Validating an implicit cognition battery in Parkinson's disease and assessing its sensitivity to pharmacological manipulation



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Thesis submitted for the degree of Master of Science (by Research) in Psychiatry

Michaelmas Term 2019

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Abstract

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Introduction: Cognitive decline is one the most common and debilitating non-motor symptoms associated with Parkinson's disease. Currently, no treatment options exist for cognitive impairment in PD, partly due to the lack of measurement tools sensitive to the subtle early cognitive changes and pro-cognitive pharmacological manipulation in the disease. Implicit cognition shows promise in detecting these otherwise overlooked changes.

Methods: Two studies were performed. One between-subject study comparing the performance of healthy controls (n=30), REM sleep behaviour disorder (n=30), a prodromal population for Parkinson's disease, and Parkinson's disease (n=30) on a previously validated battery of implicit cognitive tasks. The second was a blinded and randomized within-subject study looking at performance on the same implicit task battery in patients with Parkinson's disease (n=30) on two occasions, both 'on' and 'off' their dopaminergic medication.

Results: The first study successfully detected implicit cognitive difference in RBD individuals compared to healthy controls and Parkinson's disease, specifically on the positive location priming effect. The second study failed to detect any changes between Parkinson's patients 'on' and 'off' their medication, although there was an effect on an explicit measure of visuospatial memory.

Conclusion: These results indicate that visuospatial positive priming could be a promising avenue of future research in detecting the early cognitive changes associated with PD. These results also indicate that implicit cognition may not be sensitive to pharmacological manipulation in PD.

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1. General Introduction

1.1 Cognition

"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" Goldman et al. (2018).

This patient experience is typical of what is reported in most clinical interactions, yet patients with Parkinson's Disease (PD) and their carers report cognitive decline as one of their greatest concerns. In fact, according to the Parkinson's disease Community Choice Research Award Program, maintaining cognitive function was one of the most pressing unmet needs voiced by the PD community (Goldman et al., 2018). This is unsurprising considering that higher cognitive impairment in PD has been linked with increased placement in nursing homes (Aarsland, Larsen, Tandberg, & Laake, 2000), heightened caregiver distress (Szeto et al., 2016), higher morbidity and poorer disease outcomes including higher mortality rates (Backstrom et al., 2018). The emphasis on the treatment of the motor aspects of the disease by physicians is coupled with a lack of clinical research trials and existing therapeutic interventions for the cognitive deficits associated with PD.

Cognitive deficits are one of the most common and debilitating non-motor features of PD, often preceding the motor symptoms by many years (Naik, Kolikonda, Pittampalli, & Lippmann, 2018). Cognitive impairments in PD are diverse, non-specific and have been found to be influenced by additional factors such as social isolation, medical illness and in particular co-morbidity with depression (G. M. Halliday, Leverenz, Schneider, & Adler, 2014). Cognitive

impairments affect a large majority of PD patients and cover a broad spectrum in terms of their severity, progression rate and affected areas of functioning. They can be demarcated into four groups distributed along a chronological continuum: normal cognition, subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Parkinson's disease dementia (PDD) (Aarsland et al., 2017; Goldman et al., 2018). Patients tend to progress through the same stages of cognitive deterioration, from normal cognition to eventually developing PDD in approximately 80% of cases (Hely, Reid, Adena, Halliday, & Morris, 2008).

The first sign of cognitive impairment in PD is subjective cognitive decline (SCD) which tends to be subtle changes in daily functioning, behaviour, and mood, detected by the patient themselves or their family members. SCDs are typically undetectable using objective cognitive measures, yet have proven to reliably predict future cognitive decline in neurodegenerative diseases, specifically the development of MCI in Parkinson's (Erro et al., 2014).

The following stage in cognitive decline is the appearance of MCI, operationally defined in diagnostic and assessment guidelines by the International Parkinson and Movement Disorder Society (MDS) (Litvan et al., 2012). MCI serves as an umbrella term to define the heterogeneous cognitive deficits considered abnormal for age, which lead to the eventual development of PDD (Aarsland et al., 2017; Biundo, Weis, & Antonini, 2016). It is considered a prodromal stage of dementia, with increased risk for developing PDD (Hoogland et al., 2017), although in certain unusual cases patients revert from MCI to normal cognition (Pedersen, Larsen, Tysnes, & Alves, 2017). The processes governing the transition of MCI to other cognitive states are still unknown, specifically whether MCI and dementia function under distinctive neuropathological and genetic mechanisms, or whether they represent different stages

of severity in the same pathology (Goldman & Litvan, 2011). The frequency of MCIs are approximately 20-50% in the non-demented PD population in contrast to 4% in age-matched controls (Goldman & Litvan, 2011), however their numbers have been difficult to estimate and describe due to a lack of uniform measurement and diagnostic criteria in research studies (Zhai et al., 2016). The gold standard for diagnosis remains a comprehensive neuropsychological evaluation for the identification of MCI, yet due to time and financial cost this method is not readily accessible to the general public (Zhai et al., 2016). As such, the MoCA (Montreal Cognitive Assessment) is widely used in the PD community and has been generally accepted in both clinical and research settings as a rigourous and sensitive tool, with which to detect the between-stage differences that exist between healthy cognition, MCI and PDD (Nasreddine et al., 2005).

The transition from MCI to PDD occurs at the point in which cognitive decline interferes with normal functioning and daily activities, usually when at least two or more independent areas of cognition are impaired (Aarsland et al., 2017). Parkinson's dementia is diagnosed if the onset of dementia occurs a year or more after the onset of Parkinson's disease (Poewe et al., 2008). Patients with PD have almost a six-fold increased risk of developing dementia (Thanvi, Munshi, Vijaykumar, & Lo, 2003). Despite this high risk, there is usually a long period of MCI preceding the onset of frank dementia, lasting on average ten years but which can reach up to twenty (Aarsland et al., 2017; Hely, Reid, Adena, Halliday, & Morris, 2008). Unfortunately, once cognition has deteriorated to the point of dementia, disease progression is oftentimes too advanced for any potential disease-modifying intervention. Dementia poses a serious threat to the quality of life, independence and functioning of the sufferer, and significantly increases the

caregiver burden and health-related costs for both the individual and the healthcare system (Aarsland et al., 2017).

The clinical features of non-demented cognitive impairment in Parkinson's are varied, yet overall known to predominantly affect single non-amnestic domains, most commonly impairments in executive function (Goldman & Litvan, 2011). Other impaired domains include psychomotor speed, visuospatial abilities, language and memory translating into slowed processing, difficulty with multitasking and planning, decreased attention and concentration, impaired registration and retrieval of novel stimuli and word finding disturbances (Goldman & Litvan, 2011). These deficiencies are reflected in tasks which necessitate cognitive sequencing, planning, set maintenance or shifting to novel stimuli, registration and free recall (Alevriadou, Katsarou, Bostantjopoulou, Kiosseoglou, & Mentenopoulos, 1999; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Owen et al., 1992).

Until recently, cognition in PD has typically been under-represented in clinical practice and research. The cognitive profile of PD is heterogeneous in severity, progression and symptoms, making it difficult to quantify, track and label. However, the recognition and understanding of the profile of cognitive impairment associated with PD is increasing as a more in-depth characterisation of the phenotypes is achieved.

1.2 Medication

While no cure exists for PD, motor symptoms such as bradykinesia and rigidity are managed through anti-parkinsonian medications, the most common of which is levodopa (L-dopa). L-dopa is prescribed to almost all patients upon PD diagnosis regardless of severity, symptoms, and disease stage. It is used to replace the depleted supply of dopamine in the basal ganglia which

results from the death of dopaminergic neurons in the substantia nigra in the parkinsonian brain. Since the blood brain barrier in impermeable to dopamine, patients are instead given its amino acid pre-cursor, L-dopa, which can traverse into the central nervous system and be converted into dopamine by the enzyme aromatic l-amino acid decarboxylase. It has been the gold standard treatment for the motor symptoms of PD over the last 50 years and offers substantial relief from motor symptoms (Poewe, Antonini, Zijlmans, Burkhard, & Vingerhoets, 2010). However, certain limitations accompany levodopa treatment, such as the high dosages necessary to achieve therapy due to high levels of peripheral metabolism leaving only a small proportion of the drug to excurse an effect on the brain. To prevent this, carbidopa is prescribed alongside L-dopa to reduce the peripheral metabolism of L-dopa and increases the bioavailability of the drug in the brain. However, significant negative side-effects can accompany high dosages, usually in advanced cases where the costs of taking the drug can outweigh its benefits. This is also common in women who are usually given the same starter dose as men instead of adjusting dosage in accordance to patient weight. In these cases, uncomfortable side-effects such as dyskinesia occur, to which the physicians will respond by replacing levodopa with a dopamine agonist. Finally, as dopamine depletion is only one of the many pathological consequences of Parkinson's disease, L-dopa does not treat the full spectrum of symptoms presented by patients and there remains a pressing need to develop appropriate alternative or additive treatment methods (Hely, Morris, Reid, & Trafficante, 2005). In particular, pharmacological therapies available for the cognitive deficits associated with PD are very limited. Available treatments exist only for PDD and consist of cholinesterase inhibitors like rivastigmine. This medication counteracts the depletion of acetylcholine throughout the brain by slowing the breakdown of the already sparse chemical, enabling it to have a larger effect in individuals with PD.

Cholinesterase inhibitors have been shown to improve executive function, memory, attention, processing speed, language abilities, overall cognitive functioning as well as global impressions of cognitive change as measured by a clinician while leaving visuospatial cognition intact (Meng, Wang, Song, & Wang, 2019). No therapies currently exist for the cognitive deficits seen before the appearance of PDD making this is a priority area for research and treatment development.

While dopaminergic medication prescription is widespread, the effects of L-dopa on cognition remain unclear. Results from the studies that have explored the cognitive impact of the medications have been heterogeneous in both method and results, in part due to a lack of unified methodology to quantify cognitive impairment, both at baseline and following pharmacological intervention. One approach has been to contrast cognitive performance while 'on' vs 'off' medication. However, the results have been mixed with studies finding an improvement, no change or worsening of cognitive function with L-dopa treatment (Robbins & Cools, 2014). In addition, it has been previously shown that early stage Parkinson's is more responsive to medication than mid to late stage pathology, indicating that medication may interact with other factors, such as time since diagnosis, when altering cognitive function (Bravi et al., 1994; Manza, Amandola, Tatineni, Li, & Leung, 2017). Given that demographic data can vary greatly between cohorts, this could offer an explanation as to the contradictory findings in previous literature.

A further explanation for the inconsistent findings is that the effect of L-dopa on cognitive function is dependent on the type of cognition tested. According to the dual-syndrome

hypothesis, it has been suggested that cognitive functions mediated by the basal ganglia and associated networks may be improved by dopaminergic medication, given that the treatment is compensating for a dopaminergic deficit (Robbins & Cools, 2014). However, cognitive functions associated with prefrontal cortical networks may even be impaired by levodopa, due to dopaminergic overstimulation. Further, non-dopaminergic systems are also affected in PD, and cognitive functions associated with these networks are likely to be unaffected by dopaminergic medication.

1.3. Neurobiology

While the cause of Parkinson's disease remains unknown, it is believed to arise from an interplay of genetic and environmental factors affecting numerous fundamental cellular processes (Kalia & Lang, 2015). These changes translate into extensive large-scale pathology throughout various regions of the nervous system involving multiple neurotransmitter systems and protein aggregates, the most well characterised of which are Lewy bodies (Kalia & Lang, 2015). Lewy bodies are aggregates of misfolded ∝-Synuclein protein which accumulate in certain cells in specific areas of the brain, eventually causing highly selective neuronal loss in the locus ceruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus (G. M. Halliday et al., 2014; Kalia & Lang, 2015). The classic motor impairments which characterize PD have been attributed to the apoptosis of dopaminergic cells in the ventrolateral tier of the substantia nigra, an area which projects to the dorsal putamen of the striatum and which has been previously closely associated with motor and reward processes (Kalia & Lang, 2015). Selective dopaminergic apoptosis in this area is thought to be responsible for the tremor and bradykinesia observed in PD (Kalia &

Lang, 2015). While dopaminergic neuron loss is a normal process of aging, PD dopaminergic loss has been shown to happen in a particular order, which is different to that which is associated with traditional aging (Lang & Lozano, 1998).

Advances in our understanding of the neurobiology of PD suggest that this model of the disease may be incomplete (Parker et al., 2018). Recently, it has been shown that Lewy pathology migrates from the peripheral nervous system, specifically from the gut, up the vagus nerve and into the brain which could explain why gastrointestinal complications, such as diarrhoea and constipation, are some of the earliest reported non-motor symptom (NMS) preceding PD diagnosis (Braak, Rub, Gai, & Del Tredici, 2003; Kim et al., 2019). Lewy-body pathology has also been associated with certain NMS occurring decades before the onset of Parkinson's disease. This recent discovery builds on Braak's staging model illustrated in *Figure 1,* which delineates the neuroanatomical Lewy pathology behind each progressive stage of PD and how it spreads in a rostral manner from the brainstem until it eventually encompasses the entire brain and reaches cortical regions causing severe executive cognitive dysfunction such as dementia (Braak et al., 2003).

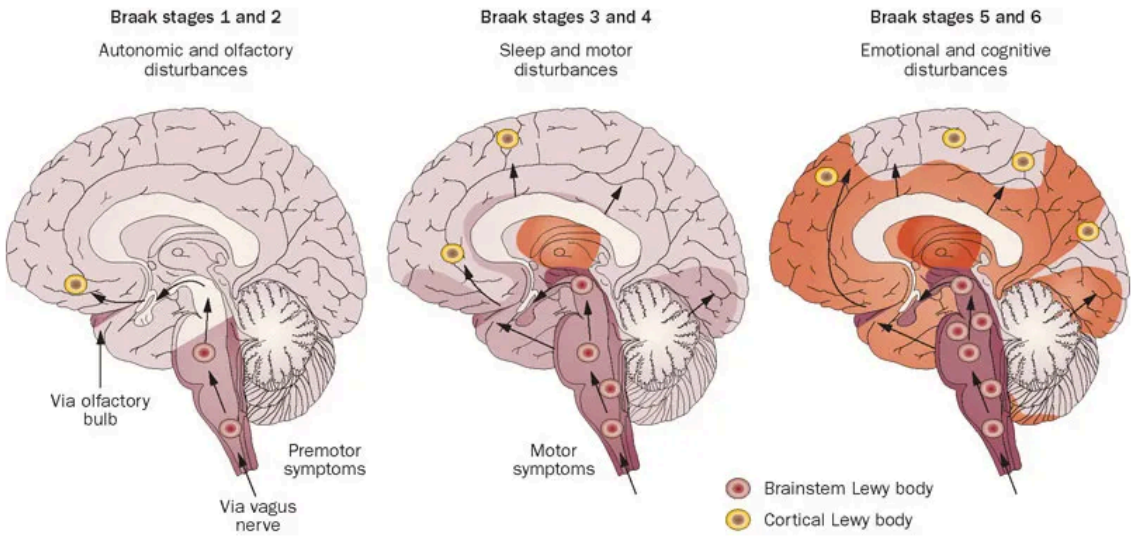


Figure 1. Braak's staging model demonstrating PD progression throughout the brain adapted from Doty (2012); G. Halliday, Lees, and Stern (2011).

While PD affects many different regions in the brain, the cognitive impairments are believed to largely stem from a fronto-striatal syndrome which affects executive function in early disease stages (G. M. Halliday et al., 2014). Animal models have shown that chronic low-dose MTPT (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treatment, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra, mimics the same deficiencies associated with mild cognitive impairment in PD in primates as it does in humans, in advance of motor impairment appearance (Schneider & Kovelowski, 1990; Schneider & Pope-Coleman, 1995; Schneider & Roeltgen, 1993). As the disease progresses, a widespread failure in neurotransmitter systems including dopaminergic, noradrenergic, serotoninergic and cholinergic systems appears (Cova & Priori, 2018). This is further suggested by post mortem observation of individuals with PDD having shown widespread neurodegeneration throughout cortical and limbic areas (G. M. Halliday et al., 2014). Basal ganglia pathology, particularly in its associative (cognitive) areas like the caudate nucleus, may also contribute to cognitive deficits (Goldman et al., 2018; G. M. Halliday et al., 2014).

In addition to the unclear aetiology of PD, the disease is marked by heterogeneity in severity, progression and symptoms. This has led to the hypothesis that there exist different subtypes of PD, and even different pathologies within PD. Clinically, labels such as “idiopathic” or “tremor-dominant” are used by physicians to diagnose patients. However, they are often based on symptoms briefly examined in clinic, in combination with patient accounts. In practice, these labels are largely overlooked, as treatment regimens remain uniform regardless of subtype or symptom characterisation. This, as well as a lack of clinical consensus, means that there is no existing reproducible methodology for diagnosing subtypes.

In research, the most widely used subtypes are tremor-dominant, akinetic-rigid and mixed; however, no fixed criteria exist to describe typology with large variability between studies in terms of subtypes used (Ma et al., 2018; Nutt, 2016; Thenganatt & Jankovic, 2014). The most recent advances in subtyping use mass data driven methods to determine clusters by symptom aggregation; these approaches have largely led to 4 subtypes which differ in terms of impairment and progression across clusters (Lawton et al., 2018; van Rooden et al., 2011). However, these phenotypes could be manifestations of varying degrees of progression of the different symptoms of Parkinson's (Nutt, 2016). The validation of these various models is important for the development of subtype-specific biomarkers and bespoke treatment options, catered to the individual's specific symptomatic profile (De Pablo-Fernandez, Lees, Holton, & Warner, 2019; Thenganatt & Jankovic, 2014).

1.4 Prodromal Phase

An interesting facet of Parkinson's disease is its long pre-diagnostic stage which can be further subdivided into three sections: the first is preclinical PD, when the neurodegenerative processes have commenced but there are no outwardly evident symptoms or signs (Berg et al., 2015). This is followed by prodromal PD, where symptoms and signs are present, but remain insufficient for diagnostic purposes. In a third and final stage, clinical PD is diagnosed in the presence of the classic motor signs. In addition to these three stages, an individual can be predisposed for PD before even having entered the pre-clinical stage by fulfilling certain genetic criteria, like LRRK2 or GBA mutations, being male, which increases your chances of developing the disease by two, or environmental factors, like exposure to pesticides (Cerri, Mus, & Blandini, 2019; Noyce, Lees, & Schrag, 2016).

