Neuropsychological Aspects: Cognition in RBD

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34.1 Introduction

It is well recognized that idiopathic rapid eye movement sleep behavior disorder (iRBD) is a major risk factor for synucleinopathies, a category of neurodegenerative diseases that includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Several risk factors and biomarkers of synucleinopathies have been identified in iRBD. Cognitive markers are particularly useful for describing iRBD subtypes (with or without mild cognitive impairment [MCI]) and to predict whether RBD patients will develop dementia first (DLB) or parkinsonism first (MSA or PD). Individuals with PD and concomitant RBD present a different clinical phenotype, with more impaired brain functional and anatomical substrates and a higher risk of presenting MCI and developing dementia.

34.2 Idiopathic RBD and Dementia Risk

DLB is the second most common cause of degenerative dementia in people older than 65 years [1]. Compared to Alzheimer's disease, DLB is associated with accelerated cognitive decline, shorter lifespan, less favorable prognosis, increased admission to residential care, and higher caregiver burden and health-related costs [1]. DLB is defined as a progressive cognitive decline with altered usual daily activities accompanied by a set of core clinical features, namely, (1) fluctuating cognition with pronounced variations in attention and alertness; (2) recurrent visual hallucinations; (3) RBD, which may precede cognitive decline; and (4) one or more

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spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, or rigidity) [2]. DLB is similar to PD with dementia (PDD), suggesting a common spectrum of Lewy body disease [2]. However, mainly for clinical purposes but also for research, a distinction between these two clinical entities has been proposed based on the temporal sequence of symptom appearance: PDD should be diagnosed when dementia occurs 1 year after a well-established PD diagnosis, whereas DLB should be diagnosed when dementia occurs before or at the same time as parkinsonism [2]. The cognitive profile of DLB patients typically involves severely impaired visuospatial abilities, attention capacities, executive functions, and, to a lesser extent, learning and memory functions [1].

Longitudinal studies in iRBD cohorts at a sleep center found an almost equivalent risk of developing parkinsonism first (PD or MSA) or dementia first (DLB). Schenck et al. [3] followed 26 patients for a mean of 14.2 years after RBD onset. Of the 21 patients who developed a neurodegenerative disease, 6 (29%) were diagnosed with dementia (3 DLB, 1 unspecified, and 2 Alzheimer's disease with autopsy-confirmed combined Alzheimer's plus Lewy body disease pathology). Another study followed 174 iRBD patients for a mean of 12 years after RBD onset [4]. Of the 53 patients who developed a synucleinopathy, 29 (55%) were diagnosed with DLB. Recently, our group published the results on a cohort of 89 iRBD patients followed for a mean of 14.6 years after RBD symptom onset. Of the 46 patients diagnosed with a synucleinopathy, 21 (46%) developed DLB [5]. Finally, Youn et al. [6] followed 84 patients for a mean of 8.2 years after RBD onset. Of the 18 patients who developed a neurodegenerative disease, 7 (39%) had dementia (4 DLB, 3 Alzheimer's disease). Thus, the risk of developing dementia (mostly DLB) in iRBD is from 29 to 55% over a period of 8–14 years following RBD symptom onset. In contrast, only a few cases of iRBD developed Alzheimer's disease, and the association between RBD and Alzheimer's disease could be considered rare [7–9]. Taken together, these previous results support that RBD patients who develop dementia would present DLB at clinical diagnosis. Moreover, the inclusion of RBD as a core clinical feature improves the diagnostic accuracy of DLB [10], and RBD is now recognized as a core clinical feature of DLB [2].

34.3 Cognitive Profile in iRBD

34.3.1 Cross-sectional Studies

Of the many cognitive domains that have been defined, a neuropsychological assessment would consider in general mainly attention, executive functions, episodic learning and memory, visuospatial abilities, language, gnosia, and praxis. Cognitive complaints are frequent in iRBD patients [11], and several studies have found lower cognitive performance in iRBD patients compared to age-, sex-, and education-equivalent healthy subjects (Table 34.1) [6, 11–19]. All studies found lower performance by iRBD patients compared to healthy subjects on a broad range of cognitive tasks used in clinical settings. However, results vary across studies according to the cognitive domains that are impaired or preserved. Several factors may explain these discrepancies, including

Table 34.1 Controlled studies on cognitive performance in idiopathic rapid eye movement sleep behavior disorder

