleep Disorders, the four criteria for RBD diagnosis^{10,11} are:

- Repeated episodes of sleep-related vocalization and/or complex motor behavior;
- Behaviors documented by polysomnography during REM sleep or presumed to occur during REM sleep based on clinical history;
- REM sleep without atonia on polysomnography;
- Sleep disturbance cannot be explained by another sleep disorder, mental illness, medication use, or substance use.

A definitive RBD diagnosis requires polysomnography. Typical polysomnography findings include REM sleep without atonia, sustained increase in muscle tone on chin electromyography, and excessive transient muscle activity in the chin or limbs.

RBD is classified as probable when abnormal REM sleep behavior is reported without documentation by polysomnography. Further, it is classified as subclinical upon finding sustained electrophysiological changes on polysomnography with no compatible history. Not all patients develop classic RBD¹¹. Patients with RBD are alert and oriented upon waking up from sleep.

Given the lengthy nature of polysomnography and its limited availability, questionnaires have been developed for RBD screening and to support a probable RBD diagnosis. The RBD screening questionnaire, which is the most widely used questionnaire, was validated in 2007. It is a 10-item self-report questionnaire with yes or no answers and a maximum score of 13 points. The Hong Kong version of the RBD questionnaire¹⁰ was validated in 2010 and consists of 13 self-assessment questions that include an “I do not know” option among the answers. It assesses the presence and severity of RBD symptoms. The Innsbruck questionnaire is simpler since it comprises nine items — seven specific for RBD and two (questions four and nine) assessing other sleep disorders. The REM Sleep Behavior Disorder Single-Question Screen was validated in 2012. It has a single question: “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?” with the possible answers being “yes” or “no”¹⁰. The Mayo Sleep Questionnaire is not specific for RBD and contains 16 questions, with one being directed at RBD. In case of a positive answer, RBD-specific sub-items should be subsequently completed¹⁰.

RBD symptoms usually start in late adulthood, with the mean age at diagnosis being 60–70 years. Most cases involve a gradual and progressive symptom onset, with a delay of several years between symptom onset and diagnosis. The prevalence of RBD in the general population and among older adults is approximately 0.5–10 and 2%, respectively. In addition, some studies have shown that the condition is more prevalent in men, while others have reported no sex-based difference¹¹. RBD can be classified as idiopathic (iRBD) when it occurs in the absence of any neurological disorders or other possible causes. Contrastingly, it is classified as secondary in case of neurodegenerative diseases, in particular, those associated with synucleinopathies, including PD, dementia with Lewy bodies, and multiple system atrophy.

In some patients, RBD occurs months or even decades before the development of motor impairment associated with neurodegenerative diseases, highlighting the need for the correct classification of iRBD. Physiological motor activity suppression during REM sleep happens in several neuronal circuits that begin in the pons and terminate on spinal cord motor neurons. A normal atonia during REM sleep results in quiet motor activity and supports sleep-related memory consolidation. Muscle atonia during REM sleep causes RBD and has an apparent association with dysfunction of the pontine nuclei of the reticular formation. However, the exact mechanism underlying this REM sleep disorder remains unclear and has been reported to involve several brainstem structures, including the locus coeruleus, subcoeruleus, periaqueductal gray matter, ventral mesopontine junction, pedunculopontine tegmental

nucleus, peri-locus coeruleus area at the pons, and bulbar nuclei (Figure 1).

A proposed hypothesis for the underlying mechanism of RBD is the specific degeneration of a population of glutamatergic neurons located in the sublateral nucleus of the pons, which are responsible for muscle atonia. Another possibility is the injury of glycinergic and GABAergic premotor neurons of the ventromedial hypothalamic nucleus. Some studies have reported the presence of Lewy bodies in the midbrain and pons areas involved in REM sleep atonia¹².

IDIOPATHIC RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

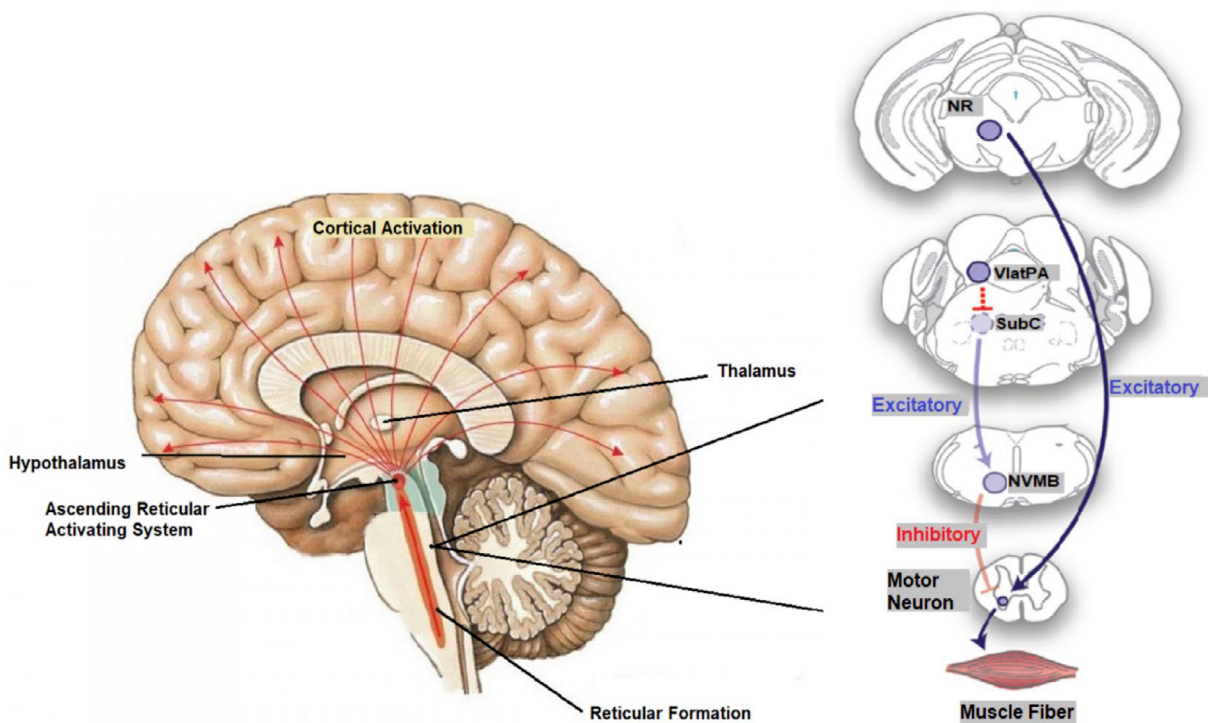
iRBD, which occurs without neurodegenerative disease, was first described in 1986, with similar phenomenological

reports being presented in the 1970s. It is characterized by central nervous system (CNS) dysfunction during sleep and wakefulness with cortical activity impairment, neuropsychological changes, and autonomic dysfunction¹³.

