Cognitive Impairment in Lewy Body Diseases: Treatments and Assessments

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Abstract

This thesis explores the efficacy, and cognitive implications of pharmacological treatments for Lewy body diseases (LBD), alongside cognitive profiling and remote assessment methodologies. A network meta-analysis of 22 randomised controlled trials, involving over 3300 patients with Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), revealed that rivastigmine is likely to be the most effective treatment for cognitive and neuropsychiatric symptoms even though it is associated with significant adverse events. Experimental studies examining the effects of rivastigmine on eye movements and reward sensitivity demonstrated significant improvements in saccadic measures but no enhancement in reward sensitivity, suggesting a limited role for cholinergic modulation in reward processing. Cognitive profiling using remote online tools detected distinct deficits in attention, executive function, memory and language among Parkinson's disease (PD) and REM sleep behavioural disorder (RBD) patients, supporting the dual syndrome hypothesis of early dopaminergic and later cholinergic dysfunctions. The feasibility of remote cognitive testing in clinical trials was confirmed, with high completion rates indicating its potential for broader application despite challenges related to technical variability. A study examining the relationship between dopaminergic function and cognitive/motor performance found a double dissociation, with cognitive measures correlating with frontal dopamine transporter (DAT) uptake and motor measures correlating with striatal DAT uptake, reinforcing the role of these networks in cognitive and motor functions. This thesis highlights the importance of individualised treatment, the development of specialised cognitive tools and the integration of remote assessments into clinical practice. Future research should focus on extended longitudinal studies and advanced imaging techniques to further elucidate the progression of cognitive decline and optimise therapeutic strategies for LBD.

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What a journey this has been! As I write these words within the iconic Radcliffe Camera, at the heart of the city of dreaming spires, I am filled with profound reflection on an extraordinary experience—one that transcends the pursuit of a DPhil. This journey has been a lifetime experience, navigated through unprecedented times, and it will remain etched in my memory forever.

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Dedication

Now, I would like to dedicate my PhD to my idol, teacher, and my late grandfather, Falah Mubarak Al Hajraf. A man who guided, inspired, and encouraged us to pursue and foster knowledge. Every day, as I would greet him on my way to and from school, he would remind me, “Take great care of your education.” He would often recite the verse of the Arab poet: “Knowledge builds homes without pillars, while ignorance destroys the homes of glory and honor.” Born on 24th August 1922, we lost him on 24th August 2015, and now, as fate would have it, I am submitting my thesis on this very anniversary. I hope I have made him proud, and that his legacy will live on, inherited by future generations. He was the best grandfather one could ask for.

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Lastly, I dedicate this work to my brothers and sisters, and to our newest family member, Hajraf Khaled.

To My Dear Parents

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and

Seeta Khaled Faisal Al Hailam

وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ ۚ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا

“If you ventured in pursuit of glory,
don’t be satisfied with less than the stars.”

Al-Mutanabbi

“Only those who will risk going too far
can possibly find out how far one can go.“

T. S. Eliot

Oxford Parkinson's Disease Centre

This DPhil project was primarily conducted at the Oxford Parkinson's Disease Centre (OPDC), established in February 2010 with a unique multidisciplinary research approach to understanding Parkinson's disease. The centre is home to the Oxford Discovery Cohort, one of the world's largest and most comprehensively characterised clinical cohorts of Parkinson's disease patients. The cohort includes over 1000 PD patients, more than 300 RBD patients, and 300 healthy controls. Unless otherwise indicated, participants in most studies within this DPhil project were drawn from the Discovery Cohort.

Data Acquisition and Contributions

The data presented in this thesis were primarily acquired by me, with the following specific exceptions and contributions:

Chapter 2 | Dr. Stephanie Hirschbichler contributed as a second reviewer for the network meta-analysis, ensuring the rigor and reliability of the review process.

Chapter 3 | The data from healthy controls used in this chapter were generously provided by Prof. Masud Husain's team and Dr. Kinan Muhammed, allowing for a comparison with the patient data I collected.

Chapter 4 |The online cognitive tool used for collecting remote cognitive data from our cohort was developed by Dr. Adam Hampshire's team at Imperial College London.

Ketone Clinical Trial: In this study, I was responsible for reviewing some patients during their initial visits and collecting online cognitive data. The motor assessments and in-clinic visits were conducted by the OPDC team, with Prof. Michele Hu and Dr. David Dearlove serving as the primary investigators.

Chapter 5 | The DAT scans discussed in this chapter were originally collected by the imaging team at the Oxford Parkinson's Disease Centre (OPDC) before I joined the team. I recruited 10 patients and conducted motor and cognitive assessments at the time of their scans. This work was done in collaboration with Prof. Masud Husain's team, who also performed additional cognitive assessments for apathy, which are not included in this thesis. Additionally, older DAT scans and associated cognitive and motor measures from the Discovery study were provided for my analysis. Descriptive reports were kindly provided by Dr. Kevin Bradley.

Abbreviations List

ACh	Acetylcholine
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer’s Disease Assessment Scale–Cognitive Subscale
ADLs	Activities of Daily Living
AEs	Adverse Events
ANOVA	Analysis of Variance
ANT	Attentional Network Task
BD	Twice a Day (Bis in die)
BDI	Beck Depression Inventory
CIBIC+	Clinician's Interview-Based Impression of Change with Caregiver Input
CHIEF-PD	Cholinesterase Inhibitors to Prevent Falls in Parkinson's Trial
CINs	Cholinergic Interneurons
ChEIs	Cholinesterase Inhibitors
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
COVID-19	Coronavirus Disease 2019
CSF	Cerebrospinal Fluid
DBS	Deep Brain Stimulation
DLB	Dementia with Lewy Bodies
D-KEFS	Delis-Kaplan Executive Function System
EEG	Electroencephalography
EMA	European Medicines Agency
FSS	Fatigue Severity Scale
GBA	Glucocerebrosidase
GPi	Globus Pallidus Interna
HADS	Hospital Anxiety and Depression Scale
HC/CON	Healthy Controls
HSD	Honestly Significant Difference
ICSD-3	International Classification of Sleep Disorders, Third Edition
iRBD/RBD	Idiopathic REM Sleep Behavior Disorder
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
LARS	Lille Apathy Rating Scale
LBD	Lewy Body Diseases
LDOPA	Levodopa
LEDD	Levodopa Equivalent Daily Dose
LRRK2	Leucine-Rich Repeat Kinase 2
MAO-B	Monoamine Oxidase B
MANCOVA	Multivariate Analysis of Covariance
mAChRs	Muscarinic Acetylcholine Receptors

MDS	Movement Disorder Society
MDS-UPDRS III	MDS Unified Parkinson's Disease Rating Scale Part III
MCI	Mild Cognitive Impairment
MDRS	Mattis Dementia Rating Scale
MIBG	Metaiodobenzylguanidine
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
NART	National Adult Reading Test
nAChRs	Nicotinic Acetylcholine Receptors
NMA	Network Meta-analysis
NMS	Non-Motor Symptoms
NMDA	N-Methyl-D-Aspartate (as in NMDA receptor antagonists)
NMSS	Non-Motor Symptoms Scale
NMSQuest	Non-Motor Symptoms Questionnaire
NPI	Neuropsychiatric Inventory
PCA	Principal Component Analysis
PD	Parkinson's Disease
PDD	Parkinson’s Disease Dementia
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PD-NC	Parkinson's Disease with Normal Cognition
PDQ	Parkinson's Disease Questionnaire
PET	Positron Emission Tomography
PIGD	Postural Instability Gait Difficulty
PPMI	Parkinson’s Progression Markers Initiative
PPN	Pedunculopontine Nucleus
QSBB	Queen Square Brain Bank
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
RCT	Randomized Controlled Trial
ROI	Region of Interest
RT	Reaction Time
SAEs	Serious Adverse Events
SCD	Subjective Cognitive Decline
SC	Superior Colliculus
SMD	Standardized Mean Difference
SPECT	Single Photon Emission Computed Tomography
STN	Subthalamic Nucleus
SUR	Standardized Uptake Ratio
tDCS	Transcranial Direct Current Stimulation
TMT-B	Trail Making Test Part B
TUG	Timed Up and Go
V-PSG	Video Polysomnography

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Chapter | 1

Chapter 1 | Introduction

1.1 Parkinson's Disease (PD)

Parkinson's disease (PD) is a multisystem, heterogeneous neurodegenerative disease, considered the second most common cause of neurodegeneration following Alzheimer's disease (AD). It is named after Dr James Parkinson from Hoxton, London, who first formally described the disease in his famous article 'An Essay on the Shaking Palsy' in 1817. Based on his observations, he defined the condition as follows:

> Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured. (Parkinson, 1817)

Nearly half a century later, Dr Jean-Martin Charcot presented a more thorough description of the disease. He gave the disease its current name and recognised slowness in executing movements (bradykinesia) rather than muscle weakness to be the cardinal feature of the condition. He was the first to describe the cognitive effects of PD, stating in his famous lectures on diseases of the nervous system in 1875, 'At a given point, the mind becomes clouded and the memory is lost' (Charcot, 1877). Much progress has been made over the last two centuries in shedding light on the disease; however, the condition is still not fully understood, and no cure has been discovered yet.

Parkinson's disease is more than a movement disorder. In addition to its four cardinal features (resting tremor, bradykinesia, rigidity and postural instability), it has cognitive, behavioural, sleep and autonomic features (Poewe, 2008). Both the phenotype and prognosis of PD show significant variation (Fereshtehnejad et al., 2015; Lawton et al., 2015; Lewis et al., 2005; Selikhova et al., 2009). PD also has a broad spectrum of cognitive features ranging from subjective cognitive decline (SCD) and mild cognitive impairment (PD-MCI) at

one end to Parkinson's disease dementia (PDD) at the other (Aarsland et al., 2021).

1.1.1 Epidemiology

PD affects around 6 to 10 million people worldwide (Dorsey et al., 2018; Maserejian N et al., 2020). Approximately 145,000 individuals in the United Kingdom have PD (0.21% of the population), and this number is expected to reach 250,000 by 2065 (Parkinson's UK, 2017). In Kuwait, around 1500 individuals (0.1% of the population) suffer from the disease (Safiri et al., 2023).

The estimated prevalence of PD in developed countries is 0.3% in the general population, increasing with age to nearly 1% in people over the age of 60 years and 3% in those over 80 years old (de Lau & Breteler, 2006; Lee & Gilbert, 2016). The overall annual incidence ranges from 5 to 35 per 100,000 people (Alves et al., 2009; Linder et al., 2010; Simon et al., 2020; Twelves et al., 2003) and could reach over 250 per 100,000 people among those over the age of 80 years (Hirsch et al., 2016).

PD tends to be more prevalent among men than among women, with men being approximately 1.5 times more likely to have the disease than women (Moisan et al., 2016; Wooten et al., 2004). This disparity may be attributed to several factors: men are often more exposed to occupational and environmental hazards that can increase the risk of developing PD (Moisan et al., 2015; Narayan et al., 2017; Ritz et al., 2016); women may benefit from the neuroprotective effect of oestrogen (Bourque et al., 2019; Saunders-Pullman, 2003); and potential genetic influences linked to the X chromosome may play a role in the disease's distribution between genders (Elbaz et al., 2016; Pankratz et al., 2002; Wooten et al., 2004).

Geographical analysis shows that PD is less prevalent in Asian and African countries than in Western nations (Dotchin et al., 2008; Marras et al., 2018; Muangpaisan et al., 2009; Okubadejo et al., 2006; Pringsheim et al., 2014; von Campenhausen et al., 2005). This trend

could be attributed either to methodological differences in study design, demographic characteristics and diagnostic criteria or to regional variations in underlying genetics or environmental factors (Abbas et al., 2018).

The prevalence and incidence of PD are significantly influenced by age, a major risk factor for the disease (Reeve et al., 2014). The increase in the ageing population worldwide with the advancement of global healthcare systems is forecasted to lead to a twofold increase in the number of individuals affected by PD within the coming 20 years, a phenomenon that could be described as a 'PD pandemic' (Dorsey & Bloem, 2018).

1.1.2 Pathophysiology

PD is a complex, heterogeneous, progressive neurodegenerative disease. Its main pathological hallmarks are the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of alpha-synuclein aggregates known as Lewy bodies and Lewy neurites (Dauer & Przedborski, 2003). Recent advances in genetics and molecular pathology have significantly enhanced our understanding of PD's pathogenesis, revealing a multifactorial aetiology that includes genetic mutations, environmental factors, abnormal protein aggregation, mitochondrial dysfunction, lysosomal and endosomal abnormalities, oxidative stress and neuroinflammation (Dickson, 2018; Morris et al., 2024; Schapira & Jenner, 2011). These insights come from studies on familial forms of PD, sporadic cases, and various cellular and animal models, highlighting the complex nature of the disease's onset and progression. Notably, familial cases account for 5-15% of PD (Balestrino & Schapira, 2020), with mutations in over 20 genes implicated in the disease, including the common Glucocerebrosidase (GBA) and Leucine Rich Repeat Kinase 2 (LRRK2) mutations (Blauwendraat et al., 2020; Tran et al., 2020).

Braak's hypothesis is a widely recognised staging system for PD progression (Braak et al., 2003). It posits a sequential involvement of brain regions starting from the lower brainstem and olfactory bulb, advancing through the midbrain, and ultimately reaching cortical areas (Figure 1.1). In other words, this hypothesis suggests that Lewy bodies follow a predictable topographical progression, potentially explaining the clinical evolution from early non-motor to later motor symptoms (Goldman & Postuma, 2014). Complementing this view, the prion-like hypothesis proposes a mechanism for the spread of the pathology where misfolded alpha-synuclein proteins propagate between neurons in a manner akin to infectious prions, facilitating the progression of PD across neural networks (Brundin et al., 2008; Brundin & Melki, 2017). This is supported by evidence of alpha-synuclein aggregates in transplanted neurons in PD patients, indicating cell-to-cell spread (Kordower et al., 2008; Li et al., 2008).

While the Braak and prion-like hypotheses offer insights into the 'where' and 'how' of PD progression, the theories of top-down versus bottom-up progression address the 'wherefrom', debating the initial site of pathological onset (Borghammer & Van Den Berge, 2019; Leclair-Visonneau et al., 2020; Van Den Berge & Ulusoy, 2022). The bottom-up theory (gut-first) aligns with Braak's staging, suggesting that PD starts in peripheral organs including the gut or the lower brain regions and ascends to the cortex, potentially explaining early autonomic and olfactory dysfunction. Conversely, the top-down theory (brain-first) suggests that PD might initiate in the cortical areas, descending to affect the brainstem and peripheral nervous system, a perspective that could account for the cognitive impairments observed in some patients early in the disease course. Integrating these theories provides a comprehensive framework for understanding PD pathology, emphasising the disease's heterogeneity and the multifaced nature of its progression.

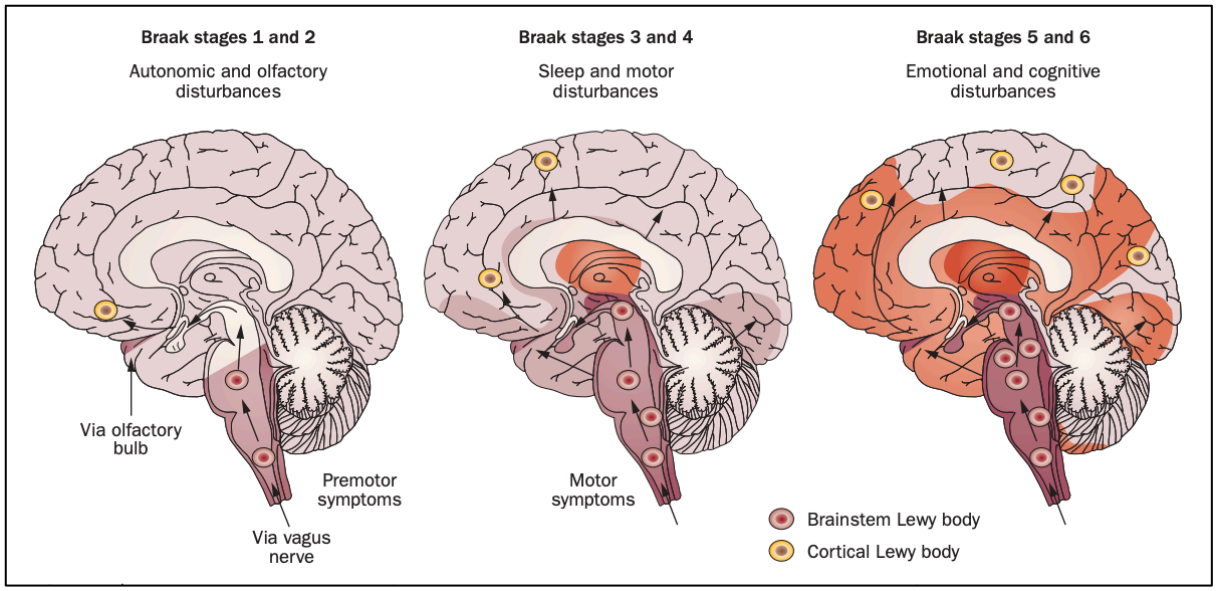


Figure 1.1 | The Braak staging system of Parkinson's Disease. This figure illustrates the Braak staging model for PD, showing the sequential spread of Lewy body pathology, beginning at the initiation sites in the medulla oblongata and olfactory bulb and progressing to late infiltration of pathology into cortical regions. The red-shaded areas highlighted the affected regions at each stage of the disease. Reproduced with permission from (Doty, 2012; Halliday et al., 2011).

1.1.3 Motor Symptomology

PD is the most common hypokinetic movement disorder, characterised by four cardinal symptoms: bradykinesia, tremor, rigidity and postural instability. Research suggests that approximately 60–80% of dopaminergic neurons in the nigrostriatal pathway are depleted by the time these hallmark motor symptoms emerge (Sveinbjornsdottir, 2016). Bradykinesia, defined as a progressive reduction in the speed and amplitude of repetitive alternating movements, is a prerequisite for diagnosis. It is often accompanied by other hypokinetic manifestations like akinesia, marked by a limited range of motion and difficulty initiating movements, and hypomimia (reduced facial expressions) (Jankovic, 2008). Tremors in PD, primarily resting tremors noticeable when the muscle is relaxed, are distinct from kinetic (observed during movement) and postural (difficulty maintaining a stable posture against gravity) tremors, which are more typical of essential tremor (Bhidayasiri, 2005). The classical PD tremor, often described as 'pill-rolling' due to its characteristic thumb and finger

motion, generally diminishes with movement and re-emerges in new static positions as a 're-emergent tremor' (Dirkx et al., 2018). Rigidity involves perceptible stiffness reported by patients, with clinicians assessing this symptom based on the resistance encountered during passive muscle stretching (cogwheel with tremor). Postural instability, a sign of later-stage PD, signifies a broader differential diagnosis when presenting early and is thus not a prerequisite for diagnosis according to the Movement Disorder Society (MDS) criteria (Postuma, Berg, et al., 2015).

Given PD's clinical variability, significant efforts have been made to categorise patients based on their motor symptoms to identify distinct phenotypes to better understand disease progression and outcomes (De Pablo-Fernández et al., 2019; Fereshtehnejad et al., 2015). Traditionally, PD clinical phenotypes have been classified into tremor-dominant and postural instability/gait difficulty categories, facilitating research into disease progression and risk factors (Stebbins et al., 2013; Thenganatt & Jankovic, 2014). A data-driven analysis of the Oxford Discovery and Tracking Parkinson's cohorts identified four distinct clusters: one with rapid motor progression and symmetrical symptoms, cognitive decline, postural hypotension, and poor olfaction; a second with mild motor symptoms and non-motor symptoms (NMS); a third marked by severe motor symptoms, sleep problems and psychological distress; and a fourth with slow progression and a tremor-dominant unilateral presentation. These phenotypes exhibit varied responses to levodopa, the standard PD treatment (Lawton et al., 2018).

To assess motor symptom severity in PD, the Hoehn and Yahr Staging Scale and the Unified Parkinson's Disease Rating Scale (UPDRS) Part III are widely used. The Hoehn and Yahr Scale delineates PD progression into five stages, from mild unilateral symptoms in Stage 1 to severe disability in Stage 5 (Hoehn & Yahr, 1967). On the other hand, the UPDRS

provides a more detailed evaluation of motor symptoms, allowing clinicians to quantify impairment and monitor disease progression over time (Goetz, Tilley, et al., 2008).

1.1.4 Non-Motor Symptomology

NMS in PD constitute a significant component of the disease's complexity and contribute substantially to overall morbidity (Pfeiffer, 2016). Evidence suggests that the impact of NMS on the quality of life may surpass that of motor symptoms (Li et al., 2010; Martinez-Martin et al., 2011; Prakash et al., 2016). Virtually every patient with PD will experience one or more NMS (Rodriguez-Blazquez et al., 2021), which, intriguingly, may manifest a decade or more prior to the onset of classical motor symptoms (Hawkes et al., 2010; Schrag et al., 2015).

NMS in PD are diverse, extending from olfactory deficits to psychiatric disturbances, sleep-related disorders, and cognitive and sensory changes (Chaudhuri, Healy, et al., 2006). Symptoms such as hyposmia are noteworthy for their potential to appear significantly before motor manifestations, providing a window for early therapeutic intervention during a critical prodromal phase (Ponsen et al., 2004). Common NMS include but are not limited to autonomic dysfunctions such as constipation, erectile dysfunction, postural hypotension and urinary symptoms (Chen et al., 2020). Sleep-related disorders, such as rapid eye movement (REM) sleep behaviour disorder (RBD) and excessive daytime sleepiness, are common and have been reported to precede motor symptoms by over a decade (Claassen et al., 2010; Pont-Sunyer et al., 2015; Savica et al., 2010). Moreover, neuropsychiatric manifestations, particularly depression, apathy and anxiety, often arise well before PD is clinically diagnosed (Schrag et al., 2015; Weintraub et al., 2022). Cognitive deficits are also common at the point of diagnosis, with estimates suggesting that 20–42% of patients exhibit PD-MCI (Weil et al., 2018) and approximately 10% may progress to PDD within 3–5 years (Williams-Gray et al.,

2007). It is also noted that NMS can fluctuate and often exhibit a temporal correlation with motor fluctuations, particularly manifesting during motor 'off' periods, which frequently correspond to the waning effects of dopaminergic medications (Martínez-Fernández et al., 2016).

Regrettably, NMS are frequently overlooked or underappreciated in routine clinical assessments, which can lead to delays in diagnosis and suboptimal patient care even though many of these symptoms are amenable to treatment and can be mitigated to improve clinical outcomes (Chaudhuri & Odin, 2010; O'Sullivan et al., 2008). To this end, specialised tools such as the Non-Motor Symptoms Questionnaire (NMSQuest) (Chaudhuri, Martinez-Martin, et al., 2006) and the Non-Motor Symptoms Scale (NMSS) (Chaudhuri et al., 2007) have been developed to enhance the recognition and management of NMS. Prioritising the early identification and comprehensive management of NMS is paramount for ameliorating patient outcomes and alleviating the broad burden of PD.

1.1.5 Assessments and Diagnosis

The diagnosis of PD primarily remains clinical, relying heavily on the assessment of motor symptoms and their progression over time. Two pivotal diagnostic criteria have been established to aid clinicians in the identification and management of PD: the Queen Square Brain Bank (QSBB) criteria established in 1992 (Hughes et al., 1992) and the MDS Clinical Diagnostic Criteria for PD introduced in 2015 (Postuma, Berg, et al., 2015). Additionally, earlier this year, two new research diagnostic criteria were introduced to biologically redefine and stage PD (Höglinger et al., 2024; Simuni et al., 2024).

Despite the availability of these clinical criteria, misdiagnosis is not uncommon, with error rates ranging from 15% to 24% across different studies (Tolosa et al., 2021). This variance is partly due to the overlap in PD symptoms with those of other forms of

parkinsonism known as ‘atypical parkinsonian syndromes’ (McFarland, 2016). A meta-analysis incorporating data from 11 clinicopathological investigations revealed that the overall accuracy of clinically diagnosing PD stands at 80.6% (Rizzo et al., 2016).

To refine diagnosis and reduce misclassification, ancillary investigations are frequently utilised (Berardelli et al., 2013). Single-photon emission computed tomography (SPECT) imaging can confirm dopamine dysfunction, a hallmark of PD, providing supportive evidence when clinical uncertainty exists. Magnetic resonance imaging (MRI) plays a crucial role in ruling out alternative causes of parkinsonism, including vascular parkinsonism and multiple system atrophy (MSA). Moreover, genetic testing becomes a valuable tool in familial PD cases, where a family history may indicate a hereditary component. These tools have now been integrated into the recent biological classification and research diagnostic criteria, together with alpha-synuclein biomarkers (Höglinger et al., 2024; Simuni et al., 2024). Overall, while clinical criteria provide the foundation for PD diagnosis, the integration of these ancillary investigations can significantly improve diagnostic accuracy, facilitating the early and appropriate management of the disease.

1.1.6 Management and Treatment

PD management is multifaceted, focusing on symptom control, quality of life and a multidisciplinary approach to care. The mainstay of symptomatic pharmacological treatment is the dopamine precursor levodopa, which has been shown to offer significant mobility benefits and improve activities of daily living (Fox et al., 2018). Recent evidence suggests that the early initiation of levodopa, especially in younger patients with prominent tremors, may provide persistent benefits over time, contrary to past concerns about the risks of early use (Gray et al., 2014). Dopamine agonists are also used as first-line therapies but come with a caveat; over 40% of patients treated with these medications may develop impulse control

disorders, which pose significant management challenges (Corvol et al., 2018). Adjunctive therapies to levodopa, such as monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors, have been employed to prolong the benefits of levodopa, particularly by reducing 'off' periods and contributing to more stable symptom control (Regensburger et al., 2023).

When conventional oral pharmacotherapy fails to adequately control symptoms, advanced therapies such as deep brain stimulation (DBS), MRI-guided focused ultrasound and levodopa-carbidopa enteral suspensions may be considered. These treatments are shown to be particularly beneficial for patients who have medication-responsive motor symptoms but suffer from complications like off periods or dyskinesia that are unresponsive to medication adjustments (Armstrong & Okun, 2020).

The role of nonpharmacological interventions cannot be overstated. They complement pharmacological treatments and may include a variety of exercises ranging from aerobic and resistance training to balance and gait exercises. These interventions, along with speech, occupational and physiotherapy, are integral to managing the motor aspects of PD and improving gait and balance (Mak et al., 2017; Ramig et al., 2018; Sturkenboom et al., 2014; Tomlinson et al., 2013). Ongoing research into high-intensity exercise suggests its potential to modify disease progression, although further study is required (Schenkman et al., 2018; van der Kolk et al., 2019).

A holistic and multidisciplinary approach is essential for the effective management of PD as it ensures that both motor symptoms and NMS are adequately addressed. The inclusion of specialists from various disciplines allows for a comprehensive treatment plan that aligns with the individual requirements and priorities of each patient (Bloem et al., 2021). Currently, no pharmacological therapies that can modify disease progression are

available. Yet, ongoing research is dedicated to developing disease-modifying therapies, highlighting the dynamic nature of PD management and the potential for future treatment breakthroughs (McFarthing et al., 2024)(Figure 1.2).

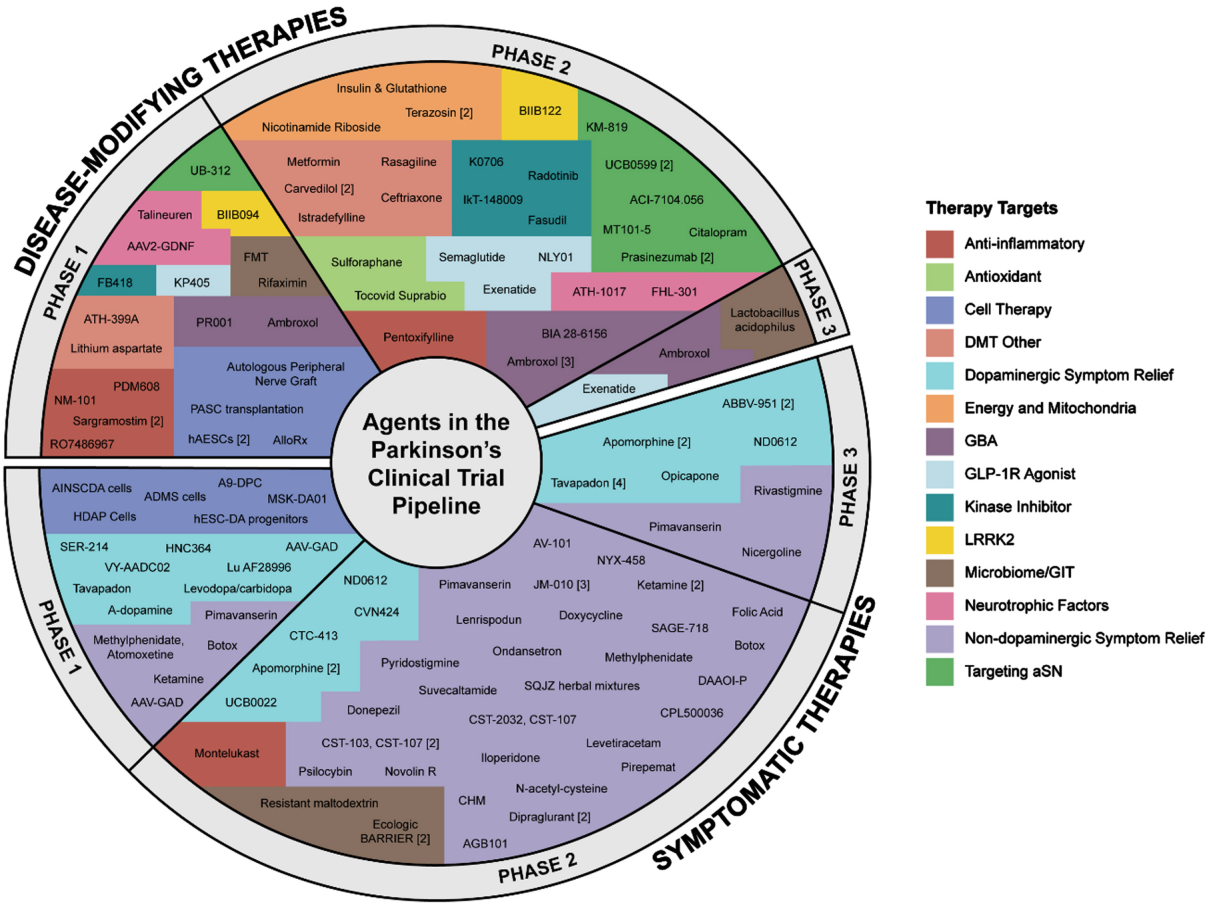


Figure 1.2 | A schematic representation of all agents currently in active clinical trials for PD, as registered on ClinicalTrials.gov (updated 31st January 2024). A toral of 107 agents are being tested across 136 trials. The pie chart illustrates the distribution of trials by phase and type: DMT [Phase 1 (16%), Phase 2 (26%), Phase 3 (2%)] and ST [Phase 1 (16%), Phase 2 (26%), Phase 3 (2%)]. Reproduced with permission from (McFarthing et al., 2024).

1.2 Cognitive Impairment in PD

Cognitive impairment is a common and complex feature of PD. It can manifest at various stages of the disease trajectory, occurring before disease onset (Fengler et al., 2017), concurrently or, commonly, years after diagnosis as the disease progresses (Gonzalez-Latapi et al., 2021). The spectrum of cognitive impairment in PD ranges from SCD and PD-MCI to its most severe form, PDD (Aarsland et al., 2021) (Figure 1.3). SCD entails self-perceived cognitive decline without objective evidence of impairment in standardised cognitive assessments and can increase the risk of subsequent PD-MCI or PDD (Dujardin et al., 2010; Erro et al., 2014; Galtier et al., 2019; Purri et al., 2020). PD-MCI, which is a transitional phase between normal cognition and dementia like in AD (Petersen et al., 1999), involves a gradual decline in cognitive function, either self-reported by the patient or noted by clinicians or informants, with discernible deficits in cognitive assessments (Weil et al., 2018). These deficits may affect single or multiple cognitive domains, including attention, memory, and executive and visuospatial functions. On the other hand, PDD entails cognitive impairment severe enough to significantly disrupt daily functioning, extending beyond the impairment caused by the motor symptoms associated with the disease (Goetz, Emre, et al., 2008). These cognitive declines in PD have significant implications for not only the patients but also their caregivers. The following quotes from (1) a patient and (2) a caregiver provide a glimpse into the profound effects of cognitive decline on their lives (Goldman et al., 2018):

(1) I wish that the doctor had told me that cognitive changes could be one of the results of the disease. My clinic visits have focused much more on physical signs and symptoms. The few times cognition has been addressed; the comments were very brief.

(2) The most bothersome is attention, which we call ‘chasing rabbits’ at our house. Early on this manifested as flitting from task to task without completion. However, cognitive symptoms have started to affect communication, which, in turn, affects our relationship.

In the following sections, we explore the complexities of cognitive impairment in PD, examining its diagnostic criteria, prevalence, clinical manifestations, underlying mechanisms and implications for patient care.

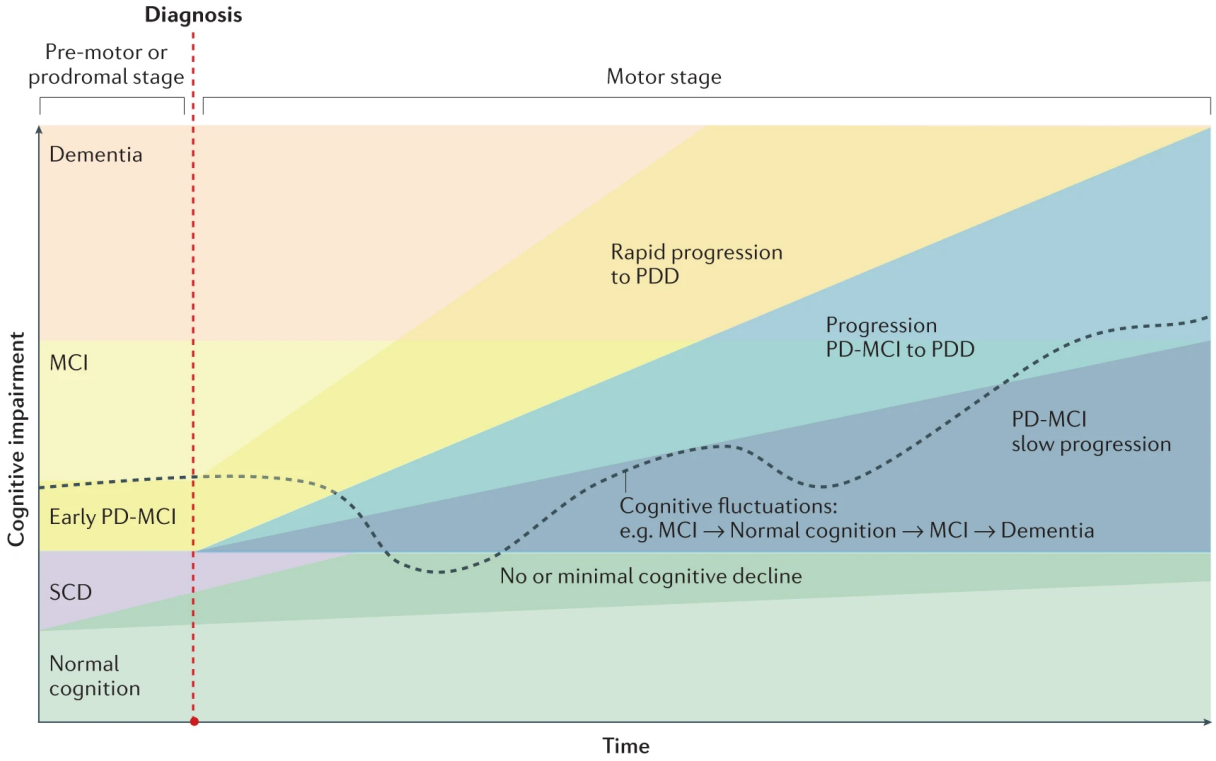


Figure 1.3 | The spectrum of cognitive impairment in PD, and the heterogenous nature of its progression over time. Reproduced with permission from (Aarsland et al., 2021).

1.2.1 Diagnostic Criteria

Establishing diagnostic criteria for PD-MCI has been challenging, with definitions and evaluations varying over time. To address this issue, the MDS outlined specific inclusion and exclusion criteria, along with guidelines for categorisation into Level I and Level II classifications (Litvan et al., 2012). The inclusion criteria are adherence to standardised diagnostic criteria for PD, the observation of a gradual decline in cognitive ability within the PD context and evidence of cognitive deficits not significantly interfering with functional independence. The exclusion criteria are the presence of PDD, other primary explanations and comorbid conditions affecting cognitive testing. The Level I (abbreviated) criteria denote

impairment on a scale of global cognitive abilities or impairment in at least two tests during a limited neuropsychological assessment, while the Level II (comprehensive) criteria involve neuropsychological testing covering two assessments within each of the five cognitive domains: attention and working memory, language, memory, executive functions and visuospatial skills. An individual meets the Level II criteria if they exhibit impairment on at least two neuropsychological tests, either within a single cognitive domain or across two different domains (Litvan et al., 2012).

In the past, PDD lacked specific and operationalised diagnostic criteria, often being categorised under 'dementia due to other general medical conditions' in the DSM IV (American Psychiatric Association, 1994), with a descriptive rather than diagnostic focus on PDD. As potential treatments for PDD emerged and clinical trials progressed, establishing precise diagnostic criteria became critical for the inclusion of homogeneous patient groups in research, understanding the natural history of PDD and conducting more accurate clinicopathological studies. Hence, the MDS assembled a Task Force to define clinical diagnostic criteria for 'possible' and 'probable' PDD in 2007 (Emre et al., 2007), which encompassed the core features, associated manifestations and exclusion criteria summarised in Table 1.1. This was followed by recommendations from the Task Force, which emphasised operationalising PDD diagnosis through a two-tiered assessment framework adaptable to the clinician's expertise and the specific clinical context. The initial level provides a straightforward battery of tests for general practitioners, while the second level offers a more detailed examination of cognitive impairments for precise diagnosis, clinical monitoring or research participation (Dubois et al., 2007).

I. Core features

(1) Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria

(2) A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

(1) Cognitive features
- Attention: impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
- Executive functions: impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
- Visuospatial functions: impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
- Memory: impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
- Language: core functions largely preserved. Word-finding difficulties and impaired comprehension of complex sentences may be present

(2) Behavioral features
- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
- Changes in personality and mood including depressive features and anxiety
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
- Excessive daytime sleepiness

III. Features which do not exclude PDD, but make the diagnosis uncertain
- Coexistence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g., presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which when present make it impossible to reliably diagnose PDD
- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  - Acute confusion due to (a) systemic diseases or abnormalities or (b) drug intoxication
  - Major depression according to DSM-IV
- Features compatible with "probable vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Table 1.1 | Summary of core features, associated clinical features, and exclusion criteria for diagnosing PDD, reproduced with permission from (Bilgiç et al., 2013; Emre et al., 2007) . **Probable PD-D:** Core features required, with typical cognitive deficits in at least two cognitive domains, presence of at least one behavioural symptom (optional), and absence of Group III and IV features. **Possible PD-D:** Core features required, with atypical cognitive impairment or Prescence of Group III features, and absence of Group IV features. Behavioural symptoms may or may not be present.

1.2.2 Prevalence

The estimated point prevalence of PDD is reported to be between 24% and 31% (Aarsland et al., 2021; Aarsland et al., 2005). Research from the famous Sydney multicentre longitudinal study indicates that the cumulative prevalence of PDD escalates with the progression of the disease to about 28% within 5 years, nearly doubling to 48% after 15 years and reaching 83% following 20 years of diagnosis (Hely et al., 2008). Different incidence rates of dementia in PD patients have been reported (Nicoletti et al., 2019; Williams-Gray et al., 2013), with a widely accepted estimate of around 100 per 1000 patient-years (Aarsland et al., 2001; Marder et al., 1995; Perez et al., 2012). This suggests that annually, nearly 10% of individuals with PD are likely to develop dementia, a rate that is four to six times higher than in those without PD (Aarsland et al., 2001; de Lau et al., 2005; Garcia-Ptacek & Kramberger, 2016; Hobson & Meara, 2004).

On the other hand, the prevalence of PD-MCI is highly variable, primarily due to the different diagnostic criteria used across studies. Using the MDS Level II criteria for newly diagnosed and early-stage PD patients, prevalence rates range from 20% to 40% (Broeders, de Bie, et al., 2013; Nicoletti et al., 2019; Pedersen et al., 2017). Further diversification arises from Yarnall et al.'s (2014) application of varying cognitive test thresholds, resulting in prevalence rates of 65.8%, 42.5% and 22.4% below 1, 1.5 and 2 standard deviations, respectively (Yarnall et al., 2014). A meta-analysis by Baiano et al. (2020) encompassing 41 studies and over 7000 PD patients estimates PD-MCI prevalence at roughly 40%, with the multiple domain subtype occurring in about 31% of cases (Baiano et al., 2020). Nicoletti et al. (2019) reported an incidence rate of 148 per 1000 patient-years for MCI among PD patients (Nicoletti et al., 2019). Moreover, a population-based study showed a cumulative

incidence of PD-MCI of 9.9% after 1 year and 28.9% after 5 years for those initially cognitively unimpaired (Pedersen et al., 2017).

1.2.3 Neurobiology and Pathophysiology

The pathophysiology and neurobiology of cognitive impairment in PD are complex and not yet fully understood. Key neuropathological features include the accumulation of Lewy bodies composed of alpha-synuclein, the presence of coexistent AD pathology with amyloid-beta plaques and neurofibrillary tau tangles, often accompanied by microvascular damage and argyrophilic inclusions (Halliday et al., 2014). These abnormal protein accumulations, particularly in cortical areas, are strongly associated with cognitive decline and dementia in PD (Smith et al., 2019). Additionally, oxidative stress, neuroinflammation and mitochondrial dysfunctions play a significant role in the cognitive impairment observed in PD (Irwin et al., 2013).

The cellular mechanisms driving PD-related cognitive impairment reflect the disease's intricate pathology, involving disruptions across multiple neural networks that progressively deteriorate over time (Gratwicke et al., 2015). While the impairment of dopaminergic circuits in the basal ganglia and prefrontal cortex, for example, contributes to cognitive decline (Narayanan et al., 2013), it does not fully account for the range of cognitive symptoms observed. Cholinergic system dysfunctions, especially in the forebrain, are also pivotal in the cognitive decline seen in PD (Bohnen & Albin, 2011). This multifaceted pathology highlights the importance of neurotransmitter systems beyond dopamine, which are explored in greater detail later in this chapter, focusing on how these dysfunctions contribute to various aspects of cognitive impairment in PD.

1.2.4 Cognitive Profile

The cognitive profile of PD is highly variable, encompassing a range of deficits that affect various cognitive domains and associated with dysfunction in multiple neurotransmitter systems (Brandao et al., 2020). This heterogeneity, observed across various studies, indicates the potential presence of distinctive cognitive phenotypes within PD (Aarsland & Kurz, 2010; Janvin et al., 2006; Watson & Leverenz, 2010). Early cognitive changes generally include attention deficits, executive dysfunctions, and alterations in visuospatial functioning (Gonzalez-Latapi et al., 2021; Muslimovic et al., 2005). Language abilities, in contrast, often remain intact and less affected (Caviness et al., 2007; Emre, 2015; Yarnall et al., 2014). However, deficits may occur in aspects of fluency (Azuma et al., 2003; Zec et al., 1999), becoming more pronounced with the progression to dementia (Henry & Crawford, 2004). Moreover, early-stage memory complaints, when present, tend to be mild and typically involve challenges with the retrieval of episodic information rather than recognition which can also present later in the disease (Bezdicek et al., 2019; Brønnick, 2015; Costa et al., 2014; Fields, 2017).

When comparing AD to PDD, the cognitive profiles reveal distinct patterns. AD is typically characterised by more pronounced deficits in declarative and episodic memory due to medial temporal pathology, evident early in disease process (Aarsland, Litvan, et al., 2003; Smirnov et al., 2020). In contrast, PDD often exhibits more substantial executive and attentional dysfunctions and visuospatial impairments, which are believed to result (as explained earlier) from dopaminergic deficits and a later cholinergic degeneration, respectively (Kehagia et al., 2010). Additionally, while language impairments are common in AD, particularly affecting semantic verbal fluency, PDD-related language deficits are often

secondary to executive or motor dysfunction rather than primary linguistic processes (Cummings et al., 1988; Emre et al., 2007; Henry et al., 2004; Reilly et al., 2010).

In an attempt to elucidate the diverse spectrum of cognitive impairment observed in PD, the 'dual syndrome hypothesis' was introduced (Kehagia et al., 2013). This framework posits that impairments manifest along two dimensions: one involves the fronto-striatal circuits and occurs early in the disease, where dopaminergic modulation leads to deficits in attention, working memory and executive functions; the other relates to deterioration in the posterior cortical regions occurring later in the disease, where significant cholinergic loss predominates, manifesting as deficits in memory, visuospatial functions and language.

The dual syndrome hypothesis was based on observations from the CamPaIGN study, which showed these two distinct patterns of cognitive impairment with the longitudinal follow-up of the incident PD cohort (Williams-Gray et al., 2009). It underscores the interplay of neurotransmitters affecting cognition in PD's progression, highlighting the value of early cognitive assessments to guide management strategies despite the lack of disease-modifying options.

1.2.5 Assessments

Assessments of cognitive impairment in PD are essential for tailoring patient care and managing the disease's progression effectively. As recommended by the MDS, initial screenings typically utilise the Montreal Cognitive Assessment (MoCA), Mattis Dementia Rating Scale Second Edition (MDRS-2) and Parkinson's Disease – Cognitive Rating Scale (PD-CRS) (Litvan et al., 2012). Among these, the MoCA is commonly used and noted for its superior sensitivity compared to the Mini-Mental State Examination (MMSE), making it a more effective tool for the early detection of cognitive decline (Hu et al., 2014). Following these screenings, comprehensive neuropsychological evaluations are conducted to delineate

the nature and extent of cognitive deficits across various domains, including memory, attention, executive functions, language and visuospatial skills. These assessments not only help in diagnosing PDD but also play a critical role in distinguishing PDD from other forms of dementia, such as AD. Online computerised versions of these assessments are also available and offer potential advantages in terms of efficiency and cost (Marras et al., 2014). Serial assessments can track cognitive changes over time, which is important for evaluating disease progression and the efficacy of treatments in randomised controlled trials (RCTs).

1.2.6 Treatment

The management of cognitive impairment in PD includes pharmacological and non-pharmacological treatments. Several RCTs have focused on dementia in PD, often including both PDD and DLB due to their clinical overlap.

Pharmacotherapy for dementia in PD primarily involves cholinesterase inhibitors (ChEIs) and is merely symptomatic. Rivastigmine is the only ChEI with definitively positive results in PDD, showing statistically significant but modest clinical effects on various cognitive and functional measures (Emre et al., 2004). It is the only drug approved by the FDA and EMA for mild-moderate PDD but not for PD-MCI. The ChEIs donepezil and galantamine were marked as 'possibly useful' by the 2019 MDS Evidence-Based Medicine Committee (Seppi et al., 2019). Donepezil has demonstrated improvements in cognitive performance in PDD patients, although the results are not consistent (Aarsland et al., 2002; Dubois et al., 2012; Ravina et al., 2005). No double-blind RCTs for galantamine in PDD have been conducted, although it has shown benefits in open-label trials (Aarsland, Hutchinson, et al., 2003; Litvinenko et al., 2008). Memantine, an NMDA receptor antagonist, is also commonly used but has been marked as 'investigational' due to mixed findings (Aarsland et al., 2009; Emre, Tsolaki, et al., 2010; Seppi et al., 2019).

Non-pharmacological approaches to managing cognitive impairment in PD encompass cognitive interventions, physical exercise and brain stimulation techniques. Cognitive training and rehabilitation, particularly multi-domain, computer-based training, have led to improvement in various cognitive functions in PD (Gavelin et al., 2022). However, a Cochrane review found no conclusive evidence supporting these benefits (Orgeta et al., 2020). Physical exercise, including aerobic and resistance exercises, may provide short-term benefits for global cognition, processing speed and executive function (da Silva et al., 2018; David et al., 2015; Picelli et al., 2016). Non-invasive brain stimulation techniques like transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have shown preliminary evidence for improving cognitive abilities, although further research is needed to establish their efficacy (Seppi et al., 2019; Trung et al., 2019). Invasive brain stimulation, specifically DBS, has been studied with mixed results. A small study has shown that bilateral DBS of the nucleus basalis of Meynert (NBM) is safe but not significantly effective in improving primary cognitive outcomes in patients with PDD, although neuropsychiatric symptoms may improve (Gratwicke et al., 2018). Similar results were found in another recent sham-controlled trial with DBS targeting the NBM in combination with the globus pallidus internus (GPi) in patients with PD-MCI (Sasikumar et al., 2022).

Numerous RCTs have been conducted or are currently in different phases for investigational pharmacological treatment, either repurposing existing drugs or exploring novel potential disease-modifying therapies. None have shown significant positive outcomes (Bayram et al., 2023; Sun & Armstrong, 2021).

1.3 Prodromal Phase of PD

1.3.1 Symptoms

The Oxford English Dictionary defines a prodrome as 'a symptom or sign, or a set of symptoms or signs, that is characteristic or premonitory of the onset of a disease; (also) an early phase of a disease in which its symptoms or signs are mild or non-specific' (OED 2024). In the context of PD, this prodromal phase is marked by mild or non-specific NMS that precede the classical motor symptoms by years (up to ~ 20 years) (Postuma & Berg, 2016). These symptoms include olfactory dysfunction, constipation, sleep disturbances such as RBD, depression, anxiety and autonomic dysfunction. In the following sections, we focus specifically on RBD, a key prodromal condition, and its cognitive manifestations.

1.3.2 RBD

RBD is a parasomnia typified by a loss of the muscle paralysis that normally occurs during the REM phase of sleep, leading to the physical enactment of dreams that may include vocalising and complex motor behaviours (Hu, 2020). Schenk and colleagues were the first to identify the disorder in humans in 1986, documenting a series of five patients who exhibited diverse sleep behaviours during REM sleep, along with increased limb twitching, irregular chin muscle control, and increased ocular activity and density (Schenck et al., 1986).

RBD is typically categorised into idiopathic RBD (iRBD), which has an unknown cause, and secondary RBD, which occurs in conjunction with other neurological disorders. iRBD is recognised as a precursor to alpha-synucleinopathies such as PD, DLB and MSA, potentially emerging up to 50 years prior to these conditions, with a median onset time of 25 years before neurodegenerative symptoms appear (Boeve et al., 2013; Claassen et al., 2010;

Postuma, Gagnon, et al., 2015). Around 50–75% of individuals with iRBD develop PD within a decade of their iRBD diagnosis, and over 80% are eventually diagnosed with a neurodegenerative disease, with an overall annual conversion rate of 6.3% (Iranzo et al., 2014; Iranzo et al., 2013; Postuma et al., 2019; Schenck et al., 2013). This challenges the term 'idiopathic' with regard to RBD and emphasises its significance as an early warning sign of these disorders, suggesting a shared pathophysiology. Therefore, it is not surprising that RBD symptoms have been observed in as many as 70% of PD patients (Zhang et al., 2017). For clarity and consistency, this thesis will henceforth use the term 'RBD' to refer specifically to iRBD.

1.3.3 Cognition in RBD

This section delves into the cognitive profile associated with RBD, highlighting how these cognitive deficits often precede and predict the development of neurodegenerative diseases.

The prevalence of cognitive impairments in individuals with RBD is notably high, often serving as an early warning sign of potential neurodegenerative diseases. Cross-sectional research has shown that up to 50% or even more of RBD patients exhibit MCI, particularly in domains such as attention and executive functions (Gagnon et al., 2009; Nagy et al., 2023). These impairments are often present even before the other clinical symptoms of neurodegeneration appear. For example, Massicotte-Marquez et al. (2008a) found that RBD patients demonstrated poorer performance in attention, executive functions and verbal memory than healthy controls (HCs) (Massicotte-Marquez, Decary, et al., 2008). In addition, Ferini-Strambi et al. (2004) identified significant deficits in visuospatial construction and learning in RBD patients (Ferini-Strambi et al., 2004).

Longitudinal studies have been pivotal in highlighting the cognitive trajectory of RBD patients. For instance, Fantini et al. (2011) assessed cognitive functions over a 2-year period, finding that RBD patients consistently performed worse than HCs in verbal memory and visuoconstruction. Additionally, a decline in visuospatial learning was noted over time (Fantini et al., 2011). Similarly, Terzaghi et al. (2013) observed significant cognitive deterioration in RBD patients over a follow-up period of approximately 43 months, particularly in visuospatial abilities (Terzaghi et al., 2013).

Génier Marchand et al. (2017) further investigated cognitive markers for the early detection of prodromal dementia in a cohort of 76 RBD patients. Their study demonstrated that cognitive tests assessing attention and executive functions could strongly predict dementia development. Patients who developed dementia first were impaired in all cognitive domains compared to those who developed parkinsonism first (Génier Marchand et al., 2017). Similar findings were revealed by Youn et al. (2016), who showed that RBD patients exhibited baseline cognitive impairments and progressive decline, with executive function deficits at baseline increasing the risk of conversion to neurodegenerative disorders (Youn et al., 2016).

Recent studies have also elucidated the cognitive profile of RBD and the prediction of future dementia. Arnaldi et al. (2021) investigated various biomarkers and their effectiveness in predicting phenoconversion in RBD patients. They found that cognitive functions, particularly attention and working memory, were strong predictors of conversion to synucleinopathies. The Trail Making Test Part B (TMT-B) emerged as a potential cost-effective first-line screening tool for identifying patients at high risk of phenoconversion, which could be valuable in the design of disease-modifying clinical trials (Arnaldi et al., 2022). Furthering this research, Joza et al. (2024) conducted a large, comprehensive, multicentre study

involving 754 RBD participants from the International RBD Study Group (iRBDSG), focusing on the progression of cognitive decline. Their findings revealed that cognitive decline in attention and executive functions began up to 10 years before phenoconversion to dementia. Performance on the TMT-B was a strong predictor of early DLB, while changes in verbal memory best differentiated between the DLB and PD subtypes of RBD phenoconversion (Joza et al., 2024).

Overall, the cognitive profile of RBD patients is characterised by significant impairments in attention, executive functions, verbal memory and visuospatial abilities. These cognitive deficits often precede the development of neurodegenerative diseases like PD and DLB, making early cognitive assessments crucial for identifying individuals at higher risk.

1.3.4 Diagnosis and Treatment

RBD diagnosis requires a comprehensive clinical evaluation that includes patient history-taking, a physical examination and specific diagnostic tests. The diagnostic criteria for RBD, as defined by the third edition of the International Classification of Sleep Disorders (ICSD-3), include repeated episodes or arousal during sleep associated with vocalisation and/or complex motor behaviours, occurring during REM sleep and confirmed by video polysomnography (V-PSG) (Sateia, 2014). Comprehensive guidelines for V-PSG, the gold standard overnight sleep study for diagnosing RBD, were recently published by iRBDSG (Cesari et al., 2022). This technique involves monitoring various physiological parameters during REM sleep to confirm the absence of muscle atonia. Video recording during PSG helps document abnormal movements and behaviours, aiding in diagnosis. It is also essential to distinguish RBD from other parasomnias, such as sleepwalking, night terrors or epilepsy, which may involve additional tests or specialist consultations.

Treatments for RBD involve both pharmacological and non-pharmacological strategies aimed at ameliorating symptoms and preventing injuries (Aurora et al., 2010). Clonazepam, a long-acting benzodiazepine, is commonly used as the treatment of choice. It enhances the effects of gamma-aminobutyric acid, promoting muscle relaxation and reducing dream enactment behaviours (Gilat et al., 2022; Schenck & Mahowald, 1990). Melatonin, a hormone regulating sleep-wake cycles, is another treatment option that helps reduce the frequency and intensity of RBD episodes (Boeve et al., 2003).

Non-pharmacological treatments include safety measures, behavioural therapy and regular monitoring (Roguski et al., 2020). Modifying the sleeping environment to prevent injuries, maintaining good sleep hygiene and using relaxation techniques can help improve overall sleep quality and reduce RBD episodes. Regular follow-ups and counselling with a neurologist or sleep specialist are essential for monitoring RBD and informing patients of the prognostic risks of neurodegenerative diseases (Gossard et al., 2023).

1.4 Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disease that falls under the umbrella of alpha-synucleinopathies, a group of diseases characterised by the abnormal accumulation of alpha-synuclein in the brain (Goedert et al., 2013). This group also includes PD, PDD and MSA, and all its members can present with varying degrees of cognitive impairment and autonomic dysfunction. DLB is characterised by cognitive impairment, attentional fluctuation, parkinsonism and visual hallucinations (McKeith et al., 2017).

The nomenclature and classification of DLB have been subjects of significant debate over the years. However, with advances in research, DLB has been recognised as a distinct clinical entity, although confusion persists, particularly when differentiating it from PDD (Gomperts, 2016; Jellinger, 2018). The historical evolution of DLB's nomenclature reflects the complexity and ongoing controversy in the field. The clinical definition of DLB has evolved to encompass several terms previously used to describe the condition. These include diffuse Lewy body disease (Kosaka et al., 1984), diffuse cortical Lewy body disease (Lewy body dementia) (Gibb et al., 1987), dementia associated with cortical Lewy bodies (Byrne et al., 1991), the Lewy body variant of AD (Hansen et al., 1990) and senile dementia of the Lewy body type (Perry et al., 1990), to name a few.

1.4.1 Prevalence and Diagnosis

Estimates of DLB prevalence show significant variation, ranging from 0.3% to 24.4% of all dementia cases and reported to be 5% in older populations (Hogan et al., 2016; Kane et al., 2018; Vann Jones & O'Brien, 2014). The reported incidence of DLB is between 0.5 and 1.6 per 1000 person-years, making up 3.2% to 7.1% of new dementia diagnoses (Hogan et

al., 2016; Vann Jones & O'Brien, 2014). However, DLB is often underdiagnosed, particularly in non-specialist settings, with significant regional variations in diagnosis rates (Kane et al., 2018; Vann Jones & O'Brien, 2014).

The DLB Consortium has updated its diagnostic guidelines for DLB, enhancing criteria that have been widely used over the past three decades (McKeith et al., 2005; McKeith et al., 1996). The revised fourth consensus criteria emphasise a clinical diagnosis supported by core features and indicative biomarkers (McKeith et al., 2017). This diagnosis necessitates the presence of progressive cognitive decline that interferes with daily functions. While memory impairment might not be prominent initially, it typically worsens with disease progression. Early signs often include notable deficits in attention, executive function, and visuoperceptual abilities. The updated criteria also reaffirm the 'one year rule' to distinguish DLB from PDD, specifying that cognitive symptoms in DLB occur before or within one year of the onset of parkinsonism.

DLB's core clinical features include cognitive fluctuations, visual hallucinations, parkinsonism and RBD. Supporting clinical features, such as hypersomnia, hyposmia, severe sensitivity to antipsychotics and transient episodes of unresponsiveness, provide further diagnostic evidence. Furthermore, indicative biomarkers include ^{123}iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy and specific neuroimaging findings, such as reduced DAT uptake in the basal ganglia as demonstrated by SPECT or positron emission tomography (PET) imaging and PSG confirmation of RBD (McKeith et al., 2017).

Despite these advances, significant gaps remain in our understanding of DLB. Further research into the underlying pathophysiology of DLB, including genetics and biomarkers, is essential to improve diagnostic accuracy. Additionally, recognising the prodromal stages of DLB is crucial as recent research has begun to define diagnostic criteria for possible or

probable MCI with Lewy bodies (MCI-LB), one of the prodromal DLB syndromes (McKeith et al., 2020). This is particularly important for creating a window of opportunity for early intervention with potential disease-modifying therapies.

1.4.2 Cognitive Profile

DLB presents a cognitive profile that is distinct from that of AD but overlaps significantly with that of PDD (Aarsland, Litvan, et al., 2003). A hallmark feature of DLB is significant fluctuation in cognitive function, often presenting as episodes of confusion, incoherent speech or pronounced daytime drowsiness (Ferman et al., 2004). These cognitive fluctuations are closely linked to disruptions in arousal and attentional processes, which constitute primary cognitive impairments in DLB (Ballard et al., 2001; Matar et al., 2020; O'Dowd et al., 2019).

DLB is characterised by severe deficits in attention and executive functions. Patients often struggle with tasks requiring sustained and selective attention, visual attention, set-shifting, planning and mental flexibility (Ala et al., 2002; Cagnin et al., 2015; Calderon et al., 2001; Doubleday et al., 2002; Park et al., 2011). These impairments are more pronounced in DLB than in AD but similar in PDD (Collerton et al., 2003; Ferman et al., 2006; Fields, 2017; Noe et al., 2004).

Visuospatial abilities are also severely affected in DLB, even in the early stages. Patients often exhibit difficulties with complex visuospatial tasks, such as object rotation, and visuoconstructive abilities, as well as visuoperceptual tasks like object recognition, which can contribute to the onset of visual hallucinations (Cagnin et al., 2015; Collerton et al., 2003; Devenyi & Hamedani, 2024; Metzler-Baddeley, 2007; Metzler-Baddeley et al., 2010; Mori et al., 2000; Mosimann et al., 2004). Studies have consistently shown that DLB

patients perform poorly on such tasks compared to those with AD, highlighting the disproportionate severity of visuospatial deficits in DLB (Cormack et al., 2004; Tiraboschi et al., 2006; Wood et al., 2013; Yoshizawa et al., 2013). Notably, a recent study demonstrated that the Fragmented Letters Test, a visuoperceptual task, can effectively distinguish between autopsy-confirmed AD and DLB, with test scores strongly reflecting the extent of Lewy body pathology (Salmon et al., 2022).

Memory impairment in DLB tends to be less severe than in AD and is often secondary to impairments in executive functions and attention (Ferman et al., 2006; Ferman et al., 2013). Patients with DLB show comparable impairment in free recall but demonstrate superior delayed recognition memory to those with AD, suggesting disruptions in retrieval mechanisms (Hamilton et al., 2004; Yoshizawa et al., 2013). This pattern is similar in PDD, where memory deficits are also less prominent early in the disease (Hanağası et al., 2016). DLB patients typically perform better on verbal memory tasks than on visual memory tasks due to their visuoperceptual difficulties (Kemp et al., 2017; Mondon et al., 2007; Noe et al., 2004; Oda et al., 2009).

In summary, the cognitive profile of DLB is marked by significant fluctuations in cognitive function, severe impairments in attention and executive functions, pronounced visuospatial deficits, and relatively preserved memory and naming abilities compared to that of AD. These features overlap substantially with those of PDD, making it crucial to consider the onset and progression of motor symptoms to differentiate the conditions according to the long-standing and arbitrary 'one year rule' (Burn et al., 2003; Fritz et al., 2016; Jellinger & Korczyn, 2018; McKeith et al., 2017). But is this enough to differentiate the two conditions? A recent study by Smirnov et al. (2020) suggested that DLB and PDD may have distinct cognitive profiles. DLB was associated with greater memory impairment, while PDD

showed more pronounced visuospatial deficits. Additionally, language function declined faster in DLB, whereas visuospatial and executive functions deteriorated more rapidly in PDD (Smirnov et al., 2020). These findings highlight the complexity of distinguishing between DLB and PDD, with ongoing controversy and debate over the sufficiency of the 'one year rule'.

1.4.3 Treatment

The management of DLB requires a multifaceted approach involving pharmacological and non-pharmacological strategies (McKeith et al., 2017). ChEIs, such as rivastigmine and donepezil, are often prescribed to address cognitive and neuropsychiatric symptoms (McKeith et al., 2000; Stinton et al., 2015). Antipsychotic medications should be used with caution due to the high risk of severe adverse reactions (McKeith et al., 1992). Non-pharmacological interventions, including physical therapy, cognitive stimulation and support for caregivers, can provide meaningful assistance to patients. However, robust evidence supporting the routine recommendation of these interventions for DLB is still limited (Connors et al., 2018; Morrin et al., 2018). Currently, all treatment options are symptomatic, and no disease-modifying treatment is available.

1.5 The Roles of Dopaminergic and Cholinergic Systems in Apathy and Attentional Deficits in Lewy Body Diseases (LBD)

1.5.1 Apathy

Apathy is a common and complex non-motor manifestation of Lewy body diseases (LBD) (Bjoerke-Bertheussen et al., 2012; Mele et al., 2020; Pagonabarraga et al., 2015). It is defined as the 'quantitative reduction of self-generated voluntary and purposeful behaviours' *(Levy & Dubois, 2006).* This loss of motivation is not ascribed to emotional distress or an altered level of consciousness (Marin et al., 1991) and is worse than the premorbid level of functioning (Robert et al., 2018). The Apathy Work Group of the International Society for CNS Clinical Trials and Methodology (ISCTM) updated the diagnostic criteria for apathy in 2021 (Miller et al., 2021). It agreed by consensus that for a diagnosis, unusual persistent symptoms (≥ 4 weeks) in at least two of the three apathy dimensions are required: diminished initiative, diminished interest and diminished emotional expression/responsiveness. These dimensions correspond to the behavioural (also known as auto-activation deficit), cognitive and emotional (affective) subtypes of apathy, respectively (Levy & Dubois, 2006; Marin et al., 1991; Stuss et al., 2000). Additionally, some authors have suggested the incorporation of a social domain/subtype (Ang et al., 2017; Sockeel et al., 2006).