Variable	Terzaghi et al.	Massicotte-Marquez et al.[a]	Gagnon et al.[a]	Marques et al.	Ferini-Strambi et al.[b]	Fantini et al.[b]	Li et al.	Youn et al.	Zhang et al.	Barder et al.
Number of patients	23	14	32	10	17	24	23	96	15	171
Age	67.0 ± 7.0	66.6 ± 7.7	65.7 ± 8.5	64.0 ± 2.9	70.0 ± 7.3	69.5 ± 7.3	72.5 ± 6.8	65.5 ± 6.7	61.7 ± 12.7	64.7 ± 9.0
Education	6.0 ± 2.0	12.2 ± 4.0	13.4 ± 3.6	10.0 ± 0.6	8.5 ± 3.4	8.6 ± 3.6	14.2 ± 2.3	12.7 ± 4.9	10.4 ± 3.7	13.7 ± 3.4
Gender, % men	91	100	78	80	76	75	83	69	73	88
Cognitive domains										
Attention	Yes	No	Yes	No	Yes	No	No	Yes	No	–
Executive functions	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Verbal learning	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	–
Nonverbal learning	Yes	–	–	–	Yes	Yes	Yes	No	No	–
Visuospatial	No	No	No	–	Yes	Yes	Yes	Yes	No	–
Language	–	–	–	–	–	–	No	–	No	–
Gnosia	–	–	–	–	–	–	–	–	–	–
Praxis	–	–	–	–	–	–	–	–	–	–

[a,b]share common participants; Yes = poorer performance for patients versus controls ($p < 0.05$); No = similar performance for patients and controls

population heterogeneity in the sociodemographic variables, recruitment bias, small sample sizes with low statistical power, and the use of diverse cognitive tasks with variable specificity to a cognitive domain and variable sensitivity to detect deficits.

Generally, the most affected cognitive domains in iRBD are attention, executive functions, and episodic memory [11–19]. Additionally, some studies have found impaired visuospatial abilities [6, 12–14], although others have not [11, 16–18]. In fact, impaired visuospatial, visuoperceptive, and nonverbal learning abilities in iRBD appear to be related to the extent of cognitive decline [12, 20–22], as has been reported for neurodegenerative diseases associated with RBD, such as PD and DLB [11, 23]. Moreover, the use of more sensitive computerized tasks might reveal visuoperceptive and visual short-term memory deficits in iRBD [15, 24, 25]. Praxis, gnosia, and language appear to be well preserved in iRBD, although these cognitive functions, or their more specific components, have received little research attention. Overall, the impaired cognitive profile observed in iRBD is similar, albeit to a lesser extent, to that observed in DLB.

Recent iRBD studies have examined other cognitive functions, including prospective memory and decision-making [[26, 27]; see Chap. 35]. Prospective memory refers to the ability to execute delayed intentions, such as remembering to attach an important document to an email or to take a pill at bedtime [28]. Significant prospective memory decline has been reported in PD patients [29, 30]. In a recent study by our group, prospective memory was assessed in iRBD using a self-administered questionnaire, a simple clinical measure (envelope test), and a laboratory general knowledge task involving perceptual cue salience [31]. All participants performed well on the questionnaires and the envelope task. However, healthy subjects showed better detection accuracy compared to iRBD patients for all high- and low-salience cues. Moreover, iRBD patients with cognitive impairment performed similarly to iRBD patients with normal cognition in the high-salience condition but showed significant difficulty in detecting low-salience cues. Thus, prospective memory difficulties in iRBD, assessed with a laboratory task, are more prominent in patients with cognitive impairment and could serve as a promising indicator of early cognitive decline in iRBD. One recent study also found evidence for a differential pattern of prospective memory impairment in iRBD with severe impairment of event-based and concurrent preservation of time-based prospective memory [32].

Most studies have focused on group differences in neuropsychological tests between healthy subjects and iRBD patients. However, the most relevant clinical variable is the proportion of iRBD patients with clinically significant cognitive impairment. A few studies have reported that a significant proportion of iRBD patients present clinically impaired cognition, particularly in terms of attention, executive functions, and episodic learning and memory [11, 16].