According to several studies, patients with iRBD present abnormalities in heart rate variability, myocardial scintigraphy, and cardiovascular autonomic reflex tests (Table 1)^{6,7,14,15,16,17,18}. Moreover, previous studies have suggested that the type and severity of these autonomic dysfunctions could predict the development of RBD-associated neurodegenerative diseases¹⁹.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER IN PARKINSON'S DISEASE

The risk of patients with iRBD developing PD or dementia is estimated to be 20 to 45% higher during the first five



Source: adapted from Fraigne et al.¹².

NR: red nucleus; VlatPA: ventrolateral periaqueductal gray matter; SubC: subcoeruleus; NVMB: ventromedial nucleus of the bulb.

Figure 1. Areas involved in rapid eye movement sleep behavioral disorder.

Table 1. Findings on idiopathic rapid eye movement sleep behavioral disorder.

Author	Year	Country	iRBD (n)	RBD diagnostic method	Findings
Postuma et al. ¹⁴	2010	Canada	99	Polysomnography	Patients with RBD showed cardiac autonomic dysfunction in both those who developed and did not develop neurodegenerative disease.
Frauscher et al. ⁶	2012	Austria	15	Polysomnography	Presence of autonomic dysfunction in patients with iRBD.

Continue...

Table 1. Continuation.

Author	Year	Country	iRBD (n)	RBD diagnostic method	Findings
Sorensen et al. ¹⁵	2013	Denmark	11	Polysomnography	Patients with RBD had attenuated sympathetic activity.
Ferini-Strambi et al. ⁷	2014	Multicenter	318	Polysomnography	Patients with iRBD had more gastrointestinal, cardiovascular, and urinary problems.
Lee et al. ¹⁶	2015	Korea	17	Polysomnography	iRBD was associated with autonomic dysfunction; predominantly, adrenergic and cardiovagal functions.
Aguirre-Mardones et al. ¹⁷	2015	Spain	44	Polysomnography	iRBD was associated with hyposmia and constipation.
Bedard et al. ¹⁸	2019	Canada	5	Polysomnography	Specific marker on positron emission tomography showed brain cholinergic alterations in patients with iRBD.

RBD: rapid eye movement (REM) sleep behavior disorder; iRBD: idiopathic RBD.

years of the parasomnia. The risk further increases over time, with >80% of men being affected after approximately three decades of RBD progression^{11,20}. A significant number of PD patients are affected by RBD; however, studies have reported varying values ranging from 15 to >70%^{8,21,22}. RBD may precede the onset of PD motor symptoms or appear with the progression of the disease, being more frequent and presenting more severe symptoms in advanced PD cases²². As shown in Table 2, most studies have assessed the clinical prevalence of RBD in PD patients; yet, few studies employed polysomnography^{1,5,8,23,24,25,26,27,28}.

Zhang et al.²² conducted a meta-analysis and meta-regression study on the prevalence of RBD in PD patients. They analyzed 28 studies published between 2010 and 2016 with a total of 8,689 PD patients. Less than half of these studies used polysomnography for RBD diagnosis, and the RBD prevalence ranged from 19.2 to 69.8%. In 2017, another Chinese group carried out a meta-analysis of RBD prevalence in patients with early-onset PD. They included eight studies with 2,462 PD patients and found a mean prevalence of 23.6% (range: 4.3–69.4%). Only one of the included studies used polysomnography for RBD diagnosis²⁹. These meta-analyses indicated a high heterogeneity among the evaluated studies²², which could have resulted from the different methodologies for RBD diagnosis, with some studies using questionnaires and others using polysomnography. Further, the studies that only used the clinical features of RBD employed different questionnaires with distinct sensitivities and specificities. Moreover, the diagnostic efficacy of the most frequently used questionnaires has not been compared. Studies on RBD prevalence also used heterogeneous populations with different ethnicities, ages, and PD duration, with RBD being more prevalent in older adults and in more advanced PD stages²¹. RBD has recurrent symptoms; however, the patient may experience no symptoms for months after a period of intense symptom manifestation. Finally, most studies on RBD prevalence were cross-sectional, which can cause confusion and

limit causality inferences. Therefore, despite numerous relevant studies, the actual prevalence of RBD in PD patients remains unknown and can only be estimated.

RBD in PD patients does not necessarily lead to disability but causes sleep disruption for the patient or bed partner, who may occasionally suffer involuntary physical aggression⁹. RBD appears to be associated with faster motor symptom progression and increased non-motor symptoms, including cognitive decline, psychiatric changes, and autonomic dysfunction. A study conducted in California and published in 2019³⁰ assessed the presence of RBD in 776 PD patients. Based on the predominant motor symptom, they were classified into the following three clinical subtypes: postural instability and gait dysfunction, tremor dominant, or indeterminate. Patients were evaluated between 2001 and 2007 and reassessed between 2011 and 2017. The total RBD prevalence was 21%. According to the Unified Parkinson's Disease Rating Scale score, patients with the postural instability and gait dysfunction subtype and RBD presented faster motor worsening. RBD patients progressed twice as fast to a score below the Mini-Mental State Examination cut-off point. As shown in Table 3, previous studies have identified an association between RBD and other non-motor symptoms of PD^{2,3,4,5,21,31,32,33,34,35,36,37,38,39,40}. These recent studies indicate that RBD is a marker of a PD subtype with more frequent and severe motor and non-motor symptoms, as well as a poor prognosis. The proposal to classify RBD as a symptom of PD or other synucleinopathies further supports the hypothesis that RBD is a PD subtype marker.