1.5.1.1 Prevalence

The prevalence of apathy in PD is generally estimated at 40% (den Brok et al., 2015), but it varies across studies, with reported rates ranging between 16.5% and 70% (Aarsland et al., 1999; Benito-León et al., 2012; Drijgers et al., 2010; Dujardin et al., 2007; Isella et al., 2002; Kulisevsky et al., 2008; Laatu et al., 2013; Monastero et al., 2013; Pluck & Brown, 2002; Rodríguez-Violante et al., 2014; Starkstein et al., 2009; Stella et al., 2009; Ziropadja et

al., 2012). This variation could be attributed to differences in the diagnostic criteria and assessment methods used, as well as PD population characteristics including comorbidities and disease severity and duration (den Brok et al., 2015; Ou et al., 2020). In DLB, the prevalence of apathy is higher, ranging from 35% up to 100% in patients with severe dementia (Breitve et al., 2018; Kazui et al., 2016; Liu et al., 2019).

1.5.1.2 Apathy and Reward Sensitivity

Several studies have proposed that insensitivity to reward could be an important element of clinical apathy (Adam et al., 2013; Bonnelle et al., 2015; Czernecki et al., 2002; Rochat et al., 2013; Schmidt et al., 2008). This has been evaluated using different approaches and experimental paradigms, mainly gambling and effort-demanding decision-making tasks (Chong et al., 2015; Cools et al., 2003; Czernecki et al., 2002; Le Bouc et al., 2016; Le Heron, Manohar, et al., 2018; Le Heron, Plant, et al., 2018; Martínez-Horta et al., 2014; Schmidt et al., 2008; Torta & Castelli, 2008; Torta et al., 2009). In these paradigms, individuals vary in their subjective assessments of whether the benefits of a specific rewarding outcome justify the risk of gambling or the physical and cognitive efforts necessary for its attainment. These experiments showed that apathetic PD patients have blunted sensitivity to reward compared to those without apathy and HCs, particularly with lower reward levels (Le Heron, Plant, et al., 2018). This was reversed to some degree with the administration of dopaminergic therapy, which enhances motivation and amplifies their willingness to make greater efforts for the same reward outcomes, emphasising a dopaminergic modulatory effect (Chong et al., 2015; Le Bouc et al., 2016).

1.5.1.3 The Role of Dopaminergic System

Apathy in LBD is mainly attributed to neurodegeneration in the fronto-striatal brain regions, encompassing dopamine-responsive areas within the basal ganglia such as the ventral striatum, and the limbic system including the anterior cingulate cortex. These areas are instrumental in fostering motivated behaviour and initiating actions, and their integrity is essential for the proper functioning of the mesolimbic dopamine pathway, which is critical for reward processing (Le Heron, Apps, et al., 2018). The role of dopamine in apathy and reward-based decision-making is well-established in both laboratory and clinical settings (Berridge & Kringelbach, 2015; Berridge & Robinson, 1998; Chong & Husain, 2016; Salamone et al., 2016; Wise, 2004). However, the high prevalence of apathy in neurodegenerative diseases, other than PD, where the dopaminergic system is mostly intact, led researchers to also explore the role of non-dopaminergic neurotransmitter systems (Bailey et al., 2016; Lanctôt et al., 2017; Nunes et al., 2013).

1.5.1.4 The Role of Cholinergic System

The cholinergic system is among those investigated in the context of apathy. It has a neuromodulatory function in the central nervous system, unlike its main excitatory role in the peripheral nervous system. This is mediated by two types of receptors: inotropic nicotinic receptors (nAChRs) and metabotropic muscarinic receptors (mAChRs) (Kruse et al., 2014; Picciotto et al., 2000). The central cholinergic neurotransmission can regulate neurotransmitter release, modulate axonal excitability, and synchronise the activity of neuronal networks (Kawai et al., 2007; Picciotto et al., 2012; Rice & Cragg, 2004; Threlfell et al., 2012). Figure 1.4 illustrates the distribution of cholinergic cell groups and their projections in the forebrain and brainstem.

The interplay between the dopaminergic afferent fibres and the cholinergic interneurons (CINs) in the basal ganglia has significant implications for motivation and reward-based decision-making (Bohnen et al., 2015; Bohnen et al., 2012; Zhou et al., 2002). In a study involving rodents, the inhibition of mAChR function within the nucleus accumbens (NAc) was found to reduce reward-seeking behaviours. Conversely, the blockade of nAChR function led to an enhancement of such behaviours. The study's findings also indicate that these behavioural changes are attributable to the cholinergic secondary modulation of dopamine release. The muscarinic antagonists diminished dopamine release, whereas the nicotinic antagonists increased dopamine output in response to reward-predictive cues (Collins et al., 2016). On the other hand, acetylcholine in the prefrontal cortical regions is crucial for attention, increasing signal-to-noise ratios and supporting reward cue detection (Everitt & Robbins, 1997; Parikh et al., 2007; Sarter et al., 2006; Sarter et al., 2005), while the anticipation of the reward timing has been linked to cholinergic activity in the primary visual cortex (Chubykin et al., 2013; Liu et al., 2015). All these mechanisms contribute to the potential role of the cholinergic pathway in apathy, motivation, reward processing and reward-guided decision-making. This was demonstrated in an RCT, which showed that the acetylcholinesterase inhibitor rivastigmine significantly relieved apathy symptoms measured using the Lille Apathy Rating Scale (LARS) compared to placebo (Devos et al., 2014).

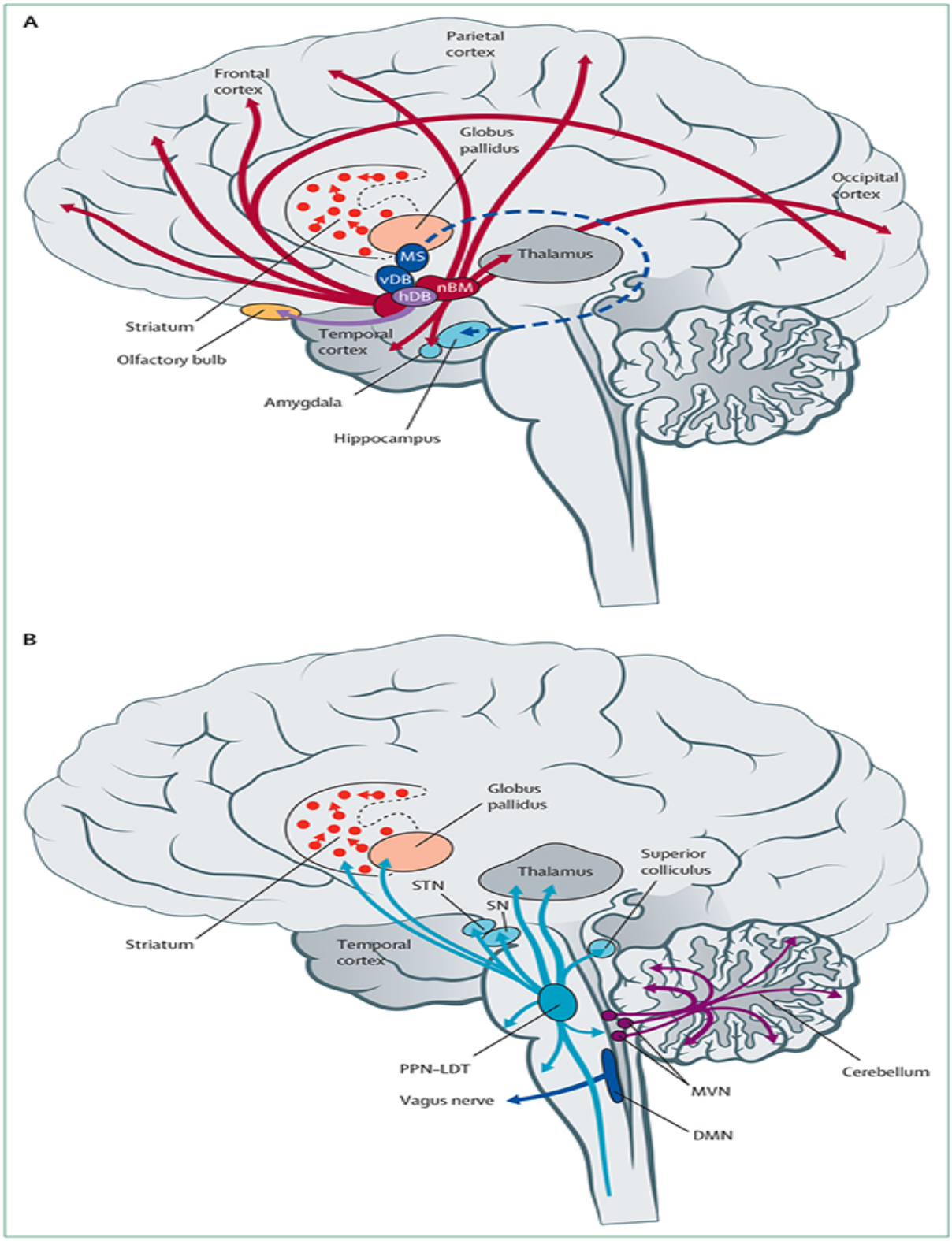


Figure 1.4 | Anatomical distribution of cholinergic cell groups and their pathways. Depiction of cholinergic neurons and their projections in the forebrain (A) and brainstem (B). Coloured arrows indicate the topographic projections originating from specific cholinergic nuclei. nBM: nucleus basalis of Meynert, hDB: horizontal limb nucleus of the diagonal band of Broca, vDB: vertical limb nucleus of the diagonal band of Broca, MS: medial septal nuclei, PPN-LDT: pedunculopontine nucleus- laterodorsal tegmental complex, SN: substantia niagra, STN: subthalamic nucleus, DMN: dorsal motor nucleus of the vagus, MVN: medial vestibular nucelus. Reproduced with permission from (Bohnen et al., 2022).

1.5.1.5 Eye-Tracking as an Objective Measure of Reward Sensitivity

A more recent approach to assess reward sensitivity objectively is through oculomotor eye-tracking reward tasks. These tasks gauge the velocity of saccadic eye movements and changes in pupil size when subjects are presented with visually based rewards. Studies involving humans and primates have indicated that both saccadic and pupillary measures can be modulated by the expected reward and the motivation level (Hikosaka et al., 2006; Manohar et al., 2015; Muhammed et al., 2020). For instance, saccades associated with rewards exhibit an increase in peak velocity compared to those without rewards. This was initially observed in primate research, where saccadic responses to food-rewarded targets were faster than those to targets without rewards (Chen et al., 2013; Kawagoe et al., 1998; Takikawa et al., 2002) Subsequent research in humans has corroborated these results, showing that when monetary incentives are introduced, the saccadic peak velocity increases with higher rewards (Chen et al., 2014; Manohar et al., 2015; Manohar & Husain, 2016). Saccadic latencies, or reaction times (RTs), were also significantly shorter in rewarded trials than in unrewarded trials (Hong & Hikosaka, 2008; Kawagoe et al., 1998; Manohar & Husain, 2016). Pupillometry, on the other hand, can provide us with a unique autonomic perspective of reward and motivation. In healthy individuals, pupils dilate more with higher reward expectations (Manohar & Husain, 2015; Murphy et al., 2011; Rudebeck et al., 2014). Hence, those saccadic and pupillary parameters can be used as behavioural indicators of reward sensitivity.

Apathy was shown to be associated with blunted pupillary and saccadic reward sensitivity in PD patients, while the effect of dopamine was demonstrated to increase both in studies comparing medication ‘on’ versus ‘off’ states (Manohar and Husain 2015;

Muhammed et al. 2016; Muhammed et al. 2021). To date, the impacts of non-dopaminergic neurotransmitters, such as acetylcholine, have not been explored using a similar eye-tracking pharmacological 'on/off' methodology. The encouraging outcomes of the rivastigmine trial by Devos et al. (2014) (Devos et al. 2014) prompted us to delve into a cholinergic investigation. We aimed to meticulously examine the effects of rivastigmine employing the definitive metric of eye-tracking reward tasks (Chapter 3). This approach contrasts with previous research, which predominantly relied on subjective tools like apathy questionnaires, clinical evaluations and interviews. The use of eye-tracking measures presents a new avenue to scrutinise apathy and the impact of pharmacological interventions with greater objectivity.

1.5.2 Attention

1.5.2.1 The Central Role of Attention in Cognitive Processes: Pathways, Types and Neuropsychological Perspectives

Attention serves as the gateway to our conscious experience, a fundamental cognitive process that is integral to our everyday functioning (Peelen & Kastner, 2014). From the moment we wake up to the last flicker of thought before sleep, attention dictates what we perceive, how we learn and the way we navigate our complex world. Hence, it is considered central to cognitive function and is extensively linked to other domains of cognition, such as working memory and executive functions (Awh et al., 1998; Diamond, 2013; Gazzaley & Nobre, 2012; Kane et al., 2001; Oberauer, 2019).

Attention operates through two distinct but interconnected pathways: the dorsal pathway, which facilitates top-down attention, and the ventral pathway, underpinning bottom-up attention (Corbetta & Shulman, 2002). The top-down attentional pathway is voluntary and selective, allowing us to consciously focus on specific elements, objects or

areas within our spatial environment. Conversely, the bottom-up attentional pathway is involuntary, reflexive and automatically triggered by the inherent salience of stimuli in our surroundings, thus acting as an interrupter that redirects our focus to important or novel events (Corbetta & Shulman, 2002; Vossel et al., 2014). Furthermore, the temporal profiles of voluntary and involuntary attention are notably different (Carrasco, 2011). Involuntary attention is rapid and transient in nature. On the other hand, voluntary attention is characterised by a slower onset but can be sustained for longer periods, allowing for goal-directed behaviour (Müller & Rabbitt, 1989; Nakayama & Mackeben, 1989).

In neuropsychology, different forms of attention, including selective, sustained, divided and executive attention, reflect the complexity of this cognitive process. Selective attention involves focusing on a specific stimulus while ignoring others (Driver, 2001). Sustained attention is the ability to maintain focus on a single task over an extended period (Sarter et al., 2001). Divided attention refers to the capacity to process multiple sources of information or perform more than one task at a time (Bouchard et al., 2023). Finally, executive attention is the type of attention used when planning, organising, problem-solving and managing complex cognitive tasks (McCabe et al., 2010). Each type of attention engages different brain regions, with the prefrontal cortex playing a crucial role in managing these attentional processes (Bahmani et al., 2019; Friedman & Robbins, 2022; Rossi et al., 2009). Another, more recent taxonomy of attention was proposed by Chun et al. (2011), who categorised it into 'external attention', involved in selecting and adjusting sensory information such as spatial locations, temporal points and specific sensory inputs, and 'internal attention', which directs and maintains internally generated information like task rules, memory and responses (Chun et al., 2011).

1.5.2.2 Attention in LBD

Deficits in attention are commonly observed in both PD and DLB (Aarsland, 2016; Ballard et al., 2002). The characteristic loss of dopamine in these conditions impacts the fronto-striatal circuitry, which is crucial for attention and executive function processes (Owen et al., 1992; Owen et al., 1995; Robbins et al., 1994). In PD, these deficits can occur early in the disease and sometimes in the prodromal phase preceding the motor symptoms (Massicotte-Marquez, Décary, et al., 2008; Muslimovic et al., 2005; Michele Terzaghi et al., 2008; Yarnall et al., 2014). They were found to be a predictor of progression to PDD in longitudinal studies (Lawson et al., 2021; Pedersen et al., 2013). They were also shown to be associated with a reduced quality of life in PD patients and negatively impact activities of daily living (Barone et al., 2009; Bronnick et al., 2006; Klepac et al., 2008; Lawson et al., 2016). Regarding DLB, fluctuation in attention is one of the four core features of the consensus DLB diagnostic criteria (McKeith et al., 2017), highlighting its significance in the disease's assessment.

1.5.2.3 The Clinical Implications of Attentional Deficits

One of the significant clinical consequences of attentional deficits in LBD is falls, which are notably prevalent in individuals with these conditions (Allan et al., 2009; Wood et al., 2002). Such deficits likely exacerbate or contribute to gait instability, a hallmark of parkinsonism, thereby increasing the likelihood of falls (Stegemöller et al., 2014). This, in turn, can lead to serious consequences, including injuries such as fractures (Genever et al., 2005; Tan et al., 2014), a heightened fear of falling with lower balance confidence (Mak & Pang, 2009; Rahman et al., 2011), loss of independence, reduced mobility and quality of life, and a greater likelihood of acute hospitalisation or admission to nursing homes (Hely et al.,

1999; Paul et al., 2017; Santos García et al., 2023; Walker et al., 2014). In a longitudinal study by Allcock et al. (2009), cognitive deficits in attention and executive function were examined for their association with fall frequency in PD patients (Allcock et al., 2009). The study found that patients with reduced attentional capacity, as measured by the Power of Attention (PoA) task, and increased variability in RTs (a sign of fluctuating attention) were at a significantly higher risk of experiencing falls. This association remained significant even after adjusting for UPDRS III motor scores, highlighting the role of attentional performance in predicting and mitigating fall risk in PD populations.

1.5.2.4 The Role of the Cholinergic System in Attention and Fall Risk

Falls in LBD patients provide a distinct lens through which to examine the complex dynamics between attention and motor integration, mediated by striatal circuity and various neurotransmitter systems. Within this framework, research findings from basic science affirm the significant role of basal forebrain cholinergic loss in PD, contributing to attention deficits and consequently elevating the risk of falls (Sarter et al., 2014). Sarter and colleagues (2014) posit that the impairment of the attentional processing of movement-related cues due to the loss of cholinergic inputs results in the deprivation of essential information to the striatal circuitry, which is typically employed for motor action selection and sequencing. In simpler terms, the simultaneous decline in cholinergic and dopaminergic activity diminishes the supervision of striatal circuitry, thereby revealing the true impact of dopamine denervation on gait and fall propensity (Kucinski et al., 2013; Sarter et al., 2014). Cholinergic PET imaging research found that thalamic cholinergic hypofunction, rather than dopaminergic pathway deterioration, is associated with a history of falls in PD patients (Bohnen et al., 2009; Müller et al., 2013). This underscores the influence of the

pedunculopontine nucleus (PPN) in managing gait and balance (Karachi et al., 2010; Pahapill & Lozano, 2000). Complementing this finding, structural imaging research has shown that degeneration of the cortical cholinergic system, particularly reductions in the volume of the NBM, is predictive of worsening gait impairments in PD (Wilson et al., 2021). This offers a potential biomarker for anticipating mobility decline and fall risk.

Transitioning from imaging to interventions, clinical trials are key in exploring how the cholinergic system influences attention in LBD, where the occurrence and characteristics of falls are used as endpoint outcome measures. An example of such trials is the ReSPonD trial (Henderson et al., 2013), which aimed to assess whether rivastigmine, an acetylcholinesterase inhibitor, could reduce gait variability in patients with PD. Conducted as a randomised, double-blind, placebo-controlled phase 2 trial, the study enrolled 130 patients who were randomly assigned to receive either oral rivastigmine or placebo capsules twice daily for 32 weeks. The results showed that patients receiving rivastigmine exhibited improved step time variability during normal walking and simple dual-task conditions compared to those on the placebo. However, gastrointestinal side effects were more common in the rivastigmine group. Consequently, a multi-centre phase 3 trial, CHIEF-PD, is now underway to confirm these findings (Neumann et al., 2021). CHIEF-PD utilises rivastigmine patches rather than capsules to potentially reduce the gastrointestinal side effects observed in the phase 2 trial. In another randomised, placebo-controlled study, researchers investigated the efficacy of another cholinesterase inhibitor, donepezil, in reducing fall frequency in individuals with PD who experience advanced postural instability. The study found that patients on donepezil had an approximately 50% decrease in fall occurrences in the 6-week duration compared to those on placebo (Chung et al., 2010).

While the previously mentioned randomised trials primarily focused on PD patients without cognitive impairment, Li et al. (2015) (Li et al., 2015) investigated the occurrence of falls in PD patients with varying cognitive function levels and evaluated the effects of rivastigmine on cognition and falling in this cohort. The study randomised 176 PD patients to receive either a placebo or rivastigmine capsules for 12 months, employing the MoCA to assess cognitive function and documenting instances of falls. The results indicated that PD patients without cognitive impairment had notably fewer falls compared to those with PD-MCI and PDD. Moreover, rivastigmine significantly improved MoCA scores and resulted in fewer falls compared to the placebo. These findings underscore the strong association between cognitive impairment severity and fall incidence in PD patients and highlight rivastigmine's potential in ameliorating cognitive decline and reducing falls within this population.

Taken together, these acetylcholinesterase inhibitor trials indicate that cholinergic augmentation is associated with a significant reduction in fall frequency, suggesting potential improvements in attentional processes.

1.6 Thesis Aims and Outline

This thesis aims to investigate the comparative efficacy and safety of pharmacological treatments for cognitive impairment in PD and DLB, with the goal of enhancing clinical practice and supporting informed decision-making regarding drug prescriptions. Additionally, it seeks to elucidate the mechanistic effects of rivastigmine on cognitive functions in PD and DLB patients. Furthermore, the thesis explores cognitive profiles and patterns in PD and RBD patients utilising remote cognitive assessments and examining correlations with DAT imaging to better understand cognitive impairment in these conditions.

1.6.1 Research Questions

1. What is the comparative efficacy and safety of current pharmacological treatments for cognitive impairment in patients with PD and DLB?
2. What are the effects of cholinergic modulation by Rivastigmine on specific cognitive domains, particularly related to apathy and attention, in patients with PD and DLB?
3. What are the distinct cognitive profiles of PD and RBD patients, and how can remote cognitive assessments be utilised effectively in clinical settings?
4. How does dopaminergic function, as measured by DAT-SPECT imaging, correlate with cognitive and motor measures in PD and RBD patients?

1.6.2 **Thesis Outline and Objectives of Experimental Chapters**

Chapter 2 |

This chapter presents a systematic review and network meta-analysis to thoroughly evaluate the efficacy and safety of pharmacological treatments, including ChEIs and NMDA receptor antagonists, for cognitive impairment in PD and DLB.

Chapter 3 |

This chapter investigates the effects of rivastigmine on specific cognitive functions such as attention and reward sensitivity in patients with PD and DLB through drug withdrawal studies using eye-tracking technology.

Chapter 4 |

This chapter explores the cognitive domains affected in PD and RBD patients using innovative online cognitive assessments. It compares the cross-sectional and longitudinal cognitive patterns of these patients with those of HCs.

Chapter 5 |

This chapter investigates the correlations between cognitive and motor measures with DAT-SPECT imaging parameters in PD and RBD patients.

Chapter | 2

Chapter 2 | Comparative Efficacy and Safety of Pharmacological Cognitive Treatments in Parkinson's Disease and Dementia with Lewy Bodies: A Systematic Review and Network Meta-analysis

2.1 Introduction

Cognitive impairment is a common non-motor manifestation of PD. At the time of diagnosis, around 25% of PD patients have some degree of cognitive impairment (Pedersen et al., 2017). Two decades later, up to 80% develop dementia (Hely et al., 2008). This has enormous social and financial implications for the patients, their caregivers and healthcare systems. To date, no cure has been discovered, and management is merely symptomatic.

The cognitive disturbances in PD and their pathology are distinct from those in AD. Nevertheless, the symptomatic treatments for PD and AD are remarkably similar. ChEIs, such as rivastigmine, donepezil and galantamine, are most commonly used. These drugs prevent the breakdown of acetylcholine by inhibiting a post-synaptic enzyme called acetylcholinesterase. This leads to an increase in the synaptic levels of acetylcholine and its duration of action, hence increasing cholinergic activity in the central nervous system (Aarsland et al., 2004). The cholinergic system is believed to be involved in many cognitive processes such as memory, attention, decision-making and executive functions (Bohnen et al., 2022; Hampel et al., 2018).

Another drug class commonly used for the symptomatic treatment of cognitive decline comprises NMDA receptor antagonists, such as memantine. They work by non-competitively blocking the glutamatergic NMDA receptor, which reduces Ca^{2+} influx, preventing and reducing potential neural excitotoxicity (Johnson & Kotermanski, 2006).

These drugs may be used in late-stage PD but are only approved by the FDA for the treatment of moderate-to-severe dementia in AD (Aarsland et al., 2021).

Previous meta-analyses have evaluated the use of ChEIs and NMDA receptor antagonists in PDD and DLB (Matsunaga et al., 2015; Meng et al., 2019; Pagano et al., 2015; Rolinski et al., 2012; Stinton et al., 2015). However, those studies were limited to direct comparisons of drugs against placebos, and the treatments were not ranked and compared. Network meta-analysis allows us to combine direct and indirect evidence from clinical trials. It can help answer more clinically relevant questions, such as which available treatment is best for a specific disease. Here, we study mild-to-moderate PDD and DLB, aiming to better inform clinical practice and decision-making by patients and doctors regarding drug prescriptions.

2.2 Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this systematic review (Page et al., 2021) and its extension for reporting the network meta-analysis (Hutton et al., 2015).

2.2.1 Search Strategy

A central research question was formulated before conducting the literature review, that is, 'What is the comparative efficacy and safety of current pharmacological treatments for cognitive impairment in PD and DLB patients?' We used the PICOS strategy shown below to construct the research question. The search was performed using the following databases: PubMed, PsycINFO, Embase, Cochrane Library of Systematic Reviews, ClinicalTrials.gov and World Health Organization International Clinical Trials Registry. The search terms and Boolean operators used are shown in Table 2.1.

Population - P	Parkin* or (Lewy body dementia or Lewy body or Dementia with Lewy bodies or DLB or LBD) or PDD or PD
Intervention - I	Treatment or drug or medication or cholinesterase inhibitor or galantamine or rivastigmine or donepezil or NMDA antagonist or memantine
Study - S	Trial or drug trial or randomized clinical trial or RCT or placebo or control*
Outcome - O	Cogniti* or memory or attention* or language or executive or MMSE or MoCA or ADAS-cog or Mattis dementia

Table 2.1 | Search terms according to PICOS strategy.

2.2.2 Study Selection Criteria

The studies in this systematic review met the following inclusion criteria: 1) The study population comprised PD patients or patients with DLB diagnosed based on clearly defined criteria; 2) The study was an interventional RCT with a follow-up length of at least 12 weeks;

3) The outcome measures included a cognitive measure, either primary (preferably) or secondary; and 4) The study was published in the English language.

2.2.3 Trial Participants and Intervention Types

The study participants were PD or DLB patients with mild-moderate cognitive impairment (MoCA or MMSE 10-26). We only included trials that assessed drugs used to treat dementia in PD and DLB. Any other intervention types, including surgical procedures, natural remedies and non-pharmacological interventions, were excluded.

2.2.4 Outcome Types

Cognitive outcome measures that assess global cognition, such as the MoCA, MMSE, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) or Mattis Dementia Rating Scale (MDRS), were included in addition to global measures of neuropsychiatric and behavioural symptoms. We also included safety and tolerability measures such as dropout rates and adverse events. Self-reported outcome measures were excluded.

2.2.5 Study Selection

The titles of all the potential studies resulting from the search strategy were carefully reviewed independently by Dr. Stephanie Hirschbichler (SH) and the author (FA). Irrelevant titles were excluded, and the abstracts of the relevant titles were reviewed. The inclusion criteria were applied, and if the abstract showed that the article met at least the first two inclusion criteria, it was included in the full article review. Then, all the full articles were examined, and only those that met all the inclusion criteria and had the approval of both reviewers were included in this systematic review. All duplicated studies were removed.

2.2.6 Data Extraction

The following data were extracted from the clinical trials included in this study:

1- The main author and the year of publication
2- The number of participants and their characteristics (age and gender and inclusion criteria)
3- The study design and duration
4- The drug and its characteristics (dose, frequency, route and duration)
5- The primary outcome measure of the study
6- The cognitive outcome measures of the study (primary or secondary)
7- The results of each outcome measure
8- The baseline and final mean ± standard deviation (SD) of each outcome measure.
9- The mean change from baseline ± SD of each outcome measure
10- The conclusion of each study

These data were extracted from the published studies independently by both reviewers. The authors were contacted for any missing data. In some studies, the SDs of continuous outcome measures were not reported, so we used the Cochrane Handbook for Systematic Reviews of Interventions to impute SDs for changes from baselines based on validated approaches (Higgins JPT, 2022). When multiple studies reported data from the same study population, the study with the most participants was used for data extraction.

2.2.7 Methods of Statistical Analysis

Meta-analysis was conducted using Review Manager (RevMan) version 5.4 with the standardised mean difference (SMD) between treatment and placebo groups. We used the mean change from baseline for all outcome measures. The results of the included studies were pooled using random effects models and presented in forest plots. The statistical heterogeneity between studies were measured using the I^2 test. Funnel plots were used to assess publication bias among the studies. We performed frequentist network meta-analyses using the Netmeta package in R statistical software version 4.2.0. Random-effects

models and SMDs between the network interventions were used also in the network meta-analyses.

2.2.8 Pairwise and Network Meta-analysis

Pairwise meta-analysis is a statistical method commonly used in evidence-based medicine and research to combine and compare the results of multiple independent studies that have similar methodologies and are addressing the same question. This method mainly focuses on comparing two interventions or treatment directly (Jansen & Naci, 2013). The primary goal is to ascertain whether one intervention is superior to another or if they are equivalently effective. This is achieved by calculating a pooled effect size, which quantifies the strength of the treatment effect across the various studies. Pairwise meta-analysis assumes homogeneity is study populations and interventions, allowing for a direct comparison. Its strength lies in its ability to increase statistical power and precision by pooling data, but it is limited by comparing only two treatments at a time and may be influenced by publication bias and heterogeneity among studies (Jansen & Naci, 2013).

To overcome the limitations of pairwise meta-analysis, network meta-analysis (NMA), also known as multiple treatments meta-analysis, extends the approach by allowing for the simultaneous comparison of multiple treatments within a single analysis (Salanti, 2012). This method integrates both direct comparisons of treatments within randomised controlled trials and indirect comparisons across trials based on a common comparator (e.g. placebo or standard treatment) (Rouse et al., 2017). It is particularly valuable in fields with numerous treatments options and limited direct head-to-head comparisons, like in our case with the cognitive treatments of Lewy Body Diseases.

The key assumptions of network meta-analysis include (Chaimani et al., 2019):

1- Transitivity: This fundamental assumption implies that the studies being combined are sufficiently similar in terms of patient populations, settings, and methods so that their results can be reasonably pooled together.
2- Consistency: This assumption requires that the direct and indirect estimates of the same comparisons are in agreement. In other words, the network should not contain any major inconsistencies or contraindications in the results from different pathways of evidence. Figure 2.1 illustrates this assumption.

Network meta-analysis is powerful for understanding the relative effectiveness of multiple treatments, but its accuracy and reliability are heavily dependent on these assumptions being met. If these assumptions are violated, the results of the analysis can be misleading. Therefore, careful consideration and assessment of these assumptions are crucial when conducting a network meta-analysis. NMA is regarded as one of the highest forms of evidence in evidence-based medicine, positioned at the top of the evidence hierarchy (see Figure 2.2) due to its ability to simultaneously compare multiple treatments.

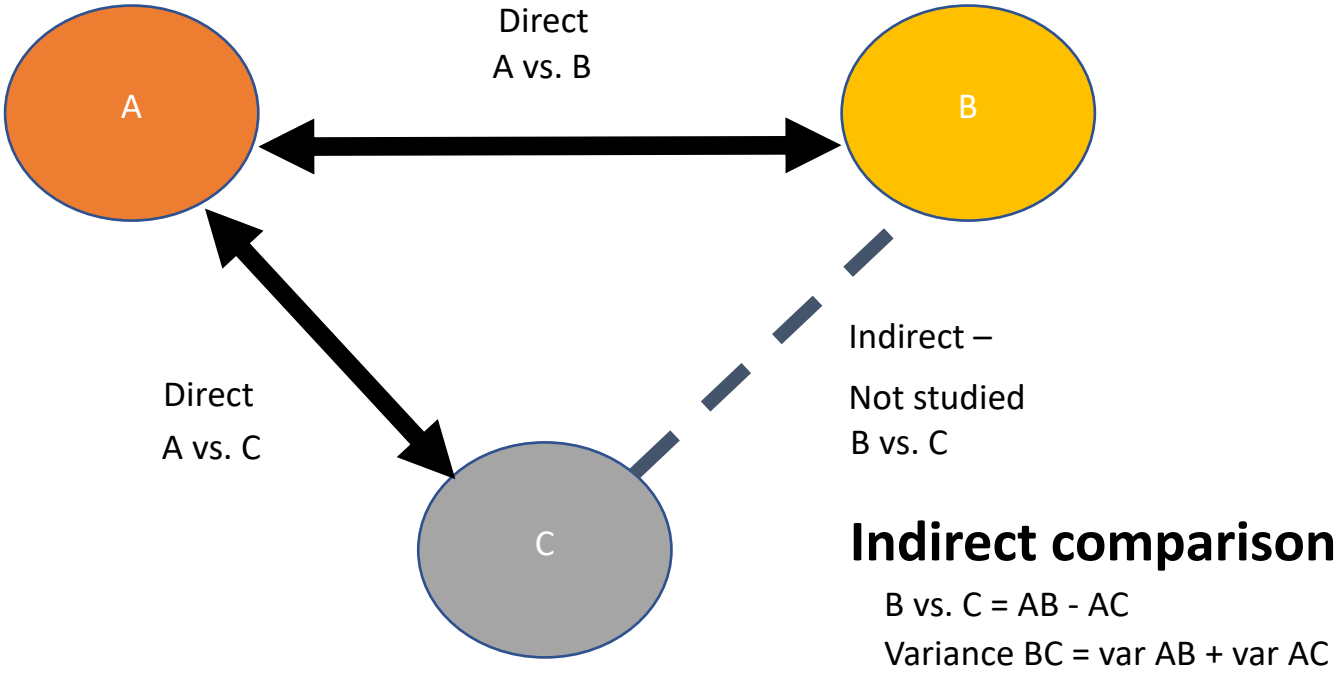


Figure 2.1 | Illustration of the consistency assumption in network meta-analysis and how the indirect comparison is calculated. where A and B treatments and A and C treatments are directly compared in heads-to-heads studies while no study compared B to C. The consistency assumption is assuming that if a is better than b and c is better than A then in the indirect estimate c is better than b. the indirect estimate is calculated as the differences in treatment effect between a and b and a and c.

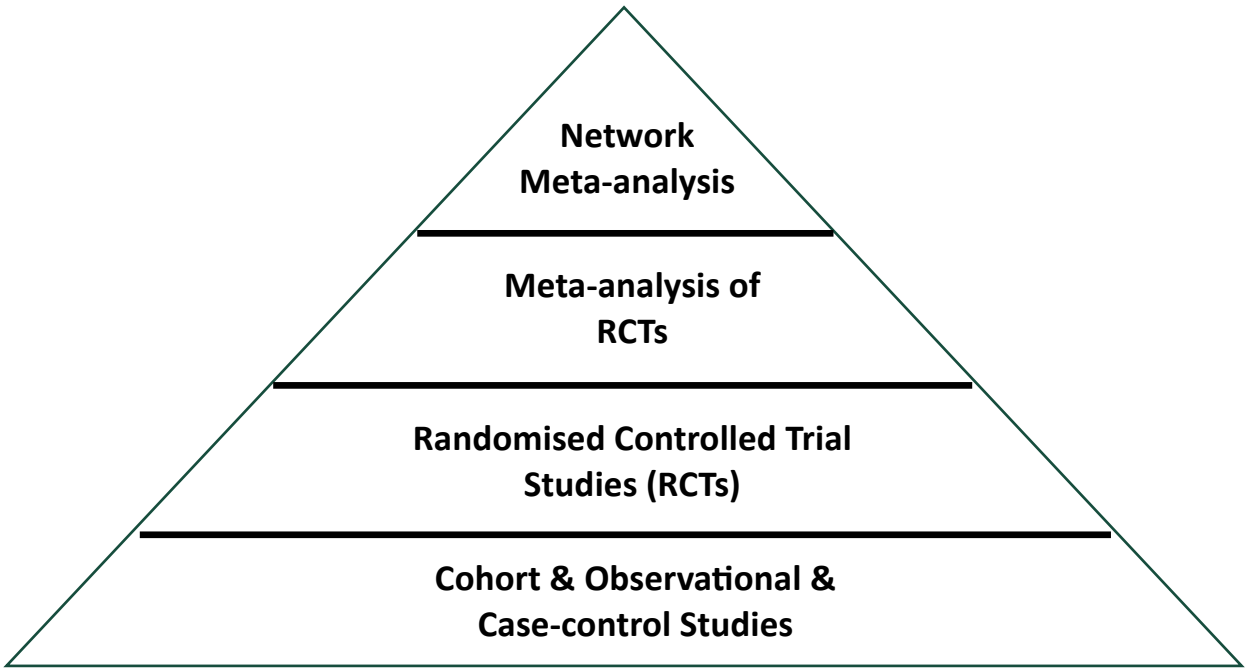


Figure 2.2 | The hierarchical levels of clinical evidence-based medicine. The network meta-analysis is the highest possible level of clinical evidence followed by meta-analysis of randomised clinical trials, then the randomised clinical trials and lastly cohort, observational and case-control studies.

2.2.9 Risk of Bias Assessment and Effect Modifiers

This study utilised the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to examine the quality of evidence across all studies (Balshem et al., 2011). To assess the risk of bias in the clinical trials, version 2 of the Cochrane Risk of Bias tool for randomised trials (RoB2) was used (Sterne et al., 2019).

As part of assessing the validity of the transitivity assumption for the network meta-analysis, we compared the distributions of the effect modifiers across the included trials using the BUGSnet package in R (Béliveau et al., 2019). These effect modifiers are characteristics of the study and patients that can be associated with the treatment outcomes. In other words, any variable that can influence the treatment effect but is not a treatment or an outcome is an effect modifier (Jansen & Naci, 2013). Hence, as the network meta-analysis involves various trials that compare different interventions, the variation in the distribution of the effect modifiers plays a dual role. First, like in standard pairwise meta-analysis, this variation can occur across studies for specific comparisons, leading to heterogeneity. Second, and uniquely to network meta-analysis, variation can exist between different comparisons, leading to inconsistency. This dual variation can critically affect the reliability of the network meta-analysis's findings. Therefore, a meticulous examination of these effect modifiers is essential to ensure the robustness and validity of the conclusions drawn from the network meta-analysis (Hutton et al., 2015).

2.3 Results

2.3.1 Search Results and Study Characteristics

Out of 2045 studies identified based on the search strategy, 22 studies met the inclusion criteria (Figure 2.3). These trials randomised a total of 3366 PDD and DLB patients to receive either a drug or placebo (except for the rivastigmine formulations comparison trials, patients were randomised to either capsule or patch). Table 2.2 shows the characteristics of the included trials. Twenty studies were randomised, placebo-controlled, double-blind studies. Two trials compared the two rivastigmine formulations, one of which was a long-term, open-label, randomised trial. Excluded studies are listed in Appendix Table 8.1.

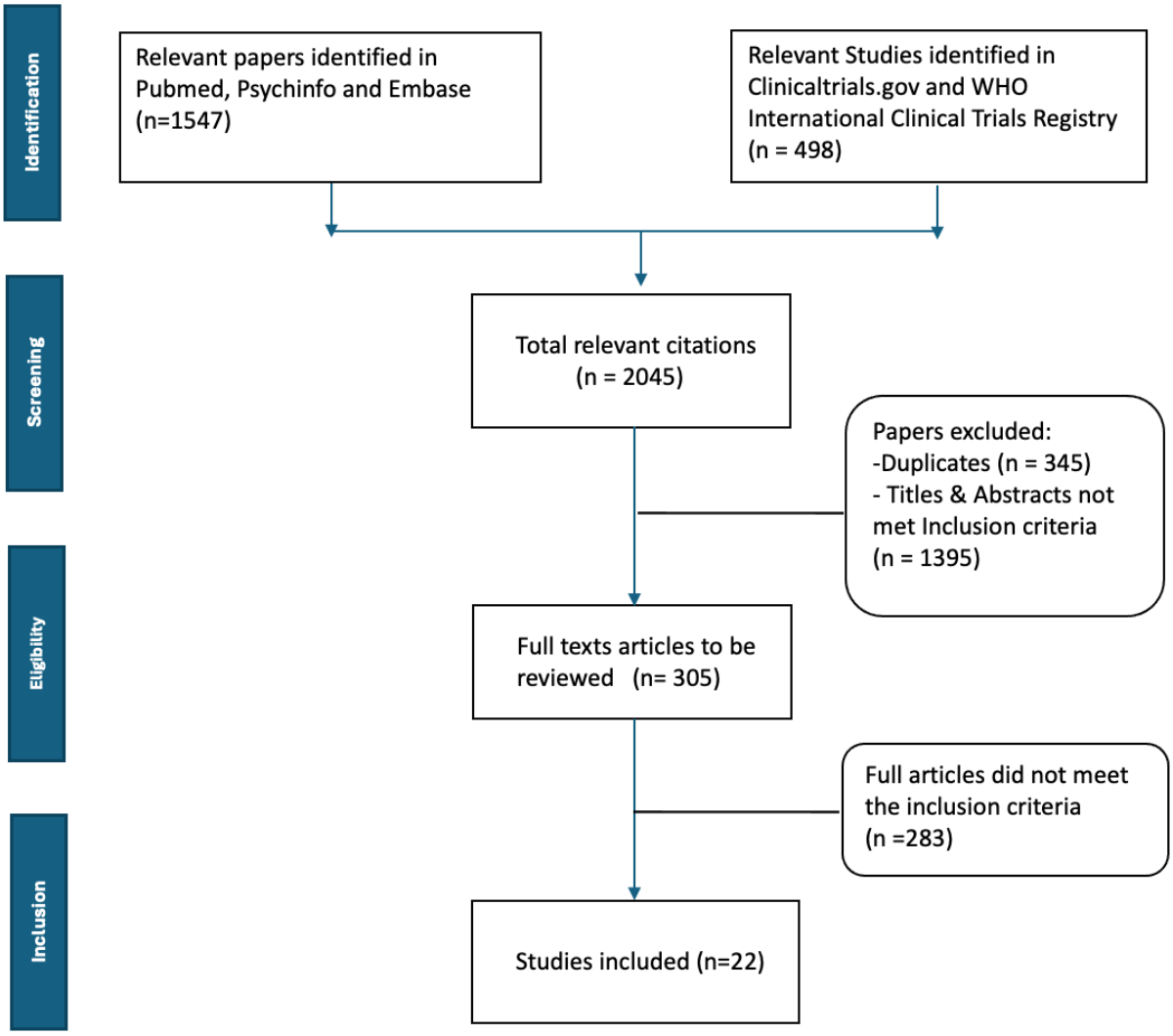


Figure 2.3 | Flowchart of the search strategy

Included studies

	Participants			Interventions						
Study	Population	Female (%)	Age mean (SD)	Drug	Comparator	Daily Dose	Drug (n)	Comparator(n)	Duration	Outcome measures
Emre 2004 (Emre et al., 2004)	Mild-Moderate PDD	35.1	72.7 (6.6)	Rivastigmine oral	Placebo	3-12 mg	362	179	24 weeks	A,B,E,G
McKeith 2000 (McKeith et al., 2000)	DLB	43.3	73.9 (6.5)	Rivastigmine oral	Placebo	3-12 mg	59	61	23 weeks	A,G
Li, 2015(Li et al., 2015)	PD-MCI (MoCA 15-25)	38.1	66.8 (12.2)	Rivastigmine oral	Placebo	3-12 mg	41	40	52 weeks	C
Emre 2014(Emre et al., 2014)	Mild-Moderate PDD	31.7	72.3 (6.3)	Rivastigmine oral	Rivastigmine patch	12 mg 4.6 – 9.5 mg/24 hrs	295	288	76 weeks	D,G
McDonald 2018(McDonald et al., 2018)	Mild-Moderate PDD	36.8	73 (5.4)	Rivastigmine oral	Rivastigmine patch	12 mg 4.6 – 9.5 mg/24 hrs	8	11	24 weeks	D,G
Mamikonyan 2015(Mamikonyan et al., 2015)	PD-MCI	21.4	64.3 (8.2)	Rivastigmine patch	Placebo	4.6 – 9.5 mg/24 hrs	14	14	24 weeks	C,E
Aarsland 2002(Aarsland et al., 2002)	Mild-Moderate PDD	7.14	71 (3.9)	Donepezil	Placebo	5 or 10 mg	14	12	20 weeks	A,F
Dubois 2012(Dubois et al., 2012)	Mild-Moderate PDD	31.66	71.9 (6.92)	Donepezil	Placebo	5 or 10 mg	377	173	24 weeks	A,B,F,G
Mori 2012(Mori et al., 2012)	DLB	65.92	78.7 (5.57)	Donepezil	Placebo	5 or 10 mg	103	32	12 weeks	A,G
Ikeda 2015(Ikeda et al., 2015)	DLB	58	77.9 (6.1)	Donepezil	Placebo	5 or 10 mg	94	44	16 weeks	A,G
Leroi 2004(Leroi et al., 2004)	Mild-Moderate PDD	34.95	68.5 (10.6)	Donepezil	Placebo	5 or 10 mg	7	9	18 weeks	A,D,G
Ravina 2005(Ravina et al., 2005)	Mild-Moderate PDD	21.05	73.6 (8.95)	Donepezil	Placebo	5-10 mg	21	20	26 weeks	A,B,D,E
MUSTARDD-PD 2016 (MUSTARDD-PD, 2016)	Mild-Moderate PDD	22.6	73.8 (8)	Donepezil	Placebo	10 mg	32	30	26 weeks	D,G
Aarsland 2009(Aarsland et al., 2009)	Mild-Moderate PDD + DLB	25	76.6 (5.95)	Memantine	Placebo	20 mg	34	38	24 weeks	A,E,G
Leroi 2009(Leroi et al., 2009)	Mild-Moderate PDD	48	75.7 (7.85)	Memantine	Placebo	20 mg	11	14	22 weeks	A,D,G
Emre 2010(Emre, Tsolaki, et al., 2010)	Mild-Moderate PDD + DLB	43.7	73.4 (6.5)	Memantine	Placebo	20 mg	96	99	24 weeks	E,G
NCT00294554 (ClinicalTrials.gov, 2017)	Mild-Moderate PDD	15	71.8 (7.4)	Memantine	Placebo	5- 20 mg	10	10	24 weeks	D,F
HEADAWAY-DLB	DLB	21.3	73.2 (6.3)	Intepirdine	Placebo	70 mg	91	89	24 weeks	B,F,G

2019(Lang et al., 2021)										
SYNAPSE 2019 (ClinicalTrials.gov, 2019)	Mild-Moderate PDD	11	73.2 (7)	SYN120	Placebo	100 mg	44	38	16 weeks	H
PRESENCE 2021 (Biglan et al., 2022)	DLB and PDD	17.2	72.6 (6.6)	Mevidalen	Placebo	75 mg QD	86	87	12 weeks	B,C,E,G
AscenD-LB 2021 (Jiang et al., 2022)	DLB	15.4	72.8 (6.9)	Neflamapimod	Placebo	40 mg TDS	46	45	16 weeks	A,G
NCT03467152 2022 (ClinicalTrials.gov, 2022)	DLB	37.2	74.5 (6.5)	Irsenontrine	Placebo	50 mg	96	92	12 weeks	A,C,E,F,G

Table 2.2 | Characteristics of the included studies **A.** Mini-Mental State Examination (MMSE), **B.** Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), **C.** Montreal Cognitive Assessment (MoCA), **D.** Mattis Dementia Rating Scale (MDRS), **E.** Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC), **F.** Clinician's interview-based impression of change with caregiver input (*CIBIC+*), **G.** Neuropsychiatric Inventory (NPI) **H.** Cognitive Drug Research (CDR)

Outcome Measures

We conducted pairwise and network meta-analyses covering the following main outcome measures:

1- Cognitive outcome measures (MoCA, MMSE and MDRS)
2- Neuropsychiatric measures (Neuropsychiatric Inventory (NPI))
3- Safety and tolerability measures (dropout rates and adverse events)

2.3.2 Cognitive Outcome Measures

2.3.2.1 Pairwise Meta-analysis

A pairwise meta-analysis was conducted on drugs with at least two trials comparing them to a placebo using cognitive outcome measures.

Cholinesterase inhibitors

Three rivastigmine studies included in this analysis used the MMSE and MoCA. The meta-analysis revealed a significant improvement in MMSE/MoCA scores with rivastigmine compared to placebo (weighted SMD = 0.29, 95% CI [0.13,0.45], z = 3.62, p = 0.0003). There was no heterogeneity between the studies, with $I^2 = 0\%$. For donepezil trials, six studies used the MMSE as an outcome measure. They showed significant improvement in MMSE with

donepezil compared to placebo (weighted SMD = 0.53, 95% CI [0.36,0.70], z = 6.13, p < 0.00001). The studies were also not heterogeneous (I^2 = 0%). The combined analysis of cognitive outcome measures in the ChEI trials revealed significant improvement in the treatment groups compared to placebo groups (weighted SMD = 0.42, 95% CI [0.27,0.56], z = 5.58, p < 0.00001). There was a small amount of heterogeneity between the trials, with I^2 = 19%. Figure 2.4 shows a forest plot of the cognitive outcome measures for rivastigmine, donepezil and combined ChEI trials.

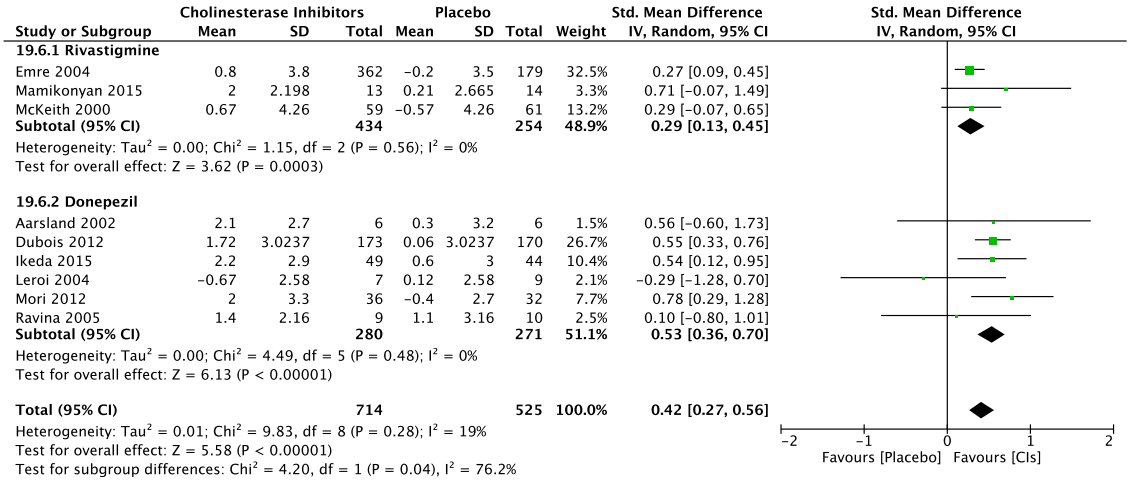


Figure 2.4 | Forest plot of the pairwise meta-analyses of the global cognitive outcome measures (ChEIs).

NMDA receptor antagonist: memantine

Two memantine RCTs included in this meta-analysis used the MMSE as an outcome measure. Memantine showed no significant difference in MMSE mean change compared to placebo (weighted SMD = 0.17, 95% CI [−0.60,0.93], z = 0.43, p = 0.67). However, the studies were highly heterogeneous (I^2 = 63%); see Figure 2.5.

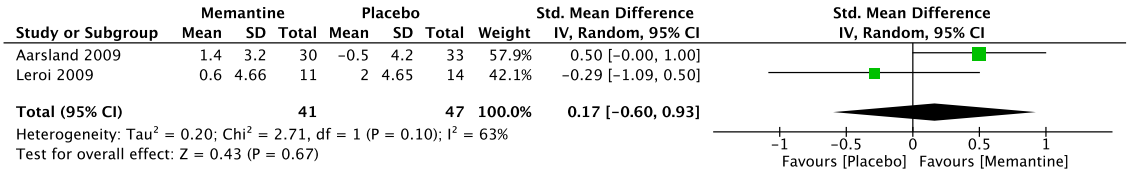


Figure 2.5 | Forest plot for the pairwise meta-analysis of the global cognitive outcome measures (memantine).

2.3.2.2 Network Meta-analysis (NMA)

The cognitive NMA comprises 19 studies that evaluate 7 drugs in addition to two forms of Rivastigmine, assessing their effects on mean changes in global cognitive assessment scores (Figure 2.6A,B). Each drug was directly compared to placebo, and there were no direct comparisons between the drugs. The two formulations of Rivastigmine were compared in two studies. Donepezil had the highest number of studies in the network, with 7 studies. Rivastigmine had 5 studies, Meantime had 2 studies, while the remaining drugs had one study each. The network includes a total of 3366 patients randomised to either a drug or a placebo (except when the two formulations of Rivastigmine were compared).

Both rivastigmine and donepezil showed statistically significant improvement in global cognitive measures compared to placebo (SMD = 0.36, 95% CI 0.14 to 0.57, SMD = 0.33, 95% CI 0.12 to 0.54 respectively). No significant differences were found between memantine (SMD = 0.26, 95% CI -0.20 to 0.71), mevidalen (SMD = 0.15, 95% CI -0.27 to 0.57), irsenontrine (SMD = 0.07, 95% CI -0.31 to 0.45), intepirdine (SMD = 0.10, 95% CI -0.30 to 0.50), neflamapimod (SMD = -0.12, 95% CI -0.71 to 0.47) and placebo. The drugs were ranked based on their P-scores as follows: rivastigmine (capsule), donepezil, memantine, mevidalen, intepirdine, irsenontrine, placebo and finally neflamapimod (Table 2.3). The Q statistics of the network showed low heterogeneity score I^2 = 18.7% [0.00% - 58.6%] with no significant heterogeneity within the designs of the network model. The funnel plot revealed no publication bias (p= 0.8716 egger) (Figure 2.9).

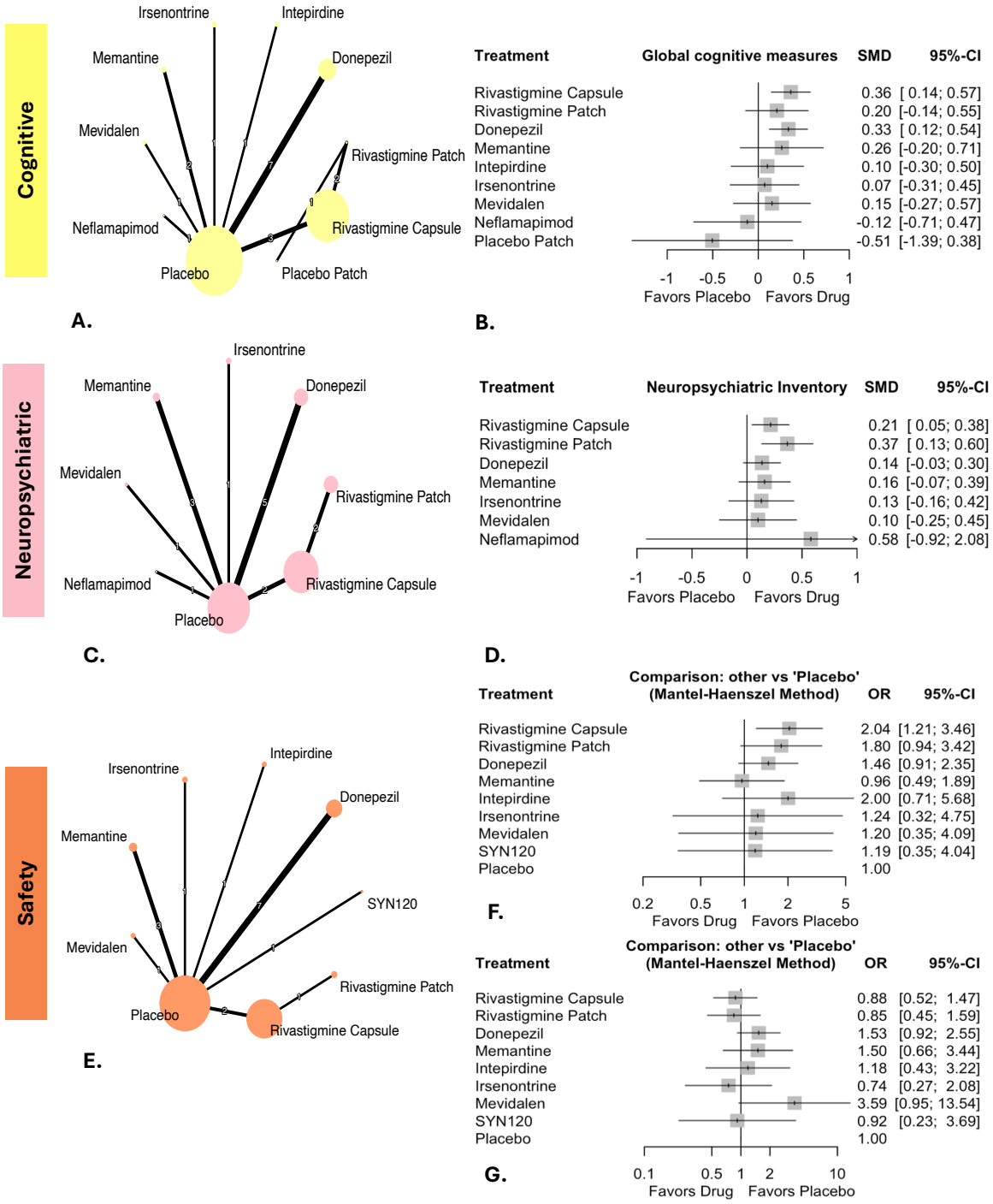


Figure. 2.6 | Net graphs and forest plots of the network meta-analyses. Net graphs **A.** (Cognitive), **C.** (Neuropsychiatric), **E.** (Safety) show the network geometries: The nodes' sizes indicate the number of participants allocated to each treatment, while treatments that are directly compared are connected with a line and its thickness corresponds to the number of trials assessing that comparison. **B.** Forest plot of the cognitive network meta-analysis with positive SMD indicates better performance than placebo (in the cognitive measures used: higher scores reflect better performance). **D.** Forest plot of neuropsychiatric measures, a positive SMD reflects improved outcomes over placebo. **F.** Forest plot of dropout rates due to adverse events, an odds ratio (OR) higher than 1 suggests a higher dropout rate, indicating worse tolerability when compared to placebo. **G.** Forest plot of serious adverse events – similarly, an OR greater than 1 signifies a higher incidence of serious adverse events, suggesting a poorer safety profile relative to placebo.

2.3.3 Neuropsychiatric Outcome Measures

The neuropsychiatric NMA comprises 15 studies that include 6 drugs, assessing their effects on mean changes in global neuropsychiatric inventory scores (NPI) (Figure 2.6C,D). Each drug was directly compared to placebo, with no head-to-head comparisons between the drugs. Rivastigmine formulations were compared against each other in two studies.

Only rivastigmine in both formulations was significantly superior to placebo in improving NPI scores [rivastigmine capsule (SMD = 0.21, 95% CI 0.05 to 0.33), rivastigmine patch (SMD = 0.37, 95% CI 0.13 to 0.60)]. The ranking of the drugs based on their P-scores was in order: rivastigmine (patch), neflamapimod, rivastigmine (capsule), memantine, donepezil, irsenontrine, mevidalen, and lastly placebo (Table 2.3). The Q statistics of the network showed low heterogeneity score I^2 = 0% [0.00% - 64.8%] with no significant heterogeneity within the designs of the network model. The funnel plot revealed no publication bias (p= 0.3848 egger) (Appendix Figure 8.2).

2.3.4 Safety Outcome Measures

Within our NMA, we assessed safety through dropout rates due to adverse events, which reflects the treatment's tolerability, and serious adverse events, including life-threatening conditions and hospitalisations, to provide a balanced safety profile.

2.3.4.1 Dropouts due to Adverse Events (AEs)

The safety NMA showed that rivastigmine capsules were the only treatment significantly linked to increased dropout rates due to adverse events, compared to placebo (OR = 2.04, 95% CI [1.21; 3.46])(Figure 2.6E,F). The treatments were ranked, from lowest to

highest dropout rates due to adverse events, based on their P-scores as follows: placebo, memantine, SYN120, mevidalen, irsenontrine, donepezil, rivastigmine (patch), intepirdine, rivastigmine (capsule)(Table 2.3). Comparison graphs showing the effect sizes for drug efficacy and tolerability are presented in Figure 2.7, and a league table with head-to-head comparisons is shown in Figure 2.8.

2.3.4.2 Serious Adverse Events (SAEs)

The safety NMA showed that when it came to the occurrence of severe adverse events, there was no significant difference between any of the treatments and placebo (Figure 2.6E,G). The treatments were ranked based on their p-scores, from least to most likely to cause severe adverse events, as follows: irsenontrine, rivastigmine (patch), rivastigmine (capsule), SYN120, placebo, intepirdine, memantine, donepezil, and mevidalen (Table 2.3).

2.3.5 Risk of Bias and Effect Modifiers

In assessing the risk of bias and potential effect modifiers, the RoB2 risk assessment tool alongside the GRADE approach was utilised to evaluate the included studies. Among the studies reviewed, two exhibited a high risk in only one component, while the remaining studies demonstrated either low or unclear risk across all the assessed components. The overall risk of bias was low for 18 studies and unclear for four studies (refer to Appendix Table 8.2 for detailed information). Additionally, potential effect modifiers such as age, baseline cognitive function, years of education, disease duration, and time since dementia diagnosis were systematically analysed across studies. The analyses revealed no meaningful heterogeneity in the distribution of these potential effect modifiers, as detailed in Appendix Figure 8.1.

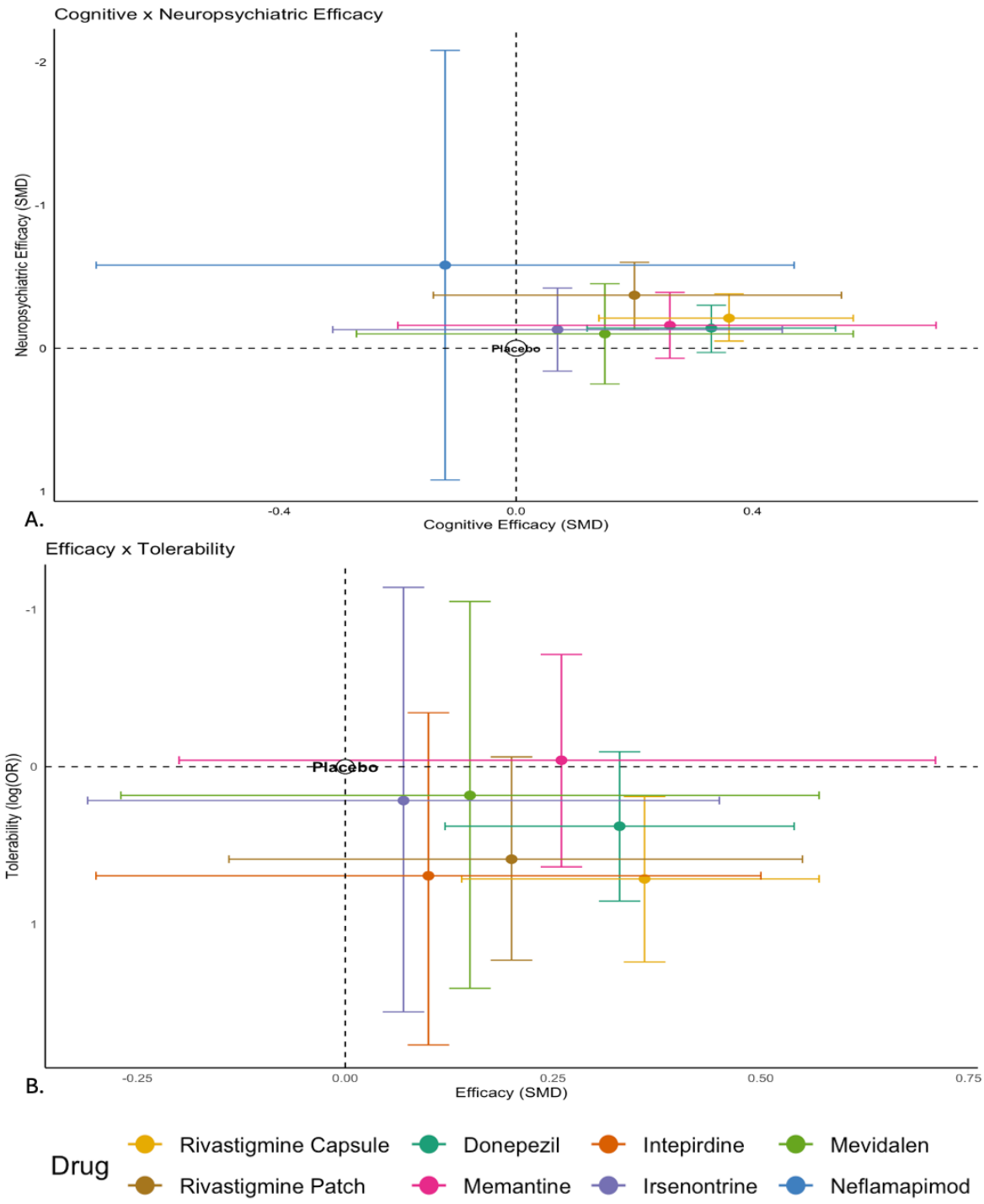


Figure 2.7 | Comparison of effect sizes for A. cognitive efficacy with neuropsychiatric efficacy and B. cognitive efficacy with tolerability (measures by dropout due to adverse events) for drugs included in our study in PDD and DLB patients. Each drug corresponds to a color, with bars showing the associated 95% confidence interval. Dashed lines indicate the position of the placebo, serving as the central reference point for the standardized mean difference (SMD). Positive efficacy effect sizes reflect an efficacy superior to placebo. Negative tolerability values, positioned higher on the y-axis, indicate better neuropsychiatric outcomes and improved tolerability.