34.3.2 Longitudinal Studies

To our knowledge, five longitudinal studies have addressed cognition in iRBD. In the first study, 24 iRBD patients and 12 healthy subjects were followed for a mean

interval of 2.2 years [12]. Patients showed poorer delayed verbal memory (story recall) and visuospatial abilities (Rey-Osterrieth Complex Figure, copy) at baseline and follow-up and poorer visuospatial attention (Corsi supraspan test) at follow-up only. The second study followed 20 iRBD patients for a mean interval of 3.6 years [33]. Cognitive performance declined in 45% of patients, mainly in visuospatial abilities, along with nonverbal logic (Raven Coloured Matrices) and attention (Attentive matrices). The third study followed 84 iRBD patients for a mean of 4.2 years [6]. At follow-up, 18 patients had developed a neurodegenerative disease, including 7 with dementia. Only poorer visual attention (Trail Making Test, part A) at baseline differentiated between disease-free patients and those who developed a neurodegenerative disease. The fourth study followed 76 iRBD patients for a mean of 3.6 years [20]. At follow-up, 34 patients had developed a synucleinopathy: 15 dementia first (DLB) and 19 parkinsonism first (PD or MSA). Cognitive performance and the proportion of patients with clinically impaired performance (z score of -1.5) were compared at baseline between patients who developed dementia first and those who developed parkinsonism first. The diagnostic value of cognitive tests for detecting prodromal dementia was also assessed. RBD patients who developed dementia first were impaired at baseline in all cognitive domains (attention and executive functions, episodic learning, and visuospatial abilities) compared to patients who developed parkinsonism first. The parkinsonism-first patients were similar at baseline to disease-free iRBD patients on all cognitive measures. In dementia-first patients, two cognitive tests assessing attention and executive functions (Stroop Color-Word Test and Trail Making Test part B) best predicted dementia (area under the curve ≥ 0.85) compared to parkinsonism-first patients and healthy individuals.

In the more recent fifth study, we compared the progression of cognitive test performance over a six-year prodromal period in three groups of RBD patients classified at their last follow-up as having PD, DLB, or still-idiopathic [34]. Cognitive performance changes over time were strongly associated with later development of dementia (DLB). Clear deficits in attention and executive functions were observed 6 years before diagnosis. Verbal episodic learning and memory deficits started later, deviating from normal approximately 5 to 6 years and becoming clinically impaired 2 years before diagnosis. Visuospatial abilities progressed variably, with inconsistent prodromal latencies. For clinical utility, the Trail Making Test (part B) best detects early prodromal DLB stages, whereas Verbal Fluency (semantic) and Rey Auditory-Verbal Learning Test are best for monitoring changes over time.

34.4 MCI in iRBD

MCI is a syndrome known to be an intermediate state between normal cognitive functioning and dementia [35]. It is characterized by a significant, objectively assessed cognitive decline that is greater than expected for education and age. No major interference with social, professional, or daily living activities should be reported. MCI can be diagnosed according to the following criteria: (1) cognitive concern reflecting a significant change in cognition reported by the patient or a

relative or a health professional, (2) objective evidence of impairment in one or more cognitive domains compared with normative age- and education-equivalent performance, (3) preserved daily life activities based on previous and actual capacities, and (4) absence of dementia [11, 35]. In addition, medication side effects and other medical (e.g., severe sleep apnea, chronic obstructive pulmonary disease) or psychiatric conditions responsible for cognitive deficits should be excluded. MCI can be classified into different subtypes according to the nature (amnestic vs. non-amnestic) and number (single-domain vs. multiple-domain) of the cognitive domains impaired [36]. MCI is a risk factor for dementia, and depending on the etiology, many MCI patients develop AD, vascular dementia, PDD, or DLB [20, 37, 38]. However, the progression of MCI is also highly variable. In the general population and in PD patients, some MCI patients progress to dementia, others return to normal cognitive functioning, and still others remain with mild cognitive deficits for many years [38–40]. Consequently, clinicians and researchers should be careful not to directly link MCI to the future development of a neurodegenerative disease, nor to automatically consider MCI as part of a neurodegenerative disease.

In a population-based sample followed prospectively for a median of 3.8 years, a substantial proportion (14/44, or 32%) of individuals with probable RBD developed MCI [41]. Sleep clinic studies have also reported a high frequency of MCI in iRBD patients [4, 5]. In a cross-sectional study of iRBD patients referred to a sleep clinic, MCI frequency as measured by standard criteria was estimated at up to 50% (16/32) compared to 8% (3/40) in healthy subjects [11]. In this study, the main MCI subtype reported was nonamnestic MCI single domain with predominant attention and executive dysfunctions. Another study confirmed these results and found a higher proportion of MCI in iRBD patients (33%, 5/15) than in healthy subjects (8%, 3/36) [18]. Very few studies have followed a cohort of iRBD patients with concomitant MCI to determine the risk of developing dementia. Molano et al. [22] followed seven iRBD patients for several years. All patients met MCI criteria and subsequently developed Lewy body disease, confirmed by autopsy [22]. In a more recent study by our group, a large cohort of iRBD patients was followed for a mean of 3.6 years to determine the predictive value of MCI for dementia [20]. Results showed that a higher proportion of patients who developed dementia first had MCI at baseline (93%, or 14/15) compared to the proportion of patients that developed parkinsonism first (42%, or 8/19).