Based on the PD model proposed by Braak et al.⁴¹, pre-symptomatic PD stages are characterized by the deposition of Lewy bodies in the dorsal pons, bulb, and olfactory nucleus. This explains why RBD precedes PD motor symptoms in some cases; nevertheless, it does not explain why many PD patients do not present RBD. Histopathological changes have been reported in patients with iRBD who did not clinically present neurological disorders. These changes included the presence of Lewy bodies in the brainstem in one

Table 2. Prevalence of rapid eye movement sleep behavior disorder in Parkinson disease patients.

Author	Year	Country	Total of PD patients	Diagnostic method	PD prevalence (%)	
Mahajan et al. ⁵	2014	USA	418	RBDSQ	27.0	
Munhoz et al. ²³	2014	Brazil	100	ICSD-RBD	58.0	
Kim et al. ²⁴	2014	Korea	202	ICSD-RBD	57.4	
Aygun et al. ¹	2014	Turkey	104	ICSD-RBD	NT	T
					45.2	54.8
Janković et al. ⁸	2015	Serbia	97	RBDQ-HK	15.5	
Alatriste-Booth et al. ²⁵	2015	Brazil	120	Polysomnography	35.1	
Swallow et al. ²⁶	2016	UK	1,719	RBDSQ	43.3	
Chahine et al. ²⁷	2016	Multicenter	423	RBDSQ	25.5	
Suzuki et al. ²⁸	2017	Multicenter	436	RBDSQ	35.1	

RBD: rapid eye movement (REM) sleep behavior disorder; PD: Parkinson's disease; ICSD-RBD: minimum criteria for RBD according to the International Classification of Sleep Disorders; NT and T: non-tremor and tremor forms of Parkinson's disease; RBDQ-HK: RBD questionnaire-Hong Kong; RBDSQ: RBD screening questionnaire.

Table 3. Findings on the presence of rapid eye movement sleep behavior disorder in Parkinson disease patients.

Author	Year	Country	Total number of PD patients	RBD (% of total)	Findings related to PD motor symptoms	Findings related to PD non-motor symptoms
Postuma et al. ³¹	2011	Canada	53	60		Cardiac autonomic denervation was not associated with PD; rather, it was associated with RBD.
Kim et al. ²¹	2014	Review	4,089	20–72		RBD was associated with hallucinations and dementia.
Mahajan et al. ⁵	2014	USA	418	27	Patients with RBD were 1.66 times more likely to present worse motor symptoms.	No depression differences between patients with and without RBD.
Fantini et al. ³²	2015	Multicenter	216	53.0		RBD was associated with an increased risk of developing impulse control disorders.
Cui et al. ³³	2017	China	403			RBD was a risk factor for anxiety development (OR: 1.029 and p-value: 0.037).
Liu et al. ⁴	2017	China	141	21.3		Patients with RBD had more anxiety, depression, constipation, hallucinations, and a higher prevalence of orthostatic hypotension.
Jozwiak et al. ³⁴	2017	Canada	93	56.9		RBD was associated with greater cognitive impairment and a higher diagnosis frequency of mild cognitive impairment.
Pagano et al. ²	2018	Multicenter	421	37.5	RBD was associated with a faster progression of PD motor symptoms.	RBD was associated with a greater risk of cognitive decline and a higher number of non-motor symptoms associated with PD, including hallucinations, pain, fatigue, constipation, and urinary problems.
Kang et al. ³⁵	2013	Systematic review			Higher frequency of RBD in the predominant non-tremor PD phenotype.	RBD was a risk factor for the development of dementia and hallucinations.
Kim et al. ³⁶	2018	Systematic review				RBD in PD patients was associated with greater disease severity and increased mortality risk; further, the authors suggested that RBD could be a PD subtype marker.

Continue...

Table 3. Continuation.

Author	Year	Country	Total number of PD patients	RBD (% of total)	Findings related to PD motor symptoms	Findings related to PD non-motor symptoms
Liu et al. ³⁷	2019	China	158	19.6		RBD was associated with cognitive decline, other sleep disorders, and anxiety.
Banks et al. ³⁸	2019	USA	100			RBD was associated with gait motor complications.
Baig et al. ³	2019	UK	921 (in the first assessment)			RBD was not associated with an increased risk of developing impulse control disorders.
Bargiotas et al. ³⁹	2019	Switzerland	64	40.0		RBD was associated with apathy and increased depressive symptom severity.
Pilotto et al. ⁴⁰	2019	Systematic review				Patients with PD and RBD had an increased risk of cognitive decline. The authors proposed the existence of a malignant PD phenotype associated with RBD and orthostatic hypotension, which could be characterized by faster progression of cognitive decline and postural instability.

RBD: rapid eye movement (REM) sleep behavior disorder; PD: Parkinson's disease; OR: Odds Ratio.

patient and decreased monoaminergic neurons in the locus coeruleus and substantia nigra in another²⁰.

A Spanish cohort study published in 2013⁴² assessed 44 patients with iRBD, of whom four remained disease-free until the end of the follow-up period. However, all four patients presented striatal abnormalities in the dopamine transporter in the neuroimaging examination, one showed transcranial ultrasonography abnormalities, and two had abnormalities in the olfactory test. Therefore, the iRBD concept remains controversial, and the use of the term “idiopathic” does not seem to be very appropriate. Alternative terms, such as cryptogenic RBD and isolated RBD, have been suggested to indicate RBD stages without other symptoms. Other authors have proposed that RBD is a symptom of alpha-synucleinopathy and not an isolated entity⁴².

AUTONOMIC DYSFUNCTION

Autonomic dysfunction or dysautonomia refers to impairment of the autonomic nervous system resulting from many different factors and diseases. Autonomic dysfunction usually manifests as more than one symptom. The most common autonomic dysfunction in PD patients is cardiovascular dysfunction with an abnormal vasovagal response, which can lead to syncope. Other common manifestations are orthostatic hypotension, constipation, neurogenic bladder, and sexual dysfunction.