The pre-diagnostic stage, characterized by the progressive destruction of dopaminergic basal ganglia neurons, is very long and usually lasts until one or more of the four classical PD motor symptoms arise. They consist of bradykinesia, rigidity, tremor and postural instability and only appear once approximately 80% of dopaminergic neurons have been lost (Cheng, Ulane, & Burke, 2010). This means that a definitive diagnosis and the subsequent start of treatment begins in the very late stages of disease progression. Even then, PD diagnosis can only be confirmed with certainty during autopsy, with a significant proportion of cases either misdiagnosed, undiagnosed or displaying a mixed phenotype encompassing multiple possible diseases. According to one study, at least 15% and up to 35% of individuals with a diagnosis of Parkinson's disease do not fulfil the strict clinical criteria of the disease upon post mortem examination (Schrag, Ben-Shlomo, & Quinn, 2002). Additionally, it has been estimated that around 20% of individuals remain undiagnosed in the community creating a large gap in treatment provision (Schrag et al., 2002).

In many cases, this late-stage or entire lack of PD diagnosis means that much of the cognitive pathology associated with PD goes undetected. One study found that 19% of patients were already suffering from objectively measurable MCI at the time of PD diagnosis (Aarsland et al., 2009). As such, it is estimated that once a disease-modifying therapy is developed, be it neuroprotective or disease-reversing such as stem cell regeneration, the current level of neuronal deterioration at diagnosis will probably be too important for the novel therapy to significantly impact the course of pathology (Noyce et al., 2016). Consequently, scientific focus has shifted to earlier detection of the disease, with growing recognition of the importance of the NMS in PD, which typically appear years before the onset of motor impairment (see *Figure 2*).

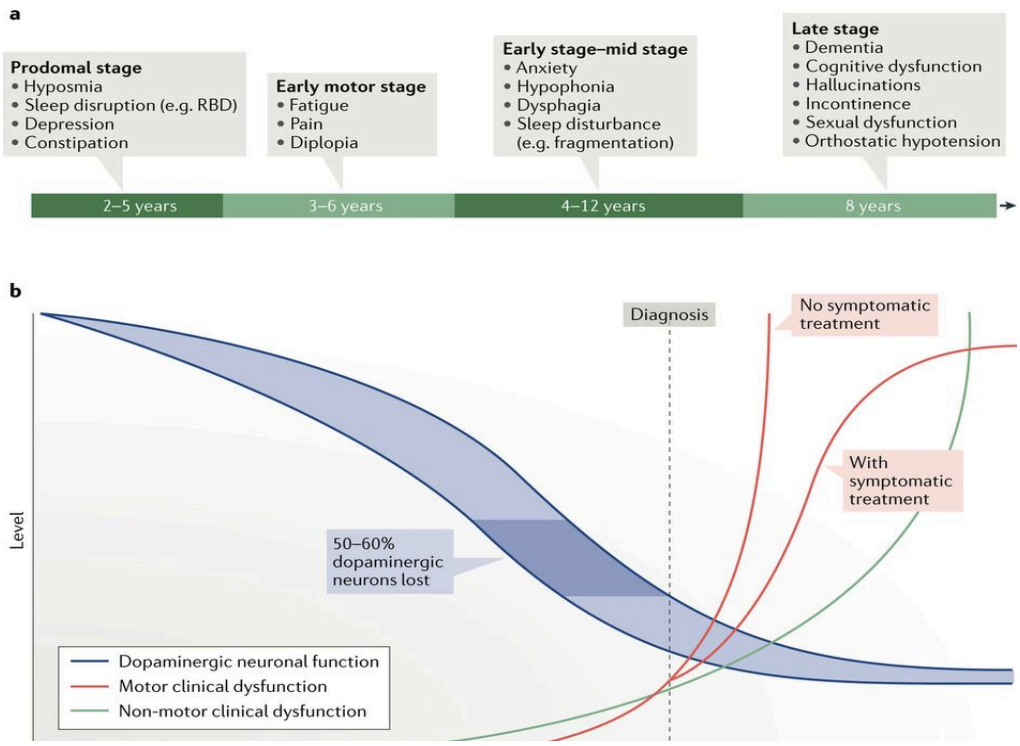


Figure 2. A timeline of the stages of prodromal Parkinson's disease (Schapira, Chaudhuri, & Jenner, 2017)

Over 50 NMS exist in PD; often these are present in the early stages of the disease, but are difficult to pinpoint due to their varied nature and high prevalence in the general population (see *Figure 3*). Approximately half of early diagnosed PD cases report suffering from one or more NMS (Baig et al., 2015). Further, while NMS are often times pervasive and greatly affect the quality of life of PD patients, more than 50% of are not identified in clinical practice and go untreated (Weintraub, Comella, & Horn, 2008). The most commonly reported NMS are autonomic functions such as incontinence but can range from fatigue, loss of olfactory sense to sleep problems and depression (Gallagher, Lees, & Schrag, 2010). Studies have also shown that PD is oftentimes preceded by diagnoses of anxiety, depression, constipation and erectile dysfunction (Noyce et al., 2016). High levels of chronic pain, fatigue and insomnia, due in part to the comorbidity of PD with sleep disturbances like REM sleep behaviour disorder (RBD), add

additional strain to the lives of PD patients and predispose them to further mental illnesses and psychiatric disturbances (Grover, Somaiya, Kumar, & Avasthi, 2015).

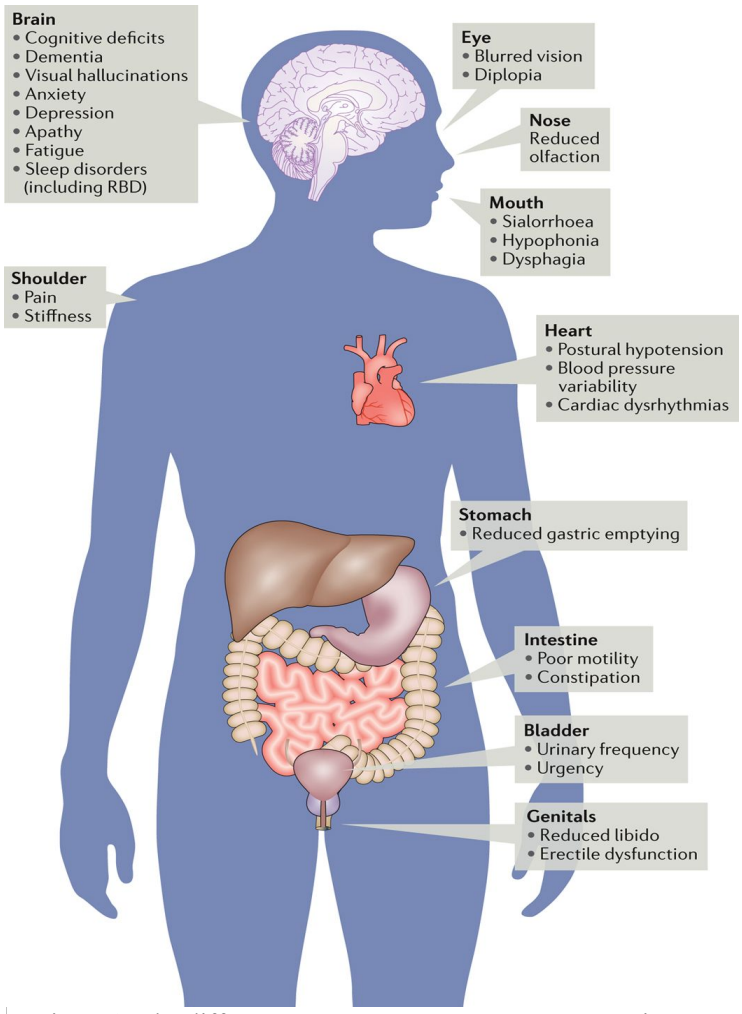


Figure 3. The different non-motor symptoms accompanying PD (Schapira et al., 2017).

The most reliable early non-motor features remain sleep disorders, specifically RBD. RBD is a parasomnia characterized by REM sleep without atonia, resulting in an abnormally high level of skeletal muscle activity (Kempfner, Jennum, Nikolic, Christensen, & Sorensen, 2013). RBD sufferers lose the sleep paralysis that usually accompanies REM sleep and have very vivid, violent dreams that they tend to "act out". The term idiopathic RBD (iRBD) is used when RBD is not yet concomitant with another disease, however the scientific community has so widely accepted RBD as an early manifestation of neurodegenerative disease that the very notion of "idiopathic" RBD has been called into question (Ferini-Strambi et al., 2004; Mahowald, 2006; Terzaghi et al., 2008). The term is still widely employed however and will be

used in this thesis to designate individuals that have received a diagnosis of RBD but not yet one for an ∝-synucleinopathy.

It has been previously shown that 25% of iRBD sufferers will convert to a neurodegenerative disease within 3 years, 40% in 5 years and long-term prospective studies indicate that that over 80% of individuals with iRBD will eventually go on to develop an ∝-synucleinopathy (Postuma, Iranzo, et al., 2015; Schenck, Boeve, & Mahowald, 2013), with 40-65% developing PD after an average of 10-15 years (Schenck et al., 2013). While RBD is rare in the general population, only affecting approximately 0.5% of individuals (Gagnon, Bertrand, & Genier Marchand, 2012), RBD is common and often under-recognised in patients with PD, estimated to be present in about half of PD cases (Rolinski et al., 2014). The close association between RBD and PD means that it is a very powerful and promising prodromal marker for PD (Postuma, Gagnon, Bertrand, Genier Marchand, & Montplaisir, 2015). However, it is important to note that patients with RBD do not always develop Parkinson's disease, with some converting to other types of synucleinopathy, including Lewy Body Dementia and multiple system atrophy (Noyce et al., 2016).

Cognitive impairments often accompany the parasomnia. Indeed, RBD patients suffer from MCI at a rate of approximately 50%, compared to the 8% in the general population, accounting for age and sex (Gagnon et al., 2009). This figure increases to 73% for PD sufferers with concomitant RBD (average time since diagnosis of 4.9 years), compared to only 11% of PD patients without RBD (average time since diagnosis of 5.8 years) (Gagnon et al., 2009). iRBD converters to PD also tend to have higher levels of cognitive impairment compared other forms of PD (Gagnon et al., 2009; Jozwiak et al., 2017; Schenck et al., 2013). This has led to the

hypothesis that RBD is associated with a specific cognitively impaired subtype of PD, characterized by a poorer cognitive outcome but also differences in autonomic and motor functioning. It is believed that the cognitive deficits observed in RBD share a similar background to those seen in Parkinson's disease including attention, executive function, decision-making, verbal episodic memory and non-verbal memory (Marques et al., 2010; Massicotte-Marquez et al., 2008; Sasai et al., 2012; Youn et al., 2016). A definitive consensus on areas affected has yet to be reached however, with visuospatial impairments in RBD still debated and a link between degree of impairment and overall cognitive decline suggested (Fantini et al., 2011; Gagnon et al., 2009; Iranzo et al., 2006; Molano et al., 2010).

1.5 Cognitive Biomarker development

Cognitive biomarkers are objective, quantifiable cognitive characteristics of a biological process (Strimbu & Tavel, 2010). They do not rely on animal models for any stage of development or validation. This is attractive due to the poor predictive validity of PD biomarkers in rodent studies, specifically their limited predictability concerning the efficacy of pro-cognitive drugs in future human research (Millan et al., 2012). Secondly, the long period between the onset of neuronal degeneration and the appearance of PD symptoms has created a rich window of opportunity in which to measure the progressive cognitive decline and the effect of novel therapeutics in prodromal groups. This is compounded by the fact that the cognitively impaired profile associated with RBD, the most frequently used prodromal population in disease monitoring and modifying treatment research, suggests that cognitive biomarkers may be particularly sensitive to early changes in this target population. Finally, measuring cognition through computer programmed tasks lends itself well to efficient, large-scale, cost-effect clinical and research implementation compared to other invasive and costly diagnostic methods like

biological or neuroimaging methods. Unlike the motor symptoms of PD which are universally measured by the MDS Unified Parkinson's Disease Rating Scale (UPDRS) developed by Fahn and Elton (1987), the gold-standard for PD motor impairment measurement, no uniform diagnostic tool currently exists for the cognitive deficits seen in RBD and early PD. This has resulted in researchers using an array of different methods and tasks to measure cognition within these pathologies, which has made it difficult to create diagnostic criteria, and to quantify and compare different studies, individuals and pathological stages of disease.

As mentioned previously, the MoCA is a used as a widespread measure of cognitive impairment used within and outside PD studies. It is an objective and general test of cognitive function, validated against the Mini-Mental State Examination (MMSE) as sensitive to the changes associated with MCI and PDD (Nasreddine et al., 2005). Further, the MoCA is more sensitive than the MMSE to the cognitive decline associated with PD and a better predictor of the future development of MCI and PD in healthy individuals (Hu et al., 2014). While this task has been validated as robust, it remains too coarse to detect mild cognitive deficiency and is mostly effective when used at later stages in the disease (Kletzel, Hernandez, Miskiel, Mallinson, & Pape, 2017). The MoCA is of limited utility as a measure of mild cognitive impairment; many individuals perform at ceiling and it is possible to use compensatory cognitive strategies to mask mild impairments (Kletzel et al., 2017). Additionally, while the MoCA can identify the differences separating healthy cognition, MCI and dementia, it is insensitive to the wide spectrum of changes happening within each group. Further, it is not adapted for use as an intermediate marker for short term change and treatment. This has created a need for a novel

experimental medicine markers that are sensitive to mild cognitive changes and pharmacological intervention.

1.6. Implicit cognition

One way to circumvent the limitations of measuring cognition using tools such as the MoCA, is to use tasks that measure implicit cognition, which are processes that are outside of full conscious awareness (understanding and remembering information without consciously exerting effort to rote learn information). Aspects of cognition are an important scaffold for everyday function and can be easily measured using computer-based tasks. Such measures are a useful alternative to clinician-based rating scales, and offer a degree of granularity and sensitivity that is lacking in these more explicit measures. Implicit measures are less vulnerable to ceiling effects and they may therefore be relatively more discriminative and sensitive to pharmacological manipulation. Additionally, since implicit tasks measures processes that are outside of full conscious awareness, they are cannot be overcome by strategies.

There is evidence that this hypothesis holds true in depression as implicit cognitive measures have been shown to be more sensitive to the subtle cognitive changes of antidepressant medication (Harmer, Cowen, & Goodwin, 2011). These measures have overcome high levels of placebo effect and can predict, following very short term treatment, the delayed clinical efficacy of SSRIs (Harmer et al., 2009). The sensitivity of implicit measures to pharmacological manipulation has also been demonstrated using pro-cognitive drugs, such as modafinil and methylphenidate, further highlighting the potential of implicit cognitive measures as effective biomarkers for use in the development of pharmacological treatments for the cognitive

impairments associated with PD (Klinge et al., 2018; Pringle, Browning, Parsons, Cowen, & Harmer, 2013). In Parkinson's disease, preliminary work has suggested that implicit measures may be more sensitive than explicit measures to the cognitive changes seen in the early stages of the disease. For example, Filoteo, Maddox, Salmon, and Song (2007) found that impaired performance on an implicit rule-learning task, but not an explicit version of the same task, is associated with poorer motor scores on the UPDRS 1.6 years later. Implicit cognition has yet to be characterised in RBD, however as previously stated some explicit measures have been shown to be as similarly impaired in PD, for example short term visual memory as demonstrated by Rolinski et al. (2016) however findings vary based on tasks and remain controversial in certain instances. Indication that implicit cognition may be affected have also been demonstrated by findings such as an overall slowing of electroencephalogram in RBD detected by Fantini et al. (2003) which researchers have attributed to early sign of central nervous system dysfunction, perhaps paralleled by subclinical cognitive deficits. Therefore, both findings in RBD and early stage PD populations indicate a potential sensitivity to implicit cognitive tasks.

The aim of this thesis is therefore to determine whether a battery of previously validated implicit cognitive tasks is sensitive to the impairments associated with early stage PD and whether it is sensitive to pharmacological manipulation. This implicit cognition task battery (ICTB) has been developed within our research group and shown to be sensitive to the effects of modafinil and more sensitive than explicit measures to the cognition enhancing properties of the dopamine agonist methylphenidate in healthy volunteers (Klinge et al., 2018; Pringle et al., 2013). Given this, and previous work suggesting that implicit measures may be particularly sensitive cognitive biomarkers within the context of treatment development, the studies described in this thesis are

designed to further investigate whether this task battery might be useful in the future development of novel therapeutic agents for PD.

This implicit task battery measures different aspects of implicit cognition including priming, contextual learning, association formation and reversal and rule generalization. To contrast these results with a measure of explicit cognition, an explicit visuospatial memory task was also administered. Given that this battery of cognitive tasks has demonstrated sensitivity to pro-cognitive pharmacological intervention and that certain paradigms in the battery have been tested in Parkinson's disease, like the acquired equivalency paradigm, a scientific interest lies in administering this implicit cognitive battery in PD, to evaluate its sensitivity to cognitive changes and its suitability as a cognitive biomarker for drug development.

The first task in the implicit battery is the location priming task. Priming is a memory effect where prior exposure to a probe stimulus influences the subsequent response to a prime stimulus. Priming effect is one of the most widespread measures of implicit cognition, with studies exploring both positive (repetition) and negative (inhibition) priming of different types such as associative, perceptual, conceptual and spatial. It is a form of implicit repetition learning where participants are tested on either their memory of a probe target (positive priming) or probe distractor stimuli (negative priming). The task used in our battery measures short term memory and reflexive reaction time using two location priming mechanisms, the negative priming (NP) component uses inhibition while the positive priming (PP) component relies on facilitation. Participants are presented with three types of trials: positive, negative and control. Negative priming trials are trials where the location of the distractor stimulus on the prime display becomes the target on the ensuing probe display. Positive priming trials represent those in which

the target stimulus location stays the same in prime and probe. Control trials are those in which the target is in a position unrelated to the probe trial. NP and PP effects are calculated by individually comparing the negative and positive trials respectively to the control trials. Results from previous literature on location priming in PD have been mixed. Troche, Trenkwalder, Morelli-Canelo, Gibbons, and Rammsayer (2006) found that negative priming effect was unchanged in PD compared to healthy individuals, while describing an enhanced priming effect for the positive trials. Another study, which looked exclusively at negative priming, found a reduction of negative priming in PD compared to healthy individuals (Filoteo, Rilling, & Strayer, 2002). Others still, have found an increased NP in PD participants (Wylie & Stout, 2002). To better understand these polarised findings within the same pathology, a joint review was conducted between Stout, Wylie, and Filoteo (2002), in which they correlated performance to a variety of clinical characteristics, thus attributing these opposite findings to the varying clinical profile of the two cohorts. This is in line with findings from Troche et al., (2006) who discovered a link between priming effect and bradykinesia as well as depression in PD, but not healthy controls, solidifying the hypothesis that priming effect may interact differentially with clinical characteristics in PD and HC. Baseline reaction time differences between healthy controls and Parkinson's patients indicate motor impairments in PD may play a role in the findings as they were demonstrated in Wylie & Stout's cohort but not that of Filoteo's.