Cognitive Efficacy (SMD)

Tolerability (OR)

Riva Cap	0.15 [-0.12; 0.42]	0.03 [-0.27; 0.33]	0.10 [-0.41; 0.60]	0.26 [-0.19; 0.71]	0.29 [-0.15; 0.72]	0.21 [-0.27; 0.68]	0.48 [-0.15; 1.10]	0.25 [-0.31; 0.80]	**0.36 [0.14; 0.57]**	**0.86 [0.01; 1.72]**
1.14 [0.78; 1.65]	**Riva Patch**	-0.13 [-0.53; 0.28]	-0.05 [-0.62; 0.52]	0.10 [-0.42; 0.63]	0.13 [-0.38; 0.64]	0.05 [-0.49; 0.60]	0.32 [-0.36; 1.01]	0.09 [-0.52; 0.71]	0.20 [-0.14; 0.55]	0.71 [-0.10; 1.52]
1.4 [0.69; 2.82]	1.23 [0.55; 2.73]	**Don**	0.07 [-0.43; 0.57]	0.23 [-0.22; 0.68]	0.26 [-0.17; 0.69]	0.18 [-0.29; 0.65]	0.45 [-0.17; 1.08]	0.22 [-0.33; 0.77]	**0.33 [0.12; 0.54]**	0.84 [-0.07; 1.74]
2.12 [0.9; 4.99]	1.87 [0.74; 4.74]	1.52 [0.67; 3.46]	**Mem**	0.16 [-0.45; 0.76]	0.19 [-0.40; 0.78]	0.11 [-0.51; 0.73]	0.38 [-0.37; 1.12]	0.15 [-0.54; 0.83]	0.26 [-0.20; 0.71]	0.76 [-0.23; 1.76]
1.02 [0.32; 3.27]	0.90 [0.26; 3.05]	0.73 [0.23; 2.30]	0.48 [0.14; 1.66]	**Intepirdine**	0.03 [-0.52; 0.58]	-0.05 [-0.63; 0.53]	0.22 [-0.49; 0.93]	-0.01 [-0.66; 0.64]	0.10 [-0.30; 0.50]	0.61 [-0.36; 1.57]
1.65 [0.39; 7.01]	1.45 [0.33; 6.46]	1.18 [0.28; 4.93]	0.78 [0.17; 3.51]	1.62 [0.30; 8.88]	**Irsenontrine**	-0.08 [-0.65; 0.49]	0.19 [-0.51; 0.89]	-0.04 [-0.68; 0.60]	0.07 [-0.31; 0.45]	0.58 [-0.38; 1.53]
1.70 [0.45; 6.46]	1.50 [0.37; 5.98]	1.22 [0.33; 4.54]	0.80 [0.20; 3.25]	1.67 [0.33; 8.34]	1.03 [0.17; 6.36]	**Mevidalen**	0.27 [-0.45; 0.99]	0.04 [-0.62; 0.70]	0.15 [-0.27; 0.57]	0.66 [-0.32; 1.63]
-	-	-	-	-	-	-	**Nef**	-0.23 [-1.01; 0.55]	-0.12 [-0.71; 0.47]	0.39 [-0.67; 1.44]
1.72 [0.45; 6.53]	1.51 [0.38; 6.04]	1.23 [0.33; 4.58]	0.81 [0.20; 3.28]	1.69 [0.34; 8.42]	1.04 [0.17; 6.43]	1.01 [0.18; 5.72]	-	**SYN120**	0.11 [-0.4; 0.62]	0.62 [-0.40; 1.63]
2.04 [1.21; 3.46]	1.80 [0.94; 3.42]	1.46 [0.91; 2.35]	0.96 [0.49; 1.89]	2.00 [0.71; 5.68]	1.24 [0.32; 4.75]	1.20 [0.35; 4.09]	-	1.1875 [0.3487; 4.0441]	**Pla**	0.51 [-0.38; 1.39]
-	-	-	-	-	-	-	-	-	-	**Pla Patch**

Figure 2.8 | League table for cognitive efficacy and tolerability. This figure illustrates head-to-head comparisons of drugs, comparing cognitive efficacy (above the diagonal) using Standardised Mean Differences (SMD) and tolerability (below the diagonal) using Odds Ratios (OR). For efficacy, and SMD higher than zero indicates better cognitive performance relative to the comparator. For tolerability, an OR higher than 1 suggest worse dropout rates due to adverse events relative to the comparator. Each cell contains effect estimates and 95% confidence intervals. Values in bold indicate statistical significance, represented by confidence intervals that don't include zero (for SMD) or 1 (for OR).

Cognitive		Neuropsychiatric		Dropout AEs		Serious AEs	
Treatment	P-score	Treatment	P-score	Treatment	P-score	Treatment	P-score
1. Rivastigmine Capsule	0.8408	Rivastigmine Patch	0.8534	Placebo	0.7634	Irsenontrine	0.7432
2. Donepezil	0.7957	Neflamapimod	0.7060	Memantine	0.7487	Rivastigmine Patch	0.7135
3. Memantine	0.6688	Rivastigmine Capsule	0.5907	SYN120	0.5834	Rivastigmine Capsule	0.6855
4. Rivastigmine Patch	0.6017	Memantine	0.4869	Mevidalen	0.5777	SYN120	0.6120
5. Mevidalen	0.5350	Donepezil	0.4376	Irsenontrine	0.5578	Placebo	0.5912
6. Intepirdine	0.4692	Irsenontrine	0.4263	Donepezil	0.4505	Intepirdine	0.4793
7. Irsenontrine	0.4285	Mevidalen	0.3767	Rivastigmine Patch	0.3293	Memantine	0.3268
8. Placebo	0.2993	Placebo	0.1225	Intepirdine	0.2848	Donepezil	0.2797
9. Neflamapimod	0.2654			Rivastigmine Capsule	0.2045	Mevidalen	0.0687
10. Placebo Patch	0.0955						

Table 2.3 | Treatment rankings based on P-scores from network meta-analyses. This table ranks treatments based on their p-scores from the network meta-analyses, assessing cognitive and neuropsychiatric efficacy, along with safety metrics including dropout due to adverse events (AEs) and serious AEs. The treatments are listed from best to worst, aiding in evaluating their overall efficacy and safety for informed clinical conditions.

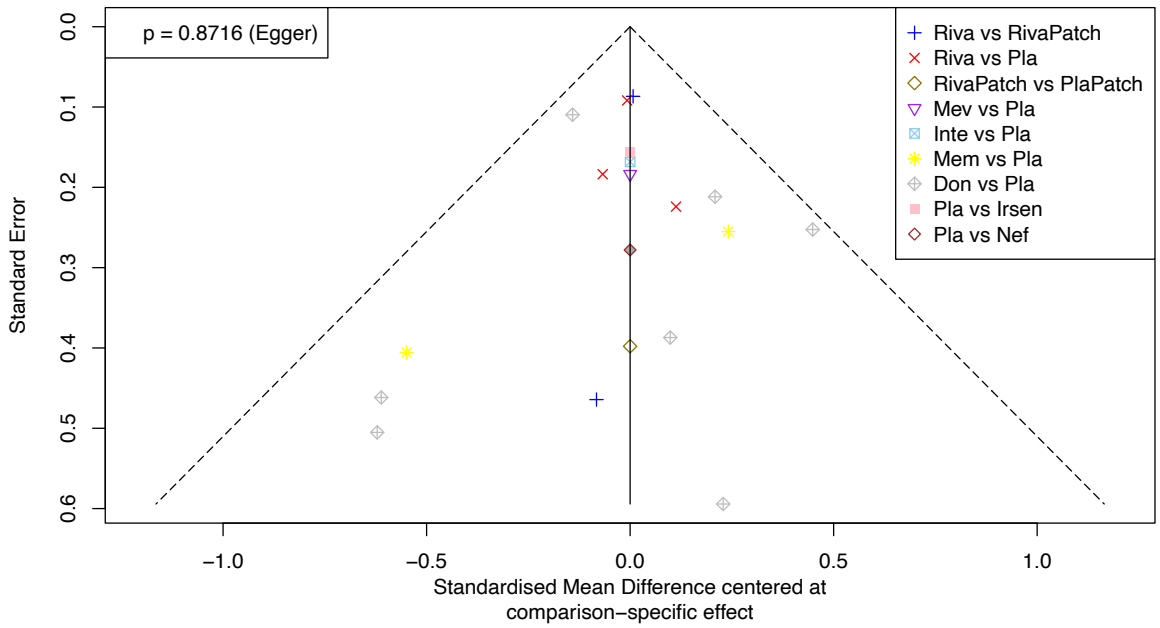


Figure 2.9 | Funnel plot of the included studies for cognitive network meta-analysis. This funnel plot shows the effects estimates of individual studies plotted against their precision, used to check for publication bias in the network meta-analysis. An egger's p-value of 0.8 suggests there is no significant publication bias.

2.4 Discussion

In this network meta-analysis, we evaluated pharmacologic treatments of Parkinson's disease dementia and dementia with Lewy bodies. We integrated findings from 22 randomized controlled studies, including over 3300 PD and DLB patients with mild-moderate cognitive impairment. According to the meta-analysis, only Rivastigmine and Donepezil significantly improved cognition. Only Rivastigmine improved neuropsychiatric symptoms. However, Rivastigmine was the only drug associated with adverse events. The results suggest that a trade-off between improving cognitive and neuropsychiatric symptoms and side effects should be carefully considered.

The study design included a comparative assessment between drugs and placebos, as well as an examination of Rivastigmine in its transdermal modality. We used change from baselines in global cognitive (MoCA, MMSE or MDRS) and neuropsychiatric (NPI) outcome measures for the network meta-analysis. Furthermore, our evaluation expanded beyond efficacy outcomes to include safety and tolerability measures, i.e. dropout rate attributable to adverse events and the incidence of serious adverse events.

The study showed that Rivastigmine is superior to the other medications in both cognitive and neuropsychiatric efficacy outcome measures. Together with Donepezil, they were the only drugs in our network meta-analysis to show statistically significant improvement in global cognition when compared to placebo with a higher effect of Rivastigmine (capsule). On the other hand, only Rivastigmine (in both formulations, capsules and patches) were shown to significantly improve the neuropsychiatric symptoms scores when compared to placebo. However, concerning safety measures, the picture was different. Rivastigmine was the only drug that showed statistically significant dropout rates due to

adverse events compared to placebo. It was ranked the last based on the p-scores. But it is important to note, that when it comes to serious adverse events that lead to life-threatening consequences or hospitalisation, there was no significant differences between Rivastigmine, placebo and the other medications.

Rivastigmine is the only FDA approved drug in Parkinson's disease dementia, and that is in agreement with our efficacy findings. Emre et al. 2004, one of the largest randomised placebo-controlled double-blinded trial in Parkinson's disease dementia which led to its approval, tested Rivastigmine capsules in 541 patients. It showed significant improvement in ADAS-cog by 2.1 points in comparison to worsening by 0.7 points in the placebo group (Emre et al., 2004). But it is apparent that this efficacy comes with its cost of mild side effects which are common with the cholinergic medications such as nausea, vomiting, and tremor (Khoury et al., 2018).

The cognitive improvement with cholinesterase inhibitors in this study is consistent with the previous pairwise meta-analyses. In addition, and similar to our findings, Stinton et al. (2015) found significant clinical but not cognitive improvement with Memantine compared to placebo in DLB and PDD patients (Stinton et al., 2015). However, neither clinical nor global cognitive improvements with memantine were found in Meng et al. (2019) (Meng et al., 2019).

In the comparative analysis of Rivastigmine's two formulations, no significant differences were found between the capsules and patches in both cognitive and neuropsychiatric measures. The capsule form, however, was the only form to demonstrate cognitive improvement over placebo. With respect to neuropsychiatric symptoms, both capsules and patches significantly outperformed placebo, with patches showing a higher effect and p-score. This suggests that although both formulations are efficacious for

managing neuropsychiatric symptoms, capsules might be preferred for their cognitive benefits. However, patches may be favoured for their lower rates of dropout due to adverse events, aligning with similar findings in Alzheimer's disease research (Darreh-Shori & Jelic, 2010; Winblad et al., 2007), indicating a better tolerance profile. These findings underscore the importance of individualising treatment based on the patient's symptom severity and their capacity to tolerate side effects. Emre et al. (2014) was the only study to compare the two formulations of Rivastigmine head-to-head in an open label randomized study. Only patients with moderate-severe dementia (MMSE < 21) showed significant improvements in the cognitive measures MDRS and MMSE with capsules in comparison to patches (Emre et al., 2014). However, the primary outcomes of the study were focused on long-term safety and tolerability. Also, the open label non-blinded design of this study poses a high risk of performance bias.

In terms of dosing and pharmacokinetics, varying dosages of Rivastigmine and Donepezil were used across the included studies, potentially affecting the outcomes. Rivastigmine exhibits different pharmacokinetics between its oral and transdermal formulations (Mercier et al., 2007). The capsule form is rapidly absorbed, with a peak plasma concentration occurring around 1 hour after ingestion, resulting in a less stable plasma level. In contrast, the transdermal patch takes approximately 8 hours to reach its peak concentration, providing a more gradual and consistent release of the drug over 24 hours. This smoother pharmacokinetic profile results in lower peak plasma concentrations and reduced fluctuations between peak and trough levels, which may explain the patch's improved tolerability (Cummings et al., 2007). On the other hand, Donepezil has a much longer half-life of approximately 70 hours (compared to 1-2 hours for Rivastigmine), allowing for once-daily dosing, which enhances patient adherence (Rogers & Friedhoff, 1998).

Cholinesterase inhibitors like Rivastigmine and Donepezil are associated with central cholinergic gastrointestinal side effects, such as nausea and vomiting, particularly during initial dose titration (Imbimbo, 2001). These side effects are believed to arise from rapid increase in acetylcholine levels caused by inhibition of cholinesterase enzymes. Administering Rivastigmine with food or using the transdermal patch can mitigate these side effects by slowing the drug's absorption and providing a more gradual increase in plasma levels (Desai & Grossberg, 2005; Khoury et al., 2018).

The transdermal patch also offers several advantages for elderly patients, who often face difficulties managing complex medication regimens and swallowing pills (Emre, Bernabei, et al., 2010). The patch's continuous drug delivery, visual reassurance of administration, and simplified dosing regimen improve treatment compliance, especially in elderly populations with multiple comorbidities.

Considering the comprehensive results from network meta-analyses, clinicians should carefully balance the potential benefits against the risks when prescribing cognitive-enhancing medications for PDD and DLB patients. Rivastigmine capsules are preferable for patients experiencing both cognitive and neuropsychiatric symptoms, provided they can tolerate the mild side effects. For patients primarily struggling with cognitive symptoms who are sensitive to side effects, Donepezil may be a more suitable choice. Alternatively, for those whose primary concerns are neuropsychiatric symptoms, Rivastigmine patch would be a better option. The better overall cognitive benefit/risk profile of Donepezil was also shown in a recent network meta-analysis of randomized controlled trials in DLB (Tahami Monfared et al., 2020).

We understand that personalized treatments might be the future of cognitive treatments also in PDD and DLB, where complex interactions of different neurotransmitter systems lead to cognitive impairment. Every patient is different and until we reach the ultimate aim of finding a cure to dementia, it is important to evaluate the current available treatments and update the treatment protocols accordingly.

A strength of this study is the use of network meta-analysis. This gave us the opportunity to combine all the current evidence to compare and rank the cognitive treatments in Lewy body disorders. Also, strict inclusion criteria were used to protect and ensure transitivity which is an important assumption of the network meta-analysis. In addition, we assessed the effect modifiers across the included studies.

There are, however, several limitations to this study that should be acknowledged. Firstly, while the use of network meta-analysis allowed us to combine the available evidence, the overall number of studies that met our inclusion criteria was limited. More specifically, many of the included trials had small sample sizes, with some studies comparing as few as 7 patients receiving the treatment to 9 patients receiving a placebo. These small sample sizes reduce the statistical power of the individual studies, making it difficult to draw robust conclusions and increasing the likelihood of variability or bias. This issue is especially important when considering the precision of treatment effect estimates, as small samples may inflate the apparent effects of an intervention or obscure true effects due to lack of sufficient data.

Second, there was considerable variability in the dosages of some drugs used across the included studies. Different studies administered varying dosages of the same drug, introducing heterogeneity into the analysis. Rivastigmine and Donepezil, in particular, have dose-dependent efficacy, with previous research indicating that higher doses can lead to

improved cognitive and behavioural outcomes (Alva et al., 2014; Anand et al., 2000; Grossberg et al., 2013; Manabe et al., 2016). However, this network meta-analysis could not account for these variations due to a lack of dose-specific studies. This limitation complicates the comparison of treatment effects, as optimal dosages for cognitive improvement in LBD are not universally established, and inconsistent dosing regimens may influence the results.

Third, some of the potential disease-modifying drugs were represented by only single studies within our analysis. This reliance on data from single studies limits the robustness and generalisability of conclusions regarding these drugs. The absence of multiple trials on specific drugs increases the risk of bias and makes it more challenging to validate their effectiveness in a broader population.

Lastly, the scarcity of head-to-head comparison studies between the various cognitive treatments posed a significant challenge. This lack of direct comparisons meant we were unable to test the direct-indirect consistency of the network meta-analysis, which is a key assumption for ensuring the validity of the findings.

In summary, while strict inclusion criteria and the assessment of effect modifiers across studies helped ensure transitivity, the small sample sizes, variability in dosages, reliance on single studies for certain drugs, and lack of direct comparisons between treatments represent key limitations in our analysis. These limitations should be considered when interpreting the findings and their generalisability to clinical practice.

2.5 Conclusion

This network meta-analyses showed that Rivastigmine capsules are likely to be most efficacious compared to other available drugs in improving global cognitive and neuropsychiatric measures in PDD and DLB patients. However, it was the least tolerable when compared to placebo and Donepezil was shown to have a better overall benefit/risk profile. Clinicians must weigh benefits and risks when prescribing a cognitive enhancer, accounting for the patient's symptomatology and capacity to tolerate the potential side effects. Further head-to-head randomized controlled trials with larger sample sizes are necessary to determine a more thorough ranking of the drugs which will ensure better treatments protocols for PDD and DLB patients.

Chapter | 3

Chapter 3 | The Cognitive Effects of Cholinergic System in Lewy Body Diseases

3.1 Introduction

3.1.1 Background

Rivastigmine is the only FDA-approved drug to treat dementia in PD. It works by increasing cholinergic activity via the dual inhibition of acetylcholinesterase and butyrylcholinesterase (Kandiah et al., 2017). In the previous chapter, the network meta-analysis revealed the superiority of rivastigmine in improving cognitive outcome measures in comparison to placebo and other drugs in PD and DLB RCTs. This observation was consistent with previous meta-analyses (Matsunaga et al., 2015; Meng et al., 2019; Pagano et al., 2015; Rolinski et al., 2012; Stinton et al., 2015; Tahami Monfared et al., 2020). The question is, how does rivastigmine mechanistically affect the different cognitive domains in LBD?

The cholinergic system has been associated with many cognitive processes, including attention, cognitive flexibility, executive functions and memory. Previous cholinergic PET studies in PD showed a correlation of these cognitive functions with global and regional brain cholinergic activity (Bohnen et al., 2015; Bohnen et al., 2006; Bohnen et al., 2012; van der Zee et al., 2021). Regarding LBD, PD and DLB have similar in vivo cholinergic imaging profiles wherein greater denervation is linked to cognitive impairment and is more common in the posterior cortical regions (Klein et al., 2010; Shimada et al., 2009). In the dual syndrome hypothesis, a late posterior-cortical cholinergic deficit was proposed with visuospatial and memory impairments presenting in patients with PDD (Kehagia et al., 2013). However, the precise mechanistic effects of rivastigmine on cognitive functions in LBD

patients remain underexplored. This chapter aims to fill this gap by examining the impact of rivastigmine on specific cognitive functions through two detailed drug withdrawal studies.

3.1.2 Aims and Objectives

The primary aim of this work was to investigate the mechanistic effects of rivastigmine on cognitive functions in patients with PDD and DLB. The objectives were as follows:

1- **Study 1: Investigating the impact of rivastigmine on eye movements and reward sensitivity using an incentivised prosaccadic task**

- To assess the impact of rivastigmine on eye movements using an incentivised prosaccadic task with saccadic and pupillometric measures
- To determine whether rivastigmine enhances motivational responses to reward (reward sensitivity) as evidenced by changes in eye movement metrics

2- **Study 2: Examining the effects of rivastigmine on attentional networks through the Attentional Network Task (ANT)**

- To evaluate the effects of rivastigmine on attentional networks using the Attentional Network Task (ANT), focusing on the alerting, orienting and executive control components of attention
- To analyse whether rivastigmine improves the efficiency of these attentional networks, thereby enhancing overall cognitive performance.

3.2 General Methods

3.2.1 Recruitment and Participants

The recruitment process started with a search of patient databases of the Oxford Department of Experimental Psychology and the OPDC, which include participants referred from clinics throughout the Thames Valley region. Eligible participants who had LBD and were prescribed rivastigmine by their treating doctors were contacted, along with HCs. All the patients had a clinical diagnosis of idiopathic PD based on the MDS (Postuma, Berg, et al., 2015)or UK Brain Bank diagnostic criteria (Hughes et al., 1992) or DLB based on the consensus diagnostic criteria (McKeith et al., 2017). Official invitation letters were sent with a participant information sheet explaining the study and its aims, objectives and rationale in detail. Participants were given the opportunity to ask questions, and written informed consent was obtained. Participants were compensated for their time and travel expenses. They were also notified that they would be eligible for additional monetary rewards based on their performance in the experimental tasks. All participants had normal or corrected-to-normal vision during the testing period, with no ophthalmic conditions that might affect eye-tracking, such as cataracts or double vision. The study had the approval of the local ethics committee and was executed in accordance with the Declaration of Helsinki.

3.2.2 Study Setting and Visit Structure

Each participant had two visits, one for each condition (ON and OFF rivastigmine). These visits were counterbalanced with block randomisation to reduce the training/learning effect bias. Ahead of the visit, an instructional email was sent to the participant regarding drug intake. For the OFF visit, the patient was instructed to withhold the capsule or patch overnight. For the ON visit, they were directed to take rivastigmine as usual. The patients were also instructed not to change any of their other medications. Each visit was preceded by a medical and drug history along with a physical examination (UPDRS III). This was followed by a MoCA assessment and an online cognitive test.

Each visit lasted around 3–4 hours and consisted of three experimental tasks. The tasks were presented in a fixed order for all participants: first, an eye-tracking prosaccadic monetarily incentivised task, followed by a reversal learning volatility task (Dice-learning), and finally, the ANT. The task order was kept consistent to avoid introducing additional variability across participants that might arise from differences in task sequencing, and to ensure comparable cognitive load across visits. Breaks were given between the tasks to reduce the burden on the participants. In this chapter, we present the findings from the first and third tasks.

3.3 Study 1 | Investigating the Impact of Rivastigmine on Eye Movements and Reward Sensitivity Using an Incentivised Prosaccadic Task

3.3.1 Introduction

Apathy is a prevalent and multifaceted NMS observed in LBD, including PD and DLB. Defined as a 'quantitative reduction of self-generated voluntary and purposeful behaviours' (Levy & Dubois, 2006), apathy significantly affects patients' quality of life and presents considerable challenges in clinical management. The underlying mechanisms of apathy in LBD are complex and involve several neurotransmitter systems, with particular emphasis on the dopaminergic and cholinergic systems.

The dopaminergic system's role in motivation and reward processing is well-documented, especially its involvement in fronto-striatal circuits that are crucial for initiating and sustaining goal-directed behaviours (Berridge & Robinson, 1998; Salamone et al., 2016). However, apathy is also prevalent in neurodegenerative conditions where dopaminergic pathways are relatively intact (Lanctôt et al., 2017), prompting research into other neurotransmitter systems, particularly the cholinergic system, which is extensively implicated in cognitive and attentional processes (Everitt & Robbins, 1997; Sarter et al., 2006).

The cholinergic system, mediated by muscarinic and nicotinic receptors, exerts a modulatory effect on neuronal activity and neurotransmitter release, particularly in regions like the basal ganglia and prefrontal cortex (Picciotto et al., 2012; Tanimura et al., 2018). These regions are integral to the regulation of motivation and reward processing, suggesting that cholinergic dysfunction might contribute to the apathetic states observed in LBD. Preclinical studies have demonstrated that manipulating cholinergic signalling in these brain

areas can significantly alter reward-seeking behaviour, highlighting a potential therapeutic target for apathy (Collins et al., 2016; Rice & Cragg, 2004).

Rivastigmine, a ChEI that enhances cholinergic transmission by preventing the breakdown of acetylcholine, has shown promise in ameliorating apathy symptoms in clinical trials involving LBD patients (Devos et al., 2014; McKeith et al., 2000). However, the mechanisms by which rivastigmine influences apathy and its effects on reward sensitivity remain poorly understood. Previous studies have primarily relied on subjective assessments of apathy, which may not fully capture the nuances of this complex symptom (Devos et al., 2014; McKeith et al., 2000).

3.3.1.1 Saccadic Eye Movements and Cholinergic System Modulation

Prosaccade eye movements are rapid, reflexive shifts in gaze toward a sudden visual stimulus, such as a target or light appearing in the periphery of the visual field (Fischer & Ramsperger, 1984; Klein & Fischer, 2005). These movements are automatic and are part of the brain's mechanism to quickly orient attention and vision toward important environmental stimuli. Prosaccades are essential for efficient visual exploration and attentional shifts, enabling individuals to focus rapidly on new objects or events in the surroundings. In contrast, antisaccades are voluntary eye movements that require the individual to look away from a visual stimulus, often used in studies to assess inhibitory control, which complements the reflexive nature of prosaccades (Munoz & Everling, 2004). The physiological control of prosaccades involves a highly coordinated network of brain regions, primarily the superior colliculus in the midbrain, the frontal eye field in the frontal cortex, and the brainstem saccade generators like the paramedian pontine reticular formation for horizontal movements and the rostral interstitial nucleus of the medial longitudinal fasciculus for vertical movements (Brodal, 2016).

The neurotransmitter systems involved in prosaccade generation highlight the importance of precise neural communication (Horn et al., 1994). Among these systems, cholinergic modulation has a particularly significant impact on saccadic eye movements, which are key measures of motivated action and attentional control. Pharmacological studies investigating cholinergic and anticholinergic drugs illustrate this influence, with reviews by Reilly et al. (2008) and Naicker et al. (2017) detailing the effects of these drugs on eye movement (Naicker et al., 2017; Reilly et al., 2008). For instance, antimuscarinic agents like hyoscine hydrobromide (scopolamine) have been shown to reduce saccadic peak velocity (Oliva et al., 1993). Additionally, nicotine, a cholinergic agonist, has been reported to improve performance in anti-saccade tasks when initial performance is suboptimal, although this benefit appears to plateau as performance stabilizes (Parr & Friston, 2019; Rycroft et al., 2006; Sherr et al., 2002).

A recent placebo-controlled, double-blind study by Grogan et al. (2024) investigated trihexyphenidyl (THP), a muscarinic antagonist, using an incentivised eye movement task to examine motivation-linked responses (Grogan et al., 2024). The results showed that participants responded faster and with greater vigour when incentives were high, but THP blunted these motivational effects, implicating muscarinic receptors in facilitating invigoration through reward.

3.3.1.2 Pupil Responses and Cholinergic System Modulation

The relationship between pupil dilation and central cholinergic modulation is well-documented, with pupil responses serving as a sensitive indicator of neuromodulatory activity related to arousal, attention, and cognitive processing. Reimer et al. (2016) demonstrated that spontaneous fluctuations in pupil diameter correlate with activity in both the cholinergic and noradrenergic systems. These two systems, however, contribute to pupil

dilation differently: phasic changes in pupil size are predominantly associated with noradrenergic activity, while more sustained dilations, such as those during continuous behavioral states like locomotion, reflect ongoing cholinergic activation (Reimer et al., 2016). This tonic cholinergic influence on pupil dilation suggests that pupillometry can effectively track cholinergic engagement over time, offering insights into attention and arousal states in both healthy individuals and clinical populations, including LBD patients.

Larsen et al. (2018) added that cholinergic neurons in the basal forebrain, which are activated during pupil dilation, may receive modulatory input from noradrenergic pathways (Larsen & Waters, 2018). This interconnected relationship implies that pupil dilation is not an isolated measure of either cholinergic or noradrenergic activity but reflects a complex neuromodulatory network. This coordination suggests that both systems play distinct but overlapping roles in supporting attentional and arousal states, making pupil responses a useful marker for tracking neuromodulatory balance in LBD, where cholinergic deficits are central to cognitive and behavioral symptoms, including apathy.

Studies in humans further validate the role of cholinergic modulation in pupil dilation, especially through pharmacological interventions that target the cholinergic system. For example, Naicker et al. (2016) conducted a placebo-controlled study in which subjects were administered various anticholinergic agents, including centrally acting drugs like hyoscine hydrobromide and promethazine. They found that hyoscine hydrobromide, a potent central anticholinergic, led to an increase in pupil diameter during cognitive tasks, reinforcing the role of central cholinergic pathways in modulating pupil size (Naicker et al., 2016). This increase was absent with peripherally acting anticholinergics, suggesting that central cholinergic activity specifically contributes to pupil dilation during mental effort. The

study underscores the potential of pupillometry to capture the effects of central cholinergic modulation on cognitive processes, offering a non-invasive measure of cholinergic function.

Given these findings and the need for more objective measures, this study aimed to investigate the impact of rivastigmine on reward sensitivity using an incentivised prosaccadic task combined with eye-tracking technology. This approach allowed for the precise measurement of saccadic eye movements and pupillary responses, which are known to reflect underlying motivational and attentional states. By comparing these parameters in patients with LBD both on and off rivastigmine, this study sought to elucidate the role of cholinergic modulation in apathy and reward processing.

Hypothesis: Rivastigmine, by enhancing central cholinergic activity, will improve reward sensitivity as measured by increased saccadic peak velocity and pupillary dilation in response to higher rewards.

3.3.2 Methods

3.3.2.1 Experimental Paradigm

We used an eye-tracking monetarily incentivised task developed by Muhammed et al. (2016) to assess the saccadic and pupillary responses to reward (Muhammed et al., 2016) (Figure 3.1). Eye movements and pupillary size were monitored with an infrared eye tracker (Eyelink 1000, SR Research). In the set-up of the experiment, the eye-tracking camera was calibrated for each participant with nine fixation points. Participants were told that the task involved measuring the speed of eye movements, and the faster they moved their eyes toward the targets, the greater the reward they would receive out of the maximum possible reward available for each trial. They were also instructed to keep their eyes as wide open as possible throughout the experiment, reduce blinking, and blink only between trials if possible.

The task comprised 270 trials organised into five blocks. Each block comprised 54 trials with breaks in between them to allow the participant to rest if required. At the start, the participants were instructed to focus on the centre of the screen for 500 milliseconds (ms) as a fixation period until they heard the reward available for each trial from the loudspeaker. The loudspeaker would play a pre-recorded auditory cue with the maximum possible reward in pence (p) '0 p, 10 p or 50 p maximum' lasting for 1200 ms. After an interval of 1400, 1500 or 1600 ms, the central disc would vanish, and a target would appear on either the left or the right side of the screen, positioned at 11' eccentricity, with a diameter of 4'. The brightness of the disc targets and the room lighting were kept the same throughout the trials to prevent any influence on pupil dilation.

The participants were given a share of the maximum reward based on their performance. Each reward level had 90 trials, making up a total of 270 trials. The reward amount was

adjusted for each trial through an exponential fall-off based on the RTs of the 20 previous trials. This adaptive approach maintained a consistent level of difficulty throughout the experiment. It considered the varying individual fatigue rates and baseline RTs. Most importantly, it ensured that all participants received an equal amount of the reward on offer. To keep the participants motivated, the reward achieved was shown immediately within the target disc at the end of each trial. In addition, positive reinforcement was administered using auditory cues: a 'bell' sound indicated a reward exceeding 10 p, while a 'cash register' sound signalled a reward surpassing 30 p. When earnings were below 10 p, no sound was played.

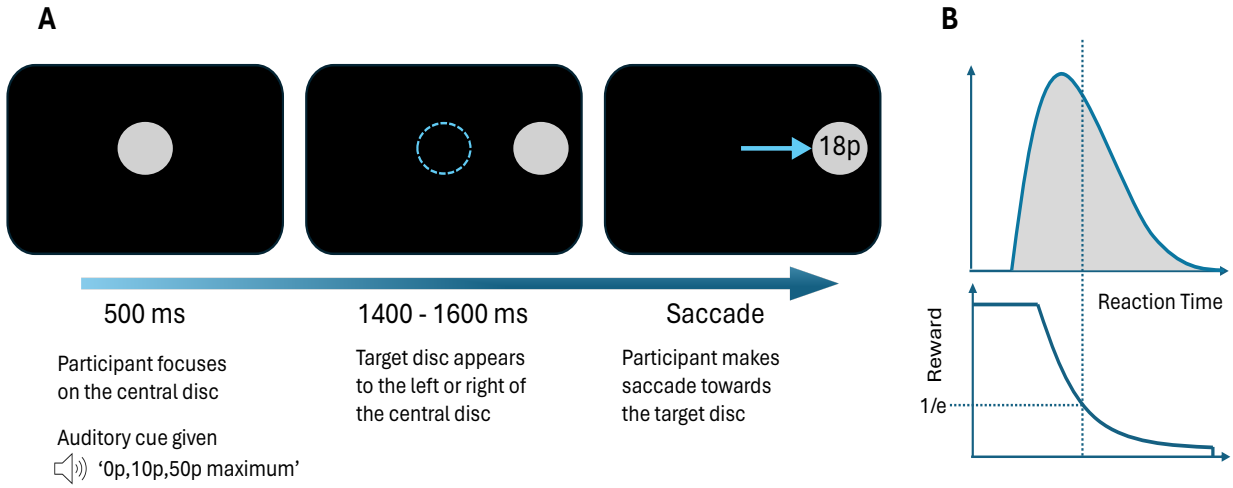


Figure 3. 1 | Schematic representation of the eye tracking task (adapted from Muhammed et al. 2016) (**A**): The experimental paradigm is illustrated here with the reward gained shown within the target disc in pence for each trial (for example 18p). (**B**): The graph shows an adaptative exponential fall-off used to calculate and dynamically adjust the reward obtained by each participant and for each trial, based on the mean reaction time from the previous 20 trials. Participants received a proportion of the maximum amount on offer dependent on performance. This meant that participants received equal reward amounts, the difficulty level was kept the same throughout the tasks, and varying individual fatigue rates and baseline reaction times were accounted for.

3.3.2.2 Eye-tracking Recording

Eye-tracking recordings were conducted in a dimly lit room, where the participants rested their chins on a chinrest distanced 60 cm from a 21' screen (1024 × 768 pixels, 100 Hz refresh). The right eye was monitored for all participants, except for two participants for whom the left eye was tracked, and eyes were sampled at the rate of 1 kHz. The presentation of stimuli occurred on a Windows computer equipped with MATLAB (from The MathWorks) and the Psychophysics Toolbox. Eye movements were assessed in real-time by the Eyelink computer online and promptly transmitted to the presentation computer to provide immediate feedback. A saccade was considered if the eye movement exceeded 2 degrees and was registered as a completed saccade if it landed within a 5-degree radius from the target's centre. The first landing point within the target area was used to determine saccade completion. RT was calculated from the moment the target appeared to the time when the saccade was deemed complete. Peak saccadic velocity was determined as the highest recorded velocity during the saccade. For pupillary data, dilation was measured as the proportional change in diameter from the average baseline pupillary diameter, recorded in arbitrary units (A.U.) by EyeLink.

3.3.2.3 Statistical Analysis

Eye tracking data analysis and statistics were performed using a modified custom-made MATLAB code and R. The saccadic parameters of interest were peak velocity, amplitude, RT and peak velocity residuals. Peak saccadic velocity was a main parameter as it showed sensitivity to reward in both human and primate studies (Manohar et al., 2015; Takikawa et al., 2002). However, with the 'main sequence' effect (Bahill et al., 1975), the amplitude was factored out in a linear regression and the peak velocity residuals were used as the primary outcome of the saccadic analysis. Only trials with successfully registered

saccades were included in the analysis. Outliers in any saccadic parameters were removed from the data. Saccades with peak velocities of 2 or more standard deviations from the mean were excluded (< 100 and > 700 degrees per second). In addition, saccades with RTs below 90 ms or above 350 ms and amplitudes lower than 3 degrees or higher than 10 degrees were excluded. A repeated-measures analysis of variance (ANOVA) using a mixed linear effect model was performed for each saccadic parameter with within-subject factors of reward (0 p,10 p and 50 p), drug (ON and OFF rivastigmine) and between-subjects random effects.

For pupillary data, interpolation was applied to fill in any pupil traces lost due to blinking. Pupillary baseline sizes were calculated as the mean of pupillary diameters at the fixation period (for 500 ms) at the beginning of each trial before the auditory cue. The pupillary response to reward was measured as the relative change in pupillary size from the mean baseline size to the epoch of interest, synchronised with the onset of the reward auditory cue. The epoch of interest was the mean pupillary size between 1400 and 2400 ms post the auditory cue.

The saccadic and pupillary reward sensitivity for each participant was characterised by the mean differences in saccadic peak velocity and pupillary diameter response between the highest reward (50 p) and the absence of reward (0 p) conditions (50 p – 0 p). The greater the difference, the higher the sensitivity to reward. To assess whether rivastigmine improved saccadic and pupillary reward sensitivity, paired t-tests were performed.

To address any potential violations of sphericity in the data, the Greenhouse–Geisser correction was applied where necessary. Spearman rank correlations were used for non-parametric questionnaire data, while Pearson correlations were performed for parametric data. For multiple comparisons, Tukey's Honest Significant Difference (HSD) adjustments

were utilised. In all the analyses, P values of less than 0.05 were considered statistically significant.

3.3.3 Results

3.3.3.1 Participant Characteristics

A total of 25 LBD patients (16 PD and eight DLB) and 31 HCs were recruited to participate in this study. One patient in the LBD group was excluded from completing the task as they were unable to attend the second visit. This patient also exhibited a high level of cognitive impairment, which affected their ability to understand the task requirements. Additionally, the task proved physically and mentally tiring for the patient, with frequent eyelid closures and difficulty maintaining focus, ultimately leading to their exclusion from the study.

The mean age of the participants was 69.1 ± 8.2 years, with no significant difference in age between patients and controls. However, differences in gender distribution were noted, with women constituting only 20% of the LBD group compared to 58% of the HC group. Around 89% of the participants were right-handed, and 11% were left-handed. There was a significant difference between patients and HCs in global cognitive status, with lower scores in patients. The mean MoCA score was 22 ± 3.5 in patients compared to 28 ± 1.5 in HCs. None of the participants had a history of other major psychiatric or neurological conditions, head injuries or neurosurgeries. Table 3.1 summarises the demographic data of the participants.

		LBD patients (N=24)	Healthy elderly controls (N=31)	p value
Age (years) Mean (SD)		71.2 (7.5)	67.5 (8.5)	0.098[1]
Gender n (%)	Female	3 (20.0%)	18 (58.1%)	0.035[2]
	Male	12 (80.0%)	13 (41.9%)	
Disease Duration Mean (SD)		3.8 (3.7)	n/a	n/a
Age at onset of symptoms (years) Mean (SD)		62.6 (7.7)	n/a	n/a
Age at diagnosis (years) Mean (SD)		66.9 (6.9)	n/a	n/a
Rivastigmine Form n (%)	Capsule	11.0 (73.3%)	n/a	n/a
	Patch	4.0 (26.7%)	n/a	
Handedness n (%)	Left	1.0 (6.7%)	4.0 (12.9%)	0.789[2]
	Right	14.0 (93.3%)	27.0 (87.1%)	
Education Years Mean (SD)		15.6 (3.2)	n/a	n/a
MoCA (total scores) Mean (SD)		22.0 (3.5)	28 (1.5)	<0.001[1]

Table 3.1 | Baseline characteristics of study participants. 1. Independent t-test 2. Pearson's Chi-squared test.

The average disease duration of the LBD participants was 3.8 ± 3.7. Only one PD patient was drug-naïve, while the rest were on dopamine replacement medications (levodopa or dopamine agonists). The average levodopa equivalent daily dose (LEDD) of the medicated patients was 662.5 ± 503.43 mg. Of the LBD patients, 73% were on rivastigmine capsules, and 27% were on rivastigmine patches. Most participants took either 3 mg or 6 mg capsules once or twice daily, while for the transdermal patches, the dosage was 9.6 mg/24 hours. PD patients were significantly older than DLB patients; otherwise, no significant differences were observed between the two patient groups regarding disease duration, gender representation, education years and MoCA scores. Table 3.2 compares the baseline characteristics of the PD and DLB patients. In the ON visits, the average number of hours from the last rivastigmine dose was 3.1 ± 2.9 hours, while in the OFF visits, the duration was 24.6 ± 5.8 hours. There was no significant difference in the MoCA scores between the ON and OFF visits (paired t-test = −0.95, p-value = 0.358); see Table 3.3.

		DLB (N=8)	PD (N=16)	Total (N=24)	p value
Age (years) Mean (SD)		67.6 (6.3)	75.4 (6.9)	71.2 (7.5)	0.039[1]
Gender n (%)	Female	2.0 (25.0%)	1.0 (14.3%)	3.0 (20.0%)	0.605[2]
	Male	6.0 (75.0%)	6.0 (85.7%)	12.0 (80.0%)	
Disease Duration (years) Mean (SD)		2.4 (2.5)	5.2 (4.4)	3.8 (3.7)	0.161[1]
Age at first symptom (years) Mean (SD)		58.8 (3.6)	65.9 (8.9)	62.6 (7.7)	0.096[1]
Age at diagnosis (years) Mean (SD)		63.7 (5.5)	70.1 (6.9)	66.9 (6.9)	0.077[1]
MoCA Total Mean (SD)		22.2 (3.5)	21.7 (3.8)	22.0 (3.5)	0.781[1]
Education Years Mean (SD)		15.8 (4.1)	15.4 (1.9)	15.6 (3.2)	0.852[1]
Handedness n (%)	Left	1.0 (12.5%)	0.0 (0.0%)	1.0 (6.7%)	0.333[2]
	Right	7.0 (87.5%)	7.0 (100.0%)	14.0 (93.3%)	
Rivastigmine Form n (%)	Capsule	5.0 (62.5%)	6.0 (85.7%)	11.0 (73.3%)	0.310[2]
	Patch	3.0 (37.5%)	1.0 (14.3%)	4.0 (26.7%)	

Table 3.2 | Baseline characteristics of the two patient groups. 1. Independent t-test 2. Pearson's Chi-squared test.

	ON (N=15)	OFF (N=15)	Total (N=30)	p value
MoCA_Total Mean (SD)	21.8 (3.4)	22.4 (3.4)	22.1 (3.3)	0.358[1]
Last_Rivastigmine_dose (hrs) Mean (SD)	3.1 (2.9)	24.6 (5.8)	13.9 (11.8)	< 0.001[1]

Table 3.3 | Comparison between ON and OFF visits. 1. Paired t-test.

3.3.3.2 Saccadic Measures

Repeated-measures ANOVAs with linear mixed-effects models were performed on the saccadic eye movement parameters: peak saccadic velocity, amplitude, RT and peak velocity residuals. The models included random effects for individual variations among the subjects and fixed effects for the drug status and reward levels.

Rivastigmine Significantly Increases the Peak Saccadic Velocity

The mean peak saccadic velocity when the patients were on rivastigmine was significantly higher than when it was being withheld ($p < 0.001$). The main effect of the drug was statistically significant, with $F(1,8954.5) = 47.89$ ($p < 0.001$). The reward also had a significant effect on peak saccadic velocity, with $F(1,8953) = 5.79$ ($p = 0.003$). However, there was no significant interaction effect of the drug and the reward on peak velocity: $F(1,8953) = 0.15$ ($p = 0.8589$). This indicates that both drug treatment and reward independently

contribute to the increase in peak saccadic velocity, while their interaction does not have a significant effect. The model accounts for individual differences and shows robust effects for the main factors of interest. Pairwise comparisons of rewards in both drug conditions showed that the statistically significant increase in peak saccadic velocity was only noticed between the 0 p and 50 p reward levels ($p = 0.02$), while no significant differences were noted between the other reward levels (0 p vs. 10 p and 10 p vs. 50 p). Overall, when compared to HCs, the mean peak saccadic velocity in patients under both drug conditions was significantly lower (Figure 3.3A). To assess the impact of rivastigmine on saccadic reward sensitivity, a paired t-test was conducted. It revealed no significant differences between the ON and OFF drug conditions ($t(23) = 0.170$, $p = 0.867$). These results suggest that rivastigmine does not influence saccadic reward sensitivity.

Rivastigmine Has a Significant Positive Effect on Saccadic Amplitude

Patients on rivastigmine had a significantly higher saccadic amplitude compared to when they were off the medication (Figure 3.3B). The main effect of the drug on the amplitude was statistically significant: $F(1,8956) = 46.45$ ($p < 0.001$). However, the main effect of the reward was not statistically significant: $F(1,8953) = 1.16$ ($p = 0.312$). There was also no significant interaction effect of drug and reward on amplitude: $F(1,8953) = 0.35$ ($p = 0.704$). Figure 3.4 shows the linear relationship between peak saccadic velocity and amplitude, highlighting the differences by drug condition and reward level.

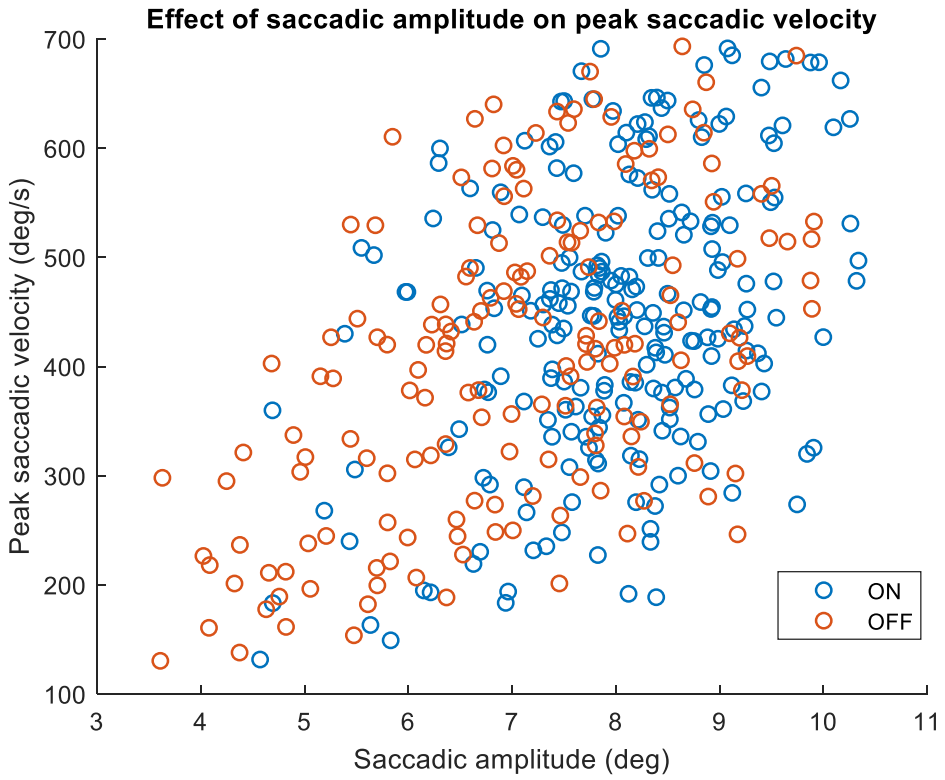


Figure 3.2 | Main Sequence. This graph shows an example of the main sequence from a single participant, illustrating the saccades recorded both ON and OFF the drug Rivastigmine. The x-axis represents the saccadic amplitude (in degrees) and the y-axis shows the corresponding saccadic velocity (in degrees/second). For all trials from all participants in the study, a linear model was fitted, showing a positive significant strong correlation between the two parameters (r= 0.53, p<2.2e-16).

Rivastigmine and Saccadic Velocity Residuals

After factoring out the main sequence effect of the amplitude on velocity (Figure 3.2), the velocity residuals were still significantly higher in the ON visits than in the OFF visits (Figure 3.3C). The linear mixed-effects model demonstrated statistically significant effects of both drug ($F(1,8976) = 9.37$, $p= 0.002$) and reward ($F(1,8976) = 5.34$, $p= 0.004$). Nevertheless, there was no significant interaction effect ($F(1,8976) = 0.06$, $p= 0.939$). Like velocity, post hoc pairwise comparisons revealed only a significant increase in velocity residuals between 0 p and 50 p.

Saccadic RT Significantly Decreases with Rivastigmine

RT is the time difference between the target onset and the onset of the saccadic completion. The model showed a significant main effect of drug ($F(1,8958) = 11.16$, $p < 0.001$) on the saccadic RT, but not of reward ($F(1,8953) = 0.75$, $p = 0.468$), and there was no interaction effect of drug and reward: $F(1,8953) = 0.14$ ($p= 0.873$); see Figure 3.3D.

To assess if the drug effect on saccadic measures was linked to a speed-accuracy trade-off, we analysed saccadic end-point variability. The linear mixed-effects ANOVA model indicated no drug effect on end-point variability ($F(1,23) = 0.64$, $p = 0.43$). There was also no significant effect of reward ($F(1,23) = 1.98$, $p=0.17$), nor was there an interaction effect between drug and reward ($F(1,23) = 0.12$, $p = 0.73$).

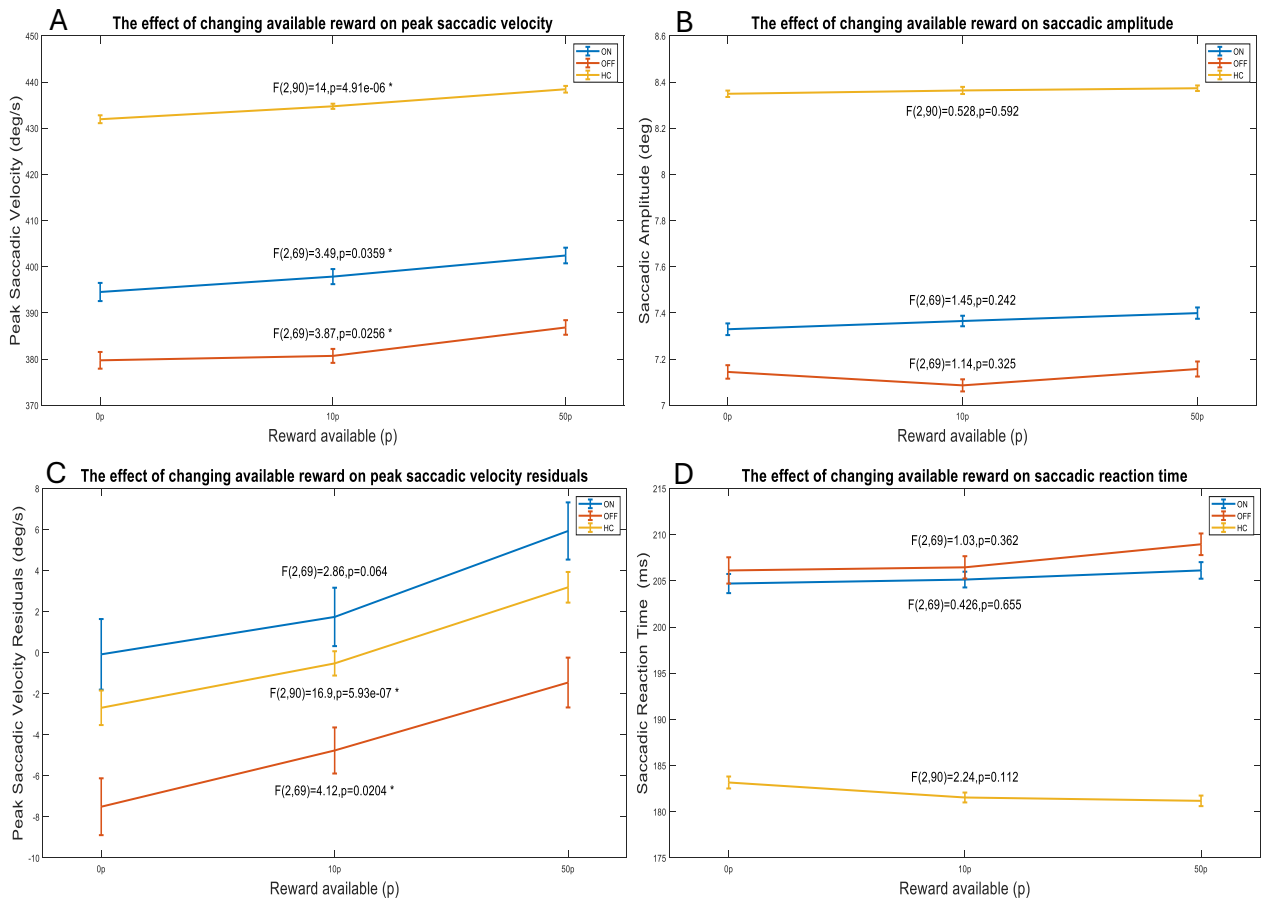


Figure 3.3 |The effects of drug on saccadic measures across different reward levels. (A) Velocity: The peak velocities were elevated in the ON state (illustrated in blue) relative to the OFF state (depicted in red), and both velocities were lower compared to HC (shown in yellow). Significant disparities in mean velocities among the various rewards were observed in both ON ($F(2,69) = 3.49$, $p = 0.0359$) and OFF states ($F(2,69) = 3.87$, $p = 0.0256$), with relatively similar reward sensitivity slopes. (B) Amplitude: This was significantly higher in the ON than in the OFF states but significantly lower than that of HCs. No statistically significant differences in amplitude were found between the different rewards in all conditions. (C) Velocity residuals: These remained significantly greater in the ON state compared to the OFF state, with HCs in between. Both the OFF state and HCs had a significant main effect of reward on velocity residuals as shown in the ANOVAs of the reward in the saccadic velocity residuals (OFF state: $F(2,69) = 4.12$, $p = 0.02$; HC: $F(2,90) = 16.9$, $p < 0.001$), while the ON state did not reach statistical significance ($F(2,69) = 2.86$, $p = 0.064$). Both states and HCs exhibited a similar trend and slope. (D) Reaction time: In HCs, this was significantly shorter than in patients, while no differences were noted between the two drug conditions. The effect of reward was not statistically significant in all conditions.

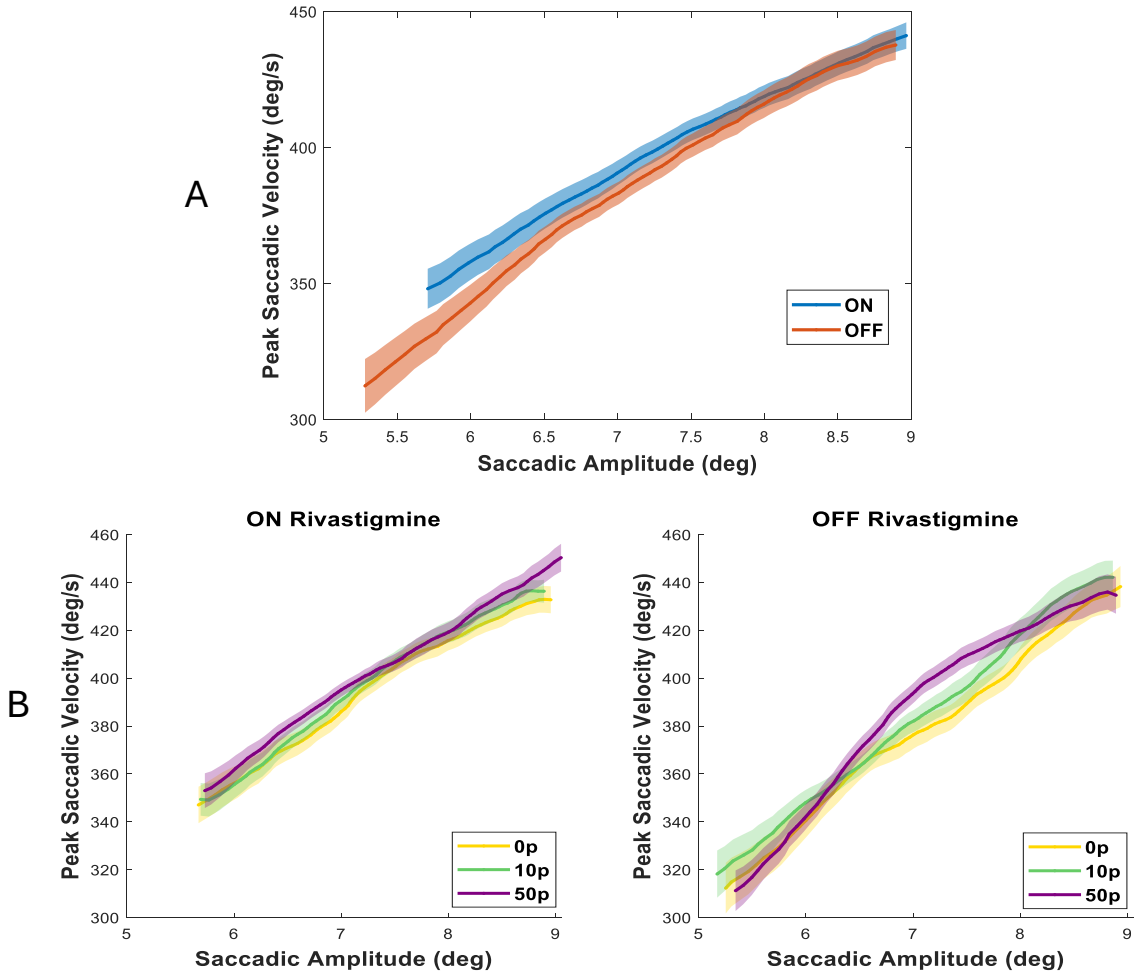


Figure 3.4 | The relationship between peak saccadic velocity and amplitude by drug and reward. (A) Drug: This conditional plot shows a linear relationship for both drug conditions, with shaded regions representing the standard error of the means. For most of the amplitude range, the ON condition exhibits a slightly higher peak saccadic velocity compared to the OFF condition, with differences more pronounced at lower amplitudes and diminishing as amplitude increases. (B) Reward: Each conditional plot (left: ON, right: OFF) shows a nearly linear relationship between saccadic amplitude and peak saccadic velocity for different reward levels: 0 p (yellow), 10 p (green) and 50 p (purple). The 50 p reward level generally exhibits the highest peak velocity across both conditions except in the OFF state (right), where at the lowest amplitudes below 6 degrees and highest amplitudes above 8 degrees, the 10 p reward level exhibits a higher peak saccadic velocity.

3.3.3.3 Pupillary Measures

The main pupillary measure of the task was the change in pupil size. The reward effect was measured as the change in the mean pupil diameter from the baseline in the fixation period at the start of the trial (of ~500 ms) to the epoch of interest, which was 1400–2400 ms after the auditory cue. The mean baseline pupil sizes in the two drug states (ON and OFF) and in HCs were similar and did not differ significantly (Figure 3.5). The same pattern was noticed for the different reward levels (0 p, 10 p and 50p) at baseline in each drug condition. In the epoch of interest, the mean pupil size was slightly larger in the ON state than in the OFF state, but no statistical significance was noted. Additionally, no statistically significant differences were observed between the mean pupil sizes in the epoch of interest with the different rewards.

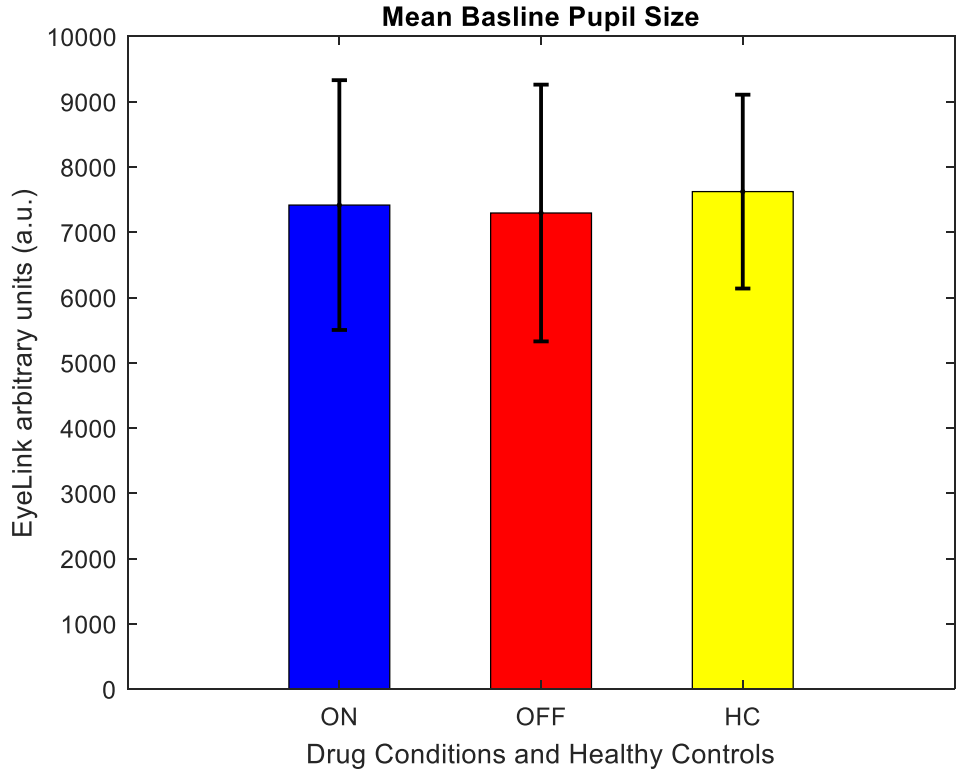


Figure 3.5 |Mean pupillary size at baseline for patients ON and OFF drug, and HC. These were measured at the fixation period in the first 500 ms of each trial before the start of the cue. The pupil sizes are measured in Eyelink units (E.U.s). No significant differences were noticed between ON (blue), OFF (red) drug condition and HC (yellow). Error bars represent SEM.

To test for the drug and reward effects on the pupillary measures, a linear mixed-effects ANOVA of the mean pupil change from baseline to the epoch of interest was conducted. It showed no main effects of drug and reward on mean pupil size change (drug: $F(1,115) = 0.086$, $p = 0.769$; reward: $F(2,115) = 1.644$, $p = 0.197$). In addition, no interaction effect was found (drug: reward - $F(2,115) = 0.333$, $p = 0.717$). Post hoc pairwise comparisons with Tukey's HSD adjustments revealed no statistically significant variances between the three reward levels ([Reward 10 p – 0 p] difference estimate 0.018, $t(125) = 0.002$, $p= 1.00$; [Reward 50 p – 0 p] difference estimate 15.682, $t(125) = 1.572$, $p= 0.262$; and [Reward 50 p – 10 p] difference estimate 15.664, $t(115) = 1.57$, $p= 0.263$). Moreover, although the mean difference noticed between 50 p and the other rewards on offer was larger, it was not statistically significant, and the reward did not modulate the pupil diameter.

The pupillary reward sensitivity was calculated as the difference between the mean pupillary size change with the maximum reward on offer (50 p) and the minimum available reward (0 p) over the specified times in the epoch of interest. A larger difference denotes higher reward sensitivity. In both ON and OFF states, no significant differences were noted between these two reward levels (Figure 3.6A,B). However, in HCs, the reward had a significant effect ($F(2,60) = 9.39$, $p < 0.001$, post hoc HSD (50 p – 0 p): $t(60) = 4.1$, $p < 0.001$); see Figure 3.6C. HCs also had significantly higher pupillary reward sensitivity compared to LBD patients in their ON state ($p = 0.045$) and borderline significance with respect to their OFF state ($p = 0.07$); see Figure 3.7A,B.

To evaluate the effect of rivastigmine on pupillary reward sensitivity, a paired t-test was performed between the ON and OFF conditions. No significant difference was observed between the two drug conditions: $t(23) = -0.122$, $p = 0.904$. Overall, these results indicate that rivastigmine did not also affect pupillary reward sensitivity.