Several brain areas modulate the activity of the autonomic nervous system, including the left amygdala,

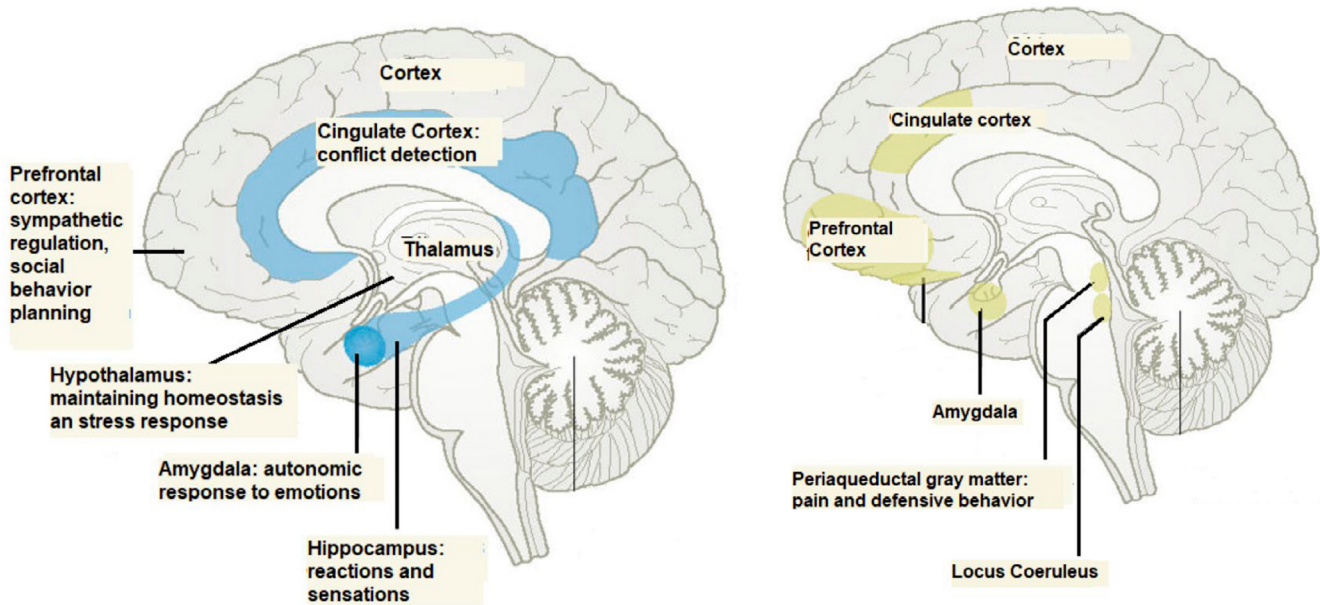
insula, periaqueductal gray matter, and cingulate cortex⁴³. These areas are distributed across the forebrain and brainstem (Figure 2).

IDIOPATHIC RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER-ASSOCIATED AUTONOMIC DYSFUNCTION

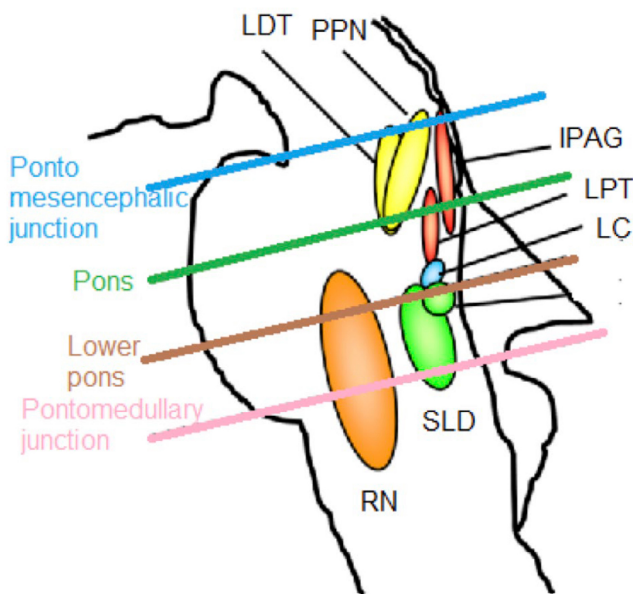
Although sleep is not regulated by the autonomic nervous system, some CNS areas regulate both systems. Therefore, sleep and autonomic system interactions might occur and can be descriptively separated into the three situations mentioned below.

First, autonomic dysfunction and sleep impairments might be induced by pathologies, including synucleinopathies with neurodegeneration of brainstem nuclei, which is involved in RBD pathogenesis and degeneration of central and peripheral autonomic regions. Second, the failure of sleep-related cardiorespiratory control mechanisms could cause or aggravate autonomic dysfunction, which might explain the high prevalence of nocturnal cardiac arrhythmia in patients with obstructive sleep apnea. Third, autonomic dysfunction could cause or aggravate a sleep disorder, as seen in familial dysautonomia. Nonetheless, the underlying pathophysiology is complex.

Autonomic cells in the hypothalamus and brainstem (Figure 3)⁴⁴ are closely associated with cells that regulate the sleep-wake cycle. Sleep is promoted by neurons in the ventrolateral preoptic nucleus of the thalamus, which secretes



Source: adapted from Fenster et al.⁴⁴.
Figure 2. Areas of the autonomic nervous system.



Source: adapted from Boeve et al.¹¹.
 LDT: laterodorsal tegmental nucleus; PPN: pedunclopontine nucleus; IPAG: periaqueductal gray matter; LPT: laterodorsal pons; LC: locus coeruleus; SLD: sublaterodorsal nucleus; RN: raphe nuclei.

Figure 3. Approximate location of important areas involved in rapid eye movement sleep behavioral disorder control and central autonomic modulation.

gamma-aminobutyric acid (GABA) and galanin neuropeptide. On the other hand, wakefulness is regulated by cholinergic and monoaminergic pathways. All these neurons are important for RBD. Monoaminergic pathways originate from the brainstem and send projections to the hypothalamus and cortex. The hypothalamus has glutaminergic and hypocretin-secreting neurons that project to all monoaminergic nuclei

and are fundamental to maintain the waking conscious state. Hypocretin-secreting neurons are important in autonomic control and send projections to various regulatory centers of the autonomic nervous system, including the solitary tract nucleus and periaqueductal gray matter⁴⁵. The lateral part of the bulb contains autonomic afferent and efferent pathways, which act on respiratory control during sleep and are associated with the pontine nuclei. Table 1 presents autonomic dysfunctions clinically associated with iRBD.

