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Cognitive changes and brain imaging in REM sleep behavior disorder

Kognitivní změny a zobrazení mozku u poruchy chování v REM spánku

Dissertation thesis

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Abstract

Isolated REM sleep behavior disorder (iRBD) is associated with a broad spectrum of symptoms, including sensory, olfactory, neuropsychiatric, motor, and cognitive impairments. Among the cognitive symptoms, deficits in memory and executive functions are most prominent, although the precise cognitive profile of iRBD remains unclear. Similarly, findings regarding structural brain changes are mixed, with meta-analyses suggesting involvement of frontal and temporal lobes and basal ganglia, yet considerable heterogeneity exists across studies. Given the early onset of sensory deficits in iRBD, recent research has begun to also investigate the interplay between sensory function, cognition, and brain morphology. This thesis aims to synthesize recent literature and address key research gaps through four original empirical studies. These studies examine the cognitive profile of iRBD, associated brain structural changes, and the relationships between cognitive, sensory, and neuroimaging measures. The results consistently highlight processing speed deficits as a core cognitive feature of iRBD, with robust associations between performance and grey matter density in the right insula and putamen. In contrast, colour discrimination deficits were not linked to cognitive functions, brain morphology, or dopaminergic depletion, instead supporting a sensory origin likely rooted in retinal pathology. Additional findings in a Parkinson's disease cohort suggest distinct neural mechanisms for dual-task gait performance. Overall, this thesis advances understanding of the complex relationships among cognitive, sensory, and structural brain changes in iRBD. The identification of processing speed impairments and their potential neuroanatomical substrates may have practical implications for early neuropsychological assessment in alpha-synucleinopathies.

Keywords: Prodromal Synucleinopathy, Cognition, REM Sleep Behavior Disorder, Colour Discrimination, Gait, Morphology, DAT-SPECT.

Abstrakt

Izolovaná porucha chování v REM spánku (iRBD) je spojena se širokým spektrem příznaků, včetně smyslových, čichových, neuropsychiatrických, motorických a kognitivních. Mezi kognitivními příznaky jsou nejvýraznější deficity paměti a exekutivních funkcí, ačkoli přesný kognitivní profil iRBD zůstává nejasný. Podobně jsou nejednotná zjištění týkající se strukturálních změn mozku, přičemž metaanalýzy naznačují postižení čelních a spánkových laloků a bazálních ganglií, avšak mezi studiemi existuje značná heterogenita. Vzhledem k časnému nástupu senzorických deficitů u iRBD se v nedávné době začal výzkum zabývat také vzájemným působením mezi senzorickými funkcemi, kognicí a morfologií mozku. Tato práce si klade za cíl shrnout nejnovější literaturu a řešit klíčové mezery ve výzkumu prostřednictvím čtyř původních empirických studií. Tyto studie zkoumají kognitivní profil iRBD, související strukturální změny mozku a vztahy mezi kognitivními, senzorickými a neurozobrazovacími parametry. Výsledky konzistentně zdůrazňují deficity v rychlosti zpracování informací jako hlavní kognitivní rys iRBD, s robustními asociacemi mezi výkonem a hustotou šedé hmoty v pravé insule a putamenu. Naproti tomu nedostatky v rozlišování barev nebyly spojeny s kognitivními funkcemi, morfologií mozku ani s dopaminergní deplecí, což spíše podporuje senzorický původ, který má pravděpodobně základ v patologických změnách na sítnici. Další zjištění na kohortě s Parkinsonovou chorobou naznačují odlišné neuronální mechanismy pro výkonnost chůze při tzv. dual-task úkolech. Celkově tato práce přispívá k pochopení komplexních vztahů mezi kognitivními, senzorickými a strukturálními změnami mozku u iRBD. Identifikace poruch rychlosti zpracování informací a jejich potenciálních neuroanatomických substrátů může mít praktické důsledky pro včasné neuropsychologické hodnocení u alfa-synukleinopatií.

Klíčová slova: Prodromální synukleinopatie, kognice, porucha chování v REM spánku, rozlišování barev, chůze, morfologie, DAT-SPECT.

Abbreviations and Definitions

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1 Introduction

1.1 REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) was first observed in animal models 60 years ago when bilateral lesions in the locus coeruleus of cats led to the loss of muscle atonia and appearance of movements during REM sleep. These lesioned cats exhibited during REM sleep dreamlike and hallucinatory behaviours, such as fighting an imagined enemy (Jouvet & Delorme, 1965).

The first documented human cases appeared 21 years later. Schenck et al. (1986) reported five patients who at the time of referral described vivid dreams accompanied by complex motor behaviours, such as vocalizing or physically acting out dream content, sometimes resulting in injuries. These episodes consistently occurred in the later hours of the night. Among the five cases, four were men and one was a woman, all over age 60. When these patients underwent clinical examination, polysomnography (PSG) revealed normal basic sleep architecture but abnormal electromyographic (EMG) activity during REM sleep. This abnormal EMG activity, reflecting the loss of normal muscle atonia (REM sleep without atonia; RWA), directly manifested as jerking or complex motor behaviours. Additionally, patients spent more time in the 3rd and 4th stages of sleep. They frequently woke up as a result of vivid dreams or real-world consequences, such as striking a wall, but upon awakening, they quickly regained full consciousness. Based on these characteristic symptoms— REM sleep retaining its basic features, the presence of abnormal motor behaviours, and the loss of normal muscle atonia during REM sleep —the authors identified this condition as a distinct parasomnia, which they termed REM sleep neurobehavioral disorders.

These symptoms have remained core diagnostic criteria in modern diagnostic manuals, though their assessment now relies on more rigorous methods. According to American Academy of Sleep Medicine (2014) there must be present a) repeated episodes of sleep related vocalization and/or complex motor behaviours, b) these behaviours are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep, c) polysomnographic recording demonstrates RWA, and d) the disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

Although parasomnia with such symptoms might be perceived as more of a nuisance than a serious condition, its prevalence in certain diseases suggests otherwise. RBD is diagnosed as a comorbid condition in approximately 45% of Parkinson's disease (PD) patients (Maggi et al., 2023; Zhang et al., 2017), up to 88% of those with multiple system atrophy (Palma et al., 2015), and up to 89% of those with dementia with Lewy bodies (DLB) (Boeve et al., 2001; Elder et al., 2022). Contrary, in the general population, the prevalence of RBD in PGS confirmed cases is estimated to be between 0.38 and 1.4% (Cicero et al., 2021; Lee et al., 2023). These prevalence rates highlight the strong association between RBD and neurodegenerative diseases and, among other things, contributed to defining RBD without other clinical signs of an underlying disease as preclinical stage of alpha-synucleinopathies, see next chapters.

In summary, RBD is defined by RWA and behaviours during REM sleep, frequently exhibiting as laughing, shouting, punching, kicking, or gesturing. It is also highly prevalent condition in alpha-synucleinopathies, but it is not exclusively present in neurodegenerations.

1.2 Classification of RBD

Although the diagnostic criteria essentially exclude other types of RBD based on criterion D—i.e., the disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use (American Academy of Sleep Medicine, 2014)—several types of RBD are commonly recognized in both clinical and research practice. Some of these are also reflected in the newer American Academy of Sleep Medicine guidelines (Howell et al., 2023a).

RBD is categorized into two main types based on its assumed cause: primary and secondary. In primary RBD, there are no comorbidities or other obvious factors contributing to RBD symptoms. Due to this absence, it was historically referred to as idiopathic RBD (Hogl et al., 2018; Manni et al., 2011). However, as research has increasingly linked this form of RBD to phenoconversion to neurodegenerative diseases, the term isolated RBD (iRBD) has been considered more appropriate (Hogl et al., 2018). In rare cases, it has also been referred to as cryptogenic RBD (Ferini-Strambi et al., 2004). In contrast, secondary (or symptomatic) RBD occurs in the presence of comorbidities such as neurodegenerative disorders, narcolepsy, stroke, and other conditions (Howell et al., 2023b; Manni et al., 2011). Some literature further distinguishes drug-induced RBD as a separate category from the secondary classification (Howell et al., 2023b).

From a diagnostic certainty perspective, RBD is typically classified as defined or probable. Probable RBD is diagnosed using methods such as questionnaires, self-reported measures, or clinical interviews without PSG. This classification is commonly used in population-based studies (Boot et al., 2012) but also appears in some clinical research (Zibetti et al., 2010). The term defined RBD is generally used only to distinguish it from probable RBD. In other contexts, terms such as iRBD or secondary RBD are used.

More recently, there has been an increasing focus on identifying early stages of various diseases, including RBD. As a result, a new category has emerged for patients who meet some but not all RBD diagnostic criteria, referred to as prodromal RBD (Cesari et al., 2022; Lee et al., 2023). Specifically, this category includes individuals who exhibit RWA at levels meeting the threshold used in RBD diagnosis, or those with two or more episodes of dream enactment behaviour (DEB) during REM sleep (Cesari et al., 2022). However, this concept is not entirely new; similar classifications were suggested decades ago under the term subclinical RBD (Boeve, 2010; Kimura et al., 1997).

1.3 iRBD as a Preclinical Stage of Alpha-Synucleinopathies

iRBD is, by definition, not linked to any obvious cause. However, the same research group that originally defined RBD soon discovered that patients with iRBD often developed neurodegenerative disorders over time. This observation led them to conduct a multicenter study, which revealed that 38% of individuals initially diagnosed with iRBD converted to Parkinson's disease or multiple system atrophy (Schenck et al., 1996).

A formal hypothesis suggesting an association between iRBD and neurodegeneration, specifically alpha-synucleinopathies, was probably first proposed by Boeve et al. (2001), and has since been tested in several longitudinal studies (Fereshtehnejad, Montplaisir, et al., 2017; Galbiati et al., 2019; Iranzo et al., 2006; Miyamoto & Miyamoto, 2018; Postuma, Gagnon, Vendette, Fantini, et al., 2009). These studies provided compelling evidence that iRBD almost exclusively progresses to alpha-synucleinopathies. For example, Boeve et al. (2001) found that iRBD predicted a synucleinopathy with a positive predictive value ranging from 91.7% to 100%, depending on the methodology used. The long-term risk of conversion has been further explored across multiple cohorts, with estimates suggesting that approximately 45% of individuals with iRBD develop a neurodegenerative disease within 10 years (Iranzo et al., 2006; Miyamoto & Miyamoto, 2018; Postuma, Gagnon, Vendette, Fantini, et al., 2009). Supporting this trend, a recent meta-analysis reported a

33.5% conversion risk at five years, which increased steadily to 96.6% after 14 years (Galbiati et al., 2019).

These findings alone offer strong support for the notion that iRBD represents a prodromal stage of alpha-synucleinopathies. Nevertheless, a key limitation is that most diagnoses in these studies were made during the patient's lifetime, without postmortem histopathological confirmation, which remains the gold standard (Cullinane et al., 2024).

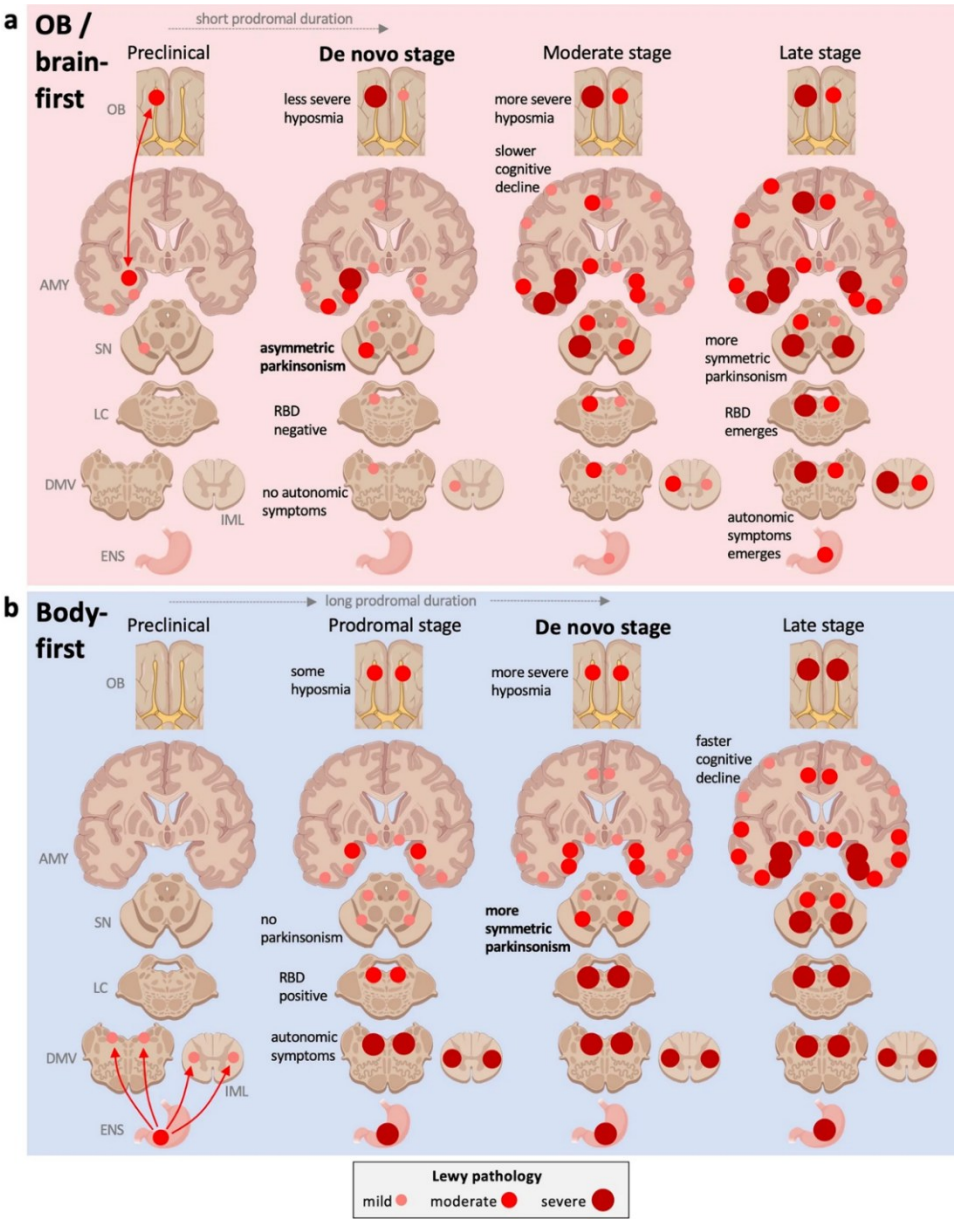
Although rare, neuropathological studies do exist (Hogl et al., 2018; Iranzo et al., 2014; Iranzo et al., 2013; Maya et al., 2024). One particularly notable study by Iranzo et al. (2013) included patients from their earlier longitudinal cohort (Iranzo et al., 2006), thus providing both long-term clinical and neuropathological data. That study demonstrated conversion from iRBD to Lewy body dementia in three male patients over the age of 70, with RBD symptoms persisting for 10 to 21 years. In all cases, the clinical diagnosis of an alpha-synucleinopathy was confirmed by postmortem pathological examination, and the neuropathological findings were consistent with standard features of Parkinson's disease and dementia with Lewy bodies. Since these patients were diagnosed during life with alpha-synucleinopathies, the findings were not unexpected. However, other studies have found neuropathological changes even in individuals who were diagnosed antemortem with iRBD and had not yet developed a clinical neurodegenerative disease. In three such cases, postmortem diagnoses included multiple system atrophy and DLB. In the DLB cases, the brainstem and, to a lesser extent, the limbic system were the most affected, with sparing of the cortex. In multiple system atrophy, the olivopontocerebellar and striatonigral regions were predominantly involved (Maya et al., 2024).

Altogether, these findings are so robust that, within the current framework, iRBD is widely regarded as a preclinical stage of alpha-synucleinopathies. As such, it can be placed temporally within the disease course. One commonly referenced model for staging is Braak staging (Braak et al., 2003). Although this model has been challenged (Borghammer & Van Den Berge, 2019; Burke et al., 2008), RBD can still be mapped onto, with meaningful practical implications. This is particularly relevant in the context of a reformulated model that distinguishes between two mutually exclusive subtypes: body-first and brain-first (Borghammer et al., 2022; Horsager et al., 2020). In the body-first subtype—more consistent with former Braak's staging—pathology is thought to originate in the enteric nervous system and progress via the peripheral autonomic nervous system, spinal cord, and brainstem to the prosencephalon. This trajectory parallels the clinical emergence of constipation, motor dysfunction, and cognitive impairment. Within this framework, RBD is believed to arise

during the stage when the pontine and medullary regions are affected, i.e., Stage 2 (see Table 1).

Figure 1

Body-first vs brain-first phenotypes



Note. From "A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease," by Borghammer, P., Just, M. K., Horsager, J., Skjaerbaek, C., Raunio, A., Kok, E. H., Savola, S., Murayama, S., Saito, Y., Myllykangas, L., & Van Den Berge, N., 2022, *NPJ Parkinsons Dis*, *8*(1), p. 6 (https://doi.org/10.1038/s41531-022-00436-2). Licensed under CC BY 4.0.

Table 1

Mapping iRBD to Braak stages of Parkinson's disease

Stage	Brain Regions Affected	Clinical Features	RBD Relevance
Stage 1	Dorsal motor nucleus of the vagus, olfactory bulb	Olfactory loss, autonomic symptoms	Not present
Stage 2	Locus coeruleus, raphe nuclei	Apathy, anxiety, depression, sleep disturbances	Strong association with RBD onset
Stage 3	Substantia nigra, amygdala	Early motor signs	RBD typically already present by this stage
Stage 4	Temporal mesocortex, thalamus	Motor symptoms, early cognitive changes	RBD may persist or worsen
Stage 5	High-order sensory association areas	Cognitive decline, visual hallucinations	RBD may coexist with other complex sleep disturbances
Stage 6	Primary sensory and motor cortex	Severe dementia, major motor impairment	Sleep severely affected; RBD part of broader dysfunction

1.4 Cognitive Impairment in RBD

Cognitive impairment is estimated to be present in approximately 30-66% of patients with iRBD (Gagnon et al., 2010; Gagnon et al., 2009; Genier Marchand et al., 2017; Joza et al., 2024; Nagy et al., 2023; Terzaghi et al., 2013). However, these estimates may be biased, as, with the exception of one population-based study, they do not rely on random sampling, often fail to account for symptom duration, and are based almost exclusively on small, non-representative samples. Additionally, there are currently no established criteria for diagnosing mild cognitive impairment (MCI) in iRBD, unlike in PD where such criteria exist (Litvan et al., 2012). Nevertheless, despite the potential biases, the prevalence of MCI in

iRBD appears to be high and its presence is a significant risk factor both for faster conversion to overt neurodegenerative disease and for greater severity of symptoms such as dementia (Arnaldi et al., 2021; Genier Marchand et al., 2017; Leitner et al., 2023). Therefore, cognitive status in iRBD is of critical importance from diagnostic, clinical trial, and patient quality of life perspectives. While it remains debated which specific cognitive domains are affected and whether a distinct cognitive profile exists, a considerable number of studies have already been conducted on the topic.

1.4.1 Cognitive Profile in RBD

Regarding impairments in specific cognitive domains, findings across studies have shown substantial heterogeneity. While some studies report deficits in visuospatial abilities, memory, language, executive functioning, verbal fluency, or attention (Campabadal et al., 2019; Ferini-Strambi et al., 2004; Gagnon et al., 2009), others have reported contrasting results, including instances where patients outperformed controls, for example, in long-term memory (Assogna et al., 2021). If any tentative conclusion can be drawn based on the frequency of reported domains, memory and executive functions appear most consistently implicated. These frequently reported deficits are supported by a recent meta-analysis, which found moderate effect sizes for impairments in memory (–0.64) and executive functions (–0.50)(Leitner et al., 2023). However, a particularly important yet often overlooked observation concerns the methodological details of the included studies: many tests categorized under executive functions primarily assess processing speed (Leitner et al., 2023).

Processing speed is considered a fundamental prerequisite for other cognitive functions, playing a crucial role in downstream processes such as attention, executive functions, and memory (Ferguson & Foley, 2024; Chiaravalloti et al., 2003). As a result, it may serve as an underlying mechanism for observed cognitive deficits in conditions such as PD (Ferguson & Foley, 2024). In light of this evidence, it is plausible that many of the cognitive deficits observed in iRBD may also be driven by reduced processing speed. Although a few studies have already identified impairments in processing speed among iRBD patients (Campabadal, Inguanzo, et al., 2020; Campabadal et al., 2019), such findings remain relatively scarce. Therefore, identifying a specific cognitive profile in iRBD remains an open question. A robust theoretical framework, integrating processing speed theory with

findings from neurosciences, needs to be developed and tested using appropriate experimental, rather than purely clinical, measures.