Contextual cueing is the second task in the implicit battery. It measures the implicit learning of contextual information and how it guides the deployment of visual attention. Participants are shown multiple arrays of the same items, some repeated and others novel. The task measures whether participants implicitly remember tasks that they have previously seen and the relative

response time of repeated arrays compared to novel ones. A previous study found that contextual cueing was impaired in PD patients, as they fail to learn repeat trials in contrast to healthy controls on repeated trials versus novel ones (van Asselen et al., 2009). In contrast, other variations of the task found that PD participants were not impaired in reaction time compared to healthy controls (Li, Diaz-Brage, Fernandez-Lago, & Fogelson, 2018; Sisk, Twedell, Koutstaal, Cooper, & Jiang, 2018). Another study did not find differential performance between cognitively normal older adults and amnesic MCI patients, but did find a relationship between reduced hippocampal volume and lower performance, which has also been linked to PD (Negash et al., 2015). These mixed findings tend to indicate that different types of measures and different versions of the contextual cueing tasks bring out a variety of different results with regards to PD.

The third task in the battery used by Klinge et al. (2018) is the acquired equivalency task adapted from Myers et al. (2003). Acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent increases generalization between them. It has been examined in animals, such as pigeons (Hall, Ray, & Bonardi, 1993) and rats (Honey & Hall, 1991; Spiker, 1956), in humans, both children (Spiker, 1956) and healthy adults, as well as in a variety of cognitive disorders like schizophrenia (Weiler, Bellebaum, Brune, Juckel, & Daum, 2009), post-traumatic stress disorder (Kostek et al., 2014) and epilepsy (Khalil, Abo Elfetoh, Moftah, & Khedr, 2015). Our team used the "Fish" variation of the task where participants were asked in a first instance to learn associations between cartoon people and fish. In a testing phase, they are then asked to recall these previously learnt associations and deduce novel ones based on rules implicitly communicated though feedback in the first phase. It examines explicit feedback learning in the acquisition phase of the task and implicit rule learning by measuring generalisation in the transfer phase of the task. It has previously been administered in

Parkinson's disease patients by Myers et al. (2003), which found improved performance in the initial explicit rule learning but worse in the implicit generalisation phase compared to healthy controls. This finding is somewhat consistent with the study from Filoteo et al. (2007), which found that implicit rule learning was impaired in Parkinson's disease, while explicit rule learning remained unaffected.

The final implicit task in the battery is the Implicit Symbol Location Prediction Task (ISLP) used in this study is a modified version of the Intra-dimensional Extra-dimensional (IDED) set shifting task which was developed by Pringle et al. (2013). The ISLP is a set-shift dot-probe task in which the location of a target stimulus is probabilistically predicted by a preceding stimulus and the rules governing the relationship between the preceding stimulus and the target change over the course of the task. This task examines implicit rule learning and reversal learning. This is done by measuring reaction time and accuracy response to a target positioned either behind an implicitly learned predictive stimuli and a decoy stimuli. In a large majority of trials, the target is placed behind a predictive shape, implicitly teaching the participant where to expect the location of the target in future trials. In a minority of trials, the target was placed behind the non-predictive stimuli. Reaction times are compared for both types of trials to evaluate whether individuals have implicitly learnt to predict the identity of the predictive shape. This dimension of the task measures implicit rule learning. Additionally, the predictive shape changes partway through the task, subdividing all trials into either acquired (first half) or reversal (second half) trials. Reaction times are compared for these two types of trials to evaluate how flexible individuals are in recoding a rule when presented with novel information. This dimension of the task evaluates reversal learning. Previously, patients with Parkinson's disease have been shown

to be impaired on the extra-dimensional portion of this task (Downes et al., 1989; Gauntlett-Gilbert, Roberts, & Brown, 1999). Another study found that performance on a set shifting task in PD was influenced by medication status, with non-medicated PD participants displaying impaired performance on multiple areas of cognitive function compared to medicated PD (Owen et al., 1993).

Finally, to compare implicit measures of cognition to an explicit baseline, the Oxford Memory Task, a measure of explicit function, was administered in parallel to the implicit battery to measure participants' ability to remember the identity of objects and their locations. This measure of explicit visuospatial memory is used to separate out different dimensions of an object (like location and identity) which are thought to be stored in different areas of memory (Pertzov, Dong, Peich, & Husain, 2012). It calculates absolute localization error, identity choice accuracy and misbinding error for a varying number of items. Specifically, this task has been shown to be sensitive to the cognitive changes associated with aging (Pertzov, Heider, Liang, & Husain, 2015) and individuals having suffered medial temporal lobe damage in patients with voltage gated potassium channel complex antibody-associated limbic encephalitis (Pertzov et al., 2013). To the best of our knowledge, none of the tasks included in the ICTB have been examined in RBD.

1.7. Synthesis

In summary, cognition in Parkinson's disease is heterogeneous, varying in terms of symptomology, severity and progression rate through different stages of pathology development. While most patients suffer from some decline in cognitive abilities, with the majority eventually developing dementia, treatment options for cognitive impairment remain largely unavailable

creating a large unmet need in the PD community. The development of cognitive treatment methods in PD is contingent on the development of novel biomarkers, which can detect early changes in cognition, are able to track progression of cognitive decline and are sensitive to pharmacological manipulation. In addition, the long prodromal phase of PD, oftentimes in which the cognitive impairments precede the motor ones by many years, represents an optimal time for disease-modifying intervention while neuronal degeneration is still limited. This prodromal period is also associated with a range of non-motor symptoms, which act as precursors to the future diagnosis of PD. One important precursor to PD is the emergence of iRBD, a parasomnia which predicts future development of neurodegenerative disease, often times PD. This makes individuals with RBD a promising population in which to study what is believed to be an early form of a cognitively impaired PD, specifically, with regards to cognitive biomarker development. Indeed, this would imply that cognitive biomarkers would be more sensitive to early cognitive changes associated with PD in a more cognitively vulnerable prodromal population. However, certain obstacles slow the development of efficient biomarker development. These include the lack of reproducibility of animal studies regarding pro-cognitive compounds, the use of compensatory strategies and large ceiling effect seen in many explicit tasks, and the lack of sensitivity to the subtle cognitive changes arising in early PD. More subtle cognitive measures offer a promising opportunity to surmount these obstacles as recent studies have established good reliability and sensitivity to the subtle cognitive changes associated with pathological states and pharmacological intervention like depression and anti-depressant medication (Harmer et al., 2011). There have also been some promising preliminary findings concerning implicit cognition in RBD and PD, however these remain very limited (Fantini et al., 2003; Filoteo et al., 2007; Myers et al., 2003; Troche et al., 2006). A battery of implicit

cognitive tasks developed with our research group has been previously shown to be sensitive to the cognitive effects of cognition enhancing drugs such as methylphenidate and modafinil in healthy individuals (Klinge et al., 2018; Pringle et al., 2013). As such, the current project examined the sensitivity of these different cognitive tasks in PD to evaluate their suitability as potential biomarkers. The aim of this thesis is to assess the sensitivity of this task battery to the early changes in cognition and pharmacological manipulation in prodromal and early stage PD. Study 1 describes a study in which performance on this battery of implicit tasks is evaluated in healthy control, REM sleep behaviour disorder and Parkinson's disease to establish the sensitivity to the cognitive changes associated with the early stages of PD. Study 2 describes a study in which the same tasks were administered to PD participants on two occasions, once 'on' and once 'off' their medication to assess this battery's sensitivity to pharmacological manipulation in PD. These studies are important steps in establishing whether these measures have the potential to act as cognitive biomarkers in future studies exploring the effects of novel potential therapeutic agents for PD.

2. Study 1: Validating a battery of implicit cognitive tests in a population of PD and RBD individuals

2.1 Introduction

As discussed previously, one of the earliest symptoms of PD is SCD, usually preceding the disease diagnosis by many years, sometimes decades. SCD remains difficult to characterize through explicit cognitive measures, which remain too coarse to detect these subjective and subtle cognitive changes. Currently, no existing measures or characterization methods exist to quantify this early cognitive change. Therefore, there is an intense interest in the scientific community to develop and validate cognitive measures sensitive to the early and subtle changes in cognition seen in the earliest stages of PD. This early detection may offer immense disease modifying potential, currently limited by the advanced neuronal degradation that accompanies late-stage diagnosis. Implicit measurement tools show promise in overcoming the obstacles currently halting explicit cognitive biomarker development, due to their heightened sensitivity in a variety of cognitive domains.

Therefore, the aim of this study will be to examine the suitability of implicit cognition as a candidate biomarker for cognitive impairment in PD, citing its sensitivity to pro-cognitive drugs and the promising results found in psychiatric disorders, including preliminary findings in Parkinson's. The battery developed by Klinge et al. (2018) will be used in this study as a measure of implicit cognition. A group of RBD patients will also be included in the study design as a prodromal group for PD. This will enable us to examine whether the cognitive changes we expect to find in the PD group are also present in this non-medicated, less pathologically advanced and cognitively vulnerable PD subset. Additionally, this implicit battery is attractive

because it examines a variety of implicit cognitive paradigms, some of which have been tested previously in PD, offering an interesting overview of implicit cognition in cognitive prodromal and early stage PD.

The aim of this cross-sectional study will be to assess the sensitivity of the implicit task battery in patients with RBD, and early stage PD. The battery of implicit measures as well as one explicit measure of cognition was administered to a group of 30 patients with PD, 30 patients with RBD and 30 healthy age-matched controls. Performance on the implicit cognitive tasks was predicted to be deteriorated in RBD and PD.

2.2 Methods

2.2.1 Participants

30 patients with Parkinson's disease, 30 patients with REM Sleep Behaviour Disorder (RBD) and 30 age-matched controls were included in the study. Participants were between the ages of 45 and 79 years. Most participants were recruited through the Oxford Parkinson's Disease Centre (OPDC) Discovery Cohort. Established in September 2010, the OPDC Discovery Cohort (http://opdc.medsci.ox.ac.uk) comprises over 1000 patients with Parkinson's, 300 healthy controls and 180 individuals thought to be 'at risk' of developing future Parkinson's (patients with RBD). 7 patients with PD were also recruited from a database held by the Experimental Psychology Department at the University of Oxford.

PD patients all met the UK PD Society Brain Bank Criteria for clinically probable idiopathic Parkinson's disease and had been diagnosed with PD within 4 years of the study. Clinical

information was pre-screened to exclude patients who had atypical parkinsonian disorders. All PD participants were currently medicated with levodopa (n=24), dopamine agonists (n=8) and/or monoamine oxidase inhibitors (n=11). The average levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010) was 720.9 ranging from 0 to 12 200. Other common medications used by this group were statins (n=9), α-adrenergic receptor antagonists (n=6), benzodiazepines (n=5), antidepressants (n=5) and β-adrenergic receptor antagonists (n=4).

RBD patients had all been diagnosed on the basis of polysomnographic evidence according to standard International Classification of Sleep Disorders-II criteria (Lapierre & Montplaisir, 1992) by a consultant specializing in sleep disorders. RBD is as an increase in tonic or phasic chin EMG activity during REM sleep and either a history of elaborate motor activity associated with dream content, or the presence of behavioural manifestations occurring during REM sleep during polysomnographic recordings. 25 of the RBD group were taking medication. The most commonly used medications were benzodiazepines (n=12), statins (n=8), antidepressants (n=7), omeprazole (n=6), melatonin (n=6), calcium channel blockers (n=4) and bronchodilators (n=4).

Healthy controls in the OPDC Discovery Cohort were recruited from partners and friends of PD patients. The most commonly used medications by this group were statins (n=5).

Exclusion criteria included: a score of less than 26 on the MoCA; current medical or psychiatric illness that would interfere with completing any of the assessments; inability to give informed consent.

One participant (RBD group) was excluded from analysis for having a MoCA score lower than 26 that was not identified until after study recruitment. This participant was replaced to ensure equal numbers between the groups.

In addition to cognitive functioning as measured by the MoCA, questionnaires assessing mood and behaviour were administered at baseline. These included the Epworth Sleepiness Scale (Johns, 1991), REM Sleep Behaviour Disorder Screening Questionnaire (Stiasny-Kolster et al., 2007), Beck Depression Inventory-II (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), State-Trait Anxiety Inventory (Spielberger & Vagg, 1984), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (Weintraub et al., 2012), Apathy Motivation Index (Ang, Lockwood, Apps, Muhammed, & Husain, 2017).

2.2.2 Design and Procedure

The study has a between-group design. The sample size was determined using G*Power (a statistical power calculator) for alpha = 0.025 (type 1 error: acceptable probability for which we will reject the null hypothesis when it is true, ½ of 0.05), beta = 0.95 (type 2 error: acceptable probability for which we fail to reject the null hypothesis when it is false) and an expected effect size of 0.7842 taken from Klinge et al. (2018) using the same implicit task battery. This gave a sample size estimate of 28. Since the previous effect size may be inflated, a sample size of 30 was agreed upon.

Individuals that fulfilled basic criteria were contacted and sent the Participant Information Sheet. If individuals agreed to participate, they were invited to attend a single research visit at either the John Radcliffe Hospital in Oxford, the Royal Papworth Hospital in Papworth, the Milton Keynes University Hospital in Milton Keynes, Wexham Park Hospital in Slough, or the Department of Experimental Psychology in Oxford. The research visits lasted a maximum of 3 hours.

At the beginning of the research visit, researchers took written informed consent, collected demographic information, administered the MoCA and collected the completed questionnaires. If the participant was eligible to take part in the study, they then completed a series of computerized cognitive tasks, including the Implicit Cognition Test Battery (ICTB), the Emotional Test Battery (ETB) and the Oxford Memory Task (OMT). The ICTB was been adapted from a previously validated battery of tasks (Klinge et al., 2018) and consists of the previously described Location Priming Task, the Contextual Cueing Task, the Acquired Equivalence Task and the Implicit Symbol Location Prediction Task. The emotional task battery is composed of the Facial Emotional Recognition Task (FERT), Emotional Categorization Task (ECAT) and the Emotional Recall Task (EREC), the results of which are not included here. All tasks were administered on a touch screen laptop with the exception of the OMT which was administered on a touch screen tablet.

Following the cognitive tests, the MDS Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987) was administered by a trained researcher. The Hopkins PD smartphone application was used to assess voice, balance, gait, finger tapping, reaction time, rest and postural tremor (Zhan et al., 2018). These results are not included in the present thesis.

2.2.3 Implicit cognitive tasks

All participants were given the same tests in the same order, as described below.

Location Priming task

In this task, adapted from Bauer, Gebhardt, Gruppe, Gallhofer, and Sammer (2012), participants were presented with displays containing an 'X' and an 'O'. These two stimuli could appear in two of four possible locations. Participants were required to indicate the position of the 'X' while ignoring that of the 'O' by tapping on one of the four quarters of the touch screen. Responses were recorded by tapping on the 'X'. Each trial began with the presentation of a fixation cross (2000 ms), followed by a prime display (2500 ms), to which participants responded. This was followed by a shorter fixation cross display (400 ms) and finally a probe display (2500 ms) that participants responded to once again. In this task, there were two critical experimental conditions, and one control condition, which were defined by the location of 'X' and 'O' in the probe display compared to the preceding prime display within the same trial. The experimental conditions were 'positive priming' in which the 'X' was presented in the same location in the prime and probe trials and 'negative priming' in which the probe display 'X' was presented in the position previously occupied by the 'O' in the prime display. The 'control' condition was when both the probe display 'X' and 'O' were presented in previously unoccupied locations. The prime and probe which were shown on the screen for the participant are displayed in *Figure 4* (adapted from Klinge et al., 2018). Participants were presented with a total of 72 test trials as well as 3 preliminary practice trials with corrective feedback. Only trials with correct responses to the prime (tapping on the 'X' during the allotted 2500 ms display time) were included in the analysis. Mean reaction time values for each condition were calculated per

participant. To assess priming effects for each participant, difference scores were calculated: negative priming (negative–control) and positive priming (control–repeat), which calculated the time lost and gained as a result of negative and positive priming respectively in comparison to the control condition. These difference scores were indicative of priming effect. Mean difference scores were then calculated for each group and compared.

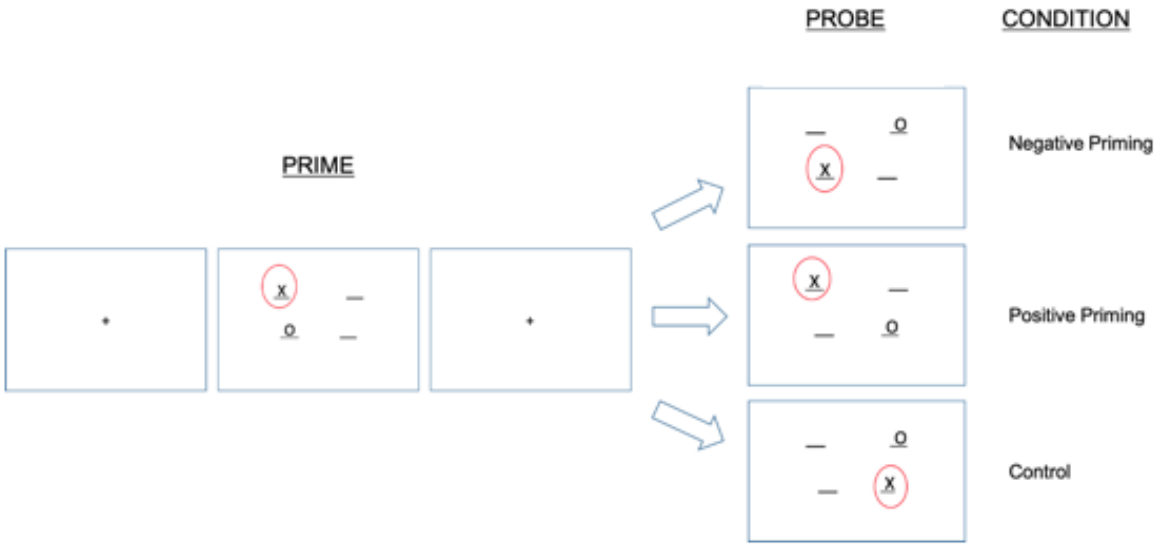


Figure 4. Example of displays for the different trial types in the location priming task. Red circles indicate the correct response.