AUTONOMIC DYSFUNCTION IN PARKINSON'S DISEASE

The prevalence of autonomic symptoms in PD patients ranges from 14 to 80%. This variability could be mainly attributed to differences in diagnostic methodology and the autonomic disorder assessed across studies. Further, several studies enrolled heterogeneous populations, while others did not use validated questionnaires⁴⁶.

Regarding the non-motor symptoms of PD, dysautonomia, including orthostatic hypotension, constipation, sialorrhea, as well as urinary and sexual dysfunction, frequently occurs at all disease stages. However, they are more common in more advanced PD stages and significantly worsen the quality of life and impair social life.

Orthostatic hypotension has a significant impact on the quality of life, as well as morbidity and mortality, in PD patients. It is characterized by a 20 mmHg decrease in systolic pressure and/or a 10 mmHg decrease in diastolic pressure when the patient goes from a dorsal decubitus to a standing position⁴⁵. Its clinical manifestations are diverse and

nonspecific and include dizziness, vertigo, blurred vision, in addition to more serious complications, such as syncope and falls. Its prevalence in PD patients ranges from 30 to 60%⁴⁷. Orthostatic hypotension can be caused by autonomic dysfunction or other conditions, including hypovolemia, physical deconditioning, and medication use. Early diagnosis of orthostatic hypotension is essential to allow the provision of behavior guidance, reassessment of medication use, and prevention of serious consequences.

Constipation is characterized by colonic and anorectal symptoms and occurs up to two decades prior to motor symptoms of PD. PD patients present with reduced intestinal motility; moreover, there can be involvement of the entire gastrointestinal tract. Approximately 50–80% of PD patients have constipation, with about 20% of them presenting constipation before the onset of motor symptoms⁴⁸. Constipation leads to functional impairment and psychosocial distress, which negatively affects the quality of life of PD patients.

Sialorrhea is characterized by excessive salivation and the inability to retain saliva within the mouth. Consequently, the patient might drool or aspirate saliva, which could even result in aspiration pneumonia. The prevalence of sialorrhea in PD patients varies from 10 to 84%⁴⁹ and is more frequent in case of ineffective medication.

Urinary tract symptoms have been recognized as non-motor complications of PD since their description by James Parkinson in 1817. They are classified as irritative, obstructive, or mixed. The most common irritative symptoms in PD patients include nocturia and frequent and urgent urination. The prevalence of urinary problems in PD patients is up to 86%⁴⁶, with nocturia being the most prevalent symptom followed by frequent and urgent urination.

Sexual function is a complex process dependent on the body's mechanical function and emotional health. Sexual dysfunction is common in PD patients and has been associated with depressive mood disorders. It is more prevalent among young male PD patients. The most common symptoms are erectile dysfunction and premature ejaculation. Erectile dysfunction has been reported in 50 to 79% of PD patients⁵⁰. The most frequent complaints of female PD patients are vaginal discomfort, lack of lubrication, and sexual dissatisfaction. Further, motor symptoms of PD, including rigidity and bradykinesia, could impair sexual activity. Clinical symptoms of autonomic dysfunctions are often subjective, difficult to diagnose, and affected by confounding factors, such as comorbidities and medication use.

For early and accurate diagnosis, autonomic reactivity tests assist in identifying autonomic dysfunctions, quantifying the deficit severity, and determining the distribution and location of the autonomic injury. Several tests assess autonomic function, including cholinergic, cardiovagal, and adrenergic sympathetic reflex autonomic responses. However, these tests are not widely available and require expensive equipment and trained personnel.

RELATIONSHIP BETWEEN RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER AND AUTONOMIC DYSFUNCTION IN PARKINSON'S DISEASE

RBD and autonomic dysfunction are correlated and common in PD patients (Table 4)^{19,51,52,53,54,55,56,57}; however, whether autonomic dysfunction is more closely associated with RBD or PD itself remains unclear. There is recent but growing evidence

Table 4. Relationship between rapid eye movement sleep behavior disorder and autonomic dysfunction in Parkinson disease patients.

Author	Year	Country	Sample	Findings
Nomura et al. ⁵¹	2013	Japan	82 PD patients	RBD was associated with orthostatic hypotension in PD patients.
Anang et al. ⁵²	2014	Canada	80 PD patients	Cardiovascular autonomic dysfunction, RBD, gait disturbances, and color discrimination ability were strong predictors of dementia development in PD patients.
Kim et al. ⁵³	2016	Korea	94 PD patients; among them, 53 had RBD	RBD in PD patients was associated with orthostatic hypotension.
Jin et al. ⁵⁴	2017	Review		The authors suggested an association of autonomic dysfunctions with RBD; moreover, this association could be a PD sign. However, they emphasize the importance of further studies to prove this hypothesis.
Kim et al. ⁵⁵	2017	Korea	160 PD patients	Patients with PD and low MIBG* uptake had a higher prevalence of RBD, orthostatic hypotension, constipation, and cognitive decline compared to those with normal uptake.
Fereshtehnejad et al. ⁵⁶	2017	Review		Patients with PD associated with RBD and autonomic dysfunction presented faster disease progression with more prominent motor symptoms in the early PD stages.

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Table 4. Continuation.

Author	Year	Country	Sample	Findings
Al-Qassabi et al. ⁵⁷	2018	Canada	150 patients (49 with iRBD, 40 with PD, 20 with atypical parkinsonism, and 41 controls)	Patients with PD and concomitant RBD had significantly lower skin sweat measurements than those with PD without RBD and controls. This finding suggests a between-subgroup difference in the peripheral alpha-synuclein deposition.
Zitser et al. ¹⁹	2019	Review		Autonomic symptoms were common in patients with RBD and reported in up to 94% of patients. The presence and severity of autonomic dysfunction symptoms in patients with RBD were associated with the risk of progression to PD. Moreover, it suggests an association of autonomic dysfunctions and RBD with a malignant PD subtype.