Another important factor to consider in characterizing the cognitive profile of iRBD is the presence of multiple phenotypes. As shown in meta-analytic studies published to date, none have accounted for the phenotypic heterogeneity of iRBD (Leitner et al., 2023; Mao et al., 2020). Yet, this consideration seems directly relevant. For instance, Litvan et al. (2012) proposed distinguishing MCI in PD based on whether deficits occur in multiple cognitive domains or only in a single domain, similar to the classification of amnestic versus non-amnestic MCI in Alzheimer's disease (Petersen, 2004). Although this may not be the most refined classification, some evidence supports this distinction in both PD (Goldman et al., 2012; Litvan et al., 2011) and iRBD (Gagnon et al., 2009). Others have simplified this categorization to a binary distinction: iRBD with or without MCI (Arnaldi et al., 2021), which is almost the same as distinguishing between cognitive and motor phenotypes (Zhang et al., 2023). More commonly, however, studies have used a longitudinal design and examined baseline cognitive differences between patients who eventually convert to neurodegenerative diseases and those who do not, or compared patients who converted to one disease with patients who converted to another disease (Genier Marchand et al., 2017; Joza et al., 2024; Postuma, Gagnon, et al., 2009a; Zhang et al., 2023). This inevitably contributes to discrepancies between cross-sectional and longitudinal studies regarding the most affected or deteriorating cognitive domains, as the cohorts assessed in each design differ (e.g., Ferini-Strambi et al., 2019; Leitner et al., 2023). Moreover, this discrepancy may imply that the most affected cognitive domain, and thus the cognitive profile, is time-dependent. A limitation of classifying patients post hoc by diagnosis following conversion is that it may not yield meaningful groupings. It is already well established that multiple phenotypes exist within PD and Alzheimer's disease (Berg et al., 2021; Fereshtehnejad, Zeighami, et al., 2017; Markello et al., 2021; Snowden et al., 2007), suggesting that treating these patient groups as homogeneous is inappropriate. Further complicating this issue is the frequent co-occurrence of multiple neuropathological processes in the same individual, as demonstrated in postmortem studies (Maya et al., 2024).

In the absence of a well-established, theory-driven classification of phenotypes, a data-driven approach, such as cluster analysis, offers a more promising alternative. Indeed, several studies have adopted this strategy. For example, Mombelli et al. (2023) identified three distinct cognitive phenotypes among patients. The first group performed poorly in all domains and showed measurable deficits in language, short- and long-term memory, and

executive functions. The second group performed comparatively worse in visuospatial abilities and long-term memory, while the third group showed relatively lower performance in short-term memory. However, only the first group exhibited mean scores below normative values on several neuropsychological tests, including the Token Test, Digit Span Forward and Backward, Rey's Word List Learning, and the copy condition of the Rey-Osterrieth Complex Figure. The other two groups, although demonstrating relative weaknesses, did not reach the threshold for clinically significant impairment. A similar clustering approach was used by Seger et al. (2023), who identified two patient groups (labelled "benign" and "aggressive") based on clinical variables. While these groups differed in subjective complaints, no significant differences were observed in objective cognitive performance.

1.4.2 Longitudinal Cognitive Decline and Risk of Dementia

As previously noted, the presence of RBD—whether isolated or secondary to a neurodegenerative condition—is associated with poorer cognitive performance. Regardless of whether cognitive deficits are subtle or meet the clinical threshold for MCI, they tend to worsen with disease progression. However, the prognosis differs depending on the cognitive status at baseline. Several studies have shown that individuals who already exhibit MCI during the iRBD stage progress more rapidly and are more likely to develop dementia earlier (Arnaldi et al., 2021; Genier Marchand et al., 2017; Joza et al., 2024; Leitner et al., 2023; Terzaghi et al., 2013). In contrast, patients with relatively preserved cognition at baseline tend to show more stable cognitive trajectories in the medium term and either do not convert or convert to a predominantly motor-first phenotype (Joza et al., 2024).

That said, this pattern may not hold across all disease stages. For instance, in cases of secondary RBD presenting in patients with mild dementia due to various neurodegenerative diseases, RBD does not appear to significantly influence the rate of dementia progression (Chwiszczuk et al., 2017). In other words, the association between RBD and poorer cognition may weaken at later stages of disease, for example, due to a floor effect.

Regarding the specific cognitive profile and the risk of phenoconversion, deficits in executive functions appear to be the strongest predictor (Leitner et al., 2023). When considering multiple phenotypes[1]—specifically, the risk of phenoconversion to a cognitive

[1] Due to significant heterogeneity in the terminology used to describe closely related phenotypes in the literature, the terms motor phenotype and cognitive phenotype are used here, for simplicity, as umbrella terms.

versus a motor phenotype—deficits across multiple cognitive domains were indicative of a higher risk of phenoconversion to the cognitive phenotype. While there was some variability depending on the particular tests used, the strongest predictors in favour of the cognitive phenotype were found in the attention domain (Stroop interference; HR = 5.62), executive function (the difference between parts A and B of the Trail Making Test; HR = 7.86), and memory (word list immediate recall; HR = 4.06) (Joza et al., 2024). A similar pattern was observed in Zhang et al. (2023), where deficits in combined measures of attention–executive and motor functions best predicted phenoconversion to the motor phenotype, whereas deficits in attention–executive functions alone were the strongest predictor of conversion to a cognitive phenotype.

Unsurprisingly, the progression rates of deficits across cognitive domains mirror the domains most predictive of phenoconversion. While in the motor phenotype there is no dominant pattern of deterioration, or it becomes detectable only shortly before phenoconversion (Foubert-Samier et al., 2020; Joza et al., 2024), in the cognitive phenotype, decline is observed earlier and across all cognitive tests, with the most pronounced impairments in attention–executive functions (Trail Making Test, Stroop – interference condition) and memory (Word list – immediate and delayed recall)(Joza et al., 2024). The same pattern was found also in other studies, for example, in Genier Marchand et al. (2018), where the greatest declines for cognitive phenotype were again in attention–executive functions (Trail Making Test, Verbal Fluency – semantic) and memory (Rey Auditory-Verbal Learning Test – total, immediate, and delayed recalls).

However, as previously discussed, this largely depends on the phenotype examined. When considering iRBD as homogenous group studies report faster decline in executive functions, attention, verbal memory or visuospatial functions, with decline in visuospatial functions being the most consistently observed (Campabadal, Inguanzo, et al., 2020; Fantini et al., 2011; Terzaghi et al., 2013; Yoo et al., 2021). When using the presence of MCI in iRBD as a classifier, different pattern emerges. Although MCI and non-MCI groups differ in the severity of deficits at both baseline and follow-up, the rate of progression does not appear to differ significantly, at least in some studies (Yoo et al., 2021).

These encompass designations such as parkinsonism-first versus dementia-first, or groups of disorders with shared dominant symptomatology (e.g., Parkinson's disease, multiple system atrophy vs. dementia with Lewy bodies, Alzheimer's disease), while acknowledging that these terms are not strictly equivalent.

1.5 Imaging in iRBD

1.5.1 Structural Imaging

Findings on structural changes in iRBD are as heterogeneous as the observed cognitive deficits. This variability is partly due to the widespread brain changes also seen in full-blown neurodegenerative diseases, and partly due to the differing structural features examined, such as volume, shape, thickness, and density.

Decreased cortical thickness has been observed in multiple brain regions, including the in anterior cingulate cortex (Rahayel et al., 2015; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), cuneus (Park et al., 2024), dorsolateral prefrontal cortex (Rahayel et al., 2022), primary motor cortex (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), fusiform gyrus (Campabadal et al., 2019; Rahayel et al., 2015), inferior frontal gyrus (Park et al., 2024), inferior parietal cortex (Rahayel et al., 2022), lateral occipital cortex (Campabadal et al., 2019; Pereira et al., 2019; Rahayel et al., 2022), lingual gyrus (Rahayel et al., 2015), middle temporal gyrus (Park et al., 2024), orbitofrontal cortex (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018; Rahayel et al., 2022), postcentral gyrus (Campabadal et al., 2019; Pereira et al., 2019), posterior temporal gyrus (Rahayel et al., 2022), superior frontal gyrus (Campabadal et al., 2019; Rahayel et al., 2015; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), superior occipital gyrus (Park et al., 2024), superior parietal cortex (Campabadal et al., 2019), or superior temporal gyrus (Park et al., 2024). Notably, no studies have reported increased cortical thickness (Rahayel et al., 2015; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018). However, some investigations have failed to detect any significant cortical thickness differences (Sarasso et al., 2024).

With regard to volume, reductions have been reported in the anterior dorsolateral prefrontal cortex (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), caudate nucleus (Park et al., 2024; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), cingulate gyrus (Han et al., 2019), cuneus (Baun et al., 2024), hippocampus (Campabadal et al., 2019), insular lobe (Han et al., 2019), middle temporal gyrus (Baun et al., 2024; Rahayel et al., 2022), nucleus basalis Meynerti (Yang & Li, 2023), olfactory cortex (Woo et al., 2023), orbitofrontal cortex (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), postcentral gyrus (Han et al., 2019; Woo et al., 2023), precuneus (Baun et al., 2024; Han et al., 2019), primary motor cortex (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018), rectus gyrus (Han et al., 2019; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018; Woo et al., 2023), Rolandic

operculum (Han et al., 2019), superior frontal gyrus (Han et al., 2019; Rahayel et al., 2015), supramarginal gyrus (Sarasso et al., 2024). Volume increases have been reported in the cerebellar posterior lobe and middle temporal gyrus (Sarasso et al., 2024).

Complementing these findings, a recent meta-analysis has provided a broader synthesis, reporting consistent volume reductions in the bilateral superior frontal gyri and gyri rectus, right temporal pole, and right caudate nucleus (see, Figure 2). Interestingly, this analysis also identified increased grey matter volume in the bilateral cerebellum and thalamus (Wang et al., 2025) (see, Figure 3), which may reflect compensatory mechanisms, individual variability in disease progression, or methodological differences across studies.

Figure 2

Regions of grey matter volume decrease in subjects with iRBD

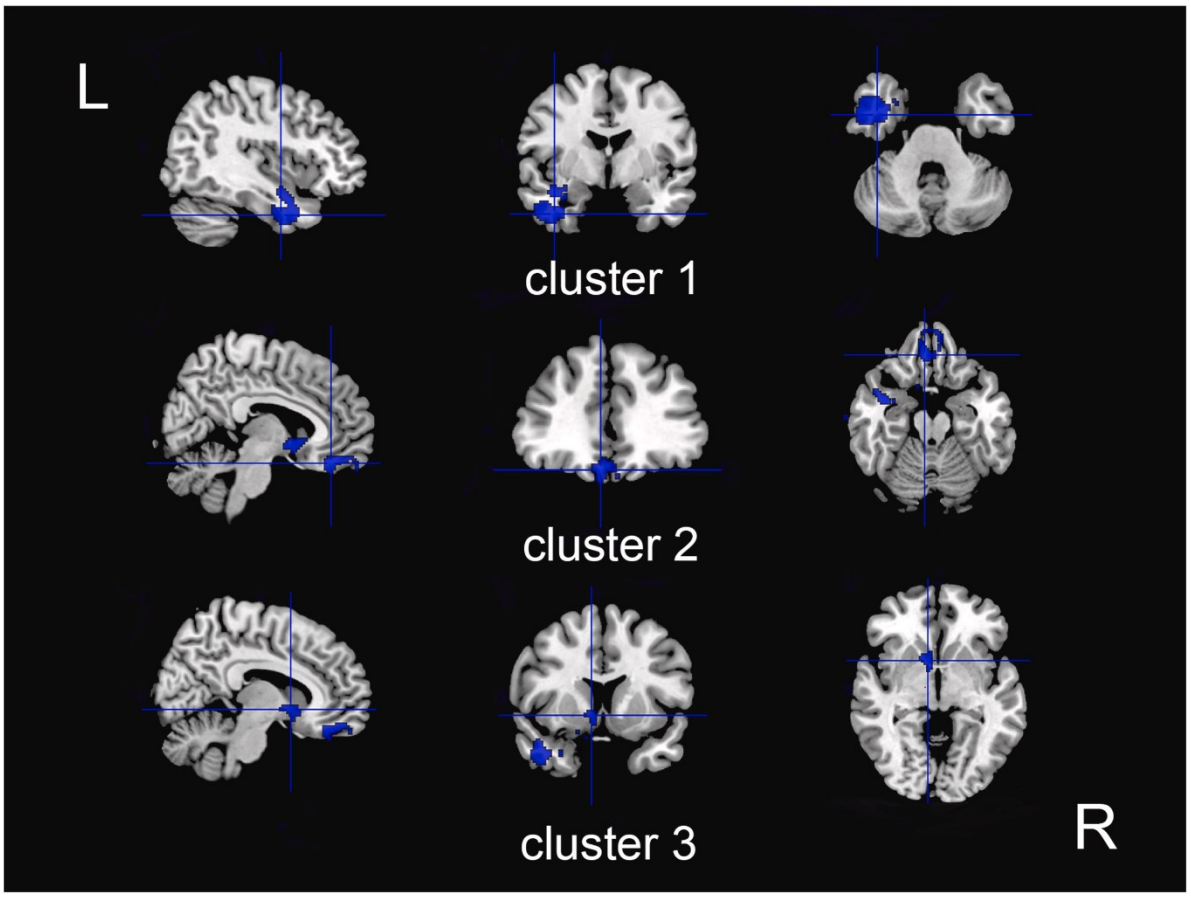


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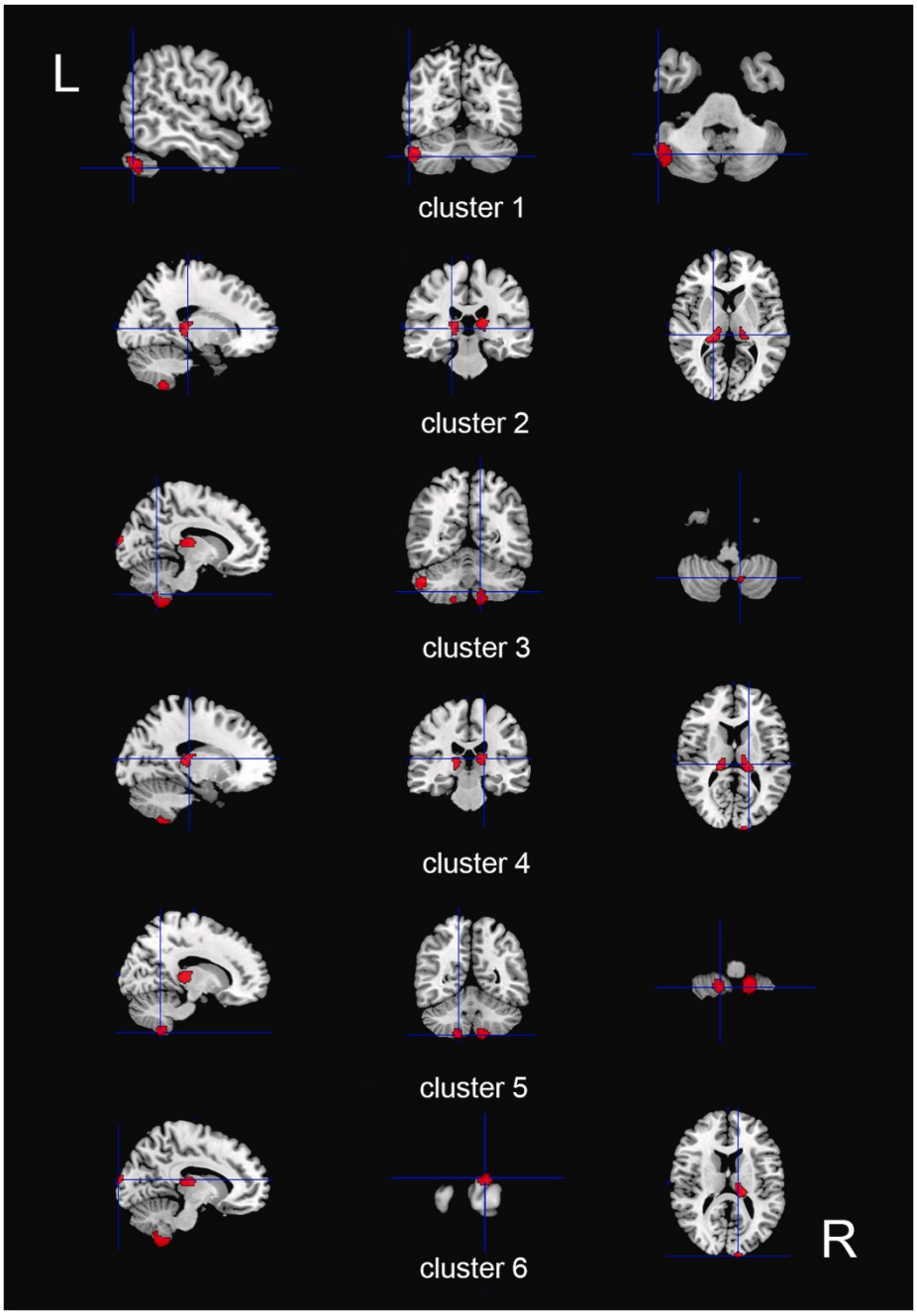
Figure 3

Regions of grey matter volume increase in subjects with iRBD



Note. Reprinted from Sleep Medicine, 126, Wang, X., Li, Y., Li, B., Shang, H., & Yang, J., Gray matter structural alterations in idiopathic rapid eye movement sleep behavior disorder: A voxel-based meta-analysis, 119., Copyright (2024), with permission from Elsevier.

Longitudinal studies have generally not detected significant volume changes over time in individuals with iRBD (Baun et al., 2024; Campabadal, Inguanzo, et al., 2020), suggesting that structural alterations may be subtle or progress slowly during the prodromal phase—particularly over relatively short follow-up periods (3 and 1.6 years, respectively). However, when analyses are restricted to specific regions of interest, such as those known

to be affected in synucleinopathies, localized volume reductions can emerge (Baun et al., 2024).

Microstructural changes and changes in shape remain understudied areas. Shape analyses, in particular, are relatively rare, though some studies have identified alterations in the pallidum (Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018) and hippocampus (Campabadal et al., 2019). Microstructural changes are typically assessed using diffusion tensor imaging (DTI), which includes parameters such as fractional anisotropy, radial diffusivity, mean diffusivity, and axial diffusivity. However, DTI has notable limitations, especially in interpreting changes in grey matter (Reveley et al., 2022; Rulseh et al., 2013).

Despite these limitations, some studies have applied DTI to grey matter. For example, Pyatigorskaya et al. (2017) reported decreased fractional anisotropy in the substantia nigra, while Alushaj et al. (2024) found increased mean diffusivity in the caudal motor substatita nigra pars compacta surface jointly for iRBD and PD. Interestingly, some other structures such as the striatum and its subregions showed alterations in iRBD but not in PD. Nevertheless, given the limitations of DTI in grey matter, these findings are less straightforward to interpret compared to those in white matter, where DTI is more commonly and reliably used.

In white matter, microstructural changes have been reported in several regions, including the fornix, internal capsule, corona radiata, and right visual stream (Unger et al., 2010), as well as the pontomesencephalic tegmentum (Scherfler et al., 2011) and anterior thalamic radiation inferior fronto-occipital fasciculus (Byun et al., 2022). Conversely, other studies found no significant differences in DTI parameters between iRBD and controls (Ohlhauser et al., 2019; Rahayel et al., 2015). Still, some studies reported unexpected findings—for instance, although neither iRBD nor PD differed significantly from controls in microstructural integrity, Ohlhauser et al. (2019) observed increased mean diffusivity in iRBD (relative to PD) across a wide range of white matter tracts: corpus callosum, the right limb of the internal and external capsule, the right superior and inferior longitudinal fasciculus, the right inferior fronto-occiptal fasciculus, the right cortical spinal tract, the right forceps major, the right corona radiata, the right tapetum and the left posterior thalamic radiation.

Underscoring the importance of these findings, especially for white matter integrity, is a recent study that sheds light on the nature of RBD. Traditionally, RBD has been considered a disorder arising from damage to grey matter structures such as the locus coeruleus, sub-coeruleus or the gigantocellular reticularis nucleus. However, a unique

lesion-based study found that nearly all lesions (92%) leading to secondary RBD were located either within or on average 3 mm from the tract connecting the locus coeruleus/sub-coeruleus and the medulla. This suggests that RBD may be best conceptualized as a disconnection syndrome, i.e., a disorder primarily involving white matter disruption (Odd et al., 2025).

Overall, there is general agreement on the presence of widespread structural changes in iRBD, primarily affecting anterior and posterior brain regions (Campabadal et al., 2021). Considering the full body of evidence, anterior regions appear to be more consistently reported. This aligns with the clinical profile of iRBD, where executive functions impairments, typically associated with anterior brain regions, are most prominent (Leitner et al., 2023).

1.5.2 Functional and Other Types of Imaging

Besides structural imaging techniques, there are many other methods used in the study of iRBD, two of which are particularly relevant and frequently applied. One is resting-state fMRI (rs-fMRI), which is widely used to assess functional connectivity, and the other is SPECT/PET, commonly employed to indirectly measure dopaminergic depletion.

One of the first rs-fMRI studies in iRBD focused on the substantia nigra, a structure well known in PD. The authors of that study discovered reduced functional connectivity between the left substantia nigra and the left putamen, and between the right substantia nigra and the right superior occipital gyrus. They also found increased functional connectivity between the right substantia nigra and the right cuneus/precuneus (Ellmore et al., 2013). Another relatively influential early study reported decreased functional connectivity in the basal ganglia and, to a lesser extent, in the cingulate and paracingulate gyri, the frontal orbital cortices, and the inferior and middle frontal gyri (Rolinski et al., 2016). These findings have been supported by more recent studies, which also demonstrate reduced functional connectivity, particularly in the basal ganglia and frontal regions. For instance, Sarasso et al. (2024) reported reduced connectivity in the left pallidum/putamen within the basal ganglia network, left calcarine sulcus, left superior and bilateral middle occipital gyri, and left middle temporal gyrus. Similarly, Woo et al. (2023) found altered functional connectivity in iRBD between the olfactory cortex and putamen and superior orbitofrontal cortex, middle cingulate cortex and paracentral lobule, and precentral gyrus. Interestingly, the same study also reported increased connectivity between the left gyrus rectus and middle occipital and

temporal cortices (Woo et al., 2023), while other studies have found decreased connectivity in these regions (Campabadal, Abos, et al., 2020).

Some studies have taken a different approach, applying graph theory to fMRI data. Graph theory allows for the analysis of complex brain networks by simplifying them into nodes (representing brain regions) and edges (representing functional interactions between those regions), providing both visual and quantitative representations of brain connectivity. Using this technique, it has been shown that iRBD patients exhibit decreased global/local efficiency and increased characteristic path length, and preserved small-worldness (S. Chen et al., 2022).