Contextual Cueing Task

In this task (adapted from Chun and Jiang, 1998), the participant was required to report the orientation of a target ('T'), which was hidden amongst an array of distractor stimuli ('L's). On half of the trials, the display array was a repeat of one previously presented and on the other half of trials the display array was novel (see *Figure 5*). On each trial, a central fixation dot is presented, followed by a stimulus array which includes the target stimulus 'T' and 11 distractor stimuli ('L's) that could appear in different orientations (rotations in all possible 90° angles). Participants were required to indicate the orientation of the target (which is rotated 90° to the left or right) by tapping either the right or left side of the screen. After a two-minute instruction

block, the task ran for approximately 6 minutes. The entire task was composed of 3 blocks of 48 trials, two blocks of which were considered training blocks in which the participants learned the task. To be included in analysis, participants were required to complete an overall minimum of 70 on 144 total task trials and 25 on 48 block 3 trials. Analysis was conducted on the third block only by calculating mean reaction time and accuracy per participant. To measure contextual learning, difference scores (novel vs repeat) were computed for the first and second half of the task. Increased accuracy and decreased reaction times in repeated trials compared with novel trials were indicative of learning.

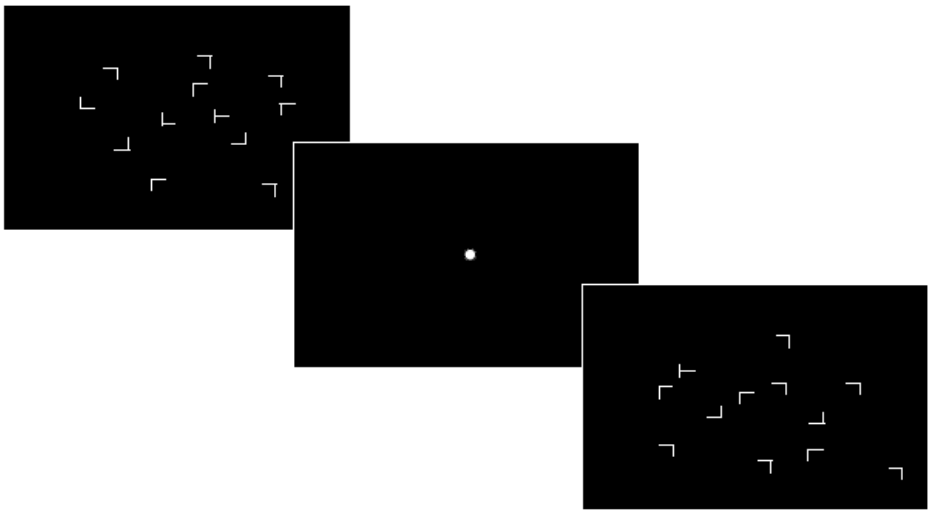


Figure 5. Example of two possible contextual cueing displays presented to participants. Response was registered by tapping either the right or left side of the screen to indicate the orientation of the "T". In both displays, a correct response would be registered if the participant were to tap on the left side of the screen.

Acquired Equivalence Task

The Acquired Equivalence Task was adapted from Myers et al. (2003) and is visually described in *Figure 6*. Performance was measured by both the initial learning in the acquisition phase and the transfer or generalization in the equivalence testing phase. Acquisition was composed of three stages: shaping, equivalence and novel consequents (see *Table 1*). Antecedent stimuli were

represented on screen as cartoon faces (a brown-haired man, a blond-haired woman, a brown-haired girl and a blond-haired boy) labelled with either A1, A2, B1 or B2. Consequents were represented as different coloured cartoon fish (yellow, red, blue and green) labelled with X1, X2, Y1 or Y2. In the first acquisition stage (shaping), a stimulus (A1) was associated with a consequent stimulus (X1), while another stimulus (B1) was associated with a different consequent (Y1). In a second acquisition stage (equivalence), novel antecedents A2 and B2 were associated with X1 and Y1 respectively. In the last phase of acquisition (novel consequents), A1 was associated with a new consequent X2 while B1 was associated with a new consequent Y2. In all acquisition phases, participants were required to learn associations through feedback that was displayed on the screen following a choice. In the case of correct choice, participants were shown the word "Correct" at the bottom of the screen. In the case of an incorrect choice, participants were shown the word "Incorrect" at the bottom of the screen.

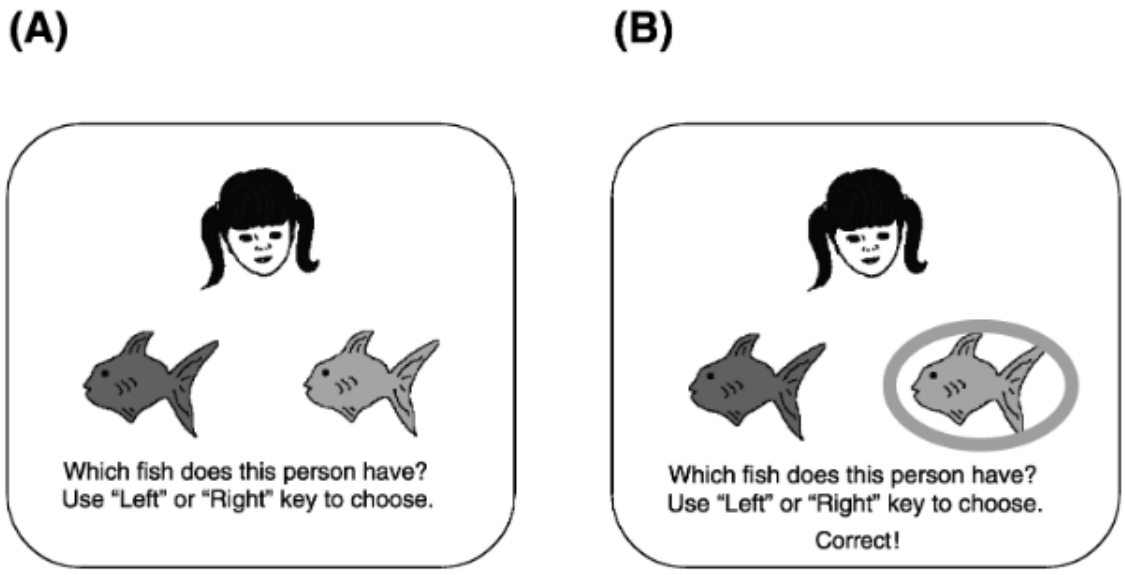


Figure 6. Example display during an acquisition trial in the acquired equivalency task. (A) Stimuli appear. (B) Participant responds and corrective feedback is given. Adapted from Myers et al. (2003).

Following the acquisition phases, participants entered the testing stage. Feedback was removed

and 48 test trials were administered: 24 trained (shaping and equivalence), 12 new trained (novel consequents) and 12 untrained. In the untrained trials, participants were tested on their generalization of the previously acquired equivalencies, specifically those outlined in the transfer phase column of *Table 1*. Participants were considered to have learned the task if they validated the novel consequents stage in a maximum of 60 trials and completed the entire acquisition stage in a maximum of 112 trials. If the participant required more than the allotted amount of trials in either the novel consequent or the acquisition stage, the task automatically moved on to the next stage and that participant was excluded from analysis.

Table 1. Acquired equivalence paradigm

Acquisition stage 1: shaping	Acquisition stage 2: equivalence	Acquisition stage 3: novel consequents	Transfer phase: equivalence testing
A1 → X1	A1→X1	A1→X1	A2→X2?
B1→Y1	A2→X1	A2→X1	B2→Y2?
	B1→Y1	A1→X2	
	B2→Y1	B1→Y1	
		B2→Y1	
		B1→Y2	

Table 1. The acquired equivalency paradigm (Collie, Myers, Schnirman, Wood, & Maruff, 2002). All associations taught to participants at each stage of the acquired equivalence task. All acquisition stages received feedback. Transfer phase trials did not receive feedback and tested associations that were never learnt but could be deduced from those learnt in acquisition.

Implicit Symbol Location Prediction Task

This task was adapted from Pringle et al. (2013) by removing the extra-dimensional portion of the task. The task was a set-shift dot-probe task in which the location of a target stimulus was probabilistically predicted by a preceding stimulus (implicit rule learning) with the predictive stimuli switching half-way through. The task was composed of 160 trials, broken up into two blocks (acquisition, reversal) of 80 trials each. Each block was divided into four quarters. In each trial, participants were presented with a central fixation cross which was then replaced with two shape stimuli, one at the top, and the other at the bottom of the screen, which were presented for 500 ms. The stimuli varied in two dimensions (colour and shape) with the two stimuli presented in a trial differing on both. All the trials within a given block of the task used stimuli with the same two shapes which were presented in one of two colours (the specific stimuli used were drawn at random from a pool of six possible shapes and colours). Following the offset of the stimuli, a probe (two small dots) was presented for 500 ms in the previous location of one of the stimuli. Participants were required to respond by tapping the dots present on screen during the probe. If participants had not responded within 1000 ms following the offset of the dot stimuli the trial was terminated (see *Figure 7*). The task included two critical manipulations: first, a specific stimulus predicted the location of the probe in 80% of the trials (16 trials per quarter), with the other 20% of trials (4 trials per quarter) being surprising 'catch trials'; second, the predictive exemplar changed between blocks. In the current task, learning across a block was inferred by comparing how much vigilance increases from the first to the last 40 trials in the block. In the initial acquisition (acq) block of the task, a particular stimulus colour, such as yellow, predicted probe location and therefore this block measured the ability of participants to learn the initial predictive properties of the stimulus. In the second reverse (rev) block,

participants were presented with identical stimuli, however, the predictive stimulus changes to the other colour (e.g. if yellow predicted the probe in the first block, green predicts its location in the second). For reaction time data, error trials were removed and mean reaction time was calculated. Reaction time vigilance was calculated as: mean reaction time for catch trials – mean reaction time for predictive trials. Accuracy vigilance was calculated as: mean accuracy for predictive trials – mean accuracy for catch trials. Both formulae resulted in a higher positive number if attention was directed towards the predictive stimuli. Learning rate was calculated as: 4th quarter vigilance – 1st quarter vigilance.

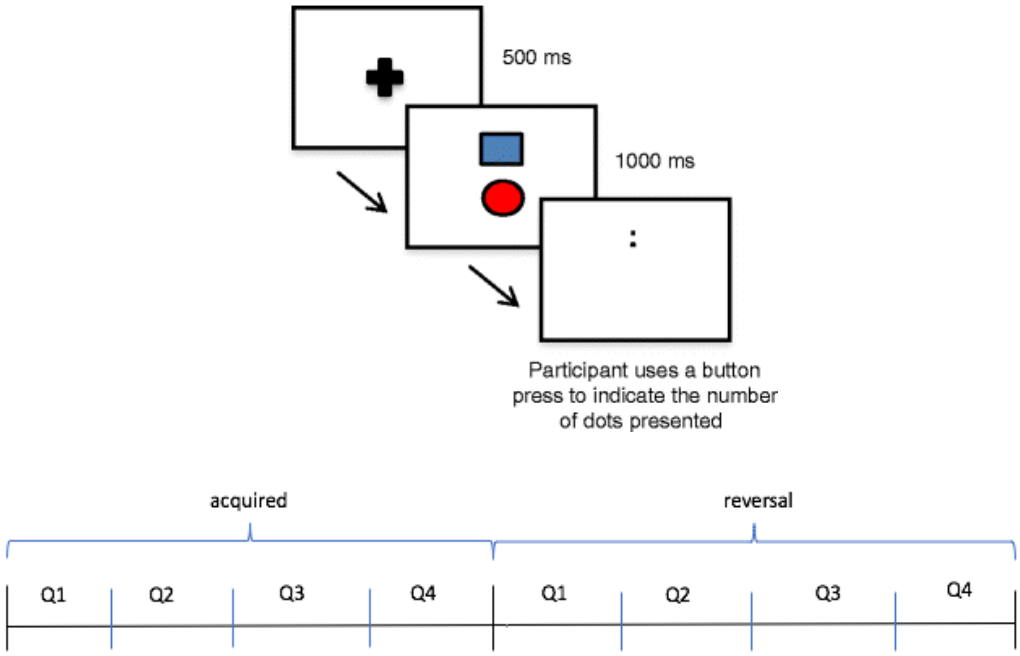


Figure 7. Display and quarter breakdown of the implicit symbol location prediction task (ISLP). Upper: Display sequence presented to participants. Participants were instructed to tap on the two dots that appear behind the blue square. Lower: The breakdown of each direction (acquired, reversal) into four quarters which were each composed of 20 trials of two conditions (16 predicted and 4 catch).

2.2.4 Explicit cognitive task

Oxford Memory Task

This task (adapted from Pertzov et al., 2015) measured explicit short term visual working memory by asking the participant to memorize the location and identity of fractals

(see *Figure 8*). Participants were shown 45 trials, 3 of which were practice trials, of either one or three fractals on a screen for 4 seconds and are then asked to identify which fractal they had previously seen in a lineup of novel shapes. They then dragged the familiar fractal to the location in which it was first seen. Performance was measured based on the accuracy of identification and distance between initial and chosen location. This was evaluated by measuring the proportion of correct selections and the absolute error (distance between the chosen position and the true position). Each fractal had a maximum width and height of 120 pixels. Stimuli were presented on a black background. Localization memory was computed by taking the distance between the centre of the target object after it had been dragged to its remembered location from the actual centre of the object in the initial memory array.

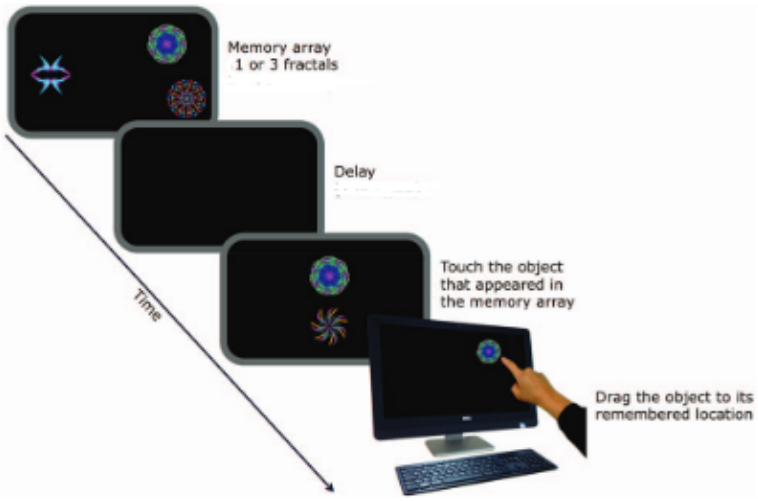


Figure 8. Oxford Memory Task display sequence.

2.2.5 Data analysis

All data were analysed using SPSS (IBM SPSS Statistics for Windows, Released 2011, Version 24. IBM Corp, Armonk, New York, USA) and graphed using R (R Core Team, 2018). Baseline measure data were non-normally distributed and compared between groups using Kruskal-Wallis

test for continuous data followed by a Dunn's Post-hoc test and chi-square tests for categorical data. For all tasks, reaction time and accuracy data were visually examined to ensure normal distribution. Outliers were determined and removed using boxplots for reaction time averages for individual participants. For the location priming and ISLP tasks, the spread of the reaction time raw data was visualized by four researchers and histograms were constructed using trial by trial reaction times to trim any tails which were not included in the normal distribution bell curve. This represented anything outside the 200-1600ms range for the ISLP and 200-2600ms range for the contextual cueing task. Combined with the exclusion of all unanswered trials, this resulted in the exclusion of 10.8% of the total trials for block 3. For the location priming, 0.4% of total trials were excluded and 1.8 % of for the ISLP. The remaining data were visually observed for normality and tested using the Shapiro-Wilk's test. Analysis was conducted using repeated measures ANOVAs with treatment group as between-subject factors and task conditions as within-subject factors. Where the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Significant interactions were explored further using independent samples t-tests with Bonferroni correction.

All demographic and questionnaire measures were evaluated for normality using visual inspection of histograms and Shapiro-Wilk's tests. All were found to be non-normally distributed. Categorical measures (gender and handedness) were compared using a chi-square test while continuous ones were compared using a Kruskal-Wallis test. Significant Kruskal-Wallis tests were followed up with Dunn's test. It has been shown that individuals with less than 12 years of education tend to display lowered performance on the MoCA (Nasreddine et al., 2005). To compensate for this difference, an additional point was added to the total MoCA score of participants who had fewer than 12 years of education.

2.3 Results

2.3.1 Questionnaire measures

Baseline demographic data were collected and compared for all three groups. Groups were well matched in terms of age, education and time since diagnosis. However, there was a significant difference in the gender balance of the three groups, which was driven by more men in the RBD group (26 men) compared with the PD (18 men) and HC (18 men) groups.

Both the RBD and PD groups reported significantly greater difficulty with non-motor experiences of daily living when compared to the HC group, as measured by the UPDRS Part 1: non-motor experiences of daily living. The PD group also had significantly higher scores than other groups on the UPDRS Part 2: Motor Experiences of Daily Living and the UPDRS Part 3: Motor examination, while there were no significant differences between the HC and RBD groups on these measures.