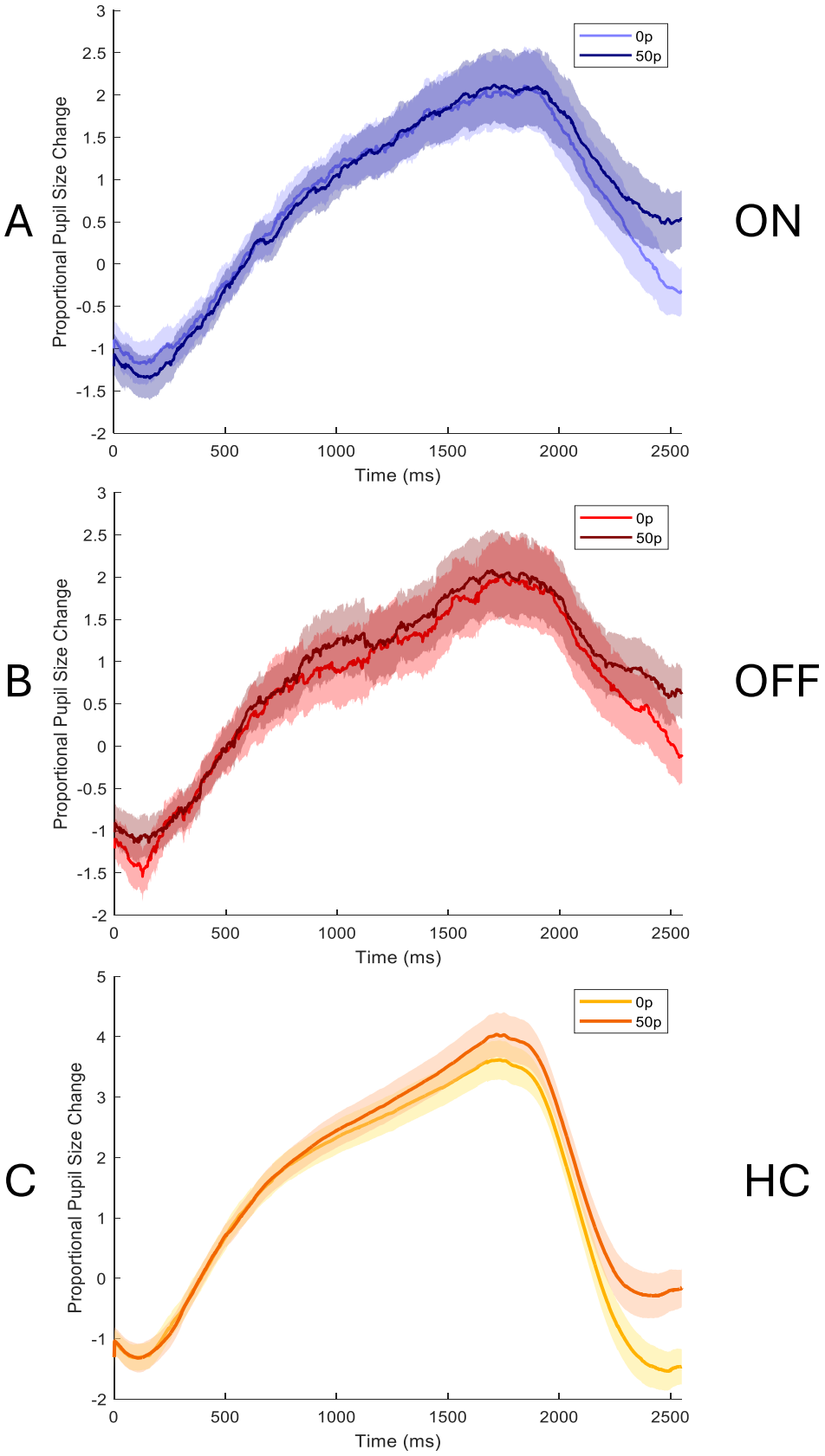


Figure 3.6 | Pupillary responses across study groups and drug conditions. Proportional changes in mean pupil sizes from baseline to the epoch of interest in the highest reward 50p and no reward (0p). In the ON (A) and OFF (B) states, no significant differences are visible between the two reward levels, although in the OFF state, 50p has a slightly higher mean compared to 0p. A significant difference is observed in HCs (C) [$t(60)=4.12$, $p=0.0003$].

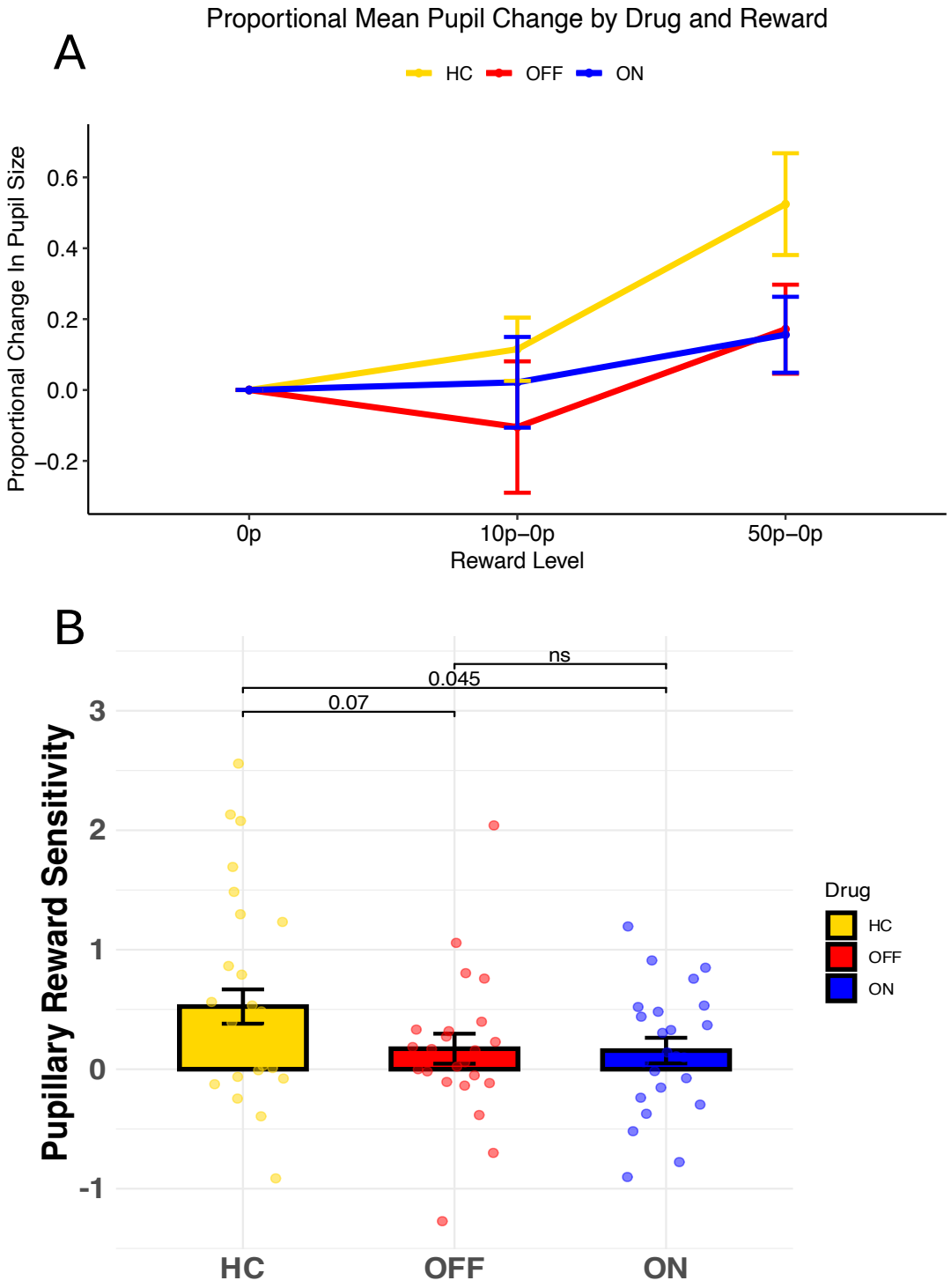


Figure 3.7 | Pupillary reward sensitivity measures across study groups and drug conditions. A) The graph shows the proportional change in pupil size across the different reward levels (0p, 10p-0p, and 50p-0p) for HCs (yellow), ON (blue) and OFF (red) drug conditions. The HCs exhibit a significant increase in pupil size for both 10p (p=0.006) and 50p reward levels (p=0.0003). In contrast, both ON and OFF conditions do not show significant differences in pupil size with increasing reward levels. B) Bar plots of pupillary reward sensitivity across study groups. Independent t-tests shows that HC have significantly higher pupillary reward sensitivity than ON (p=0.045) and higher than OFF with marginal significance (p=0.07). A paired t-test between ON and OFF showed no statistically significant difference (p=0.9). The jittered points, coloured according to drug condition, indicate pupillary reward sensitivity for individual participants.

3.3.4 Discussion

This study sought to determine the impact of the cholinergic medication rivastigmine on eye movements and reward sensitivity in patients with LBD. We used a pro-saccadic eye-tracking task to evaluate reward sensitivity and tested patients on and off the drug. We hypothesised that rivastigmine would increase reward sensitivity, as indexed by saccadic and pupillary responses, either through a direct effect on central cholinergic pathways or indirectly via the modulation of dopaminergic pathways. The results showed no interaction effect between drug and reward on participants' performances. This rejects our hypothesis of the cholinergic effect on reward sensitivity. However, the findings revealed significant independent effects of the drug and reward on the saccadic eye movement measures, even after adjusting for the main sequence effect.

3.3.4.1 Invigoration of Saccadic Velocity and Amplitude by Rivastigmine

Peak saccadic velocity exhibits a significant increase with the administration of rivastigmine. It is posited that this increase may be attributed to the drug's effect on saccadic amplitude, which also shows a significant increase with the drug. This amplitude change is a part of the main sequence effect, a well-established direct relationship between saccadic amplitude and velocity (Bahill et al., 1975). When this effect was controlled for, the influence of rivastigmine on increased saccadic velocity remained significant. In addition, we observed that saccadic RT (latency) was significantly shorter (faster) with rivastigmine, while increased reward levels did not produce any changes. These saccadic findings may be explained by the role of the cholinergic system in saccadic eye movement generation. The superior colliculus (SC), which is essential for saccade initiation, receives cholinergic inputs from the PPN (Beninato & Spencer, 1986; Hall et al., 1989; Martinez-Gonzalez et al., 2011). PPN neurons

are active during saccadic tasks in primates and stimulate SC neurons to initiate saccades (Kobayashi et al., 2002; Kobayashi et al., 2001; Okada & Kobayashi, 2009). Supporting this, pharmacological studies have demonstrated the significant impact of cholinergic modulation on saccadic measures. For instance, nicotine, a cholinergic agonist, significantly reduced saccadic RT when injected into the primate SC (Aizawa et al., 1999; Watanabe et al., 2005). Similarly, a recent randomised controlled study showed that the acute administration of galantamine, a ChEI, significantly decreased saccadic RT (Baakman et al., 2022). In contrast, the use of anticholinergic drugs, like procyclidine, hyoscine hydrobromide and promethazine, was found to reduce saccadic amplitude and velocity and increase latency (Glue, 1991; Reilly et al., 2008), highlighting the critical role of cholinergic activity in these processes.

On the other hand, levodopa was found to prolong saccadic latencies (Bakhtiari et al., 2020; Hood et al., 2007; Lu et al., 2019; Michell et al., 2006). However, it showed no effect on other saccadic measures, such as peak velocity and amplitude, and may even decrease them (Lu et al., 2019; Muhammed et al., 2016). Conversely, DBS of the subthalamic nucleus (STN) or GPi led to significantly faster saccadic RTs in PD patients (Antoniades et al., 2012; Antoniades et al., 2015; Bakhtiari et al., 2020; Temel et al., 2009; Yugeta et al., 2010). This effect of DBS might be due to its influence on non-dopaminergic systems, including PPN cholinergic projections to the STN and GPi (Bevan & Bolam, 1995; Clarke et al., 1997; Woolf & Butcher, 1986). Overall, this suggests that dopaminergic modulation can have varying effects, unlike cholinergic modulation, which improved all saccadic measures in our study. It is important to note that the positive effect of rivastigmine on eye movement measures could have significant implications for patients' daily activities that require split-second

attention, such as driving or crossing the street, even though the drug does not improve reward sensitivity.

3.3.4.2 Rivastigmine and Pupillary Measures

In terms of the pupillary measures, despite the anticipated miotic effect of rivastigmine, our study found no significant differences between the two drug conditions in the mean change in pupil diameter from baseline to the epoch of interest (~1400–2400 ms post-auditory cue). This could be masked by the effect of rewards on these pupillary measures as shown in previous studies (Manohar & Husain, 2015; Muhammed et al., 2021; Van Slooten et al., 2018). In addition, LBD patients exhibited reduced pupillary sensitivity to reward compared to HCs, consistent with our earlier findings (Manohar & Husain, 2015; Muhammed et al., 2016).

3.3.4.3 The Effects of Reward on Saccadic Measures

Monetary incentives significantly increase peak saccadic velocity in both medicated and non-medicated states, with this increase persisting as significant even when controlling for the amplitude's contribution as per the main sequence, while the lack of an effect of reward on saccadic RT observed in our study aligns with our previous findings in the dopaminergic study (Muhammed et al., 2016).

3.3.4.4 Rivastigmine Did Not Improve Sensitivity to Reward

Despite its positive effects on saccadic measures, rivastigmine had no effect on reward sensitivity, indexed by both pupillary and saccadic reward sensitivity. Several possible explanations can account for this outcome.

First, reward processing is primarily regulated by the dopaminergic system. The cholinergic system probably has a limited role in evaluating reward, and the secondary signalling of dopamine with striatal cholinergic interneurons is less potent. This could explain why rivastigmine, which enhances cholinergic function, did not significantly impact reward sensitivity. Furthermore, the potential role of other neurotransmitter systems, such as the serotonergic and noradrenergic systems, in PD apathy has also been shown (Hezemans et al., 2022; Maillet et al., 2016), with potential therapeutic effects of noradrenergic drugs seen in other neurodegenerative diseases (Costello et al., 2024; David et al., 2022). For example, a recent randomised placebo-controlled trial termed the Apathy in Dementia METhylphenidate (ADMET) trial 2, demonstrated that methylphenidate significantly improved apathy symptoms in patients with AD (Mintzer et al., 2021).

Second, although rivastigmine has been shown to improve apathy in clinical trials, such as a study by Devos et al. on patients with PD using the Lille Apathy Rating Scale (LARS) (Devos et al., 2014) and one by McKeith et al. on patients with DLB using the NPI (McKeith et al., 2000), our study did not reveal a significant enhancement in reward sensitivity. Both LARS (Sockeel et al., 2006) and NPI (Cummings et al., 1994) are inherently subjective, relying on semi-structured interviews, which might have influenced the reported improvements. The improvement in apathy seen in these trials may be due to rivastigmine's cognitive effects (Emre et al., 2004) or its ability to enhance attention (Wesnes et al., 2005) rather than a direct effect on reward sensitivity. This suggests that while rivastigmine may alleviate some symptoms associated with apathy, it does so through different mechanisms.

Third, the population tested in our study had early MCI. Cholinergic imaging studies showed that cortical cholinergic levels correlate inversely with cognitive decline (Bohnen et al., 2018; Bohnen et al., 2006). Hence, patients with early-stage disease or mild cognitive decline

exhibit less cholinergic degeneration compared to those with severe dementia (Hilker et al., 2005; Klein et al., 2010; Okkels et al., 2023). This disparity in cholinergic system integrity may explain why our study did not detect statistically significant effects on reward sensitivity measures. Additionally, the capacity of ChEIs to improve reward sensitivity may rely on the baseline cholinergic activity. If the cholinergic activity is already elevated, an additional increase in acetylcholine levels might not yield further benefits.

The pharmacokinetics of rivastigmine vary between capsule and patch formulations, with plasma concentration peaks and troughs potentially influencing our findings. Rivastigmine capsules reach peak plasma levels within an hour post-ingestion, creating a rapid but temporary rise, while the patch provides more stable plasma concentrations with peak levels occurring around eight hours post-application (Emre, Bernabei, et al., 2010; Lefèvre et al., 2008). Notably, the variability in capsule intake timing on 'ON' visits (from 6-10 am, with visits generally starting at 10 am) could result in differing plasma peaks for each participant. This timing variation may influence how the drug's effects are reflected in eye movement metrics, such as saccadic velocity and amplitude. For instance, if the capsule was taken closer to the 10 am visit, a stronger peak effect might enhance cholinergic stimulation and associated eye movements. Meanwhile, for participants who took it earlier, plasma levels could have begun to decline, leading to potentially different eye movement patterns compared to those observed with a patch that maintains stable plasma levels.

3.3.4.5 Study Limitations

Our study has several limitations. First, the study's non-blinded, open-label nature may have predisposed it to performance bias, particularly since participants were aware of their medication condition. This awareness could potentially motivate patients to perform according to their expectations of the drug's efficacy, perhaps striving for improved outcomes when they knew they were in the ON state. However, the potential for reporting bias – arising from the researcher's knowledge of the patients' drug conditions during data analysis – is minimised by the objective metrics provided by the eye-tracking task.

Second, the recruitment process faced significant hurdles, primarily due to the challenges presented by the COVID-19 pandemic and the vulnerable health status of potential participants. Several patients, already contending with the progressive and debilitating effects of dementia, could not sustain participation beyond the initial session or were altogether unable to attend due to their declining health. This limitation restricted our sample to those individuals within the Thames Valley region who could both travel to the study venue and endure the demands of the lengthy, 4-hour testing procedure. Consequently, this may have introduced both attrition and pre-screening biases, rendering our sample potentially less reflective of the broader LBD patient population across the region. Finally, the patients were on dopamine during the testing sessions and were not asked to withhold their dopaminergic medications, which could affect the study outcomes as dopamine was found in previous studies to increase reward sensitivity measured by the saccadic and pupillometric measures used in our study. This could have masked the effect of rivastigmine in improving reward sensitivity.

3.3.5 Conclusion and Future Directions

In conclusion, our findings suggest that the cholinergic drug rivastigmine does not significantly enhance reward sensitivity. This highlights the limited role of the cholinergic system in reward processing compared to the dopaminergic system. However, rivastigmine significantly improved saccadic eye movement measures, with positive implications for patients' daily activities. Our research employed an eye-tracking task, offering an objective measure of response to rivastigmine. Integrating such objective measures into clinical trials could provide deeper insights into its effects, and by extension, the cholinergic system's role in modulating reward sensitivity and apathy. Furthermore, future research should focus on understanding the interactions between the neurotransmitter systems to better elucidate their respective contributions to apathy, cognitive functions and therapeutic outcomes.

3.4 Study 2 | Examining the Effects of Rivastigmine on Attentional Networks through the Attentional Network Task

3.4.1 Introduction

3.4.1.1 Rationale and Background

Attention is a fundamental cognitive process that influences our conscious experience and everyday functioning (Peelen & Kastner, 2014). In LBD, including PD and DLB, deficits in attention are prevalent and have significant clinical implications, such as an increased risk of falls (Allan et al., 2009; Wood et al., 2002). The cholinergic system, particularly through its influence on the basal forebrain and cortical structures, plays a crucial role in modulating attention (Bohnen et al., 2009; Sarter et al., 2014). Rivastigmine, an acetylcholinesterase inhibitor, has been shown to enhance cognitive functions by increasing cholinergic activity, but its specific effects on attentional networks within LBD populations are not fully understood. This study sought to address this gap by examining the effects of rivastigmine on attentional performance using the ANT.

3.4.1.2 Cholinergic System and Attentional Network Task (ANT)

Posner and Petersen's (1990) taxonomy of attention defines three distinct networks – alerting, orienting, and executive control- each responsible for specific aspects of attention and supported by distinct neural structures. These networks collectively form the basis for attentional processes and interact with various neurotransmitter systems, particularly the cholinergic system (de Souza Almeida et al., 2021; Posner & Petersen, 1990; Posner & Rothbart, 2023).

Alerting Network

The alerting network is fundamental for achieving and sustaining a state of heightened vigilance, enabling individuals to respond effectively to stimuli. It can be further divided into tonic alertness, the long-term state of readiness influenced by circadian rhythms and maintained throughout sustained tasks, and phasic alertness, a brief and immediate response to specific warning cues (Callejas et al., 2005; Fan et al., 2009). While the alerting network is mainly influenced by the noradrenergic system, cholinergic modulation plays an indirect role in supporting overall attentional states, particularly by interacting with the orienting network during specific attentional shifts (Fan et al., 2009). The neuroanatomical basis of the alerting network includes right hemisphere circuits and frontal, parietal, and thalamic areas, which respond dynamically to both internal and external demands (Fan et al., 2009; Posner & Petersen, 1990).

Orienting Network

The orienting network facilitates selective focus on relevant information by enabling shifts in attention between stimuli and enhancing processing in specific sensory channels. This network, particularly influenced by the cholinergic system, has three main components: disengaging from the current focus (parietal lobe), shifting attention (midbrain regions), and re-engaging on a new target (pulvinar) (Pacheco-Unguetti et al., 2011; Posner & Petersen, 1990). Cholinergic activity, especially through muscarinic receptors, is critical in orienting tasks as it enhances attentional focusing and selective attention by modulating activation within the frontoparietal network (Klinkenberg et al., 2011). Nicotine, which enhances cholinergic transmission, has been shown to improve orienting and selective attention response times (Meinke et al., 2006; Thiel & Fink, 2008; Thiel et al., 2005), while cholinergic

antagonist can decrease the neural activity typically seen in orienting tasks (Klinkenberg et al., 2011).

Executive Control Network

The executive control network is involved in managing conflicts and complex decisions, which are necessary in tasks requiring inhibitory control, planning, and error monitoring (Fan et al., 2002). It often uses the flanker task, where participant focus on a central target while ignoring adjacent stimuli (flankers) that may introduce interference (Eriksen & Eriksen, 1974). The cholinergic system supports this network, though to a lesser extent than the dopaminergic and serotonergic systems, by enhancing signal-to-noise ratios, allowing for more precise conflict resolution and monitoring (Fan et al., 2009; K. Kim et al., 2019). Additionally, in conditions that heightened attentional demand, cholinergic modulation enhances activation in prefrontal and parietal areas, underscoring its role in sustaining attention during challenging tasks (Klinkenberg et al., 2011).

3.4.1.3 Previous Research on Rivastigmine and Attention

Previous RCTs have indicated that rivastigmine can improve attention and executive functions in patients with PDD and DLB (Emre et al., 2004; McKeith et al., 2000). However, the primary outcomes of these trials were often global cognitive measures, with attention typically assessed as a secondary outcome.

A study by Wesnes et al. (2005) is among the few specifically assessing the effects of cholinergic medications on attention. This 24-week, randomised, double-blind, placebo-controlled trial involved 487 patients with PDD across multiple centres. The study uniquely focused on assessing the effect of rivastigmine on attention, utilising the Cognitive Drug Research (CDR) computerised cognitive assessment at baseline, and then again at 16 and 24

weeks following treatment initiation. The findings highlighted rivastigmine's superiority over placebo across various dimensions of attention, including sustained and focused attention, response consistency and central processing speed (Wesnes et al., 2005). These results underscore the potential of rivastigmine to enhance specific aspects of attention, which this study aimed to explore further using the ANT.

3.4.1.4 Hypotheses and Objectives

Here, we hypothesised that rivastigmine will enhance attentional network efficiency. The primary objective was to compare attentional performance when patients are on and off rivastigmine, with a specific focus on how the drug influences the efficiency of the alerting, orienting and executive control networks.

3.4.2 Methods

3.4.2.1 Experimental Paradigm

For the second task in our series examining the effects of rivastigmine, we employed an adapted version of the ANT originally developed by Fan in 2002 (Fan et al., 2002). This task incorporates the cued RT paradigm introduced by Posner in 1980 (Posner, 1980) and the flanker task concept designed by Eriksen and Eriksen in 1974 (Eriksen & Eriksen, 1974). The test is designed to concurrently assess the alerting, orienting and executive control networks, which are central components of Posner and Petersen's neurocognitive model of attention proposed in 1990 (Posner & Petersen, 1990). For this task, the Inquisit (Millisecond) software was utilised, running a modified ANT script authored by Katja Borchert (Borchert, 2013).

The task consisted of four segments: an initial practice round of approximately 2 minutes, followed by three subsequent experimental blocks, each nearing 5 minutes in duration. The entire task amounted to around 20 minutes, inclusive of short breaks between blocks. The practice block included 24 trials where participants received feedback on their performance, including speed and accuracy, to acclimate them to the task requirements. The experimental block consisted of 96 trials, bringing the total number of trials to 288. Each block was an amalgamation of 48 different conditions, derived from a combination of four cue types, three flanker conditions, two target locations and two target directions. Each condition was presented twice to the participants throughout the block (Figure 3.8).

During the task, each trial commenced with the presentation of a fixation cross at the centre of the screen for 400 ms to anchor the participants' gaze in preparation for the arrows. Participants were encouraged to maintain their focus on the cross throughout the task's duration. Following the fixation period, a central arrow was displayed either above, on

or below this cross and oriented either to the right or to the left for a maximum duration of 1700 ms. Occasionally, this central arrow was flanked by additional arrows on each side, which could be aligned in the same or opposite direction as the central arrow; for instance:

< < > < <

The primary focus for participants was to identify the direction of the central arrow. Responses were to be registered using the keyboard, with the 'E' key denoting a leftward-pointing central arrow and the 'I' key denoting a rightward-pointing one. Participants were instructed to respond as quickly and accurately as possible, with the index fingers placed ready on the keys. Both RTs and accuracy were recorded to calculate the efficacy of the attentional networks.

In certain trials, a black star briefly flashed on the screen for 100 ms before the arrow appeared, serving as a cue. The position of the star announced the imminent appearance of the arrow: a star placed centrally or both above and below the cross indicated that the arrow would appear shortly without specifying a location. In contrast, a star appearing solely above or below the cross not only signalled that the arrow would appear soon but also specified its subsequent location. The task was administered in a dimly lit room to minimise distractions and optimise visual clarity. Participants were seated comfortably with a 13.5' screen positioned 30 cm in front of them, ensuring that the visual stimuli were within an optimal range for attentional assessment.

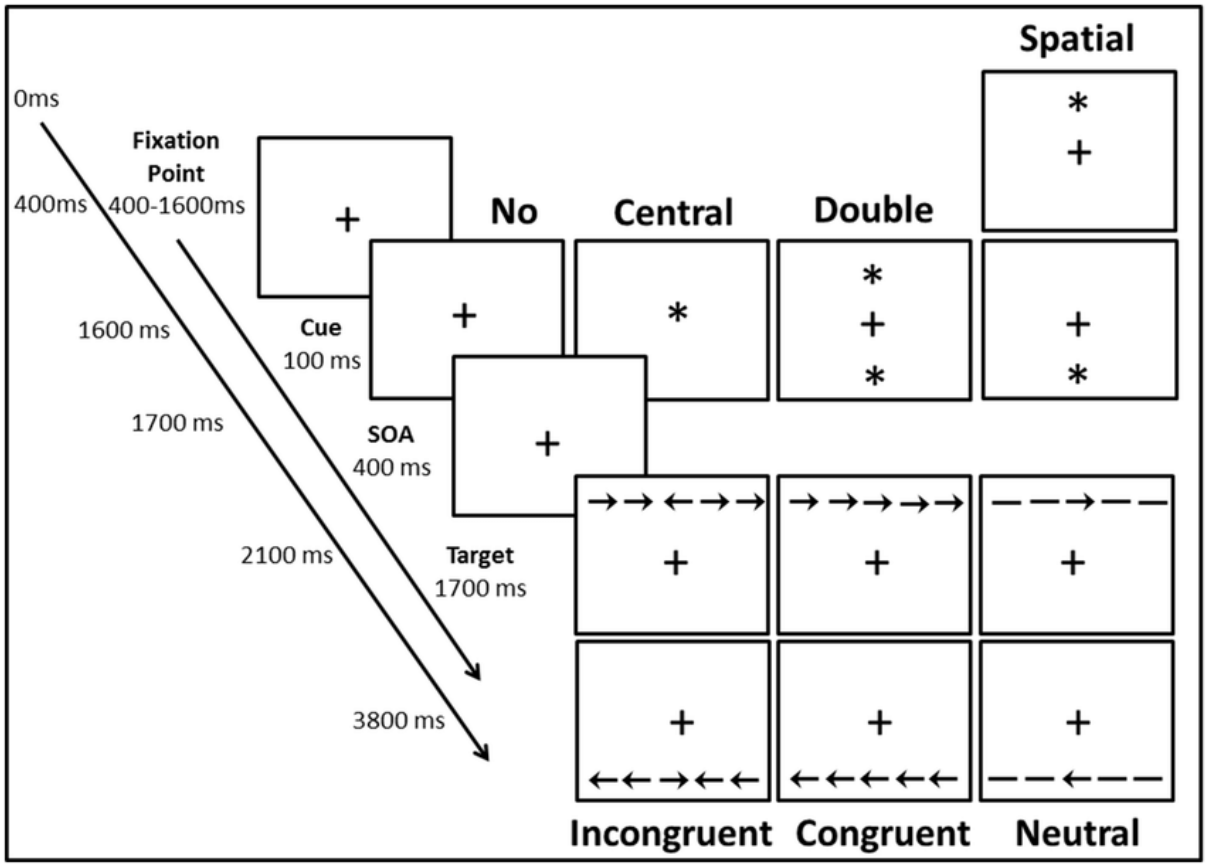


Figure 3.8 | Schematic representation of the Attentional Network Task (ANT) paradigm. *The sequence includes a fixation cross (400-1600ms), followed by a cue (no cue, center cue, double cue, or spatial cue) (100ms) and the target display consisting of a central arrow flanked by congruent or incongruent distractors (1700ms). Participants are required to indicate the direction of the central arrow as quickly and accurately as possible. The task assesses alerting, orienting, and executive control components of attention. Reproduced with permission from (Pérez et al., 2014).*

3.4.2.2 Statistical Analysis

We conducted a comprehensive statistical analysis to understand the effects of rivastigmine on attentional performance. The analysis began with the calculation of descriptive statistics, specifically mean and SD for both accuracy percentages and RTs across all trials. These trials were then categorised into various conditions: four cue types (central cue, no cue, double cue and spatial cue) and three flanker conditions (congruent, incongruent and neutral), both separately and in combination. This descriptive overview was prepared separately for each drug state, namely when patients were on or off the drug.

RTs were processed by removing outliers (latencies outside 200–1200 ms) and including only correct trials. Missed trials, where no response was recorded, were excluded from reaction

time analysis but were retained for the accuracy analysis as errors. RTs were log-transformed to meet the assumptions of parametric testing.

To evaluate the overall impact of the drug on attentional performance, we employed a linear mixed-effects model. The model included drug status and cue and flanker conditions as fixed effects, with a random intercept included to account for the repeated measures within each patient. This analysis was crucial to understanding not just the main effects of the drug but also its interaction with different task conditions. Instances of significant interactions led us to conduct post hoc analyses with Tukey's HSD adjustments, offering a nuanced understanding of the drug's effect under varying experimental scenarios.

A key aspect of our analysis involved assessing the efficiency of the three attentional networks – executive control, orienting and alerting. Efficiency was calculated by subtracting the RTs between specific conditions, as follows:

1. Executive Control Efficiency = RT incongruent – RT congruent
2. Orienting Efficiency = RT central cue – RT spatial cue
3. Alerting Efficiency = RT no cue – RT double cue

These efficiency values were then compared between the drug conditions using paired t-tests to identify any significant changes attributable to the drug. We applied the same approach to accuracy scores, where the efficiency metrics were based on accuracy percentages instead of RTs.

We conducted further exploratory analyses to investigate each cue and flanker condition and their interactions within the ANT conditions. Mean RT and accuracy between drug conditions were compared using paired Student's t-tests and Wilcoxon signed-rank tests.

Prior to these analyses, we rigorously checked whether our data adhered to the assumptions required for each statistical test, such as normality and sphericity. Where these assumptions were not met, we either adjusted our approach through statistical correction or opted for non-parametric methods.

3.4.3 Results

3.4.3.1 Baseline Characteristics

A total of 17 LBD patients participated in this study, divided into nine PD and eight DLB patients. However, only 10 participants (five PD and five DLB) completed the ANT during both visits. Seven patients were either unable to complete the task or missed the entire second visit. These excluded participants faced significant cognitive challenges that hindered their ability to understand or complete the ANT. The task was particularly demanding for these patients, both in terms of cognitive processing and attention, making it difficult for them to fully engage or follow through with the requirements.

The demographic and clinical characteristics of each group in the cohort are presented in Table 3.4. The mean age of all participants was 71.5 ± 7.2 years, with an average MoCA score of 21.8 ± 3.4 reflecting the overall cognitive function across the cohort. The gender distribution was predominantly male (82.4%; 17.6% female). Participants had completed an average of 16 ± 3.4 years of education. The majority were right-handed, accounting for 94.1% of all participants. The patients were already receiving rivastigmine as part of their treatment regimen, with the form and dosage determined by their treating physicians. Twelve patients (70.6%) were on the capsule form, with a dosage ranging from 1.5 mg BD to 4.5 BD. Meanwhile, five patients (29.4%) were using the transdermal patch,

with a dosage ranging from 4.6 mg/day to 13.3 mg/day. None of the participants had a history of neurosurgery, major head injury or major psychiatric illnesses.

Statistical analysis using independent t-tests and Pearson's chi-squared tests revealed a significant mean age difference between the two groups, with PD patients being notably older than DLB patients ($p = 0.028$). This age discrepancy was the only significant statistical difference identified, as no other baseline characteristics, including MoCA scores, years of education, gender distribution, handedness and the form of rivastigmine used, showed statistically significant differences. This highlights the homogeneity of the groups regarding cognitive and demographic features apart from the noted variation in age. However, the baseline characteristics of patients who completed the study revealed no differences between the two patient groups, including in their age (Appendix Table 8.3). This allows for a cohesive evaluation of their combined performance on the ANT, specifically examining the effects of rivastigmine across the cohort.

	DLB (N=8)	PD (N=9)	Total (N=17)	p value
Age mean (SD)	67.6 (6.3)	75.0 (6.3)	71.5 (7.2)	0.028[1]
Gender Female	2.0 (25.0%)	1.0 (11.1%)	3.0 (17.6%)	0.453[2]
Male	6.0 (75.0%)	8.0 (88.9%)	14.0 (82.4%)	
Education Years mean (SD)	15.8 (4.1)	16.2 (2.9)	16.0 (3.4)	0.783[1]
Handedness Left	1.0 (12.5%)	0.0 (0.0%)	1.0 (5.9%)	0.274[2]
Right	7.0 (87.5%)	9.0 (100.0%)	16.0 (94.1%)	
MoCA_Total mean (SD)	22.2 (3.5)	21.4 (3.4)	21.8 (3.4)	0.639[1]
Age_at_first_symptom mean (SD)	58.8 (3.6)	65.0 (8.3)	62.5 (7.3)	0.108[1]
Age_when_diagnosed mean (SD)	63.7 (5.5)	68.8 (7.5)	66.4 (6.9)	0.165[1]
Rivastigmine_Form Capsule	5.0 (62.5%)	7.0 (77.8%)	12.0 (70.6%)	0.490[2]
Patch	3.0 (37.5%)	2.0 (22.2%)	5.0 (29.4%)	

Table 3.4 | Baseline characteristics of study participants. 1. Independent t-test 2. Pearson's Chi-squared test

Each participant was scheduled as part of the recruitment to undergo two research visits (on and off rivastigmine). Table 3.5 presents the differences between the ON and OFF visits in terms of MoCA scores and the interval since the last dose of rivastigmine. As anticipated and in accordance with the study protocol, there was a significant difference in the time elapsed since the last dose of rivastigmine between the ON condition (mean 3.5 hours, SD 3.4) and the OFF condition (mean 24.8 hours, SD 6.8), confirming adherence to the study design and enabling a valid comparison of the ANT performance with and without the drug. This temporal distinction is crucial as it ensures that any observed differences in attentional networks can be attributed to the effects of rivastigmine, while the consistency in MoCA scores between visits indicates stable global cognitive function throughout the study period.

	OFF (N=10)	**ON (N=10)**	**Total (N=20)**	**p value**
MoCA Total Score				0.138[1]
Mean (SD)	23.0 (3.3)	22.0 (3.3)	22.5 (3.3)	
Last Rivastigmine dose (hrs)				< 0.001[1]
Mean (SD)	24.8 (6.8)	3.5 (3.4)	14.2 (12.0)	

Table 3.5 | Comparison between the two drug conditions visits in terms of total MoCA scores and the time since the last Rivastigmine dose for the patients who completed ANT in both visits. 1.Paired t-test

3.4.3.2 ANT Results

The overall mean RT for the correct trials when the participants were on the drug was 771.4 ± 210.1 ms, which was slightly shorter than that of the OFF state (794.0 ± 196.8 ms); however, this difference was not statistically significant ($p = 0.112$). Similarly, the overall accuracy during the ON state was 90.4 ± 8.3%, higher than in the OFF state (85.7 ± 8.0%), but this increase also did not reach statistical significance ($p = 0.135$). Figure 3.9 illustrates these comparisons of mean RT and accuracy. Table 3.6 summarises the overall results for each

drug condition, detailed by each cue and flanker condition. Detailed ANT results are provided in Tables 8.4 and 8.5 in the Appendix.

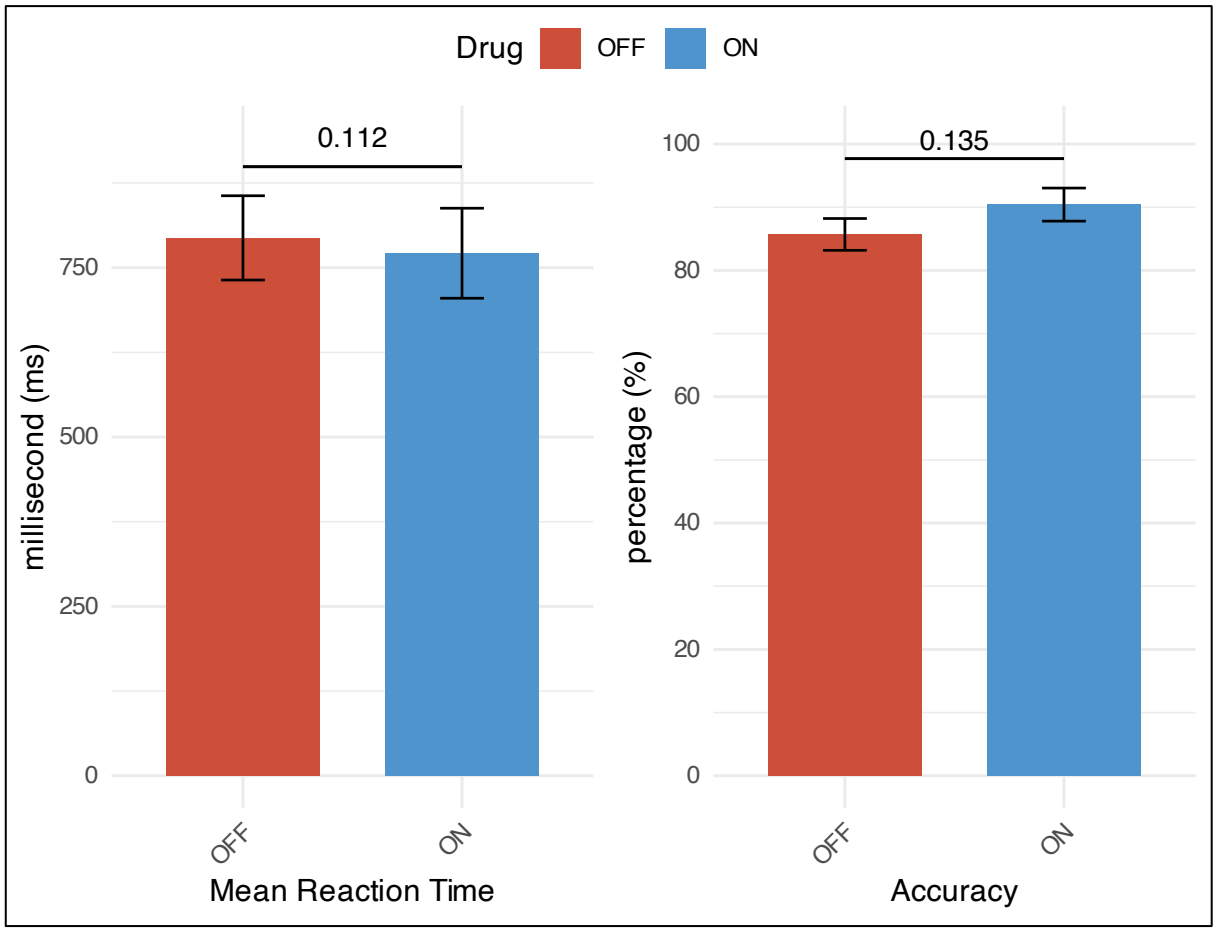


Figure 3.9 | Overall mean reaction time (for the correct trials) and accuracy in all the ANT trials for each drug condition. P-value of the paired t-tests.

		Mean Reaction Time			Accuracy		
		ON (N=10)	OFF (N=10)	Statistics[1]	ON (N=10)	OFF (N=10)	Statistics[1]
	Overall	771.4 (210.1)	794.0 (196.8)	t(9)= -1.7,p= 0.112	90.4 (8.3)	85.7 (8.0)	t(9)= 1.6,p=0.135
Cue	**No**	813.3 (214.0)	832.2 (193.8)	t(9)= -1.5,p= 0.156	90.7 (8.8)	84.0 (9.6)	t(9)= 2.2,p= 0.058
	Centre	773.8 (206.6)	801.5 (204.9)	t(9)= -1.5,p= 0.148	90.6 (8.6)	85.4 (8.2)	t(9)= 1.6,p= 0.131
	Double	755.6 (202.7)	770.4 (188.6)	t(9)= -0.7,p= 0.480	89.9 (9.0)	87.9 (7.0)	t(9)= 0.5,p= 0.578
	Spatial	742.7 (220.2)	773.0 (208.1)	t(9)= -2.1,p= 0.061	90.6 (8.6)	85.4 (9.3)	t(9)= 1.6,p= 0.141
Flanker	**Congruent**	733.8 (202.4)	768.0 (203.7)	t(9)= -2.5,p= 0.036	92.8 (6.8)	92.7 (5.7)	t(9)= 0.1,p= 0.958
	Incongruent	861.7 (237.5)	920.9 (219.1)	t(9)= -1.1,p= 0.310	85.7 (14.7)	76.1 (23.1)	t(9)= 1.3,p= 0.242
	Neutral	730.2 (202.1)	745.6 (191.3)	t(9)= -0.9,p= 0.359	92.7 (8.7)	88.2 (8.6)	t(9)= 3.3,p= 0.010

Table 3.6 |Mean reaction time and accuracy ON and OFF Rivastigmine across different cue and flanker conditions. *1. Paired t-test*

Mean RTs

A linear mixed-effects model with repeated-measures ANOVA was employed to investigate the impact of rivastigmine on the RTs within the ANT paradigm. Within-subject factors included in the model were drug status, cue condition and flanker condition, while between-subject variability was accounted for by random effects of the subjects. The analysis revealed no statistically significant main effect of drug status on RTs: $F(1,4818) = 0.11$, $p = 0.74$. Significant effects were observed for both cue and flanker conditions when considered separately (cue: $F(1,4818) = 41.1$, $p < 0.001$; flanker: $F(1,4818) = 73.6$, $p < 0.001$), in addition to their interaction ($F(1,4818) = 4.03$, $p = 0.04$). However, the two-way interactions between the drug status and both the cue ($F(1,4818) = 0.08$, $p = 0.38$) and flanker conditions ($F(1,4818) = 0.20$, $p = 0.66$), as well as the three-way interaction between them ($F(1,4818) = 0.42$, $p = 0.57$) were found to be statistically non-significant.

Accuracy

A generalised linear mixed model (logistic) was employed to investigate the effects of drug status and cue and flanker condition on the probability of correct responses (accuracy). The analysis included a random intercept to account for the individual variability among the 10 patients, with the model parameters estimated using maximum likelihood (Laplace approximation).

The model revealed a statistically significant main effect of the flanker condition on accuracy ($\chi^2(1) = 6.68$, $p = 0.01$). However, the main effects of drug status ($\chi^2(1) = 0.61$, $p = 0.44$) and cue condition ($\chi^2(1) = 1.02$, $p = 0.31$), as well as the two-way interactions between drug status and flanker condition ($\chi^2(1) = 0.10$, $p = 0.75$) and drug status and cue condition ($\chi^2(1) = 0.18$, $p = 0.67$), and the three-way interaction among drug status, cue condition and flanker condition ($\chi^2(1) = 0.01$, $p = 0.91$) were not statistically significant.

The Effect of Rivastigmine on the Efficiency of ANT Networks

The efficiency of ANT networks under the influence of rivastigmine was assessed by calculating alerting, orienting and executive control effects for each patient on and off the drug. The analysis revealed no significant differences between the drug conditions across all ANT networks (alerting effect: $t(9) = -0.208$, $p = 0.84$; orienting effect: $t(9) = 0.162$, $p = 0.875$; executive control (conflict) effect: Wilcoxon (W) = 33, $p = 0.625$; Figure 3.10). Similarly, the efficiency of ANT accuracy networks was evaluated. The analysis indicated no significant differences between the drug conditions across all networks (alerting effect: $t(9) = -1.608$, $p = 0.142$; orienting effect: $t(9) = -0.74$, $p = 0.478$; executive control (conflict) effect: $W = 10$, $p = 0.084$). However, there was a trend towards improvement in executive control with the drug, indicating borderline significance (Figure 3.11).

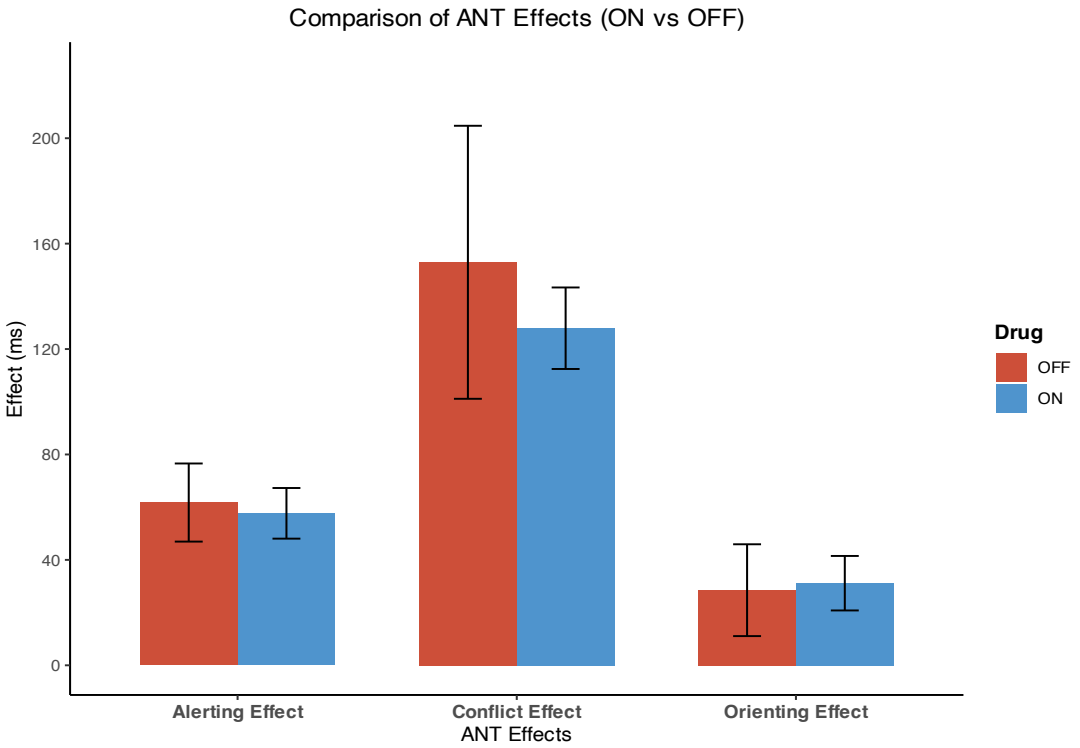


Figure 3.10 | Comparison of the ANT effects ON and OFF Rivastigmine. *The graph displays mean effect values for Alerting, Executive (Conflict), and Orienting effects as assessed by the ANT). Error bars indicate the standard error of the mean. Red bars represent the mean effect values when Rivastigmine is not administered (OFF), and blue bars indicate values when the medication is in effect (ON). Lower scores better conflict efficiency, while larger differences suggest more efficient orienting and alerting networks.*

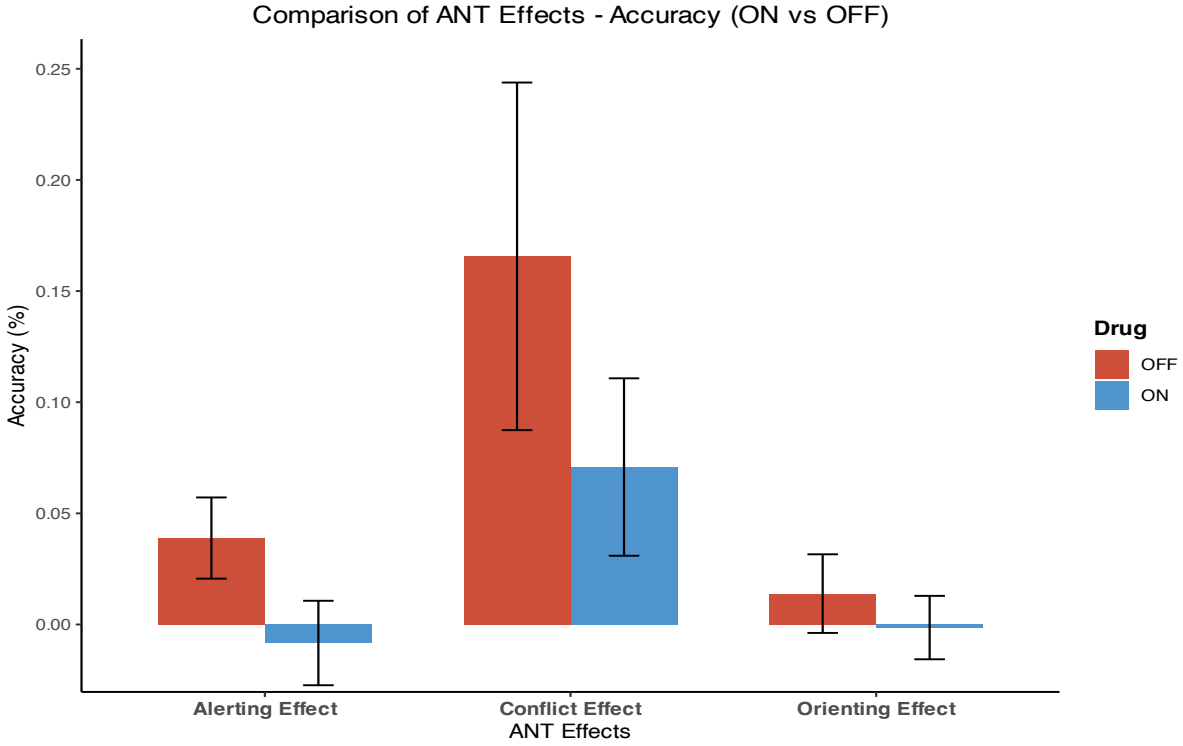


Figure 3.11 | Comparison of the ANT effects for accuracy ON and OFF Rivastigmine. *The graph displays mean effect values for Alerting, Executive (Conflict), and Orienting effects as assessed by the ANT. Error bars indicate the standard error of the mean. No significant differenced were observed between the drug status in all networks, although there was a trend towards more efficient executive control with borderline significance when patients where on Rivastigmine. Lower: better conflict, higher: better the others.*

3.4.3.3 Additional Analyses

We conducted additional exploratory analyses to delve into each cue and flanker condition, as well as their interactions in ANT conditions, comparing mean RT and accuracy between drug conditions using paired Student's t-tests and Wilcoxon signed-rank tests.

In the mean RT analyses for the overall cue and flanker conditions, only the congruent flanker condition showed significant improvement with faster RTs when rivastigmine was used ($t(9) = -2.45$, $p = 0.036$; Figure 3.12). In the specific ANT conditions, both the centre cue congruent and spatial cue congruent conditions demonstrated faster mean RTs in the ON state ($t(9) = -2.3$, $p = 0.047$ and $t(9) = -2.75$, $p = 0.022$, respectively). No significant differences were noted in the other ANT conditions (Figure 3.13).

The same analyses were conducted for accuracy. A significant improvement in accuracy was found in the neutral flanker condition in the ON state ($t(9) = 3.27$, $p = 0.010$; Figure 3.14). In the specific ANT conditions, significant improvements in accuracy when patients were on rivastigmine were observed in the no cue incongruent condition ($W = 28$, $p = 0.022$), the no cue neutral condition ($t(9) = 2.41$, $p = 0.039$) and the centre cue neutral condition ($t(9) = 2.67$, $p = 0.026$; Figure 3.15).

These analyses provided insight into how rivastigmine affects different aspects of attentional RT and response accuracy under various conditions, highlighting specific scenarios where the drug significantly improved performance. Given the exploratory nature of these analyses, multiple comparisons correction was not applied, as the objective was to generate hypotheses rather than to test them.

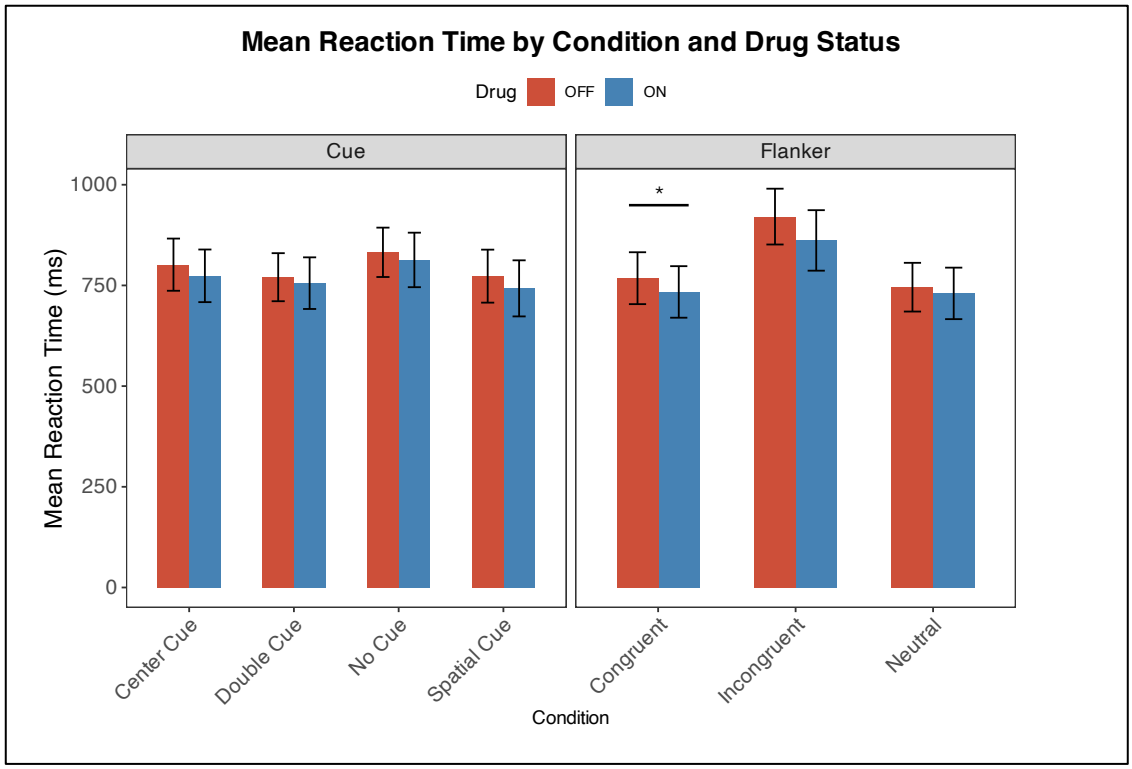


Figure 3.12 | Mean reaction time by condition and drug status. The bar chart shows the mean reaction times (in milliseconds) for four cue conditions (no cue, centre cue, double cue and spatial cue) and three flanker conditions (neutral, congruent and incongruent) ON (blue) and OFF (red) rivastigmine. Error bars represent 1 ± SEM. * unadjusted $p < 0.05$.

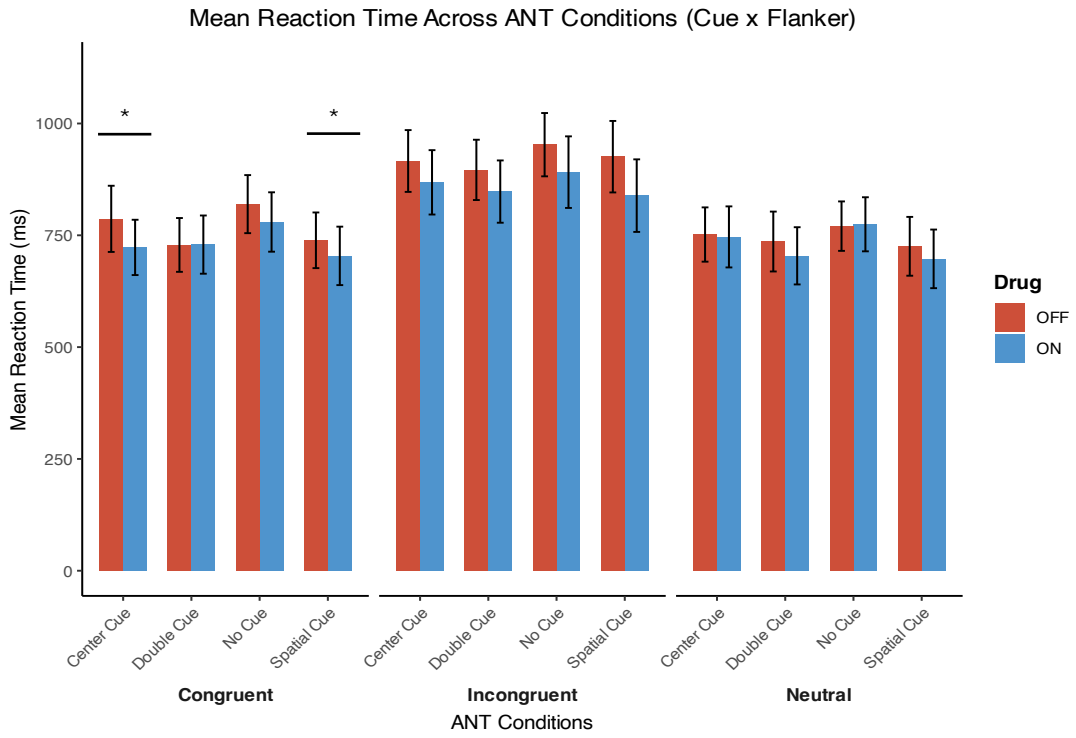


Figure 3.13 | Mean reaction time across different ANT conditions segmented by drug status. The bar chart illustrates the mean reaction times (in milliseconds) for four cue conditions (no cue, centre cue, double cue and spatial cue) within three flanker types (neutral, congruent and incongruent) ON (blue) and OFF (red) rivastigmine. Error bars represent 1 ± SEM. * unadjusted $p < 0.05$.

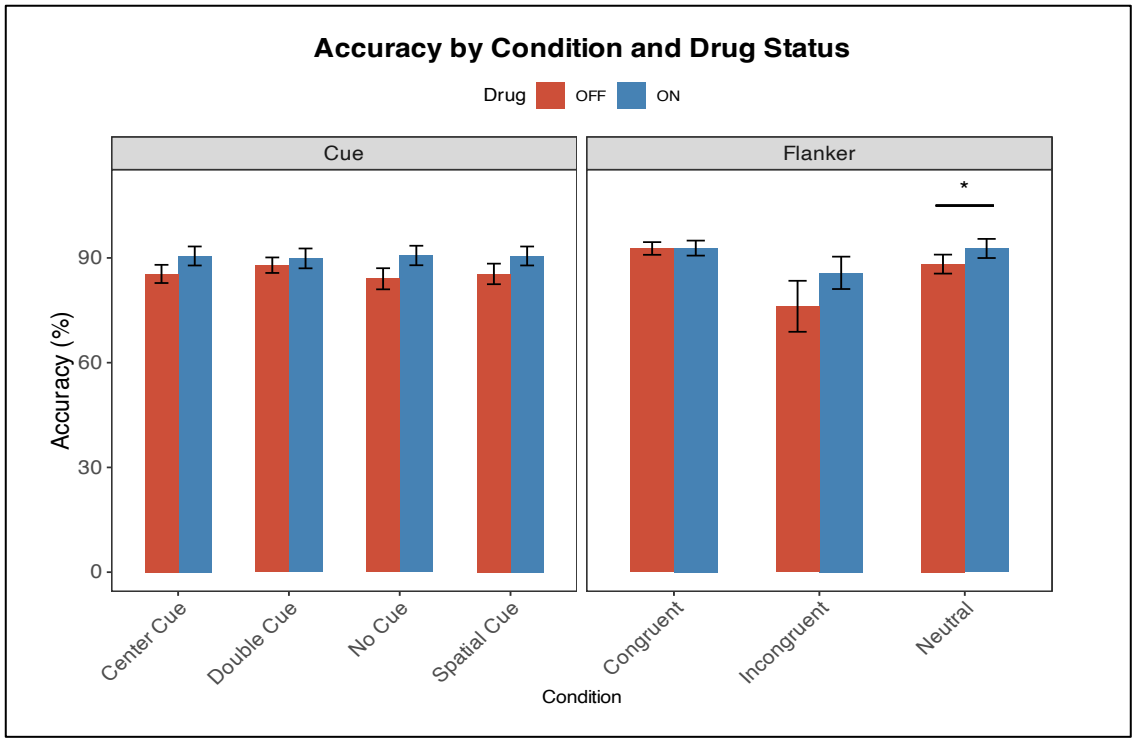


Figure 3.14 | Accuracy by condition and drug status. The bar chart presents the mean accuracy percentages for four cue conditions (no cue, centre cue, double cue and spatial cue) and three flanker conditions (neutral, congruent and incongruent) ON (blue) and OFF (red) rivastigmine. Error bars indicate 1 ± SEM. *unadjusted $p < 0.05$.

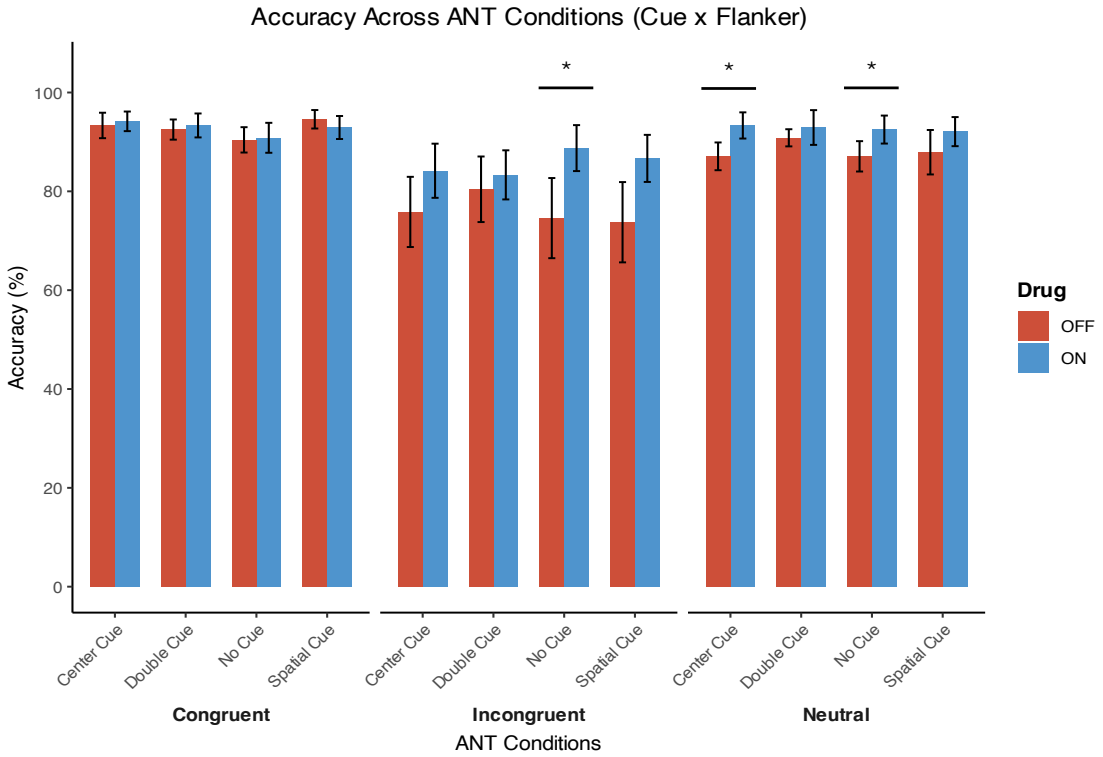


Figure 3.15 | Accuracy percentages across different ANT conditions segmented by drug status. The bar chart displays the mean accuracy rates for four cue conditions (no cue, centre cue, double cue and spatial cue) within three flanker types (neutral, congruent and incongruent) ON (blue) and OFF (red) rivastigmine. Error bars indicate 1 ± SEM. * unadjusted $p < 0.05$.