While this does not cover the entire body of literature on rs-fMRI, these studies reveal patterns similar to those observed in structural imaging, with widespread changes in the basal ganglia, as well as in frontal, temporal, and occipital regions. However, some bias may be present, as many studies used a region of interest (ROI) approach, which has become less favoured in more recent research.

Currently, there are no meta-analyses on functional connectivity in iRBD, so strong conclusions cannot yet be drawn. However, two systematic reviews have reached conclusions consistent with the findings described here. Churchill et al. (2024) concluded that the most prominent alterations are found in the brainstem nuclei, basal ganglia, frontal and occipital lobes, and in whole-brain network measures. Similarly, Campabadal et al. (2021) based on their review of existing studies, concluded that functional connectivity is disrupted within the basal ganglia, as well as in cortico-striatal and cortico-cortical networks.

This overall picture is complemented by SPECT/PET studies, which also indicate altered functioning of the basal ganglia and brainstem, albeit from a different perspective. Nigrostriatal dopamine is a key neuromodulator for both striatal and extrastriatal functioning, and it can be indirectly measured presynaptically or postsynaptically using SPECT/PET (Rommelfanger & Wichmann, 2010; Yamada et al., 2016). In PD, the loss of dopaminergic cells in the substantia nigra is well recognized, primarily for causing motor symptoms due to the loss of modulatory effects on the basal ganglia, particularly the striatum (Latif et al., 2021). Consequently, this approach has been extensively applied to iRBD. It has been shown that the striatal-occipital ratio, both averaged and hemispheric, is decreased in iRBD and, more interestingly, this decrease progresses gradually from iRBD to the later stages of PD. Specifically, the region with the most reduced striatal-occipital ratio was shown to be the posterior putamen, and irrespective of the region, the most affected hemisphere was the right (Huang et al., 2020). Abnormal SPECT/PET findings in the

putamen, caudate nucleus, or globus pallidus have also been consistently confirmed in other studies (Arnaldi et al., 2015; Arnaldi et al., 2023; Lovdal et al., 2024; Pilotto et al., 2024).

Although SPECT with the 123I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane tracer is most frequently used, primarily for estimating dopaminergic depletion in the basal ganglia, it can also be utilized for whole-brain analysis, with the consideration that up to 70% of the signal outside the striatum may arise from serotonergic transporters (Koch et al., 2014). In one such analysis, it was shown that iRBD patients with and without abnormal SPECT results differed from controls in specific binding ratios in the insula, and those with abnormal SPECT also showed differences in the right thalamus (Pilotto et al., 2024). The authors of that study suggests that neurotransmitter imbalance in the insula, particularly in the anterior part, might underlie deficits in high-level cognitive control, and abnormalities in the thalamus might serve as a classifier distinguishing PD from DLB. However, more evidence is needed; for example, Arnaldi et al. (2015) did not find any differences in the thalamus.

Altogether, SPECT/PET studies provide relatively consistent findings suggesting dopaminergic depletion in the basal ganglia, particularly in the putamen. This conclusion is also supported by the only existing meta-analysis (Bauckneht et al., 2018). However, it should be noted that the vast majority of SPECT/PET studies are conducted on samples of 20 or fewer participants and employ highly variable imaging methodologies, raising significant concerns about reliability. Furthermore, for some reason, it is common practice to dichotomize samples into "normal" or "abnormal" based on SPECT results. This practice directly contradicts statistical recommendations, as artificial categorization leads to a loss of information and variability (Altman & Royston, 2006; Naggara et al., 2011). All these methodological issues likely contributed to some very unusual findings; for example, in the meta-analysis, the SBR in the caudate appeared to be a relatively good marker with high sensitivity and specificity in all comparisons between controls, iRBD, PD with iRBD, and PD without iRBD—except for the comparison between iRBD and PD without iRBD, where the AUC was 0.59, while in all other cases it was above 0.82 (Bauckneht et al., 2018).

1.6 Association of Imaging and Cognition in RBD

Association studies can generally be classified into those using only screening instruments and those employing comprehensive neuropsychological batteries. The former approach does not allow for distinguishing associations between imaging parameters and specific

cognitive domains. However, it is used in the majority of studies and provides information about the association between imaging and a “cumulative” cognitive deficit across domains. This cumulative measurement may increase statistical sensitivity when several domains are affected, since deficits can summate. In contrast, studies using comprehensive neuropsychological batteries are more sensitive for detecting associations with specific cognitive deficits and allow for more straightforward interpretation in relation to imaging parameters. Most studies of both types focus on associations with structural imaging parameters, thus also elaborate here.

Screening instruments such as the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination typically show weak or non-significant associations with regional grey or white matter volumes (Baun et al., 2024; M. Chen et al., 2022; Rahayel et al., 2015). This is expected, as these tools are designed to provide a broad assessment of cognitive functioning are therefore less likely to correlate strongly with specific brain regions—unless the total score is disproportionately influenced by a single cognitive domain. In contrast, it can be rather assumed that stronger associations would be observed with global brain metrics, such as total grey or white matter volume. However, to the best of the author’s knowledge, no such studies have yet been conducted in iRBD.

Nevertheless, several studies do report associations between MoCA scores and regional grey or white matter parameters. For instance, MoCA scores have been linked to cortical thinning in the bilateral insula, the right temporal cortex and the left posterior temporal cortex, or volume of nucleus basalis of Meynert (Rahayel et al., 2022; Yang & Li, 2023). Although the original authors did not interpret the association between cortical thinning and MoCA in terms of some meaningful construct beyond “global cognition”, it can be cautiously speculated that the relationship was primarily driven by deficits in MoCA subtests such as phonemic fluency, word recall, digit subtraction, and trail making, representing memory and executive functions. This is supported by evidence linking the insula to executive functions (Billeke et al., 2020) and the temporal cortex to memory and language processing, particularly word repetition (Mesulam et al., 2019). Further support comes from findings that iRBD patients with cognitive impairment differ from those without it on MoCA subtests trail making, phonemic fluency, and word recall—subtests that also discriminate well between controls and PD patients (Miyamoto & Miyamoto, 2023; Roalf et al., 2016). The association between MoCA scores and the nucleus basalis of Meynert is somewhat more straightforward to interpret. This cholinergic nucleus is known to modulate widespread cortical areas and is affected in alpha-synucleinopathies (Koulousakis et al.,

2019; Oswal et al., 2021). While its degeneration may not be linked to a specific cognitive domain with MoCA test, its broad modulatory role provides a logical basis for its association with overall MoCA performance.

Studies using comprehensive neuropsychological batteries—although theoretically better suited to detect domain-specific associations—have also produced largely negative or inconclusive results regarding shape, volume, or cortical thickness (Campabadal et al., 2019; Park et al., 2024; Sarasso et al., 2024; Yang & Li, 2023).

Among studies with significant findings, one stands out in terms of the number of detected associations. Rahayel, Postuma, Montplaisir, Genier Marchand, et al. (2018) found that MRI parameters (volume, surface area, or cortical thickness) were associated with attention and executive functions (frontal medial superior, dorsolateral paracentral, sensorimotor, fusiform, lingual, cuneus), learning and memory (temporal pole, anterior superior, posterior lingual and fusiform, insula, cuneus, hippocampus) and visuospatial functions (frontal medial superior, paracentral, prefrontal, temporal middle, posterior lingual, fusiform, insular, precuneus, cuneus, lateral occipital, lateral occipital, hippocampus). Thus, associations were found across all examined cognitive domains. The authors highlighted notable overlaps in the occipital cortex and hippocampus and interpreted these findings as reflecting the prominence of these regions in the pathophysiology of synucleinopathies. This interpretation could be extended to propose that the observed associations reflect not only structure-function relationships, but broader disease processes that produce shared variance, which statistically manifest as correlations between specific cognitive functions and imaging parameters.

The reasons why such widespread associations are not observed in other studies remain unclear. Possible explanations include cognitive and imaging methodologies, sample characteristics (e.g., iRBD phenotypes, or disease duration), or statistical approaches (e.g., use of single cognitive tests rather than latent variables).

Despite the general inability to replicate all these associations, some partial overlaps exist. For example, Pereira et al. (2019) found an association between memory and cortical thinning in the left superior temporal, left caudal middle frontal, right superior frontal and right lateral occipital gyri, and between visuospatial functions and the left fusiform. Nevertheless, other studies report entirely different associations, such as between memory and accumbens volume (Park et al., 2024), attention/executive functions and various subcortical and cortical regions including the midbrain and insula, internal capsule, putamen, pallidum, thalamus, orbitofrontal cortex, and anterior part of the right temporal lobe

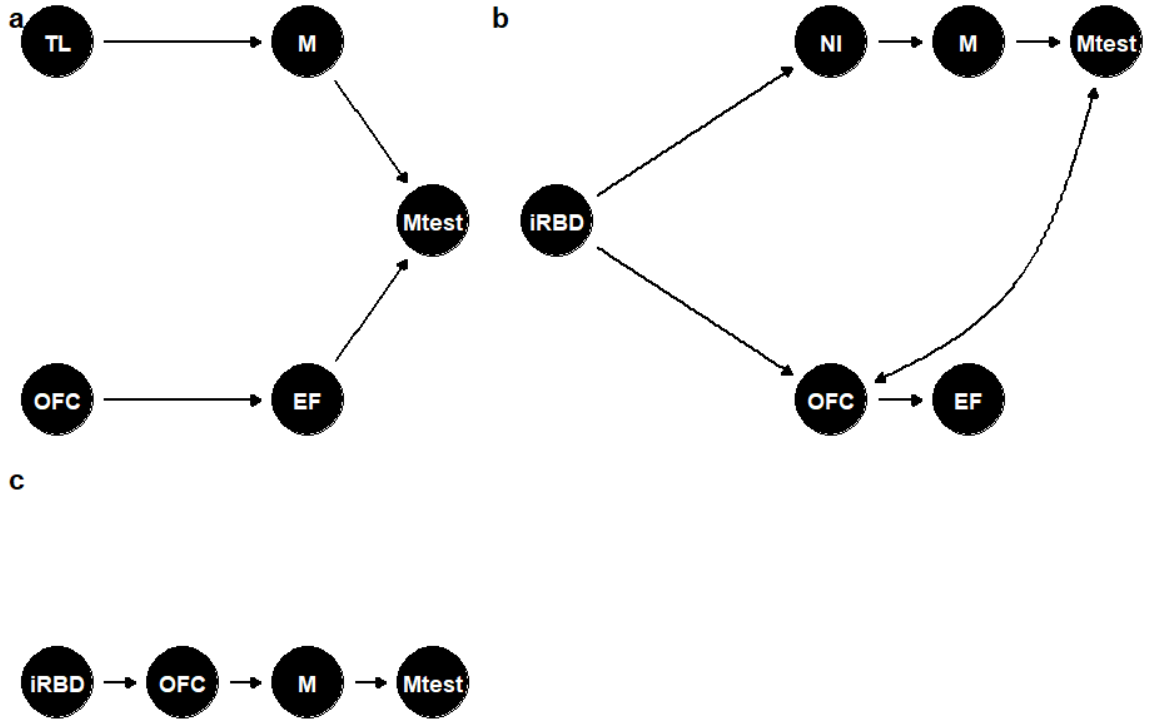
(Remillard-Pelchat et al., 2022), visuospatial functions and the left superior colliculus (Remillard-Pelchat et al., 2022), or attention and cholinergic basal forebrain (Woo et al., 2025).

Altogether, these findings are heterogeneous and difficult to interpret. Given that the majority of studies fail to detect significant associations, it can be speculated that, in the iRBD stage, structural and cognitive changes are subtle, inconsistent, and therefore challenging to identify. When associations are found, they most commonly involve memory, visuospatial, and executive functions, and regions within the frontal, temporal, and occipital lobes. Compared to simple group differences, interpretation of these associations is further complicated by statistical considerations—particularly the distinction between correlation and causation—and by the fact that many studies are exploratory in nature. Without an a priori hypothesis linking a specific cognitive function to a specific brain region, the interpretation of findings—for example, an association between a memory test and the orbitofrontal cortex—becomes especially problematic. At least four scenarios are possible in such a case. The memory test may tap executive functions, which are driven by the orbitofrontal cortex. While the observed association may reflect a genuine causal link, the conclusion that the orbitofrontal cortex is directly responsible for memory deficits in iRBD would be incorrect (see, Figure 4a). Second, despite statistical corrections (e.g., for multiple comparisons), spurious associations may occasionally reach the conventional significance threshold (typically $p < 0.05$). Third, disease processes might cause volume reductions in the orbitofrontal cortex that share variance with performance on memory tests. However, the memory impairment itself may result from a parallel neurodegenerative mechanism, such as neurotransmitter imbalances, thereby producing an indirect, unrecognized relationship due to methodological limitations (see, Figure 4b). Forth, the orbitofrontal cortex may indeed play a role in memory, representing a genuine causal relationship and leading to the correct conclusion that orbitofrontal dysfunction leads to memory deficits in iRBD (see, Figure 4c).

Some of these interpretive challenges can be partially addressed by modelling latent constructs, however, this approach is often unfeasible due to, among other factors, the large sample sizes required. Another strategy is to use meta-analyses, which can help identify reliable patterns by assuming that consistently replicated associations reflect true underlying relationships. Nevertheless, no such study exists to date.

Figure 4

An example of the limitations of interpreting the association between magnetic resonance imaging and cognitive functions



Note. TL = temporal lobe; M = memory; Mtest = memory test; OFC = orbito-frontal cortex; EF = executive functions; NI = neurotransmitter imbalance; iRBD = isolated REM sleep behavior disorder. a) performance on memory test is influenced by both memory and executive functions, which rely on the integrity of the temporal and orbitofrontal cortices. b) performance on memory test is driven by memory processes that depend on neurotransmitter balance but shows correlations with orbitofrontal cortex parameters. c) performance on memory test is driven by memory processes that depend on the orbitofrontal cortex.

2 Aims and Hypotheses

This thesis addresses long-standing questions regarding cognitive deficits in the early stages of alpha-synucleinopathies and their relationship to brain imaging. Specifically, it will seek to characterise the cognitive profile of individuals with early stages of alpha-synucleinopathies and to identify the specific cognitive domains that are impaired in these conditions. Furthermore, it will examine the relationship between cognitive deficits and their underlying neuroanatomical substrates. Finally, it will explore the interplay between cognitive functions, sensory functions, and brain imaging findings.

A broad and integrative research strategy will be applied across four studies to achieve these aims. Rather than examining isolated clinical groups, the studies will include various subpopulations within the spectrum of alpha-synucleinopathies, including individuals with iRBD, iRBD with (iRBD-MCI) or without MCI (iRBD-NC), patients with de novo PD, and healthy controls (CON). This approach will allow for a comprehensive examination of the cognitive and neuroanatomical features characteristic of early alpha-synucleinopathies and will also enable the systematic testing of the following hypotheses:

- H_1: Patients with alpha-synucleinopathies exhibit a distinct cognitive impairment profile.
- H_2: Cognitive deficits in alpha-synucleinopathies are associated with specific brain imaging findings.
- H_3: Patients with alpha-synucleinopathies show neuropathophysiological changes detectable through brain imaging.
- H_4: Colour discrimination deficits observed in alpha-synucleinopathies can be explained by impairments in cognitive functions.
- H_5: Colour discrimination deficits observed in alpha-synucleinopathies are associated with specific brain imaging findings.

Each of the four studies will then address distinct but complementary aspects of these hypotheses.

2.1 Study 1: Cortical and Subcortical Morphometric Changes in Relation to Cognitive Impairment in iRBD

The specific cognitive profile of patients with iRBD remains uncertain, although it is assumed that executive functions and memory are the most prominently affected domains (Leitner et al., 2023). Similarly, the neuroanatomical basis of cognitive deficits is still under investigation, with findings remaining inconclusive (Park et al., 2024; Pereira et al., 2019; Rahayel, Postuma, Montplaisir, Genier Marchand, et al., 2018; Rahayel et al., 2021; Woo et al., 2025). The same applies to structural imaging studies, which have yielded inconsistent results regarding region-specific brain alterations (Campabadal, Inguanzo, et al., 2020; Campabadal et al., 2019; Park et al., 2024; Pereira et al., 2019; Rahayel et al., 2015; Rahayel, Postuma, Montplaisir, Bedetti, et al., 2018). Thus, based on the available literature, three main research questions arise: Is there a specific cognitive profile characteristic of iRBD? (*RQ 1.1*); Are there common and detectable brain structural changes in iRBD? (*RQ 1.2*); How are cognitive deficits and structural brain changes related? (*RQ 1.3*).

All three research questions will be addressed in the first study (Mala et al., 2024), which is designed to test hypotheses H_1, H_2, and H_3.

2.2 Study 2: Interplay Between Cognitive Deficits, Colour Vision, and Brain Imaging in iRBD

Visual deficits are among the earliest markers of iRBD, and by extension, alpha-synucleinopathies, with some deficits appearing up to five years before clinical diagnosis (Dall'Antonia et al., 2018; Fereshtehnejad et al., 2019). Among these, impairments in colour discrimination are particularly well-documented (Dusek et al., 2019; Fereshtehnejad et al., 2019; Kim et al., 2024; Li et al., 2019; Postuma, Gagnon, et al., 2009b). Although these impairments might initially be regarded as purely sensory in nature, colour discrimination and other visual deficits are often linked to cognitive functioning (Bertrand et al., 2012; Li et al., 2019; Rahayel, Postuma, Montplaisir, Genier Marchand, et al., 2018; Zarkali et al., 2021). Moreover, in the specific case of colour discrimination, the underlying biological substrates remain uncertain. Proposed mechanisms include both sensory-level changes—such as ganglion cell layer loss, macular thinning, neurodegeneration of amacrine cells, and alterations in white matter pathways including the corona radiata and visual stream (Ortuno-Lizaran et al., 2020; Polo et al., 2016; Unger et al., 2010)—as well as higher-level processing

changes, including widespread cortical and subcortical alterations and dopaminergic depletion (Colzato et al., 2014; Rahayel, Postuma, Montplaisir, Genier Marchand, et al., 2018).

To further elucidate these issues, the second study (Havlik et al., in press) is designed to investigate the relationship between colour discrimination deficits and both cognitive and neurobiological markers in iRBD. Specifically, it addresses whether cognitive functions account for differences in colour discrimination between iRBD and controls *(RQ 2.1*), the colour discrimination deficit in iRBD is related to dopaminergic denervation *(RQ 2.2*), and performance in colour discrimination can be explained by morphometric parameters of cerebral grey and white matter *(RQ 2.3*). This study will address hypotheses H_1, H_4, and H_5.

2.3 Study 3: Memory Profile in iRBD

The cognitive profile can be assessed at the level of broad cognitive domains; however, more detailed analyses can help elucidate the elementary psychological mechanisms underlying cognitive deficits in iRBD. For instance, two main hypotheses have been proposed to explain memory impairment. The *retrieval hypothesis* posits that core memory processes—such as encoding, consolidation, and retention—are relatively preserved, but memory deficits arise due to impairments in executive or attentional functions that hinder information retrieval. In contrast, the *core memory deficit hypothesis* suggests that the memory impairment stems from disruptions in the core memory processes themselves (Troster & Fields, 1995). Several studies have examined these hypotheses in iRBD populations (Gagnon et al., 2009; Shin et al., 2019; Terzaghi et al., 2013), but the results are mixed, with some findings supporting each hypothesis. Consequently, the question of whether memory impairment in iRBD is secondary to deficits in other cognitive functions remains unresolved *(RQ 3.1)*. To address this, the third study (Wenke et al., 2022) will further investigate H_1. Specifically, it will examine whether the observed memory deficits can be attributed to impairments in attention and executive functioning, thereby contributing to the ongoing debate between retrieval-based and core memory deficit mechanisms.

2.4 Study 4: Effect of Cognitive Load on Gait Performance and Its Neurobiological Correlates

Patients with PD exhibit significant impairments in gait parameters, including speed, cadence, and stride length, whereas such impairments are subtle or non-significant in individuals with iRBD (Ehgoetz Martens et al., 2019; Zanardi et al., 2021). As previously noted, cognitive impairment is present in both groups. In both PD and iRBD, studies have shown that introducing a cognitive load during walking leads to changes in gait parameters that differ from those observed in healthy controls, suggesting a specific interaction between cognitive and motor systems (Ehgoetz Martens et al., 2019; Varalta et al., 2015). fMRI studies have demonstrated distinct patterns of brain activation under dual-task conditions: PD patients show altered activity in the ventroposterior putamen (Nieuwhof et al., 2017) , while iRBD patients exhibit reduced BOLD signal in the dorsal caudate nucleus and decreased functional connectivity between motor areas and subcortical regions (Ehgoetz Martens et al., 2020).

While some functional parameters have been identified in the few existing fMRI studies, it remains unclear whether structural brain alterations also reflect the effects of cognitive load during gait *(RQ 4.1)*. Although the most straightforward approach to answering this question would be to examine the iRBD group within the context of this dissertation, several key limitations arise. First, although heterogeneity in cognitive changes, brain morphology, and their associations is observed in both iRBD and PD, this heterogeneity is more pronounced in iRBD due to its preclinical nature (Baiano et al., 2020; Boeve, 2010; Campabadal et al., 2021; Fang et al., 2020; He et al., 2020; Leitner et al., 2023; Wallace et al., 2022; Wang et al., 2025). Second, an exploratory study in iRBD would carry a higher risk of false-positive findings due to this variability. Third, no such structural imaging study exists even in more advanced stages of the disease, which would further complicate the interpretation of any results. Forth, unlike PD, iRBD diagnosis is not accompanied by definitive biological or imaging markers that confirm underlying α-synucleinopathy, increasing the likelihood of sample heterogeneity, as patients may eventually convert to PD, MSA, or DLB. Therefore, the fourth study (Krupicka et al., 2024) adopts a stepwise research strategy and aims to elucidate the mechanisms underlying the interplay between cognitive performance and gait in the context of de novo PD. This study will serve as a pilot for subsequent potential investigations in iRBD that directly addresses this research question.