Depression, as measured by the BDI, was also significantly higher in both RBD and PD groups compared with the HC group. There was also a significant difference between the groups in self-reported impulsivity, as measured by the QUIP, which was driven by significantly increased impulsivity in the RBD group compared with the HC group. There were no significant differences between groups in terms of trait anxiety, sleepiness and MoCA. Further demographic characteristics across all three groups are summarised in *Table* 2.

Table 2. Study 1 demographic and questionnaire measures

	HC (n=30)	RBD (n=30)	PD (n=30)	Overall p-value	RBD vs PD	RBD vs HC	HC vs PD
Gender M:F	18:12	26:4	18:12	0.036	-	-	-
Age	65.3 (9.0)	64.3 (9.0)	64.7 (7.4)	0.861	-	-	-
Education	4.2 (2.5)	3.0 (2.8)	4.1 (2.0)	0.096	-	-	-
Time since diagnosis	N/A	34.0 (21.9)	39.6 (9.0)	0.5117	-	-	-
UPDRS I	3.8 (3.1)	8.6 (4.8)	9.0 (5.2)	<0.001	1	<0.001	<0.001
UPDRS II	0.5 (1.1)	2.6 (3.3)	9.0 (5.8)	<0.001	<0.001	0.032	<0.001
UPDRS III	4.7 (3.1)	7.6 (4.5)	22.3 (9.8)	<0.001	<0.001	0.179	<0.001
MoCA	29.0 (5.3)	27.8 (4.1)	28.4 (1.4)	0.285	-	-	-
ESS	5.4 (3.1)	6.5 (4.4)	5.5 (4.1)	0.595	-	-	-
RBD	1.9 (1.5)	10.0 (2.5)	5.4 (3.2)	<0.001	<0.001	<0.001	0.001
BDI	4.4 (5.4)	10.8 (9.8)	9.4 (5.4)	<0.001	1	0.002	0.001
QUIP	0.1 (0.3)	0.4 (0.5)	0.3 (0.5)	0.036	0.576	0.030	0.617
TRAIT	44.2 (3.2)	45.2 (9.2)	42.5 (7.4)	0.365	-	-	-

Table 2. All overall P-values for healthy controls (HC), REM sleep behaviour disorder (RBD) and Parkinson's Disease (PD) were calculated using the Kruskal-Wallis test with the exception of gender, calculated using a chi-square test. Post-hoc tests were all conducted using Dunn's test for pairwise comparisons. Education was evaluated in number of years post-secondary. Time since diagnosis was calculated in months. Tests administered were the Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA) adjusted for years of education, Epworth Sleepiness Scale (ESS), REM Sleep Behaviour Disorder (RBD), Beck's Depression Inventory (BDI), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) and the Trait Anxiety Inventory (TRAIT). Data shown are in mean (SD).

2.3.2 Implicit cognitive tasks

Location Priming Task

To check whether there were baseline differences between the groups in reaction times, all three conditions were aggregated and raw overall mean reaction time from the location priming task were entered into a one-way ANOVA with a between-subjects factor of group. The conditions were not shown to differ significantly between groups [$F(2,87)=1.15$, $p=0.322$] and as such differences in baseline reaction times were considered negligible.

The mean negative and positive priming difference measures were entered into a repeated

measures ANOVA with prime type (two levels: negative, positive) as the within-subjects factor and group as the between-subject factor. There was a significant main effect of prime type [$F(1,87)=36.03$, $p<0.001$, $\eta_p^2=0.293$] with participants showing a significantly greater positive priming effect (mean: 51.33ms; sd: 51.62ms) than negative priming effect (mean: 11.84ms; sd: 26.20ms). There was no main effect of group [$F(2,87)=1.33$, $p=0.270$], but there was a significant interaction between group and prime type [$F(2,87)=3.43$, $p=0.037$, $\eta_p^2=0.073$].

To further understand the significant interaction between group and prime type, two independent one-way ANOVAs were conducted for negative and positive priming. This revealed non-significant differences for the negative prime type [$F(2,89)=1.55$, $p=0.217$] and marginally significant differences for the positive prime type [$F(2,89)=2.87$, $p=0.062$] (*Figure 9*).

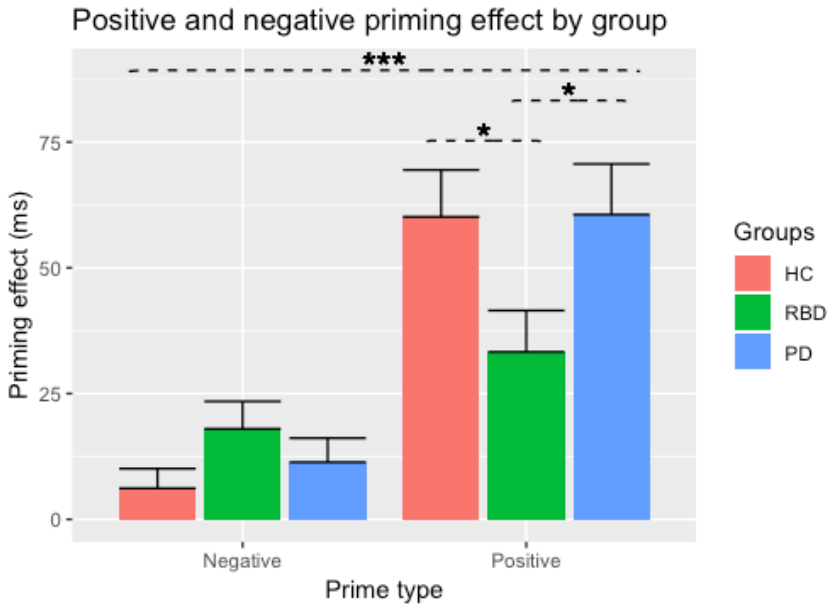


Figure 9. Priming effect for the location priming task in milliseconds was calculated for healthy controls (HC), REM sleep behaviour disorder (RBD) and Parkinson's Disease (PD) as follows: individual negative priming effect=individual negative condition reaction time mean-individual control condition mean reaction time; positive priming effect=individual control condition reaction time mean-individual positive priming reaction time mean. Error bars represent standard error.

To further understand the marginally-significant main effect of group for positive priming, follow-up independent sample t-tests were conducted which revealed that positive priming was

significantly decreased in the RBD group compared with the HC [$t(58)=2.16, p=0.035$] and PD [$t(58)=2.10, p=0.040$] groups. There was no significant difference in positive priming between the HC and PD groups [$t(58)=0.03, p=0.974$].

To investigate whether the decreased priming in the RBD group was driven by the concurrent usage of benzodiazepines, which are known to have a cognition impairing effect (Crowe & Stranks, 2018), a further analysis was conducted to test whether priming differed between participants who were taking clonazepam (n=17) and those who weren't (n=73). There was no difference between these two groups in terms of negative priming [t(88)=1.88, p=0.063] or positive priming: [t(88)=0.58, p=0.561].

Finally, to ensure the validity of the reaction times values, accuracy was compared using a repeated measures ANOVA with prime type as the within-subject factor and group at the between subject factor. Results indicate that there were no significant main effects of prime type [$F(1, 87)=0.94, p=0.335$] or group [$F(2, 87)=1.31, p=0.274$], nor a prime type to group interaction: $F(2, 87)=1.20, p=0.308$.

Contextual Cueing

Five participants (PD:3, RBD:1, HC:1) were not included in this analysis. One individual (PD) asked to stop midway through while another one's file was corrupted (HC). Three individuals (PD:2, RBD:1) did not meet the minimum required amount of valid trials for both total task (70) and block 3 only (25) and were excluded from further analysis. Analysis was run on 27 PD, 29 RBD, 29 HC.

To ensure that there were no baseline reaction time differences between the groups, a one-way ANOVA was run for overall mean reaction time responses and overall mean accuracy as within-subject factors and group as a between subject variable. There was no main effect of group for reaction time [$F(2,82)=0.22$, $p=0.803$] or accuracy [$F(2,82)=0.01$, $p=0.986$].

To measure contextual cueing, a repeated measures ANOVA was carried out using reaction times for block 3. Condition (two levels: novel, repeat) was used as a within-subjects factor and group as a between-subject variable. While there was a different patternicity displayed by the RBD group compared to the PD and HC, no main effect of group was detected [$F(2,82)=0.51$, $p=0.602$] (*Figure 10*). As expected, there was a significant main effect of condition [$F(2,82)=7.41$, $p=.008$, $\eta_p^2=0.083$] with participants responding on average more slowly to the novel measures (mean: 1.13s; sd: 0.20s) than the repeated ones (mean: 1.11s; sd: 0.19s). The group by condition interaction was not significant [$F(2,82)=1.95$, $p=0.149$].

A further analysis was conducted using a repeated measures ANOVA carried out for accuracy focused on block 3, with condition (two levels: novel, repeat) as the within-subject factor and group as the between-subject variable. Once again, there was no significant main effect of group [$F(2,82)=0.36$, $p=0.697$] and no significant main effect of condition [$F(2,82)=3.28$, $p=0.074$], although there was a numerical difference in accuracy across the conditions in the expected direction, with participants responding less accurately on the novel arrays (mean: 80%; sd:1%) than the repeated arrays (mean: 82%; sd:1%). There was no significant group by condition interaction [$F(2,82)=0.91$, $p=0.408$].

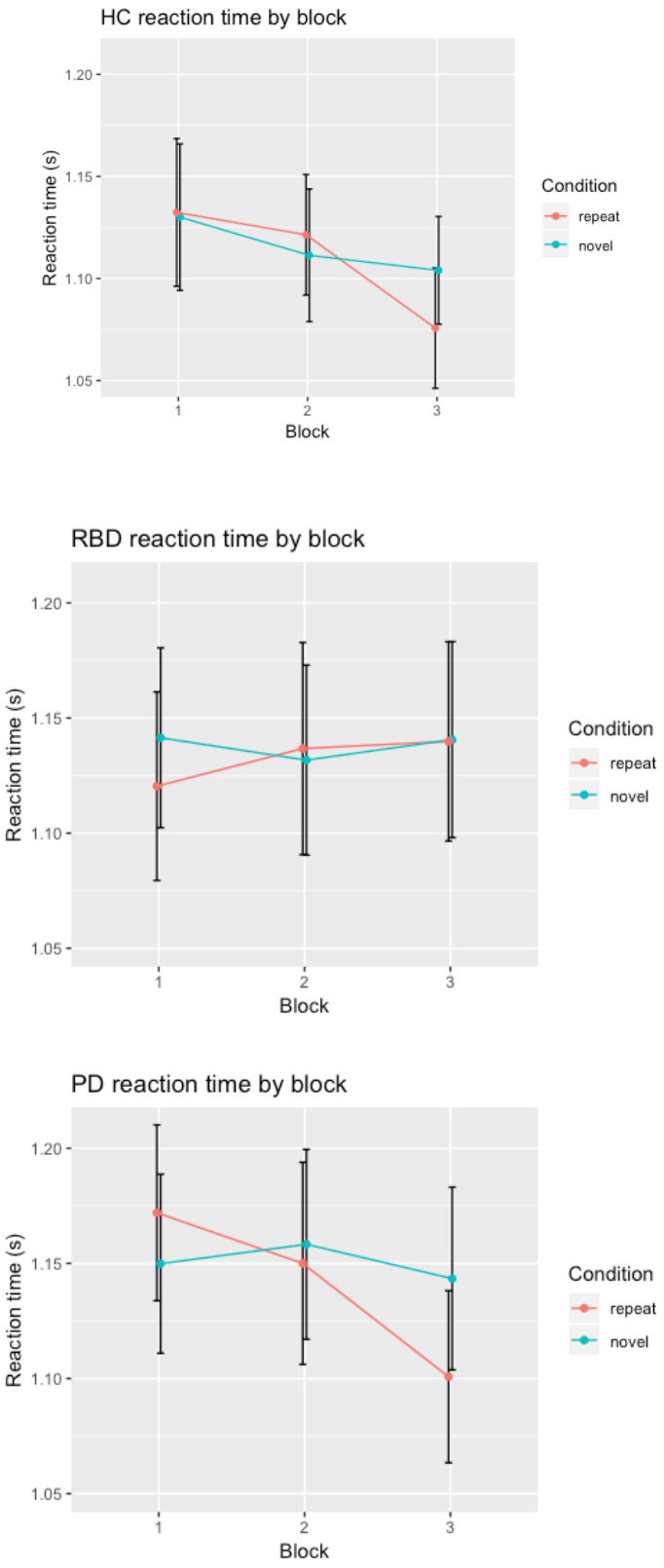


Figure 10. Priming effect for the contextual cueing task by group. Calculated for healthy controls (HC), REM sleep

behaviour disorder (RBD) and Parkinson's Disease (PD) in seconds as follows: overall accuracy priming effect=individual average repeat accuracy-individual average novel accuracy; reaction time priming effect=individual mean novel reaction time-individual mean repeat reaction time. Error bars represent standard error.

Acquired Equivalency Task

Eight participants (PD:3, RBD:3, HC:2) were excluded for failing to reach criterion, by not completing the training in fewer than the maximum allowed trials (maximum 60 on novel consequents and 112 on total acquisition). Analysis was conducted on the remaining seventy-nine participants (PD:27, RBD:27, HC:28).

The number of acquired trials (shaping + equivalence + novel consequents) were entered into a one-way ANOVA with group as a between subject factor. There was no significant main effect of group [$F(2,79)=1.97$, $p=0.146$] (*Figure 11*).

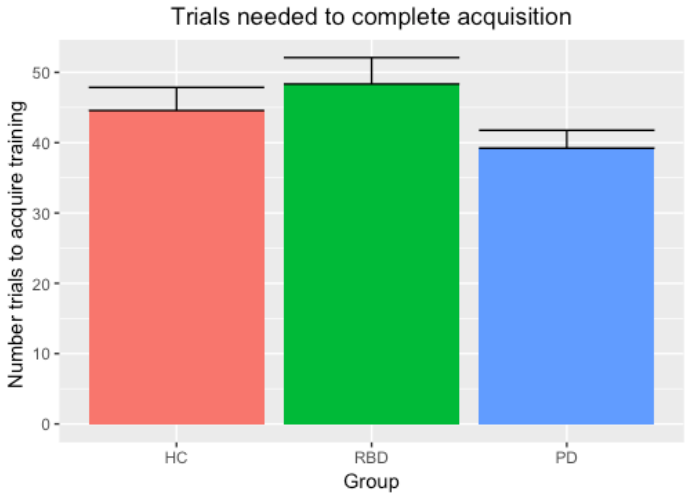


Figure 11. Number of trials necessary to complete acquisition training by group. Acquired equivalency task with acquired trials=shaping+equivalence+novel consequents. Averaged by group for healthy controls (HC), REM sleep behaviour disorder (RBD) and Parkinson's Disease (PD). Error bars represent one standard error.

A repeated measures ANOVA was run for transfer trials with test type (two levels: retention, untrained) as the within subject variables and group as the between subject factor. There was a

significant effect of test type [$F(1,79)=1910.51$, $p<0.001$, $\eta_p^2=0.960$], with individuals performing on average more accurately on trials that they had previously learnt (mean: 88%; sd: 14%) versus novel trials (mean: 61%; sd: 30%) (see *Figure 12*). However, there was no significant main effect of group [$F(2,79)=0.87$, $p=0.424$], or group by trial type interaction [$F(2,79)=0.13$, $p=0.881$].

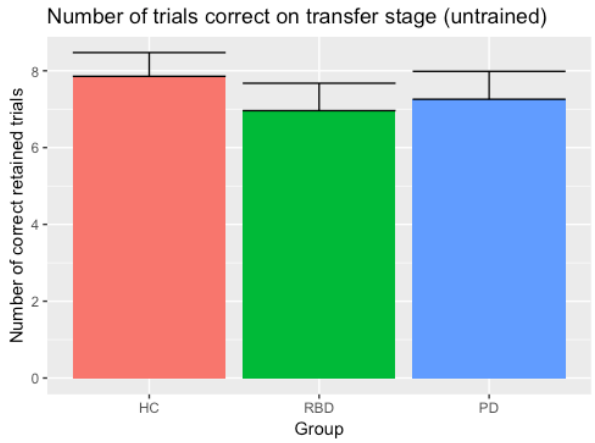


Figure 12. Number of correct trials on transfer testing by group. Averages by group for healthy controls (HC), REM sleep behaviour disorder (RBD) and Parkinson's Disease (PD) for acquired equivalency task. Error bars represent one standard error.

Implicit Symbol Location Prediction Task

One participant (RBD) was excluded for not having any correct trials in one block. Analysis was conducted on the remaining eighty-nine participants (PD:30, RBD:29, HC:30).

Mean reaction times were entered in a repeated measures ANOVA with direction (two levels: acquisition, reversal) and condition (two levels: catch, predicted) as within subject factors and a between subject factor of group. There was also a significant main effect of direction [$F(1,86)=30.64$, $p<0.001$, $\eta_p^2=0.263$] (see *Figure 13*). This was driven by smaller reaction times on reversal trials (mean: 770 ms; sd: 150ms) compared to acquired trials (mean: 803 ms; sd:

476ms). There were no significant main effect of condition [$F(1,86)=2.56$, $p=0.113$] or group [$F(2,86)=0.01$, $p=0.991$] and no interactions of main effects.

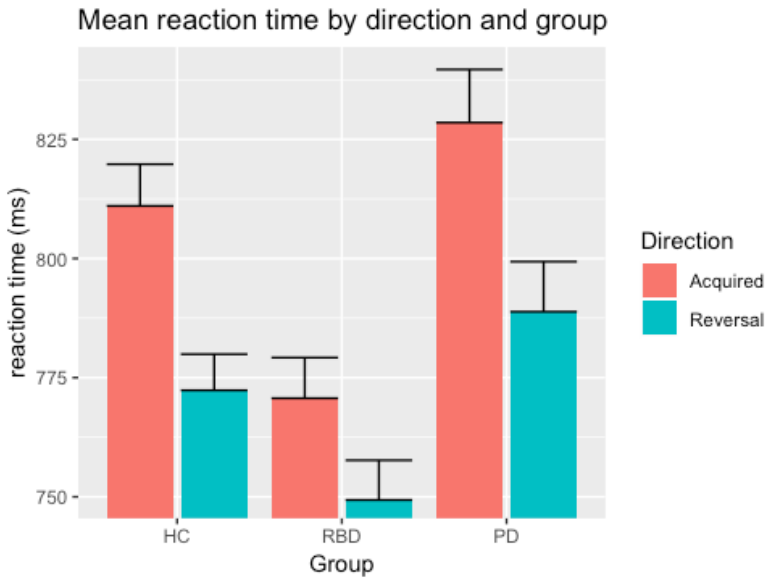


Figure 13. Mean reaction time for the implicit symbol location prediction task by direction. Averages in milliseconds for healthy controls (HC), REM sleep behaviour disorder (RBD) and Parkinson's Disease (PD) by direction. Error bars represent standard error.