RBD: rapid eye movement (REM) sleep behavior disorder; PD: Parkinson's disease; iRBD: idiopathic RBD; MIBG: metaiodobenzylguanidine, assessed through myocardial scintigraphy.

on the correlation of some non-motor symptoms with RBD as a risk factor for iRBD progression to PD. This could indicate that autonomic dysfunctions associated with RBD might be a preclinical PD marker⁵⁴. Previous studies have revealed a significant impact of PD non-motor symptoms on the quality of life, including depression, cognitive decline, and sleep disorders. Studies have even reported that non-motor symptoms have a greater impact on the quality of life than motor symptoms⁵⁸.

The various clinical presentations of PD, associations between motor and non-motor symptoms, and prognoses support the hypothesis that PD subtypes could be classified according to the predominant phenotype, severity, and prognosis markers. These findings substantiate the PD subclassification based on the predominant motor symptom and the presence of non-motor symptoms indicative of a more severe disease form. The coexistence of RBD and autonomic

dysfunctions is associated with the phenotypic conversion to PD, non-motor symptoms (e.g., cognitive decline), and faster progression of motor symptoms, collectively describing what previous studies have termed the malignant PD form¹⁹.

In PD, autonomic dysfunction is related to worse quality of life regardless of disease duration, cognitive decline, or motor symptom severity⁵⁹. Evidence suggests an association of autonomic dysfunctions, specifically, early-onset dysfunctions, with faster progression of cardinal PD symptoms and reduced survival⁶⁰.

Therefore, assessing RBD and autonomic dysfunction from PD onset could contribute to patient management with respect to both pharmacological and non-pharmacological treatments. Further, it could allow managing patient expectations, especially in cases of greater severity and more reserved prognosis.

References

1. Aygun D, Turkel Y, Onar MK, Sunter T. Clinical REM sleep behavior disorder and motor subtypes in Parkinson's disease: a questionnaire-based study. *Clin Neurol Neurosurg*. 2014 Apr;119:54-8. <https://doi.org/10.1016/j.clineuro.2014.01.011>
2. Pagano G, De Micco R, Yousaf T, Wilson H, Chandra A, Politis M. REM behavior disorder predicts motor progression and cognitive decline in Parkinson disease. *Neurology*. 2018 Sep;91(10):e894-e905. <https://doi.org/10.1212/WNL.0000000000006134>
3. Baig F, Kelly MJ, Lawton MA, Ruffmann C, Rolinski M, Klein JC, et al. Impulse control disorders in Parkinson and RBD: A longitudinal study of severity. *Neurology*. 2019 Aug;93(7):e675-e687. <https://doi.org/10.1212/WNL.0000000000007942>
4. Liu Y, Zhu XY, Zhang XJ, Kuo SH, Ondo WG, Wu YC. Clinical features of Parkinson's disease with and without rapid eye movement sleep behavior disorder. *Transl Neurodegener*. 2017 Dec;6:35. <https://doi.org/10.1186/s40035-017-0105-5>
5. Mahajan A, Rosenthal LS, Gamaldo C, Salas RE, Pontone GM, McCoy A, et al. REM sleep behavior and motor findings in Parkinson's disease: a cross-sectional analysis. *Tremor Other Hyperkinet Mov (N Y)*. 2014 Jun;4:245. <https://doi.org/10.7916/D84B2ZDF>
6. Frauscher B, Nomura T, Duerr S, Ehrmann L, Gschliesser V, Wenning GK, et al. Investigation of autonomic function in idiopathic REM sleep behavior disorder. *J Neurol*. 2012 Jun;259(6):1056-61. <https://doi.org/10.1007/s00415-011-6298-0>
7. Ferini-Strambi L, Oertel W, Dauvilliers Y, Postuma RB, Marelli S, Iranzo A, et al. Autonomic symptoms in idiopathic REM behavior disorder: A multicentre case-control study. *J Neurol*. 2014 Jun;261(6):1112-8. <https://doi.org/10.1007/s00415-014-7317-8>
8. Janković M, Svetel M, Kostić V. Frequency of REM sleep behavior disorders in patients with Parkinson's disease. *Vojnosanit Pregl*. 2015 May;72(5):442-6. <https://doi.org/10.2298/vsp130501006j>
9. Munhoz RP, Moro A, Silveira-Moriyama L, Teive HA. Non-motor signs in Parkinson's disease: a review. *Arq Neuropsiquiatr*. 2015 May;73(5):454-62. <https://doi.org/10.1590/0004-282X20150029>
10. Högl B, Stefani A. REM sleep behavior disorder (RBD): Update on diagnosis and treatment. *Somnologie (Berl)*. 2017;21(Suppl 1):1-8. <https://doi.org/10.1007/s11818-016-0048-6>
11. Boeve BF. REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. 2010 Jan;1184:15-54. <https://doi.org/10.1111/j.1749-6632.2009.05115.x>

12. Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM sleep at its core - circuits, neurotransmitters, and pathophysiology. *Front Neurol*. 2015 May;6:123. <https://doi.org/10.3389/fneur.2015.00123>
13. Fantini ML, Ferini-Strambi L, Montplaisir J. Idiopathic REM sleep behavior disorder: Toward a better nosologic definition. *Neurology*. 2005 Mar;64(5):780-6. <https://doi.org/10.1212/01.WNL.0000152878.79429.00>
14. Postuma RB, Lanfranchi PA, Blais H, Gagnon JF, Montplaisir JY. Cardiac autonomic dysfunction in idiopathic REM sleep behavior disorder. *Mov Disord*. 2010 Oct;25(14):2304-10. <https://doi.org/10.1002/mds.23347>
15. Sorensen GL, Mehlsen J, Jennum P. Reduced sympathetic activity in idiopathic rapid-eye-movement sleep behavior disorder and Parkinson's disease. *Auton Neurosci*. 2013 Dec;179(1-2):138-41. <https://doi.org/10.1016/j.autneu.2013.08.067>
16. Lee H, Cho YW, Kim HA. The severity and pattern of autonomic dysfunction in idiopathic rapid eye movement sleep behavior disorder. *Mov Disord*. 2015 Nov;30(13):1843-8. <https://doi.org/10.1002/mds.26416>
17. Aguirre-Mardones C, Iranzo A, Vilas D, Serradell M, Gaig C, Santamaria J, et al. Prevalence and timeline of nonmotor symptoms in idiopathic rapid eye movement sleep behavior disorder. *J Neurol*. 2015 Jun;262(6):1568-78. <https://doi.org/10.1007/s00415-015-7742-3>
18. Bedard MA, Aghourian M, Legault-Denis C, Postuma RB, Soucy JP, Gagnon JF, et al. Brain cholinergic alterations in idiopathic REM sleep behaviour disorder: a PET imaging study with (18) F-FEOBV. *Sleep Med*. 2019 Jun;58:35-41. <https://doi.org/10.1016/j.sleep.2018.12.020>
19. Zitser J, During EH, Chiaro G, Miglis MG. Autonomic impairment as a potential biomarker in idiopathic REM-sleep-behavior disorder. *Auton Neurosci*. 2019 Sep;220:102553. <https://doi.org/10.1016/j.autneu.2019.05.005>
20. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*. 2013 Aug;14(8):744-8. <https://doi.org/10.1016/j.sleep.2012.10.009>
21. Kim YE, Jeon BS. Clinical implication of REM sleep behavior disorder in Parkinson's disease. *J Parkinsons Dis*. 2014;4(2):237-44. <https://doi.org/10.3233/JPD-130293>
22. Zhang X, Sun X, Wang J, Tang L, Xie A. Prevalence of rapid eye movement sleep behavior disorder (RBD) in Parkinson's disease: a meta and meta-regression analysis. *Neurol Sci*. 2017 Jan;38(1):163-70. <https://doi.org/10.1007/s10072-016-2744-1>
23. Munhoz RP, Teive HA. REM sleep behaviour disorder: how useful is it for the differential diagnosis of parkinsonism? *Clin Neurol Neurosurg*. 2014 Dec;127:71-4. <https://doi.org/10.1016/j.clineuro.2014.09.014>
24. Kim YE, Yang HJ, Yun JY, Kim HJ, Lee JY, Jeon BS. REM sleep behavior disorder in Parkinson disease: association with abnormal ocular motor findings. *Parkinsonism Relat Disord*. 2014 Apr;20(4):444-6. <https://doi.org/10.1016/j.parkreldis.2013.12.003>
25. Alatraste-Booth V, Rodríguez-Violante M, Camacho-Ordoñez A, Cervantes-Arriaga A. Prevalence and correlates of sleep disorders in Parkinson's disease: a polysomnographic study. *Arq Neuropsiquiatr*. 2015 Mar;73(3):241-5. <https://doi.org/10.1590/0004-282X20140228>
26. Swallow DM, Lawton MA, Grosset KA, Malek N, Smith CR, Bajaj NP, et al. Variation in recent onset parkinson's disease: implications for prodromal detection. *J Parkinsons Dis*. 2016 Mar;6(2):289-300. <https://doi.org/10.3233/JPD-150741>
27. Chahine LM, Xie SX, Simuni T, Tran B, Postuma R, Amara A, et al. Longitudinal changes in cognition in early Parkinson's disease patients with REM sleep behavior disorder. *Parkinsonism Relat Disord*. 2016 Jun;27:102-6. <https://doi.org/10.1016/j.parkreldis.2016.03.006>
28. Suzuki K, Okuma Y, Uchiyama T, Miyamoto M, Sakakibara R, Shimo Y, et al. Impact of sleep-related symptoms on clinical motor subtypes and disability in Parkinson's disease: a multicentre cross-sectional study. *J Neurol Neurosurg Psychiatry*. 2017 Nov;88(11):953-9. <https://doi.org/10.1136/jnnp-2017-316136>
29. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. *BMC Neurol*. 2017 Feb;17:23. <https://doi.org/10.1186/s12883-017-0795-4>
30. Duarte Folle A, Paul KC, Bronstein JM, Keener AM, Ritz B. Clinical progression in Parkinson's disease with features of REM sleep behavior disorder: a population-based longitudinal study. *Parkinsonism Relat Disord*. 2019 May;62:105-11. <https://doi.org/10.1016/j.parkreldis.2019.01.018>
31. Postuma RB, Montplaisir J, Lanfranchi P, Blais H, Rompre S, Colombo R, et al. Cardiac autonomic denervation in Parkinson's disease is linked to REM sleep behavior disorder. *Mov Disord*. 2011 Jul;26(8):1529-33. <https://doi.org/10.1002/mds.23677>
32. Fantini ML, Macedo L, Zibetti M, Sarchioto M, Vidal T, Pereira B, et al. Increased risk of impulse control symptoms in Parkinson's disease with REM sleep behaviour disorder. *J Neurol Neurosurg Psychiatry*. 2015 Feb;86(2):174-9. <https://doi.org/10.1136/jnnp-2014-307904>
33. Cui SS, Du JJ, Fu R, Lin YQ, Huang P, He YC, et al. Prevalence and risk factors for depression and anxiety in Chinese patients with Parkinson disease. *BMC Geriatr*. 2017 Nov;17:270. <https://doi.org/10.1186/s12877-017-0666-2>
34. Jozwiak N, Postuma RB, Montplaisir J, Latreille V, Panisset M, Chouinard S, et al. REM sleep behavior disorder and cognitive impairment in Parkinson's disease. *Sleep*. 2017 Aug;40(8):zsx101. <https://doi.org/10.1093/sleep/zsx101>
35. Kang SH, Yoon IY, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. *Sleep*. 2013 Aug;36(8):1147-52. <https://doi.org/10.5665/sleep.2874>
36. Kim Y, Kim YE, Park EO, Shin CW, Kim HJ, Jeon B. REM sleep behavior disorder portends poor prognosis in Parkinson's disease: A systematic review. *J Clin Neurosci*. 2018 Jan;47:6-13. <https://doi.org/10.1016/j.jocn.2017.09.019>
37. Liu H, Ou R, Wei Q, Hou Y, Cao B, Zhao B, et al. Rapid eye movement behavior disorder in drug-naïve patients with Parkinson's disease. *J Clin Neurosci*. 2019 Jan;59:254-8. <https://doi.org/10.1016/j.jocn.2018.07.007>
38. Banks SJ, Bayram E, Shan G, LaBelle DR, Bluett B. Non-motor predictors of freezing of gait in Parkinson's disease. *Gait Posture*. 2019 Feb;68:311-6. <https://doi.org/10.1016/j.gaitpost.2018.12.009>
39. Bargiotas P, Ntafouli M, Lachenmayer ML, Krack P, Schubach WMM, Bassetti CLA. Apathy in Parkinson's disease with REM sleep behavior disorder. *J Neurol Sci*. 2019 Apr;399:194-8. <https://doi.org/10.1016/j.jns.2019.02.028>
40. Pilotto A, Romagnolo A, Tuazon JA, Vizcarra JA, Marsili L, Zibetti M, et al. Orthostatic hypotension and REM sleep behaviour disorder: impact on clinical outcomes in alpha-synucleinopathies. *J Neurol Neurosurg Psychiatry*. 2019 Nov;90(11):1257-63. <https://doi.org/10.1136/jnnp-2019-320846>
41. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. Mar-Apr 2003;24(2):197-211. [https://doi.org/10.1016/s0197-4580\(02\)00065-9](https://doi.org/10.1016/s0197-4580(02)00065-9)
42. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valdeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: Study in 174 patients. *PLoS One*. 2014 Feb;9(2):e89741. <https://doi.org/10.1371/journal.pone.0089741>
43. Beissner F, Meissner K, Bar KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci*. 2013 Jun;33(25):10503-11. <https://doi.org/10.1523/JNEUROSCI.1103-13.2013>