3 Materials and Methods

The methods used in the presented studies varied and are described in detail below. However, all studies were conducted at the Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague. Ethical approval was obtained from the ethics committee of this institution, and all procedures were carried out in accordance with applicable standards (American Educational Research Association et al., 2014) and with the 1964 Helsinki Declaration. Written informed consent was obtained from all participants.

3.1 Study 1: Cortical and Subcortical Morphometric Changes in Relation to Cognitive Impairment in iRBD

3.1.1 Participants

Video-PSG confirmed iRBD patients were diagnosed at the Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague in accordance with the International classification of sleep disorders, third edition (American Academy of Sleep Medicine, 2014). Participants eligible for inclusion were over 50 years of age and had completed at least eight years of formal education. Patients were excluded if they had a diagnosed overt neurodegenerative disease, dementia, narcolepsy, epilepsy, encephalitis, drug induced RBD, head injury, or focal brain lesion indicative of secondary RBD. Patients were classified based on their MCI status. The CON group was recruited from the general community via social media and web advertisement and was matched to have age, education, and sex comparable to the iRBD group. All CONs underwent a detailed medical interview, neuropsychological examination and video-PSG. Exclusion criteria were neurological or psychiatric disease (e.g., Parkinson's disease, epilepsy, schizophrenia, depression, anxiety, history of stroke or major head trauma), alcohol or drug addiction, chemotherapy or radiotherapy, major somatic illness (cancer, symptomatic coronary heart disease etc.), sleep disorders (untreated sleep apnea, insomnia, narcolepsy), major hearing and vision problems, and cognitive deficit.

3.1.2 Neuropsychological Assessment

MoCA was used to screen cognition and the Czech adaptation of the National Adult Reading Test (NART)(Krámská, 2014) to estimate premorbid intelligence level. Furthermore, both groups were evaluated by a complex neuropsychological. Specifically, the following tests were administered: Rey Auditory Verbal Learning Test (RAVLT; memory)(Bezdicek et al., 2014), Memory Binding Test (MBT; memory)(Buschke, 2014), abbreviated Memory for Intentions Screening Test (MIST; memory)(Raskin et al., 2010), Trail Making Test (TMT; attention/working memory, executive functions)(Bezdicek et al., 2012), Letter-Number Sequencing from Wechsler Adult Intelligence Scale, Third Revision (LNS; attention/working memory)(Wechsler, 2010), Prague Stroop Test (PST; executive functions)(Bezdicek et al., 2015), Verbal fluency (VF; language/executive functions)(Nikolai et al., 2015), Clock Drawing Test (CDT; visuospatial functions)(Kopecek et al., 2016), MoCA Cube (visuospatial functions)(Kopecek et al., 2016), Grooved Pegboard Test (GPT; the speed of processing)(Kløve, 1963), and Symbol Digit Modalities Test (SDMT; the speed of processing) (Smith, 1982).

3.1.3 MRI Acquisition and Preprocessing

For a full MRI data processing pipeline, see the source article (Mala et al., 2024). Briefly, Morphometry analysis was performed on T1-weighted 3D Magnetization-Prepared Rapid Acquisition with Gradient Echo images. The segmentation was done by Hammers atlas resulting in segmentation of intracranial volume, total grey matter and total white matter for each subject as well as the absolute values for 34 different brain regions. For voxel-wise analysis, the modulated, normalized grey matter segments were smoothed using a Gaussian kernel with an 8 -mm3 full width at half maximum. Voxel-based morphometry (VBM) was performed with the smoothed grey matter volume maps. Deformation-based morphometry (DBM) was performed with the smoothed Jacobian determinants. Smoothing was performed with the same settings as for VBM.

3.1.4 Statistical Analyses

Between-group comparisons of MRI parameters were conducted using a general linear model with age and sex as covariates. For VBM analyses, total intracranial volume was included as an additional covariate. The statistical map for between-group comparison was

thresholded at $p < 0.05$ statistical level, corrected for multiple comparisons using the family-wise error rate. Correlational analyses between cognitive test performance and brain morphology (including VBM, DBM and ROI analyses) included cognitive test scores as an additional covariate in the model. Neuropsychological test scores were transformed to approximate a normal distribution and imputed where missing. For each subject, *z*-scores were calculated, and principal component analysis (PCA) with varimax rotation was applied to derive component scores. Between group differences (CON vs iRBD vs iRBD-NC vs iRBD-MCI) in these scores were assessed using nested ANOVA. The resulting *p* values were corrected for multiple comparisons using the Benjamini–Hochberg procedure. Analyses were conducted using R implemented in RStudio and CAT12.

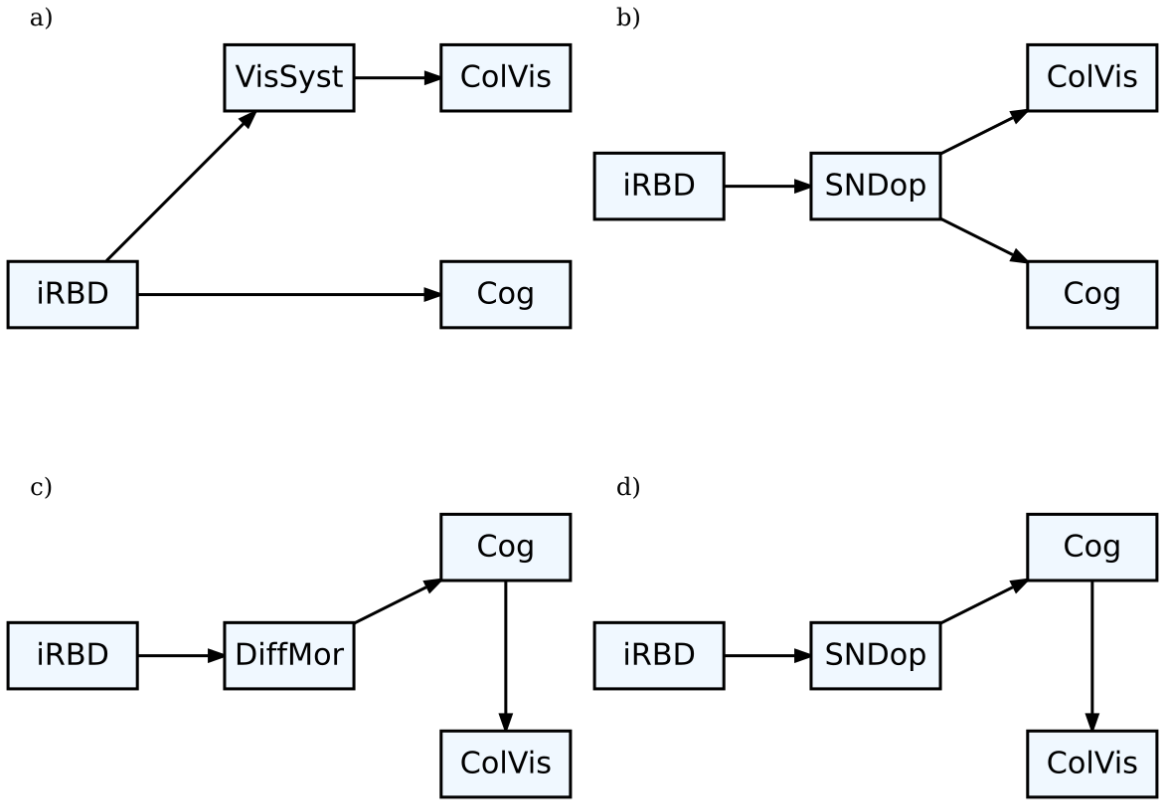
3.2 Study 2: Interplay Between Cognitive Deficits, Colour Vision, and Brain Imaging in iRBD

3.2.1 Causal Assumptions and Interpretation Criteria

Based on existing literature, several competing causal assumptions (illustrated in Figure 5) were formulated to represent hypothetical mechanisms underlying colour discrimination deficits. First, colour discrimination impairment may result from structural disturbances within the visual system (Polo et al., 2016; Unger et al., 2010). Second, the colour discrimination deficit may be an indirect consequence of diffuse morphological brain changes, with cognitive impairment acting as a mediator in the pathway from structural alterations to visual dysfunction (Bertrand et al., 2012). Third, both cognitive and colour discrimination deficits may share a common underlying cause, namely dopaminergic depletion in the basal ganglia (Colzato et al., 2014). Finally, it is also possible that cognitive functions mediate the effect of basal ganglia dopaminergic depletion on colour discrimination (Colzato et al., 2014).

In the original study, several a priori criteria were established to guide the interpretation of results; however, only two are directly relevant to the present thesis: a) meaningful mediation effect of cognitive functions is the presence of statistically significant results in at least two psychological tests within the same cognitive or motor domain, or a significant result in a test that measures multiple domains (e.g., MoCA); b) any statistically significant association between colour discrimination and MRI parameters is considered substantively meaningful, as it may reflect distinct underlying mechanisms.

Figure 5
Competing causal assumptions



Note. In all models represented in this figure it is assumed that demographic variables age, sex and education level constitute common causes of iRBD, cognition, colour discrimination and sample selection. VisSyst = visual system; ColVis = colour vision; Cog = cognition; SNDop = substantia nigra dopamine; DiffMorf = diffuse morphological changes.

3.2.2 Participants

To test the hypothesis regarding colour discrimination, a group of patients with video-PSG confirmed iRBD and CON group were recruited through non-probabilistic sampling methods between 2015 and 2024 as part of a larger study conducted at the General University Hospital in Prague. Both iRBD and CON participants underwent comprehensive neurological and neuropsychological assessments. Only patients with iRBD diagnosed according to the International Classification of Sleep Disorders, third edition (American Academy of Sleep Medicine, 2014), and without clinical signs of overt parkinsonism or dementia, were included. Exclusion criteria for both groups included a history of head injury,

narcolepsy, severe untreated psychiatric symptoms (e.g. depression or mania), drug-induced RBD, or focal brain lesion indicative of secondary RBD. Additionally, participants in the CON group were required to be free of RBD and MCI, with the latter determined according to Level I criteria (Litvan et al., 2012).

3.2.3 Neuropsychological Assessment

Both groups underwent the MoCA as a screening measure, followed by the same comprehensive neuropsychological battery used in Study 1. In brief, six cognitive domains were assessed: memory, attention/working memory, executive functions, language, visuospatial functions, and processing speed. Furthermore, motor functioning was assessed using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, part III (MDS-UPDRS), for the purpose of testing secondary hypotheses.

3.2.4 Colour Discrimination Assessment

Binocular colour discrimination was assessed using the Farnsworth-Munsell 100-Hue Test (FM-100)(Farnsworth, 1957). The goal in this test is to arrange 85 coloured caps in a sequence that follows a smooth transition of hues between two fixed reference caps, replicating the natural progression of the colour spectrum. The caps are divided into four trays representing different segments of the spectrum: red-yellow (RY), yellow-green (YG), green-blue (GB), and blue-red (BR). Four subscores (one for each tray) and one total error score (TES).) are calculated based on the deviation of each cap from its correct position in the sequence. The FM-100 test was administered in a dark room without windows under artificial lighting provided by a 1440 lm, 6,500 K incandescent lamp.

3.2.5 MRI Data Acquisition and Preprocessing

MRI data acquisition and preprocessing were conducted in same line as in Study 1. In brief, MRI scans were acquired on a 3T MRI scanner (Siemens Skyra 3T, Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. High-resolution T1-weighted 3D Magnetization-Prepared Rapid Acquisition with Gradient Echo images were obtained in the axial plane with the following parameters: repetition time (TR), 2,200 ms; echo time (TE), 2.4 ms; inversion time (TI) 900 ms; flip angle (FA) 8°; field of view (FOV) 230×197×176 mm; spatial resolution 1x1x1 mm3. T1-weighted images were preprocessed using the

Computational Anatomy Toolbox (CAT12, v12.8.2) implemented in SPM12 (v7771) within Matlab. Preprocessing included segmentation, normalization, and modulation of grey matter images. Data quality was assessed via CAT12 quality check pipeline, with a minimum segmentation rating of C+ required. Visual inspection was also performed to exclude images with artefacts or misalignment. The resulting modulated, normalized grey matter maps were smoothed with an 8 mm^3 full width at half maximum Gaussian kernel for VBM analysis.

3.2.6 Dopamine Transporter Imaging

The integrity of nigrostriatal dopaminergic functioning was assessed exclusively in the iRBD group due to ethical and technical constraints, using DAT-SPECT with [123I]-2-b-cabomethoxy-3b-(4-iodophenyl)-N-(3fluoropropyl) nortropane (DaTscan®, GE Healthcare) as the radiopharmaceutical. The procedure followed the guidelines of the European Association of Nuclear Medicine (Darcourt et al., 2010), employing standardized acquisition and reconstruction parameters as previously described in detail (Dusek et al. 2019). Semi-quantitative analysis of images was performed using the DaTQUANT V2 software. The specific to non-displaceable binding ratios (SBR) were determined in the bilateral striatum, caudate, and putamen using the formula (nucleus uptake – background uptake)/background uptake, with bilateral occipital lobes serving as the background reference region. Mean striatal, caudate, and putamen SBRs from both hemispheres were analysed.

3.2.7 Statistical Analyses

All variables were first transformed to ensure consistent directionality for easier interpretation, for example, errors in the FM-100 test were aligned with the direction of scores such as the number of words recalled in the RAVLT. To compare groups in colour discrimination and to examine relationships between colour discrimination, cognitive performance, and MRI parameters, a series of models was fitted. These included generalized linear models (GLM) with gamma-distributed errors and a log link function, or with an inverse Gaussian distribution; Tobit models with a Gaussian distribution and robust standard errors implemented in the R package Survival (version 3.6.4)(Therneau, 2024); and ordinary least squares (OLS) regressions. Selected models were subsequently entered into mediation analyses to assess the potential mediating effect of cognition on colour discrimination. An overview is provided in Table 2.

Table 2

Overview of statistical tests used in Study 2

Hypothesis / Research Question	Method / Model	Outcome Variable	Predictor Variables / Covariates
Group differences in colour discrimination	• GLM (Gamma distribution, log link) • Tobit model (Gaussian, robust *SE*s)	• FM-100 TES score • FM-100 subscores	Group, Age, Sex, Education
Effect of iRBD on colour discrimination through cognition (mediation)	Two-stage regression approach: • Stage 1: Regress cognitive variables on predictors • Stage 2: Regress FM-100 on group, cognition, and interaction	Mediator: cognitive variables Outcome: FM-100 scores	Group, Age, Sex, Education + Interaction term: Group × Cognitive variables
	• GLM (inverse Gaussian, for pos. skewed cognitive data) • Tobit (for MoCA, MDS-UPDRS) • OLS (for other variables)	Psychological variables	Group, Age, Sex, Education

Association of colour discrimination with dopamine transporter imaging	• GLM (Gamma distribution, log link) • Tobit model (Gaussian, robust *SE*s)	• FM-100 TES score • FM-100 subscores	SBRs (Striatum, Caudate, Putamen), Age, Sex, Education (iRBD group only)
Association of colour discrimination with MRI data (VBM)	• Multiple regression model • Full factorial model (interaction)	FM-100 scores	Group, TIV, Age, Sex, Education + Interaction term: Group × MRI

Note. GLM = generalized linear models; FM-100 = Farnsworth-Munsell 100-Hue Test; MoCA = Montreal Cognitive Assessment Czech version; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, part III; OLS = ordinary least squares regressions; *SE* = standard error; TES = total error score; SBR = specific to non-displaceable binding ratios; TIV = total intracranial volume.

In each analysis, except analyses of descriptive variables, *p* values were corrected for multiple comparisons using the Benjamini-Hochberg procedure. Analyses were conducted using R (4.3.3) implemented in RStudio (2024.12.1.563) and CAT12 (12.8.2).

3.3 Study 3: Memory Profile in iRBD

3.3.1 Participants

The iRBD and CON groups were recruited using the same non-probabilistic methods, diagnostic criteria, and within the same institution as in Studies 1 and 2. Inclusion criteria for this study were as follows: age >50 years and >8 years of formal education. Exclusion criteria for both groups included a history of neurological or psychiatric conditions (e.g., stroke, major head trauma, epilepsy, schizophrenia, multiple sclerosis or delirium), a history of alcohol or substance abuse, current radio- or chemotherapy, significant cardiovascular health conditions (uncontrolled diabetes mellitus, myocardial infarction, etc.) or with uncorrected visual or hearing deficits. Additionally, individuals in the CON group were required to show no significant cognitive impairment or symptoms of depression relative to normative standards (Ciharova et al., 2020; Kopecek et al., 2016).

3.3.2 Methods and Operationalization

A comprehensive neuropsychological battery assessing memory, attention/processing speed, working memory, executive functions, motor speed, and prospective memory was administered to both groups. However, to address the specific aims of the study, only the MBT, RAVLT, PST, LNS, and SDMT were included in the analyses. Specifically, three items from the RAVLT, six items from the MBT, and one item from each of the remaining tests were analysed. Theoretical implications are detailed in Table 3. In sum, poorer performance across encoding, delayed recall, and relational binding tasks would support the core memory hypothesis, whereas selective impairment in free recall, alongside preserved cued recall and recognition, would support the retrieval (attention/executive dysfunction) hypothesis. Recognition deficits alone would not clearly distinguish between the two, as they may reflect either core memory impairment or executive dysfunction at encoding due to uncontrolled encoding strategies. Intact performance on a paired-associate task, which supports both encoding and retrieval and taps relational binding, would argue against core memory deficits. Finally, if attentional/executive functions or processing speed significantly mediate memory performance, this would further support the attentional/executive dysfunction hypothesis.

Table 3

Cognitive outcomes and their theoretical relevance to memory hypotheses in iRBD

Outcome	Theoretical implications				
	Core memory deficit			Executive deficit	
	encoding	retention	binding	encoding	retrieval
RAVLT-IR	*	-	na	*	*
RAVLT-DR	*	*	na	*	*
RAVLT-Rec.	*	*	na	*	-
MBT-IR-TIP	*	-	-	-	-
MBT-IR-PIP	*	-	*	-	-
MBT-IFR	*	-	na	-	*
MBT-DR-TIP	*	*	-	-	-
MBT-DR-PIP	*	*	*	-	-
MBT-DFR	*	*	na	-	*

Note. * = The hypothesis (column) implies deficit in iRBD patients on this measure (row); – = The hypothesis (column) implies intact performance iRBD patients on this measure (row); DFR = delayed free recall in MBT; IFR = immediate free recall in MBT; MBT = Memory Binding Test; MBT-DR = Delayed Cued Recall in MBT; MBT-IR = Immediate Cued Recall in MBT; na = The hypothesis (column) offers no prediction with respect to the performance of iRBD patients on this measure (row); PIP = Total number of Pairs cued recalled in the Paired condition; RAVLT = Rey Auditory Verbal Learning Test; RAVLT-DR = delayed (free) recall; RAVLT-IR = T1-T5 free recall; RAVLT-Rec. = Recognition (number of correct responses from 15 true positives and 35 distractors); TIP = Total number of Items cued recalled in the Paired condition.

3.3.3 Statistical Analyses

Bayesian multivariate GLM with Student-t error terms were used to assess memory performance (RAVLT and MBT) in relation to iRBD status, sex, and age. Models were fitted using the R package *brms* with default priors. Mediation analysis was conducted for memory outcomes showing significant group differences, using LNS, PST, and SDMT as mediators. The probability of direction to assess effect existence and the percentage in the region of practical equivalence (ROPE) for practical significance were reported. A probability of direction > 95% suggests a possible effect (similarly to one-sided p value < .05), while a ROPE > 97.5% indicates a negligible one. 95% highest density posterior probability intervals (PPI) were also provided to support interpretation. The statistical analysis was performed using the software environment for statistical computing R version 4.0.5 (R Core Team, 2021).

3.4 Study 4: Effect of Cognitive Load on Gait Performance and Its Neurobiological Correlates

3.4.1 Participants

Participants included patients diagnosed with PD at the Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital in Prague, based on the Movement Disorder Society clinical diagnostic criteria for PD (Postuma et al., 2015). In addition, CON participants were also included, recruited from the general population using non-probabilistic sampling methods. All participants were required to have at least 9 years of formal education, MoCA score of 24 or higher, and a full score (3 points) on the MoCA Serial 7 Subtraction Task, indicating no cognitive impairment on the task also used

as a competing condition in the dual-task walking paradigm. Participants were excluded if they had major hearing and vision problems or a diagnosis of dementia. Furthermore, CON participants were excluded if they had any neurological or psychiatric disorders, used psychoactive substances, had concurrent oncological or other serious somatic illnesses, or showed signs of REM sleep behavior disorder.

3.4.2 Measures

All participants underwent neuropsychological examination covering attention and working memory, executive functions, language, delayed recall, and visuospatial functions. The MoCA was used to screen cognitive and motor performance. Gait was assessed using the expanded Timed Up & Go Test (TUG)(Wall et al., 2000), involving standing up, walking 10 m, turning, returning, and sitting down. TUG was completed twice. A 5.15 m GAITRite® pressure walkway (CIR Systems Inc.) was positioned 2.43 m from the chair to capture gait parameters during the straight walk. Gait was assessed under two conditions: (i) single-task (ST) and (ii) dual-task (DT) with serial subtraction (counting down from 100 by sevens). Gait speed, stride length, and cadence were analysed (Zampieri et al., 2010). MRI acquisition and preprocessing followed the same protocol as in Studies 1 and 2, focusing exclusively on VBM.