Learning rate, calculated as the difference between the 4th quarter and 1st quarter vigilance, was analysed in a repeated measures ANOVA with direction as a within-subject factor and group as a between subject factor. There was no significant main effect of direction [$F(1,86)=0.30$, $p=0.587$] or group [$F(2,86)=0.01$, $p=0.991$] and no significant group by direction interaction [$F(2,86)=0.48$, $p=0.620$].

Accuracy rates were very high across all groups on this task. PD had the lowest average accuracy (96%), while HC and RBD scored higher (99%). A repeated measures ANOVA was carried out for accuracy with direction (two levels: acquisition, reversal), condition (two levels: catch, predicted) as within subject factors and a between subject factor of group. There was no significant main effect of direction [$F(1,86)=2.23$, $p=0.139$] or condition [$F(1,86)=0.16$,

p=0.692] and no significant interactions between group and direction or condition. There was, however, a significant main effect of group [$F(2, 86)=4.77$, p=0.011] which was driven by lower accuracy in the PD group compared with the control group [$t(58)=2.23$, p=0.03] and the RBD group [$t(58)=2.23$, p=0.002].

2.3.3 Explicit cognitive task

Oxford Memory Task

Data were lost for three PD participants due to computer malfunction, therefore the analysis was run on 30 HC, 30 RBD and 27 PD.

Identification performance is the ratio of correct fractal choice trials to total trials in the two-alternative forced choice. A repeated measures ANOVA on identification performance was run with condition (two levels: one fractal, three fractal) as a within-subjects factor and group as a between-subjects factor. There was a significant main effect of condition, reflecting worse identification performance when three fractals were presented compared to one, [$F(1,84)=211.80$, $p<0.001$, $\eta_p^2=0.716$], however performance did not differ between groups as indicated by a non-significant effect of group [$F(1,84)=0.43$, p=.576] and group by condition interaction [$F(1,84)=0.989$, p=0.983].

Absolute error is the distance between the reported location and the true location of the fractal. Trials with incorrect identification were excluded from further analysis. A repeated measures ANOVA was run with condition (one or three fractals) as the within-subjects factor and group as a between-subjects factor. There was a significant main effect of condition on absolute error [$F(1,84)=320.92$, $p<0.001$, $\eta_p^2=0.793$], with the three-fractal trials showing a higher rate of error.

Once again, performance did not differ between groups, as indicated by a non-significant effect of group [$F(1,84)=0.94$, $p=0.678$] and group by condition interaction [$F(1,84)=0.76$, $p=0.903$].

2.4 Discussion

The aim of this study was to determine whether a previously validated battery of implicit cognitive tasks was sensitive to the impairments seen in prodromal and early stage PD. The task battery identified a deficit in the RBD group on priming effect, with a significant reduction in positive priming compared to the other two groups. The impairment seen in the RBD group was specific to the priming task and there were no differences in task performance between groups on the other tasks in the implicit battery, nor on the explicit visuospatial task. Interestingly, there were no impairments in performance in the PD group on any of the tasks used in this study.

Demographic data were relatively evenly matched between groups except for the gender disparity in the RBD group which had more males (26) than females (4). This proportion is reflective of the parasomnia's incidence in the general population with 85% of the diagnoses occurring men (Bodkin & Schenck, 2009). Depression (BDI) was also present in higher levels in PD and RBD compared to HC. This finding replicates a study by Barber et al. (2017) in which BDI scores were compared in the three groups with similar results to ours. Our findings are also in line with average depression incidence in general population and in PD. Slightly less than half of individuals with PD are thought to suffer from concomitant depression (Marsh, 2013). This is compared to 10% in general population (Lim et al., 2018). RBD is also associated with higher levels of depression than in PD without RBD (Rolinski et al., 2014).

In terms of task performance, the RBD group exhibited significantly reduced positive spatial priming and selective attention compared to the other two groups. This is surprising given that the neurodegeneration is more pronounced in PD compared to RBD. In addition, cognitive deficits associated with PD have been linked to impaired inhibition processes and an increase in positive priming effect (Troche et al., 2006). Plomhause et al. (2014) found no differences in visual selective attention in iRBD compared to HC and PD with and without RBD, but did find some impaired intermediate visuoperceptive processing in both iRBD and concomitant RBD. While the existence of impaired visuoperceptive processing in RBD could explain our findings and has been seen in other studies (Fantini et al., 2011; Ferini-Strambi et al., 2004; Iranzo et al., 2006), it remains controversial (Gagnon et al., 2012; Gagnon et al., 2009; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008).

Contrary to the study hypothesis, results indicate an overall lack of impairment in the PD group in the implicit task battery. This finding contributes to the mixed literature on implicit cognition in PD. Previous positive findings have already been described in the general introduction, however there also exists some negative findings in spatial attention and contextual cueing with unimpaired performance on implicitly-learned spatial attention in PD (Li et al., 2018; Sisk et al., 2018) as well as impaired performance compared to HC (van Asselen et al., 2009). Li et al. (2018) also found unimpaired reaction times in both explicit and implicit contextual sequence prediction, however found significant differences in functional connectivity and P3b latency of HC and PD. This implicates the insensitivity of the task itself in favour of other types of implicit detection methods.

Throughout the ISLP, PD participants performed less accurately than the two other groups. It is unclear why these baseline differences did not emerge in the rest of the battery. Since the ISLP was the last task to be administered in the visit as well as the longest one, it could be that the PD participants were starting to tire following the lengthy visit and that this group are more susceptible to fatigue. Pringle et al. (2013) discussed the long testing time of their dimensional task, suggesting it may be measuring attention span and stamina instead of true reaction time or accuracy. Further, it is worth noting that accuracy approached ceiling for both HC and RBD, making differences between groups very small. This is one of the reasons for which reaction time is the standard outcome measure for dot-probe tasks (Thomson, McIntyre, MacLeod, & Keelan, 1986).

Excluding the deficits seen in the positive priming task, both the RBD and PD groups displayed unimpaired performance on the implicit task battery. These findings are contrary to our hypothesis proposing that implicit cognitive tasks may be more sensitive to the subtle cognitive changes seen in prodromal and early stage Parkinson's disease. A possible explanation for this result is our pre-selection for cognitively fit individuals through the minimum MoCA cutoff of 26 at screening. The stringent inclusion criteria shaped our cohort to be exceptionally cognitively fit, with MoCA scores very high throughout the three groups. In our cohort, the average PD group MoCA was 28.73. This figure is much higher than previously recorded MoCAs seen in PDD (16.9), PD patients with MCI (23.2), cognitively normal PD patients (26.7) and even healthy controls (27.2) (Dalrymple-Alford et al., 2010). This high cutoff was established to exclusively examine the sensitivity of the task battery to impairments undetectable by standard, explicit clinical tools such as the MoCA. However, as discussed in the general

introduction, the progress of cognitive impairment in Parkinson's is rarely linear and varying types of cognitive impairments have a high probability of coincidence, especially once PD has been diagnosed and neuronal degradation is significantly advanced. As such, it very possible that by excluding PD individuals with any objective cognitive impairment, we excluded all individuals with implicit cognitive impairment. Future studies could investigate the same battery of tasks in patients with a more typical MoCA and investigate the association between MoCA and performance on implicit tasks.

An alternative explanation for the null findings is that through our adaptation of the battery introduced by Klinge et al. (2018), the task battery may have lost a degree of its sensitivity. The shortening of the tasks is a possible desensitizing factor, specifically with regards to the contextual cueing and the ISLP. The contextual cueing task was shortened into 3 blocks of 48 trials totalling 144 trials, whereas all previous studies administered much longer versions (Chun & Jiang, 1998; Klinge et al., 2018; Negash et al., 2015; van Asselen et al., 2009). For example, 720 trials were administered in the source study by Chun and Jiang (1998) and 420 in the study by Klinge et al. (2018) from which the task was directly adapted. In the study by Chun & Jiang (1998), partipants perform identically in the two conditions until the first epoch (120 trials). To mitigate this discrepancy, our analysis was only conducted on the final block of the task. However, this may still not have been enough to filter out the learning trials and witness the contextual cueing effect as it develops throughout the task.

In the ISLP, the extra-dimensional set-shifting portion was removed from the IDED leaving only the intra-dimensional reversal learning (e.g. only switching between two colours). Much of the

previous literature examining this task has found deficits in PD particularly on the set-shifting portion of the task (Cools, Barker, Sahakian, & Robbins, 2001) particularly during extra-dimensional (e.g. switching from colour to shape) set-shifting (Downes et al., 1989; Gauntlett-Gilbert et al., 1999). This indicates that the shortening may have also been a factor in the lack of results seen in this task.

Finally, given that the neurodegeneration is more pronounced in PD compared to RBD, the attenuated impairment seen in this group in Study 1 is surprising. These results could simply be indicating chance findings, revealing the tasks to be insensitive to the early cognitive changes present in RBD and PD. The differential performance between RBD and PD could be a result of the dopaminergic medication masking the impairments seen in PD or the cognitively impaired profile of the RBD group compared to PD. As seen in the introduction, the effects of pharmacological manipulation in PD are unclear on both explicit and implicit cognition and RBD has been associated with heightened cognitive impairment both in its idiopathic and concomitant states. Both these hypotheses could be viable explanations for the results seen in Study 1 and will be further examined in Study 2.

3. Study 2: Assessing the sensitivity of the implicit task battery to pharmacological manipulation in people with Parkinson's disease

3.1 Introduction

To validate this battery as a cognitive biomarker candidate for PD, it is essential to establish its sensitivity to pharmacological manipulation. Therefore, Study 2 will test task performance in individuals with PD on two occasions, once 'on' and once 'off' of their dopaminergic medication, with the hypothesis that performance on the implicit task battery will be impaired while participants are 'off' their medication compared to while they are 'on'. It is expected that the non-medicated visit performance in Study 2 will mimic the RBD group performance in Study 1. Given that the RBD group displayed a significantly reduced positive priming effect in the location priming task, we expect to see a reduced positive priming effect in the non-medicated state in Study 2. This reduction in priming effect is opposite to the heightened priming effect seen in the pro-cognitive drugs modafinil and methylphenidate on the spatial priming task (Harmer et al., 2011; Pringle et al., 2013).

Study 2 will also offer the potential to examine whether the different performances seen in RBD and PD in Study 1 are due to medication differences between the two groups by examining whether individuals with PD differ in their performance while 'on' and 'off' medication. If the performance on these tasks differs based on medication, this will demonstrate that the battery is sensitive to dopaminergic medication in PD. Given the findings in Study 1, it is expected that performance will increase on the medicated visit compared to the non-medicated visit, with the dopaminergic medication conferring a pro-cognitive effect to PD patients, masking the cognitive impairments that by contrast become visible in the non-medicated RBD group in Study 1. If the

performance is unaffected by the change in medicated sates, iRBD participants could be displaying a functionally different cognitive impairment compared to those seen in PD. Alternatively, it could be that by selecting for the RBD group, we are selecting for a cognitively impaired prodromal subtype of the disease that performs worse on these implicit tasks. This group may also exist in PD, however does not appear to reduce the performance of the PD group due to 'dilution' with other non-cognitive subtypes.

The same tasks as those described in Study 1 were administered to a group of 30 patients with PD on two separate occasions: one visit while they were "on" their physician-prescribed dopaminergic medication, and one visit when they were "off". It was predicted that cognitive dysfunction would be apparent using our implicit test battery in prodromal and early stages of disease progression compared to healthy controls. In consistency with Study 1, we also investigated whether a more explicit test of visuospatial memory is sensitive to the functional connectivity changes witnessed between medicated states.

3.2 Methods

3.2.1 Participants

30 patients with Parkinson's disease were included in the study. Participants were aged between 50 and 75 years. All participants were recruited through community by advertising through a variety of Parkinson's specific groups such as the local Parkinson's UK branch events, exercise classes and various online groups.

All participants had been diagnosed with Parkinson's disease within 6 years of study recruitment. To confirm the diagnosis of PD, potential participants were asked to bring the letter issued by the NHS confirming their diagnosis to the screening visit. Additional details such as the exact diagnosis given in the NHS letter and prescriptions were examined by research assistants to exclude patients who had dementia and atypical parkinsonian disorders. In cases where the diagnosis was uncertain, a neurologist on the research team was consulted to determine inclusion eligibility on a case by case basis.

Additional exclusion criteria include: a score of less than 26 on the MoCA; a score of 3 or more on any of the tremor measures of the UPDRS; current medical or psychiatric illness that would interfere with completing any of the assessments; inability to give informed consent.

Questionnaires assessing mood, anxiety symptoms and perceived cognitive function were administered at baseline. These included the Epworth Sleepiness Scale (Johns, 1991), REM Sleep Behaviour Disorder Screening Questionnaire (Stiasny-Kolster et al., 2007), Beck Depression Inventory-II (Beck et al., 1961), Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), State-Trait Anxiety Inventory (Spielberger & Vagg, 1984), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (Weintraub et al., 2012), Apathy Motivation Index (Ang et al., 2017).

3.2.2 Design and Procedure

The study has a within-group design. Individuals living with Parkinson's disease, different from those recruited for Study 1 and who fulfilled basic criteria, were contacted and sent the

Participant Information Sheet. If individuals agreed to participate, they were invited to attend a preliminary screening visit which they completed while 'on' their dopaminergic medication. If they were found to be eligible, participants were invited to take part in two further research visits, one on their dopaminergic medication ("ON") and one off ("OFF") in which they would complete the same set of tasks previously outlined in Study 1. The order of these visits was counterbalanced across participants using a randomization schedule stratified by gender; 16 participants completed their ON visit first and 14 completed their OFF visit first. Two researchers were needed to administer the study to a participant. The researcher who administered the screening visit was responsible for randomising, communicating the medication schedule and withdrawal procedure to the participant. This enabled the second researcher to conduct the two research visits while blind to the participant's medicated state, to eliminate any bias during their interactions with the participant. All visits were held at the Warneford Hospital in Oxford. The screening visit lasted approximately 1 hour and research visits lasted between 2 and 3 hours.

At the beginning of the screening visit, researchers took written informed consent, collected demographic information, administered the MoCA and the motor portion of the UPDRS. If participants fulfilled scoring criteria for the MoCA and the UPDRS, they were found to be eligible to take part in the study. Following the screening visit participants were given a set of questionnaires to fill out before the first research visit. In each research visit, participants completed the same battery of tasks as used in Study 1: the Implicit Cognition Test Battery (ICTB), the Emotional Test Battery (ETB) and the Oxford Memory Task (OMT). The ICTB included the Location Priming Task, the Contextual Cueing Task, the Acquired Equivalence

Task and the Implicit Symbol Location Prediction Task (see Study 1 for task details). The ETB included the Facial Emotional Recognition Task (FERT), Emotional Categorization Task (ECAT) and the Emotional Recall Task (EREC), the results of which are not included here. All tasks were administered on a touch screen laptop with the exception of the OMT which was administered on a touch screen tablet. Following the cognitive tests, the UPDRS was administered by a trained researcher. The Hopkins PD smartphone application was used to assess voice, balance, gait, finger tapping, reaction time, and rest and postural tremor (Zhan et al., 2018). These results are not included in the present thesis.

3.2.3 Medication withdrawal

Medication withdrawal varied based on medication type. If individuals were on L-dopa, they were asked to omit the dose on the morning of their research visit making their last dose taken before the visit that of the evening dose of the previous day, termed "overnight withdrawal". If the participant was on dopaminergic agonists, they were asked to allow for a 24h period off the medication before their research visit, making their last dose the one of the morning prior to the visit. The average withdrawal time in Study 2 was 15 hours and 52 minutes with a median of 15 hours and 40 minutes. This indicates that our participants on their 'off' visit had respected the 12-hour minimum generally used in other 'on' vs. 'off' studies. Only one participant was below this minimum having only withdrawn from medication for 11 hours.

3.2.4 Tasks and Data Analysis

All tasks and data analysis were identical to those used in Study 1.

3.3 Results

3.3.1 Questionnaire measures

Baseline demographic data were collected for all 30 participants, with participants scoring in the normal range for all measures. All PD participants were medicated with L-dopa (n=28) or dopamine agonists (n=7), with a number of participants on both (n=5). The minimum cutoff score used for the MoCA was 26, in line with what is considered the cutoff for "normal" cognition (Nasreddine et al., 2005). Similarly to Study 1, the average MoCA score was 28.2, indicating our sample was exceptionally cognitively fit likely as a result of our selective screening process. The average BDI score measuring for depression was 9 on a scale of 0-63, indicating a minimally depressed cohort. Similarly, participants scored an average of 37 for trait anxiety on a scale of 20-80, indicating low levels of anxiety. The average L-dopa equivalent daily dose (LEDD) (Tomlinson et al., 2010) was 360.3 ranging between 100 and 820. Other common medications currently used by this group were statins (n=6), steroids (n=8), antidepressants (n=7) and hypertension medication (n=6) and acid reflux medication such as omeprazole (n=5). The UPDRS was measured on three occasions, once at screening, and once during each research visit. All demographic information is outlined in *Table* 3.

Table 3. Study 2 demographic and questionnaire measures.

	n=30
Gender (M:F)	14:16
RBD converters (Y:N)	2:28
Age	65.1 (6.6)
Education	4.6 (2.1)
LEDD	360 (174)
Time since diagnosis	41.1 (22.5)
Time since appearance of symptoms	201.1 (420.8)
MoCA	28.2 (1.2)
ESS	6.5 (4.5)
RBDSQ	6.1 (4.0)
BDI	8.9 (6.9)
QUIP	0.5 (1.0)
TRAIT anxiety	34.6 (9.4)
UPDRS III	23.4 (11.0)
Hoehn & Yahr stage	2.3 (0.9)

Table 3. P-values calculated using a chi-square test. Time since diagnosis was calculated in months. Tests administered were the Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA) on a scale of 30 – adjusted for years of education, Epworth Sleepiness Scale (ESS) has a range of 0-24, REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ), Beck's Depression Inventory (BDI) has a range of 0-63, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), a 13-point scale, and the Trait Anxiety Inventory (TRAIT) has a range of 20-80. Education is measured in years above the age of 16. Time since diagnosis and appearance of symptoms is measured in months. UPDRS III and Hoehn & Yahr stage as measured at screening visit.