3.4.4 Discussion

This study, to the best of our knowledge, represents the inaugural effort to evaluate the impact of rivastigmine on ANT performance among patients with LBD through an on- and off-drug approach. The findings revealed no significant effect of rivastigmine on the overall mean RTs and accuracy rates. When examining attentional networks as delineated by the neurocognitive framework of Posner and Petersen (1990) (Posner & Petersen, 1990) and empirically evaluated by Fan et al. in 2002 (Fan et al., 2002), rivastigmine did not enhance performance specifically related to these attentional networks. However, a trend of a positive effect of the drug was observed in the accuracy executive control network, suggesting potential benefits for tasks requiring conflict resolution and higher-order cognitive control.

Previous studies found that rivastigmine can enhance attention and executive functions in PDD patients, including improving scores in tasks that assess cognitive flexibility (set-shifting), planning and problem-solving (Emre et al., 2004; Poewe et al., 2006; Schmitt et al., 2010; Wesnes et al., 2005). However, Schmitt et al. (2011), in a post hoc analysis of the EXPRESS trial study (Emre et al., 2004), reported significant improvements in all tasks within the D-KEFS except for the Color-Word Interference subtest, which assesses cognitive inhibitory control, where no effect of rivastigmine was found (Schmitt et al., 2010). Similarly, in a recent drug withdrawal study in PDD and DLB patients, Fallon et al. (2023) found no effect of rivastigmine withdrawal on inhibitory control. Patients on the drug showed improvements in trials that required maintaining information without the need to ignore or discard irrelevant details. However, no such improvement was observed in trials that involved ignoring or updating information (Fallon et al., 2023). This contrasts with the trend observed in our study, which, although present, did not reach statistical significance. On the

other hand, dopamine is believed to play a crucial role in cognitive control through its action in the prefrontal cortex (Ott & Nieder, 2019).

The absence of a discernible impact of rivastigmine on attentional networks may be due, in part, to the limited size of our sample. Additionally, the specific characteristics of our patient population could contribute to these findings. Our participants were in the early stages of cognitive decline, exhibiting only mild symptoms. The literature suggests that cholinergic denervation is correlated with the severity of cognitive impairment and is more pronounced in later stages of neurodegenerative conditions such as PDD and DLB (Bohnen et al., 2018; Okkels et al., 2024; Perry et al., 1985). Consequently, the cholinergic system may still have a sufficient functional reserve in the early stages of these diseases, mitigating any observable deficits when the drug is not administered. This functional reserve could account for the lack of noticeable improvement when patients are on the medication.

In addition, it is important to consider that the patients with PDD in our study and some DLB patients were concurrently receiving dopamine replacement therapy. This concurrent treatment may confound the results as it is known to potentially have both positive and negative effects on cognitive functions (Cools et al., 2001; Molloy et al., 2006). These mixed effects might obscure any cholinergic influences on attentional capacities. Therefore, the interplay between the dopaminergic and cholinergic systems warrants closer scrutiny to fully understand the nuances of pharmacological interventions regarding attentional networks in patients with LBDs.

Further investigation into the pharmacological formulations of rivastigmine should be considered in the context of attentional network performance. Our network meta-analysis study in Chapter 2 showed that capsules ranked higher based on P-scores than patches in improving global cognitive outcome measures.

The exploratory analyses provided further insights into specific conditions where rivastigmine might have a positive effect. Notably, significant improvements in RTs for the centre cue congruent and spatial cue congruent conditions indicate that rivastigmine enhances attentional speed in less demanding tasks. This suggests that the drug may be particularly beneficial for faster responses in situations where the task is straightforward or the stimuli are less conflicting.

On the other hand, the improvements in accuracy for the no cue incongruent, no cue neutral and centre cue neutral conditions suggest that rivastigmine is beneficial for correct responses in more challenging tasks with higher cognitive demands. These findings indicate that while rivastigmine improves attentional speed in simpler tasks, it also enhances accuracy in tasks that are more complex and demanding.

The observed trends and specific condition improvements can have important clinical implications. Rivastigmine's potential to enhance specific aspects of attention could translate into better management of daily activities for patients with LBD. Improved attentional control can reduce the likelihood of falls, a common and serious issue in these populations (Allcock et al., 2009; Sarter et al., 2014; Yarnall et al., 2011). Moreover, the potential benefits for executive control suggest that rivastigmine could aid in tasks requiring planning, problem-solving, and multitasking, thereby enhancing overall quality of life.

However, these exploratory findings should be interpreted with caution. Multiple comparisons were not corrected for, increasing the risk of Type I errors. Additionally, the linear mixed-effects model showed no significant interaction effect between drug status, cue and flanker conditions.

Participants' timing in resuming their capsule or patch administration for 'ON' visits introduces variability in plasma levels at testing, potentially impacting cholinergic-driven

attentional responses and task performance. Given the pharmacokinetic differences between the rapid onset of capsules and steady release profile of patches (Emre, Bernabei, et al., 2010), such timing variability may influence performance in attention tasks differently across participants. Tasks requiring fast responses may see differential effects based on proximity to peak plasma concentrations. The capsule's rapid onset might create sharp, transient cognitive enhancements, which could affect attentional scores variably depending on when the capsule was taken. By contrast, the patch's steady release reduces these fluctuations, likely promoting more consistent attentional outcomes. For future studies, aligning administration timing more closely to testing may help reduce variability and clarify comparative effects of each formulation on attentional and cognitive measures.

3.4.4.1 Limitations

In any research endeavour, acknowledging and understanding the work's limitations is crucial for accurately interpreting the results and guiding future research. This pilot study, aimed at exploring the effect of rivastigmine on attention in LBD patients, offers valuable preliminary insights but is not without constraints. The following sections discuss these limitations and their implications for the study's outcomes and future research directions.

Implications of a Small Sample Size

A primary limitation of this study is its small sample size, consisting of only 10 PD and DLB patients. This was largely due to recruitment challenges exacerbated by the COVID-19 pandemic and the vulnerable nature of the study population. Such a limited sample size may affect the generalisability of the findings, potentially limiting their applicability to the broader PD and DLB populations. Additionally, the reduced statistical power inherent to smaller samples may impact the detection and interpretation of significant differences or trends within the data.

Impact of the COVID-19 Pandemic

The COVID-19 pandemic posed unique challenges to this study, influencing both participant accessibility and data collection methodologies. Issues such as ethical considerations in working with high-risk groups during a pandemic and logistic constraints imposed by public health measures likely introduced unforeseen biases and limitations. These factors need to be considered when evaluating the study's methodology and interpreting its results.

Working with a Vulnerable Population

Conducting research with a vulnerable group, such as PD and DLB patients experiencing cognitive decline, necessitates careful consideration. This aspect of the study presented certain ethical and practical challenges, potentially limiting the scope and depth of data collection. For example, regarding the ANT, some patients could not understand the instructions, hence could not complete it. These challenges underline the importance of sensitive handling and interpretation of the data, considering the specific needs and conditions of the participants.

3.4.4.2 Concluding Remarks and Future Directions

Despite these limitations, this pilot study provides preliminary evidence suggesting that rivastigmine may enhance specific aspects of attentional performance in patients with LBD. While the overall effects were not statistically significant, the trends observed in RTs under less cognitively demanding conditions and accuracy under more challenging conditions indicate potential cognitive benefits. These findings warrant further investigation with larger samples to confirm the therapeutic potential of rivastigmine in improving attentional networks in LBD patients.

Chapter | 4

Chapter 4 | Online Cognitive Assessments in Lewy Body Diseases

4.1 Introduction

In this chapter, we explored the cognitive profiles of PD and RBD patients using the Cognitron online cognitive assessment platform. Through three studies, we investigated the distinct cognitive domains affected by these conditions, analysed cross-sectional and longitudinal cognitive patterns, and evaluated the feasibility of utilising remote cognitive assessments in clinical trial settings.

4.1.1 Aims and Objectives

Aim: To map the cognitive profiles of PD and RBD using remote online cognitive tools.

Objectives:

1- Assessing the cognitive domains affected by PD and RBD (Study 1)

- To utilise the Cognitron platform to measure performance in various cognitive domains, including attention, executive functions, memory, language and visuospatial functions
- To compare cognitive performance between PD, RBD and HC groups in the Oxford Discovery study

2- Evaluating the specificity of cognitive deficits (Study 1)

- To identify the specific cognitive tasks on which PD and RBD patients perform worse than HCs
- To determine if any specific cognitive tasks can distinctly differentiate PD from RBD

3- Analysing cross-sectional cognitive patterns (Study 2)

- To compare the performance in each cognitive task relative to the overall cognitive performance within each group
- To identify areas of cognitive strengths and weaknesses in PD, RBD and HC groups

4- Investigating longitudinal changes in cognitive function (Study 2)

- To track changes in cognitive performance over time within PD and RBD groups
- To compare these changes to determine if cognitive decline rates differ between the two conditions

5- Assessing the use of remote cognitive testing in an RCT setting (Study 3)

- To evaluate the feasibility and practicality of implementing online cognitive battery in a clinical trial setting
- To gather participant feedback and identify potential barriers to the use of remote cognitive testing in this context

4.2 Study 1 | Cognitive Profiling of Patients with Parkinson's Disease and Rapid Eye Movement Sleep Behavioural Disorder in the Oxford Discovery Cohort Using Remote Cognitive Assessments

4.2.1 Introduction

Cognitive impairment is a prevalent non-motor manifestation of LBD. At the time of diagnosis, around 25–30% of PD patients exhibit MCI (Caccappolo & Marder, 2015), with over 80% progressing to dementia as the disease advances (Hely et al., 2008). This cognitive decline is distressing for both patients and their caregivers, significantly impacting their quality of life and increasing caregiver burden (Lawson et al., 2016; Leroi et al., 2012).

Cognitive changes can occur early in the prodromal phase of PD (Fengler et al., 2017; Muslimovic et al., 2005). RBD is considered a prodromal biomarker of alpha-synucleinopathies including PD, MSA and DLB (Barone & Henchcliffe, 2018). Thus, it can serve as a unique window of opportunity for early dementia intervention and clinical trials. The most affected cognitive domains in RBD are executive functions, verbal memory, attention and visuospatial functions (Fantini et al., 2011; Massicotte-Marquez, Decary, et al., 2008; Terzaghi et al., 2013). PD patients with RBD have an increased MCI diagnosis frequency, more impaired cognitive functions, and a higher risk of dementia in comparison to PD patients without RBD (Gagnon et al., 2009; Jozwiak et al., 2017).

Cognitive deficits in PD are not an exception to the heterogeneous nature of the disease, involving multiple neurotransmitter systems (Brandao et al., 2020). Kehagia and colleagues proposed the dual syndrome hypothesis, which consists of two clinical presentations: 1) early fronto-striatal executive and attentional dysfunctions caused by dopaminergic deficits in non-demented PD patients and 2) late posterior-cortical deficits with visuospatial and memory impairments caused by cholinergic deficits occurring in

patients with PDD (Kehagia et al., 2013). This hypothesis was based on observations from the CamPaIGN study, which revealed these two distinct patterns of cognitive impairment with the longitudinal follow-up of their incident PD cohort (Williams-Gray et al., 2009).

In studying cognitive impairment associated with PD and RBD, it is critical to employ assessment tools that are tailored to the distinct cognitive profiles of these conditions. While screening tests such as the MoCA, MMSE and MDRS are commonly used and validated, they are not specific for LBD (Goldman et al., 2018; Kulisevsky & Pagonabarraga, 2009). Unlike AD, where episodic memory and language are predominantly affected early on, cognitive decline in PDD typically presents with deficits in attention and executive and visuospatial functions, often with speech remaining intact (Brønnick, 2015; Smirnov et al., 2020).

Given these differences, there is a compelling need for PD-specific cognitive tools that are efficient, easy to deliver and interpret, and time-saving, particularly in remote or under-resourced areas where travel to clinics can be impractical or impossible. The COVID-19 pandemic has further crystallised the importance of such tailored, remote cognitive testing options (Owens et al., 2020). The heightened risk of virus transmission during in-person visits has made these tools indispensable, particularly for older individuals and those living with neurodegenerative diseases who face increased vulnerability. Hence, digital platforms, such as Cognitron, can be invaluable in such circumstances, providing ongoing cognitive assessment capabilities in the absence of traditional face-to-face, clinic-based evaluations amidst lockdowns and healthcare resource reallocation (A. Hampshire et al., 2021; Zhao et al., 2022). Moreover, the advent of computerised testing has brought about the advantage of allowing for more frequent cognitive assessments with fewer learning effects often associated with repeat testing (Goldberg et al., 2015). This enhances the tests' ability to sensitively track any decline in cognitive function over time (Brooker et al., 2020).

Cognitron has been validated in extensive populations, including hundreds of thousands of HCs and diverse disease cohorts (Del Giovane et al., 2023; Hampshire et al., 2024; Jolly et al., 2020; Shibata et al., 2024; Taquet et al., 2024), offering a promising alterative for delineating the cognitive profiles of PD and RBD. The use of such digital tools can facilitate early diagnosis and the prediction of cognitive decline, which is crucial for timely intervention with future potential disease-modifying therapies to either halt or slow disease progression.

This study was designed to map out the specific cognitive profiles of PD and RBD using online cognitive assessments provided by Cognitron, which span various cognitive domains. It is posited that individuals with PD will exhibit poorer performance, particularly in tasks assessing attention and executive functions, while those with RBD will show difficulties in visuospatial and memory-related tasks.

4.2.2 Methods

4.2.2.1 Participants

Participants were recruited from the OPDC Discovery cohort study, primarily from the Thames Valley region. The cohort includes PD patients who fulfil the UK Brain Bank criteria for probable PD (Hughes et al., 1992), prodromal PD patients with RBD diagnosed via polysomnography based on the International Classification of Sleep Disorders (ICSD) criteria (Sateia, 2014) and HCs with no known neurological disorders. Inclusion required a MoCA score equal to or greater than 26, indicative of adequate cognitive functioning, with the assessment obtained from the latest Discovery visit and no older than 18 months prior to the current study's enrolment phase. Participants were excluded if they had severe unaddressed vision or hearing problems that could interfere with the online test platform, major psychiatric or neurological disorders other than those specified for inclusion (e.g. active psychosis, severe depression) or cognitive impairment indicated by a MoCA score of 25 or less. Official invitation letters were sent to participants explaining the study and its objectives and rationale. Written informed consent was obtained from the participants in the clinic for remote cognitive testing in general, and specific electronic consent was obtained for this study. Prior approval was obtained from the local research ethics committee in accordance with the Declaration of Helsinki and national legislation.

4.2.2.2 Cognitive Tasks

We employed an online cognitive battery consisting of 13 tasks selected from the Cognitron platform, which was validated within our cohort (Bălăeţ et al., 2024; Adam Hampshire et al., 2021). These tasks included Motor Control, Manipulations in Two Dimensions, Target Detection, Blocks, Emotion Discrimination, Trail Making, Switching Stroop, Spatial Span, Digit Span, Word Definitions, Verbal Analogies, Prospective Memory – Immediate, and

Prospective Memory – Delayed, encompassing a diverse range of cognitive domains (illustrated in Table 4.1 and Figure 4.1). The tasks were designed and programmed using HTML5 and JavaScript and hosted on the Cognitron server, which was developed and deployed on the Amazon EC2 platform. With support from the National Institute for Health and Care Research (NIHR), the platform was optimised for remote testing, making it accessible to older individuals and patient groups.

The online cognitive battery was sent via email to the participants, who were identified by a specific ID provided by the Discovery study. The tests took around 30–45 minutes to complete. Participants were instructed not to change any of their usual medications or daily routines and advised to find a quiet place and a suitable time of the day when they tended to perform at their best to complete the tests. It was also recommended that they use a desktop computer and a mouse if possible. To cover both visual and verbal memory, we used a verbal memory task for the prospective early and delayed memory tasks in the first phase of data collection and a visual memory task in the second phase.

Cognitive domain	Task	Difficulty grade
Attention and Working Memory	Target Detection	1
	Trail Making Task	1
	Digit Span	2
	Spatial Span	2
Executive Functions	Emotional Discrimination	1
	Switching Stroop	2
Language	Word Definitions	3
	Verbal Analogies	3
Memory	Prospective Memory immediate recall	2
	Prospective Memory delayed recall	3
Visuospatial	2D Manipulations	1
	Blocks	3
Motor	Motor Control	1

Table 4.1 | Overview of cognitive tasks used in the battery, along with their associated cognitive domains and difficulty grades. *Note: The listed cognitive domain is the primary one, though each task may involve multiple cognitive domains.*

The cognitive tasks are described in more detail below:

1. *Prospective Memory – Immediate (Verbal)*

This Prospective Memory task assesses immediate verbal memory. The participant is initially presented with a series of English words on the screen (Figure 4.1K). These words are presented sequentially in a pseudo-random order, each displayed for 1000 ms with an inter-word interval of 200 ms. Subsequently, a list of 24 random words is shown, which includes words from the initial set (accounting for 50% of the words shown). The participant is then given the option to decide whether each of these words was previously displayed by clicking 'Yes' or 'No'. The primary outcome measure is the total number of correct answers. The secondary outcome measure is the median RT of the correct answers.

2. *Target Detection*

The Target Detection task evaluates visual spatial attention and executive functions. A target shape is initially presented to the participant on the left side of the screen, with a probe area on the right side (Figure 4.1C). After a 3000 ms delay, the probe area begins to populate with various shapes. The participant's challenge is to identify and click on the target shape while disregarding the distractor shapes. Shapes are introduced every 1000 ms, and a subset of shapes within the probe area is removed concurrently at the same interval. This process repeats for a total of 120 cycles of shape addition and removal. The target shape is introduced among the new shapes in a pseudo-random pattern, occurring approximately 12 times out of every 20 cycles. The primary performance measure in this task is the total number of successfully clicked target shapes. The secondary measure is the mean RT.

3. *Emotion Discrimination*

The Emotion Discrimination assessment evaluates the participant's capacity to recognise and differentiate between facial expressions of emotion. Images of two individuals are shown, each displaying a specific emotion, such as happiness, neutrality, anger or fear (Figure 4.1G). The task is to determine whether the emotions conveyed by both individuals are identical or dissimilar. The trials differ depending on the emotions depicted and whether the individuals display matching or conflicting emotional expressions. The task consists of 50 trials, with each correct answer equalling one point, and the overall score represents the outcome measure. A secondary measure is the median RT.

4. *2D Manipulation*

The 2D Manipulation test assesses the participant's ability to mentally manipulate objects in a spatial context. A 6 × 6 target grid featuring coloured squares is displayed at the screen's top, while four additional grids with coloured squares are presented below (Figure 4.1F). Among these grids, one is an exact match to the target grid, although it is rotated by either 90, 180 or 270 degrees. The other three grids are slightly different from the target grid. The participant must quickly and accurately identify the grid that matches the target. They have 3 minutes to complete as many trials as possible. For every correct response, their total score increases by one point. The primary outcome measure is the total number of correctly identified matches divided by the total number of trials completed. A secondary measure is the median RT.

5. *Digit Span*

The Digit Span task is derived from the verbal working memory part of the Wechsler Adult Intelligence Scale developed by Wechsler in 1955 (Wechsler, 1955). The participant is shown a series of digits appearing on the screen one after another (Figure 4.1A). They are

then required to reproduce the sequence of numbers by inputting them using an on-screen numeric keypad. The difficulty increases progressively: for every accurately recalled sequence, the length of the subsequent sequence increases by one. The examination concludes when three consecutive errors are made at a specific sequence length. The primary metric of interest is the maximum sequence length that can be accurately recalled, with a maximum possible length of 20. A secondary measure is the median RT.

6. *Spatial Span*

The Spatial Span test evaluates spatial short-term memory. It is based on the well-known Corsi Block Tapping test developed by Corsi in 1972 (Corsi, 1973). The participant is presented with a 4 × 4 grid of 16 squares (Figure 4.1B). In each trial, a sequence of these squares is illuminated, with each square remaining lit for 1500 ms with an inter-stimulus interval of 0 ms. The task is to select the squares in the exact order in which they were highlighted. The test's complexity increases step-by-step: each time the sequence is correctly recollected, the subsequent sequence's length is augmented by one. The task concludes when three consecutive errors are made at a specific sequence length. The primary measure of interest here is the maximum sequence length that can be accurately recalled. A secondary outcome measure is the median RT.

7. *Word Definitions*

The Word Definitions test examines the participant's language skills using word definitions. The participant encounters 21 different words, each with four descriptive statements (Figure 4.1I). The task is to identify the statement that offers the correct definition of the word, responding as quickly and accurately as possible. The participant is given a time frame of 20 seconds to select a definition for each word. The presented words have a range of usage frequencies in written English (both rarely and commonly used terms

are included). For every correct answer, one point is added to the overall score. The primary measure of performance is the total score attained. A secondary measure is the median RT of correct trials.

8. Blocks

The Blocks task assesses the individual's ability to solve spatial puzzles by rearranging the blocks. The participant is presented with a grid of coloured blocks on the left side of the screen (Figure 4.1E). On the right side, there is a black silhouette composed of a subset of the shapes found on the left. The objective is to manipulate the blocks on the left to match the silhouette on the right by removing specific blocks. These blocks fall by gravity, meaning they fall when removed. The test consists of 15 trials of varying difficulty. The level of complexity is controlled by two factors: the number of blocks that need to be removed (one, two or three blocks) and the number of blocks required to fall to achieve the target silhouette. Each trial concludes when either the participant successfully replicates the target silhouette (a correct trial) or when an incorrect block is removed (an incorrect trial). The primary measure of performance is the total number of correct trials. A secondary measure is the median RT.

9. Verbal Analogies

The Verbal Analogies test assesses language, particularly semantic reasoning abilities. Participants are shown two written relationships and must determine whether they share the same type of association or not (e.g. 'Close is to distant as common is to unique'; Figure 4.1J). They express their decision by selecting 'True' or 'False' options provided beneath the written analogies. Throughout the sequence of trials, the analogies vary in terms of semantic proximity to control the difficulty level, and the types of associations shift. Participants aim to answer as many questions as they can within a timespan of 3 minutes to achieve the

highest possible score. Each correct response contributes one point to the overall score, while each incorrect response deducts one point. The key performance metric of interest is the total score obtained. A secondary measure includes the median RT of correct trials.

10. Prospective Memory – Delayed (Verbal)

This task is linked to the Prospective Memory – Immediate (verbal) task and measures the delayed memory recall. Participants are presented with written words shown previously in the immediate task and are asked to indicate whether they have seen these words before by pressing 'Yes' or 'No' buttons. Every correct response contributes one point to the overall score. The primary outcome measure for this task is the total score obtained. A secondary measure is the median RT of the correct answers.

11. Trail Making Test (TMT)

The Trail Making Test (TMT) evaluates attention and executive function. It is an adaptation of the traditional TMT Parts A and B (Figure 4.1D). In Part A, participants are presented with numbered circles on the screen and asked to click on the circles in ascending order, commencing with 1 and progressing through to 26. Part B introduces circles that contain both numbers and letters. The challenge here is to alternate between clicking on numbers and letters, starting with 1, followed by A, then 2, then B and so forth until 13 and M are reached. The key outcome measure for this task is the summary score, calculated as the average of the mean RTs for numbers and letters. Secondary outcome measures include the mean RTs for numbers and letters separately.

12. Switching Stroop

The Switching Stroop task is a modified version of the well-known Stroop colour and word test, originally developed by Stroop in 1935 (Stroop, 1935). It has been widely used in neuropsychology to assess executive function, attention and the capacity to inhibit cognitive interference.

In this adapted version, participants are shown a red or blue box positioned in the centre of the screen (Figure 4.1H). Adjacent to this box, the words 'RED' and 'BLUE' are written in red or blue ink on either side. At the top of the screen, a specific rule is provided, which can be 'INK' or 'TEXT'. When the rule is 'INK', participants are required to click on the word with the ink colour that matches the central box colour. When the rule is 'TEXT', the objective shifts to selecting the word that describes the colour of the central box. For both rules, the trials can be congruent or incongruent. Congruent trials, where the text and ink colour match, are more automatic tasks. However, in the incongruent trials, participants are challenged to perform a less automated task by choosing an ink colour (e.g. when the rule is INK) while inhibiting the interference caused by the more automated task of reading the word. This capacity to inhibit cognitive interference is known as the Stroop effect (MacLeod, 1991). For each correct response, participants earn one point, contributing to their overall score. The primary measure of performance for this task is the total score achieved, which reflects the ability to navigate the Stroop effect. A secondary measure is the median RT.

13. Prospective memory – Immediate (Objects)

This Prospective Memory task assesses visual memory. Participants are shown a sequence of 20 objects, each displayed for 2000 ms with an inter-stimulus interval of 500 ms (Figure 4.1L). The challenge is to memorise as many objects as possible during this initial presentation. Afterwards, each object is presented again within a grid containing seven

distractors, which vary in similarity to the target object along three dimensions: item (whether the image depicts the same object as the target), precision (whether the image matches the target's pose or artistic style) and misattribution (whether the image is flipped right or left). The primary outcome measure is the total number of points collected, which are awarded as follows for each trial: no points for an incorrect item, one point for the correct item, two points for the correct item and precision, and three points for the correct item, precision and no misattribution. A secondary measure includes the median RT.

14. Prospective Memory – Delayed (Objects)

This Prospective Memory task focuses on assessing the participants' delayed recall memory regarding the objects shown in the prior task. It is positioned as the final task in the battery, while the previous task is one of the first. Hence, it serves to measure memory retention over time. The participant is presented with the same task as described above; however, the encoding period is removed. The objects are shown in a grid and the participants are asked to click on the object that exactly matches one of the objects shown in the previous task. The key outcome measure is the cumulative number of points achieved, as described in the previous task. A secondary measure includes the median RT.

15. Motor Control

This task tests the participant's speed and accuracy in clicking target objects, measuring motor function, perceptual processing and response execution. The participant is instructed to use a mouse (or, if not possible, the touchscreen) to keep clicking on targets (red circles) that pop up in different locations as quickly and accurately as they can (Figure 4.1M). They are presented with 30 stimuli, with each stimulus appearing immediately (0 ms delay) after the response to the previous one. The primary outcome measure is the mean RT of the correct clicks.

4.2.2.3 Baseline Measures

Baseline cognitive, neuropsychiatric and motor measures were captured as part of the Discovery study clinics. Cognitive function was assessed using the MoCA and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Phonemic and semantic fluency tests were used to evaluate verbal fluency. Neuropsychiatric status was measured using the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI). Motor function was assessed using the UPDRS III and the Purdue Pegboard Test.

4.2.2.4 Statistical Analysis

All data analyses in this study were performed using R and Jamovi. Independent t-tests and chi-squared tests were used to assess baseline demographic differences between the study groups. For each cognitive task, one-way ANOVA was conducted to compare group means for primary (summary scores) and secondary (RT) outcome measures. Equivalent non-parametric tests were used whenever necessary for non-normally distributed variables.

The summary scores and mean RTs from the cognitive tasks were corrected for age, gender and total education years using simple linear regression. These corrected scores were then converted to standardised z-scores, and Cohen's d effect sizes were calculated to measure between-group differences compared to HCs for each cognitive task. We utilised Cohen's recommended coefficients to quantify effect sizes: d = 0.2 (small), 0.5 (medium) and 0.8 (large) (Cohen, 1988). Hierarchical clustering was performed to organise the different cognitive variables based on similarities. Principal component analysis (PCA) was used to reduce the dimensionality of the data, with five components set in anticipation of the five cognitive domains. Each component score was used as a global composite score for a specific cognitive domain, and groups were compared based on their mean composite

scores to create a cognitive profile for each study group. Additionally, correlation tests were conducted between the MoCA scores and the composite scores. Metacognition was also assessed for each task, with participants rating their performance from 0–100%. Means were compared across groups, and Pearson correlation was used to correlate these ratings with the performance summary scores for each task.

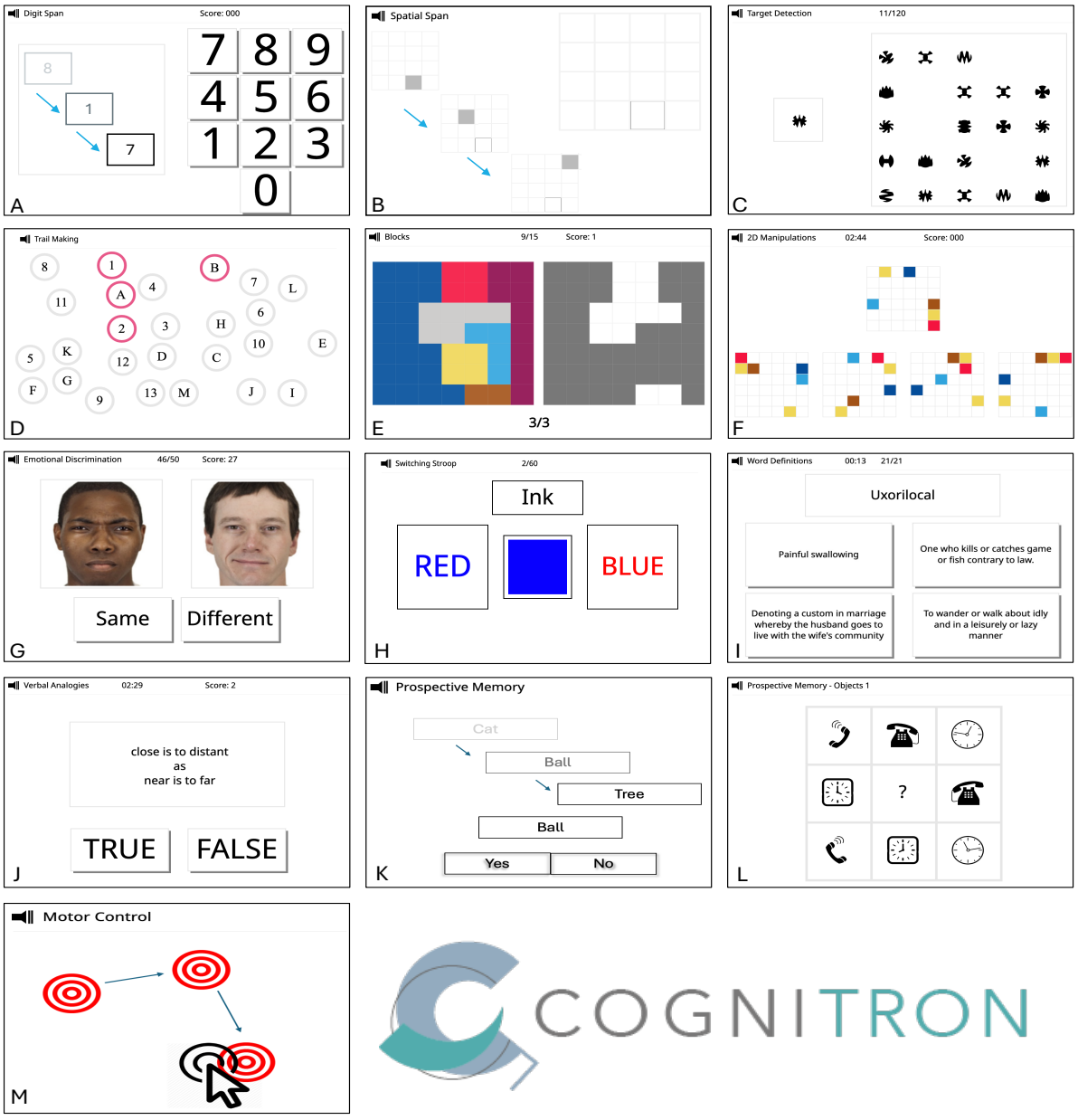


Figure 4.1 | Illustration of the cognitive tasks included in the online battery. A. Digit Span **B.** Spatial Span **C.** Target Detection **D.** Trail Making Test (TMT)**E.** Blocks **F.** 2D Manipulation **G.** Emotion Discrimination **H.** Switching Stroop **I.** Word Definitions **J.** Verbal Analogies **K.** Prospective Memory (verbal) **L.** Prospective memory – Objects (visual) **M.** Motor Control

4.2.3 Results

4.2.3.1 Participants

A cohort of 222 participants underwent cognitive testing, including 89 patients with PD, 61 with RBD and 72 HCs (CON). Table 4.2 outlines their demographic details. The participants had an average age of 67.8 years (SD = 9.2), with those in the CON group being significantly older than their counterparts in other groups. A significant predominance of men was observed in the RBD group (91.8%), whereas the PD and CON groups displayed nearly balanced gender distributions. The average disease duration for PD patients was 9.3 years (SD = 2.9), with the majority (over 75%) being in Hoehn and Yahr Stage 2 of disease severity. Regarding premorbid cognitive performance measured by NART IQ scores, the RBD group had significantly lower scores compared to the CON group. However, no significant differences were found among the groups regarding education level, handedness and ethnicity.

4.2.3.2 Baseline Cognitive, Neuropsychiatric and Motor Measures

We examined the baseline cognitive, neuropsychiatric and motor measures of the study groups (Table 4.3). Regarding cognitive measures, significantly lower baseline MoCA scores were found in the RBD group compared to the PD and CON groups. However, no significant differences were found in IQCODE, phonemic and semantic fluency scores. Regarding the neuropsychiatric measures (HADS and BDI), depression levels were significantly higher in PD patients compared to the RBD and CON groups, while anxiety levels were significantly higher in both PD and RBD patients in comparison to the CON group. In terms of motor measures, UPDRS III, as expected, indicated more severe impairment in PD patients; nevertheless, no differences were observed in motor dexterity as assessed by the Purdue Pegboard Test.

Measure	PD (N=89)	RBD (N=61)	CON (N=72)	Total (N=222)	p value
Age					0.027[1]
Mean (SD)	65.8 (8.5)	67.0 (9.6)	69.7 (9.2)	67.4 (9.2)	
Gender					< 0.001[2]
Female	43.0 (48.3%)	5.0 (8.2%)	38.0 (52.8%)	86.0 (38.7%)	
Male	46.0 (51.7%)	56.0 (91.8%)	34.0 (47.2%)	136.0 (61.3%)	
Disease Duration					
Mean (SD)	9.3 (2.9)	NA	NA	NA	
Hoehn & Yahr PD Stage					< 0.001[2]
0	0.0 (0.0%)	61.0 (100.0%)	70.0 (100.0%)	131.0 (59.5%)	
1	12.0 (13.5%)	0.0 (0.0%)	0.0 (0.0%)	12.0 (5.5%)	
2	69.0 (77.5%)	0.0 (0.0%)	0.0 (0.0%)	69.0 (31.4%)	
3	8.0 (9.0%)	0.0 (0.0%)	0.0 (0.0%)	8.0 (3.6%)	
Full Scale IQ NART					0.033[1]
Mean (SD)	117.9 (5.1)	115.9 (5.2)	119.0 (6.8)	117.4 (5.6)	
Verbal IQ NART					0.033[1]
Mean (SD)	121.0 (4.8)	119.1 (4.9)	122.0 (6.4)	120.6 (5.2)	
Performance IQ NART					0.033[1]
Mean (SD)	118.3 (3.4)	117.0 (3.4)	119.0 (4.5)	118.0 (3.7)	
Total Education					0.546[1]
Mean (SD)	15.6 (3.4)	15.5 (3.7)	16.1 (3.0)	15.7 (3.4)	
Handedness					0.914[2]
Right	78.0 (88.6%)	54.0 (88.5%)	43.0 (93.5%)	175.0 (89.7%)	
Left	6.0 (6.8%)	4.0 (6.6%)	2.0 (4.3%)	12.0 (6.2%)	
Both	4.0 (4.5%)	3.0 (4.9%)	1.0 (2.2%)	8.0 (4.1%)	
Ethnicity					0.410[2]
White - British	84.0 (94.4%)	59.0 (96.7%)	69.0 (95.8%)	212.0 (95.5%)	
Other	5.0 (5.6%)	2.0 (3.3%)	3.0 (4.2%)	10.0 (4.5%)	

Table 4.2 | Baseline demographic data of participants across study groups. 1. Linear Model ANOVA 2. Pearson's Chi-squared test

Measure	PD (N=89)	RBD (N=61)	CON (N=72)	Total (N=222)	p value
MoCA					0.002[1]
Mean (SD)	28.0 (1.3)	27.8 (1.3)	28.6 (1.4)	28.1 (1.4)	
Phonemic Fluency					0.110[1]
Mean (SD)	49.7 (13.4)	44.7 (11.4)	48.4 (15.5)	47.7 (13.1)	
Semantic Fluency					0.717[1]
Mean (SD)	41.4 (10.8)	40.0 (8.7)	41.4 (10.9)	40.9 (10.1)	
UPDRS III					< 0.001[1]
Mean (SD)	28.8 (12.4)	6.5 (3.9)	2.9 (2.6)	18.7 (14.9)	
Purdue Pegboard					0.600[1]
Mean (SD)	30.1 (16.5)	32.9 (6.7)	32.2 (9.3)	32.1 (10.4)	
BDI					< 0.001[1]
Mean (SD)	10.4 (5.8)	6.8 (5.8)	5.2 (6.3)	7.7 (6.4)	
HADS Depression					< 0.001[1]
Mean (SD)	5.0 (3.2)	2.8 (2.9)	1.9 (2.5)	3.4 (3.2)	
HADS Anxiety					< 0.001[1]
Mean (SD)	5.5 (3.7)	4.1 (4.1)	2.6 (2.7)	4.1 (3.7)	
IQCODE					0.194[1]
Mean (SD)	51.2 (4.3)	50.8 (5.3)	49.8 (3.2)	50.6 (4.3)	

Table 4.3 | Baseline cognitive, neuropsychiatric and motor measures of participants across study groups. 1. Linear Model ANOVA

Online Cognitive Battery

4.2.3.3 Primary Outcome Measures (Summary Scores)

The univariate ANOVA conducted on the raw summary scores indicated statistically significant differences among the study groups in several cognitive tasks, including Trail Making, Target Detection, Emotion Discrimination, Word Definitions, Verbal Analogies, Prospective Memory – Immediate (verbal) and Motor Control. Adjustments for age, gender and education did not affect the significance of these findings, except for the Emotion Discrimination task, which did not maintain significance post-adjustment. Interestingly, the Switching Stroop task emerged as significantly different among the groups only after the adjustments. Table 4.4 summarises the ANOVA results for the cognitive summary scores.

Subsequent post hoc comparisons using the Tukey's HSD (and Dwass–Steel–Critchlow–Fligner pairwise comparisons for the non-parametric Kruskal–Wallis ANOVAs) refined these observations.

PD vs. CON

PD patients demonstrated significantly poorer performance in several tasks compared to the CON group. PD patients had significantly lower scores in Target Detection ($t(212) = -3.91$, $p < 0.001$) and Switching Stroop ($t(212) = -2.60$, $p = 0.027$). Additionally, they were significantly slower in the TMT ($W = -5.43$, $p < 0.001$). Language tasks, such as Verbal Analogies ($t(212) = -4.53$, $p < 0.001$), indicated significantly decreased scores among PD patients, while Word Definitions scores were lower but with borderline significance ($W = -3.05$, $p = 0.078$). PD patients also scored significantly worse on the Prospective Memory –Immediate (verbal) task ($t(111) = -3.77$, $p < 0.001$) but not on its delayed version. However, no significant differences were observed in the visual memory tasks. As expected, PD patients performed significantly worse than the CON group on the Motor Control task ($W = -4.48$, $p = 0.004$).

RBD vs. CON

RBD patients also showed several areas of poorer performance compared to the CON group but with fewer significant differences than PD patients. RBD patients had lower scores in both Trail Making ($W = -3.01$, $p = 0.085$) and Digit Span ($W = -3.13$, $p = 0.069$) but with borderline statistical significance. Regarding language tasks, RBD patients had significantly lower scores in both Verbal Analogies ($t(212) = -4.19$, $p < 0.001$) and Word Definitions ($W = -3.43$, $p = 0.04$). They also scored lower than CON in the Prospective Memory – Immediate (verbal) task, again with borderline statistical significance ($t(111) = -2.36$, $p = 0.052$). Yet, like PD patients, they showed no significant differences in the delayed version or the visual

memory tasks. In Motor Control, no significant differences were noted between RBD and CON (W = 1.07, p = 0.729).

PD vs. RBD

PD and RBD patients did not show significant differences in the performance of any cognitive task. The only significant difference was the expected worse motor performance among PD patients (W = −4.89, p = 0.002).

Several tasks did not show significant differences among the study groups, including the Spatial and Digit Span tasks, visuospatial tasks (Blocks and Manipulations 2D), and the Emotion Discrimination task. Additionally, no significant differences were observed in the immediate and delayed visual memory tasks. Cohen's d effect sizes were calculated to quantify the differences between patient groups and CON, expressed as SDs, as shown in Figure 4.2.

Task Summary Score Mean (SD)	**PD (N=89)**	**RBD (N=61)**	**CON (N=72)**	**Total (N=222)**	**ANOVA**	**p value**
Motor Control	1338.0 (597.6)	1099.0 (425.5)	1145.3 (431.5)	1209.8 (512.4)	$\chi^2(2)=15.81^c$	**< 0.001**
Manipulations 2D	19.6 (7.8)	19.4 (7.7)	21.5 (7.8)	20.2 (7.8)	$F(2,212)=2.46^a$	0.088
Target Detection	39.1 (18.1)	41.6 (15.2)	47.6 (15.7)	42.6 (16.9)	$F(2,212)=7.65^a$	**< 0.001**
Blocks	7.8 (3.4)	7.7 (3.2)	8.7 (3.0)	8.1 (3.2)	$F(2,212)=1.87^a$	0.157
Emotion Discrimination	41.7 (4.2)	41.2 (3.5)	42.8 (3.1)	41.9 (3.7)	$F(2,135)=3.35^b$	0.067
Trail Making	70357.1 (42597.7)	71033.2 (48260.6)	52382.4 (13994.5)	64713.2 (38615.8)	$\chi^2(2)=14.31^c$	**< 0.001**
Switching Stroop	48.8 (6.6)	48.9 (6.1)	50.8 (6.3)	49.5 (6.4)	$F(2,212)=3.63^a$	**0.028**
Spatial Span	5.0 (1.2)	5.2 (1.1)	5.3 (1.1)	5.2 (1.1)	$F(2,212)=2.78^a$	0.064
Digit Span	7.0 (2.2)	6.3 (2.8)	6.8 (2.2)	6.8 (2.4)	$\chi^2(2)=5.12^c$	0.077
Word Definitions	17.0 (3.2)	16.9 (2.7)	18.3 (2.5)	17.4 (2.9)	$\chi^2(2)=7.08^c$	**0.029**
Verbal Analogies	16.6 (10.2)	15.6 (9.3)	22.9 (10.1)	18.4 (10.4)	$F(2,212)=12.46^a$	**< 0.001**
Prospective Verbal Memory - Immediate	21.4 (1.6)	21.8 (1.8)	22.6 (1.3)	21.9 (1.7)	$F(2,111)=7.18^a$	**0.001**
Prospective Verbal Memory - Delayed	20.1 (1.6)	19.4 (2.1)	20.4 (2.0)	20.0 (1.9)	$F(2,109)=1.12^a$	0.331
Prospective Visual Memory - Immediate	45.4 (6.8)	44.7 (9.8)	47.8 (7.2)	46.1 (7.8)	$F(2,98)=1.51^a$	0.226
Prospective Visual Memory - Delayed	42.7 (8.0)	41.9 (11.4)	45.8 (7.6)	43.6 (8.9)	$F(2,49.9)=2.2^b$	0.141

Table 4.4 | Summary scores of the online cognitive battery tasks compared across the study groups with ANOVAs and p-values adjusted for age, gender, and education years. a. Fisher's ANOVA (equal variance) b. Welch's ANOVA (unequal variance) c. Kruskal-Wallis ANOVA (non-parametric)

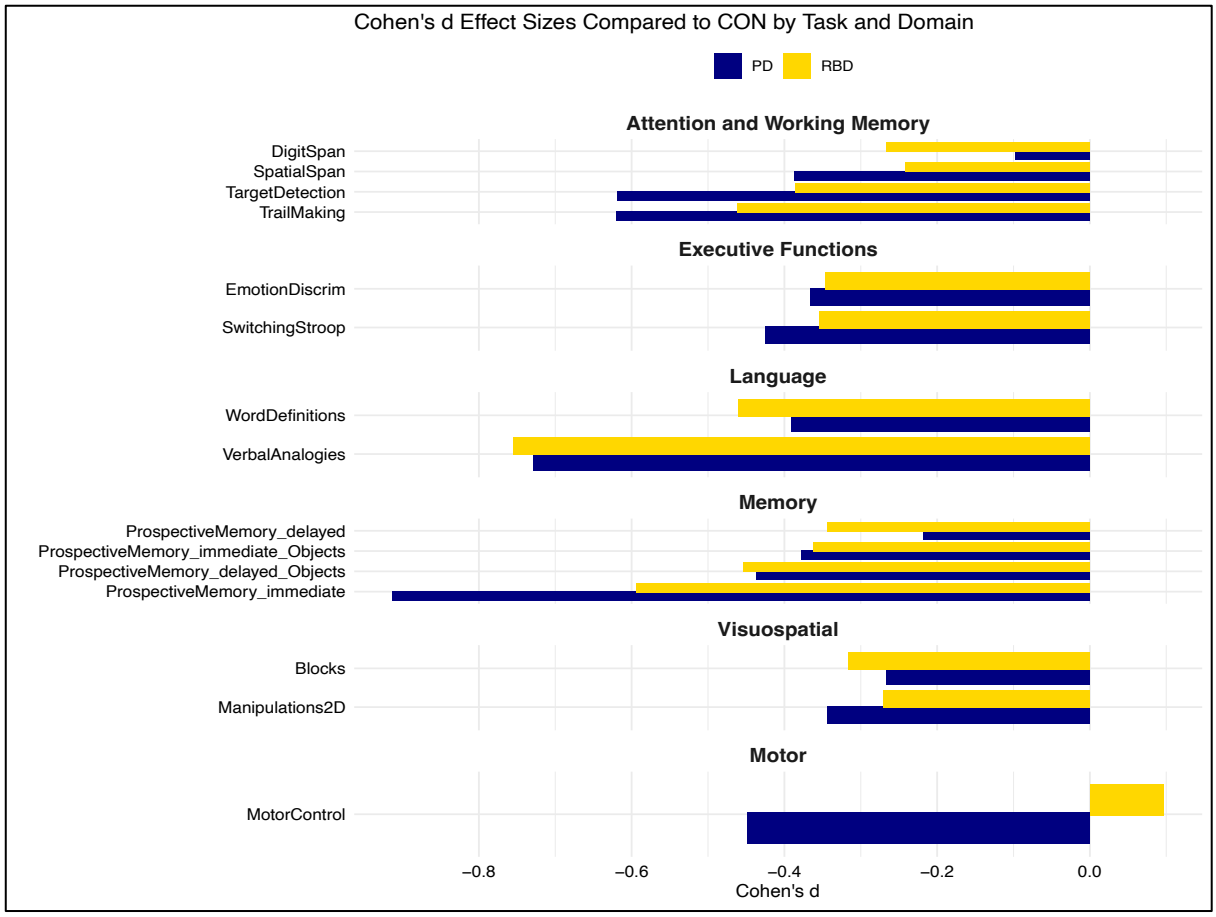


Figure 4.2 | Cohen's d effect sizes illustrating the differences between patient groups (PD (blue) and RBD (yellow)) and CON in summary scores, expressed as SD. Negative values indicate worse performance in patient groups compared to CON.

4.2.3.4 Secondary Outcome Measures (RTs)

Univariate Kruskal–Wallis ANOVAs were conducted to analyse the RTs of the study participants while they performed the tasks (secondary outcome measures). The analysis revealed significant differences among the study groups in eight specific tasks: Target Detection, Switching Stroop, Word Definitions, Verbal Analogies, Prospective Memory – Delayed (verbal), Prospective Memory – Delayed (visual), Trail Making (both letters and numbers) and Motor Control (Table 4.5). Dwass–Steel–Critchlow–Fligner pairwise comparisons showed that PD patients were significantly slower than the CON group in Target Detection ($W = -4.90$, $p = 0.002$), Switching Stroop ($W = -3.40$, $p = 0.043$), Digit Span ($W = -3.61$, $p = 0.029$) and both parts of the TMT (numbers: $W = -3.42$, $p = 0.041$ and letters: $W =$

−5.14, $p < 0.001$). On the other hand, RBD patients were significantly slower than the CON group only in the letters part of the TMT ($W = -3.92$, $p = 0.016$).

Regarding language tasks, PD patients took significantly longer than the CON group to answer the Verbal Analogies questions ($W = -3.81$, $p = 0.019$), while RBD patients spent significantly longer than the CON group on answering the Word Definitions questions ($W = -4.84$, $p = 0.002$). However, no significant differences were found between the two patient groups regarding these tasks. Regarding the memory tasks, PD patients had significantly longer RTs for correct responses compared to the CON group for both delayed verbal ($W = -4.14$, $p = 0.010$) and visual ($W = -4.53$, $p = 0.004$) memory tasks. Additionally, the median RT for delayed verbal memory tasks was higher among PD patients than among RBD patients, with borderline significance ($W = -3.26$, $p = 0.055$). On the other hand, the median RT for delayed visual memory tasks was higher among RBD patients than in the CON group but failed to reach statistical significance ($W = -2.92$, $p = 0.097$). However, no significant differences were observed among the study groups in the immediate versions of the tasks. Furthermore, post hoc comparisons revealed no significant differences in RTs among the study groups for the Manipulations 2D, Emotion Discrimination, Blocks and Spatial Span tasks. Effect sizes, expressed as Cohen's d, were computed to measure the difference in RTs between patient groups and CON, reported in SD, as illustrated in Figure 4.3.

Task Reaction Time Mean (SD) ms	PD (N=89)	RBD (N=61)	CON (N=72)	Total (N=222)	ANOVA	p value
meanRT_MotorControl	1338.0 (597.6)	1099.0 (425.5)	1145.3 (431.5)	1209.8 (512.4)	$\chi^2(2)=15.81^a$	**< 0.001**
medRT_Manipulations2D	5745.2 (2018.1)	6476.2 (2838.3)	5943.0 (2142.7)	6016.3 (2325.0)	$\chi^2(2)=2.09^a$	0.352
meanRT_TargetDetection	2074.2 (455.6)	1966.7 (436.2)	1902.7 (421.0)	1989.1 (443.6)	$\chi^2(2)=12.69^a$	**0.002**
medRT_Blocks	4378.6 (1567.3)	4608.0 (1715.4)	4026.7 (1404.1)	4324.3 (1567.4)	$\chi^2(2)=4.22^a$	0.121
medRT_EmotionDiscrim	2261.7 (572.9)	2287.1 (499.7)	2252.9 (588.0)	2266.1 (555.6)	$\chi^2(2)=1.27^a$	0.531
meanNumberRT_TrailMaking	42375.1 (10395.1)	43591.8 (12656.6)	41719.3 (11913.0)	42490.6 (11556.8)	$\chi^2(2)=6.23^a$	**0.044**
meanLetterRT_TrailMaking	69983.1 (26378.5)	69224.3 (23776.6)	60877.9 (18816.3)	66723.0 (23608.8)	$\chi^2(2)=14.51^a$	**< 0.001**
medRT_SwitchingStroop	2705.2 (730.0)	2663.0 (705.2)	2602.4 (608.1)	2658.8 (682.2)	$\chi^2(2)=6.37^a$	**0.041**
medRT_SpatialSpan	5041.7 (1590.6)	4691.4 (1341.8)	4705.5 (1223.3)	4832.7 (1413.0)	$\chi^2(2)=2.38^a$	0.304
medRT_DigitSpan	6713.5 (2275.0)	5957.9 (1699.9)	5870.2 (1766.9)	6231.3 (1999.1)	$\chi^2(2)=7.16^a$	**0.028**
medRT_WordDefinitions	5152.8 (1653.5)	5849.9 (1774.7)	4684.3 (1823.5)	5191.9 (1794.6)	$\chi^2(2)=12.49^a$	**0.002**
medRT_VerbalAnalogies	4272.7 (1173.3)	4203.0 (874.5)	3952.9 (1049.9)	4146.9 (1063.2)	$\chi^2(2)=7.39^a$	**0.025**
medRT_correct_VerbalMemory_immediate	1060.2 (217.5)	1095.3 (211.7)	1077.8 (181.0)	1076.8 (203.6)	$\chi^2(2)=0.77^a$	0.681
medRT_correct_VerbalMemory_delayed	1061.3 (253.0)	1028.3 (178.3)	1023.1 (143.6)	1039.5 (200.9)	$\chi^2(2)=10.01^a$	**0.007**
medRT_correct_VisualMemory_immediate	9643.8 (4082.4)	9308.4 (3561.8)	8748.5 (4771.0)	9244.7 (4207.2)	$\chi^2(2)=3.21^a$	0.201
medRT_correct_VisualMemory_delayed	4998.8 (2037.7)	4049.6 (1620.2)	3803.5 (1993.1)	4331.2 (1978.5)	$\chi^2(2)=12.49^a$	**0.002**

Table 4.5 | Reaction times of the online cognitive battery tasks compared across the study groups with ANOVAs and p-values adjusted for age, gender, and education years. a. Kruskal-Wallis ANOVA (non-parametric).

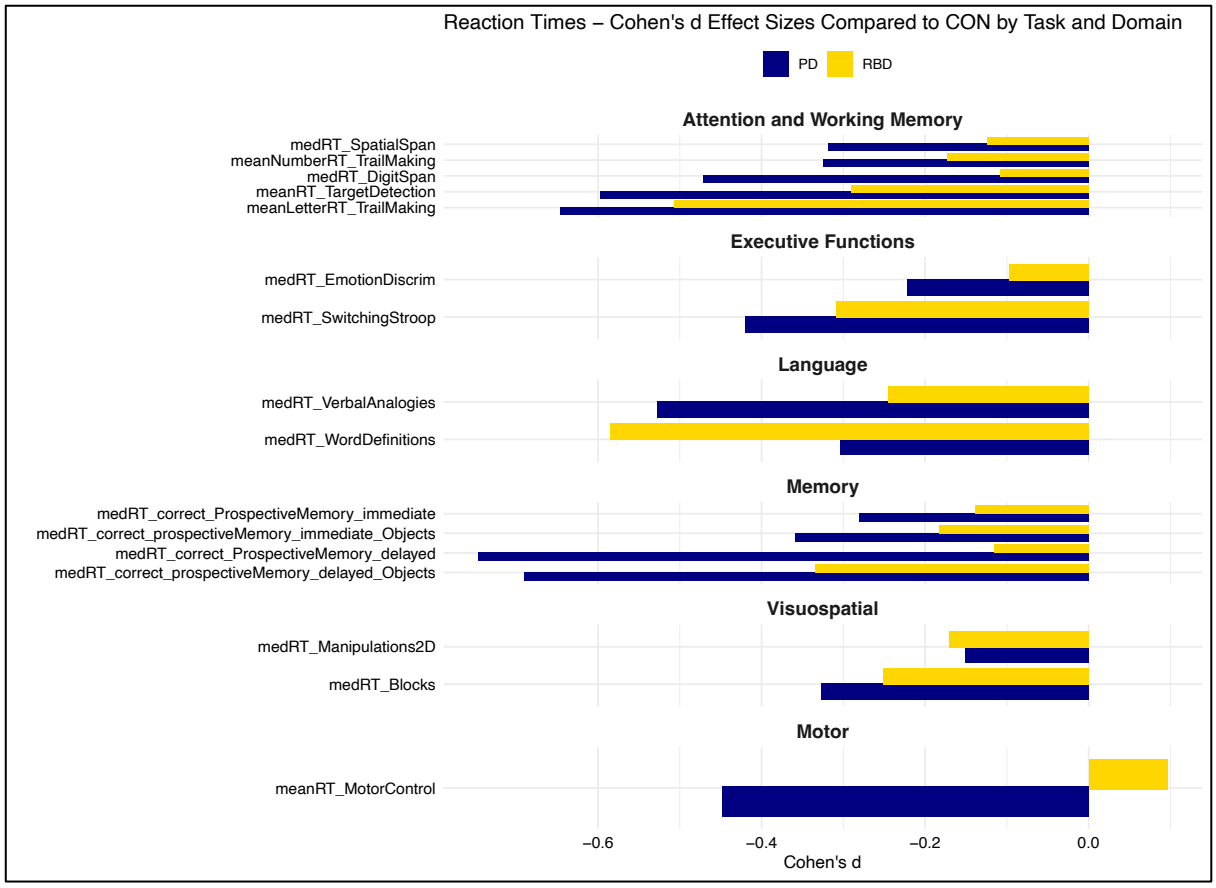


Figure 4.3 | Cohen's D effect sizes illustrating the differences in reaction times between patient groups (PD (blue) and RBD (yellow)) and HC, expressed in SD. *Negative values indicate slower reaction times in patient groups compared to HC.*

4.2.3.5 Perceived Performance (Metacognition)

Figure 4.4 presents the mean perceived performance (expressed as a percentage) for each study group across different cognitive tasks. Figure 4.5 shows the correlations between perceived performance and actual performance, serving as an index of metacognition. The highest correlations were noted in the memory tasks.

4.2.3.6 Hierarchical Clustering

Figure 4.6 shows the correlation matrix and hierarchical clustering of the cognitive tasks, revealing distinct grouping and relationships among these tasks.

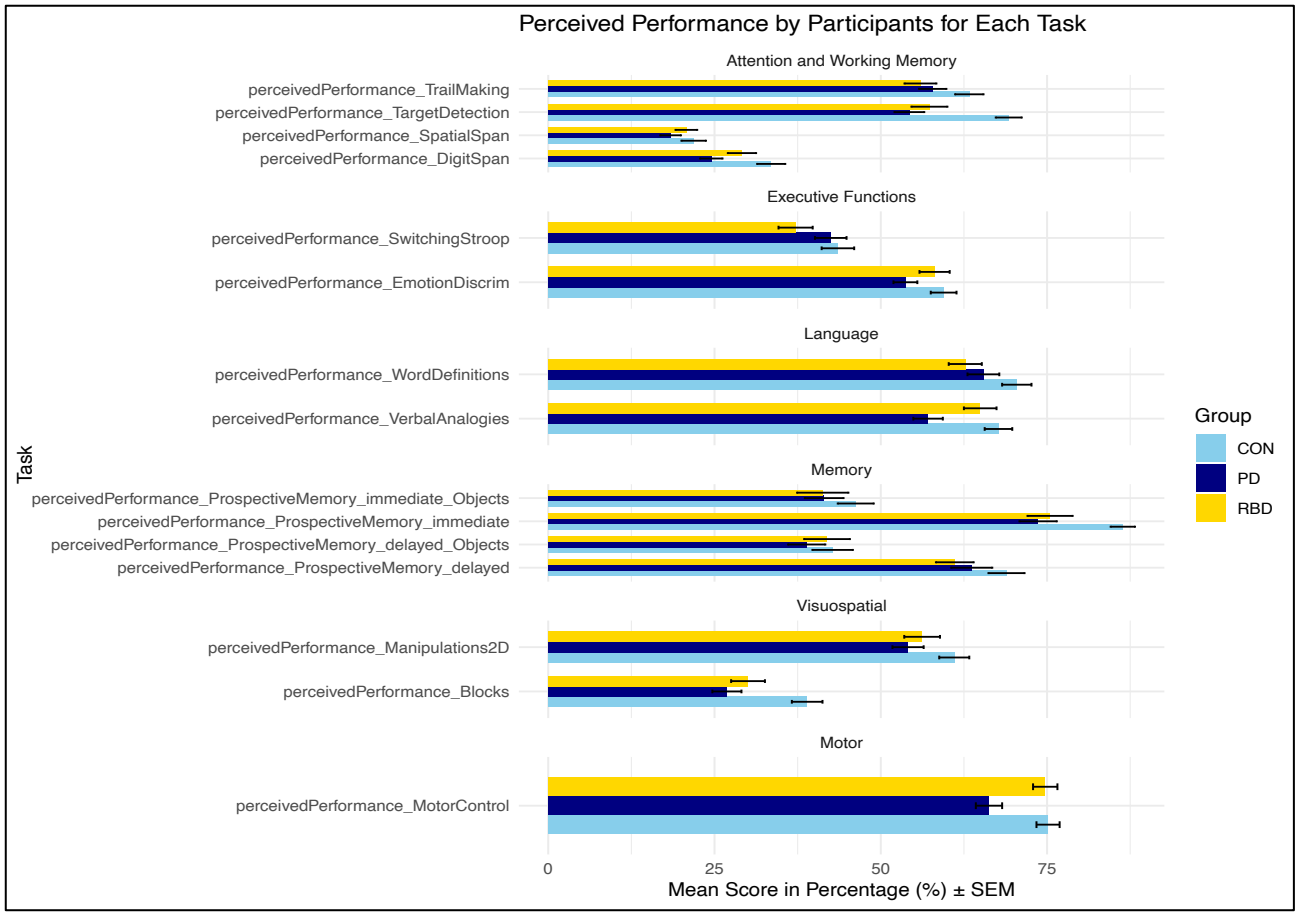


Figure 4.4 | Mean perceived performance of study groups across different cognitive tasks, expressed as a percentage (out of 100%). Error bars represent the standard error of the mean (SEM).

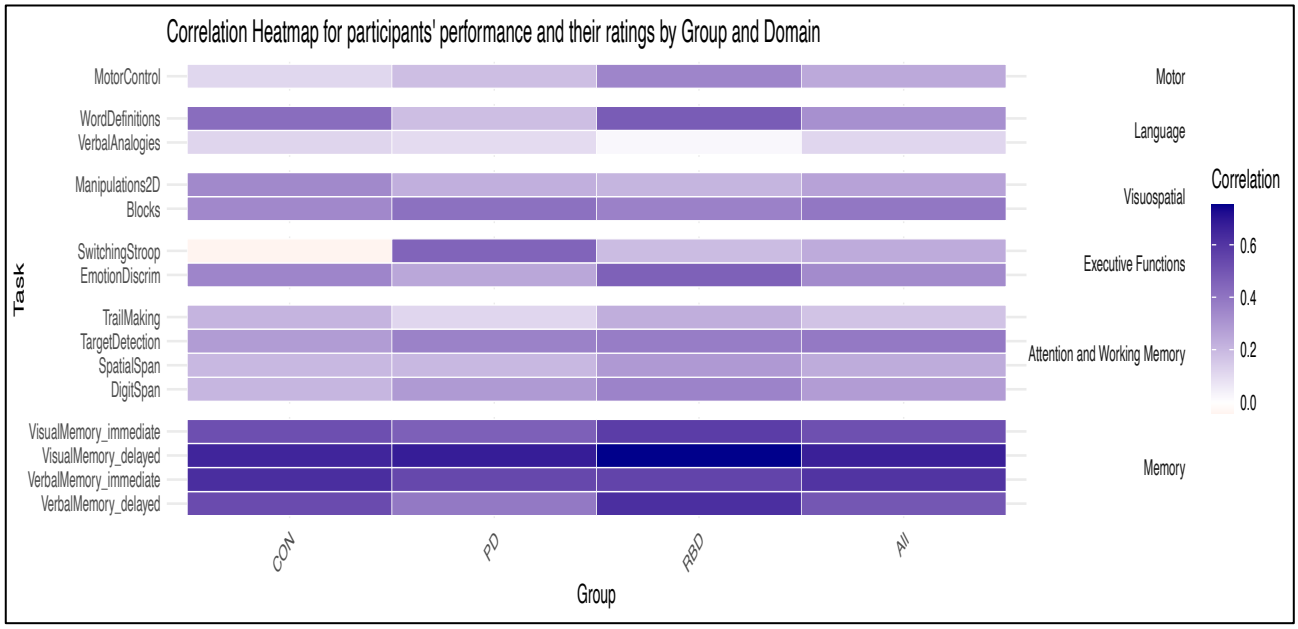


Figure 4.5 | Correlations between perceived and actual performance. Darker purple indicates stronger correlations. For all participants, all the tasks except Verbal Analogies, exhibit statistically significant Pearson correlations ($p<0.01$), with the highest correlations observed in the memory tasks. In PD, non-significant correlations were found in Motor Control, TMT, Spatial Span, and delayed verbal memory and language tasks. In RBD and HC, non-significant correlations were noted in Verbal Analogies and Switching Stroop, with an additional non-significant correlation in motor control for HC.