3.4.3 Statistical Analyses

Dual-task cost (DTC) was calculated as:

$$DTC = \frac{(DTvalue - STvalue)}{STvalue}$$

To quantify cognitive–motor interference, PCA of DTC parameters was conducted in CONs. Based on the first PCA component, PD participants were classified as having normal (>10th percentile of CON) or impaired dual-task cost (≤10th percentile). Group differences in gait parameters were analysed using a general linear model with age and sex as covariates. VBM analysis was performed using a multiple regression model with the covariate DTC (speed or stride length or cadence), total intracranial volume, age, and sex. The statistical map for the correlation analysis was thresholded at cluster level at the statistical level $p < 0.05$ corrected

by family-wise error. The CON subgroup with impaired dual-task cost was excluded from all statistical analyses due to the low number of participants.

4 Results

4.1 Study 1: Cortical and Subcortical Morphometric Changes in Relation to Cognitive Impairment in iRBD

Mala, C., **Havlik, F.***, Mana, J., Nepozitek, J., Dostalova, S., Ruzicka, E., Sonka, K., Keller, J., Jech, R., Dusek, P., Bezdicek, O., & Krupicka, R. (2024). Cortical and subcortical morphometric changes and their relation to cognitive impairment in isolated REM sleep behavior disorder. *Neurol Sci, 45*(2), 613-627. https://doi.org/10.1007/s10072-023-07040-z

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4.1.1 Sample Characteristics

After excluding participants with missing data or meeting exclusion criteria, 63 patients with iRBD and 36 CON were included in the analyses. The iRBD group was further divided based on the presence of MCI: 27 patients (43%) were classified as iRBD-MCI, and 36 as iRBD-NC. Additional descriptive information is provided in Table 4.

Table 4

Socio-demographic and clinical characteristics of samples in Study 1

	CON[a] (n = 36)	iRBD[b] (n = 63)	iRBD-MCI[c] (n = 27)	iRBD-NC[d] (n = 36)
Age, years[†]	63.76 (7.15)	66.73 (6.59)	65.09 (6.76)	67.96 (6.27)
Education, years	15.22 (3.27)	14.75 (3.02)	14.81 (3.05)	14.69 (3.03)
Sex, male %	83	90	92	89
Symptom duration, years	–	6.87 (7.90)	8.18 (10.07)	5.89 (5.74)
MoCA[†]	25.53 (2.01)	24.21 (2.57)	23.33 (2.48)	24.86 (2.46)
NART[†]	120.58 (9.43)	118.21 (9.36)	115.30 (9.37)	120.39 (8.86)
MDS-UPDRS-III[†]	3.44 (4.36)	6.37 (5.49)	6.22 (5.72)	6.47 (5.40)
BDI-II[†]	4.03 (3.10)	9.32 (7.53)	7.84 (5.84)	10.41 (8.48)
STAI-X1[†]	31.33 (5.92)	36.71 (9.19)	35.88 (5.33)	37.32 (11.27)
STAI-X2[†]	32.83 (6.61)	39.63 (8.97)	38.16 (7.22)	40.71 (10.03)

	CON[a] (n = 36)	iRBD[b] (n = 63)	iRBD-MCI[c] (n = 27)	iRBD-NC[d] (n = 36)
ESS	6.14 (3.80)	7.25 (4.40)	7.72 (4.94)	6.91 (4.01)
SINBAR score[†,††]	5.77 (2.80)	49.09 (24.35)	48.96 (29.47)	49.20 (19.74)
Tonic RWA index[†,††]	0.93 (0.90)	18.60 (21.26)	20.67 (24.53)	16.91 (18.42)
Phasic RWA index[†,††]	3.77 (2.26)	25.21 (16.80)	24.78 (17.88)	25.57 (16.15)
Mixed RWA index[†,††]	0.40 (0.53)	10.29 (15.32)	10.37 (12.91)	10.22 (17.24)

Note. CON = healthy controls; iRBD = isolated rapid eye movement sleep behavior disorder; MCI = mild cognitive impairment; NC = normal cognition; Symptom duration = time between the subjective onset of iRBD symptoms and assessment; MoCA = Montreal Cognitive Assessment Czech version; NART = National Adult Reading Test; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, part III; BDI-II = Beck Depression Inventory, Second Edition; STAI = State-Trait Anxiety Inventory (state anxiety, X1) and (trait anxiety, X2); ESS = Epworth Sleepiness Scale; RWA = REM without atonia.

[†] significant differences between CON, iRBD-NC, and iRBD-MCI

[††] iRBD (n = 58), iRBD-MCI (n = 26), iRBD-NC (n = 32)

4.1.2 MRI Differences Between Groups

VBM, DBM and the comparison of ROI volumes yielded no significant between group differences. However, ROI analyses showed a trend toward lower volumes in the cuneus, cerebellum, lingual gyrus, putamen, nucleus accumbens, and regions of the parietal and temporal lobes in the iRBD-MCI group, and in the right cerebellum in the iRBD-NC group, compared to CON, see Table 5.

Table 5

ROI volumes defined by Hammers' atlas with a statistical trend for significant between-group differences in Study 1

	T-value	Z-value	*p*
CON > iRBD total			
left Cuneus	2.36	2.32	0.010
left Cerebellum	2.01	1.98	0.024
right Cerebellum	2.11	2.08	0.019
left Inferior Lateral Parietal Lobe	1.83	1.80	0.035
right Lingual Gyrus	2.19	2.16	0.015

	T-value	Z-value	*p*
right Lateral Occipital Lobe	1.87	1.85	0.032
CON > iRBD-NC			
Right Cerebellum	1.71	1.69	0.046
CON > iRBD-MCI			
Left Cuneus	2.43	2.36	0.009
Left Superior Parietal Gyrus	2.29	2.23	0.013
Inferior Lateral Parietal Lobe	1.90	1.86	0.031
Nuccleus Accubens	1.88	1.84	0.033
Left Anterior Medial Temporal Lobe	1.81	1.78	0.037
Left Cerebellum	1.78	1.75	0.040
Right Cerebellum	1.82	1.79	0.037
Left Putamen	1.77	1.74	0.041
Right Lingual Gyrus	2.66	2.58	0.005

Note. p values uncorrected. CON = healthy controls; iRBD = isolated rapid eye movement sleep behavior disorder; MCI = mild cognitive impairment; NC = normal cognition.

4.1.3 Cognitive Differences Between Groups

No significant differences were found between the basic groups (CON vs. iRBD) or between iRBD-NC and CON. However, the iRBD-MCI group performed significantly worse than both CON and iRBD-NC in measures of episodic memory (MIST – time-based, MBT – Total Delayed Free Recall), attention/working memory (TMT-A), executive functions (PST – interference, TMT-B), processing speed (SDMT, PST – Dots); and language (VF – letter K). Analysis on PCA components did not reveal significant group differences across any level of classification. Nevertheless, trends toward lower performance in the processing speed/executive functions and episodic memory components were observed prior to correction for multiple comparisons.

4.1.4 Correlations Between Cognitive Tests and Brain Morphometry

Across all analyses (VBM, ROI, DBM), significant correlations were consistently observed between TMT-A performance and structural measures in the right insula and putamen. Additionally, VBM revealed further associations for: TMT-A (regions of temporal superior lobe and left cerebellar hemisphere); TMT-B (primarily amygdala, hippocampus and

parahippocampal gyrus); right-hand GPT (regions in the occipital and parietal lobe of the left hemisphere); RAVLT 1–5 (precentral, postcentral and supramarginal gyrus of the left hemisphere, insula, hippocampus and temporal lobe of the right hemisphere); and PCA component psychomotor speed (regions in the rostral vermis and adjacent parts of both cerebellar hemispheres), see Figure 6.

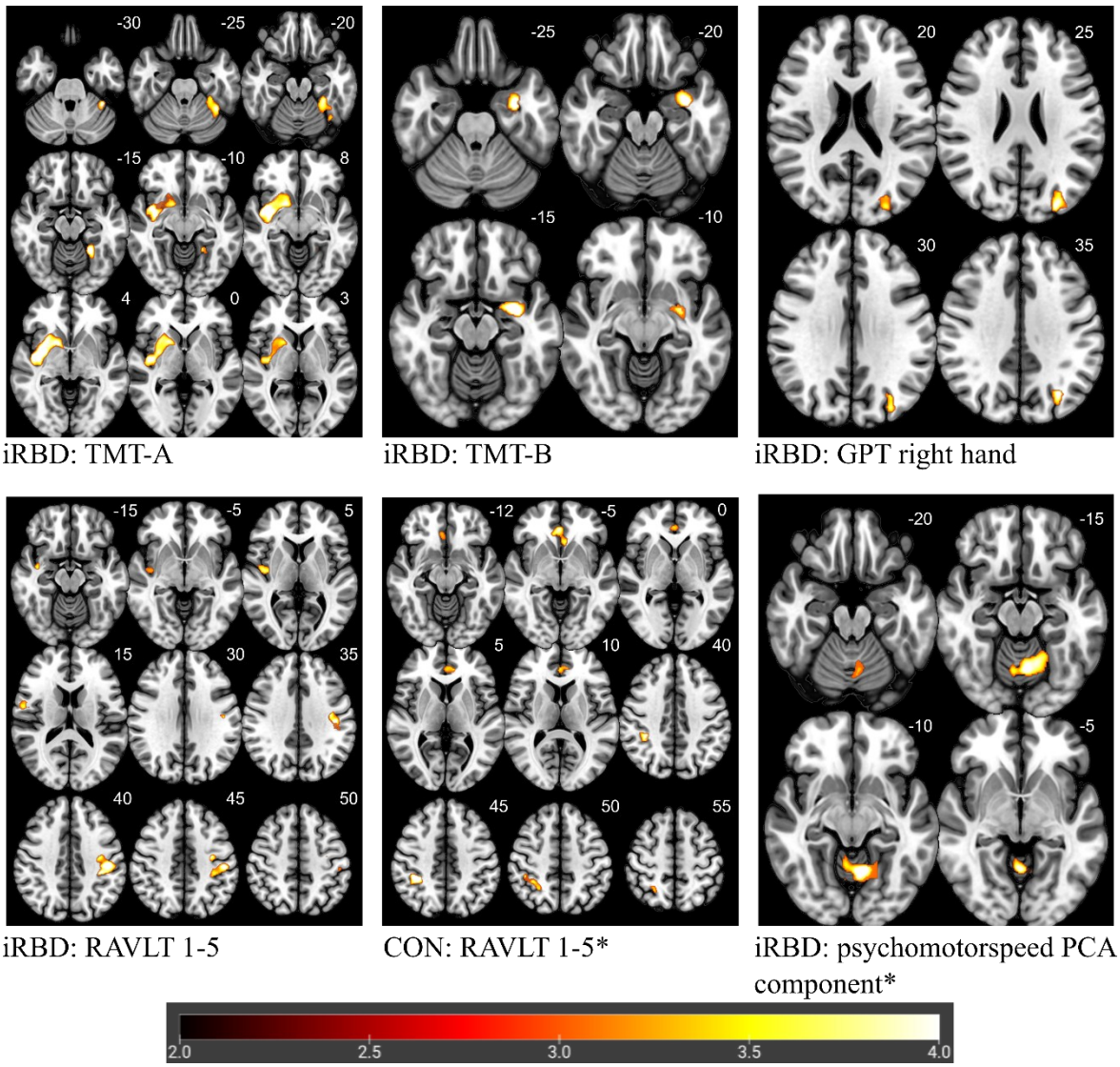
ROI-based analysis additionally identified significant correlations between: TMT-A and the bilateral nucleus accumbens, left putamen; RAVLT 1–5 with the pallidum, nucleus accumbens, insula; and PCA component psychomotor speed with the left cerebellum, temporal lobe, and insula, see Table 6.

DBM analysis revealed additional correlations between: TMT-A and a cluster involving the pallidum, caudate and superior temporal lobe; right-hand GPT and the middle/superior occipital lobe and the superior parietal lobe, see Figure 7.

Analysis of ROI volumes with interaction terms revealed significantly different regression slopes between iRBD and CON only for TMT-A in relation to the left precentral gyrus, right insula, and right putamen, see Figure 8.

Figure 6

Correlation between performance in cognitive tests and brain morphology analysed with VBM in Study 1



Note. Highlighted significant clusters thresholded at $p < 0.05$ at cluster level, corrected for family wise error. Colour scale represents the decimal logarithm of *p*-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right). Lower values of Psychomotor speed (PCA component) indicate better cognitive performance. CON = healthy controls; iRBD = isolated rapid eye movement sleep behavior disorder; TMT-A = Trail Making Test, part A; TMT-B = Trail Making Test, part B; GPT = Grooved Pegboard Test; RAVLT 1-5 = Rey Auditory Verbal Learning Test 1-5, PCA = principal components analysis.

* indicating negative correlation

Table 6

ROI-based analysis of the correlation between performance in cognitive tests and brain regional volumes segmented by Hammers atlas in Study 1

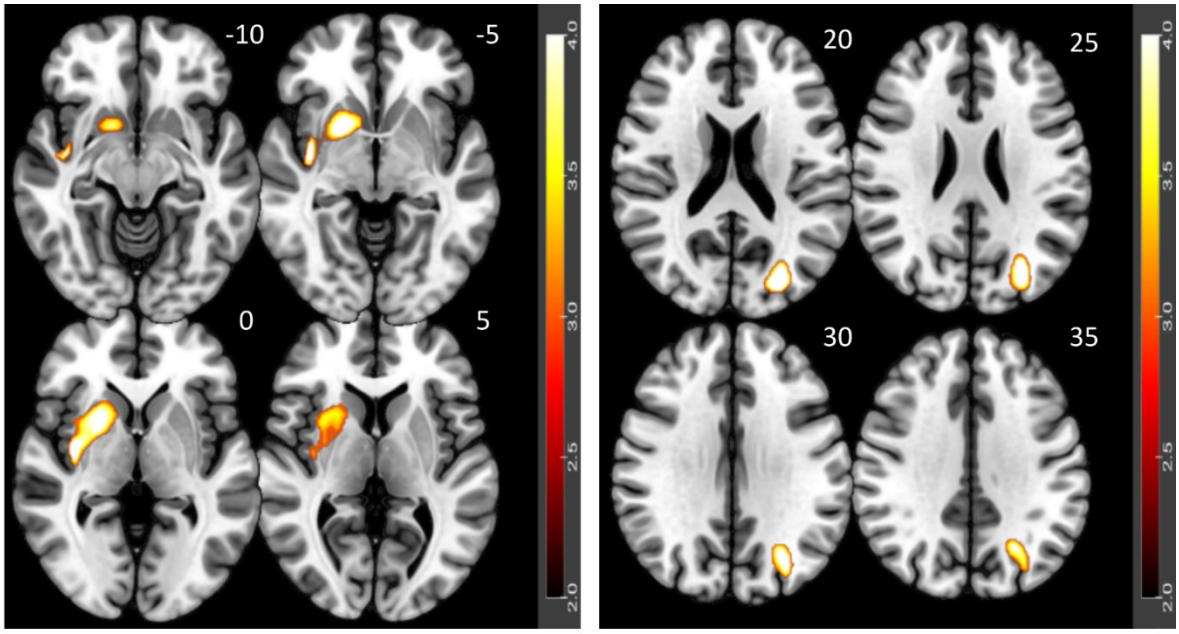
	iRBD		CON	
	r	*p*	*r*	*p*
TMT-A				
Right Putamen*	0.407	0.001	-0.033	0.852
Right Insula*	0.366	0.003	-0.123	0.482
Right Nucleus Accumbens*	0.364	0.003	0.012	0.943
Left Nucleus Accumbens*	0.364	0.004	-0.062	0.725
Left Putamen*	0.365	0.004	-0.074	0.671
Left Precentral Gyrus*	0.330	0.009	-0.176	0.311
Left Insula*	0.311	0.014	-0.130	0.456
GPT (left hand)				
Right Insula*	0.434	<0.001	-0.174	0.318
GPT (right hand)				
Right Insula*	0.314	0.013	-0.265	0.124
RAVLT 1-5				
Right Pallidum *	0.469	<0.001	0.015	0.931
Left Pallidum*	0.404	0.001	0.113	0.518
Left Nucleus Accumbens*	0.399	0.001	-0.262	0.128
Right Insula*	0.402	0.001	-0.272	0.115
Left Brainstem*	0.354	0.002	-0.279	0.105
Right Superior Parietal Gyrus	0.376	0.003	-0.369	0.029
Right Brainstem*	0.373	0.003	-0.249	0.149
Right Nucleus Accumbens	0.357	0.004	-0.480	0.004
Right Precentral Gyrus	0.362	0.004	-0.541	0.001
Left Insula*	0.352	0.005	-0.274	0.112
Left Nucleus Caudate*	0.354	0.005	-0.254	0.141
Right Nucleus Caudate*	0.348	0.006	-0.230	0.184
Left Inferior Lateral Parietal Lobe	0.343	0.006	-0.345	0.043
Left Precentral Gyrus	0.335	0.008	-0.348	0.040
Right Posterior Temporal Lobe*	0.328	0.009	-0.219	0.206
Right Cuneus*	0.327	0.010	0.199	0.253

	iRBD		CON	
	r	*p*	*r*	*p*
Left Postcentral Gyrus	0.327	0.010	-0.552	0.001
Right Lingual Gyrus*	0.322	0.011	0.149	0.349
Right Inferior Lateral Parietal Lobe*	0.307	0.015	-0.237	0.170
Right Fusiform Gyrus*	0.295	0.020	-0.064	0.717
Left Posterior Temporal Lobe*	0.293	0.021	-0.198	0.255
Left Superior Parietal Gyrus*	0.274	0.031	-0.140	0.424
Psychomotor speed (PCA component)				
Left Cerebellum*	-0.390	0.002	-0.043	0.804
Left Anterior Temporal Lobe, Medial Part*	-0.360	0.004	-0.101	0.562
Left Insula*	-0.310	0.014	0.104	0.551

Note. Pearson correlation coefficients adjusted for age for all significant associations in RBD subjects are shown ($p < 0.05$, FDR corrected). Corresponding correlation coefficients *r* and *p* values in CON are shown for comparison. Lower values of Psychomotor speed (PCA component) indicate better cognitive performance. iRBD = Isolated rapid eye movement sleep behavior disorder; CON = healthy controls; TMT-A = Trail Making Test, part A; GPT = Grooved Pegboard Test; RAVLT 1-5 = Rey Auditory Verbal Learning Test 1-5, PCA = principal components analysis.

Figure 7

Correlation between performance in cognitive tests and brain morphology analysed with DBM in Study 1



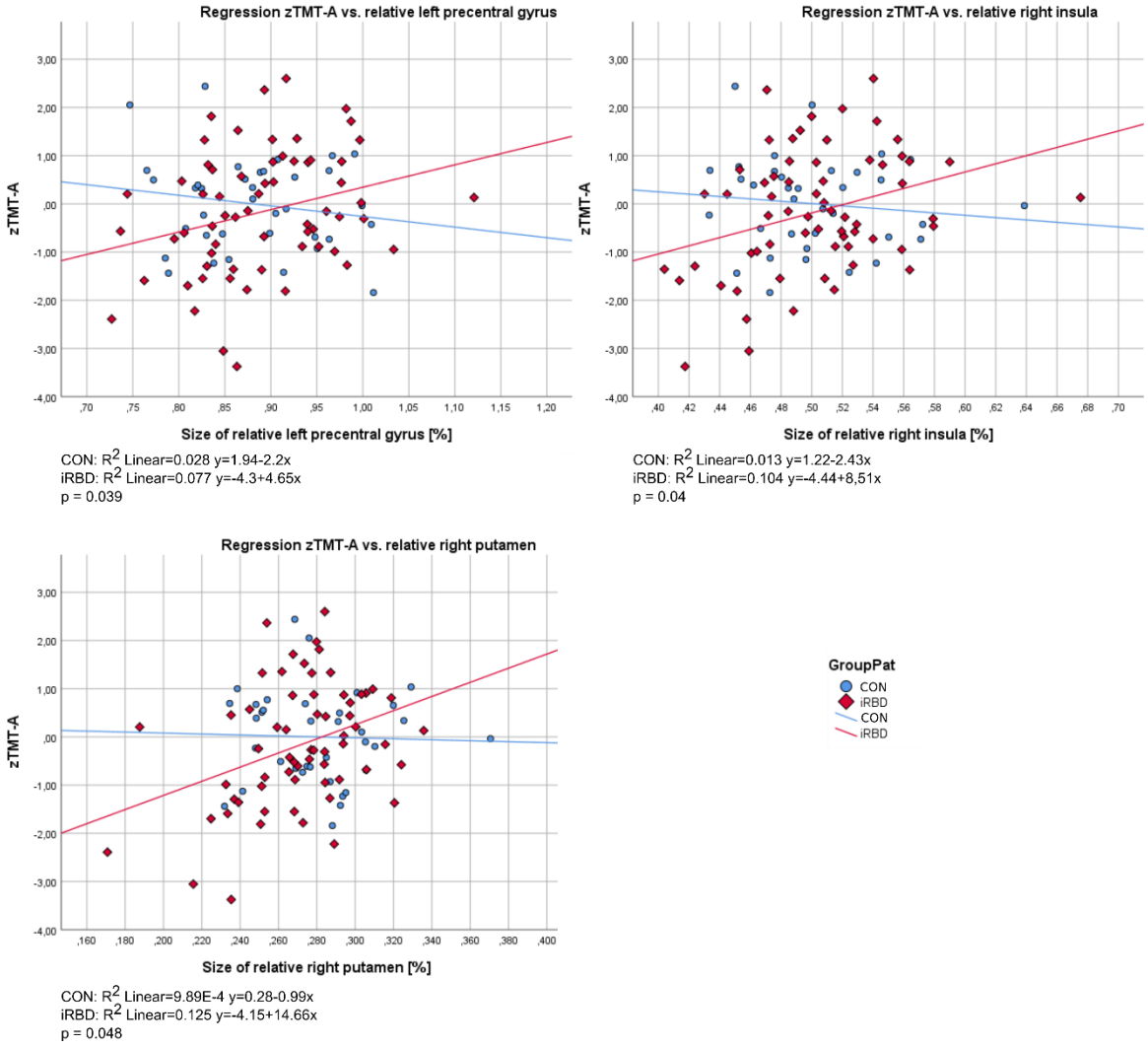
iRBD: TMT-A

iRBD: GPT right hand

Note. Highlighted significant clusters thresholded at p <0.05 at the cluster level, corrected for family-wise error. The colour scale represents the decimal logarithm of p-level. Z-coordinates in the Montreal Neurological Institute space (in millimetres) are indicated next to each slice (top right). iRBD = isolated rapid eye movement sleep behavior disorder; TMT-A = Trail Making Test, part A; GPT = Grooved Pegboard Test.