This withdrawal period did not impact the UPDRS III as motor measures did not vary greatly between research visits. On their ON visit, participants displayed an average UPDRS III of 26.3 while on the OFF one the average was 26.7.

3.3.2 Implicit cognitive tasks

Location priming

The data from one participant were lost. Analysis was conducted on the remaining 29 participants.

To check whether there were baseline differences in reaction time between the two visits, mean reaction times for both the on and off visit were entered into a paired sample t-test. The two states did not differ significantly [$t(1,28)=0.54$, $p=0.592$] and as such differences in baseline reaction times between states were considered negligible. The same analysis was done for accuracy with non-significant results [$t(1,28)=1.14$, $p=0.264$].

The mean negative priming effect, calculated by subtracting the control trial average from the negative trial average, and positive priming effect, calculated by subtracting the positive trials average from the control trial average were entered into a repeated measures ANOVA with prime type (two levels: negative, positive) and medication (two levels: on and off medication) as within-subject factors, visit order was included as a between-subject factor. There was a significant main effect of prime type [$F(1,27)=39.47$, $p<0.001$, $\eta_p^2=0.594$], which reflected a greater positive priming effect (mean: 67.65ms; sd: 53.85ms) than negative priming effect (mean: 7.99ms; sd: 27.19ms), see *Figure 14. T*here was no main effect of medication status [$F(1,27)=0.15$, $p=0.700$], visit order [$F(1,27)=1.64$, $p=0.211$], or interaction between medication and prime type [$F(1,27)=2.69$, $p=0.113$] or medication and visit order [$F(1,27)=0.92$, $p=0.345$]. In order to examine the specific hypothesis of this study, that positive priming would be decreased in participants when they withdrew from their medication, a paired-sample t-tests comparing positive priming on- and off-medication was performed and revealed no significant effect of medication status [$F(1,28)=1.23$, $p=0.230$].

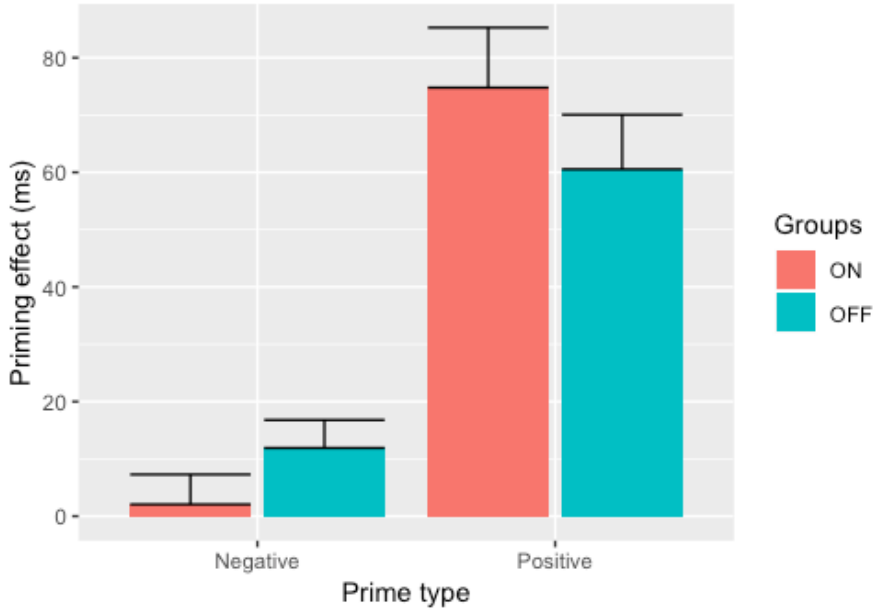


Figure 14. Positive and negative priming effect by medication for the location priming task. Priming effect in milliseconds was calculated for Parkinson's disease patients as follows: individual negative priming effect=individual negative condition reaction time mean-individual control condition mean reaction time; positive priming effect=individual control condition reaction time mean-individual positive priming reaction time mean. Error bars represent standard error.

Contextual Cueing

One participant declined take part in the task. Another did not respond on the majority of their First Visit trials. They were both excluded from analysis. Analysis was run on 28 participants.

To ensure that there were no baseline reaction time or accuracy differences between the two medicated states, a paired sample t-test was conducted between ON and OFF overall reaction times and accuracy. There was no main effect of medication for reaction time [$t(1,27)=1.28$, $p=0.210$] or accuracy [$t(1,27)=1.43$, $p=0.164$].

To measure contextual cueing, a repeated measures ANOVA was carried out using reaction times for block 3 only. Condition (two levels: novel, repeat) and medication were used as within-subject factors and visit order as a between-subject variable. There were no significant main effects of medication [$F(1,26)=1.38$, $p=0.251$], condition [$F(1,26)=1.82$, $p=0.189$] or visit

order [$F(1,26)=2.25$, $p=0.145$], and no significant interactions between medication and condition [$F(1,26)=0.22$, $p=0.644$], visit order and condition [$F(1,26)=1.80$, $p=0.191$], or visit order and medication [$F(1,26)=3.104$, $p=0.090$], see *Figure 15.*

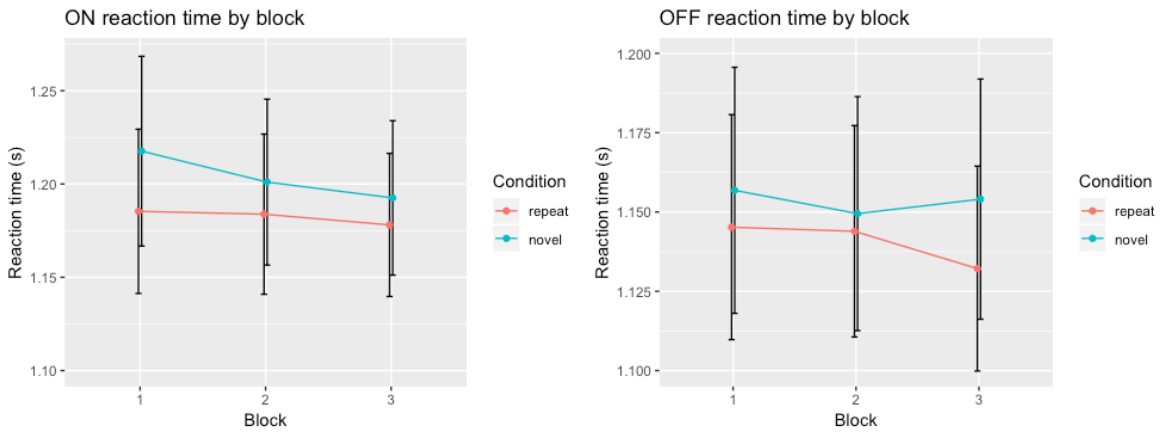


Figure 15. Priming effect for the contextual cueing task by medication. Parkinson's patients ON and OFF their dopaminergic medication in milliseconds. Error bars represent standard error.

Similarly, accuracy was analysed with a repeated measures ANOVA carried out for block 3. There were no significant differences in accuracy between medicated states [$F(1,26)=0.77$, $p=0.387$], no differences in condition [$F(1,26)=0.13$, $p=0.724$] and no differences in visit order [$F(1,26)=1.45$, $p=0.239$] . The medication by condition interaction was also non-significant [$F(1,26)=0.02$, $p=0.904$] as was visit order by medication [$F(1,26)=0.66$, $p=0.425$].

Acquired Equivalency Task

Six participants were excluded from the analysis because they took more than 60 trials to complete the novel consequents portion of the acquisition stage (2 during the OFF visit and 4 during the ON visit). The novel consequents portion is the last phase of learning, in which

participants are presented with novel fish stimuli with which to associate with known cartoon characters.

A repeated measures ANOVA was run for number of trials to learn acquisition, with medication as a within subject variable and visit order as between subject variable. There was no significant main effect of medication [$F(1,22)=0.07$, $p=0.797$] or visit order [$F(1,22)=0.77$, $p=0.391$], however there was a significant interaction between medication and visit order [$F(1,22)=5.56$, $p=0.028$, $\eta_p^2=0.202$] (see *Figure 16)*. This significant medication by visit order interaction was driven by relatively poorer performance (greater number of trials to complete the acquisition phase) in participants OFF medication when the OFF visit was performed first but not when the OFF visit was second (see *Figure 16*), although the difference in performance between the two medication was not significant for Visit One [$t(1,13)=0.69$, $p=0.503$] or Visit Two [$t(1,13)=0.19$, $p=0.852$].

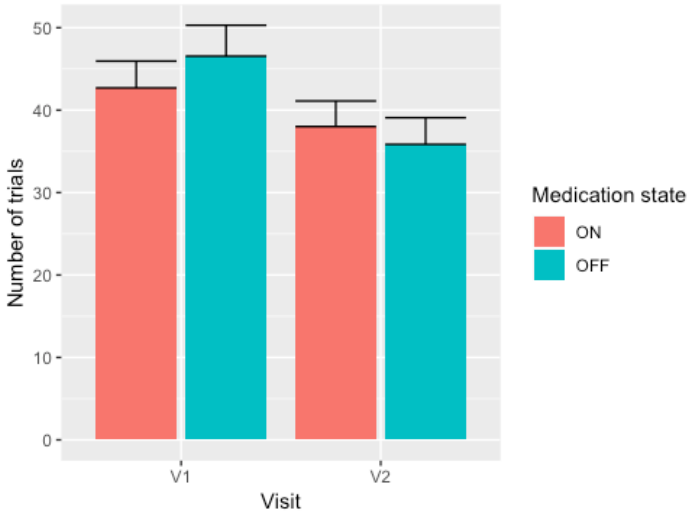


Figure 16. Number of trials necessary to complete the acquisition phase by medication. Acquired equivalency task (acquired trials=shaping+equivalence+novel consequents) for Parkinson's participants both ON and OFF their dopaminergic medication, averaged by visit. Error bars represent one standard error.

A repeated measures ANOVA was run for number of correct retention trials in the testing phase, with medication as within factor and visit order as the between subject factor. There was no

significant main effect for medication [$F(1,22)=0.81$, $p=0.379$], visit order [$F(1,22)=3.81$, $p=0.064$] or interaction between medication and first visit order [$F(1,22)=0.02$, $p=0.878$].

A repeated measures ANOVA was run for number of correct untrained trials in the testing phase, with medication as within factor and visit order as the between subject factor. There was no main effect of medication [$F(1,22)=3.60$, $p=0.071$], visit order [$F(1,22)=1.29$, $p=0.268$] or interaction between medication and first visit [$F(1,22)=0.40$, $p=0.535$].

Implicit Symbol Location Prediction Task

Mean reaction times were entered in a repeated measures ANOVA with direction (two levels: acquisition, reversal), condition (two levels: catch, predicted), and medication (two levels: on, off) as the within subject factors and visit order as a between subject factor. This revealed no significant main effect of medication [$F(1,28)=0.01$, $p=0.925$] or visit order [$F(1,28)=0.07$, $p=0.791$]. However, there were significant main effects of condition [$F(1,28)=13.14$, $p=0.001$, $\eta_p^2=0.319$], and direction [$F(1,28)=9.21$, $p=0.005$, $\eta_p^2=0.248$], which were driven by smaller reaction times on reversal and predictive trials in contrast to acquired and catch trials.

There was also a significant four-way interaction of medication by condition by direction by visit order [$F(1,28)=4.33$, $p=0.047$, $\eta_p^2=0.134$]. To follow up this interaction, acquired and reversal trials were separated. A repeated measures ANOVA was run with medication and condition as the within-subject factors and visit order as a between subject factor for acquired trials. No

significant main effect of medication [$F(1,28)=0.03$, $p=0.857$] or visit order [$F(1,28)=0.001$, $p=0.982$] was found. A main effect of condition was detected [$F(1,28)=6.04$, $p=0.020$, $\eta_p^2=0.177$], with participants displaying worse performance on catch (mean: 873ms; sd: 267ms) versus predicted (mean: 857ms; sd: 345ms) trials. There was no significant interaction between medication and condition [$F(1,28)=0.38$, $p=0.541$] or medication and visit order [$F(1,28)=1.90$, $p=0.180$]. The same analysis was performed for reversal trials. No significant main effect of medication [$F(1,28)=0.10$, $p=0.753$], condition [$F(1,28)=2.21$, $p=0.148$], or visit order [$F(1,28)=0.04$, $p=0.839$] was detected. No interaction between medication and condition [$F(1,28)=0.24$, $p=0.625$] was detected. However, there was a significant interaction between medication and visit order [$F(1,28)=4.44$, $p=0.044$, $\eta_p^2=0.137$], which was driven by faster reaction times in the OFF medication condition, but only on the second study visit (see *Figure 17)*. Two paired-sample t-tests were run comparing the reversal trial reaction times while 'on' and 'off' for each visit. No significant differences were found for Visit One [$t(1,13)=0.17$, $p=0.503$] or Visit Two [$t(1,13)=0.55$, $p=0.595$].

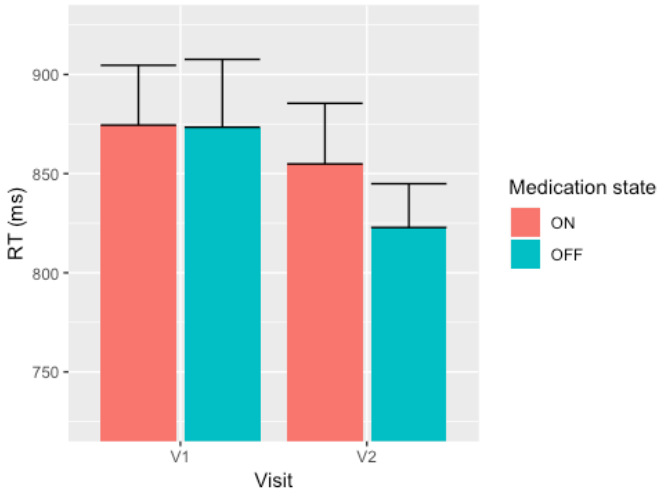


Figure 17. Mean reaction time for reversal trials in the implicit symbol location prediction task by medication. For Parkinson's patients 'on' and 'off' their dopaminergic medication in milliseconds. Error bars represent standard error.

Vigilance is the difference between the mean catch and predictive trials. A repeated measures ANOVA was run with vigilance measures using direction and medication as within subject variables and visit order as between subject variable. There was no significant main effect of medication [$F(1,28)=0.002$, $p=0.968$], direction [$F(1,28)=1.02$, $p=0.322$] or visit order [$F(1,28)=1.72$, $p=0.200$], or significant interaction between medication and direction [$F(1,28)=0.29$, $p=0.595$].

Learning rate, as calculated by the difference between the 4th and 1st quarter vigilance, was analysed in a repeated measures ANOVA with direction and medication as within-subject factor, visit order as a between-subject factor. There was no significant main effect of direction [$F(1,28)=0.37$, $p=0.547$], medication [$F(1,28)=0.27$, $p=0.605$] or visit order [$F(1,28)=0.01$, $p=0.945$] and no significant interaction between medication and direction [$F(1,28)=0.99$, $p=0.328$].

Accuracy rates were very high across both ON (mean: 97%; sd: 1%) and OFF (98%; sd: 1%) conditions on this task. A repeated measures ANOVA was carried out with medication, condition and direction as within subject factors and visit order as a between subject factor. There was no significant main effect of direction [$F(1,28)=0.21$, $p=0.651$], medication [$F(1,28)=1.88$, $p=0.181$] or visit order [$F(1,28)=0.01$, $p=0.937$]. There was a significant main effect of condition [$F(1,28)=5.23$, $p=0.030$, $\eta_p^2=0.157$] with an overall lower accuracy for catch trials (mean: 96%; sd: 6%) versus predicted trials (98%; sd: 3%). There were no significant interactions.

Vigilance on accuracy measures was entered into a repeated measures ANOVA with medication and condition as within subject factors and visit order as a between subject factor. There was no

significant main effect for direction [$F(1,28)=0.51$, $p=0.480$], medication [$F(1,28)=0.08$, $p=0.783$] or visit order [$F(1,28)=0.03$, $p=0.867$]. There were no significant interactions.

Learning rates on accuracy measures were entered into a repeated measures ANOVA with medication and direction as within subject factors and visit order as a between subject factor. There was a significant main effect for direction [$F(1,28)=9.92$, $p=0.004$, $\eta_p^2=0.262$] with a mean learning rate of -0.035 (sd: 0.084) for acquired trials versus 0.070 (sd: 0.147) for reversal indicating no learning is taking place. There was no significance main effect of medication status [$F(1,28)=0.44$, $p=0.513$] or visit order [$F(1, 28)=0.86$, $p=0.361$]. There were no significant interaction, however there was a marginal interaction between medication and visit order [$F(1,28)=3.99$, $p=0.056$].

3.3.3 Explicit cognitive tasks

Oxford Memory Task

Data for 3 participants were missing for one of the visits. Analysis was run on the remaining 27 participants.

Identification performance is the ratio of correct fractal choice trials to total trials in the two-alternative forced choice. A repeated measures ANOVA on identification performance was run with condition (two levels: one fractal, three fractal) and medication as within-subject factors and visit order as a between-subjects factor. There was a significant main effect of condition [$F(1, 25)=84.42$, $p<0.001$, $\eta_p^2=0.772$] with increased accuracy in the 1 fractal condition (mean: 99%, sd: 2%) compared to the 3 fractal condition (mean: 86%, sd: 7%). There was also a marginally significant effect of medication [$F(1, 25)=3.20$, $p=0.086$] with participants displaying

increased identification accuracy while ON medication compared to OFF. Visit order was non-significant [$F(1, 25)=0.07$, $p=0.794$].