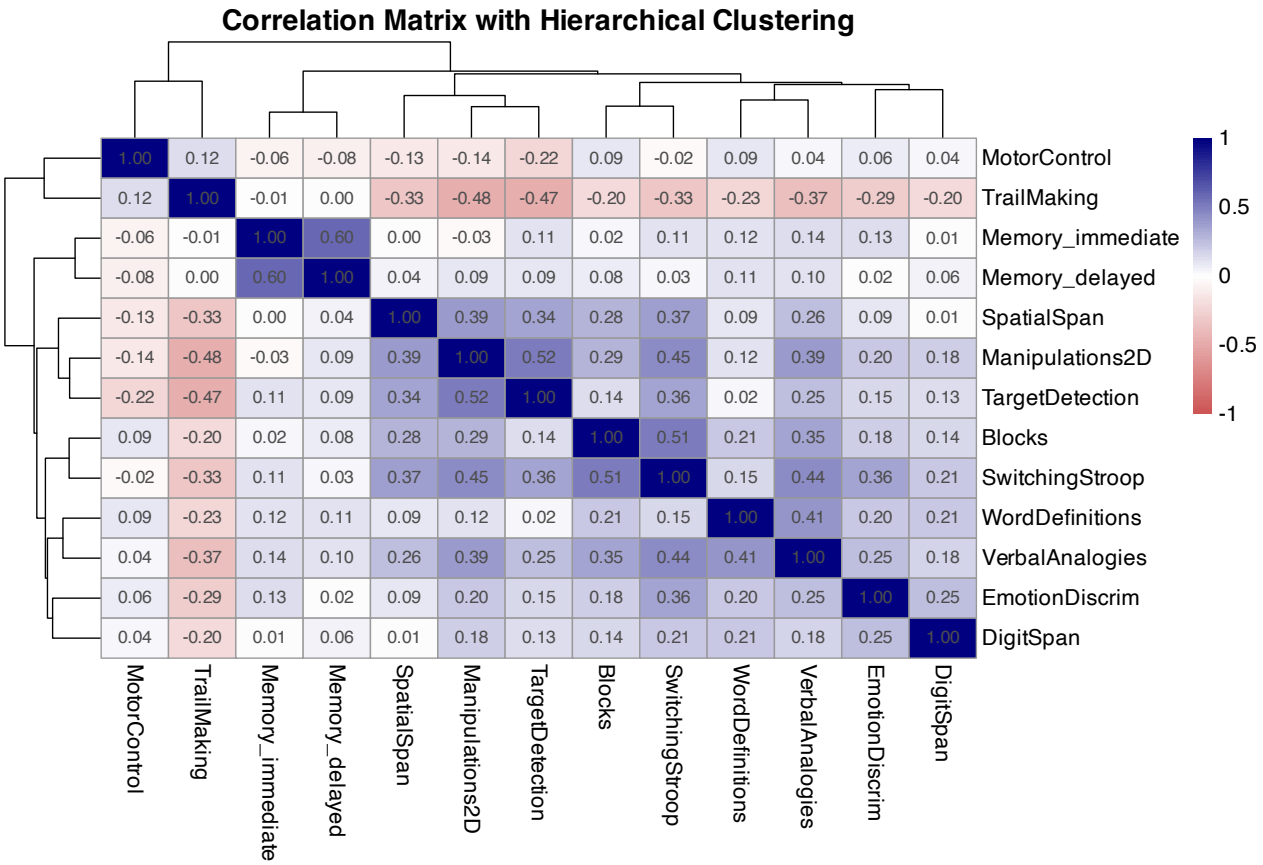


Figure 4.6 | Correlation matrix with hierarchical clustering of cognitive tasks in the online battery. The correlation matrix shows the relationship between cognitive tasks after standardising the primary performance scores. Note that Motor Control and Trail Making are RT measures, where higher scores indicate worse performance, and therefore negatively correlated with the other tasks. Hierarchical clustering reveals distinct groupings among these tasks, highlighting clusters of related cognitive abilities.

4.2.3.7 Principal Component Analysis

PCA with varimax rotation was applied to reduce the dimensionality of the dataset, with five components set to correspond to the anticipated cognitive domains (Table 4.6). These components explained 70% of the variability in the data (Table 4.7). The first component exhibited the highest loadings for attentional and working memory tasks, including Target Detection, Manipulations 2D, Trail Making and Spatial Span. The second component showed the highest loadings for visuospatial and executive functions tasks, namely Blocks and Switching Stroop. The third component was most strongly associated with memory tasks, while the fourth component had the highest loadings for language tasks.

Finally, the fifth component was characterised by loadings in Emotion Discrimination and Digit Span tasks.

Component Loadings

	Component					
	1	2	3	4	5	Uniqueness
zAdjusted_SummaryScore_TargetDetection	0.831					0.276
zAdjusted_SummaryScore_Manipulations2D	0.745					0.354
zAdjusted_SummaryScore_TrailMaking	-0.722					0.329
zAdjusted_SummaryScore_SpatialSpan	0.558					0.434
zAdjusted_SummaryScore_Blocks		0.844				0.250
zAdjusted_SummaryScore_SwitchingStroop		0.732				0.255
zAdjusted_Memory_immediate			0.895			0.190
zAdjusted_Memory_delayed			0.883			0.213
zAdjusted_SummaryScore_WordDefinitions				0.905		0.156
zAdjusted_SummaryScore_VerbalAnalogies				0.625		0.354
zAdjusted_SummaryScore_DigitSpan					0.757	0.396
zAdjusted_SummaryScore_EmotionDiscrim					0.727	0.392

Table 4.6 | PCA component loadings.

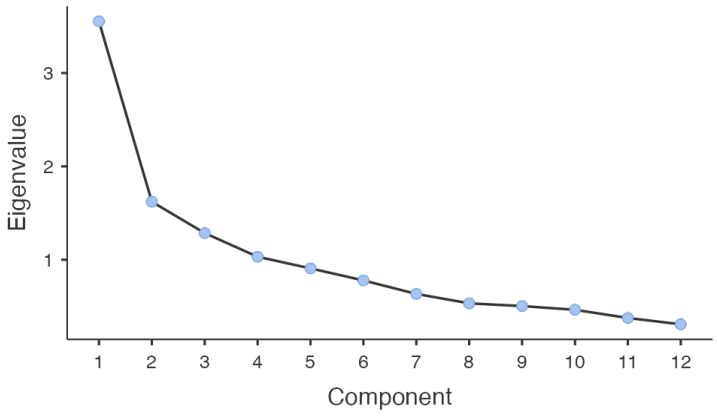


Figure 4.7 | PCA scree plot.

Component	SS Loadings	% of Variance	Cumulative %
1	2.32	19.3	19.3
2	1.71	14.2	33.6
3	1.62	13.5	47.1
4	1.38	11.5	58.6
5	1.37	11.4	70.0

Table 4.7 | PCA summary.

4.2.3.8 Cognitive Profiles

To delineate the cognitive profiles of the study groups, the first four PCA components with eigenvalues greater than 1 were used as global composite scores for the corresponding cognitive domains (Figure 4.7). Univariate ANOVAs on these scores were performed to differentiate the study groups based on cognitive domain scores (Figure 4.8A). The first component (Attention and Working Memory; $F(2,202) = 5.1$, $p = 0.007$), the third component (Memory; $F(2,119) = 5.5$, $p = 0.005$) and the fourth component (Language; $F(2,129) = 6.5$, $p = 0.002$) significantly differentiated the groups, whereas the second component (Visuospatial and Executive Functions) did not show significant differences between the groups ($F(2,202) = 0.99$, $p = 0.372$). Post hoc comparisons revealed that for PCA global attention and working memory scores, only PD patients had significantly lower scores compared to the CON group ($t(202) = -3.19$, $p = 0.005$). For both memory and language global PCA scores, both PD (Memory: $t(134) = -3.14$, $p = 0.005$; Language: $t(141) = -2.60$, $p = 0.028$) and RBD (Memory: $t(102) = -2.42$, $p = 0.045$; Language: $t(104) = -3.23$, $p = 0.005$) groups showed significant underperformance compared to the CON group (Figure 4.8B). No significant differences were observed between the PD and RBD groups across all global PCA cognitive scores.

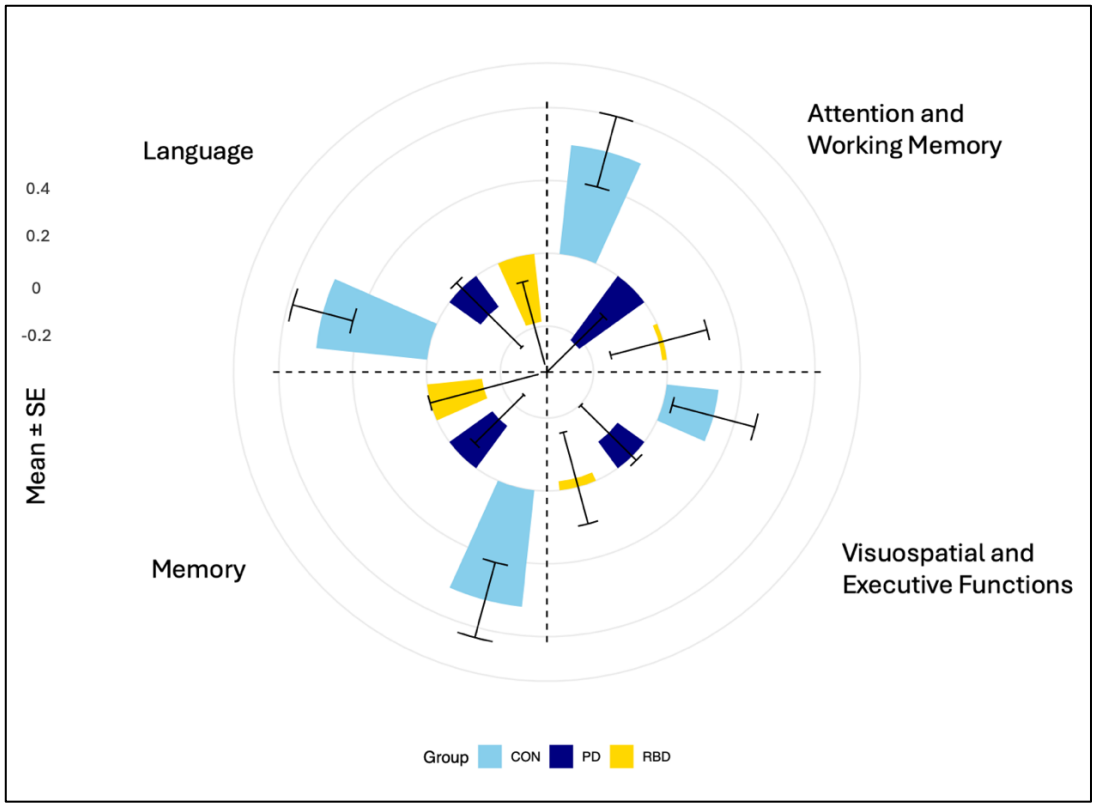


Figure 4.8A | Cognitive profiles of study groups based on PCA composite scores. The radar graph is divided into four quadrants, each representing a distinct cognitive domain based on PCA composite scores. Within each quadrant, the mean PCA composite scores of the study groups are compared using bars (PD: blue, RBD: yellow, HC: sky blue). Error bars represent ± 1 SEM.

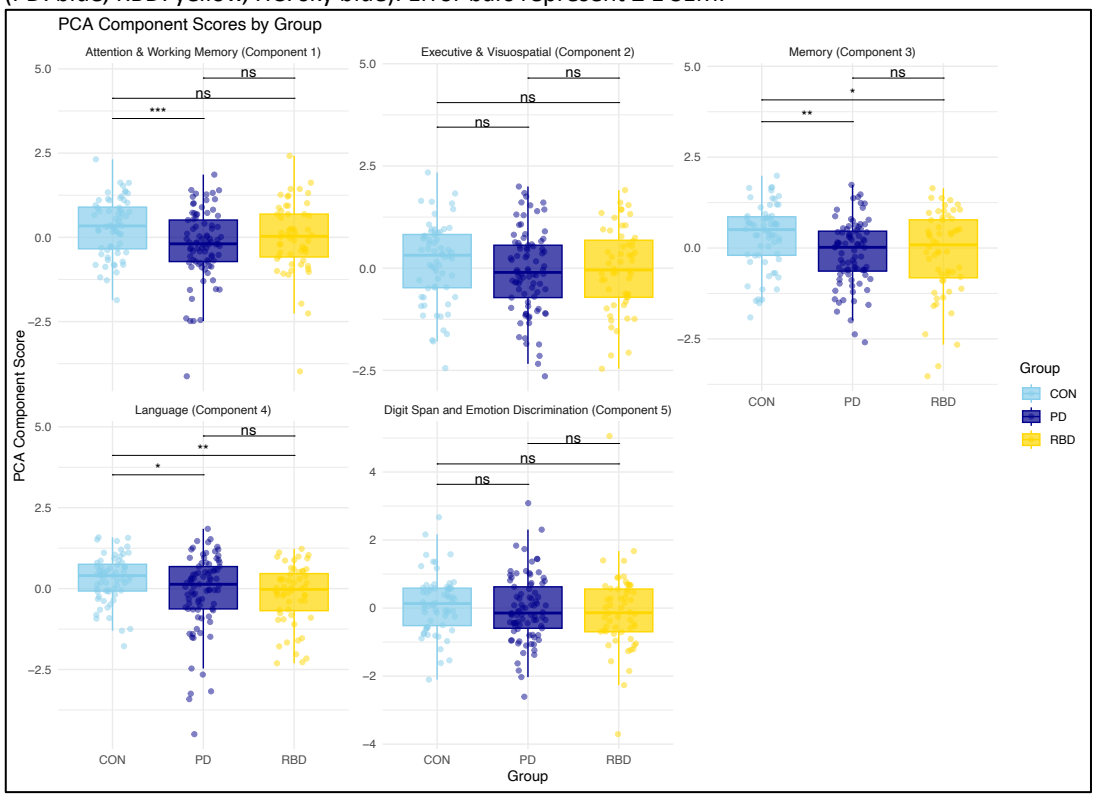


Figure 4.8B | PCA component scores by group. The boxplots illustrate the distribution of PCA component scores across the three groups: PD (blue), RBD (yellow) and HC (sky blue), with the median and interquartile range. Individual scores are displayed as jittered points. Significant differences between groups means are highlighted with annotated p-values.

4.2.3.9 Correlation Analysis between PCA Composite Scores and MoCA Scores

The Pearson correlation analysis of the PCA cognitive composite scores with the total MoCA scores revealed significant correlations for three PCA component scores. Specifically, the strongest correlation was observed with PCA Component Score 3 (Memory: r = 0.22, p = 0.006), followed by PCA Component Score 2 (Visuospatial and Executive Functions: r = 0.19, p = 0.013), and PCA Component Score 4 (Language: r = 0.17, p = 0.033). In contrast, no significant correlations were found for PCA Component Scores 1 and 5 (Figure 4.9).

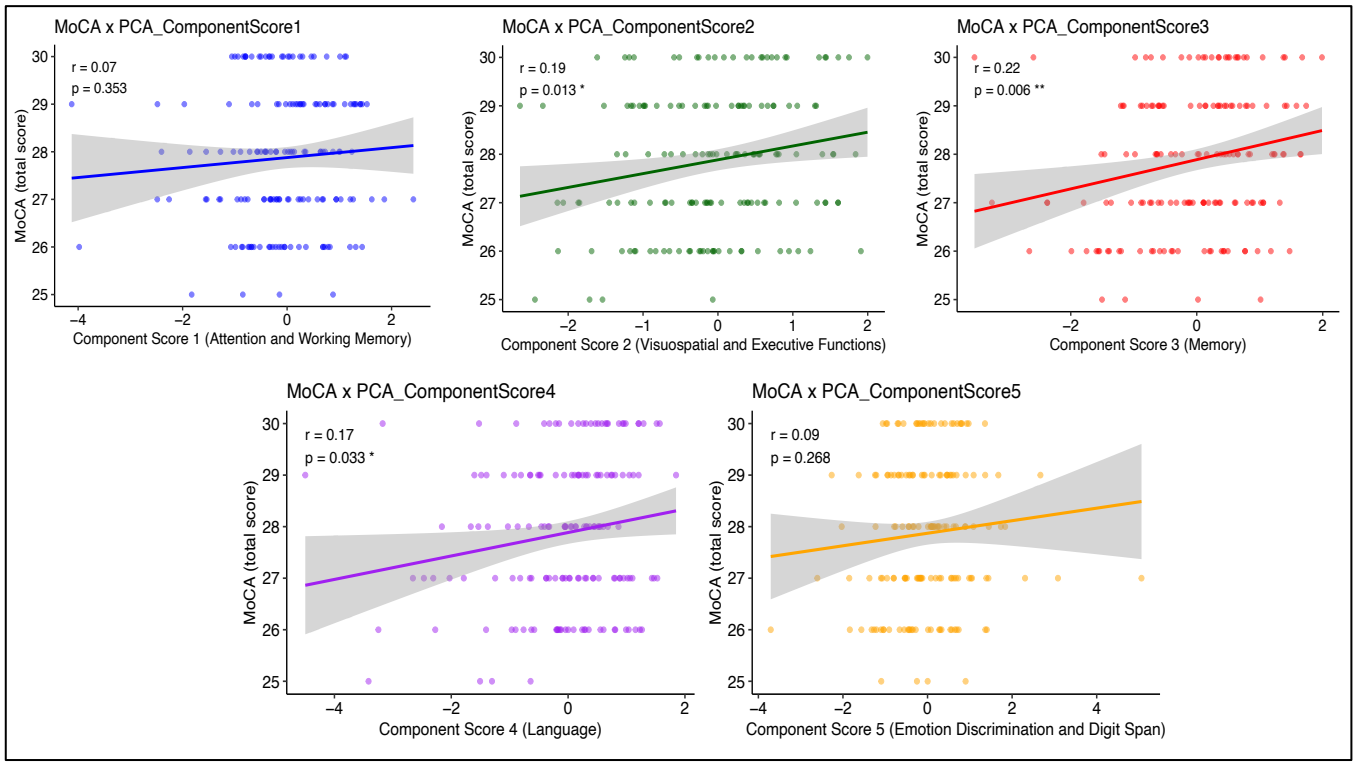


Figure 4.9 | Correlations of the total MoCA scores with the PCA component scores.

4.2.3.10 Sensitivity Analyses

To evaluate motor effects on the cognitive composite scores and determine if the observed impairments in patient groups are due to motor rather than cognitive impairments, ANCOVAs were performed on each PCA composite score, with the Motor Control task included as a covariate. The results revealed a significant motor effect on only the first composite score (Attention and Working Memory: $F(1,201) = 10.21$, $p = 0.002$); however, the group effect remained statistically significant ($F(2,201) = 3.01$, $p = 0.04$). For the fourth score (Language), a borderline significant motor effect was observed ($F(1,201) = 3.53$, $p = 0.062$), with the group effect remaining significant ($F(2,201) = 5.31$, $p = 0.006$). No motor effects were detected on the remaining scores.

4.2.4 Discussion

This study aimed to delineate the cognitive profiles of patients with PD and its prodromal phase, RBD, using remote online cognitive tools. We found that only PD patients had significantly worse scores in attention and working memory domains than CON, while both patient groups had significantly worse cognitive performances in memory and language domains compared to CON. No cognitive test, however, significantly differentiated PD from RBD, indicating comparable levels of cognitive impairments in both groups. These impairments in cognitive functions in RBD were not surprising and are consistent with the findings of previous studies (Bezdicek et al., 2018; Fantini et al., 2011; Massicotte-Marquez, Décary, et al., 2008; Rolinski et al., 2016; M. Terzaghi et al., 2008).

Our study found that PD patients exhibited significantly worse performance compared to CON in attentional and executive function tasks, such as the TMT, Target Detection and Switching Stroop. These results are in line with the literature (Brønnick, 2015; Dirnberger & Jahanshahi, 2013) and support the dual syndrome hypothesis (Kehagia et al., 2013), which posits that anterior fronto-striatal dopaminergic system-mediated cognitive deficits occur early in PD and are linked to attentional and executive dysfunction, whereas posterior cholinergic system-mediated cognitive deficits are associated with visuospatial and memory impairments that develop as the disease progresses.

Interestingly, our findings indicated that RBD patients underperformed relative to CON in memory and language cognitive domains. This also could be explained by the same dual hypothesis regarding cholinergic system-mediated cognitive deficits, supported by molecular imaging studies involving cholinergic PET scans. These studies have demonstrated severe cholinergic deficits in RBD patients compared to CON (Gersel Stokholm et al., 2020), as well as greater cholinergic denervation in PD patients with RBD compared to those

without RBD (Kotagal et al., 2012). Moreover, PD patients with premotor RBD were found to have greater cholinergic denervation compared to those with post-motor RBD (Kanel et al., 2022). In addition, the body-first vs brain-first model for the spread of alpha-synuclein pathology in LBD may provide another angle for explaining these results. Studies comparing the body-first phenotype of LBD, where RBD precedes motor symptoms, with the brain-first phenotype, where motor PD appears first, have shown early cholinergic deficits, albeit starting in the peripheral nervous system, with a higher degree of cognitive impairment in the body-first type (Borghammer et al., 2021; Horsager et al., 2020; Horsager et al., 2022).

In terms of specific cognitive tasks, previous studies have shown that RBD patients perform worse than CON in the Digit Span task (M. Terzaghi et al., 2008). Our study found a similar result, although with borderline statistical significance. Conversely, PD patients did not differ from CON in their digit span performance. Bohnen et al. (2006) showed a robust correlation between digit span and cortical AchR activity in PD patients with and without dementia, indicating that reduced cholinergic activity is associated with poorer digit span performance (Bohnen et al., 2006). This suggests that similar cholinergic deficits may underlie the digit span impairments observed in RBD patients. Furthermore, the reduced memory composite scores observed in RBD patients compared to CON may be linked to these cholinergic deficits. A recent study using both cholinergic PET and structural T1 MRI found that basal forebrain integrity completely mediated the relationship between hippocampal acetylcholine levels and performance in delayed memory tasks (Crowley et al., 2024). Additionally, another functional MRI study showed a correlation between the functional connectivity of the NBM in the basal forebrain and memory performance in RBD patients with MCI (Byun et al., 2022). These neurotransmitter deficits could explain the small differences in the cognitive profiles observed in our study between the early PD and RBD

groups. PD patients demonstrated more attentional deficits, which are associated with greater dopaminergic deficits. In contrast, RBD patients exhibited more pronounced impairments in memory compared to controls, which are associated with greater cholinergic deficits.

The absence of significant differences between PD and RBD in all cognitive tasks' summary scores might suggest similar levels of cognitive impairment and a potentially shared underlying pathology, albeit at different stages. In terms of anterior dopaminergic system-related cognitive dysfunction, RBD patients' scores fell between those of CON and PD patients, indicating that RBD may represent an earlier temporal stage of PD regarding these deficits. Furthermore, RBD, as a risk factor for dementia (Postuma et al., 2012) typically associated with cholinergic dysfunction in PD (Hall et al., 2014; Müller & Bohnen, 2013), may begin with earlier cholinergic deficits that progress over time, ultimately contributing to worse cognitive outcomes in PD patients with RBD compared to those without RBD, as shown in previous studies (Jozwiak et al., 2017; Kamble et al., 2019; Marion et al., 2008).

The attentional tasks in our battery represent a range of tasks with varying cognitive challenges and difficulties, with Digit and Spatial Span tasks considered simple attention tasks, while Target Detection and Trail Making (mainly Part 2, letters and numbers) are more complex, cognitively demanding tasks. PD patients performed significantly worse in only the complex attentional tasks, which can possibly be attributed to executive dysfunction related to fronto-striatal dopaminergic deficits that are more prominent than in RBD (Kehagia et al., 2013; Watson & Leverenz, 2010).

In terms of the secondary measures in our study, the PD group had longer RTs than other groups in most of the cognitive battery tasks. This was more prominent in complex attentional tasks (Target Detection and TMT-B) and tasks that required executive functions,

such as Switching Stroop and Verbal Analogies. This is in agreement with the literature, although often debated, where bradyphrenia (slowness in cognitive processing speed) is common in PD and independent of bradykinesia (motor slowness) (Goldman et al., 1998; Johnson et al., 2004; Pate & Margolin, 1994; Vlagsma et al., 2016).

Metacognition was also assessed in this study. The correlations between perceived and actual performance were high for most tasks, especially memory tasks. This indicates that patients were aware of their cognitive difficulties, which has important implications for their general safety and everyday activities.

Using online remote cognitive tests offers several benefits, including increased accessibility for participants who may have mobility issues, live in remote areas, or, as in our case, are vulnerable during pandemic times (Owens et al., 2020). Additionally, the convenience of completing assessments in a familiar environment can reduce test anxiety and improve performance accuracy.

However, this study has certain strengths and limitations. Its strengths include the use of a comprehensive cognitive battery to assess a wide range of cognitive domains and the inclusion of both PD and RBD patients to compare cognitive profiles across disease stages. Its limitations include potential biases related to self-reported data and the reliance on remote testing, which may introduce variability in testing conditions and participant engagement.

4.2.5 Conclusion

In conclusion, this study provides valuable insights into the cognitive profiles of PD and RBD patients using remote online cognitive assessments. Our findings indicate that PD patients perform significantly worse in attention and working memory domains compared to CON, while both PD and RBD patients show impairments in memory and language domains. Future large longitudinal studies are essential to further delineate the cognitive decline in PD and RBD over time. Such research will deepen our understanding of the progression of cognitive impairments and aid in identifying earlier markers of cognitive decline, facilitating timely interventions to improve patient outcomes.

4.3 Study 2 | Cross-sectional and Longitudinal Patterns of Cognitive Impairment in Patients with Lewy Body Diseases

4.3.1 Introduction

The first study in this chapter was a cross-sectional analysis of the study groups based on their performance in the online cognitive battery. This initial study focused on participants with MoCA scores of 26 and above, ensuring a relatively high baseline of cognitive function. However, to gain a more comprehensive understanding of cognitive performance across a broader spectrum, our second study included participants with lower MoCA scores.

In the present study, we first examined the cognitive performance of each group individually by comparing how they performed on each task to their overall performance across all tasks. This approach allowed us to identify areas where participants excelled or struggled within the context of their cognitive abilities rather than making direct comparisons between groups.

Subsequently, we investigated the longitudinal changes in the cognitive performance of each group over an 18-month period. These data, collected remotely as part of the larger Discovery study clinics, enabled us to track and analyse the progression of cognitive changes over time within each group and compare these trajectories across the different groups. By including a wider range of participants and focusing on both cross-sectional and longitudinal analyses, this study aimed to provide a more nuanced understanding of cognitive performance dynamics in our participant cohorts.

4.3.2 Methods

4.3.2.1 Participants

The recruitment method for this study closely followed the approach used in the previous study, detailed above. The present study mainly differs in its inclusion criteria, enrolling participants with MoCA scores below 26 and thus ignoring the previous exclusion criterion. The cognitive battery was administered as part of the broader Discovery study, in which patients are followed up every 18 months. Written informed consent was obtained from all participants in the clinic.

4.3.2.2 Cognitive Tasks

The online cognitive battery in this study was the same as the one used in the first study and comprised 13 cognitive tasks: Motor Control, Manipulations in Two Dimensions, Target Detection, Blocks, Emotion Discrimination, Trail Making, Switching Stroop, Spatial Span, Digit Span, Word Definitions, Verbal Analogies, Prospective Memory – Immediate (Objects) and Prospective Memory – Delayed (Objects) (Figure 4.1). These tasks cover a wide range of cognitive domains. For the memory tasks, some participants completed the verbal versions, so the scores for these tasks were standardised using z-scores to ensure comparability.

4.3.2.3 Statistical Analysis

For the cross-sectional analysis in this study, we aimed to compare the performance in each task to the overall performance. To do this, mean scores were calculated for each participant across the 13 cognitive tasks using their z-scores. Subsequently, the difference from the mean score was determined for each task for each participant, ensuring that the sum of these differences for each participant equalled zero. For each study group, mean scores for each task were then calculated to compare performance in individual tasks to

overall performance. One-sample t-tests were performed to test the difference between each task score and the mean score. A P value of 0.05 was considered statistically significant. To account for multiple comparisons, Bonferroni's correction was applied.

As secondary analyses for the cross-sectional part of the study, we compared the performance in the online cognitive tasks between participants based on their cognitive status. Participants with PD were categorised using the MDS Level 1 MCI criteria into the MCI (PD-MCI) and normal cognition (PD-NC) groups; similarly, RBD patients were categorised into the RBD-MCI and RBD-NC groups based on their MoCA scores (with scores below 26 indicating MCI). Independent t-tests were used to compare cognitive performance between these groups.

For the longitudinal analysis, we utilised a multivariate analysis of covariance (MANCOVA) to examine changes in cognitive performance over time. Tasks were treated as dependent variables, with age included as a covariate. Group (PD, RBD, CON) and visit (baseline, follow-up) were used as fixed factors. This analysis allowed us to assess the interaction between time and group, identifying significant changes in cognitive performance across the 18-month period. When significant interactions or main effects were found, post hoc tests were performed to determine which specific groups or time points differed from the others.

4.3.3 Results

4.3.3.1 Baseline Characteristics

A total of 281 participants completed the online cognitive battery (113 PD, 80 RBD and 88 CON). The mean age of the participants was 68.5 ± 9.2 years, and 63% were male. CON participants were significantly older than participants in the other groups. Both PD and CON groups had similar male and female representation, while the RBD group had a predominance of men (over 90%). The participants had a mean MoCA score of 27.2 ± 2.3. the RBD group scored significantly lower in both the MoCA and NART IQ assessments than the other groups. Table 4.8 summarises the baseline characteristics of the study participants.

	PD (N=113)	RBD (N=80)	CON (N=88)	Total (N=281)	p-value
Age	67.3 (9.1)	67.7 (9.3)	70.9 (9.1)	68.5 (9.2)	0.014[1]
Gender Female Male	46.0% 54.0%	8.8% 91.2%	50.0% 50.0%	36.7% 63.3%	< 0.001[2]
Disease duration	9.4 (2.8)	n/a	n/a	n/a	
Hoehn & Yahr stage 1 2 3	 12.0 (10.6%) 87.0 (77.0%) 14.0 (12.4%)	n/a	n/a	n/a	
MoCA	27.1 (2.3)	26.8 (2.2)	27.8 (2.1)	27.2 (2.3)	0.010[1]
Full scale IQ NART	118.1 (5.0)	115.6 (5.2)	118.3 (7.2)	117.3 (5.6)	0.011[1]
Verbal IQ NART	121.1 (4.7)	118.9 (4.9)	121.4 (6.8)	120.4 (5.3)	0.011[1]
Performance IQ NART	118.4 (3.3)	116.8 (3.4)	118.6 (4.8)	117.9 (3.7)	0.011[1]

Table 4.8 | Baseline characteristics of study participants. 1. Linear Model ANOVA 2. Pearson's Chi-squared test

4.3.3.2 Cross-Sectional Cognitive Patterns of Study Groups Relative to their Overall Performance

To compare the cross-sectional cognitive patterns of the study groups, the mean differences of the cognitive tasks from the overall cognitive performance were compared using one-sample t-tests, with Bonferroni's correction applied for multiple comparisons.

In the CON group, significant differences were observed only in Verbal Analogies, with scores being higher than the overall performance ($t(81) = 2.17$, $p = 0.033$); however,

significance was lost after Bonferroni correction (Figure 4.10A). In the PD group, none of the tasks showed significant differences compared to the mean overall cognitive score. However, Digit Span scores showed a trend towards higher scores ($t(109) = 1.72$, $p = 0.087$; Figure 4.10B). In the RBD group, the Motor Control task showed significantly better scores ($t(76) = 3.08$, $p = 0.003$) that remained significant even after Bonferroni correction (adjusted $p = 0.039$; Figure 4.10C). Figure 4.10D illustrates the cognitive patterns of all the study groups.

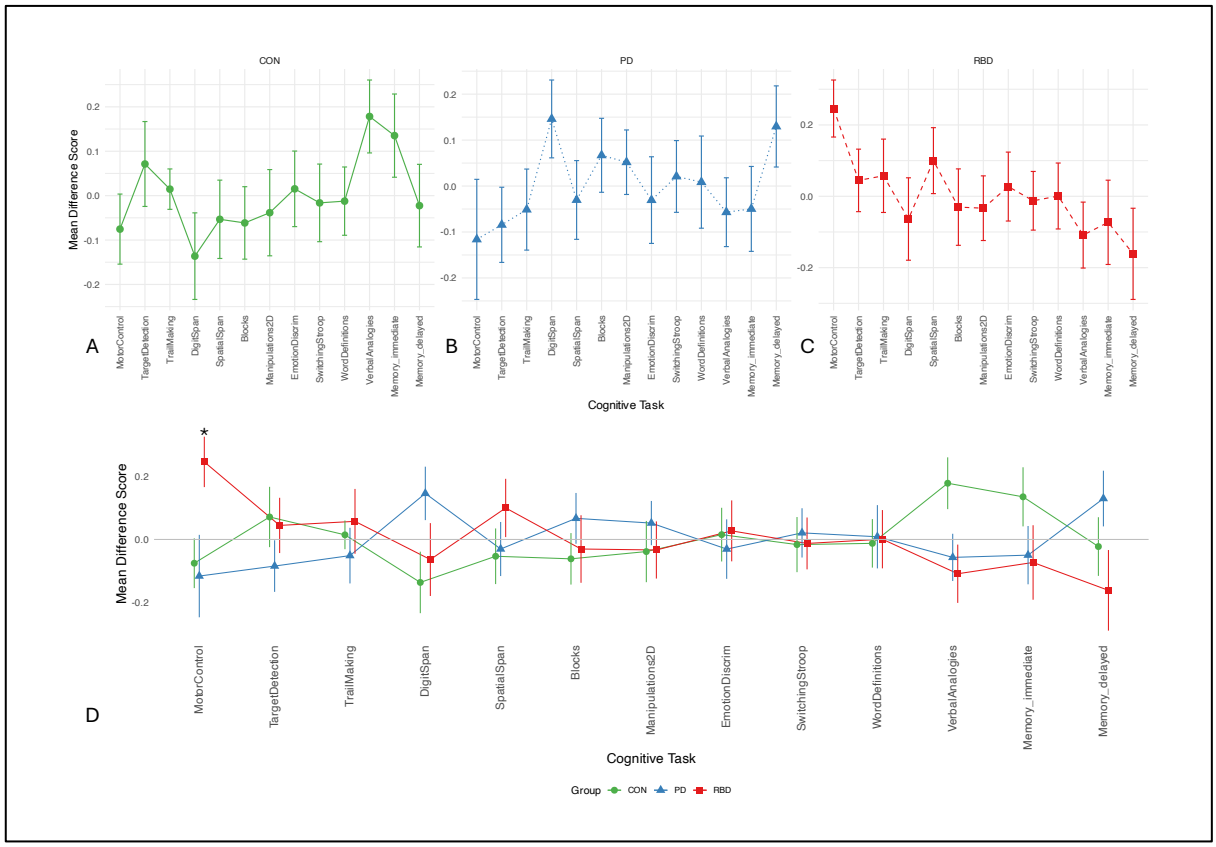


Figure 4.10 | Cross-sectional cognitive pattern relative to the overall performance in each study group: CON (A), PD (B), RBD (C), and a combined graph (D) to illustrate comparisons.
*adjusted p-value < 0.05

4.3.3.3 Secondary Analyses

Comparisons of Online Cognitive Performances Based on MoCA Cognitive Status

Study participants were divided into two groups based on their MoCA scores: MCI (MoCA < 26) and NC (MoCA ≥ 26). The baseline characteristics of these groups are presented in Table 4.9. Independent t-tests were conducted to compare cognitive performance across various tasks. Significant differences were observed for three tasks, with the MCI group performing worse: Prospective Memory – Delayed ($t(127) = -3.4$, $p < 0.001$), Emotion Discrimination ($t(266) = -2.3$, $p = 0.023$) and Spatial Span ($t(266) = -1.9$, $p = 0.048$). However, after adjusting for multiple comparisons, only the Prospective Memory – Delayed task remained statistically significant, with the MCI group scoring lower than the NC group (adjusted $p = 0.01$); see Figure 4.11. Mean scores for all MCI and NC participants are detailed in Appendix (Table 8.6).

PD-MCI vs. PD-NC

Twenty-three PD patients (20.35%) had MCI based on Level 1 MDS criteria, while 90 PD patients had NC. Table 4.9 shows the baseline characteristics of these patients. The mean summary scores for each cognitive task were compared between these groups and showed no significant differences (Figure 4.12). Detailed mean scores for each PD group are provided in Appendix (Table 8.7).

RBD-MCI vs. RBD-NC

The same MoCA cutoff of 26 was used to categorise RBD patients, resulting in 18 RBD-MCI (22.78%) and 61 RBD-NC patients. Table 4.9 displays the baseline characteristics of these groups. Significant differences were observed for only one task: Prospective Memory – Delayed ($t(36) =$, $p = 0.038$), with the RBD-MCI group having lower scores than the RBD-NC group (Figure 4.13). However, after adjusting for multiple comparisons, this difference did

not remain statistically significant (adjusted p = 0.49; Table 4). Detailed mean scores for each RBD group can be found in Appendix (Table 8.8).

	PD (N=113)			RBD (N=79)		
	PD-MCI (N=23)	**PD-NC (N=90)**	Difference p-value	**RBD-MCI (N=18)**	**RBD-NC (N=61)**	Difference p-value
Age	72.7 (9.3)	65.9 (8.5)	0.001[1]	70.1 (8.4)	67.0 (9.6)	0.218[1]
Gender Female Male	39.1% 60.9%	47.8% 52.2%	0.458[2]	5.6% 94.4%	8.2% 91.8%	0.710[2]
Disease duration	9.8 (2.3)	9.3 (2.9)	0.427[1]	n/a	n/a	
Hoehn & Yahr stage 1 2 3	 0.0 (0.0%) 17.0 (73.9%) 6.0 (26.1%)	 12.0 (13.3%) 70.0 (77.8%) 8.0 (8.9%)	0.024[2]	n/a	n/a	
MoCA	23.7 (2.1)	28.0 (1.3)	< 0.001[1]	23.6 (1.4)	27.8 (1.3)	< 0.001[1]
Full scale IQ NART	119.1 (4.6)	117.8 (5.1)	0.315[1]	114.9 (5.4)	115.9 (5.2)	0.549[1]
Verbal IQ NART	122.2 (4.3)	120.9 (4.8)	0.315[1]	118.2 (5.1)	119.1 (4.9)	0.549[1]
Performance IQ NART	119.2 (3.1)	118.3 (3.4)	0.315[1]	116.4 (3.6)	117.0 (3.4)	0.549[1]

Table 4.9 | Baseline characteristics of PD-MCI vs. PD-NC and RBD-MCI vs. RBD-NC. 1. Linear Model ANOVA 2. Pearson's Chi-squared test

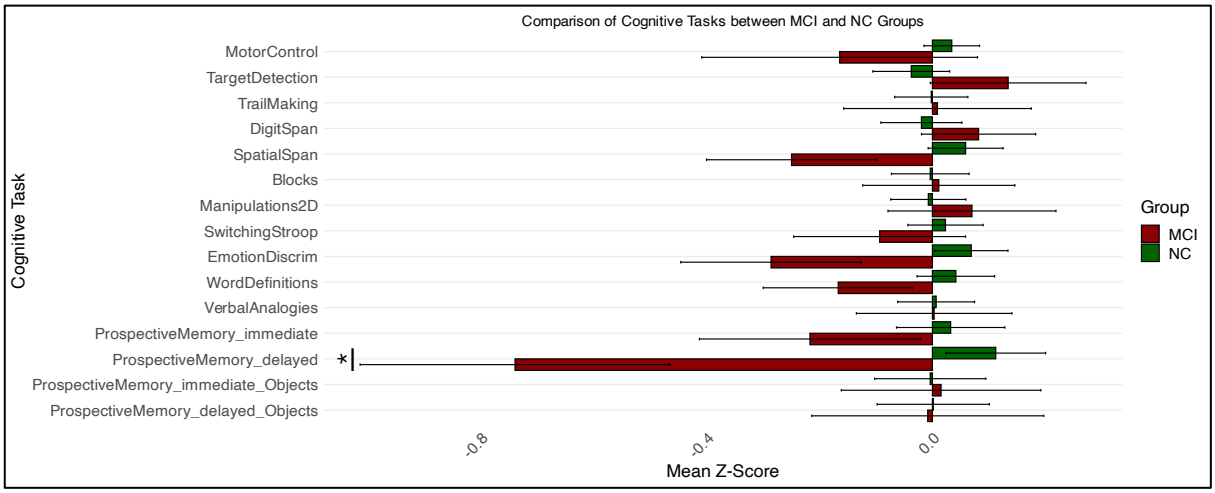


Figure 4.11 | Comparison of performance in cognitive tasks among all study participants categorized based on their MoCA scores (MCI vs. NC). *adjusted p<0.05

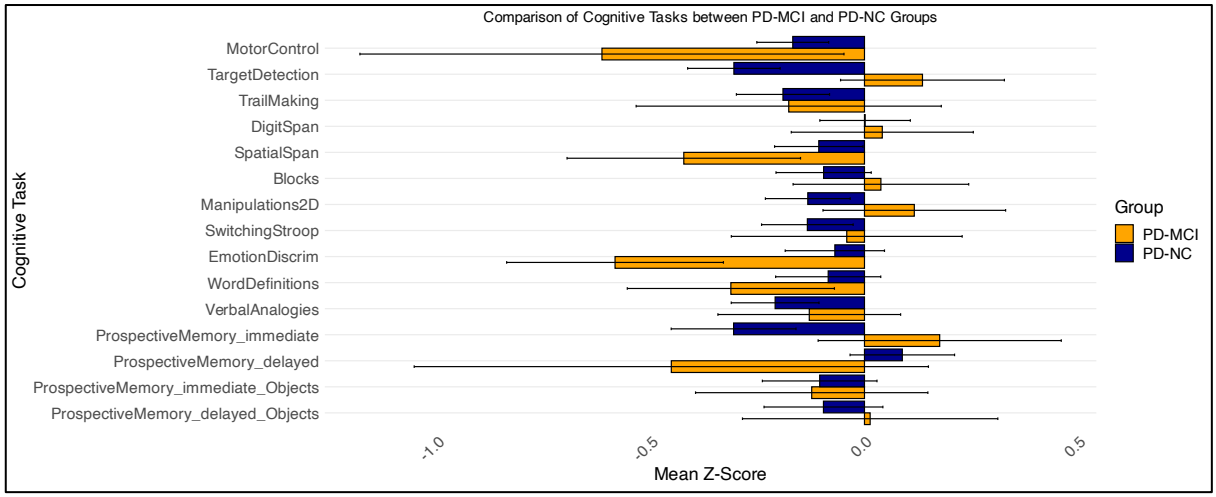


Figure 4.12 | Comparison of performance in cognitive tasks between PD-MCI and PD-NC. No significant differences observed in the mean z-scores between the two groups.

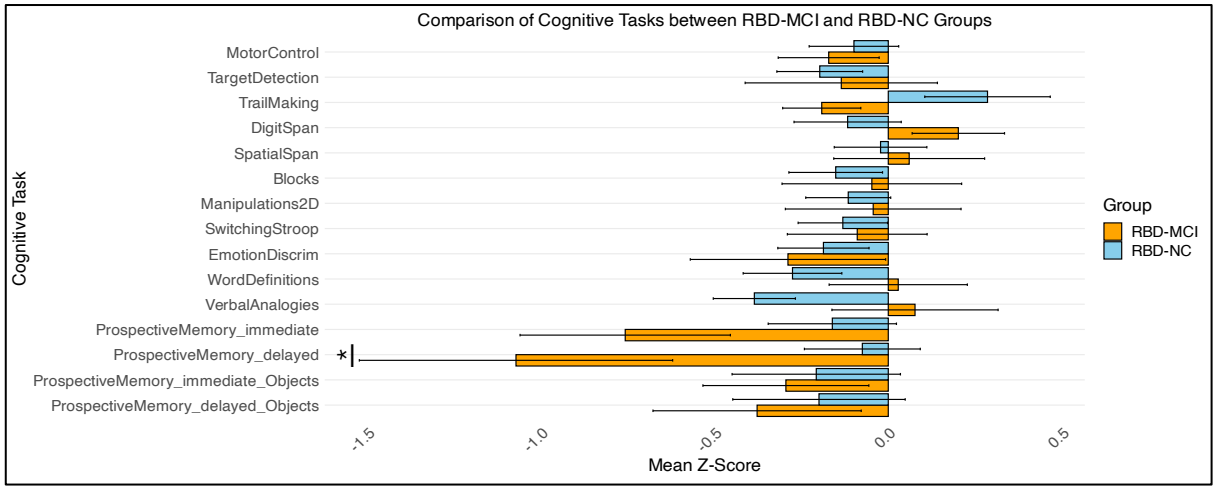


Figure 4.13 | Comparison of performance in cognitive tasks between RBD-MCI and RBD-NC. *unadjusted p<0.05

4.3.3.4 Longitudinal Changes in Cognitive Function

To assess the longitudinal cognitive pattern of change across the study groups, a MANCOVA was conducted on the 13 tasks from the online cognitive battery using longitudinal data from 52 participants (16 PD, 18 RBD and 18 CON) with a mean interval between the two assessments of 21.83 ± 0.5 months (Table 4.10). The model included group

and visit as fixed factors, with age as a covariate. The multivariate model did not show an overall visit and group interaction effect but showed significant effects of group and age. The univariate analysis showed a significant group x visit interaction effect for only one task, Digit Span. Post hoc pairwise comparisons showed that this effect was specific to PD patients, with a significant decrease in Digit Span scores in the second visit compared to the first visit (mean difference −2.00, 95% CI [−3.8,−0.22], p = 0.028). Significant age effects were noted for most tasks, while group effects were significant for the language tasks and the delayed memory task (Tables 4.11 and 4.12). Figure 4.14 illustrates the difference in mean scores for the cognitive tasks between the two time points for each group.

	PD (N=16)	RBD (N=18)	CON (N=18)	Total (N=52)	p-value
Age	69.5 (7.5)	62.7 (8.4)	63.9 (9.9)	65.5 (9.0)	0.054[1]
Gender Female Male	56.2% 43.8%	0% 100%	66.7% 33.3%	40.4% 59.6%	< 0.001[2]
Disease duration	7.5 (1.6)	n/a	n/a	n/a	
Hoehn & Yahr stage 1 2 3	 2.0 (12.5%) 13.0 (81.2%) 1.0 (6.2%)	n/a	n/a	n/a	
MoCA	28.2 (1.7)	28.3 (1.6)	26.9 (1.8)	27.8 (1.8)	0.037[1]
Full scale IQ NART	118.3 (7.6)	118.4 (3.7)	115.2 (4.8)	117.1 (5.0)	0.178[1]
Verbal IQ NART	121.3 (7.1)	121.5 (3.5)	118.4 (4.5)	120.3 (4.7)	0.178[1]
Performance IQ NART	118.6 (5.0)	118.7 (2.5)	116.5 (3.2)	117.8 (3.3)	0.178[1]
Total Education Years	13.2 (1.0)	12.9 (1.1)	12.8 (1.3)	13.0 (1.1)	0.583[1]
Time Between Visits	2.0 (0.5)	1.8 (0.6)	1.6 (0.5)	1.8 (0.6)	0.059[1]

Table 4.10 | Baseline characteristics of participants who completed the longitudinal study.
1.Linear Model ANOVA 2. Pearson's Chi-squared test

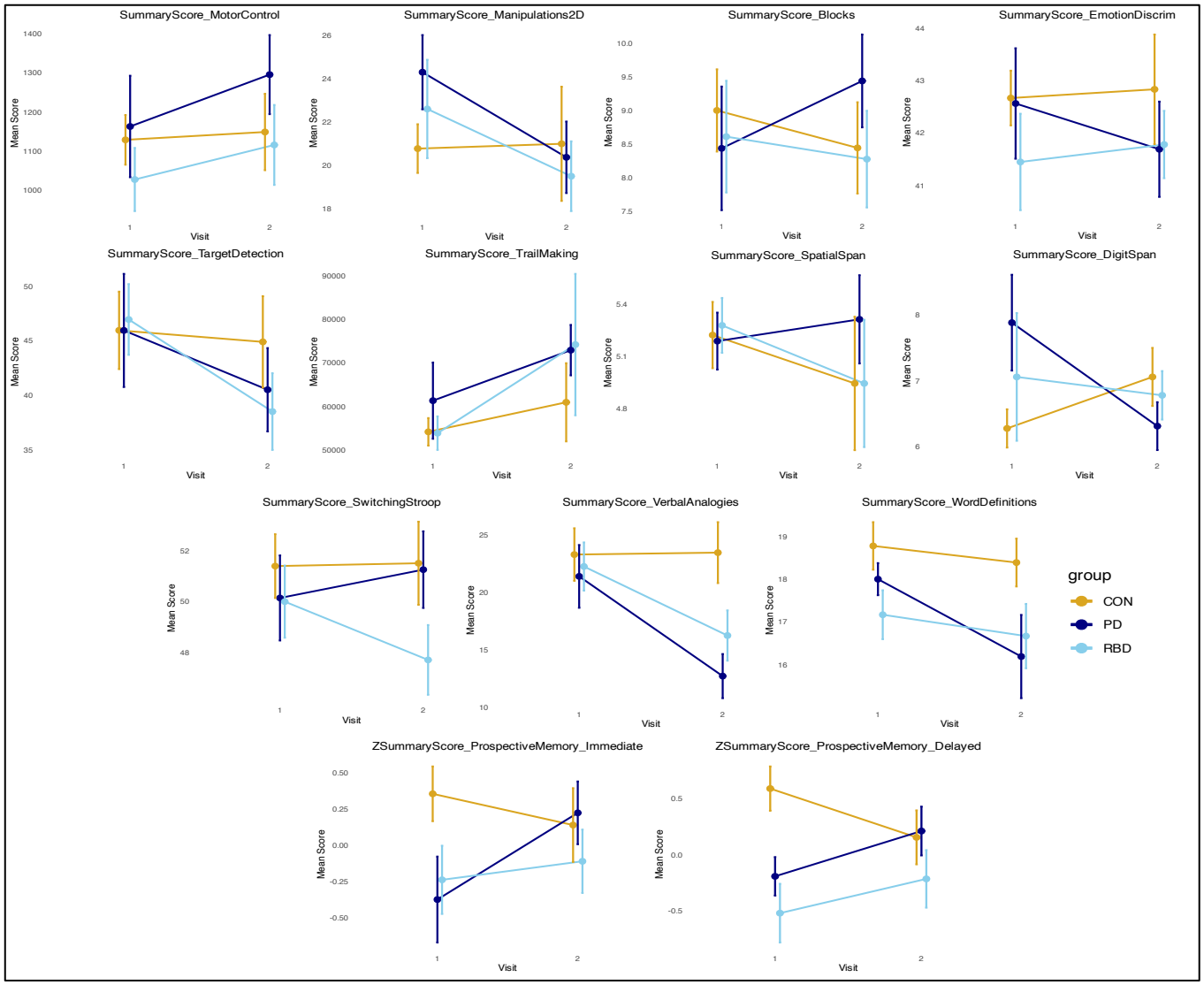


Figure 4.14| Longitudinal differences in mean scores for cognitive tasks over two time points across study groups. Mean scores represent summary scores for all cognitive tasks, where higher scores indicate better performance, except for Motor Control and Trail Making tasks, where lower scores (in milliseconds) indicate better performance.

Multivariate Tests

		value	F	df1	df2	p
group	Pillai's Trace	0.444	1.692	26	154	0.027
	Wilks' Lambda	0.597	1.721	26	152	0.023
	Hotelling's Trace	0.607	1.750	26	150	0.020
	Roy's Largest Root	0.456	2.699	13	77	0.004
Visit	Pillai's Trace	0.104	0.679	13	76	0.778
	Wilks' Lambda	0.896	0.679	13	76	0.778
	Hotelling's Trace	0.116	0.679	13	76	0.778
	Roy's Largest Root	0.116	0.679	13	76	0.778
group ✻ Visit	Pillai's Trace	0.259	0.881	26	154	0.634
	Wilks' Lambda	0.755	0.880	26	152	0.636
	Hotelling's Trace	0.305	0.879	26	150	0.638
	Roy's Largest Root	0.216	1.279	13	77	0.244
age	Pillai's Trace	0.381	3.598	13	76	<.001
	Wilks' Lambda	0.619	3.598	13	76	<.001
	Hotelling's Trace	0.615	3.598	13	76	<.001
	Roy's Largest Root	0.615	3.598	13	76	<.001

Table 4.11 | MANCOVA Multivariate tests for the longitudinal cognitive data.

Univariate Tests

	Dependent Variable	Sum of Squares	df	Mean Square	F	p
group	SummaryScore_motorControl	308343.5173	2	154171.7587	0.9896	0.376
	SummaryScore_manipulations2D	11.6637	2	5.8318	0.0995	0.905
	SummaryScore_targetDetection	288.6013	2	144.3006	0.6290	0.535
	SummaryScore_blocks	0.4717	2	0.2358	0.0274	0.973
	SummaryScore_emotionDiscrim	44.9621	2	22.4811	1.9605	0.147
	LogSummaryScore_trailMaking	0.1173	2	0.0586	2.6299	0.078
	SummaryScore_switchingStroop	106.4756	2	53.2378	1.7661	0.177
	SummaryScore_spatialSpan	0.3681	2	0.1840	0.1461	0.864
	SummaryScore_digitSpan	2.6906	2	1.3453	0.2402	0.787
	SummaryScore_wordDefinitions	55.3743	2	27.6871	3.5914	0.032
	SummaryScore_verbalAnalogies	870.6240	2	435.3120	4.9196	0.009
	ZSummaryScore_prospectiveMemory_immediate	1.8203	2	0.9102	1.1023	0.337
	ZSummaryScore_prospectiveMemory_delayed	8.8824	2	4.4412	5.2408	0.007
Visit	SummaryScore_motorControl	52498.6804	1	52498.6804	0.3370	0.563
	SummaryScore_manipulations2D	99.5695	1	99.5695	1.6982	0.196
	SummaryScore_targetDetection	536.5164	1	536.5164	2.3388	0.130
	SummaryScore_blocks	0.8132	1	0.8132	0.0946	0.759
	SummaryScore_emotionDiscrim	1.1442	1	1.1442	0.0998	0.753
	LogSummaryScore_trailMaking	0.0963	1	0.0963	4.3178	0.041
	SummaryScore_switchingStroop	12.5880	1	12.5880	0.4176	0.520
	SummaryScore_spatialSpan	0.0487	1	0.0487	0.0387	0.844
	SummaryScore_digitSpan	3.0431	1	3.0431	0.5434	0.463
	SummaryScore_wordDefinitions	16.8475	1	16.8475	2.1853	0.143
	SummaryScore_verbalAnalogies	409.1492	1	409.1492	4.6240	0.034
	ZSummaryScore_prospectiveMemory_immediate	0.0740	1	0.0740	0.0896	0.765
	ZSummaryScore_prospectiveMemory_delayed	0.0184	1	0.0184	0.0218	0.883
group ✻ Visit	SummaryScore_motorControl	22830.2782	2	11415.1391	0.0733	0.929
	SummaryScore_manipulations2D	166.5109	2	83.2555	1.4200	0.247
	SummaryScore_targetDetection	628.6463	2	314.3231	1.3702	0.259
	SummaryScore_blocks	5.8452	2	2.9226	0.3399	0.713
	SummaryScore_emotionDiscrim	19.0756	2	9.5378	0.8318	0.439
	LogSummaryScore_trailMaking	0.0975	2	0.0488	2.1865	0.118
	SummaryScore_switchingStroop	42.6172	2	21.3086	0.7069	0.496
	SummaryScore_spatialSpan	1.1721	2	0.5860	0.4653	0.629
	SummaryScore_digitSpan	35.7344	2	17.8672	3.1906	0.046
	SummaryScore_wordDefinitions	9.0446	2	4.5223	0.5866	0.558
	SummaryScore_verbalAnalogies	347.8144	2	173.9072	1.9654	0.146
	ZSummaryScore_prospectiveMemory_immediate	1.9712	2	0.9856	1.1936	0.308
	ZSummaryScore_prospectiveMemory_delayed	2.7341	2	1.3671	1.6132	0.205
age	SummaryScore_motorControl	982085.0491	1	982085.0491	6.3039	0.014
	SummaryScore_manipulations2D	578.3689	1	578.3689	9.8644	0.002
	SummaryScore_targetDetection	3202.7773	1	3202.7773	13.9615	<.001
	SummaryScore_blocks	13.8845	1	13.8845	1.6147	0.207
	SummaryScore_emotionDiscrim	21.5426	1	21.5426	1.8786	0.174
	LogSummaryScore_trailMaking	0.2959	1	0.2959	13.2706	<.001
	SummaryScore_switchingStroop	392.7961	1	392.7961	13.0303	<.001
	SummaryScore_spatialSpan	2.1693	1	2.1693	1.7224	0.193

Table 4.12 | MANCOVA Univariate tests for the longitudinal cognitive data.

4.3.4 Discussion

This study is an extension of the previous study, including participants with a broader cognitive spectrum. We compared the performance of 281 participants (113 PD, 80 RBD and 88 CON) cross-sectionally on each task of the online cognitive battery relative to their overall performance. RBD patients performed significantly better in the Motor Control task relative to their overall performance. None of the other groups showed differences in any tasks relative to their overall performance. We also examined longitudinal changes in 52 participants from the same groups followed up for approximately 22 months. Only the PD group showed a significant decline in one task, Digit Span (a working memory task), at the follow-up visit.

The superior performance of RBD patients in Motor Contol compared to the other cognitive tasks in the battery is expected and indicates that cognitive impairment precedes motor impairment in RBD. This finding aligns with previous cognitive studies on RBD, which demonstrated impairment across multiple cognitive domains (Fengler et al., 2017; Gagnon et al., 2012). This trajectory extends from the prodromal phase in RBD to the PD phase, where PD patients with RBD exhibit worse cognitive performance than those without RBD (Jozwiak et al., 2017; Rolinski et al., 2014).

The longitudinal follow-up of the study groups revealed a deterioration only in Digit Span scores for PD patients. The lack of a significant performance decline in other tasks could be due to the relatively short follow-up period as a previous systematic review of longitudinal cognitive studies of PD found medium-to-strong effect sizes only with follow-up periods of 4 years or more (Roheger et al., 2018). Longitudinal studies on RBD have found significant cognitive deterioration across multiple domains, correlated with the duration of follow-up (Terzaghi et al., 2013; Youn et al., 2016). These studies typically had follow-up

periods averaging 43 months. However, Fantini et al. (2011) demonstrated significant cognitive decline in visuospatial and memory functions with a follow-up period comparable to that in our study, that is, 24 months (Fantini et al., 2011). Notably, the participants were older than those in our study. Hence, the relatively low mean age of the participants might have influenced the lack of significant longitudinal changes, as older age has been shown to accelerate cognitive decline over longer follow-up periods (Muslimović et al., 2007). Disease severity also predicts deterioration in cognitive functions (Stepkina et al., 2010), and most PD patients in our study were in the early stages of the disease (Hoehn and Yahr Stage 2 and below).

Regarding the specific significant decline in Digit Span performance in PD patients, a previous longitudinal study with a 3-year follow-up period did not find changes in Digit Span forward scores but found tasks like Digit Symbol, Trail Making and Switching Stroop to be more sensitive to longitudinal changes (Muslimović et al., 2009). This contradicts our findings; however, the same study with a 5-year follow-up showed significant declines in several cognitive tasks, including digit span (Broeders, Velseboer, et al., 2013). These findings illustrate the complexity of cognitive impairment in PD, which is heterogeneous not only in profile and timing but also in the rate of cognitive decline.

The results from the longitudinal segment of this study underscore the importance of conducting extended follow-ups on larger cohorts of PD and RBD patients. Comprehensive neuropsychological assessments over longer periods are essential to better delineate the progression of cognitive decline in these groups.

A key factor to consider in interpreting the results of this study is the difference in patient selection for remote versus in-person cognitive assessments. In-person studies often benefit from a more controlled environment, where researchers can ensure that participants

fully understand instructions and are closely monitored throughout the tasks. This control can minimize variability related to environmental factors, distractions, or technology issues, which are inherent in remote testing environments (Gallagher et al., 2023). Furthermore, in-person recruitment may attract participants who are more comfortable with clinical settings or have more advanced disease symptoms, as they are already engaged with healthcare providers for in-person visits. This could lead to a sample with potentially greater cognitive or physical impairments. Additionally, in-person studies, particularly longitudinal cohort research, often attract participants who are more motivated and engaged (Collins et al., 2022). Repeated interactions with the research team can foster a strong sense of personal investment, encouraging higher adherence to study protocols and consistent participation. This increased motivation might positively influence their performance during cognitive tasks.

In contrast, remote studies can provide greater accessibility, allowing participants from diverse geographic regions to participate without needing to travel (Requena-Komuro et al., 2022). This may lead to a sample that includes individuals in earlier disease stages or those likely to seek in-person care. However, remote studies also present challenges in ensuring consistency of testing conditions, as participants complete tasks in varied home environments with protentional distractions or technical difficulties that could influence performance. Moreover, participants in remote studies might be more technologically adept, introducing a selection bias toward individuals with higher cognitive functioning in tasks involving technology, which could influence the results of cognitive batteries like the one used in our study.

In our study, while the remote nature of the cognitive battery allowed us to include a larger and more geographically diverse sample, it also introduced potential variability in task performance due to factors such as internet connectivity, technological proficiency, and the home environment's influence on attention and engagement. Future studies should consider these differences, particularly when comparing results from remote and in-person studies. Standardizing remote testing conditions and further investigating the impact of participant motivation and environment on performance will be essential to ensuring the reliability and validity of cognitive assessments in remote settings.

4.3.4.1 Strengths and Limitations

A strength of this study is its longitudinal aspect, which allowed for the observation of changes in cognitive performance over time. This longitudinal component provided valuable insights into the progression of cognitive decline in PD and RBD patients. Additionally, the cross-sectional part of the study included participants with lower MoCA scores, offering a more comprehensive view of cognitive impairment across a broader range of cognitive abilities. However, the study also has several limitations. In the longitudinal part, each group (PD, RBD and CON) had relatively small sample sizes, which may limit the generalisability of the findings. The follow-up period was relatively short (approximately 22 months), which might not be sufficient to capture the full progression of cognitive decline. Moreover, a selection bias is present as the study included younger and less disabled patients who were in the early stages of the disease and had good baseline cognitive functions. This selection bias may limit the applicability of the results to a broader and more diverse PD and RBD population.

4.3.4.2 Conclusion

This study extends previous research by including patients across a broader cognitive spectrum and comparing their performance cross-sectionally and longitudinally. The cross-sectional analysis of cognitive patterns revealed that RBD patients performed significantly better in motor function tasks relative to their overall performance, while other groups showed no significant differences across tasks. The longitudinal analysis highlighted a significant decline in Digit Span task performance in the PD group over a 22-month period. Further research with more diverse and larger cohorts, along with extended follow-up durations, is necessary to confirm these findings and enhance our understanding of cognitive impairment progression in PD and RBD.

4.4 Study 3 | The Use of an Online Cognitive Battery in a Randomised Controlled Trial of a Ketone Ester Drink (Delta G) in Parkinson's Disease: A Feasibility Study

4.4.1 Introduction

Ketosis is a metabolic state where the body utilises fats as its primary energy source, leading to the production of ketone bodies (Kolb et al., 2021). This state can be achieved through fasting or a ketogenic diet, which is characterised by low carbohydrate and high fat intake. Research conducted in vitro and using mouse models of PD demonstrated a potential neuroprotective role of ketone bodies (Kashiwaya et al., 2000; Tieu et al., 2003). Clinical RCTs in PD patients have shown that a ketogenic diet significantly improves motor symptoms, as measured by the UPDRS (Phillips et al., 2018; Vanitallie et al., 2005). Additionally, some studies suggest that ketone bodies can enhance cognitive functions such as attention and memory in older individuals and those with neurodegenerative diseases, including PD (Jensen et al., 2020; Krikorian et al., 2019; Ota et al., 2016; Taylor et al., 2018).

Despite these potential benefits, maintaining a fasting regimen or ketogenic diet is challenging. To address this issue, the Clarke group at the University of Oxford developed a ketone ester supplement named Delta G. This supplement effectively raises the levels of ketone bodies in the blood without dietary restrictions. It is safe and well-tolerated (Clarke et al., 2012) and has been shown to improve energy metabolism and endurance performance in athletes (Cox et al., 2016) and PD patients (Norwitz et al., 2020).

Building on these promising findings, the third study in this chapter aimed to evaluate the feasibility of using the online cognitive battery that was validated and used in the previous two studies in an RCT. This trial sought to determine whether ketone drinks can alleviate both motor symptoms and NMS of PD.

4.4.2 Methods

4.4.2.1 Study Design and Ethical Approval

This study was a longitudinal, single-blind, randomised, placebo-controlled trial designed to evaluate the efficacy of a ketone ester drink (Delta G) in alleviating the symptoms of PD. It was conducted at the John Radcliffe Hospital, Oxford, UK, from January 2020 to July 2023 in accordance with the Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). Ethical approval was obtained from the NHS Health Research Authority (reference: 19/SC/0138). The study was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN64294760) and the Integrated Research Application System (IRAS ID: 256914).

4.4.2.2 Participants and Intervention

Participants

Eligible participants included patients with a diagnosis of PD at Hoehn and Yahr Stages 1 or 2, aged between 40 and 80 years, on levodopa, and fluent in English. Exclusion criteria included communication impairments or any disorder that could put the participant at risk or bias the study results, as determined by the Chief Investigator.