Figure 8

Linear regression plots of brain regional volumes associated with the performance of TMT-A in Study 1



Note. p value for difference of regressions slopes between iRBD and CON is shown in every graph. CON = healthy controls; iRBD = isolated rapid eye movement sleep behavior disorder; z = z-score; TMT-A = Trail Making Test, part A.

4.1.5 Manuscript Contribution

I administered a portion of the neuropsychological assessments, managed the neuropsychological data, operationalized the research question, conducted the statistical analyses of the psychological data, wrote portions of the manuscript, and presented the

results. Accordingly, I share equal contribution to this article with the first author, Ing. Christiane Malá, Ph.D.

4.2 Study 2: Interplay Between Cognitive Deficits, Colour Vision, and Brain Imaging in iRBD

Havlik, F.*, Malá, C., Dusek, P., Mana, J., Lorenzo Y Losada Ibarburu, V., Dostálová, S., Nepožitek, J., Peřinová, P., Růžička, E., Krupicka, R., Šonka, K., & Bezdicek, O. (in press). Colour Discrimination Deficit in REM Sleep Behavior Disorder: An Analysis of Dopaminergic Depletion, Cognition, and Brain Morphology. *Journal of Neural Transmission*.

* main and corresponding author

Bibliometrics according to WOS: $IF_{2023} = 3.2$; Q2

4.2.1 Sample Characteristics

The final sample included 77 CONs and 73 patients with iRBD, except for the DAT-SPECT analysis, where the iRBD sample was reduced to 66 due to missing data. Of the iRBD participants, 25% were classified as iRBD-MCI and 23% as having abnormal DAT-SPECT results. The two groups differed significantly in all clinical and demographic variables; therefore, age, sex, and education were included as covariates in the main analyses. A detailed sample description is provided in Table 7.

Table 7

Socio-demographic and clinical characteristics of iRBD patients and controls in Study 2

	CON (*N*=77)			iRBD (*N*=73)			*p*
	M	*Mdn*	*SD*	*M*	*Mdn*	*SD*	
Age, years	60.08	59.60	10.68	66.60	66.90	7.09	<.001
Sex, females %	–	37.66	–	–	8.22	–	<.001
Education, years	16.14	17.00	3.50	14.40	13.00	3.19	.002
RBD duration, years	–	–	–	7.38	5.00	9.00	-
MCI, negative %	–	100	–	–	75.34	–	-
DAT-SPECT, negative %	–	-	–	–	77.27	–	-
SBR putamen	–	–	–	2.44	2.34	0.57	-

	CON (*N*=77)			iRBD (*N*=73)			*p*
	M	*Mdn*	*SD*	*M*	*Mdn*	*SD*	
SBR caudate	–	–	–	2.84	2.80	0.55	-
MoCA	26.43	26.00	2.00	23.67	24.00	2.83	<.001
BDI-II	3.81	3.00	3.63	9.33	8.00	7.80	<.001
STAI-X1	30.74	31.00	6.57	36.92	34.00	9.92	<.001
STAI-X2	32.13	32.00	6.72	39.39	38.00	9.37	<.001
MDS-UPDRS-III	3.86	3.00	3.41	6.16	4.00	5.76	.016
FM-100 (TES)	50.16	40.00	37.14	83.21	72.00	48.63	<.001
FM-100 (RY)	6.68	4.00	8.93	15.34	10.00	19.43	<.001
FM-100 (YG)	13.17	12.00	11.33	20.71	20.00	14.03	<.001
FM-100 (GB)	18.16	16.00	15.49	27.75	24.00	18.33	<.001
FM-100 (BR)	12.16	10.00	10.97	19.40	20.00	11.70	<.001

Note. MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; BDI-II = Beck Depression Inventory, Second Edition; STAI = State-Trait Anxiety Inventory; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, part III; FM-100 = Farnsworth-Munsell 100 Hue Colour Vision Test; TES = total error score; RY = red-yellow; BR = blue-red; YG = yellow-green; GB = green-blue.

4.2.2 Group Differences in Colour Discrimination

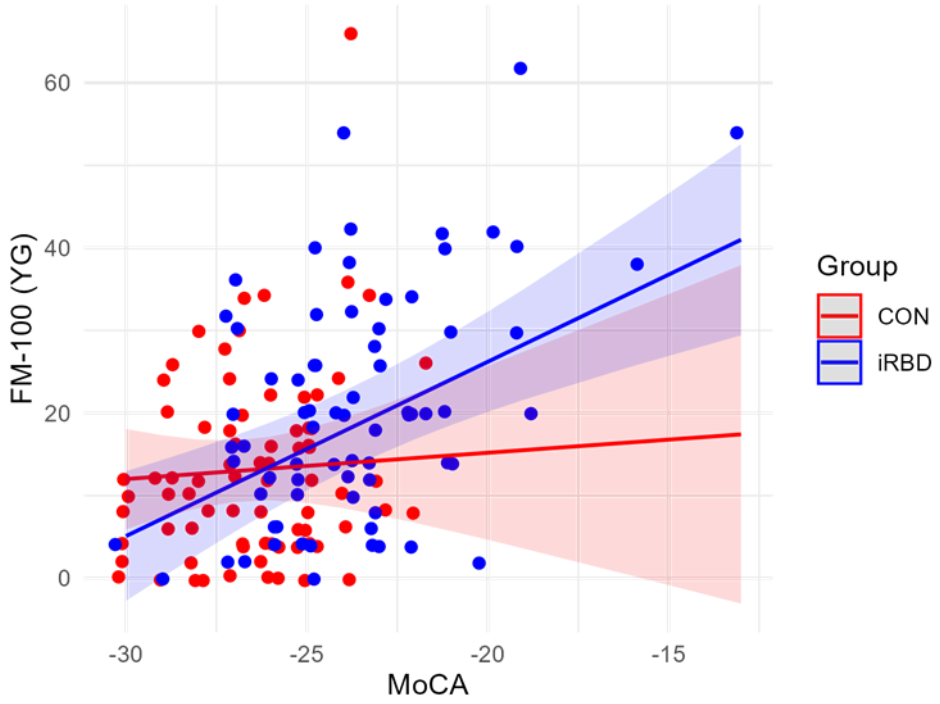
A diagnosis of iRBD was significantly associated with poorer performance on the FM-100 test. Specifically, iRBD patients had higher total error scores, $B = 0.294$, $SE = 0.114$, $t = 2.578$, $p = .011$, 95% CI[0.070, 0.516], and more errors in the red-yellow spectrum, $B = 8.599$, $SE = 3.215$, $z = 2.674$, $p = .007$, after controlling for demographic variables. On average, this corresponds to approximately 34% worse overall colour discrimination and an increase of about 9 error points in the red-yellow spectrum compared to CON.

4.2.3 Effect of iRBD on Colour Discrimination Through Cognition

Mediation analysis testing the pathway iRBD → MoCA → Colour Discrimination revealed a significant indirect effect of iRBD on FM-100 yellow-green spectrum through MoCA, ACMA = 3.717, $SE = 1.270$, $p < .001$, 95% CI[1.480, 6.493]. This mediation effect was also significantly greater in the iRBD group compared to CON, $t = 3.189$, $p = .041$, see Figure 9.

Figure 9

Group × MoCA interaction in mediation analysis of group and FM-100 (YG) with MoCA mediator



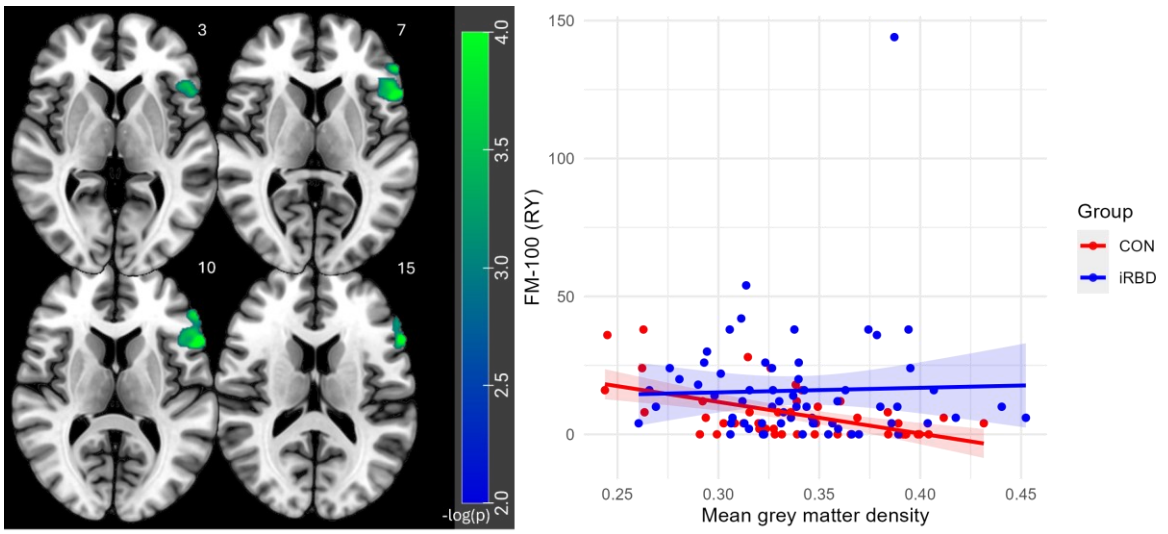
Note. For better display, the points are depicted with additional variability of .3. FM-100 = Farnsworth-Munsell 100 Hue Colour Vision Test; YG = yellow-green; MoCA = Montreal Cognitive Assessment.

4.2.4 Association of Colour Discrimination with Imaging Data

Performance on the FM-100 green-blue spectrum was significantly associated with the caudate SBR, B = 15.040, SE= 4.795, z = 3.137, p = .002, 95% CI[5.642, 24.438]. In the FM-100 red-yellow spectrum model (VBM), a significant interaction was found between group and the volume of the left inferior frontal gyrus (pars triangularis and opercularis), indicating a positive dependence for CON and none for RBD (corrected p = .014). However, this effect was no longer significant after the removal of one outlier (corrected p = .182), see Figure 10.

Figure 10

VBM analysis with full factorial model examining the effects of group and volume on FM-100 scores, including group × volume interaction terms



Note. Significant cluster for steeper dependence of iRBD vs. CON with FM-100 (RY). Z-coordinates in the Montreal Neurological Institute space (in millimetres) are indicated next to each slice (top right).

4.2.5 Manuscript Contribution

I administered a portion of the neuropsychological assessments, managed the neuropsychological data, formulated research questions, conducted all statistical analyses except for the VBM analysis, wrote the manuscript, and presented the results.

4.3 Study 3: Memory Profile in iRBD

Wenke, Š., Mana, J., **Havlík, F.**, Cohn, M., Nikolai, T., Buschke, H., Nepožitek, J., Peřinová, P., Dostálová, S., Ibarburu Lorenzo Y Losada, V., Růžička, E., Šonka, K., Dušek, P., & Bezdicek, O. (2022). Characterization of memory profile in idiopathic REM sleep behavior disorder. *Journal of Clinical and Experimental Neuropsychology*, *44*(3), 237-250. https://doi.org/10.1080/13803395.2022.2107182

Bibliometrics according to WOS: IF_{2022} = 2.2; Q3

4.3.1 Sample Characteristics

iRBD and CON participants differed in age, sex, and screening measures of cognition and neuropsychiatric symptoms (probability of direction > 95%). Therefore, all main analyses

were adjusted for the effects of age and sex. A full description of the sample is provided in Table 8.

Table 8
Clinical, demographic and screening measures of individuals with iRBD and CON group in Study 3

	Group							
	iRBD (*N* = 82)			CON (*N* = 49)			iRBD vs. CON	
	M	*Md*	*SD*	*M*	*Md*	*SD*	*pd* (%)	%inR
Sex (men, %)	87.80			75.51			96.20	37.49
Age (years)	66.65	67.07	7.49	63.05	66.08	8.23	99.20*	2.00
Education (years)	14.50	13.50	3.15	14.94	14.00	3.22	78.10	31.00
Caucasian (%)	100.00			100.00			-	
iRBD duration (years)	7.98	5.29	9.85	-			-	
MoCA[†]	23.69	24.00	2.82	25.48	25.00	2.42	100.00*	0.00
NART	19.02	17.00	9.96	15.83	14.00	10.40	95.60*	10.00
BDI-II[↑]	9.73	8.00	7.68	4.41	4.00	3.37	100.00*	0.00
STAI-X1	37.37	35.00	9.81	31.53	32.00	6.31	100.00*	0.00
STAI-X2	40.07	39.00	9.06	32.47	32.00	6.94	100.00*	0.00
ESS	7.46	7.00	4.16	5.86	6.00	3.63	-	
AHI	12.25	7.75	14.03	19.78	15.70	16.16	-	
MDS-UPDRS-III	6.33	4.00	5.68	3.53	3.00	4.01	-	
MDS-UPDRS-II	3.09	2.00	4.65	0.73	0.00	1.37	-	
DaTscan (n/bl/ua/ba/nd)		36/19/8/11/8			-		-	
Antidepressants only (%)		11.28			-		-	
Anxiolytics only (%)		4.51			-		-	
Combined (ad+ax; %)		4.51			-		-	

Note. %inR = Probability that the true value lies within a Region of Practical Equivalence (± .10 × SD); ad = antidepressants; AHI = apnea-hypopnea index; ax = anxiolytics; ba = bilaterally abnormal; BDI-II = Beck Depression Inventory (25 (30%) of iRBD patients with BDI-II > 12), Second Edition; bl = borderline; CON = controls; DaTscan = dopamine transporter imaging using single-photon emission computed tomography; ESS = Epworth Sleepiness Scale; iRBD = patients with idiopathic REM Sleep Behavior Disorder; Md = median; MDS-UPDRS-II and III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, Part II and III; MoCA = Montreal Cognitive Assessment; n = normal; NART = National Adult Reading Test; nd = not

done; *pd* = Probability of direction; STAI = State-Trait Anxiety Inventory X1 (state anxiety) and X2 (trait anxiety); ua = unilaterally abnormal; Bayesian estimation was used for between-groups comparisons; ††comparing the group is inappropriate because the measure was as an exclusion criterion in controls.
* *pd* > 95% approximately corresponds to one-sided $p < .05$ threshold

4.3.2 Results of Group Comparisons and Mediation Analyses

According to data and multivariate GLM model, there is a 98.62% probability that individuals with iRBD recall fewer words than CON on the RAVLT-DR task ($b = -0.37$, 95% PPI [−0.69, −0.05]). The probability that this difference falls within a negligible range (±0.1 standardised effect size, i.e., within the ROPE) was 4.98%. Mediation analysis revealed a significant indirect effect of iRBD on RAVLT (delayed recall) through SDMT ($b = -0.10$, 95% PPI [−0.23, −0.00]). Full results are presented in Table 9 and Table 10.

Table 9

Results of a multivariate GLM analysis probing the effect of iRBD on memory measures controlled for effects of age and sex

Outcome	*b*	95% PPI	Probability(RBD < CON)	% in ROPE
RAVLT-IR	−0.24	[−0.52, 0.07]	94.60	15.62
RAVLT-DR	**−0.37**	**[−0.69, −0.05]**	**98.62**	**4.98**
RAVLT-Rec.	−0.12	[−0.40, 0.18]	79.65	37.05
MBT-IR-TIP	0.02	[−0.26, 0.28]	46.00	53.12
MBT-IR-PIP	0.02	[−0.28, 0.34]	44.20	48.20
MBT-IFR	−0.21	[−0.54, 0.15]	88.92	21.90
MBT-DR-TIP	−0.05	[−0.32, 0.26]	62.18	48.70
MBT-DR-PIP	−0.04	[−0.37, 0.28]	60.75	45.05
MBT-DFR	−0.16	[−0.48, 0.16]	83.30	30.20

Note. Cases in bold indicate outcomes for which the 95% PPI of iRBD effect excluded zero; % in ROPE = Probability that the true value lies within a Region of Practical Equivalence (± 0.10); *b* = effect size, i.e., the median GLM parameter representing the difference between performance of iRBD patients and controls on standardizes scale when controlling for age and sex; DFR = delayed free recall in MBT; PPI = Highest density posterior probability interval; IFR = immediate free recall in MBT; MBT = Memory Binding Test; MBT-DR = Delayed Cued Recall in MBT; MBT-IR = Immediate Cued Recall in MBT; PIP = Total number of Pairs cued recalled in the Paired condition; Probability (RBD < CON) = Probability that iRBD patients perform worse than healthy controls; RAVLT = Rey Auditory Verbal Learning Test; RAVLT-DR = delayed (free) recall;

RAVLT-IR = T1-T5 free recall; RAVLT-Rec. = Recognition (number of correct responses from 15 true positives and 35 distractors); TIP = Total number of Items cued recalled in the Paired condition.

Table 10

Results of the mediation analysis of RAVLT (delayed recall) when controlling for the effects of age and sex in Study 3

Outcome	Predictor	Effect	*b*	95% PPI	*pd* (%)	% in ROPE
RAVLT-DR	iRBD	direct	−0.17	[−0.50, 0.19]	84.05	28.90
	PST-IC	**mediator**	**0.21**	**[0.03, 0.40]**	**98.88**	**11.70**
		indirect	−0.03	[−0.12, 0.02]	90.42	92.42
	LNS	mediator	0.08	[−0.09, 0.27]	82.60	55.88
		indirect	−0.02	[−0.12, 0.04]	80.30	94.80
	SDMT	**mediator**	**0.21**	**[0.03, 0.39]**	**98.90**	**12.85**
		indirect	**−0.10**	**[−0.23, −0.00]**	**98.75**	**52.00**
PST-IC	iRBD	total	−0.19	[−0.46, 0.09]	91.35	24.70
LNS	iRBD	total	−0.35	[−0.74, 0.02]	96.40	9.07
SDMT	**iRBD**	**total**	**−0.51**	**[−0.88, −0.15]**	**99.85**	**1.25**

Note. Cases in bold indicate outcomes for which the 95% PPI of iRBD effect excluded zero; % in ROPE = Probability that the true value lies within a Region of Practical Equivalence (± 0.10), the ROPE was not set-up for indirect effects because they represent interaction effects and commonly used effect size of ± 0.10; *b* = the median generalized linear model parameter representing the effect of predictor standardized outcome when controlling for age and sex (when the outcome is PST-IC, LNS or SDMT) or age, sex, PST-IC, LNS and SDMT (when the outcome is RAVLT-DR); iRBD = patients with idiopathic REM Sleep Behavior Disorder; LNS = Letter-Number Sequencing; Prop. mediated = proportion mediated; PST-IC = Prague Stroop Test, interference condition; RAVLT-DR = Rey Auditory Verbal Learning Test, delayed (free) recall; SDMT = Symbol Digit Modalities.

4.3.3 Manuscript Contribution

I administered a portion of the neuropsychological assessments, managed the neuropsychological data, and assisted with original draft writing and revisions during the review process.

4.4 Effect of Cognitive Load on Gait Performance and Its Neurobiological Correlates

Krupicka, R., Mala, C., Netukova, S., Hubena, T., **Havlik, F.**, Bezdicek, O., Dusek, P., & Ruzicka, E. (2024). Impaired dual-task gait in Parkinson's disease is associated with brain morphology changes. *Journal of Neural Transmission*, *131*(12), 1389-1395. https://doi.org/10.1007/s00702-024-02758-2

Bibliometrics according to WOS: $IF_{2023} = 3.2$; Q2

4.4.1 Sample Characteristics

Data from 64 drug-naïve de-novo PD patients and 47 CONs were analysed. A full description of the sample is provided in Table 11. Splitting the sample based on the first PCA component resulted in a subsample of 44 PD patients with normal DTC (25 males, mean age 58.6 ± 12.2 years, MoCA 26.6 [1.9, 24–30], MDS-UPDRS III 24.3 [9.7, 6–43]) and a subsample of 20 PD patients with abnormally increased DTC (11 males, mean age 57.3 ± 13.0 years, MoCA 26.4 [1.4, 24–29], MDS-UPDRS III 36.2 [14.5, 14–70]).

Table 11

Clinical characteristics of participants in Study 4

	PD	CON	*p* value
Male sex	34/64 (53%)	29/47 (62%)	0.44
Age (years)	58.2 (12.3, 33–81)	60.4 (9.2, 43–75)	0.31
Symptom duration (years)	1.7 (1.3, 0.1–5.3)	n/a	n/a
MoCA	26.5 (1.75, 24–30)	26.5 (1.72, 24–30)	0.96
TMT-B	91 (40, 44–213)	80 (23.8, 42–149)	0.1
MDS - UPDRS III	28.0 (12.6, 6–70)	n/a	n/a

Note. Data are mean (SD, range) or number/sample size (%) including *p* values analysed using t-test or Mann–Whitney U-test. MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; n/a = not applicable; PD = Parkinson's disease; TMT-B = Trail Making Test, Part B.