In addition, there was a significant condition by medication interaction [$F(1, 25)=5.14$, $p=0.032$, $\eta_p^2=0.171$]. This was further investigated by performing separate paired-sample t-tests for the 1 and 3 fractal conditions separately. This revealed no significant effect of medication for the 1-fractal condition [$t(1, 26)=0.49$, $p=0.631$]. However, on the 3-fractal condition there was a significant effect of medication [$t(1, 27)=2.15$, $p=0.041$], which was driven by reduced accuracy in participants OFF medication (see *Figure 18*).

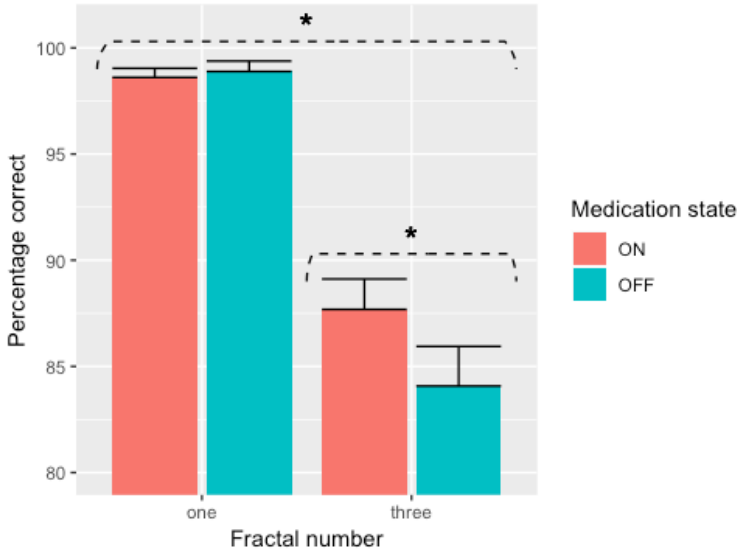


Figure 18. Mean object identification accuracy for the Oxford memory task by medication. Parkinson's patients ON and OFF their dopaminergic medication. Error bars represent standard error.

Absolute error is the distance between the reported location and the true location of the fractal. Trials with incorrect identification were excluded from further analysis. A similar analysis was conducted to that of the identification performance, whereby a repeated measures ANOVA was

run with number of fractals and medication as the within-subject factors and visit order as a between-subject factor. There was a significant main effect of condition on absolute error [$F(1,25)=135.12$, $p<0.001$, $\eta_p^2=0.844$], with a higher absolute error for the 3 fractal condition (mean: 160.23; sd: 47.70) compared to the 1 fractal condition (mean: 54.61; sd: 19.40) . There was no significant main effect of medication [$F(1,25)=0.04$, $p=0.851$] or visit order [$F(1,25)=0.39$, $p=0.536$], and no significant medication by condition interaction [$F(1,25)=0.04$, $p=0.854$] or medication by visit order interaction [$F(1,25)=0.22$, $p=0.642$].

3.4 Discussion

The aim of this study was to examine whether a battery of implicit cognitive tasks was sensitive to pharmacological manipulation in PD by comparing performance in PD individuals while 'on' and 'off' their medication. Contrary to our hypothesis, there was no significant effect of medication withdrawal on measures of implicit cognition, including spatial priming. However, there was an effect of medication withdrawal on an explicit measure of visuospatial object memory, with the 'off' visit resulting in less accurate performance compared to the 'on' one. When considering these findings, it is important to note that the UPDRS motor scores did not differ between the two visits indicating that the withdrawal did not induce significant motor impairment. This implies that the pharmacological manipulation undergone by participants was mild. A positive aspect of this consistency is that we can ascertain that these fluctuations did not impact reaction time and accuracy through slowing or tremor on the 'off' visit. Since the average withdrawal time was 15 hours and 52 minutes, the participants were well above the minimum 12 hours used for an experimental withdrawal manipulation.

One explanation for the differences in UPDRS scores is the selection of low tremor individuals during the recruitment process resulting in limited motor fluctuations between the 'on' and 'off' states. To ensure the safety of the participants, only individuals with a tremor score below 3 during the 'on' medication screening visit were included in the study. However, this is standard practice and the same cut off was used in other studies which found disparities in the 'on' and 'off' states. In addition, medication withdrawal is more pronounced in the early-stages of PD with these sufferers displaying higher sensitivity to DA medication compared to later-stage sufferers. This is thought to be because of the large number of dopaminergic neurons still present in the early stages of the disease, offering more targets on which the dopaminergic medication to exert its effects upon (Bravi et al., 1994; Manza et al., 2017). As mentioned previously, it could be that through our stringent selection criteria of high-MoCA, low-tremor individuals, an inadvertent sorting of participants occurred, composing our cohort of individuals with little fluctuation and therefore some medication insensitivity influencing our results. Alternatively, it is possible that cognitive changes did indeed surface throughout the short overnight withdrawal period but that tasks were not sensitive enough to the changes that did arise. Previous studies have successfully detected 'on' and 'off' changes using a 12-hour withdrawal period (Szewczyk-Krolikowski et al., 2014). Finally, while the UPDRS did not vary between visits, certain changes were detected in the explicit task, as well as the acquisition stage of the acquired equivalency task and the reversal trials of the ISLP, indicating that the medication withdrawal was pronounced enough for certain cognitive changes to arise.

A pattern of interaction between visit order and medication emerged in Study 2. This interaction was apparent in the number of trials needed to learn the acquired portion of the equivalency task

and reaction time on the ISLP. A better performance was seen on the second visit when the first visit had been 'on' medication. This seems to indicate that learning was taking place between the first and the second visit, and that this learning was facilitated by dopaminergic medication specifically during initial exposure to the task in Visit One. This is supported by the well-established notion that dopaminergic medication enables the brain to learn to make better choices through feedback reward pathways (Schultz, 2006), indicating that participants were 'learning" how to perform well on the task through feedback. Specifically, dopamine release has been linked to long term potentiation in the hippocampus during encoding of novel information (Roggenhofer et al., 2010). This could explain why no improvements were detected in the testing stage immediately following the acquisition stage and why improvement in only the reversal trial reaction times were detected in the ISLP. Implications for future research may involve a longer delay between the two visits to mitigate this between-visit learning effect. Alternatively, a research schedule whereby participants are administered the dopaminergic medication in the Visit Two would remove the dopaminergic learning effect altogether, however visit randomisation would then be impossible.

Further to the above findings, significant differences arose in the OMT, the explicit task examining visuospatial memory. Results indicate a significant interaction between medication and fractal condition, with individuals OFF medication demonstrating worse performance on the 3-fractal condition than individuals ON medication with no difference in the 1-fractal trials in identification accuracy. Pertzov et al. (2015) found that performance in the 3-fractal condition on both the identification and the localisation portions of the task successfully differentiated between age groups with older individuals displaying decreased performance compared to their

younger counterparts. This finding is relevant to our cohort as the average age of participants was 65 years. Indeed, the role of dopaminergic neuronal loss in aging is well-documented. It has previously been shown that the cognitive differences observed between younger and older healthy adults can be remediating by dopaminergic medication, both under the form of *d*-amphetamine (AMPH) (Garrett et al., 2015) and L-dopa (Shohamy & Wimmer, 2013). In certain cases, older participants under the influence of dopaminergic medication even outperformed adults off medication regardless of age. This is in line with results from Study 1, as PD patients 'on' medication outperformed both RBD and HC in the feedback learning acquisition stage of the acquired equivalency task. This raises the question of whether the observed deficiencies seen on the OMT were due to the nature of the task being explicit or due to the age sensitivity of the task, with deficits caused by senescence in our older cohort and remedied by the dopaminergic medication on task performance over time.

In terms of the other implicit tasks, neither the location priming nor the contextual cueing task detected any significant differences between groups. Priming effect has been shown to be selectively sensitive to methylphenidate intervention in men (Klinge et al., 2018), with an increased positive priming effect in the male experimental group only when tested against methylphenidate. This could explain the lack of findings in the gender-matched Study 2 cohort in comparison to the male-dominated RBD group in Study 1. Similarly, contextually guided spatial attention did not detect differences between the two visits. van Asselen et al. (2009) found an impairment on contextual cueing in PD compared to healthy controls, however medication was not reported in this study.

To summarise, significant differences emerged on explicit visuospatial measures of shedding some light on the sensitivity of implicit compared to explicit cognition function in medicated and un-medicated PD, specifically that explicit tasks may be more sensitive to the pharmacological effect of dopaminergic medication in the disease. Further evidence points to the importance of positive feedback and reward-based learning and age when evaluating performance 'on' and 'off dopaminergic medication. The next step in this research program will be to administer the same battery of implicit tasks to a drug naive population of RBD patients, to avoid all possible residual pharmacological effects stemming from the dual visit setup of this study. Since the feasibility of recruiting a drug-naive population of PD patients is low, administering the battery in a group of RBD participants both ON and OFF medication, who have never been exposed to dopaminergic medication, would constitute a promising alternative, especially given the significant differences in performance that arose from the RBD group in the first study.

4. General Discussion

In the present studies, we investigated whether a battery of implicit cognitive tasks would be sensitive to the cognitive changes associated with prodromal and early stage PD as well as the pharmacological manipulation in early PD. To investigate this, we used a battery of implicit cognitive tasks which have been validated as sensitive to pro-cognitive pharmacological manipulation (Harmer et al., 2011; Klinge et al., 2018).

In Study 1, we examined whether there were differences in task performance between a group of individuals with REM sleep behaviour disorder, a group with Parkinson's Disease and a group of healthy age-matched controls. In Study 2, we investigated whether this battery was sensitive to dopaminergic pharmacological challenge, by comparing task performance in patients with Parkinson's disease 'on' and 'off' their medication. Study 1 examined the hypothesis whereby RBD and PD participants would display worse performance on implicit measures compared to healthy controls. Study 2 examined the hypothesis whereby individuals 'off' dopaminergic medication would be impaired compared to when they were 'on'.

Findings from Study 1 indicate that PD and HC groups performed similarly, while the RBD group were impaired on certain implicit functions. Most notably, the RBD group displayed impaired positive priming compared to HC and PD. Study 2 results indicate that medication status did not impact performance across implicit tasks, with participants performing similarly while 'on' and 'off' their dopaminergic medication. However, significant differences between the two pathologies did emerge in measures of explicit visuospatial memory, with performance on the 'off' visit being poorer than the 'on' one. These results are contrary to our initial

hypothesis and indicate that explicit forms of visuospatial memory, specifically object identification, display heightened sensitivity to pharmacological manipulation in PD compared to implicit cognition.

The main significant finding in Study 1 was the difference between the RBD and PD groups concerning positive priming effect. Since the three groups did not differ significantly in terms of MoCA or the explicit visuospatial memory task, it can be said that implicit cognition in the form of spatial positive priming is more sensitive than measures of explicit cognition like visuospatial memory when differentiating between RBD and both HC and PD, confirming our initial hypothesis for Study 1. Additionally, the difference observed between RBD and PD in positive priming led us to believe that medication could affect positive priming performance, noting the dopaminergic medication prescribed to the PD group but not RBD. Alternatively, it was hypothesized that the difference could be due to differing underlying cognitive mechanisms in the two pathologies.

To further explore the role of medication in the prodromal and early stage PD, as well as examine the importance of medication in our findings from Study 1, the same battery was administered to PD participants 'on' and 'off' their medication. The findings of Study 2 revealed no medication difference between the two groups on the implicit cognition measures, lending support to the theory in which different pathological mechanisms, such as subtypes, are driving the observed results. This is furthered by only 2 participants in Study 2 being RBD converters, indicating two quasi-distinct pathological groups. Specifically, Study 2 revealed that explicit cognition under the form of visuospatial identity of short term memory was more sensitive to the

cognitive changes associated with dopaminergic medication in PD. Deficits were detected in the 'off' medication state on accuracy and reaction time of reversal trials of the ISLP as well as the feedback based acquisition portion of the acquired equivalency task. It is possible that the nature of these tasks enabled dopaminergic medication to facilitate performance, specifically since dopaminergic medication has been linked to enabling the encoding of novel information based long term potentiation, for example in feedback learning. It has also been shown to remedy some of the cognitive deficits seen in older individual, interacting with the OMT's previously established sensitivity to age-related cognitive deficits.

As such, the results from Study 2 indicate that it was most likely not a medication effect which governed the RBD and PD differences in priming seen in Study 1. This left the alternative hypothesis of different pathological mechanisms governing the priming effect in both groups. Previous literature on the pathophysiology of RBD link the disease to a specific degeneration of a sub-population of glutamatergic neurons specifically responsible of muscle atonia, localized in the caudal pontine sublaterodorsal tegmental nucleus (SLD) (Luppi et al., 2011). In the temporal staging system of PD initially brought forth by Braak et al. (2003) and described in further detail in the general introduction, ∝-synuclein pathology begins in the medulla of the brain and advances through distinct stages to the more rostral structures. The SLD brain region associated with RBD pathology corresponds to the 2nd stage in the model, whereas the motor symptoms associated with PD development correspond to the 3rd and 4th stage and dementia to the 4th and 6th (see *Figure* 1). As such, there is an overlap of brainstem nuclei degeneration in PD and RBD, however not every PD patient develops RBD, and to a much lesser extent than the degree to which individuals with RBD go on to develop PD. The difference could lie in the degree of

spread of the synucleinopathy and subsequent neuronal degradation in each brain region, however more research is needed to elucidate this. Nonetheless, this model marries RBD and PD under the same pathological mechanisms, with degradation ratio for each brain region separating out the different functional subtypes. Under this model, the differences observed in our study while not indicative of two completely differing pathological mechanisms could have been related to differences in degeneration patterns differences.

In addition, priming effect has also been known to vary in PD in correlation with other clinical factors such as depression and time since diagnoses (Manza et al., 2017; Troche et al., 2006). Especially relevant to our findings is the link between bradykinesia and priming effect observed in PD (Troche et al., 2006). Since baseline RBD has also been significantly linked to future development of bradykinesia (Bugalho & Viana-Baptista, 2013), a potential three-way link between RBD, bradykinesia and priming effect could exist, with the same mechanism governing the development of RBD also responsible for the differences seen in priming compared to the PD group. Since the tegmental area is directly implicated in the development of RBD and bradykinesia, it could be that the degradation of this area is responsible for the deficits seen in positive priming in RBD but not PD. Additionally, the differential implication of the direct and indirect dopaminergic pathways in positive and negative priming respectfully could be responsible for the difference in witnessed by group and prime type. In Study 2, the importance of clinical factors in influencing performance has also been highlighted, with the sensitivity of explicit cognitive tasks to the interaction between dopaminergic medication and age. This could be due to the known overlapping implication of the hippocampus in visuospatial explicit memory, aging and the dopamine mediated reward pathway.

In summary, the differences between RBD and PD groups on implicit cognition could be related to differential neuronal degeneration patterns in both types of pathology. Similarly, explicit cognitive mechanism such as visuospatial identification in Study 2 could be particularly sensitive to aging and the repairing effect of dopaminergic medication. Correlational analyses with clinical factors in both explicit and implicit tasks offer insights into the specific brain regions which could be governing the impaired mechanisms.

Some important limitations should be considered when interpreting our findings. In both studies, a MoCA score outside the normal range was an exclusion criteria to ensure we were only detecting the subtle cognitive deficits that were otherwise undetectable via explicit means. However, this artificially raised our average MoCA score. It is possible that the high inclusion MoCA, selected for individuals with no cognitive deficits, could have biased our results. In addition, the overall shortening of the contextual cueing task and the removal of the extra-dimensional portion in the implicit symbol location priming task, may have reduced the sensitivity and power to detect existing differences. However, these changes were made to shorten the visit and reduce any effect of tiredness that may have interfered with performance. Finally, while screening measures were taken to ensure that our cohort of participants were either healthy, had a diagnosis of RBD via a polysomnographic test or a PD diagnosis via a letter from a consultant, the existence of psychopathology in our healthy controls or the common diagnosis of depression in PD and RBD that we did not control for but has been found to interact with the implicit tasks, may have influenced our findings. Additionally, the heightened sensitivity to pharmacological manipulation of these tasks make them susceptible to other psychoactive medication, which a proportion of patients were taking in both studies. Similarly, some of these

tasks have been shown to be sensitive to other demographic factors such as gender in the case of the location priming task, which could have influenced our findings. Another limitation is that the small sample size of 30 participants may not have had sufficient statistical power to detect differences between the different groups, limiting our findings. A larger study cohort may have been able to explore in more detail some of the trend level effects we describe here.

For Study 2, the short withdrawal period and lack of difference in the UPDRS scores between visits indicated the limited the importance of our intervention which could have contributed to our limited results. However, previous studies have successfully detected changes both in the UPDRS and other methods by using the overnight withdrawal. Manza et al. (2017), surveyed a range of 42 medication withdrawal studies, with an average 'on' score of 30.43 and an average 'off' score of 19.83. These figures are in line with previous literature on the medication responsiveness of the motor symptoms of PD, which varies depending on medication type and clinically important difference (Bordelon et al., 2011; Shulman et al., 2010). Bordelon et al. (2011) also compared medication responsiveness of motor symptoms accross the three traditional PD subtypes: tremor dominant, akinetic-rigid and mixed. This yielded no statistically significant differences disqualifying the explanation of subtype filtering through the MoCA cutoff. As mentioned previously, an explanation for this unchanged UPDRS could be the selection of participants with low baseline UPDRS scores selecting participants with insensitivity or little fluctuation.

Our findings provide preliminary evidence for the sensitivity of implicit cognition in the form of positive priming to the changes existing in RBD, a prodromal form of PD. However, this thesis

did not provide evidence for heightened sensitivity of implicit versus explicit cognition to the effects of dopaminergic medication in PD. Instead, there is some evidence indicating explicit memory under the form of visual identification to be more sensitive measure of pharmacological manipulation in PD. Paired with the previous literature on implicit cognition, these findings support the theory brought forth by Troche et al. (2006) questioning the direct impairment of inhibition in PD, instead highlighting the importance of the interaction of a variety of clinical factors when evaluating cognition in Parkinson's. With the example of location priming, directly conflicting results have been previously explained by correlations with clinical factors such as bradykinesia and depression. At present, these studies have not provided the evidence necessary to validate this battery of cognitive tasks as cognitive biomarkers of early cognitive decline and pharmacological manipulation in Parkinson's. Nonetheless, a next step in this research course could be to examine the effects of this task battery on dopaminergic medication to drug-naive RBD participants, to contextualize the difference in findings of Study 1 concerning RBD and PD.

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