Recruitment and Randomisation

Participants were recruited via an advertisement on the OPDC website, posters in university departments, emails to departmental mailing lists and word of mouth in clinics. After obtaining informed consent, participants were block-randomised to either the ketone ester group or the placebo control group to ensure equal group sizes. Randomisation was

performed using a computer-generated sequence, and allocation was concealed until interventions were assigned.

Intervention

The intervention group received a ketone ester drink (Delta G), while the control group received a taste-matched isocaloric placebo drink. Both drinks were consumed four times daily for 1 month. Each dose consisted of 15 ml of the assigned drink (10 ml for participants weighing less than 60 kg, based on the recommended dosages). Baseline measurements were taken over a 2-week period (Weeks −2 to 0), followed by the intervention phase (Weeks 0 to 4) and a follow-up phase (Weeks 4 to 6) to monitor any lasting effects.

4.4.2.3 Outcome Measures

Primary Outcome Measures

Motor measures

- Overall motor symptom severity: assessed using the MDS-UPDRS in the 'off' state at Weeks 0 and 4 and 'off' and 'on' the drink (1 hour after drink intake) to test acute effects.
- Motor activity and gait: measured with a continuous activity monitor (Axivity AX3) worn on the lower back for 7 days before (Weeks −2 to −1) and during the intervention (Weeks 2 to 3).
- Motor skills: assessed daily using the OPDC digital smartphone application.

Cognitive measures

- In-clinic cognitive testing: global cognitive functions were assessed using the MoCA, and selective attention was evaluated using the Stroop colour-word task. Both assessments were conducted at Weeks 0, 4 and 6.

- Remote cognitive testing: conducted using the Cognitron cognitive battery encompassing 13 tasks: Motor Control, Manipulations in Two Dimensions, Target Detection, Blocks, Emotion Recognition, Trail Making Task, Switching Stroop, Spatial Span, Digit Span, Word Definitions, Verbal Analogies, Prospective Memory – Immediate and Prospective Memory – Delayed (Figure 4.1). Data were collected at Weeks −2 (baseline), 4 (primary endpoint) and 6.

  Other measures

- Fatigue: evaluated weekly via phone using the Fatigue Severity Scale during a randomly timed compliance call.
- Quality of life: assessed using the PDQ-39 questionnaire for participants and the PDQ-Carer questionnaire for their carers at Weeks 0, 4, and 6.
- Sleep disorders: evaluated using the REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) at Weeks 0, 4 and 6.
- Olfaction: assessed using the Sniffin' Sticks 16-odour identification test at Weeks 0, 4 and 6.

  Secondary Outcome Measures

- Biomarkers: blood samples were collected in the fasting state at Weeks 0, 2, 4 and 6 to measure the levels of uric acid, glucose, fructosamine, insulin, lipids, C-reactive protein and inflammatory cytokines.
- Compliance: monitored through weekly random phone calls to ask participants about their last consumption of the study drink and to measure blood ketone levels by fingerstick.
- Participant feedback: collected at Week 4 using a consumer-style questionnaire to capture subjective experiences with the drink.

- Adverse events: recorded and reported as per the study protocol.

4.4.2.4 Statistical Analysis

Data were analysed using intention-to-treat principles. The primary analysis compared the mean change from baseline to Week 4 between the ketone ester and placebo groups using independent t-tests. Subsequently, repeated-measures ANCOVA was performed using baseline values as covariates to assess changes over time within and between groups. Statistical analyses were conducted using SPSS and R. A P value < 0.05 was considered statistically significant, and for multiple comparisons, adjustment was used.

4.4.2.5 Funding

The study was funded by TdeltaS Ltd., a spin-out company from the University of Oxford. The funding source had no role in the study design, data collection, analysis, interpretation, or writing of the report.

4.4.3 Results

4.4.3.1 Study Population

A total of 20 PD patients were randomised equally into the ester drink or placebo groups, with 14 participants completed the trial (Figure 4.15). The mean age of the participants was 67.2 ± 11 years. Among the 14 participants, 11 were male. Baseline characteristics, including motor and cognitive measures, showed no significant differences between the groups (summarised in Table 4.13).

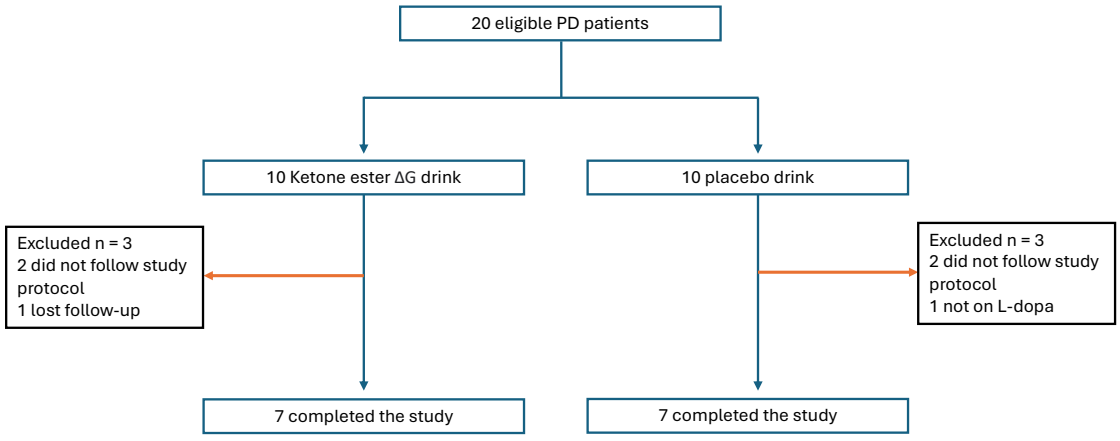


Figure 4.15 | Flow diagram displays the randomisation and progress of participants through the trial

4.4.3.2 Outcome Measures

Motor measures

There were no significant differences in the primary motor measures between patients who received the ketone ester drink and those who received the placebo. In the ketone group, the mean UPDRS III total score increased from baseline to week 4 by 4.2 ± 11.8, whereas placebo group showed a mean increase of 2 ± 6.7 (Figure 4.16). This difference was not statistically significant (p= 0.69), even after adjusting for baseline values (p=0.54). Table 4.14 summarises the efficacy results for the motor measures.

Baseline measures	Ketone (N=7)	Placebo (N=7)	Total (N=14)	p value
Age				0.258[1]
Mean (SD)	63.7 (13.8)	70.6 (6.6)	67.2 (11.0)	
Gender				0.515[2]
Male	6.0 (85.7%)	5.0 (71.4%)	11.0 (78.6%)	
Female	1.0 (14.3%)	2.0 (28.6%)	3.0 (21.4%)	
Total UPDRS III OFF score				0.123[1]
Mean (SD)	24.9 (11.4)	16.4 (7.1)	20.6 (10.1)	
Total UPDRS III ON score				0.189[1]
Mean (SD)	22.0 (13.6)	13.5 (6.2)	18.1 (11.3)	
Total UPDRS II score				0.667[1]
Mean (SD)	10.0 (5.3)	8.9 (4.4)	9.4 (4.7)	
Total clinician UPDRS II score				0.510[1]
Mean (SD)	2.6 (2.0)	2.0 (1.0)	2.3 (1.5)	
Total UPDRS IV score				0.355[1]
Mean (SD)	7.1 (4.6)	5.0 (3.2)	6.2 (4.0)	
MoCA total score				0.441[1]
Mean (SD)	26.7 (3.4)	28.0 (2.6)	27.4 (3.0)	

Table 4.13 | Baseline characteristics of the study participants. 1. Linear Model ANOVA 2. Pearson's Chi-squared test

Cognitive Measures

In-clinic cognitive assessments revealed no significant differences between the two groups (Table 4.15). The mean change in the MoCA score from baseline to Week 4 was 0.7 ± 1.6 for the ketone group and 0.9 ± 2.3 for the placebo group.

Remote cognitive testing indicated a borderline significant difference in only one task, Spatial Span. The mean score increased by 0.8 ± 1.3 from baseline to Week 4 in the ketone group and decreased by 0.5 ± 0.8 in the placebo group ($p = 0.076$). However, after adjusting for baseline scores as a covariate, this difference was not statistically significant ($p = 0.115$). No statistically significant differences were found between the groups in the remaining remote cognitive tasks, both in summary scores (Table 4.16) and RTs (Table 4.17).

Other Measures

The other primary measures in the study showed no significant differences between the study groups, apart from the Fatigue Severity Scale, which demonstrated a borderline significant increase in the ketone group (0.5 ± 0.9) compared to the placebo group (−0.5 ± 1; ($p = 0.071$). However, this borderline significance disappeared when baseline scores were included as a covariate in the ANCOVA ($p = 0.135$).

Acute Effects of the Ketone Ester Drink on UPDRS III

To evaluate the acute effect of the ketone drink on UPDRS III scores, a linear mixed-effects model was employed. The model included study group (ketone or placebo), drink status (ON or OFF) and study visit as fixed effects, with participant ID as a random effect. The interaction effect between drink status and group was not statistically significant ($F(1,27.98) = 0.0086$, $p = 0.93$). However, the main effect of drink status (ON or OFF) approached borderline significance ($F(1,27.98) = 4.14$, $p = 0.0515$), indicating a possible placebo effect.

Participant Feedback on Remote Cognitive Testing

Participant feedback on the remote online cognitive battery, as detailed in Appendix Table 8.9, highlights varying levels of ease, user-friendliness, and willingness to reuse the method, along with insightful comments for improvement.

	N	Mean change from baseline	t-test	p	ANCOVA	p
UPDRS III OFF (total)						
Ketone	6	4.2 ± 11.8	t(11) = 0.42	0.69	F(1,10) = 0.39	0.54
Placebo	7	2 ± 6.7				
UPDRS III ON (total)						
Ketone	6	3.5 ± 9.6	t(10) = 0.52	0.61	F(1,9) = 0.38	0.55
Placebo	6	1.2 ± 5.3				
UPDRS IV (total)						
Ketone	6	0.3 ± 2.7	t(10) = 1.06	0.32	F(1,9) = 3.08	0.11
Placebo	6	-1.3 ± 2.8				
UPDRS II (total)						
Ketone	6	-1.8 ± 1.9	t(11) = -0.23	0.82	F(1,10) = 0.03	0.87
Placebo	7	-1.6 ± 2.1				
Clinician UPDRS II						
Ketone	6	-0.7 ± 1	t(11) = -1.69	0.12	F(1,10) = 3.19	0.104
Placebo	7	0.1 ± 0.7				

Table 4.14 | Primary motor efficacy results. *Independent samples t-tests and ANCOVAs with baseline values as covariates*

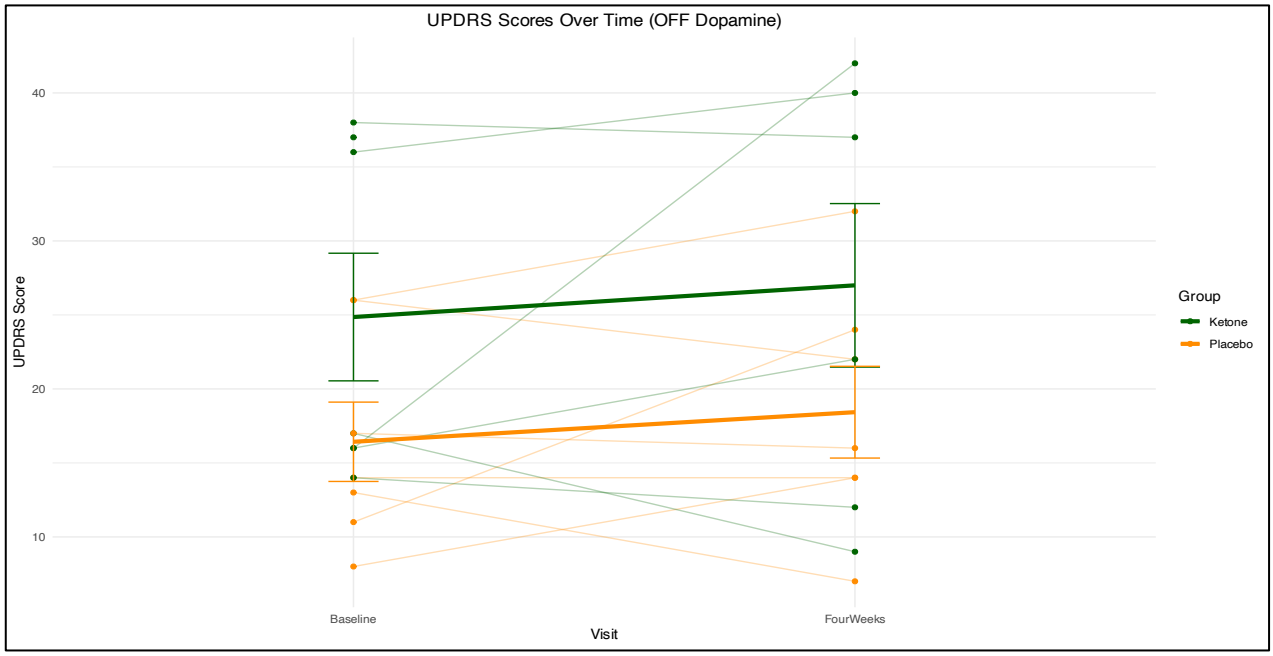


Figure 4.16 | UPDRS scores by drink condition and visit. *This figure illustrates the UPDRS scores (OFF dopaminergic medications) of participants for the baseline and endpoint visit at week 4. The line plots, with transparent lines, show individual subject trajectories over time. Bold lines represent the mean UPDRS scores for each group, accompanying by error bars indicating 1 ± SEM. The Ketone group is depicted in dark green, and the Placebo group in dark orange, allowing for a clear comparison of the treatment effect over time. No significant differences were noticed between the groups or the visits for each group.*

	N	Mean change from baseline	t-test	p	ANCOVA	p
MoCA (total)						
Ketone	6	0.7 ± 1.6	t(11)= -0.17	0.87	F(1,10)= 0.22	0.65
Placebo	7	0.9 ± 2.3				
Stroop word colour						
Ketone	6	-3.2 ± 10.7	t(11)= -0.25	0.81	F(1,10)= 0.25	0.63
Placebo	7	-0.7 ± 22.4				

Table 4.15 | Primary in-clinic cognitive efficacy results. *Independent samples t-tests and ANCOVAs with baseline values as covariates*

Summary Scores	N	Mean change from baseline	t-test	p	ANCOVA	p
Motor Control						
Ketone	5	-159.1 ± 93.6	t(9)= 0.83	0.43	F(1,8)= 0.15	0.71
Placebo	6	-1007 ± 2252				
Manipulations 2D						
Ketone	5	3.4 ± 6.8	t(9)= 0.56	0.59	F(1,8)= 0.13	0.73
Placebo	6	1.7 ± 3.1				
Target Detection						
Ketone	5	1.8 ± 18.5	t(9)= -0.05	0.96	F(1,8)= 0.37	0.56
Placebo	6	2.3 ± 17.8				
Blocks						
Ketone	5	-0.8 ± 3.6	t(11)= -0.17	0.87	F(1,8)= 0.14	0.72
Placebo	6	2.2 ± 2.2				
Emotion Recognition						
Ketone	5	-0.4 ± 1.9	t(9)= -1.69	0.125	F(1,8)= 0.10	0.76
Placebo	6	0.2 ± 3.4				
Trail Making Task						
Ketone	5	-8005 ± 3621	t(9)= -0.996	0.345	F(1,8)= 1.31	0.29
Placebo	6	7098 ± 33434				
Switching Stroop						
Ketone	5	2.6 ± 4.8	t(9)= -1.624	0.139	F(1,8)= 0.17	0.69
Placebo	6	8 ± 6				
Spatial Span						
Ketone	5	0.8 ± 1.3	t(9)= 2.01	0.076	F(1,8)= 3.13	0.115
Placebo	6	-0.5 ± 0.8				
Digit Span						

Summary Scores	N	Mean change from baseline	t-test	p	ANCOVA	p
Ketone	5	2.8 ± 3.9	t(9)= 1.69[a]	0.124	F(1,8)= 1.14	0.32
Placebo	6	0.0 ± 1.1				
Word Definitions						
Ketone	4	0.8 ± 1.9	t(8)= 1.375	0.206	F(1,7)= 2.34	0.17
Placebo	6	-1.3 ± 2.6				
Verbal Analogies						
Ketone	5	5.2 ± 10.6	t(9)= 0.535	0.606	F(1,7)= 0.06	0.82
Placebo	6	1.7 ± 11.1				
Prospective Memory - Immediate						
Ketone	6	2.8 ± 3.3	t(10)= -0.23	0.823	F(1,9)= 0.02	0.89
Placebo	6	3.8 ± 10.2				
Prospective Memory - Delayed						
Ketone	5	11.2 ± 24.4	t(9)= 0.751	0.472	F(1,7)= 0.03	0.87
Placebo	6	3.3 ± 8				

Table 4.16 | Primary remote testing cognitive efficacy results (summary scores). *Independent samples t-tests and ANCOVAs with baseline values as covariates*

Reaction times	N	Mean change from baseline	t-test	p	ANCOVA	p
Motor Control						
Ketone	5	-159.1 ± 93.6	t(9)= 0.83	0.43	F(1,8)= 0.15	0.71
Placebo	6	-1007 ± 2252				
Manipulations 2D						
Ketone	5	-1637 ± 1861	t(9)= -0.85	0.42	F(1,8)= 0.13	0.73
Placebo	6	-868 ± 1096				
Target Detection						
Ketone	5	194 ± 248	t(9)= 0.99	0.35	F(1,8)= 0.37	0.56
Placebo	6	-82.5 ± 577				
Blocks						
Ketone	5	879 ± 1228	t(9)= 1.15	0.28	F(1,8)= 0.14	0.72
Placebo	6	-517.5 ± 2457				
Emotion Recognition						
Ketone	5	-276 ± 200	t(9)= -1.5	0.17	F(1,8)= 0.10	0.76
Placebo	6	-134.5 ± 108				
Trail Making Task numbers						

Reaction times	N	Mean change from baseline	t-test	p	ANCOVA	p
Ketone	5	-7706 ± 8758	t(9)= -0.39	0.70	F(1,8)= 1.31	0.29
Placebo	6	-5258 ± 11343				
Trail Making Task letters						
Ketone	5	-8305 ± 4277	t(9)= -1.01	0.34	F(1,8)= 1.31	0.29
Placebo	6	19454 ± 60982				
Switching Stroop						
Ketone	5	0.9 ± 337	t(9)= 1.276	0.23	F(1,8)= 0.17	0.69
Placebo	6	-249 ± 312				
Spatial Span						
Ketone	5	289 ± 2090	t(9)= 1.58	0.15	F(1,8)= 3.13	0.115
Placebo	6	-1210 ± 968				
Digit Span						
Ketone	5	1343 ± 3411	t(9)= 1.63	0.14	F(1,8)= 1.14	0.32
Placebo	6	-1538 ± 2235				
Word Definitions						
Ketone	4	-352 ± 1608	t(8)= -1.19	0.27	F(1,7)= 2.34	0.17
Placebo	6	824 ± 1486				
Verbal Analogies						
Ketone	5	-56.6 ± 595	t(9)= 1.26	0.24	F(1,7)= 0.06	0.82
Placebo	6	-438 ± 373				
Prospective Memory - Immediate						
Ketone	6	-1671 ± 2870	t(10)= 1.41	0.19	F(1,9)= 0.02	0.89
Placebo	6	-6309 ± 7534				
Prospective Memory - Delayed						
Ketone	5	-298 ± 419	t(9)= -0.097	0.93	F(1,7)= 0.03	0.87
Placebo	6	-253 ± 855				

Table 4.17 | Secondary remote testing cognitive efficacy results (reaction times).
Independent samples t-tests and ANCOVAs with baseline values as covariates

4.4.4 Discussion

4.4.4.1 Feasibility of Remote Cognitive Testing in RCTs

The primary aim of this study was to assess the feasibility of using an online remote cognitive battery in an RCT. The results indicate a high level of feasibility, with 11 out of 14 participants (78.6%) completing assessments at both baseline and the primary endpoint visit at Week 4. Additionally, all participants completed at least one test, demonstrating the practicality and accessibility of remote cognitive testing in a clinical trial setting. When tested at an additional third time point in Week 6, seven participants (50%) completed the assessments, suggesting that two time points are optimal and practical for most participants, whereas increasing the number to three may pose additional challenges.

Previously, various computerised cognitive assessments, including the Cognitive Drug Research (CDR) (Biglan et al., 2022; Emre et al., 2004; Fernandez et al., 2023; Wesnes et al., 2005), Cambridge Neuropsychological Test Automated Battery (CANTAB) (Standaert et al., 2017), The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Folkerts et al., 2018) and NeuroTrax (Mamikonyan et al., 2015), have been utilised in RCTs for PD and DLB. These assessments targeted specific cognitive domains such as attention and memory. In contrast, the online cognitive battery used in our study encompassed all the cognitive domains. Additionally, while these assessments were conducted in person, ours was administered remotely.

4.4.4.2 Efficacy of a Ketone Ester Drink in Alleviating PD Symptoms

The study found no significant differences in primary motor and cognitive measures between the ketone and placebo groups. The mean change in the UPDRS III total score at Week 4 was not significantly different between the ketone and placebo groups, with a lack

of an acute significant effect of the drink. Both groups showed a borderline significant effect when assessed 1 hour after having either the ketone or the placebo drink, which could potentially be attributed to a placebo effect. Interestingly, a previous study demonstrated that the same drink improved exercise endurance in PD patients (Norwitz et al., 2020). This suggests that while the drink may enhance exercise capacity, it does not seem to have a positive effect on motor symptoms. Therefore, it could potentially be used as an adjunct to exercise therapy, which is deemed to be useful in managing PD (Mak et al., 2017).

The cognitive measures, such as the MoCA score and the online cognitive battery tasks, showed no significant changes. One online task that assessed spatial span exhibited a borderline significant difference that was not sustained after adjusting for baseline scores, highlighting the lack of significant cognitive improvements following ketone ester drink intake. This, however, should be interpreted with caution due to the small sample size.

4.4.4.3 Benefits of Remote Cognitive Testing in Clinical Trials

Remote cognitive testing offers several advantages in clinical trials, particularly in terms of accessibility and convenience for participants (Perin et al., 2020). This approach can reduce the burden on participants by allowing them to complete assessments from their homes, potentially increasing adherence and reducing dropout rates. Additionally, remote testing can facilitate the inclusion of a more geographically diverse sample, enhancing the generalisability of the findings.

On the other hand, the unsupervised nature of these assessments can pose challenges. For example, participants might encounter technical difficulties, such as an unstable internet connection or difficulties using the testing platform. Ensuring that the testing environment is free from distractions may also pose a challenge, which could affect

performance (Bauer et al., 2012). Furthermore, the lack of standardisation, along with variations in participants' hearing and vision, can introduce variability in the data (Phillips et al., 2020). Hence, different participants might take the test in vastly different settings, impacting their performance and the consistency of results. To mitigate these issues, optional strategies such as visits from nurses, caregiver supervision and telecommunication through video calls can be implemented. These measures can help ensure the reliability of the assessments and provide additional support to participants, thereby maintaining the integrity of the data.

This study has several limitations. The COVID-19 pandemic caused delays and hindrances to participant recruitment, resulting in a final sample size of 14 instead of the calculated 48. The limited sample size reduced the statistical power to detect significant differences between the study groups. Furthermore, while the study could demonstrate feasibility, the lack of significant findings regarding motor and cognitive measures for the ketone drink suggests that future studies with larger sample sizes and longer intervention periods may be necessary to explore the potential benefits of this intervention.

In conclusion, this study supports the feasibility of using online cognitive testing in clinical trials and highlights the need for further research to adopt, optimise and validate this approach. Despite the challenges faced, particularly due to the COVID-19 pandemic, the study provides valuable insights into the practical implementation of remote cognitive assessments and their potential benefits in clinical trials.

4.5 Conclusion and Future Directions

This chapter explored cognitive impairment in PD and RBD patients, emphasising the need for specialised cognitive assessment tools tailored to these conditions. The study highlights several key findings and suggests future directions for research and clinical practice.

Key Findings

1. **Cognitive impairment in PD and RBD**

- PD patients show significant deficits in attention and executive functions, consistent with the dual syndrome hypothesis that posits early fronto-striatal and later posterior-cortical dysfunctions.
- RBD patients exhibit cognitive impairments predominantly in memory and visuospatial domains, aligning with early cholinergic deficits.
- Both PD and RBD patients show comparable levels of cognitive impairment, suggesting a shared underlying pathophysiology.

2. **Assessment tools and methodologies**

- Traditional cognitive assessment tools like the MoCA, MMSE and MDRS, while useful, lack specificity for LBD.
- Digital platforms like Cognitron provide a feasible alternative to traditional assessments, especially during situations like the COVID-19 pandemic where remote testing is advantageous.
- Remote cognitive assessments are validated and can be effectively used to monitor cognitive decline over time.

3. **Longitudinal patterns of cognitive decline**

- Longitudinal follow-up revealed significant performance declines in specific cognitive tasks such as Digit Span in PD patients over a period of 22 months.
- The absence of significant differences in other tasks might be due to the relatively short follow-up period and the young age of the participants.

4. **Feasibility of remote cognitive testing in clinical trials**

- Remote cognitive testing demonstrated high feasibility in an RCT setting, with 78.6% of participants completing the two assessment time points.
- The study found no significant improvement in motor and cognitive symptoms following ketone ester supplementation in PD patients, although remote testing proved practical and accessible.

Future Directions

1. **Development and validation of PD-specific cognitive tools**

- The continued development and validation of cognitive assessment tools specific to PD and RBD are crucial. These tools should be tailored to detect subtle changes in the cognitive domains affected by these conditions.
- Implementing and validating these tools in diverse and larger cohorts, including those in advanced stages of disease, is essential.

2. **Longitudinal studies with extended follow-up**

- Future research should focus on extended longitudinal studies, for example, with follow-up periods longer than 4 years, to capture the full trajectory of cognitive decline in PD and RBD.
- These studies should include a broader range of participants, including older individuals and those with different disease severities.

3. **Integration of remote cognitive assessments in clinical practice**

- Expanding the use of remote cognitive assessments in clinical practice can improve accessibility, especially in under-resourced or remote areas.
- Ensuring the reliability and standardisation of these assessments through caregiver supervision or telecommunication support can enhance data integrity.

4. **Addressing technical and environmental variability in remote testing**

- Future studies should address the variability introduced by different testing environments and participants' technical abilities.
- Developing comprehensive guidelines and protocols for remote cognitive testing is crucial.

In conclusion, this chapter underscores the importance of specialised cognitive assessments in PD and RBD and highlights the value of remote testing in both research and clinical practice.

Chapter | 5

Chapter 5 | Neuroimaging Cognitive Correlates in the Oxford Discovery Cohort

5.1 Introduction

5.1.1 DAT Imaging and Cognition in LBD

PD is a progressive neurodegenerative disorder characterised by the loss of dopamine-producing neurons, leading to motor symptoms such as tremor, rigidity and bradykinesia, as well as NMS including cognitive impairment. DaTSCAN, a SPECT imaging technique using ^{123}I-ioflupane (^{123}I-FP-CIT), is commonly used in clinical practice to support the diagnosis of PD by visualising and quantifying the density of presynaptic dopamine transporter (DAT) in the brain (Booij et al., 1997; Djang et al., 2012; Kägi et al., 2010). It has received approval from both the FDA and the EMA for clinical use in diagnosing suspected parkinsonian syndromes (O'Brien et al., 2014). A normal DaTSCAN result has been incorporated into the MDS diagnostic criteria as an absolute exclusion criterion for PD (Postuma, Berg, et al., 2015).

Despite the well-documented relationship between striatal DAT levels and motor symptoms (Benamer et al., 2000; Seibyl et al., 1995), research exploring the correlation between DAT levels in both striatal and extrastriatal regions and cognitive functions is limited.

5.1.1.1 Striatal DAT Studies in PD

The dense dopaminergic innervation of the striatum, encompassing the caudate nucleus and putamen, makes this region the primary focus of DAT studies, some of which have also examined cognitive measures. For example, a longitudinal study from the Parkinson's Progression Markers Initiative (PPMI) cohort demonstrated that DAT imaging

parameters, such as reduced caudate uptake and asymmetry, and to a lesser extent, putamen asymmetry, predicted cognitive impairment with good accuracy over 2 years in newly diagnosed PD patients, particularly when added to age, RBDSQ and University of Pennsylvania Smell Identification Test (UPSIT) hyposmia scores, and CSF biomarkers (Schrag et al., 2017). Another incident PD cohort study with a longer follow-up period exceeding 5 years revealed an association between reduced striatal DAT binding at baseline and a higher risk of cognitive impairment (Ravina et al., 2012).

A more recent study utilising DaTSCAN imaging data from 344 PPMI PD patients revealed significant correlations between various baseline NMS and DAT uptake values at baseline and follow-up. Among these symptoms, RBD had the strongest correlation, with notable associations also observed in the memory and visuospatial cognitive domains (Liu et al., 2020). In addition, a study by Chung et al. (2018) found that drug-naïve PD patients with MCI exhibited significantly lower striatal DAT binding compared to patients with normal cognition. The study also revealed that DAT availability in the caudate, ventral striatum and, to a lesser degree, the anterior putamen was positively correlated with composite cognitive scores for working memory and attention, executive functions, and visuospatial abilities. Conversely, DAT availability in the posterior putamen showed no association with cognitive function (Chung et al., 2018). Instead, nigroputaminal impairment was more closely linked to the severity of PD motor symptoms (Nobili et al., 2010).

Building on these findings, Arnaldi et al. (2017) showed that DAT-SPECT caudate uptake, combined with resting EEG, can predict cognitive decline in drug-naïve de novo PD patients, reinforcing the strong association between caudate DAT binding and cognitive functions (Arnaldi et al., 2017). Similarly, Yousaf and colleagues (2019) demonstrated that reduced caudate DAT-SPECT uptake, in conjunction with CSF biomarkers (reduced CSF Ab42 and

increased total CSF tau), is associated with a 65% risk of cognitive decline in drug-naïve de novo PD patients over a 3-year follow-up period (Yousaf et al., 2019).

In Chapter 1, we reviewed some of the roles of the dopaminergic system in cognition. This system is integral to high-level cognitive processes, including executive functions, attention, working memory, cognitive control and learning, mainly due to its influence on fronto-striatal circuits. In DAT studies, deficits in executive functions were shown to be correlated with decreased striatal DAT uptake (H. Kim et al., 2019; Nobili et al., 2010; Pellecchia et al., 2015; Siepel et al., 2014). Several other studies also showed the relationship between reduced striatal DAT availability, particularly in the caudate, and cognitive dysfunction (Ekman et al., 2012; Kübler et al., 2017).

5.1.1.2 Extrastraital DAT Studies in PD

While the striatum has been the focal point of PD DAT-SPECT studies, recent studies have begun to explore the role of dopaminergic dysfunction beyond the striatum despite the lower signal intensity. A study involving 623 PPMI participants revealed reduced DAT uptake in the frontal, temporal and posterior cortical regions of PD patients compared to HCs. This reduction was progressive over 1 year and significantly correlated with cognitive function (Sampedro et al., 2021). Other studies also looked at extrastriatal regions, including the frontal cortex, using DAT-SPECT in PD patients; however cognitive correlations were not assessed (Frosini et al., 2015; Kaasinen et al., 2015; Son et al., 2016).

5.1.1.3 DAT Studies in RBD

DAT-SPECT has been utilised to identify dopaminergic deficits in individuals with RBD, providing valuable insights into its role as a prodromal stage of PD. Around 40% of RBD patients exhibit abnormal DAT-SPECT imaging (Iranzo et al., 2010), which is shown to be highly effective in predicting short-term progression to clinically defined alpha-

synucleinopathies, including PD (Arnaldi et al., 2024; Iranzo et al., 2017; Jennings et al., 2017; Li et al., 2017; Miyamoto et al., 2020). Furthermore, PD patients with RBD showed a faster reduction in striatal DAT binding compared to those without RBD (Cao et al., 2020).

In terms of its correlation with cognitive function, one study showed no significant differences in cognitive scores between RBD patients with and without abnormal DAT-SPECT findings (Chahine et al., 2019). However, another study found that RBD patients with MCI (RBD-MCI) had significantly lower caudate and putamen DAT specific binding ratios than cognitively normal RBD patients (Mattioli et al., 2021). In addition, a large multicentre study employed a Bayesian classifier to predict the development of dementia or parkinsonism in RBD patients based on clinical and DAT-SPECT baseline features. It found that patients with lower MMSE scores and higher asymmetry in caudate DAT uptake were more likely to develop dementia, while those with the opposite pattern were more likely to develop parkinsonism (Arnaldi et al., 2021).

5.1.2 Aims and Objectives

This study aimed to investigate the correlations between cognitive and motor measures with DAT-SPECT parameters in the Oxford Discovery Cohort. We hypothesised that cognitive measures would correlate positively with frontal and caudate DAT uptake values and negatively with caudate left-right asymmetry DAT scores. Conversely, we expected motor measures to exhibit negative correlations with striatal DAT uptake values. Furthermore, we posited that striatal DAT uptake values in RBD patients will be lower than those in HCs but higher than in individuals with PD. In contrast, left-right asymmetry scores in RBD patients were expected to be higher than in HCs, yet lower than in PD patients. We also anticipated that in RBD patients, striatal DAT uptake values will be lower in qualitatively abnormal DAT-SPECT scans compared to normal ones.

5.2 Methods

5.2.1 Recruitment

A total of 66 participants, comprising 25 PD patients, 37 patients with RBD and four HCs were prospectively recruited from the Oxford Discovery cohort. PD diagnosis was made by a neurologist based on UK Brain Bank criteria or a clinical diagnosis of probable idiopathic PD (Hughes et al., 1992). RBD diagnosis was based on polysomnography following ICSD criteria (Sateia, 2014). The exclusion criteria for RBD included evidence of dementia or motor parkinsonism. HCs must have no known history of neurological or psychiatric disorders. Ethical approval was obtained, and written informed consent was secured from all participants.

5.2.2 Cognitive and Motor Data Collection

Participants underwent combined clinical examination and cognitive assessments on the day of the scan or within the preceding 12 months. Clinical examination by a neurologist included the use of the MDS-UPDRS part III (Goetz, Tilley, et al., 2008) and additional OPDC smartphone-based digital assessments (Arora et al., 2018). Cognitive assessments encompassed the MoCA (Nasreddine et al., 2005) and verbal phonemic and semantic fluency tests.

5.2.3 Imaging Methods

5.2.3.1 DAT-SPECT/CT Imaging Protocol

Acquisition and Thyroid Uptake Prevention

DAT SPECT/CT scans were obtained following a standardised clinical protocol at the Department of Nuclear Medicine, Churchill Hospital, Oxford. To prevent thyroid uptake, participants received 120 mg of potassium iodide 1 hour before and 24 hours after injecting 185 MBq ± 10% of ^{123}I- FP-CIT (DaTscanTM injection, GE Healthcare). DAT SPECT/CT images

were captured 3 hours after injection using a Discovery 670 gamma camera (GE Healthcare). The SPECT acquisition involved 120 projections, each lasting 30 seconds, with a 128 × 128 matrix.

CT Imaging Parameters

For CT imaging, a 16-slice helical acquisition was performed at 120 KV, 40 mA, and a noise index of 30.

SPECT/CT Reconstruction

The acquired data underwent reconstruction using HERMES Hybrid Recon^{TM} (HERMES Medical Solutions, AB Stockholm) with OSEM (15 iterations, four subsets and integrated attenuation correction from CT), collimator resolution recovery and Monte Carlo scatter correction.

5.2.4 Imaging Analysis

Utilising the BRASS software from HERMES, data analysis involved registering reconstructed images to a standard template (Figure 5.1A,C). Uptake ratios were calculated for regions of interest (ROIs) in the striatal (both sides of the caudate and putamen) and extrastriatal (frontal) regions using the occipital region as the reference (Figure 5.1B). A blinded, experienced nuclear medicine radiologist (Dr Kevin Bradley) reviewed the scans and provided descriptive reports, categorising findings as normal, generalised reduction, asymmetric, caudate asymmetry or borderline. For the classification of the DAT scans from RBD patients, scans that were labelled ‘borderline’ were combined with those labelled ‘normal’ to form the ‘RBD Normal’ group, while the remaining scans were classified as ‘abnormal’, forming the ‘RBD Abnormal’ group.

Asymmetry measurements:

From the calculated uptake ratios, additional variables were derived, including the mean caudate, mean putamen, caudate: putamen ratio. Percentage asymmetry was calculated for caudate, putamen and whole striatum (both sides of caudate and putamen) as follows:

$$\textbf{\% Asymmetry} = \left(\frac{\text{abs(Left[ROI]} - \text{Right [ROI])x 100}}{\text{mean [ROI]}}\right)$$

This calculation provided key insights into the laterization of dopaminergic deficits in different groups.

5.2.5 Statistical Analysis

Statistical analyses, performed using the R program, included chi-square tests for dichotomized variables, independent samples t-tests for continuous variables in pairwise group comparisons. DAT Standardised Uptake Ratios (SURs) were corrected for age using the HERMES BRASS software. Spearman rank coefficients were computed to evaluate the correlations between DAT SURs and both cognitive and motor measures, encompassing all three participant groups: PD, RBD, and Control.

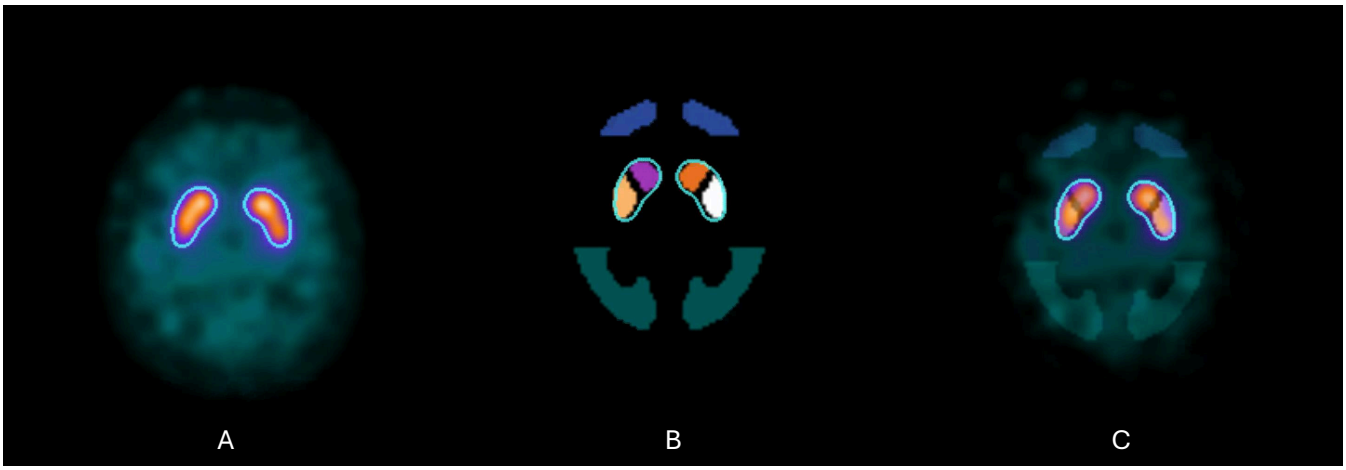


Figure 5.1 | Process of registration and templates used in DAT-SPECT analysis using Hermes BRASS software. A. A single DAT-SPECT image registered to the standard template. B. Defined ROIs for quantifying the DAT-SPECT signals in the putamen (white, yellow), caudate (orange, purple), frontal region (blue), and occipital reference range (dark green). C. Template ROIs on the DAT-SPECT image in panel A.

5.3 Results

5.3.1 Baseline Characteristics of Participants

Table 5.1 provides an overview of the baseline characteristics of the study participants, including cognitive and motor measures. The average age of the participants is 66 ± 8.8 years, with 83.3% being male. Cognitive measures showed no significant differences between the groups, with an overall mean MoCA score of 26 ± 2.9. Similarly, there was no significant differences in age and the Timed Up and Go (TUG) test results across the groups.

As anticipated, participants with PD exhibited significantly worse scores in motor measures compared to the other groups. Notably, the Control group, consisting of only four participants had a different gender distribution with all participants being female. In contrast, both patient groups (PD and RBD) had a similar male predominance.

	PD (N=25)	RBD (N=37)	Control (N=4)	Total (N=66)	p value
Age (years)					0.377[1]
Mean (SD)	68.0 (10.4)	64.9 (7.9)	64.7 (3.0)	66.0 (8.8)	
Gender (n(%))					< 0.001[2]
F	6.0 (24.0%)	1.0 (2.7%)	4.0 (100.0%)	11.0 (16.7%)	
M	19.0 (76.0%)	36.0 (97.3%)	0.0 (0.0%)	55.0 (83.3%)	
UPDRS III (total score)					< 0.001[3]
Mean (SD)	34.0 (13.7)	4.2 (3.3)	1.8 (1.5)	14.8 (16.9)	
Purdue pegboard (total score)					< 0.001[3]
Mean (SD)	25.3 (9.3)	32.9 (4.8)	34.8 (4.3)	30.4 (7.5)	
Timed up and go (seconds)					0.850[3]
Mean (SD)	9.6 (3.3)	8.9 (1.8)	9.0 (2.9)	9.1 (2.4)	
UPDRS II (total score)					< 0.001[3]
Mean (SD)	11.9 (8.9)	2.2 (3.3)	1.0 (0.8)	5.1 (7.1)	
MoCA (total score)					0.545[3]
Mean (SD)	26.0 (3.4)	25.9 (2.5)	27.0 (2.9)	26.0 (2.9)	
Phonemic Fluency (total score)					0.968[1]
Mean (SD)	44.6 (19.3)	43.5 (13.1)	44.0 (21.1)	43.9 (15.9)	
Semantic Fluency (total score)					0.674[1]
Mean (SD)	38.3 (14.4)	39.2 (10.2)	44.0 (6.8)	39.2 (11.7)	

Table 5.1 | Baseline characteristics of the study participants. Demographics and clinical motor and cognitive measures. 1. Linear Model ANOVA 2. Pearson's Chi-squared test 3. Kruskal-Wallis ANOVA

5.3.2 Comparing DAT SPECT Outcome Measures Across Study Groups

The DAT SURs from the five different SPECT ROIs were compared across the groups using independent t-tests. Figure 5.2 showed DAT samples from study participants. In the frontal region, the SURs were similar across all groups, with no significant differences (Figure 5.3A). However, in the basal ganglia regions, on both sides of the caudate and putamen, PD patients exhibited significantly lower values compared to both the RBD and Control groups. On the other hand, RBD patients displayed intermediate values for all these regions, with significantly lower values than Control and higher values than PD patients (Figure 5.3B-E).

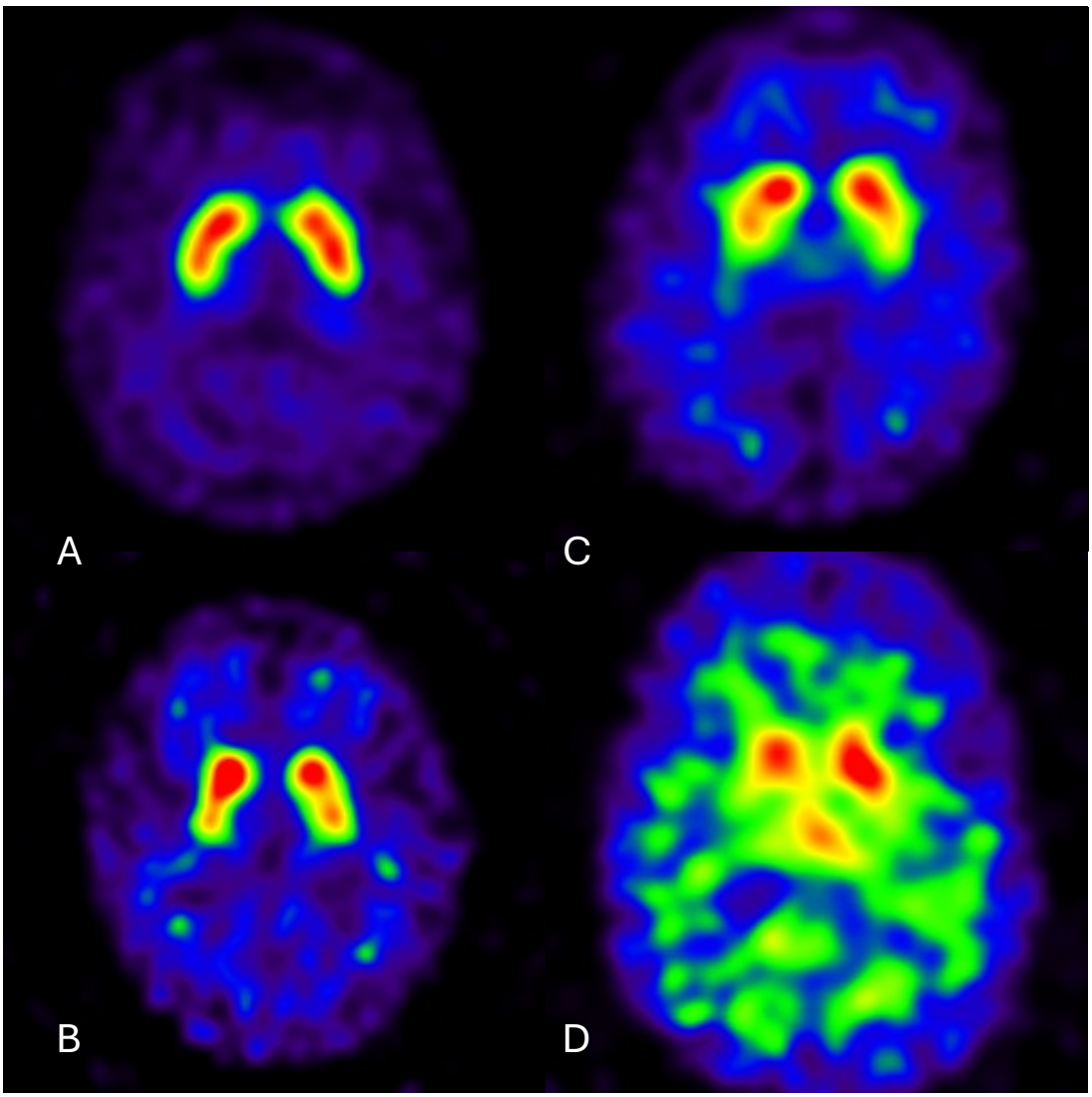


Figure 5.2 | DAT-SPECT images from four different participants, demonstrating the spectrum of abnormal patterns observed. A. Control B. RBD Borderline DAT C. RBD Abnormal DAT D. Advanced PD

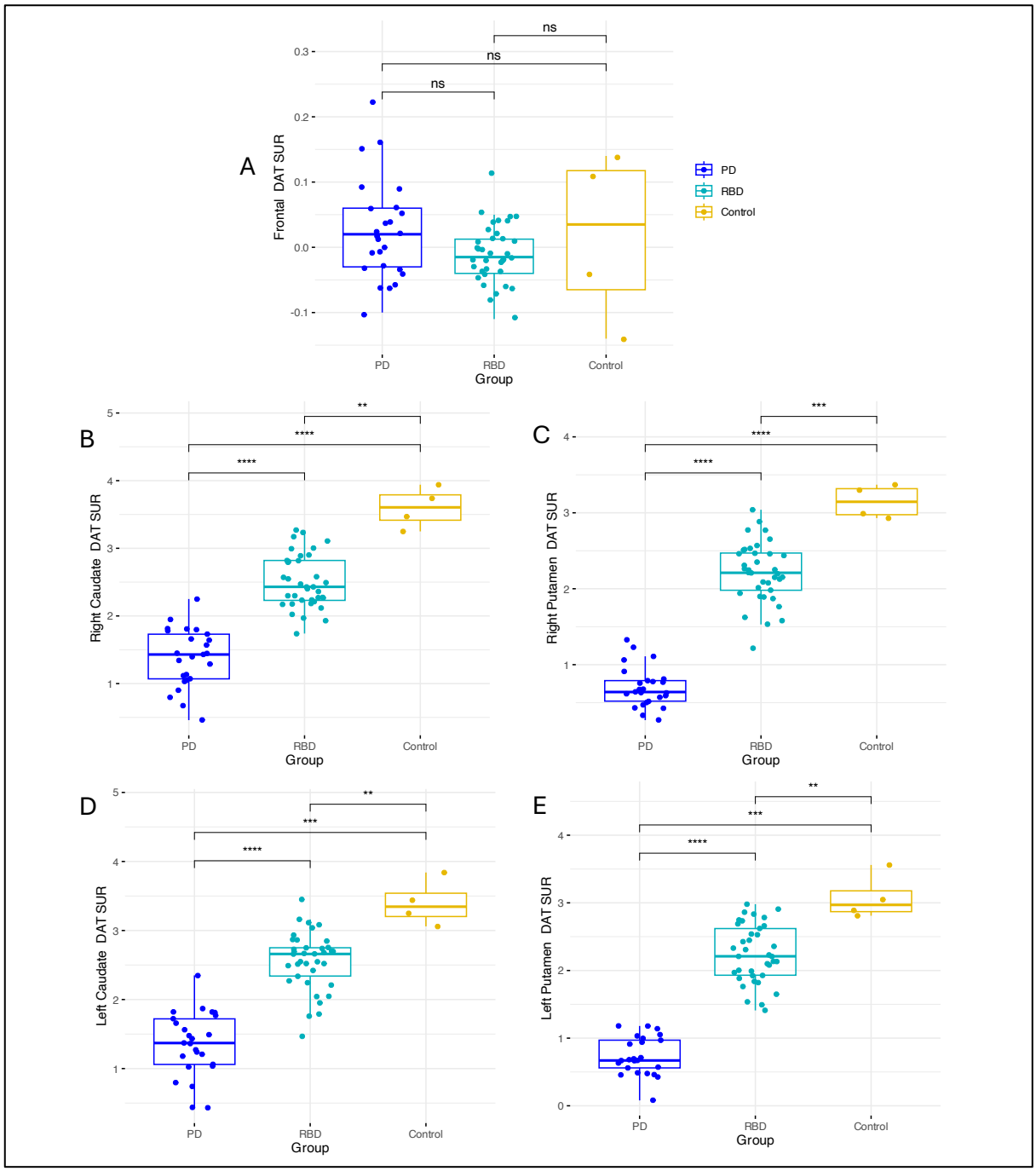


Figure 5.3 | DAT SURs across the study groups in the five different ROIs. A. Frontal, B. Right Caudate, C. Right Putamen, D. Left Caudate, E. Left Putamen. (P-values: > 0.05 ns, <0.05 *, <0.01 **, <0.001 ***, < 0.0001 ****)

5.3.3 Correlations of DAT SURs with Cognitive Measures

Spearman rho correlations were performed between DAT SURs and cognitive measures. Total MoCA scores showed a significant positive correlation with DAT SURs in the frontal ROI (r_s= 0.34, p=0.0052). No significant correlations were observed of the striatal ROIs with the total MoCA scores (Figure 5.4). When comparing the frontal DAT SURs in participants grouped based on their MoCA scores, those with MoCA scores of 26 and above had significantly higher frontal DAT SURs (p=0.033) (Figure 5.5). Additional exploratory analyses were performed for phonemic and semantic fluency scores which revealed no significant correlations with any of the DAT SPECT ROI SURs (Appendix Figure 8.3 and 8.4). Asymmetry measures, including caudate asymmetry, showed no significant correlations with MoCA (Figure 5.6).

5.3.4 Correlations of DAT SURs with Motor Measures

Spearman rho correlations were performed to evaluate the relationship between DAT SURs and motor measures (UPDRS III and OPDC smartphone assessments). Significant negative correlations were observed between DAT SURs in the striatal regions and UPDRS III total scores ($p < 0.001$; Figure 5.7). Similarly, the mean dominant hand scores from the OPDC smartphone motor assessment showed significant negative correlations with DAT SURs in the same regions ($p < 0.001$; Figure 5.8). No significant correlation was observed between DAT SURs in the frontal ROI and both motor measures.

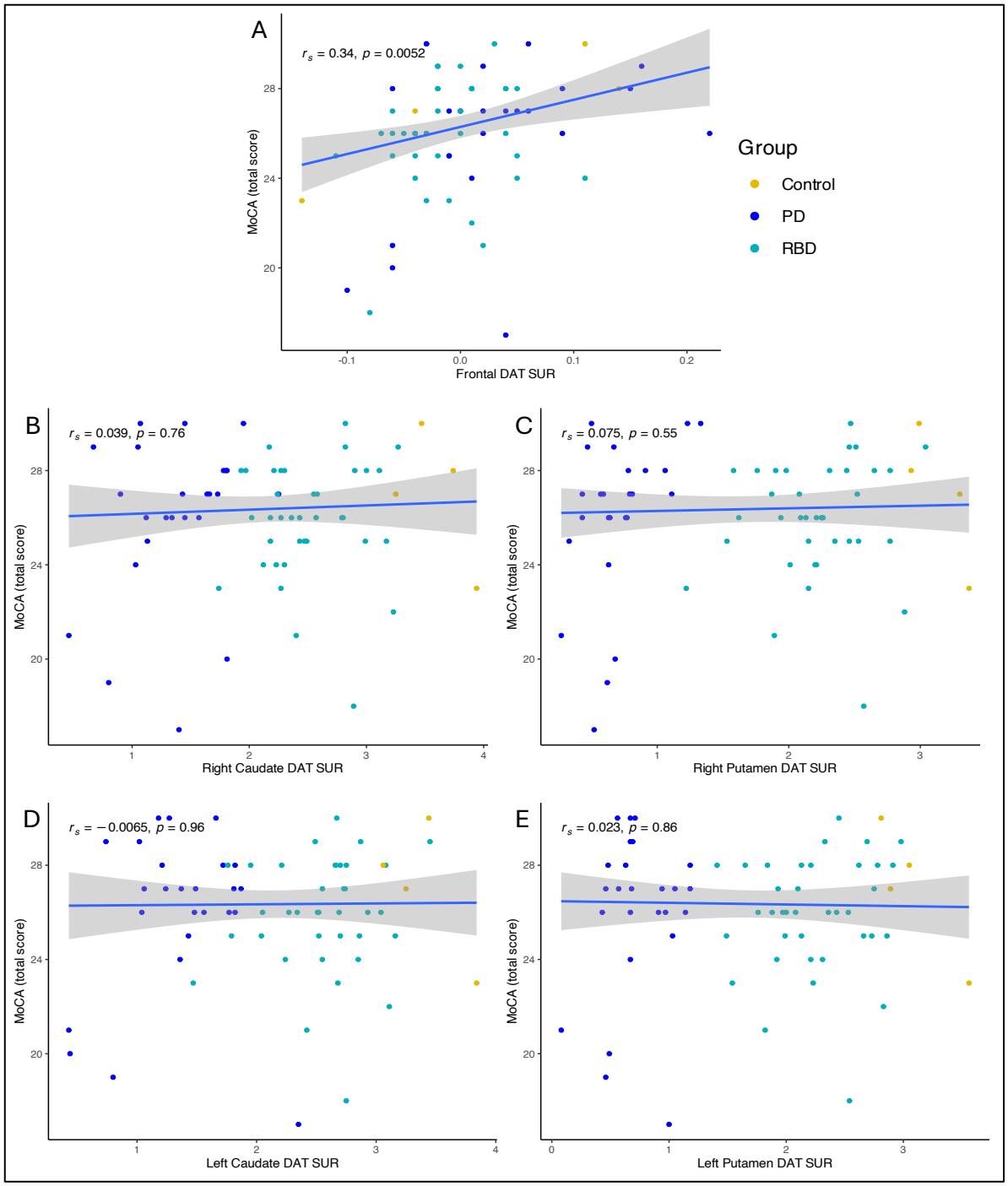


Figure 5.4 | Correlations of MoCA total scores and the DAT SURs from the five different ROIs. A. Frontal, B. Right Caudate, C. Right Putamen, D. Left Caudate, E. Left Putamen.

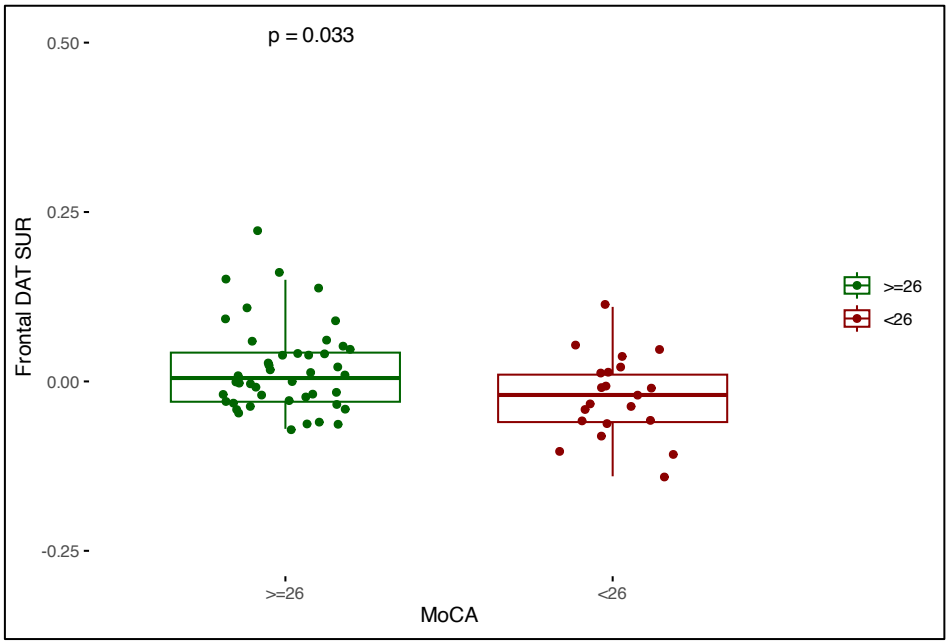


Figure 5.5 | Comparison of Frontal DAT SURs based on MoCA scores.

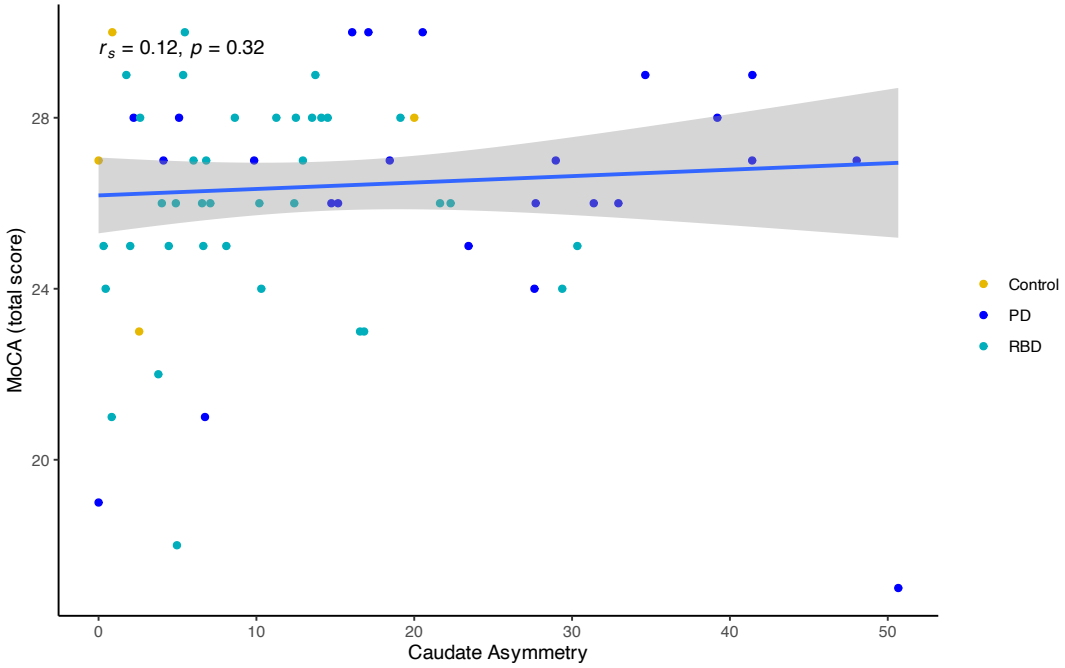


Figure 5.6 | Scatter plot illustrating the lack of significant correlation between caudate asymmetry and MoCA total scores.

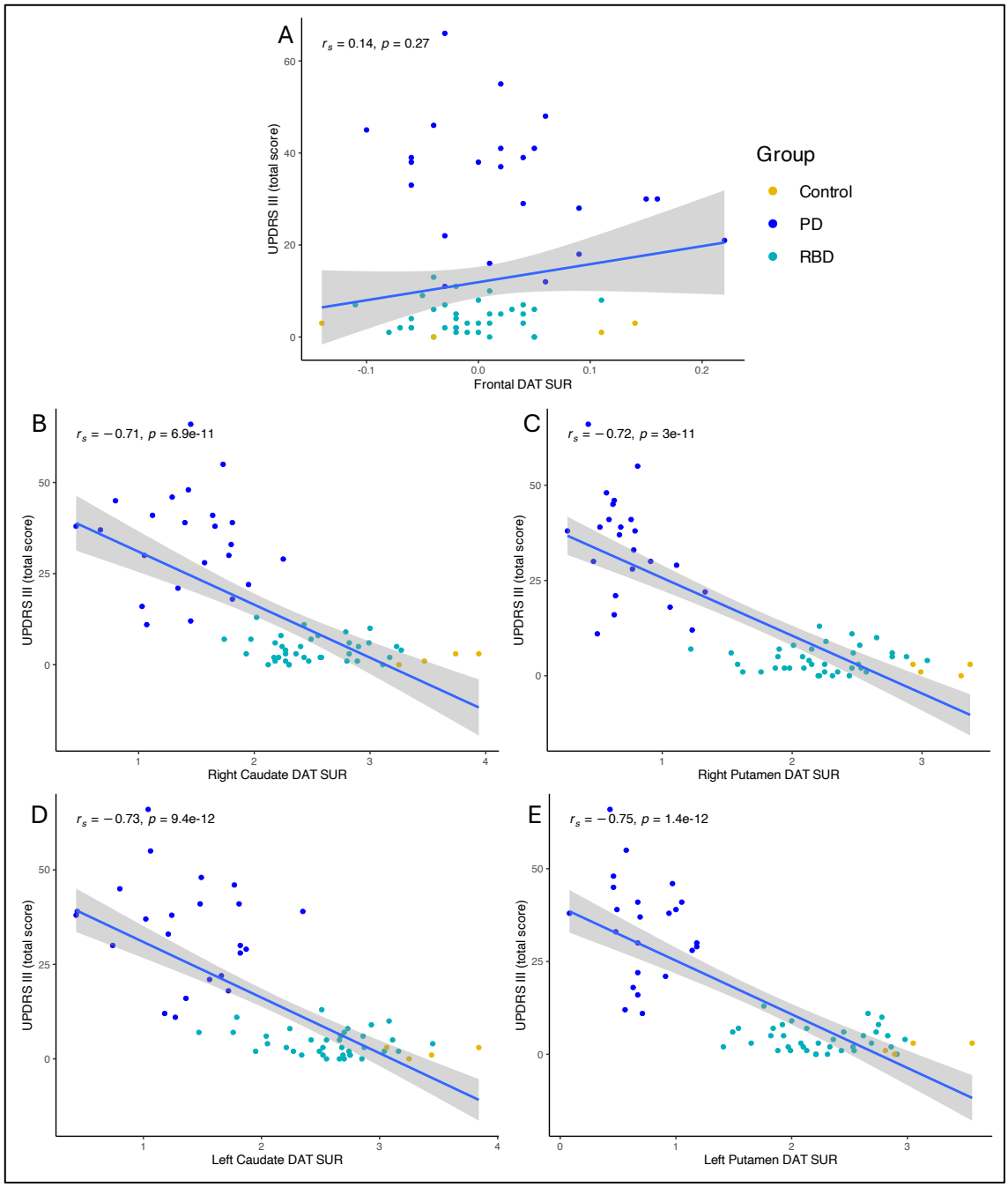


Figure 5.7 | Correlations of UPDRS III total scores and the DAT SURs the five different ROIs.
A. Frontal, B. Right Caudate, C. Right Putamen, D. Left Caudate, E. Left Putamen.