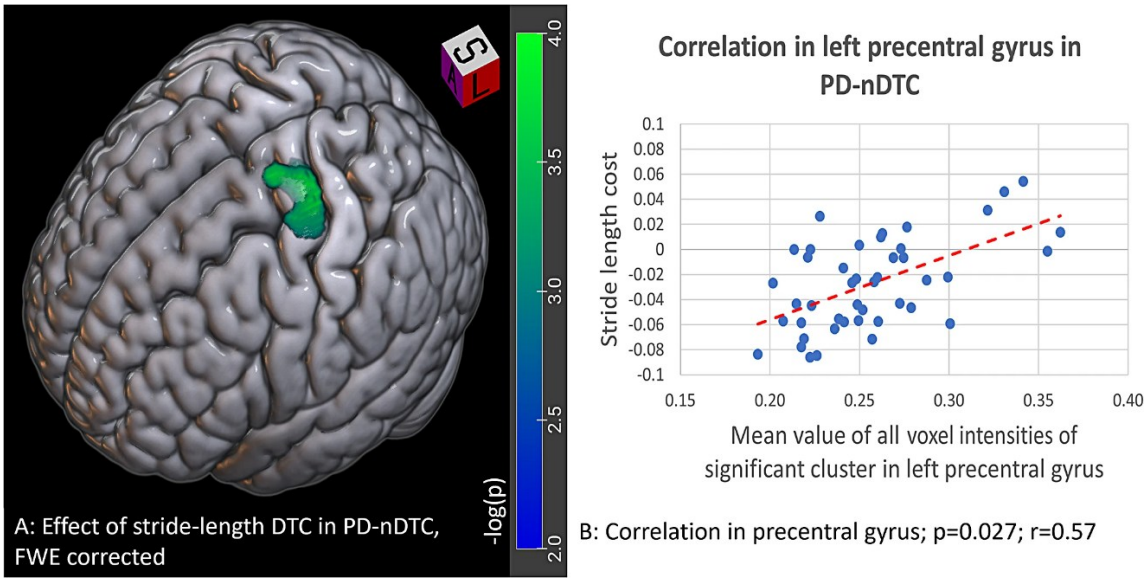
4.4.2 Results of Gait and VMB Analyses

In relevance to this dissertation, it was found that PD patients were more affected by cognitive load, as reflected by greater DTC, during gait across all parameters (speed, p = 0.007; stride length, p = 0.014, and cadence, p = 0.029). This difference was also evident at the level of a latent factor, as the groups differed significantly in PCA scores on the first component (p = 0.007).

At the level of subgroups with and without impaired DTC, no significant differences were found in the VBM analysis. However, each group showed distinct correlations between DTC measures and grey matter density. In the group without impaired DTC, stride-length DTC was positively correlated with grey matter density in the left primary motor cortex (r = 0.57, p = 0.03)(Figure 11). In contrast, the group with impaired DTC showed a negative correlation between cadence DTC and grey matter density in the right lingual gyrus (r = -0.35, p = 0.02)(Figure 12). None of these correlations, nor any others, were replicated in the CON group or in the PD group as a whole.

Figure 11

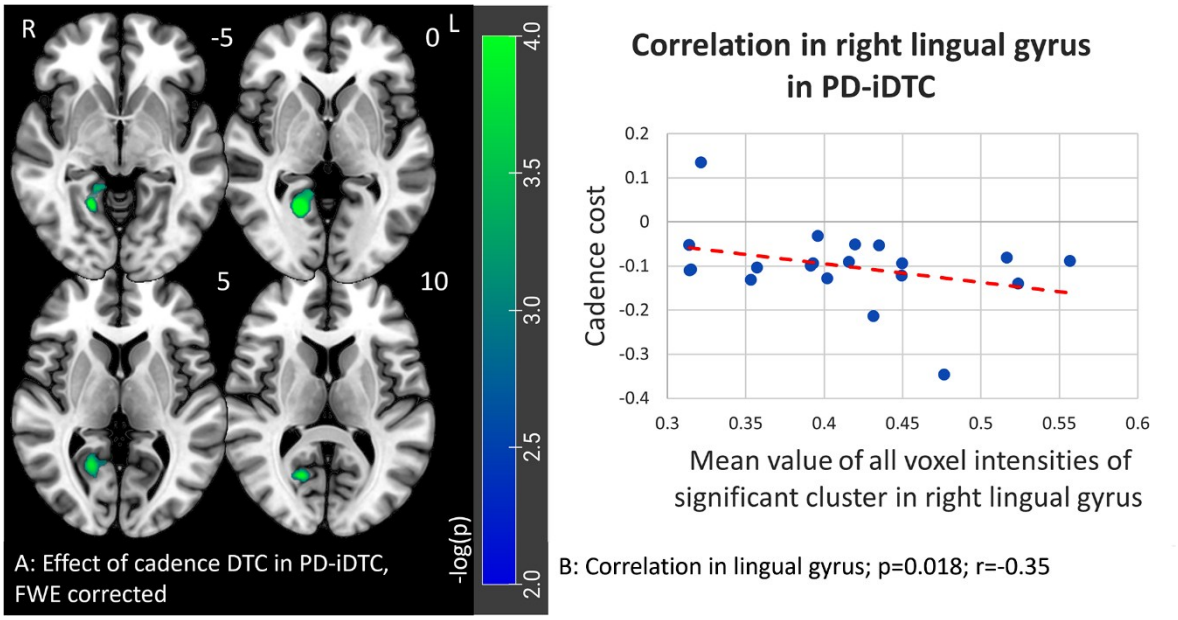
Results of the correlation analysis of brain morphometry with DTC of gait parameters for PD without gait cognitive impairment in Study 4



Note. PD-nDTC = PD without gait cognitive impairment. The colour scale represents the negative decimal logarithm of the p value. A: Significant cluster in the left precentral gyrus for a positive correlation with stride length DTC in PD-nDTC, p_{FWE} = 0.027. B: Correlation of grey matter density in the significant cluster in the precentral gyrus with stride length DTC.

Figure 12

Results of the correlation analysis of brain morphometry with DTC of gait parameters for PD with gait-cognitive impairment



Note. PD-nDTC = PD without gait cognitive impairment. The colour scale represents the negative decimal logarithm of the *p* value. A: Significant cluster in the right lingual gyrus for a negative correlation with cadence DTC in PD-iDTC, p_{FWE} = 0.018. B: Correlation of grey matter density in the significant cluster in the lingual gyrus with cadence DTC.

4.4.3 Manuscript Contribution

I administered a portion of the neuropsychological assessments, managed the neuropsychological data, and contributed to the interpretation of the results from a neuropsychological perspective. I also assisted with manuscript revisions during the review process.

5 Discussion

5.1 Study 1: Cortical and Subcortical Morphometric Changes in Relation to Cognitive Impairment in iRBD

In Study 1, no significant differences in brain morphology were found between the iRBD and CON groups. Additionally, iRBD patients, when MCI status was not taken into account, did not differ from CONs in cognitive performance. Furthermore, associations between cognitive performance and imaging measures varied depending on the specific MRI parameter. Nevertheless, a consistent association between performance on the TMT-A and the right insula and putamen was observed across all analytical approaches (VBM, ROI, DBM).

Study 1 is therefore quite unique, as to the author's knowledge, it is the only study that did not detect any between-group differences in brain morphology, even after splitting the iRBD group based on the presence of MCI. As stated in the Introduction, most studies have reported differences in the frontal and temporal lobes as well as the basal ganglia, findings that were also supported by a recent meta-analysis (Wang et al., 2025). These results raise important questions about the reasons behind the absence of significant findings in the present study.

Two primary explanations can be considered. First, it is possible that no morphological differences exist between the groups. Second, such differences may exist but were not detected in this study. Supporting the first explanation is evidence from longitudinal studies, which suggest that significant morphological progression is unlikely over short time periods (Baun et al., 2024; Campabadal, Inguanzo, et al., 2020). Thus, if patients are assessed in very early stages of the disease, structural brain changes may not yet be present, and any cognitive deficits may be primarily driven by factors such as neurotransmitter imbalance. Notably, the iRBD patients in this sample had a median disease duration of five years since symptom onset. Further support for the first explanation comes from the consistency of findings across all three analytical approaches (VBM, ROI, DBM), each targeting different structural parameters, yet all yielding non-significant results. Additionally, this study included a relatively large iRBD sample (n = 63), compared to approximately 25 subjects typically included in similar studies (Wang et al., 2025).

In contrast, the second explanation—that morphological differences do exist but were not detected—is supported by several findings. Some regions showed statistically significant differences before correction for multiple comparisons, including the right cerebellum in iRBD-NC, and the cuneus, cerebellum, lingual gyrus, putamen, nucleus accumbens and parts of parietal and temporal lobes in iRBD-MCI group compared to CONs (ROI analysis). Moreover, the existing literature includes exclusively studies reporting significant structural alterations in iRBD (Campabadal et al., 2021; Wang et al., 2025).

Based on the overall pattern of results, the author of this thesis leans toward the second explanation, despite the plausibility of the first. It seems unlikely that the sample in this study differs fundamentally from those in previous research. Nonetheless, in line with the findings of Study 1, there is insufficient evidence to support the third hypothesis formulated in the Aims and Hypotheses section. Therefore, within the context of this thesis, it is concluded that there are no detectable morphological differences between iRBD patients and CONs.

Contrary to the MRI analyses, the analyses of neuropsychological variables yielded significant results. While iRBD and CON groups did not differ overall, introducing MCI status as an additional variable revealed a consistent pattern indicating a processing speed deficit in the iRBD-MCI group. Although this might appear to contradict the frequently reported cognitive profile—typically characterized by memory and executive functions deficits (Leitner et al., 2023)—the opposite is actually true. As demonstrated in the most recent meta-analysis, the majority of executive functions tests used to characterize the cognitive profile of iRBD are, in fact, measures of processing speed or include a substantial processing speed component (Leitner et al., 2023). In this sense, Study 1 supports the notion that processing speed deficits are a dominant feature of the iRBD cognitive profile.

The overall pattern of the above analyses complements the findings on the associations between cognitive performance and brain morphology. Although several significant associations were identified—including with neuropsychological measures such as the TMT, GPT, RAVLT, and the PCA-derived psychomotor speed component—the most consistent and interpretable associations involved the TMT-A and grey matter density in the right insula and putamen. The TMT-A is widely recognized as a measure of psychomotor speed and has been linked to basal ganglia function in alpha-synucleinopathies (Botzung et al., 2019; Hanakawa et al., 2017), as also observed in the present study. Whether this relationship reflects a causal mechanism—i.e., TMT-A performance being driven by structural changes in the insula and putamen—or merely a shared source of variance remains

an open question. Nonetheless, the central role of TMT-A in iRBD research is well established. Prior studies have consistently shown that individuals with iRBD perform worse than controls on the TMT-A (Campabadal et al., 2019; Leitner et al., 2023), and the same applies to structural differences in the insula and putamen (Campabadal et al., 2021; Rahayel, Postuma, Montplaisir, Genier Marchand, et al., 2018). Taken together, these findings support the assumption that deficits in processing speed—as measured by the TMT-A—may be underpinned by structural disturbances in the basal ganglia and insula. Accordingly, based on the results from Study 1, it can be concluded that there is evidence for specific associations between cognitive functioning and brain morphology, thus supporting the second hypothesis formulated in the Aims and Hypotheses section.

These conclusions must be interpreted in light of certain limitations. There are no standardized criteria for diagnosing MCI in RBD, so a broad neuropsychological battery and a −1.5 *z*-score cutoff (commonly used in PD) were applied. The cross-sectional, exploratory design also limits interpretation. Finally, depression and anxiety were not included as covariates in order to measure the overall effect of iRBD.

5.2 Study 2: Interplay Between Cognitive Deficits, Colour Vision, and Brain Imaging in iRBD

In Study 2, differences in colour discrimination scores were observed. Furthermore, a significant mediation effect of MoCA on performance in the FM-100 (yellow-green) spectrum was found. Analysis of SBR and FM-100 revealed a positive association between FM-100 (green-blue) and caudate SBR, and a similar pattern was observed for brain morphology—specifically, the left inferior frontal gyrus (pars triangularis and opercularis) and FM-100 (red-yellow).

Until now, no other study has examined the nature of colour discrimination in iRBD as comprehensively as the present one. One of the initial hypotheses postulated that cognitive functions may play a role in colour discrimination performance (Bertrand et al., 2012), as such tasks may require planning, response maintenance, or attentional control. Although a significant mediation effect of MoCA was observed for the FM-100 yellow-green spectrum this effect was not found for any of the scores on which iRBD participants performed worse. Thus, there is insufficient evidence to support this hypothesis.

Why the mediating effect was observed only for the FM-100 yellow-green subscore—and not for TES score, where group differences were evident—remains an open

question. To author's knowledge, no other study has directly tested the relationship between colour discrimination and cognition in iRBD. Some indirect evidence can be inferred from studies on iRBD and other alpha-synucleinopathy populations, which report correlations between colour discrimination and clinical variables such as motor symptoms, olfaction, or visuo-constructional functions, often yielding medium to large effect sizes (Bertrand et al., 2012; Diederich et al., 2020; Kim et al., 2024; Li et al., 2019; Matar et al., 2019; Muller et al., 1998; Postuma, Gagnon, et al., 2009b). Given the wide range of such correlations across unrelated functional domains, it is more likely that these reflect shared variability due to disease progression rather than a causal relationship. In this context, the observed mediation effect in Study 2 may have arisen by chance or may represent non-specific, widespread effects of the disease.

A similar argument applies to the two remaining findings—associations with structural morphology and SBR in the caudate. Neither FM-100 score associated with these parameters showed group-level differences between iRBD and CON. The VBM analysis revealed a significant association only within the CON group, and this association disappeared after removal of a single outlier. The left inferior frontal gyrus is not typically linked to colour discrimination, although Siuda-Krzywicka et al. (2021) suggest that it may contribute via frontal-temporal network interactions. While dopamine depletion in the caudate is not directly implicated in colour processing, it may influence colour discrimination indirectly via its established role in cognition (Grahn et al., 2008) , implying a potential mediation chain: iRBD → caudate dopamine → cognition → colour discrimination. However, this pathway was not supported by the mediation analyses.

Taken together, a more plausible explanation is that colour discrimination deficits in iRBD originate from retinal changes, such as loss of ganglion cells, macular thinning, or degeneration of amacrine cells (Ortuno-Lizaran et al., 2020; Polo et al., 2016). Unfortunately, these retinal changes were not assessed in Study 2, which represents a key limitation. Additional limitations include: the absence of a CON for the DAT-SPECT analysis due to ethical and technical constraints; reliance solely on the FM-100 as the measure of colour discrimination; lack of complementary tests assessing perceptual processing or retinal structure (e.g., optical coherence tomography); and baseline demographic differences between the study groups.

5.3 Study 3: Memory Profile in iRBD

Study 3 was designed to enrich the literature on the cognitive profile of iRBD, specifically contributing to the ongoing debate between the retrieval deficit hypothesis and the core memory hypothesis. The former attributes memory deficits to impairments in other cognitive functions (e.g., attention, executive control), while the latter posits deficits in encoding, consolidation, and retention as primary.

Several mutually complementary findings were observed that align with predefined criteria supporting the retrieval deficit hypothesis. A significant difference between iRBD and CON was observed on a single memory measure (RAVLT delayed recall), and this effect was mediated by processing speed, as measured by the SDMT. Retention was impaired in iRBD (RAVLT delayed free recall), while recognition performance—where retrieval is externally supported—was comparable between iRBD and CON, and cued recall (MBT) remained preserved. These findings collectively provide robust support for the retrieval deficit hypothesis. Nevertheless, a somewhat unexpected result was that performance was not mediated by executive functions but by processing speed. However, as demonstrated in Study 1 and in the meta-analysis by Leitner et al. (2023), tests of processing speed and executive functions often overlap, making this result consistent with literature reporting executive or attentional deficits, as well as studies supporting the retrieval deficit hypothesis in iRBD (Bezdicek et al., 2018; Leitner et al., 2023; Marcone et al., 2019; Terzaghi et al., 2019; Youn et al., 2016).

Still, in light of mixed findings from studies on patients in more advanced stages of disease, such as early PD or DLB (Bezdicek et al., 2019; Cohn et al., 2016; Edelstyn et al., 2015; Chiaravalloti et al., 2014), the retrieval hypothesis might benefit from refinement. A "cascading retrieval hypothesis" is proposed, wherein free recall is impaired early due to its high attentional and executive demands, while cued recall and associative binding remain relatively spared. These latter deficits would emerge later as the disease progresses to early PD or DLB.

As no brain imaging was conducted in this study, and Study 1 found no significant differences in brain morphology, the neural substrates underlying retrieval deficits remain speculative. Although the question has been raised since the 1990s (Troster & Fields, 1995), definitive answers are still lacking. For example, most recent meta-analysis found both frontal and temporal lobes regions are affected in iRBD (Wang et al., 2025), and Rahayel, Postuma, Montplaisir, Genier Marchand, et al. (2018) found that attention and executive

functions were associated with frontal medial superior, dorsolateral paracentral, sensorimotor, fusiform, lingual, and cuneus, but also showed that learning and memory was associated with temporal pole, anterior superior, posterior lingual and fusiform, insula, cuneus, and hippocampus. These findings underscore the need for future studies adopting the current paradigm in combination with neuroimaging methods.

The study has several limitations. First, participant selection was indirect via advertisements, which may have introduced selection bias and limited representativeness. Second, individual matching was not used to avoid reducing the iRBD sample size. Third, only a prospective longitudinal follow-up can determine whether iRBD will develop associative memory deficits, particularly in cases converting to mixed PD and AD pathology. Fourth, free and cued recall may not fully capture retrieval or associative deficits. Fifth, differences across memory indices might reflect confounding factors or measurement error between paradigms (RAVLT vs. MBT). Sixth, although Stroop interference was not a mediator, executive functions are multifaceted and other measures might be. Finally, mood was not included in the analyses, although severe psychiatric conditions were excluded.

5.4 Effect of Cognitive Load on Gait Performance and Its Neurobiological Correlates

In Study 4, it was found that PD patients were more affected by cognitive load during gait, specifically in terms of speed, stride length, and cadence. This effect remained evident even when gait parameters were modelled as a latent factor. Furthermore, among patients less affected by the additional cognitive load, stride-length DTC was positively correlated with grey matter density in the left primary motor cortex. In contrast, in the other group, cadence DTC showed a negative correlation with grey matter density in the right lingual gyrus.

These findings suggest the presence of distinct neural mechanisms underlying dual-task performance in PD. In patients with normal DTC, a positive correlation between stride-length DTC and grey matter density in the left precentral gyrus—the primary motor cortex—may indicate that these individuals are able to prioritize motor control under cognitive load, as has also been demonstrated in cognitively unimpaired PD patients (Johansson et al., 2021). This supports the idea that preserved structure (compensatory neuroplasticity) in motor regions facilitates compensation during dual-tasking, allowing for maintenance of gait parameters despite added cognitive demands. In contrast, patients with increased DTC exhibited a negative correlation between cadence DTC and grey matter density in the right lingual gyrus. This region is involved in visual imagery and spatial-symbolic processing and

may be recruited during the mental arithmetic component of the dual-task (Bogousslavsky et al., 1987). The inverse relationship suggests that reduced structural integrity in the lingual gyrus might shift attentional resources toward the cognitive task at the expense of motor control, contributing to greater dual-task costs on gait cadence. Of note, atrophy of occipital cortex including lingual gyrus has been consistently reported in this population (Wilson et al., 2019) and was associated with severity of symptoms (Burton et al., 2004; Tessitore et al., 2012; Watanabe et al., 2013).

A limitation of the study is the absence of data on patients' performance in the concurrent cognitive task. Additional concerns include potential variability in patients' motivation and understanding of instructions, as well as intra-individual variability in gait during assessment. Another limitation is the unequal subgroup sizes, particularly the smaller impaired DTC group, which raises the possibility that observed correlations may be driven by individual morphological differences within this subgroup.

Despite these limitations, this study sets a clear direction for future research on iRBD. Until now, research on iRBD in this area has been at significant risk of false positive results, as is well known based on consistently heterogeneous findings in the literature (Campabadal et al., 2021; Leitner et al., 2023; Wang et al., 2025) and from the results observed in this thesis (Study 1 and Study 2), which indicate very subtle and sporadic differences in brain morphology, with only rare correlations with cognitive performance. Furthermore, although a specific interaction between cognitive and motor systems has already been suggested in both PD and iRBD (Ehgoetz Martens et al., 2019; Varalta et al., 2015), and further supported by fMRI findings (Ehgoetz Martens et al., 2020), no testable hypothesis regarding the involvement of brain morphology had previously been formulated. This study provides a unique, testable hypothesis involving specific brain regions that may also play a role in iRBD. Additionally, it serves as a pilot study, offering valuable methodological insights for future research. One such example is the recording of performance on a concurrent cognitive task, which allows for more detailed and meaningful analyses. Another is the recommendation to prefer longitudinal designs that can account for different types of phenotypic conversion.

5.5 General Discussion

Based on previous literature and research gaps, five hypotheses were formulated. To the first hypothesis that patients with alpha-synucleinopathies exhibit a distinct cognitive impairment

profile were dedicated Study 1 (Mala et al., 2024), partially Study 2 (Havlik et al., in press) and Study 3 (Wenke et al., 2022).