A comprehensive neuropsychological assessment is the most effective way to detect MCI. However, this involves a time-consuming exam that requires specialized training, which is often unavailable in clinical sleep practice. Effective MCI screening tests in iRBD would therefore be useful. Three screening tests have been tested in small cohorts for their ability to detect MCI in iRBD [42–44]: the Montreal Cognitive Assessment or MoCA [45], the Mini-Mental State Examination [46], and the Mattis Dementia Rating Scale [47]. The Mattis Dementia Rating Scale (cutoff score <141/144 indicating MCI) and MoCA (cutoff score <26/30 indicating MCI) show superior psychometric properties to the Mini-Mental State Examination. Nevertheless, due to its short administration time (5–10 min), its validated alternative versions (allowing retesting), the fact that it is available free of charge, and the fact that it does not require specialized training, the MoCA (http://www.mocatest.org/)

appears to be the most appropriate screening test for detecting MCI in iRBD. However, results should be validated in larger cohorts and in other countries with different cultures and languages.

The presence of cognitive impairment in a subgroup of iRBD patients suggests distinct clinical phenotypes and patterns of neurodegeneration. Only a few studies have investigated whether RBD patients show different cerebral functioning according to their cognitive status. Using quantitative EEG, Iranzo et al. [48] followed for a mean of 2.4 years 23 iRBD patients, including 10 who developed MCI, 13 who remained cognitively normal, and 10 healthy subjects. They recorded baseline EEG activity during wakefulness in the central and occipital areas and found higher absolute theta and delta power in iRBD patients who later developed MCI compared with healthy subjects, but no significant differences between the two RBD groups. Sasai et al. [49] examined 31 iRBD patients and found as their main results relationships among lower scores on the MoCA, olfactory dysfunction, and higher EEG delta spectral power during REM sleep in the occipital region. Rodrigues Brazète et al. [50] compared waking EEG activity in 42 iRBD patients, including 23 with MCI and 19 without MCI, and in 37 healthy subjects. iRBD patients with MCI had a higher slow-to-fast frequency ratio than iRBD patients without MCI and healthy subjects, mainly in the posterior regions (parietal, temporal, and occipital). iRBD patients without MCI were similar to healthy subjects.

Vendette et al. [51] investigated 20 patients with iRBD, including 10 with MCI and 10 without MCI, and 20 healthy subjects, using single-photon emission computed tomography (^{99mc}Tc-ethylene cysteinate dimer). Compared to healthy subjects, both iRBD groups had hypoperfusion in the frontal lobes. In addition, iRBD patients with MCI showed additional hypoperfusion in temporal, parietal, and occipital areas compared to RBD patients without MCI and healthy subjects. Taken together, these results indicate a more altered pattern of functional cerebral activity in iRBD patients with concomitant MCI, with hypoperfusion, and with EEG slowing, mainly in posterior regions. This functional activity pattern resembles that found in iRBD patients at risk for neurodegenerative disease, in DLB patients, and in PD patients at risk for dementia [52–58], providing new potential markers for increased risk of developing DLB in RBD patients with MCI. A recent study also found an association between cognitive dysfunction and pareidolias in iRBD patients [59]. Pareidolias are complex visual illusions of meaningful objects deriving from ambiguous forms embedded in visual scenes and a potential surrogate indicator of visual hallucinations, a core clinical feature of DLB [2].