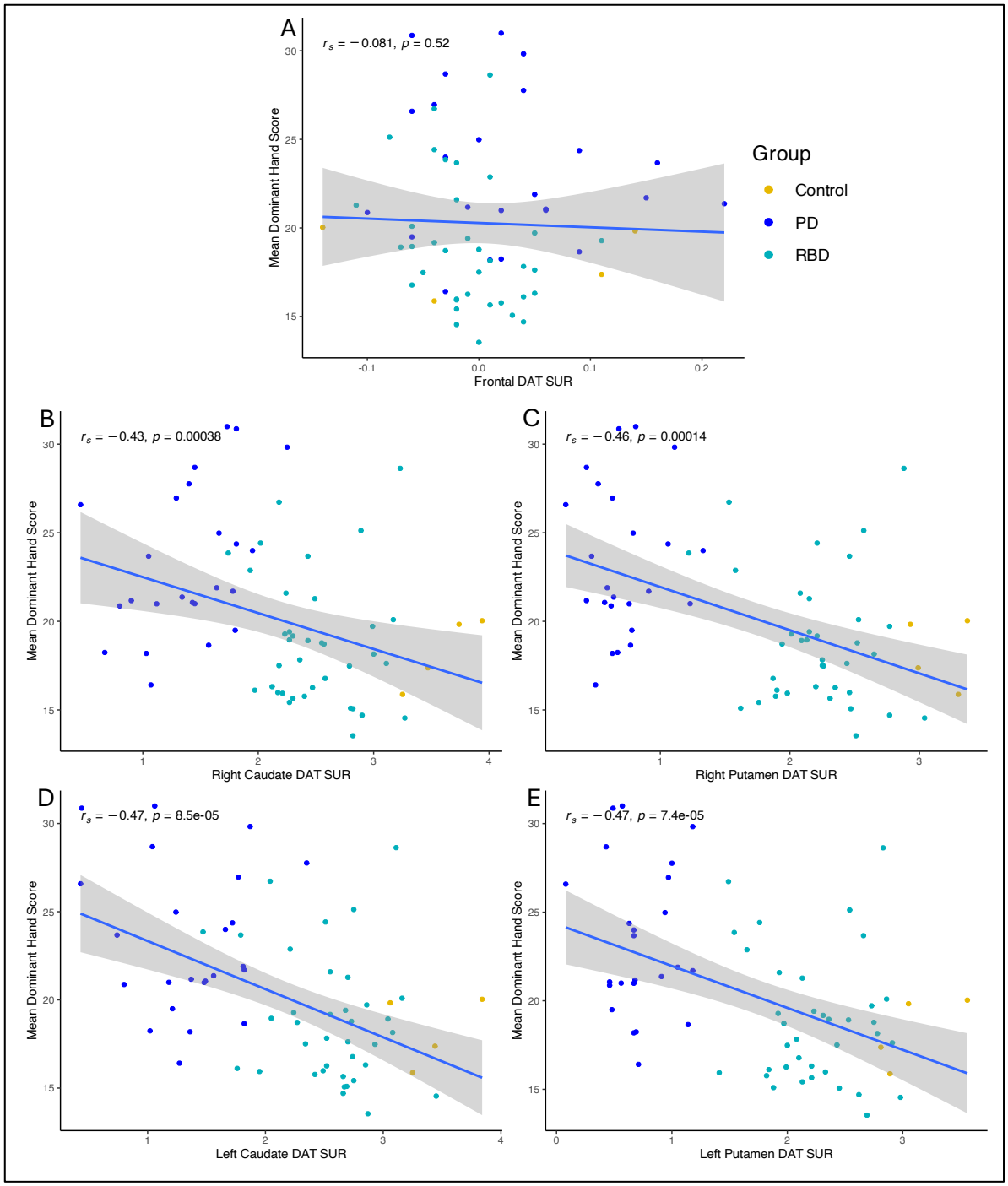


Figure 5.8 | Correlations of mean dominant hand scores (OPDC smartphone motor assessments) and the DAT SURs the five different ROIs. A. Frontal, B. Right Caudate, C. Right Putamen, D. Left Caudate, E. Left Putamen.

5.3.5 Comparing the Asymmetry Measures in DAT-SPECT Across PD and RBD

Building upon the findings related to DAT uptake values in different brain regions (ROIs), we further examined the asymmetry measures in the caudate, putamen and whole striatum across the two primary study groups: PD and RBD (categorised into RBD with abnormal DAT-SPECT (RBD Abnormal) and RBD with normal DAT-SPECT (RBD Normal)). Table 5.4 summarises the demographic characteristics and motor and cognitive performances across the different labelled DAT-SPECT categories in RBD.

In addition to asymmetry measures, we compared the mean DAT uptake in the caudate and putamen and the caudate-to-putamen ratio across the groups. As shown in Figure 5.9, Panels A and B demonstrate that PD patients exhibit significantly lower mean DAT uptake in both the caudate and putamen compared to the RBD Abnormal and RBD Normal groups, with the RBD Abnormal group showing intermediate values between PD and RBD Normal groups. As seen in Panel C, the mean caudate-to-putamen ratio is significantly higher in the PD group compared to both RBD groups, with the RBD Abnormal group having a significantly higher ratio than the RBD Normal group, further highlighting the distinct patterns of dopaminergic dysfunction among these groups.

5.3.5.1 Caudate and Putamen Asymmetry

As illustrated in Figure 5.6 Panels D and E, asymmetry measures in the caudate and putamen were significantly higher in the PD group compared to both the RBD Abnormal and the RBD Normal groups. Specifically, the putamen asymmetry was significantly higher in the PD group ($p= 0.00027$), indicating more pronounced lateralisation of dopaminergic deficits, a hallmark of PD progression. Similarly, the caudate asymmetry in the PD group was notably elevated ($p= 0.01$). While RBD Abnormal group exhibited intermediate asymmetry values

compared to PD and RBD Normal groups, no statistically significant differences were notes between the two RBD groups.

5.3.5.2 Whole Striatum Asymmetry

The asymmetry in the whole striatum (Figure 5.9, Panel F) showed a similar pattern with PD patients displaying the highest asymmetry scores, significantly higher than both RBD groups (p = 4.3e-06). This finding reinforces the concept that lateralised dopaminergic loss is more characteristic of PD. In RBD patients, particularly those with abnormal DAT-SPECT, the asymmetry is less pronounced but still present compared to normal DAT-SPECT scans, with borderline significance.

	Asymmetric (N=8)	Borderline (N=5)	Caudate asymmetry (N=2)	Generalised reduction (N=4)	Normal (N=16)	Total (N=35)	p value
Age							0.316[1]
Mean (SD)	63.1 (6.6)	71.4 (6.2)	62.8 (0.8)	66.4 (6.9)	62.9 (9.3)	64.6 (8.1)	
Range	53.5 - 74.4	60.6 - 76.6	62.2 - 63.3	57.9 - 74.8	42.0 - 75.9	42.0 - 76.6	
Gender							0.874[2]
F	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	0.0 (0.0%)	1.0 (6.2%)	1.0 (2.9%)	
M	8.0 (100.0%)	5.0 (100.0%)	2.0 (100.0%)	4.0 (100.0%)	15.0 (93.8%)	34.0 (97.1%)	
Total UPDRS III at closest visit to scan							0.359[1]
Mean (SD)	2.9 (2.8)	5.6 (5.1)	1.0 (1.4)	5.2 (2.9)	4.7 (3.3)	4.3 (3.4)	
Range	1.0 - 9.0	0.0 - 13.0	0.0 - 2.0	1.0 - 7.0	0.0 - 11.0	0.0 - 13.0	
Mean Dominant hand score							0.237[1]
Mean (SD)	16.7 (1.5)	19.4 (3.6)	16.1 (0.2)	21.0 (5.1)	19.3 (4.0)	18.8 (3.7)	
Range	15.1 - 18.9	15.7 - 24.4	16.0 - 16.3	16.1 - 26.7	13.5 - 28.6	13.5 - 28.6	
MoCA Total							0.847[1]
Mean (SD)	25.8 (2.2)	27.0 (0.7)	26.5 (3.5)	25.5 (2.1)	25.6 (3.1)	25.9 (2.5)	
Range	21.0 - 28.0	26.0 - 28.0	24.0 - 29.0	23.0 - 28.0	18.0 - 30.0	18.0 - 30.0	
Phenomic Fluency Total							0.636[1]
Mean (SD)	46.8 (13.0)	49.8 (6.2)	39.0 (4.2)	40.0 (12.7)	40.9 (15.7)	43.3 (13.3)	
Range	28.0 - 64.0	42.0 - 57.0	36.0 - 42.0	25.0 - 51.0	13.0 - 69.0	13.0 - 69.0	
Semantic Fluency Total							0.764[1]
Mean (SD)	42.1 (9.0)	41.2 (7.6)	43.5 (0.7)	34.5 (10.5)	38.8 (12.2)	39.7 (10.3)	
Range	29.0 - 55.0	32.0 - 53.0	43.0 - 44.0	20.0 - 44.0	18.0 - 67.0	18.0 - 67.0	

Table 5.2 | Baseline characteristics and cognitive/motor performance across different DAT-SPECT classifications in RBD patients. 1. Linear Model ANOVA 2. Pearson's Chi-squared test

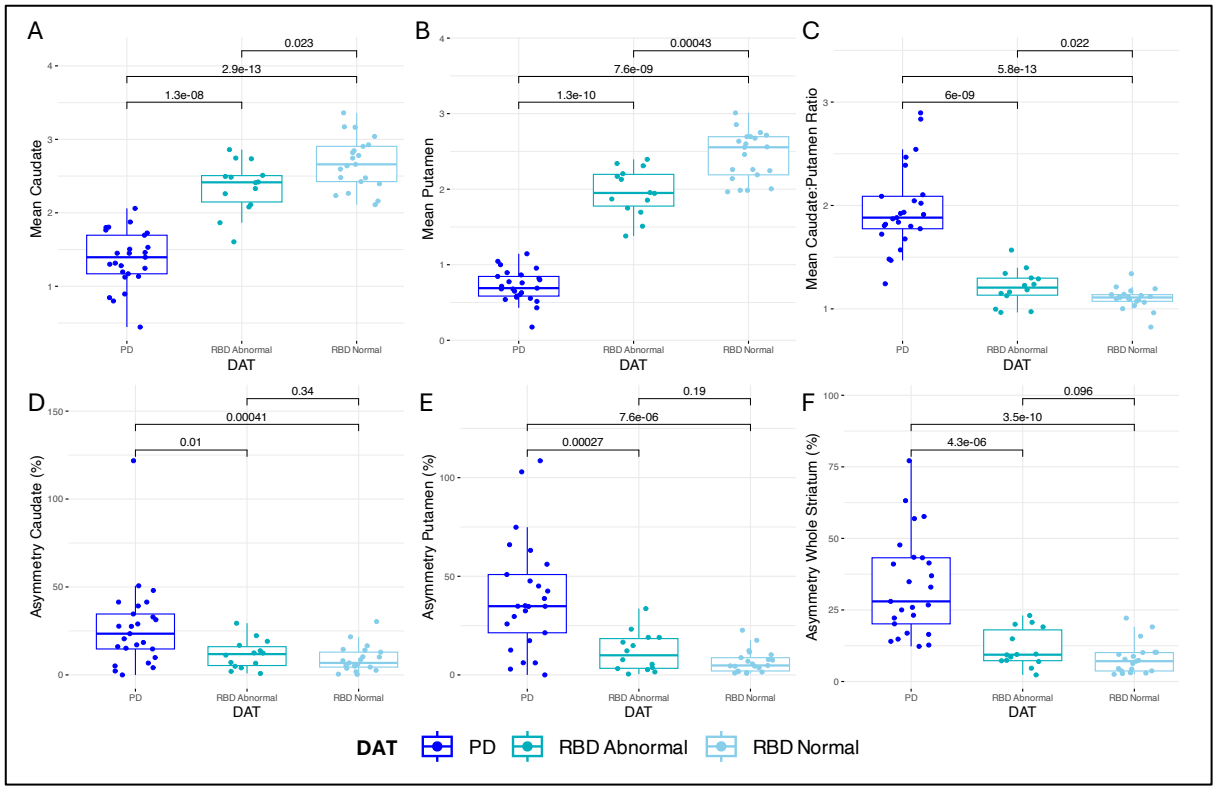


Figure 5.9 | Comparison of DAT-SPECT mean uptake and asymmetry measures across PD, RBD Abnormal, and RBD Normal groups. The box plots illustrate the distribution of both mean uptake and asymmetry measures across different regions of interest: A. Mean caudate, B. Mean putamen, C. Mean caudate-to-putamen ratio, D. Asymmetry in the caudate, E. Asymmetry in the putamen, and F. Asymmetry in the whole striatum. Statistical significance between the groups is indicated by p-values.

5.4 Discussion

This study sought to examine the relationships between DAT-SPECT measures and cognitive and motor functions in participants from the Discovery cohort including 25 PD patients, 37 RBD patients and four healthy controls. The findings demonstrated a double dissociation in the correlations observed. Specifically, the cognitive measure, MoCA scores, exhibited significant correlation with frontal DAT SURs but showed no significant correlations with striatal DAT SURs. Conversely, motor measures, such as UPDRS III and smartphone motor scores, displayed significant correlations with Striatal DAT SURs, while no significant correlations were found with frontal DAT SURs.

MoCA scores exhibited a positive correlation with only the frontal DAT SUR, while the hypothesis predicted significant correlations with both frontal and caudate DAT SURs, as well as caudate asymmetry. This finding can be attributed to the role of dopamine in cognition mainly within the fronto-cortical striatal networks, which are often affected early in PD patients and are associated with attentional and executive dysfunction (Arnsten & Dudley, 2005; Cools, 2011; Kehagia et al., 2013). Despite the lower DAT signal in the extrastriatal regions, the observed correlation was significantly positive.

The lack of significant correlation with caudate DAT SURs and caudate asymmetry in this study, unlike the findings of previous studies (Ekman et al., 2012; Nobili et al., 2010; Pellecchia et al., 2015) could be due to the use of MoCA as a global cognitive screening measure. In contrast, those previous studies used tests that primarily assess attention/working memory, or executive functions, which have been positively correlated with DAT uptake in the caudate nucleus. This nucleus, part of the associative striatum, has its dorsal region connected to the dorsolateral prefrontal cortex, which is involved in these

cognitive functions (Levy et al., 1997; Postuma & Dagher, 2006; Riley et al., 2011; Yeterian & Pandya, 1991).

Similar results have been observed in other molecular imaging studies, particularly those using PET, which offers higher sensitivity and selectivity for dopamine quantification with picomolar and nanomolar ranges (Rahmim & Zaidi, 2008). For example, Rinne et al. (2000) showed no significant correlation between caudate DAT PET values and the MMSE, another global screening measure for cognition, but significant correlations with executive function and attentional tasks (Rinne et al., 2000). Other PET studies also revealed similar associations between dopaminergic denervation in the caudate nucleus and dysfunctions in those cognitive domains (Jokinen et al., 2009; Polito et al., 2012; van Beilen et al., 2008).

The significant inverse correlations between the motor measures and striatal DAT uptake in our study are consistent with previous imaging studies using both DAT-SPECT and PET (Li et al., 2018; Liu et al., 2018; Simuni et al., 2018; Son et al., 2016). This emphasises the well documented role of striatum and, mainly, putamen in PD motor manifestations.

We observed significant differences in both mean DAT uptake and asymmetry measures between the RBD Normal and RBD Abnormal groups, suggesting that these metrics may help distinguish between RBD patients at different stages of neurodegeneration. The gradation of asymmetry, from highest in PD to lowest in RBD Normal, further supports the idea of a continuum of dopaminergic neurodegeneration that spans from RBD to PD. Importantly, this continuum could potentially serve as a biomarker for the early identification and stratification of patients at higher risk of transitioning from RBD to clinically defined PD, particularly those with abnormal DAT-SPECT scans.

Strengths and limitations

The strength of this study lies in its exploration of both striatal and extrastriatal DAT regions utilising a well-phenotyped cohort with a good number of participants from both RBD and PD groups.

However, the study does have several limitations. The resolution and sensitivity of DAT-SPECT are limited compared to those of other molecular nuclear imaging techniques such as PET, which may impact the accuracy and detail of the neuroimaging findings. Additionally, the use of the MoCA as a global cognitive measure without a detailed neuropsychological assessment for each cognitive domain could overlook specific cognitive impairments, particularly those related to executive functions and attention/working memory, which are often dopaminergic in nature (Kehagia et al., 2013). The study also did not include participants with MCI from both PD and RBD groups, limiting its ability to explore the full spectrum of cognitive impairment within these conditions. Furthermore, the lower number of healthy controls, partly due to recruitment difficulties and concerns over radiation exposure with DAT-SPECT, reduces the statistical power and generalisability of the findings when comparing them to patient groups. Finally, some of the cognitive and motor measures were collected within a 12-month period but not at the same time or in close proximity to the DAT scans, potentially missing critical temporal correlations between these measures and DAT scan results.

5.5 Conclusion and Recommendations for Future Studies

This study provides significant insights into the relationship between DAT-SPECT measures and both cognitive and motor functions in participants from the Discovery cohort, including PD and RBD patients. The findings highlight a distinct dissociation in these correlations. Cognitive measures, specifically the MoCA scores, showed significant positive correlations with DAT uptake in the frontal region but not in the striatal regions. Conversely, motor measures, including UPDRS III and OPDC smartphone motor scores, exhibited significant negative correlations with DAT uptake in the striatal regions but not in the frontal region. These dopaminergic results reinforce the role of fronto-cortical striatal networks in cognitive functions and the well-documented involvement of the striatum, particularly the putamen, in motor manifestations of PD.

Recommendations For Future Studies

Future studies should incorporate detailed neuropsychological assessments targeting specific cognitive domains, especially executive functions, attention and working memory. This approach would provide a more granular understanding of the dopaminergic contributions to cognitive impairments in PD and RBD. Additionally, including more participants with mild-moderate and severe cognitive impairment from both PD and RBD groups would help explore the full spectrum of cognitive impairments and their correlation with DAT uptake, offering a broader perspective on disease progression.

Leveraging imaging techniques with higher resolution and sensitivity, like PET, could enhance the accuracy and detail of neuroimaging findings. PET imaging, with its picomolar and nanomolar range sensitivity for dopamine quantification, may provide more precise insights into the dopaminergic system's role in cognition and motor functions. Additionally,

ensuring that cognitive and motor measures are collected in closer temporal proximity to the DAT scans would improve the accuracy of correlations between these measures and DAT uptake values, thereby capturing critical temporal dynamics. Moreover, conducting longitudinal studies with extended follow-up periods would help track the progression of dopaminergic deficits and their impact on cognitive and motor functions over time, providing valuable insights into disease progression and potential therapeutic targets.

By addressing these recommendations, future research can build on the findings of this study to further elucidate the complex relationships between dopaminergic dysfunction, cognitive impairment and motor symptoms in PD and RBD, ultimately contributing to improved diagnostic and therapeutic strategies.

Chapter | 6

Chapter 6 | General Discussion

6.1 Overview

This thesis has presented a comprehensive exploration of current pharmacological treatments for PDD and DLB, as well as the cognitive impairments associated with these conditions and their prodromal phase in RBD. The studies conducted spanned network meta-analyses, cholinergic experimental investigations into eye movement, apathy, reward sensitivity, and attentional networks. Additionally, cognitive profiling using online tools was performed, along with dopaminergic neuroimaging correlates of cognitive and motor measures using DAT-SPECT among patients in the Discovery cohort.

6.2 Pharmacological Treatments for PDD and DLB

The network meta-analyses presented in Chapter 2 evaluated the efficacy of various pharmacological treatments for PDD and DLB. Rivastigmine emerged as the most likely efficacious drug for improving both cognitive and neuropsychiatric symptoms, which is consistent with its FDA approval for PDD (Emre et al., 2004). However, the findings also highlighted a significant trade-off between efficacy and tolerability, as rivastigmine was associated with higher dropout rates due to adverse events. On the other hand, donepezil was identified as a viable alternative, offering a better overall benefit/risk profile. These findings underscore the importance of individualized treatment approaches, where the benefits of cognitive and neuropsychiatric symptom improvement must be carefully weighed against the potential for adverse effects.

The comparative analysis of rivastigmine's two formulations (capsules and patches) revealed no significant differences in cognitive efficacy between the two, though the patch formulation was associated with a lower dropout rate, suggesting better tolerability. This

aligns with previous research in AD, where transdermal formulations have shown a better safety profile (Darreh-Shori & Jelic, 2010; Winblad et al., 2007). These results emphasise the need for clinicians to consider patient preferences and tolerability when prescribing cholinesterase inhibitors, particularly for those sensitive to gastrointestinal side effects.

In our examination of existing studies in this chapter, particularly through the lens of clinical trials, we have identified several critical challenges. A notable issue is the lack of standardisation across different levels, including diagnostic criteria, assessment methods, and trial designs. Additionally, there is inconsistency in how clinical trials handle PDD and DLB; some studies combine participants from both conditions, while others separate them into distinct trials or trial arms. These variations present significant obstacles to the comparison of studies, which in turn complicates the synthesis of evidence-based recommendations for clinical practice. Addressing these methodological disparities is essential for enhancing the quality of clinical trials, advancing the field and ensuring that clinical decisions are informed by robust and comparable data (Bayram et al., 2023; Goldman et al., 2020).

We know that the ultimate goal in the treatment of neurodegenerative diseases including Lewy body diseases is to develop disease-modifying therapies that can not only halt the disease but potentially reverse the progression of the disease. Such therapies are likely to be rooted in personalised medicine, which would specifically target underlying pathogenic mechanisms. This could involve interventions aimed at misfolded proteins such as alpha synuclein, tau, amyloid beta, modulation of various neurotransmitter systems including cholinergic, dopaminergic, noradrenergic, serotonergic pathways, as well as addressing genetic factors like mutations in GBA1, LRRK2, and SNCA genes (Charvin et al., 2018; Hung & Schwarzschild, 2020; Ntetsika et al., 2021; Poewe et al., 2020). However, until

these groundbreaking treatments are realised, it remains crucial to rigorously evaluate and refine the current therapeutic options to optimise clinical outcomes and update the treatment protocols accordingly.

6.3 Rivastigmine, Eye Movement and Reward Sensitivity

The studies presented in Chapter 3 investigated the effects of rivastigmine on eye movements, attention and reward sensitivity in Lewy body diseases. By utilising eye-tracking technology, we were able to simultaneously study the drug's motor and motivational effects, which are primarily associated with the dorsal and ventral striatum, respectively (Threlfell & Cragg, 2011). Rivastigmine significantly enhanced saccadic measures, including peak velocity and amplitude, highlighting its positive motor effect. However, contrary to our hypothesis, it did not enhance reward sensitivity, suggesting that its role in modulating motivation may be limited.

This outcome implies that the cholinergic system might play a limited role in reward processing, a function predominantly regulated by the dopaminergic system. The lack of improvement in reward sensitivity, despite the positive effects on saccadic measures, indicates that the apathy-related benefits of rivastigmine reported in previous clinical trials (Devos et al., 2014; McKeith et al., 2000), might be more attributable to enhancements in attention and cognitive functions (Emre et al., 2004; Rolinski et al., 2012; Wesnes et al., 2005), or possibly through affecting a different mechanism of apathy, rather that directly influencing reward sensitivity, which has been shown to be diminished in apathetic patients (Le Heron, Manohar, et al., 2018; Muhammed et al., 2016).

The observed improvements in saccadic eye movements could have significant practical implications for daily real-world situations that demand quick and precise visual responses, such as driving or avoiding obstacles. These improvements may also contribute to

a reduction in falls – a common issue in PD – aligning with the potential positive effects of rivastigmine demonstrated in previous clinical trials focused on gait and mobility (Henderson et al., 2016; Li et al., 2015). Our research, by employing an eye-tracking task as an objective measure, underscores the importance of integrating such measures into clinical trials rather than the currently used subjective measures of apathy. This approach could offer a deeper understanding of rivastigmine's effects and elucidate how the cholinergic system, along with other neurotransmitter systems, influences both reward sensitivity and apathy.

6.4 Cognitive Profiles in PD and RBD

The distinct cognitive profiles observed in PD and its prodromal phase, as represented by RBD, compared to healthy controls underscore the more pronounced attentional deficit associated with PD. PD patients exhibited significant impairments in attention and executive functions, particularly in tasks that demand higher cognitive control, such as Trail Making test and Stroop task. In contrast, RBD patients showed more pronounced impairments in memory and language domains, consistent with cholinergic deficits. The dual syndrome hypothesis, which posits early dopaminergic-mediated deficits in attention and executive functions and later cholinergic-mediated impairments in memory and visuospatial functions, provides a plausible framework for understanding these findings (Kehagia et al., 2013). The absence of significant differences between PD and RBD in cognitive domains suggests a shared underlying pathology, with RBD representing an earlier stage of dopaminergic related cognitive decline. The insights into the cognitive profiles of PD and RBD patients highlight the need for targeted cognitive assessments that can differentiate between these stages and guide early interventions.

6.5 Remote Cognitive Testing and Longitudinal Assessment

The feasibility of using remote cognitive assessments in clinical trials and longitudinal studies was explored in Chapter 4. The studies demonstrated that remote testing is not only practical but also offers several advantages, including increased accessibility and convenience for participants. This approach is particularly relevant in the context of the COVID-19 pandemic, which has highlighted the need for flexible and scalable assessment methods in clinical practice (Owens et al., 2020).

However, the studies also identified challenges, such as potential variability in testing conditions and the technical abilities of participants. Despite these challenges, the high completion rates observed in the remote cognitive assessments suggest that this method could be integrated more widely into clinical practice and research, provided that adequate support and standardisation protocols are in place.

The longitudinal findings, though limited by a short follow-up period, underscore the need for extended studies to capture the full trajectory of cognitive decline in PD and RBD.

6.6 Relationship Between Dopaminergic Function (DAT-SPECT) and Cognitive/Motor Performance

Chapter 5 explored the relationship between DAT-SPECT measures and cognitive/motor functions in PD and RBD patients. The findings revealed a double dissociation, with cognitive measures correlating with frontal DAT uptake and motor measures correlating with striatal DAT uptake. This supports the role of the fronto-cortical straital networks in cognition and the well-established involvement of the striatum, particularly the putamen, in the motor symptoms of PD (Cools, 2011; Kehagia et al., 2013).

The lack of significant correlations between caudate DAT uptake and global cognitive measures, such as the MoCA, suggests that more specific cognitive tasks targeting executive

functions and attention may be necessary to detect dopaminergic deficits in these regions. This finding aligns with previous research showing that detailed neuropsychological assessments are more sensitive in detecting cognitive impairments associated with caudate dysfunction (Polito et al., 2012; Rinne et al., 2000).

These findings emphasise the importance of considering both striatal and extrastriatal dopaminergic pathways when assessing the impact of PD on cognitive and motor functions. Future studies should integrate more detailed neuropsychological assessments and advanced imaging techniques to further elucidate these complex relationships and improve diagnostic accuracy.

6.7 Strengths, Limitations, and Future Directions

This thesis has several strengths, including the use of network meta-analysis, objective eye-tracking measures, and the integration of remote cognitive testing. However, it also has limitations, such as small sample sizes in some studies, potential biases in remote assessments, and the challenges of generalising findings from a limited population.

Future research should focus on the development and validation of disease-specific cognitive tools for PD and RBD, incorporating detailed neuropsychological assessments and advanced imaging techniques like PET to enhance the accuracy of findings. Extended longitudinal studies with larger and more diverse cohorts are necessary to fully understand the progression of cognitive and motor impairments in these conditions.

Additionally, the integration of remote cognitive assessments into clinical practice could improve patient monitoring and intervention strategies, especially in under-resourced or geographically isolated areas.

6.8 Conclusion

In conclusion, this thesis has provided valuable insights into the pharmacological treatment of cognitive symptoms in Lewy body diseases, the cognitive profiles of PD and RBD patients, and the feasibility of remote cognitive assessments.

The findings emphasise the importance of individualised treatment approaches, the need for specialised cognitive assessment tools, and the potential of remote testing in clinical research and practice. By addressing the limitations and pursuing the suggested future directions, further research can contribute to improved diagnostic and therapeutic strategies for LBD.

Chapter | 7

Chapter 7 | References

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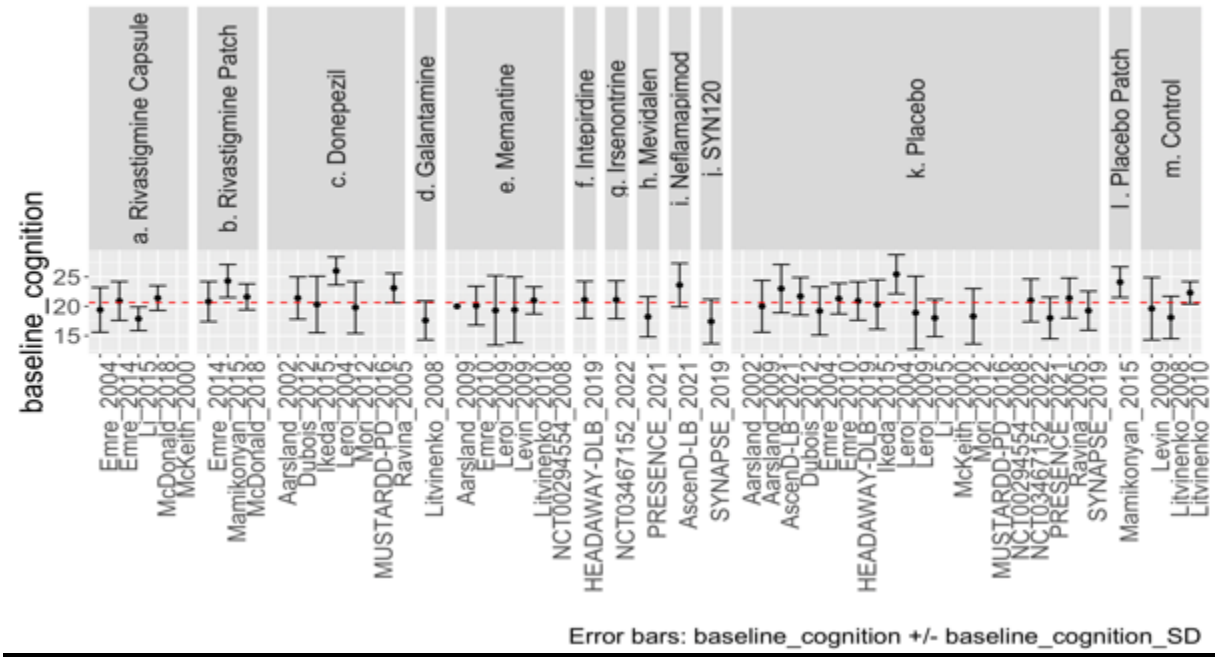
Chapter | 8

Chapter 8 | Appendix

8.1 Supplementary Information for Chapter 2

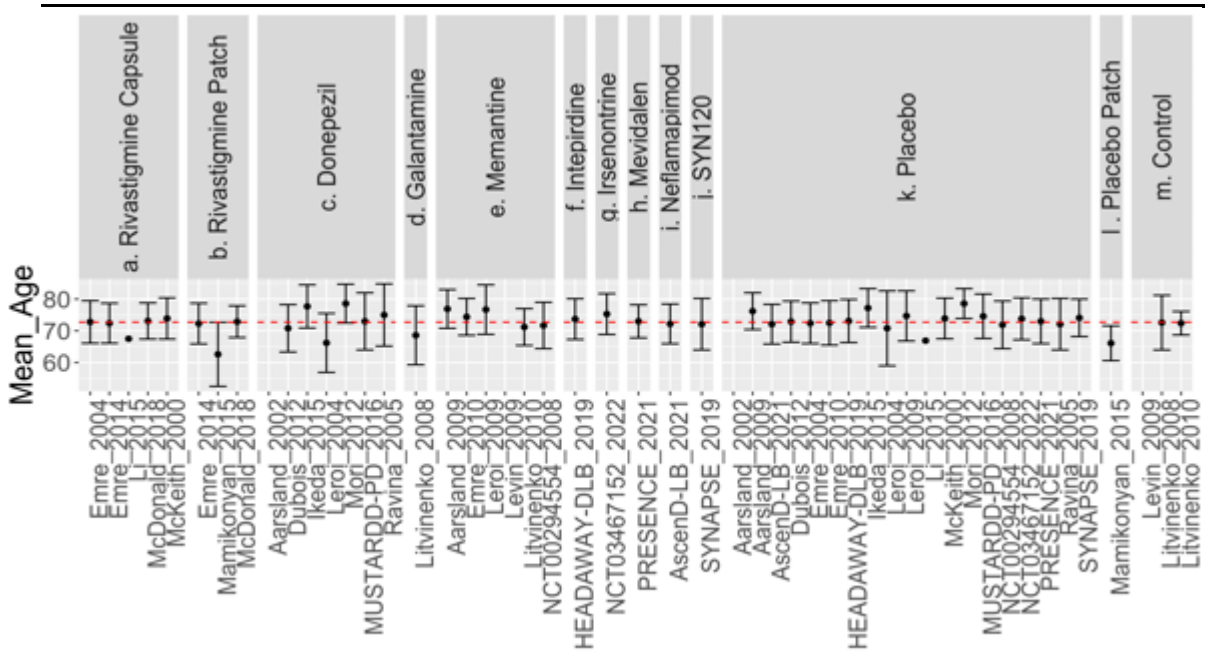
Figure 8.1 | Assessment of the distribution of potential effect modifiers across the included trials in the network meta-analysis.

- **Baseline cognition (Panel A)**



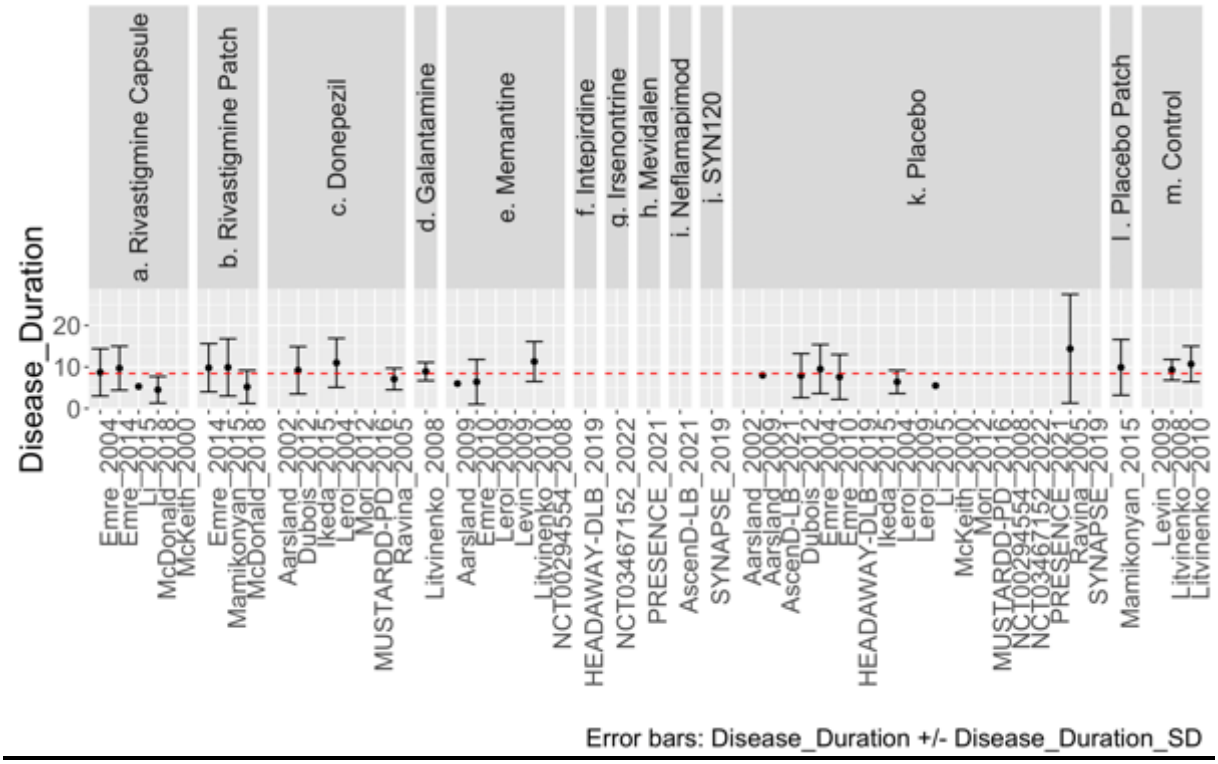
Error bars: baseline_cognition +/- baseline_cognition_SD

- **Mean Age (Panel B)**



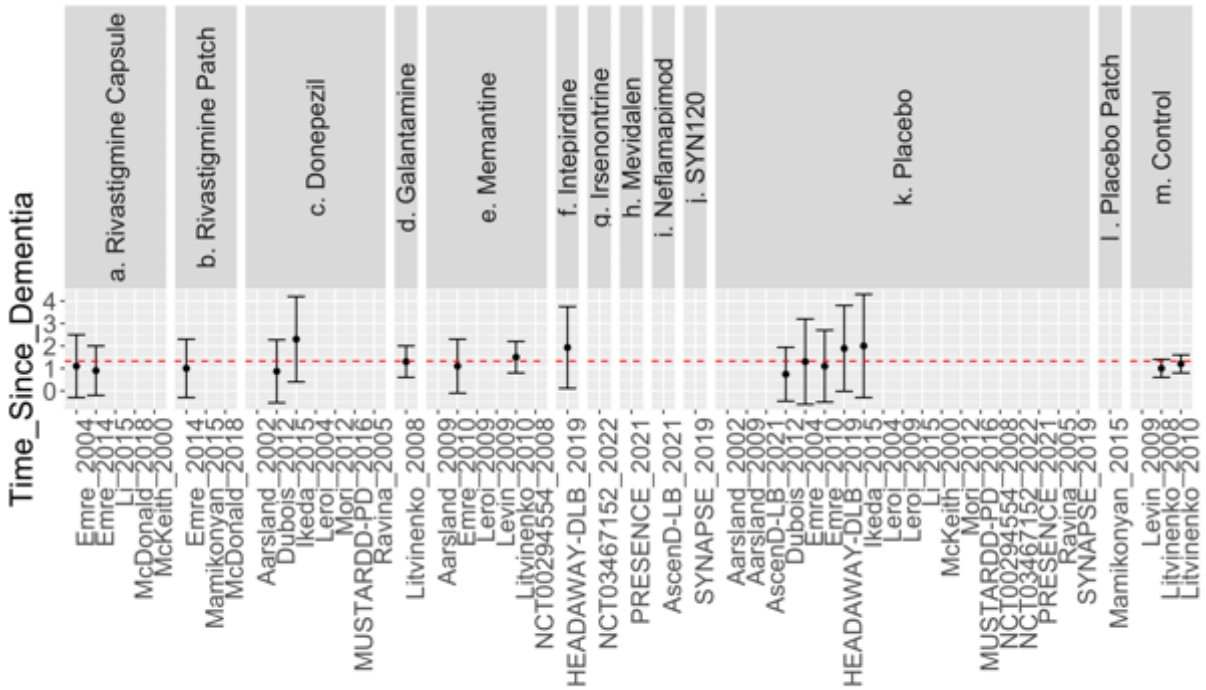
Error bars: Mean_Age +/- SD

- **Disease Duration (Panel C)**



Error bars: Disease_Duration +/- Disease_Duration_SD

- **Time since dementia (Panel D)**



Error bars: Time_Since_Dementia +/- Time_Since_Dementia_SD

Table 8.1 | Excluded studies from the network meta-analysis study with the reasons of exclusion

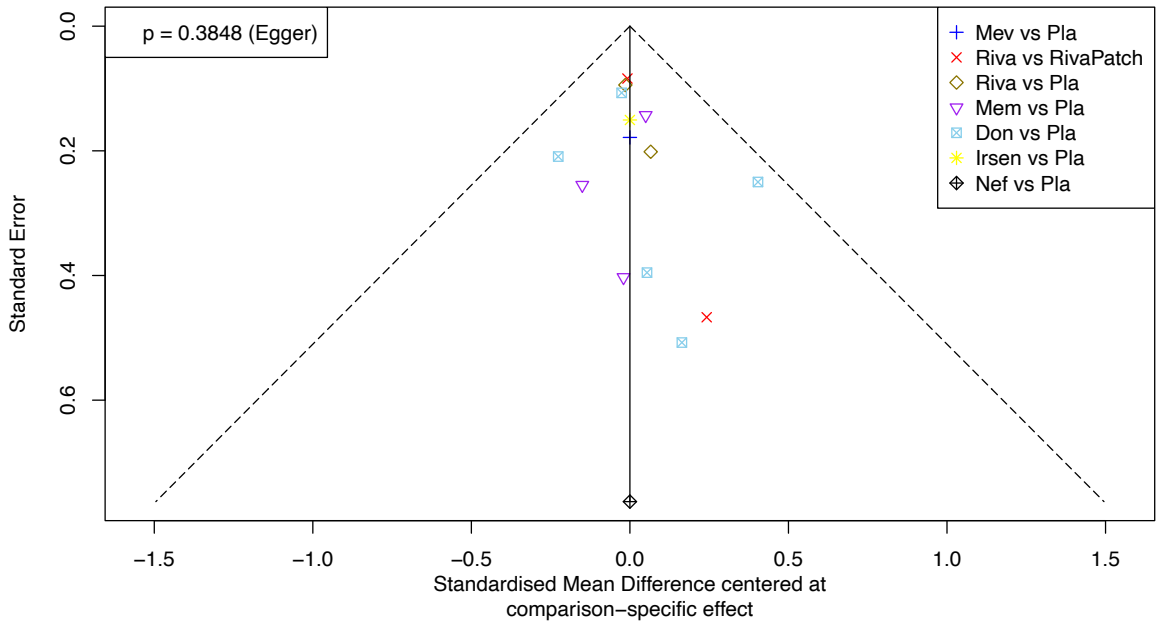
Study	Reason of Exclusion
Reading 2001	Open label non-randomized study
Giladi 2003	Open label non-randomized study
Fogelson 2003	Open label non-randomized study
Dujardin 2005	Add on study of Emre et al. 2004
Poewe 2006	Add on study of Emre et al. 2004
Burn 2006	Add on study of Emre et al. 2004
Ceravolo 2006	Open label neuroimaging study
Barone 2008	Add on study of Emre et al. 2004
Schmitt 2010	Post-hoc Analysis of Emre et al. 2004
Giacopo 2012	Outcome measures – (1st: RBD episodes)
Possin 2013	Open label neuroimaging study
Devos 2014	Study population (PD with apathy and no cognitive impairment)
Oh 2015	Open label non-randomized study
Henderson 2016	Study population (PD with falls and no cognitive impairment)
Moretti 2017	Open label non-randomized study & Study population
Espay 2021	Post-hoc Analysis of Emre et al. 2004
Mierlo 2021	Study population (PD with visual hallucinations)
Shea 1998	>20 years old – Open label non-randomized study
Samuel 2000	>20 years old – Open label non-randomized study
Minett 2003	Open label non-randomized study
Beversdorf 2004	Data not available
Thomas 2005	Open label non-randomized study
Linazasoro 2005	Open label non-randomized study & Study population (non-demented PD)
Muller 2006	Open label non-randomized study
Rowan 2006	Data not available
Chung 2010	Study population - Outcome measures
Sawada 2018	Study population (non-demented PD)
Stuart 2020	Intervention types (Donepezil + Levodopa) Outcome measures
Aarsland 2003	Open label non-randomized study
Edwards 2007	Open label non-randomized study
Grace 2008	Study population (non-demented PD)
Litvinenko 2008	Open label non-placebo-controlled study
Leroi 2009	Outcome measures
Larsson 2010	Post-hoc Analysis of Aarsland et al. 2009
Johansson 2011	Extension open label study of Aarsland et al. 2009
Ondo 2011	Study population (non-demented PD)
Wesnes 2015	Outcome measures
Tsai 2014	Significant differences between study arms baseline data & study length (8 weeks)
Pagan 2016	Open label non-placebo non-controlled safety study
Lemay 2004	Study population (non-demented PD)
Hangasi 2011	Study population (non-demented PD)
Levin 2009	Open label non-placebo-controlled study
Litvinenko 2009	Open label non-placebo-controlled study

Table 8.2 | Cochrane RoB2 Risk of Bias assessment of the included studies, with the overall certainty of evidence using the GRADE approach. GRADE evaluates Risk of Bias, Inconsistency, Indirectness, Imprecision and Publication bias and we here include the overall Certainty of Evidence to the RoB2 table as a summary of those measures. It is represented as: ⊕⊕⊕⊕ for high quality, ⊕⊕⊕⊖ for moderate quality, ⊕⊕⊖⊖ for low quality, and ⊕⊖⊖⊖ for low quality evidence.

Study	Randomisation Process	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the Reported Results	Overall	GRADE (Certainty of Evidence)
Emre 2004							⊕⊕⊕⊕
McKeith 2000							⊕⊕⊕⊕
Emre 2014							⊕⊕⊖⊖
McDonald 2018							⊕⊕⊖⊖
Mamikonyan 2015							⊕⊕⊕⊖
Aarsland 2002							⊕⊕⊕⊕
Dubois 2012							⊕⊕⊕⊕
Mori 2012							⊕⊕⊕⊖
Ikeda 2015							⊕⊕⊕⊕
Leroi 2004							⊕⊕⊕⊕
Ravina 2005							⊕⊕⊕⊖
Aarsland 2009							⊕⊕⊕⊕
Leroi 2009							⊕⊕⊕⊖
Emre 2010							⊕⊕⊕⊕
Li 2015							⊕⊕⊖⊖
MUSTARDD-PD 2016							⊕⊕⊖⊖
HEADAWAY-DLB 2019							⊕⊕⊕⊕
SYNAPSE 2019							⊕⊕⊕⊖
PRESENCE 2021							⊕⊕⊕⊕
AscenD-LB 2021							⊕⊕⊕⊕
NCT00294554 2017							⊕⊕⊖⊖
NCT03467152 2022							⊕⊕⊕⊕

Low Risk
Unclear Risk
High Risk

Figure 8.2 | Funnel plot of the included studies for neuropsychiatric network meta-analysis. This funnel plot shows the effects estimates of individual studies plotted against their precision, used to check for publication bias in the network meta-analysis. An egger's p-value of 0.3848 suggests there is no significant publication bias.



8.2 Supplementary Information for Chapter 3

8.2.1. Study 2 | Examining the Effects of Rivastigmine on Attentional Networks through the Attentional Network Task

Table 8.3 | Baseline characteristics of study participants who completed the two visits 1.
Independent t-test 2. Pearson's Chi-squared test

	DLB (N=5)	PD (N=5)	Total (N=10)	p value
Age mean (SD)	68.7 (8.0)	75.4 (6.9)	72.0 (7.9)	0.195[1]
Gender Female	1.0 (20.0%)	1.0 (20.0%)	2.0 (20.0%)	1.000[2]
Male	4.0 (80.0%)	4.0 (80.0%)	8.0 (80.0%)	
Education Years mean (SD)	14.2 (2.3)	14.6 (1.5)	14.4 (1.8)	0.752[1]
Handedness Left	1.0 (20.0%)	0.0 (0.0%)	1.0 (10.0%)	0.292[2]
Right	4.0 (80.0%)	5.0 (100.0%)	9.0 (90.0%)	
MoCA_Total mean (SD)	22.6 (2.4)	21.4 (4.3)	22.0 (3.3)	0.600[1]
Age_at_first_symptom mean (SD)	59.0 (5.3)	67.6 (8.8)	64.4 (8.5)	0.182[1]
Age_when_diagnosed mean (SD)	65.0 (6.2)	72.4 (5.9)	69.1 (6.9)	0.110[1]
Rivastigmine_Form Capsule	3.0 (60.0%)	4.0 (80.0%)	7.0 (70.0%)	0.490[2]
Patch	2.0 (40.0%)	1.0 (20.0%)	3.0 (30.0%)	

Table 8.4 | Mean RT (ms) across drug conditions for each cue x flanker condition

	OFF (N=10)	ON (N=10)	Statistics	p value
meanRT_correctCongruentNC				0.07[1]
Mean (SD)	819.7 (205.3)	779.8 (210.0)	t(9)= -2.05	
Range	543.5 - 1073.5	494.8 - 1039.8		
meanRT_correctIncongruentNC				0.174[1]
Mean (SD)	952.6 (223.8)	891.2 (253.1)	t(9)= -1.48	
Range	580.4 - 1239.4	593.8 - 1229.4		
meanRT_correctNeutralNC				0.816[1]
Mean (SD)	770.5 (174.8)	774.6 (191.2)	t(9)= -0.24	
Range	512.9 - 1000.5	555.0 - 989.1		
meanRT_correctCongruentCC				0.047[1]
Mean (SD)	786.8 (234.0)	722.9 (195.5)	t(9)= -2.30	
Range	472.7 - 1112.5	493.3 - 1016.2		
meanRT_correctIncongruentCC				0.420[1]
Mean (SD)	916.2 (218.5)	868.4 (227.6)	t(9)= -0.85	
Range	539.3 - 1161.2	585.8 - 1138.6		
meanRT_correctNeutralCC				0.846[1]
Mean (SD)	751.7 (191.9)	746.4 (215.8)	t(9)= -0.20	
Range	483.3 - 1053.8	499.5 - 1007.3		
meanRT_correctCongruentDC				0.975[1]
Mean (SD)	728.5 (190.3)	729.2 (205.8)	t(9)= 0.03	
Range	473.0 - 946.4	467.6 - 1037.5		
meanRT_correctIncongruentDC				0.476[1]
Mean (SD)	896.3 (213.2)	847.8 (220.2)	t(9)= -0.74	
Range	577.9 - 1238.8	572.4 - 1166.6		
meanRT_correctNeutralDC				0.366[1]
Mean (SD)	736.1 (211.7)	704.1 (202.3)	t(9)= -0.95	
Range	454.2 - 1071.7	473.5 - 1007.7		
meanRT_correctCongruentSC				0.022[1]
Mean (SD)	738.8 (196.8)	704.0 (206.6)	t(9)= -2.75	
Range	486.8 - 1021.5	452.5 - 983.9		
meanRT_correctIncongruentSC				0.217[1]
Mean (SD)	925.8 (252.7)	838.7 (256.6)	t(9)= -1.33	
Range	575.3 - 1241.0	506.4 - 1171.4		
meanRT_correctNeutralSC				0.114[1]
Mean (SD)	725.4 (208.0)	697.3 (207.2)	t(9)= -1.75	
Range	464.0 - 995.4	434.4 - 952.4		

Table 8.5 | Accuracy (%) across drug conditions for each cue x flanker condition

	OFF (N=10)	ON (N=10)	Statistics	p value
propCorrect_congruentNC				0.882[1]
Mean (SD)	90.4 (8.1)	90.8 (9.6)	t(9)= 0.15	
Range	75.0 - 100.0	70.8 - 100.0		
propCorrect_incongruentNC				0.014[2]
Mean (SD)	74.6 (25.6)	88.7 (14.7)	W= 36	
Range	16.7 - 95.8	54.2 - 100.0		
propCorrect_neutralNC				0.039[1]
Mean (SD)	87.1 (9.7)	92.5 (9.0)	t(9)= 2.41	
Range	62.5 - 95.8	75.0 - 100.0		
propCorrect_congruentCC				0.693[1]
Mean (SD)	93.3 (8.1)	94.2 (6.3)	t(9)= 0.41	
Range	75.0 - 100.0	83.3 - 100.0		
propCorrect_incongruentCC				0.338[1]
Mean (SD)	75.8 (22.5)	84.2 (17.3)	t(9)= 1.01	
Range	16.7 - 95.8	50.0 - 100.0		
propCorrect_neutralCC				0.026[1]
Mean (SD)	87.1 (8.9)	93.3 (8.4)	t(9)= 2.66	
Range	75.0 - 100.0	75.0 - 100.0		
propCorrect_congruentDC				0.758[1]
Mean (SD)	92.5 (6.5)	93.3 (7.7)	t(9)= 0.32	
Range	83.3 - 100.0	75.0 - 100.0		
propCorrect_incongruentDC				0.709[1]
Mean (SD)	80.4 (21.0)	83.3 (15.7)	t(9)= 0.39	
Range	25.0 - 95.8	45.8 - 95.8		
propCorrect_neutralDC				0.464[1]
Mean (SD)	90.8 (5.5)	92.9 (11.1)	t(9)= 0.76	
Range	79.2 - 100.0	62.5 - 100.0		
propCorrect_congruentSC				0.574[1]
Mean (SD)	94.6 (5.9)	92.9 (7.4)	t(9)= -0.58	
Range	83.3 - 100.0	75.0 - 100.0		
propCorrect_incongruentSC				0.138[2]
Mean (SD)	73.7 (25.7)	86.7 (15.1)	W = 42.50	
Range	8.3 - 95.8	50.0 - 100.0		
propCorrect_neutralSC				0.186[1]
Mean (SD)	87.9 (14.2)	92.1 (9.3)	t(9)= 1.43	
Range	54.2 - 100.0	70.8 - 100.0		

8.3 Supplementary Information for Chapter 4

Table 8.6 | Mean summary scores of the online cognitive tasks for MCI vs. NC participants

	Cognitive Status	N	Mean	SD	SE
MotorControl	MCI	51	1415.35	1212.48	169.7810
	NC	217	1192.93	497.14	33.7480
Manipulations2D	MCI	51	19.51	8.37	1.1720
	NC	217	20.29	7.85	0.5329
TargetDetection	MCI	51	43.06	16.62	2.3269
	NC	217	42.75	17.17	1.1656
Blocks	MCI	51	7.90	3.18	0.4457
	NC	217	8.10	3.23	0.2194
EmotionDiscrim	MCI	51	40.08	4.27	0.5986
	NC	217	41.88	3.72	0.2525
TrailMaking	MCI	51	69234.72	49597.12	6944.9855
	NC	217	64874.80	39277.23	2666.3122
SwitchingStroop	MCI	51	48.18	6.69	0.9363
	NC	217	49.59	6.33	0.4296
SpatialSpan	MCI	51	4.75	1.25	0.1745
	NC	217	5.18	1.12	0.0759
DigitSpan	MCI	51	6.69	1.63	0.2284
	NC	217	6.80	2.33	0.1579
WordDefinitions	MCI	51	16.96	2.65	0.3715
	NC	217	17.43	2.87	0.1947
VerbalAnalogies	MCI	51	17.16	10.10	1.4143
	NC	217	18.35	10.42	0.7074
ProspectiveMemory_immediate	MCI	17	21.35	1.41	0.3424
	NC	114	21.86	1.66	0.1551
ProspectiveMemory_delayed	MCI	17	18.29	2.47	0.5988
	NC	112	20.01	1.91	0.1809
ProspectiveMemory_immediate_Objects	MCI	34	44.71	7.67	1.3146
	NC	103	46.07	7.85	0.7735
ProspectiveMemory_delayed_Objects	MCI	30	42.27	9.65	1.7623
	NC	95	43.60	8.92	0.9151

Table 8.7 | Mean summary scores of the online cognitive tasks for PD-MCI vs. PD-NC

	PD-MCI (N=23)	PD-NC (N=90)	Total (N=113)	p value
SummaryScore_MotorControl				0.077[1]
Mean (SD)	1711.9 (1799.9)	1309.5 (565.7)	1386.3 (937.0)	
SummaryScore_Manipulations2D				0.877[1]
Mean (SD)	20.0 (7.6)	19.7 (7.8)	19.8 (7.7)	
SummaryScore_TargetDetection				0.349[1]
Mean (SD)	43.0 (14.7)	39.0 (18.3)	39.8 (17.7)	
SummaryScore_Blocks				0.986[1]
Mean (SD)	7.9 (3.0)	7.8 (3.4)	7.8 (3.3)	
SummaryScore_EmotionDiscrim				0.017[1]
Mean (SD)	39.0 (4.3)	41.5 (4.3)	41.0 (4.4)	
SummaryScore_TrailMaking				0.600[1]
Mean (SD)	77290.6 (67318.1)	71128.3 (42830.7)	72304.8 (48150.5)	
SummaryScore_SwitchingStroop				0.812[1]
Mean (SD)	48.3 (7.6)	48.7 (6.7)	48.7 (6.8)	
SummaryScore_SpatialSpan				0.104[1]
Mean (SD)	4.5 (1.4)	5.0 (1.1)	4.9 (1.2)	
SummaryScore_DigitSpan				0.564[1]
Mean (SD)	6.6 (2.1)	6.9 (2.2)	6.9 (2.1)	
SummaryScore_WordDefinitions				0.425[1]
Mean (SD)	16.4 (3.1)	17.0 (3.2)	16.9 (3.2)	
SummaryScore_VerbalAnalogies				0.778[1]
Mean (SD)	15.8 (9.7)	16.5 (10.3)	16.3 (10.1)	
SummaryScore_ProspectiveMemory_immediate				0.418[1]
Mean (SD)	22.0 (1.2)	21.4 (1.6)	21.4 (1.6)	
SummaryScore_ProspectiveMemory_delayed				0.171[1]
Mean (SD)	19.0 (2.8)	20.1 (1.6)	20.0 (1.7)	
SummaryScore_ProspectiveMemory_immediate_Objects				0.388[1]
Mean (SD)	43.6 (7.9)	45.4 (6.8)	44.9 (7.1)	
SummaryScore_ProspectiveMemory_delayed_Objects				0.765[1]
Mean (SD)	42.0 (9.5)	42.8 (8.0)	42.6 (8.4)	

1. Linear Model ANOVA

Table 8.8 | Mean summary scores of the online cognitive tasks for RBD-MCI vs. RBD-NC

	RBD-MCI (N=18)	RBD-NC (N=61)	Total (N=79)	p value
SummaryScore_MotorControl				0.775[1]
Mean (SD)	1056.3 (257.6)	1087.6 (425.5)	1080.6 (392.8)	
SummaryScore_Manipulations2D				0.787[1]
Mean (SD)	20.1 (8.5)	19.5 (7.6)	19.6 (7.8)	
SummaryScore_TargetDetection				0.821[1]
Mean (SD)	42.7 (18.6)	41.7 (15.5)	41.9 (16.1)	
SummaryScore_Blocks				0.718[1]
Mean (SD)	8.1 (3.4)	7.7 (3.3)	7.8 (3.3)	
SummaryScore_EmotionDiscrim				0.723[1]
Mean (SD)	40.9 (4.0)	41.2 (3.5)	41.2 (3.6)	
SummaryScore_TrailMaking				0.169[1]
Mean (SD)	54334.4 (16394.4)	71214.2 (49073.7)	67438.5 (44382.8)	
SummaryScore_SwitchingStroop				0.875[1]
Mean (SD)	49.2 (5.0)	49.0 (6.0)	49.0 (5.8)	
SummaryScore_SpatialSpan				0.765[1]
Mean (SD)	5.3 (1.0)	5.2 (1.1)	5.2 (1.1)	
SummaryScore_DigitSpan				0.287[1]
Mean (SD)	7.2 (1.2)	6.5 (2.7)	6.6 (2.4)	
SummaryScore_WordDefinitions				0.290[1]
Mean (SD)	17.7 (2.1)	16.9 (2.8)	17.1 (2.6)	
SummaryScore_VerbalAnalogies				0.074[1]
Mean (SD)	20.2 (10.2)	15.4 (9.4)	16.5 (9.7)	
SummaryScore_ProspectiveMemory_immediate				0.239[1]
Mean (SD)	20.8 (1.1)	21.8 (1.7)	21.6 (1.7)	
SummaryScore_ProspectiveMemory_delayed				0.038[1]
Mean (SD)	17.2 (2.3)	19.5 (2.2)	19.2 (2.3)	
SummaryScore_ProspectiveMemory_immediate_Objects				0.823[1]
Mean (SD)	43.9 (6.8)	44.6 (10.0)	44.4 (9.0)	
SummaryScore_ProspectiveMemory_delayed_Objects				0.679[1]
Mean (SD)	40.2 (9.1)	41.9 (11.4)	41.4 (10.7)	

1. Linear Model ANOVA

Table 8.9 | Participant feedback on the use of the remote online cognitive battery in the Ketone study: Ratings of ease of use, user-friendliness, willingness to reuse, and additional comments.

Participant ID	1. How easy or difficult was it for you to complete the online cognitive tests? (Rate 1-5, with 1 being very difficult and 5 being very easy)	2. How user-friendly did you find the overall process? (Rate 1-5, with 1 being not user-friendly at all and 5 being very user-friendly)	3. Would you be happy to use this method again to track cognitive changes over time? (Rate 1-5, with1 being very unhappy and 5 being very happy)	4. Do you have any additional comments or suggestions for improving the online cognitive testing experience?
KET001	3	2	4	I am not a regular user of a laptop or pc therefore my first attempts were hampered by that and also my Parkinson's affected my dexterity on the keyboard. This may well have had an impact on the results.
KET002	2	4	3	I did find the questions fairly hard
KET003	3	2	4	I found some of the explanations for the cognitive tests quite confusing and it wasn't until I tried them that I understood what was required. I also found it slightly frustrating that there was no summary or feedback at the end of the tasks to see how I got on
KET004	3	3	2	I was very anxious when doing the online tests. My tremor (right hand) became quite pronounced and on several occasions my fingers hit the wrong key ! There seemed no way of going back and correcting these

				mistakes. After the first attempt I used a mouse and that made it a little easier. By the third online test I was a bit happier, but I did not enjoy this experience.
KET005	5	5	5	Yes please - I'd love to do that every X months, as long as you share the results with me! I thought it worked well. I can see how people uncomfortable with IT might have found it a challenge.
KET006	4	2	3	The process was initially very tedious if I am honest, but once I was used to it - it was a breeze and I could do that regularly now.
KET007	3	3	5	
KET008	4	5	5	I only have a tablet so had to use my partners computer, thus took a few minutes to set up the tests. I found the test challenging but interesting.
KET009	4	4	4	I have one point. Some of the questions had items which were off the page of my laptop using Microsoft Edge as a browser which made answering difficult
KET010	4	5	5	

8.4 Supplementary Information for Chapter 5

Figure 8.3 | Correlations of phonemic fluency total scores and age-corrected DAT SURs across the different ROIs.

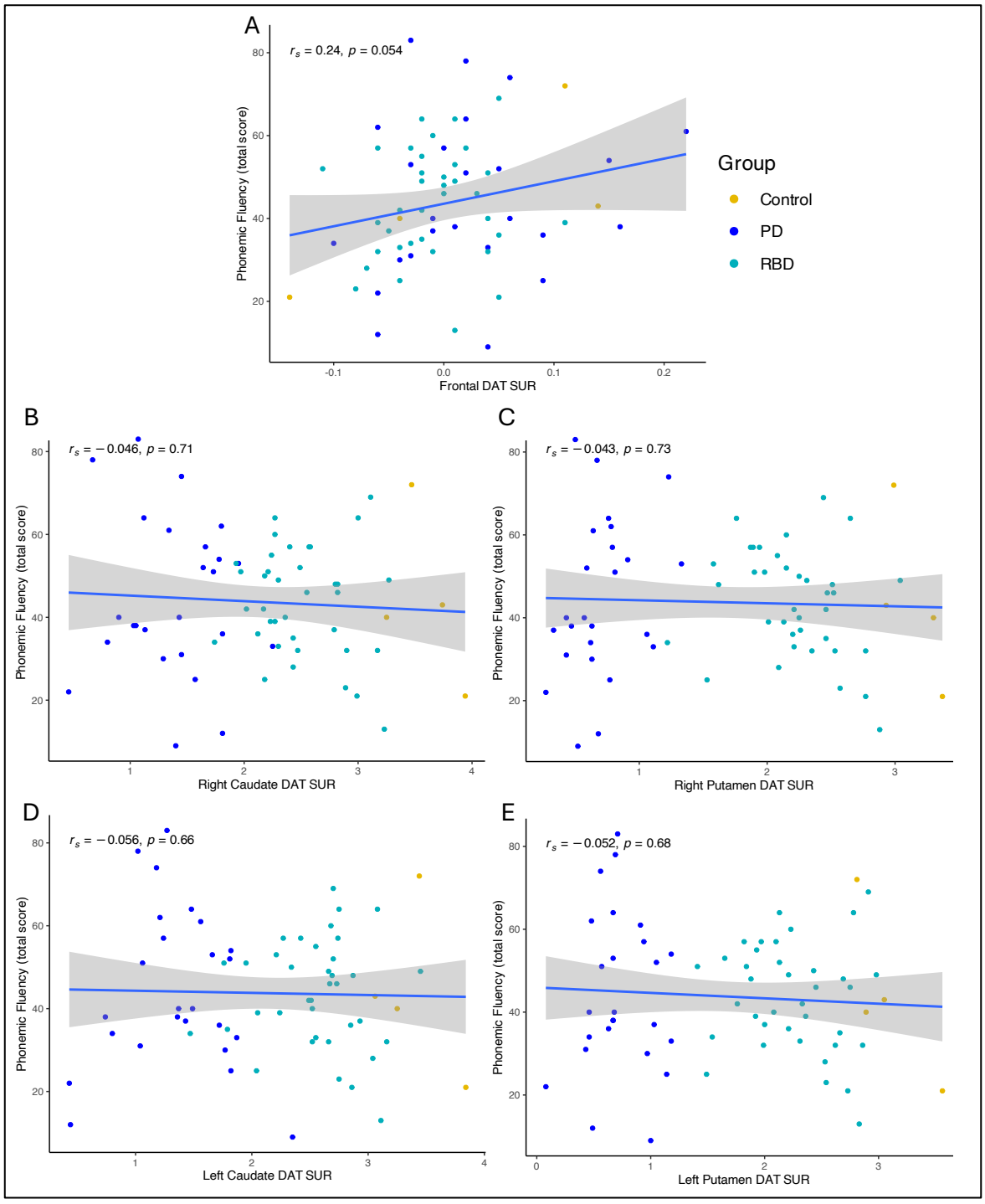


Figure 8.4 | Correlations of semantic fluency total scores and age-corrected DAT SURs across the different ROIs.