All these studies indicate the existence of a specific cognitive profile in patients with iRBD, largely consistent with recent findings (Leitner et al., 2023). Both Study 1 and Study 3 demonstrated deficits suggestive of disturbances in processing speed, which may underlie impairments observed in other cognitive domains. Although the construct of processing speed remains under theoretical scrutiny (Chiaravalloti et al., 2003; Kail & Salthouse, 1994; Mashburn et al., 2024; Salthouse, 1996, 2000), it is generally conceptualized as comprising multiple components—input, internal, and output—corresponding to sensory, cognitive, and motor processes, respectively (Mahurin, 2008). In PD, it has been shown that patients perform worse than controls across all components; however, after accounting for shared variance among tasks, significant differences remain only in motor function and simple perception/sustained alertness (Arroyo et al., 2021), suggesting that impairments are primarily linked to output and internal components. Moreover, recent evidence indicates that processing speed may account for a substantial portion of the variance observed in tests of other cognitive domains, particularly executive functions and memory (Ferguson & Foley, 2024; Leitner et al., 2023; Loffler et al., 2024). For example, Tam and Schmitter-Edgecombe (2013) found that processing speed explains a significant portion of the variance in scores on the commonly used memory test, the Brief Visuospatial Memory Test. Similarly, Loffler et al. (2024) fitted a model that fully explained executive functions through processing speed. Comparable findings have also been reported in studies on alpha-synucleinopathies (Ferguson & Foley, 2024; Grossman et al., 2002). Although the present studies did not employ methodologies to assess specific components of processing speed, the findings are consistent with the view that processing speed is altered in alpha-synucleinopathies and may contribute to, or even underlie, some of the cognitive deficits observed in iRBD.

The overall picture of the cognitive profile is further complemented by Study 2, which contributed to the first hypothesis primarily by showing that the functions underlying performance in classical colour discrimination tests—such as the FM-100—do not dominate the cognitive profile in iRBD. Although, this finding is somewhat surprising, given that deficits in visuospatial and visuoconstructional functions are frequently reported in iRBD (Fantini et al., 2011; Leitner et al., 2023; Wang et al., 2024).

The second hypothesis, proposing that cognitive deficits in alpha-synucleinopathies are associated with specific brain imaging findings, was addressed in Study 1, partially in Study 2, and in Study 4.

In Study 1, consistent and interpretable associations were observed between cognitive performance in TMT-A and grey matter density in the right insula and putamen, across multiple modalities (VBM, ROI, DTI). Additional significant associations were also found for other cognitive tests (TMT-B, GPT, RAVLT, and a PCA-derived psychomotor speed component), supporting a broader cognitive-neuroanatomical link. In Study 2, likely spurious and difficult-to-interpret associations were identified between FM-100 colour discrimination scores (formerly hypothesized in this context to be partly influenced by cognitive factors) and imaging markers in both VBM and DAT-SPECT analyses. Study 4 demonstrated that additional cognitive load during gait (specifically serial subtraction by sevens from one hundred) in PD patients was associated with grey matter density in the right lingual gyrus and the left primary motor cortex, depending on PD subgroup (impaired, respectively unimpaired DTC). These findings have three main implications.

First, there are detectable associations between cognitive functioning and brain morphology in iRBD. These associations align with the cognitive profile of iRBD, which is predominantly characterized by deficits in processing speed. It is therefore postulated that the insula and putamen may represent a potential neurobiological substrate of processing speed deficit. This interpretation fits well with findings in PD, where impairments are primarily observed in motor functions and simple perception/sustained alertness components of processing speed (Arroyo et al., 2021), and with evidence that the insula and putamen are involved in vigilance/attention, and motor functions (Fu et al., 2022; Klugah-Brown et al., 2023; Utter & Basso, 2008). Second, colour discrimination does not appear to be linked to brain regions involved in higher-order cognitive processing, thereby indirectly suggesting that cognitive functions are not significantly involved. This supports the hypothesis that impairments in colour discrimination are primarily driven by retinal changes, as proposed in earlier studies (Ortuno-Lizaran et al., 2020; Polo et al., 2016). Lastly, examining the nature of cognitive deficits using dual-task paradigms and VBM analysis in iRBD is feasible. Future studies should further investigate the roles of the lingual gyrus and primary motor cortex, both of which may also plausibly contribute to the processing speed deficits observed in iRBD (Kraft et al., 2020; Lakhani et al., 2014).

The last two hypotheses—namely, that colour discrimination deficits observed in alpha-synucleinopathies can be explained by impairments in cognitive functions, and that these deficits are associated with specific brain imaging findings—were addressed in Study 2. As noted above, neither the mediation analyses nor the VBM and DAT-SPECT results yielded meaningfully interpretable findings. These results most strongly support the

hypothesis that colour discrimination deficits stem from alterations in early phases of sensory processing (Ortuno-Lizaran et al., 2020; Polo et al., 2016). Nonetheless, alternative explanations cannot be entirely ruled out. For instance, there may be a specific association between performance on the FM-100 green-blue subtest and dopaminergic depletion, which could indirectly relate to cognitive functioning, as suggested by Colzato et al. (2014). Additionally, some direct links between dopaminergic depletion and colour processing have been observed in animal models (Govindaiah & Cox, 2005), which may also be relevant in the human context.

In conclusion, studies 1, 2, and 3 were conducted on largely overlapping samples of patients, all recruited from the same neurological centre, and employed similar methods for cognitive assessment. As such, some of the consistent findings—particularly those indicating processing speed deficits or morphological changes—may, to some extent, be influenced by these shared methodological and sampling characteristics. Consequently, the generalizability of the results to broader iRBD populations may be limited. However, this concern is tempered by the observation that the present findings—aside from the null results concerning group differences in brain morphology—are largely consistent with those reported in meta-analyses involving diverse populations (Leitner et al., 2023; Wang et al., 2025). Moreover, they align well with current theoretical models of disease progression in alpha-synucleinopathies (Borghammer et al., 2022; Horsager et al., 2020).

6 Conclusions

This thesis aimed to examine five hypotheses concerning the cognitive profile and neural underpinnings of alpha-synucleinopathies, particularly iRBD, by using data from four studies.

First, converging evidence from Studies 1, 2, and 3 supports the existence of a distinct cognitive impairment profile in individuals with iRBD. Across studies, deficits in processing speed emerged as a consistent and dominant feature, aligning with recent meta-analyses and theoretical models. Although the construct of processing speed remains conceptually debated, it is increasingly recognised as a multidimensional construct with sensory, cognitive, and motor components. The observed pattern of deficits suggests that impairments in iRBD—and by extension in early alpha-synucleinopathies—may be driven by disruptions in the internal (perception/sustained alertness) and output (motor) components of this construct. These impairments may also underlie or amplify deficits in other cognitive domains, particularly executive functions and memory.

Study 2 further contributed to the characterisation of cognitive profile in iRBD by showing that performance on classical colour discrimination tests, such as the FM-100, does not appear to be affected by cognitive functions. This finding contrasts with prior reports giving colour discrimination in association with executive functions.

Second, support for hypothesis that cognitive deficits in alpha-synucleinopathies are associated with specific brain imaging findings was provided primarily by Study 1 and Study 4. Study 1 identified robust and interpretable associations between cognitive performance and grey matter density in the right insula and putamen across multiple imaging modalities. These regions are implicated in attention/vigilance and motor control and may represent key neural substrates of processing speed deficit. Study 4 extended this evidence by demonstrating that dual-task gait paradigms in PD patients also relate to structural changes in the lingual gyrus and primary motor cortex, regions that may likewise contribute to slowed cognitive-motor integration.

In contrast, hypotheses that colour discrimination deficits reflect cognitive impairments and are associated with brain imaging markers were not supported. Study 2 found no meaningful associations between FM-100 scores and either cognitive performance or structural and functional brain measures. These findings instead point toward a sensory origin of colour discrimination deficits, consistent with prior evidence of retinal pathology in alpha-synucleinopathies. Nevertheless, potential links between dopaminergic depletion

and specific aspects of colour processing—such as the green-blue spectrum—remain plausible and warrant further investigation, especially in light of findings from experimental and animal models.

Finally, it must be acknowledged that Studies 1–3 were conducted on overlapping samples, all recruited from the same clinical centre and assessed using comparable cognitive measures. While this methodological consistency strengthens internal validity, it may also limit the generalizability of the findings. However, the results are largely consistent with those reported in meta-analyses based on diverse populations and align well with contemporary models of disease progression in alpha-synucleinopathies. These converging lines of evidence underscore the relevance of processing speed as a central cognitive construct in the prodromal and early clinical stages of these disorders and highlight the importance of integrating cognitive and neuroimaging approaches in future research.

7 Summary

The isolated (iRBD) form of REM sleep behavior disorder (RBD) is associated with a wide range of symptoms, including sensory, olfactory, neuropsychiatric, motor, and cognitive. Among the cognitive symptoms, deficits in memory and executive functions are the most prominent; however, the specific cognitive profile of iRBD remains under debate. Similarly, uncertainty applies to morphological brain changes. While meta-analyses suggest that these changes primarily affect the frontal and temporal lobes as well as parts of the basal ganglia, findings across studies remain inconsistent. Consequently, research examining the association between cognitive performance and brain structure in iRBD is highly heterogeneous, with many studies reporting non-significant results in comparison to controls. Additionally, given that sensory deficits are among the earliest manifestations of iRBD, recent research has begun to explore the interplay between sensory function, cognition, and brain morphology. In light of these unresolved questions, this thesis aims to provide an overview of the most recent findings and to enrich the literature through the results of four original studies addressing the aforementioned research gaps.

The theoretical part of this thesis provides a brief overview of the history of RBD research and current classification systems. It further outlines the evolution of the concept of iRBD as a preclinical stage of alpha-synucleinopathies. Subsequent chapters review current knowledge on the cognitive profile and brain structural changes in iRBD, with particular emphasis on the heterogeneity of phenotypes and their implications for understanding the disorder.

The empirical part of the thesis aims to advance the field through four original studies that address the following research questions: is there a specific cognitive profile characteristic of iRBD?; are there common and detectable brain structural changes in iRBD?; how are cognitive deficits and structural brain changes related?; do cognitive functions account for differences in colour discrimination between iRBD and controls?; is the colour discrimination deficit in iRBD related to dopaminergic denervation?; can be performance in colour discrimination explained by morphometric parameters of cerebral grey and white matter?; is memory impairment in iRBD secondary to deficits in other cognitive functions?; reflects structural brain alterations the effects of cognitive load during gait?.

Across these studies, deficits in processing speed consistently emerged as a dominant feature, in line with recent meta-analyses and theoretical models. Although no group-level morphological differences were detected, robust and interpretable associations were found

between cognitive performance and grey matter density in the right insula and putamen across multiple imaging modalities. Furthermore, hypotheses suggesting that colour discrimination deficits reflect cognitive impairments or are associated with brain imaging markers were not supported. Study 2 revealed no meaningful associations between colour discrimination and either brain morphology or dopaminergic depletion. These findings instead point toward a sensory origin of colour discrimination deficits, consistent with prior evidence of retinal pathology in alpha-synucleinopathies.

Additionally, findings from the Parkinson's disease sample suggest the presence of distinct neural mechanisms underlying dual-task performance—that is, the interaction between cognitive load and gait—providing further insight into the cognitive–motor interplay in alpha-synucleinopathies.

Taken together, the results presented in this thesis shed new light on the interplay between cognitive profile, sensory functions, and MRI findings in iRBD. While some findings warrant follow-up in future studies, others—such as the identification of processing speed deficits and their potential neuroanatomical correlates—may already hold practical implications for neuropsychological diagnostics.

8 Souhrn

Izolovaná (iRBD) forma poruchy chování v REM spánku (RBD) je spojena se širokou škálou příznaků senzorických, čichových, neuropsychiatrických, motorických a kognitivních. Mezi kognitivními příznaky jsou nejvýraznější deficity paměti a exekutivních funkcí; specifický profil kognitivní poruchy u iRBD však zůstává předmětem výzkumu. Obdobně je tomu v bádání o morfologických změnách v mozku u těchto osob. Ačkoli metaanalýzy naznačují, že změny postihují především čelní a spánkové laloky a části bazálních ganglií, zjištění napříč studiemi zůstávají rozporuplná. V důsledku toho je výzkum zkoumající souvislost mezi kognitivním výkonem a strukturou mozku u iRBD značně heterogenní, přičemž mnoho studií uvádí nesignifikantní výsledky ve srovnání s kontrolami. Vzhledem k tomu, že smyslové deficity patří k nejčasnějším projevům iRBD, začal být předmětem recentního výzkumu také vzájemný vztah mezi smyslovými funkcemi, kognicí a morfologií mozku. Vzhledem k těmto nevyřešeným otázkám je cílem této práce poskytnout přehled nejnovějších poznatků a obohatit literaturu o výsledky čtyř původních studií, které se zabývají výše uvedenými mezerami ve výzkumu.

Teoretická část této práce poskytuje stručný přehled historie výzkumu RBD a současných klasifikačních systémů. Dále nastiňuje vývoj konceptu iRBD jako preklinického stadia alfa-synukleinopatií. Následující kapitoly podávají přehled současných poznatků o kognitivním profilu a strukturálních změnách mozku u iRBD se zvláštním důrazem na heterogenitu fenotypů a jejich důsledky pro pochopení této poruchy.

Empirická část práce si klade za cíl rozšířit poznání v oboru prostřednictvím čtyř původních studií, které se zabývají následujícími výzkumnými otázkami: Existuje specifický kognitivní profil charakteristický pro iRBD?; existují u iRBD společné a zjistitelné strukturální změny mozku?; jak spolu souvisí kognitivní deficity a strukturální změny mozku?; odpovídají kognitivní funkce za rozdíly v rozlišování barev mezi iRBD a kontrolami?; souvisí deficit barevného rozlišování u iRBD s dopaminergní denervací?; lze výkonnost v rozlišování barev vysvětlit morfometrickými parametry šedé a bílé hmoty mozkové?; je zhoršení paměti u iRBD sekundární k deficitu jiných kognitivních funkcí?; a odráží strukturální změny mozku účinky kognitivní zátěže během chůze?.

Ve všech těchto studiích se jako dominantní rys konzistentně objevovaly deficity v rychlosti zpracování informací, což je v souladu s nedávnými metaanalýzami a teoretickými modely. Ačkoli nebyly zjištěny žádné morfologické rozdíly na úrovni skupin, byly nalezeny robustní a interpretovatelné asociace mezi kognitivním výkonem a hustotou šedé hmoty v

pravé insule a putamenu napříč různými zobrazovacími modalitami. Dále nebyly potvrzeny hypotézy, které by naznačovaly, že deficity v rozlišování barev odrážejí kognitivní poruchy nebo jsou spojeny s markery zobrazování mozku. Studie 2 neodhalila významné souvislosti mezi rozlišováním barev a morfologií mozku ani dopaminergní deplecí. Tato zjištění spíše ukazují na senzorický původ deficitů v rozlišování barev, což je v souladu s předchozími důkazy o patofyziologických změnách na sítnici u alfa-synukleinopatií.

Kromě toho zjištění na vzorku pacientů s Parkinsonovou chorobou naznačují přítomnost odlišných nervových mechanismů, které jsou podkladem výkonu v tzv. dual-task úkolech, tj. interakcí mezi kognitivní zátěží a chůzí, což poskytuje další vhled do kognitivně-motorické interakce u alfa-synukleinopatií.

Celkově výsledky prezentované v této práci vrhají nové světlo na souhru mezi kognitivním profilem, senzorickými funkcemi a morfologickými nálezy MRI u iRBD. Zatímco některá zjištění je vhodné ověřit v budoucích studiích, jiná, jako například identifikace deficitů rychlosti zpracování a jejich potenciálních neuroanatomických korelátů, mohou mít již nyní praktický význam pro neuropsychologickou diagnostiku.

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10 List of Publications

10.1 Publications Related to the Thesis

1. Mala, C., **Havlik, F.**, Mana, J., Nepozitek, J., Dostalova, S., Ruzicka, E., Sonka, K., Keller, J., Jech, R., Dusek, P., Bezdicek, O., & Krupicka, R. (2024). Cortical and subcortical morphometric changes and their relation to cognitive impairment in isolated REM sleep behavior disorder. *Neurol Sci, 45*(2), 613-627. https://doi.org/10.1007/s10072-023-07040-z **[equal contribution, corresponding author, WOS: IF$_{2023}$ = 2.7; Q2]**
2. **Havlik, F.**, Malá, C., Dusek, P., Mana, J., Lorenzo Y Losada Ibarburu, V., Dostálová, S., Nepožitek, J., Peřinová, P., Růžička, E., Krupicka, R., Šonka, K., & Bezdicek, O. (in press). Colour Discrimination Deficit in REM Sleep Behavior Disorder: An Analysis of Dopaminergic Depletion, Cognition, and Brain Morphology. *Journal of Neural Transmission*. **[corresponding author, WOS: IF$_{2023}$ = 3.2; Q2]**
3. Wenke, Š., Mana, J., **Havlík, F.**, Cohn, M., Nikolai, T., Buschke, H., Nepožitek, J., Peřinová, P., Dostálová, S., Ibarburu Lorenzo Y Losada, V., Růžička, E., Šonka, K., Dušek, P., & Bezdicek, O. (2022). Characterization of memory profile in idiopathic REM sleep behavior disorder. *Journal of Clinical and Experimental Neuropsychology*, *44*(3), 237-250. https://doi.org/10.1080/13803395.2022.2107182 **[WOS: IF$_{2022}$ = 2.2; Q3]**
4. Krupicka, R., Mala, C., Netukova, S., Hubena, T., **Havlik, F.**, Bezdicek, O., Dusek, P., & Ruzicka, E. (2024). Impaired dual-task gait in Parkinson's disease is associated with brain morphology changes. *Journal of Neural Transmission*, *131*(12), 1389-1395. https://doi.org/10.1007/s00702-024-02758-2 **[WOS: IF$_{2023}$ = 3.2; Q2]**

10.2 Publications Unrelated to the Thesis

Hlavnicka, J., Mana, J., Bezdicek, O., Cihak, M., **Havlik, F.**, Skrabal, D., Bartosova, T., Sonka, K., Ruzicka, E., & Dusek, P. (2025). Four questions to predict cognitive decline in de novo Parkinson's disease. *NPJ Parkinsons Dis, 11*(1), 91. https://doi.org/10.1038/s41531-025-00958-5 **[WOS: IF$_{2023}$ = 6.7; Q1]**

Bezdicek, O., Mana, J., Ruzicka, **F., Havlik**, F., Fecikova, A., Uhrova, T., Ruzicka, E., Urgosik, D., & Jech, R. (2022). The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation.

Frontiers in Aging Neuroscience, 14, 886491. https://doi.org/10.3389/fnagi.2022.886491 **[WOS: IF$_{2022}$ = 4.8; Q2]**

Havlik, F., Michalec, J., Kalisova, L., Dechterenko, F., Chlebovcova, M., Vaskovicova, M., & Bezdicek, O. (2021). The normative data study of the Czech MATRICS consensus cognitive battery. *Clinical Neuropsychologist*, 1-15. https://doi.org/10.1080/13854046.2021.1962410 **[WOS: IF$_{2021}$ = 4.37; Q1]**

Havlik, F., Mana, J., Dusek, P., Jech, R., Ruzicka, E., Kopecek, M., Georgi, H., & Bezdicek, O. (2020). Brief Visuospatial Memory Test-Revised: normative data and clinical utility of learning indices in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 42*(10), 1099-1110. https://doi.org/10.1080/13803395.2020.1845303 **[WOS: IF$_{2020}$ = 2.47; Q3]**

Bezdicek, O., Michalec, J., Kalisova, L., Kufa, T., Dechterenko, F., Chlebovcova, M., **Havlik, F.**, Green, M. F., & Nuechterlein, K. H. (2020). Profile of cognitive deficits in schizophrenia and factor structure of the Czech MATRICS Consensus Cognitive Battery. Schizophr Res, 218, 85-92. https://doi.org/10.1016/j.schres.2020.02.004 **[WOS: IF$_{2020}$ = 4.93; Q1]**

11 List of Figures

12 List of Tables

13 Supplement

1. Mala, C., **Havlik, F.**, Mana, J., Nepozitek, J., Dostalova, S., Ruzicka, E., Sonka, K., Keller, J., Jech, R., Dusek, P., Bezdicek, O., & Krupicka, R. (2024). Cortical and subcortical morphometric changes and their relation to cognitive impairment in isolated REM sleep behavior disorder. *Neurol Sci, 45*(2), 613-627. https://doi.org/10.1007/s10072-023-07040-z **[equal contribution, corresponding author, WOS: IF_{2023} = 2.7; Q2]**
2. **Havlik, F.**, Malá, C., Dusek, P., Mana, J., Lorenzo Y Losada Ibarburu, V., Dostálová, S., Nepožitek, J., Peřinová, P., Růžička, E., Krupicka, R., Šonka, K., & Bezdicek, O. (in press). Colour Discrimination Deficit in REM Sleep Behavior Disorder: An Analysis of Dopaminergic Depletion, Cognition, and Brain Morphology. *Journal of Neural Transmission*. **[corresponding author, WOS: IF_{2023} = 3.2; Q2]**
3. Wenke, Š., Mana, J., **Havlík, F.**, Cohn, M., Nikolai, T., Buschke, H., Nepožitek, J., Peřinová, P., Dostálová, S., Ibarburu Lorenzo Y Losada, V., Růžička, E., Šonka, K., Dušek, P., & Bezdicek, O. (2022). Characterization of memory profile in idiopathic REM sleep behavior disorder. *Journal of Clinical and Experimental Neuropsychology*, *44*(3), 237-250. https://doi.org/10.1080/13803395.2022.2107182 **[WOS: IF_{2022} = 2.2; Q3]**
4. Krupicka, R., Mala, C., Netukova, S., Hubena, T., **Havlik, F.**, Bezdicek, O., Dusek, P., & Ruzicka, E. (2024). Impaired dual-task gait in Parkinson's disease is associated with brain morphology changes. *Journal of Neural Transmission*, *131*(12), 1389-1395. https://doi.org/10.1007/s00702-024-02758-2 **[WOS: IF_{2023} = 3.2; Q2]**