44. Fenster RJ, Lebois LAM, Ressler KJ, Suh J. Brain circuit dysfunction in post-traumatic stress disorder: from mouse to man. *Nat Rev Neurosci*. 2018 Sep;19(9):535-51. <https://doi.org/10.1038/s41583-018-0039-7>
45. Miglis MG. Autonomic dysfunction in primary sleep disorders. *Sleep Med*. 2016 Mar;19:40-9. <https://doi.org/10.1016/j.sleep.2015.10.001>
46. McDonald C, Winge K, Burn DJ. Lower urinary tract symptoms in Parkinson's disease: Prevalence, aetiology and management. *Parkinsonism Relat Disord*. 2017 Feb;35:8-16. <https://doi.org/10.1016/j.parkreldis.2016.10.024>
47. Palma JA, Gomez-Esteban JC, Norcliffe-Kaufmann L, Martinez J, Tijero B, Berganzo K, et al. Orthostatic hypotension in Parkinson disease: how much you fall or how low you go? *Mov Disord*. 2015 Apr;30(5):639-45. <https://doi.org/10.1002/mds.26079>
48. Yu QJ, Yu SY, Zuo LJ, Lian TH, Hu Y, Wang RD, et al. Parkinson disease with constipation: clinical features and relevant factors. *Sci Rep*. 2018 Jan;8(1):567. <https://doi.org/10.1038/s41598-017-16790-8>
49. Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's disease: a review. *Parkinsonism Relat Disord*. 2014 Nov;20(11):1109-18. <https://doi.org/10.1016/j.parkreldis.2014.08.013>
50. Bronner G, Vodusek DB. Management of sexual dysfunction in Parkinson's disease. *Ther Adv Neurol Disord*. 2011 Nov;4(6):375-83. <https://doi.org/10.1177/1756285611411504>
51. Nomura T, Inoue Y, Kagimura T, Nakashima K. Clinical significance of REM sleep behavior disorder in Parkinson's disease. *Sleep Med*. 2013 Feb;14(2):131-5. <https://doi.org/10.1016/j.sleep.2012.10.011>
52. Anang JB, Gagnon JF, Bertrand JA, Romenets SR, Latreille V, Panisset M, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology*. 2014 Sep;83(14):1253-60. <https://doi.org/10.1212/WNL.0000000000000842>
53. Kim JS, Park HE, Oh YS, Lee SH, Park JW, Son BC, et al. Orthostatic hypotension and cardiac sympathetic denervation in Parkinson disease patients with REM sleep behavioral disorder. *J Neurol Sci*. 2016 Mar 15;362:59-63. <https://doi.org/10.1016/j.jns.2016.01.020>
54. Jin H, Zhang JR, Shen Y, Liu CF. Clinical significance of REM sleep behavior disorders and other non-motor symptoms of Parkinsonism. *Neurosci Bull*. 2017 Oct;33(5):576-84. <https://doi.org/10.1007/s12264-017-0164-8>
55. Kim JS, Park HE, Park IS, Oh YS, Ryu DW, Song IU, et al. Normal 'heart' in Parkinson's disease: is this a distinct clinical phenotype? *Eur J Neurol*. 2017 Feb;24(2):349-56. <https://doi.org/10.1111/ene.13206>
56. Fereshtehnejad SM, Postuma RB. Subtypes of Parkinson's disease: what do they tell us about disease progression? *Curr Neurol Neurosci Rep*. 2017 Apr;17(4):34. <https://doi.org/10.1007/s11910-017-0738-x>
57. Al-Qassabi A, Pelletier A, Fereshtehnejad SM, Postuma RB. Autonomic sweat responses in REM sleep behavior disorder and Parkinsonism. *J Parkinsons Dis*. 2018;8(3):463-8. <https://doi.org/10.3233/JPD-181357>
58. Kadastik-Eerme L, Rosenthal M, Paju T, Muldmaa M, Taba P. Health-related quality of life in Parkinson's disease: a cross-sectional study focusing on non-motor symptoms. *Health Qual Life Outcomes*. 2015 Jun;13:83. <https://doi.org/10.1186/s12955-015-0281-x>
59. Mendoza-Velásquez JJ, Flores-Vázquez JF, Barrón-Velázquez E, Sosa-Ortiz AL, Illigens BW, Siepmann T. Autonomic dysfunction in alpha-synucleinopathies. *Front Neurol*. 2019 Apr;10:363. <https://doi.org/10.3389/fneur.2019.00363>
60. De Pablo-Fernandez E, Tur C, Revesz T, Lees AJ, Holton JL, Warner TT. Association of autonomic dysfunction with disease progression and survival in Parkinson disease. *JAMA Neurol*. 2017 Aug;74(8):970-6. <https://doi.org/10.1001/jamaneurol.2017.1125>