The pathophysiology of MCI and cognitive impairment in iRBD remains poorly understood. Some studies have reported neuroanatomical and neurochemical deficits in iRBD. Indeed, white matter integrity loss and lower gray matter volume and thinning in cortical and subcortical regions are well documented in iRBD patients [60–65]. Neural loss has also been reported in several cortical and subcortical structures in iRBD [7, 66, 67]. In addition, nigrostriatal and nigrocaudate dopaminergic deafferentation have been reported in iRBD [68–70], while the serotoninergic systems remain intact [69]. Cholinergic and noradrenergic systems have been understudied in iRBD. One study used transcranial magnetic stimulation (short latency

afferent inhibition) and suggested cholinergic dysfunction in some iRBD patients who developed cognitive impairment [71]. However, none of these studies looked for the presence of MCI or cognitive impairment in their RBD population. In a recent study, we investigated cortical and subcortical gray matter abnormalities underlying cognitive deficits in iRBD patients with (n=17) or without (n=35) MCI and 41 healthy subjects [72]. Patients with MCI had cortical thinning in the frontal, cingulate, temporal, and occipital cortices, and abnormal surface contraction in the lenticular nucleus and thalamus. Patients without MCI had cortical thinning restricted to the frontal cortex. Lower performance in cognitive domains was associated with cortical and subcortical abnormalities in iRBD patients. In PD, the presence of a dysexecutive syndrome seems to be associated with dopaminergic dysfunction, whereas the development of dementia would be related to cholinergic degeneration [73, 74]. Interestingly, cholinergic dysfunction has also been related to RBD in PD [75]. Based on the strong associations between PD, RBD, and cognitive impairment, we may hypothesize that both dopaminergic and cholinergic deficiencies could be related to cognitive impairment in iRBD.

34.5 Cognitive Decline in PD Associated with RBD

A substantial proportion of PD patients have cognitive impairment, and approximately 75% will develop dementia during the course of PD [76]. RBD is also a frequent feature of PD, affecting 33–46% of patients [77, 78]. The existence of a distinct and more impaired cognitive profile in nondemented PD patients based on the presence of RBD is controversial [79]. Indeed, some studies have found in PD with RBD poorer cognitive performance and higher MCI frequency than in PD without RBD and healthy subjects [11, 15, 18, 80–86], whereas others have not [87–93]. However, most of these studies have methodological limitations that could explain the divergent results, including small sample size, use of screening tests only with poor sensitivity to measure cognition and that do not allow MCI diagnosis, absence of a healthy subject group to better interpret the results, and absence of polysomnography to diagnose RBD. Our group recently examined with a complete neuropsychological assessment 162 participants, including 53 PD patients with RBD confirmed by polysomnography, 40 PD patients without RBD, and 69 healthy subjects [94]. PD patients with RBD had poorer and clinically impaired (z score of -1.5) performance on several cognitive tests and domains compared to PD patients without RBD and healthy subjects, who performed similarly on all cognitive measures. Moreover, MCI diagnosis frequency in PD patients with RBD (66%, or 35/53) was almost threefold that of PD patients without RBD (23%, or 9/40).

The presence of more severe cognitive decline in PD patients with RBD has been supported by other studies showing more specific brain anatomical and functional changes in PD patients with RBD. Indeed, several studies using waking quantitative EEG, event-related potentials, neuropathological exam, anatomical magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography have reported brain dysfunctions in PD with RBD compared to

PD without RBD and healthy subjects [75, 80, 95–103]. Other studies have identified a distinct clinical subtype in PD related to the presence of RBD, with higher risk for dementia, dysautonomia, freezing of gait, falls, symmetric disease, a non-tremor-dominant PD subtype, and hallucinations [37, 104–112]. Taken together, these results indicate more severe and widespread neurodegeneration in PD patients with RBD, which is related to a more altered clinical phenotype, including the presence of cognitive decline.

34.6 Conclusion and Further Directions

Cognitive impairment is a major feature of iRBD, and it increases the risk of developing DLB. iRBD patients with MCI present a more severe and widespread pattern of impaired brain functioning, which suggests underlying neurochemical and neuroanatomical correlates. Patients with PD and concomitant RBD are at higher risk for cognitive decline. Thus, both iRBD patients with cognitive impairment and PD patients with RBD should receive targeted medical attention to better detect and monitor impairment and to enable the development of management interventions for cognitive decline and its consequences.

Future studies on cognition in iRBD should use a greater variety of tests to more deeply assess a wider range of language components (e.g., naming, reading, writing, understanding, and pragmatism) and higher executive functions (e.g., planning, problem solving, inhibition control) as well as procedural learning, judgment capacities, praxis, gnosis, and activities of daily living. Neuroimaging studies could investigate the presence of different patterns of neuroanatomical and neurochemical dysfunction underlying cognitive impairment in iRBD. In addition, the effectiveness of diverse management interventions for cognition, for example, cognitive training, physical exercise, and neuroprotection agents, should be tested in iRBD patients in the near future.

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