Making it Count: Novel Behavioural Tasks to Quantify Symptoms of Dementia with Lewy Bodies

Joseph Phillips

School of Psychology, Western Sydney University

A thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy
School of Psychology

Supervisors:

Associate Professor Ahmed A. Moustafa
Western Sydney University

Professor Simon J. G. Lewis
University of Sydney

Associate Professor Gabrielle Weidemann
Western Sydney University

Declarations

This thesis was supported by the Australian Postgraduate Award

Acknowledgements

Firstly, I would like to thank all the patients and participants who generously gave up their time to participate in our research. I hope the data that we collected will provide the foundation to improve future work in dementia with Lewy bodies resulting in positive outcomes for patients with this poorly understood disease.

I would like to thank my supervisors who were critical to the completion of this thesis. Especially Professor Simon Lewis, the amount of time and energy you gave me during my candidature was phenomenal. You were there to hold up my successes, help me learn from the non-successes and to give me a kick in the ass when focus started to drift. I don't think this thesis would have gotten to where it is without your guidance and insight. I would also like to thank Associate Professor Ahmed Moustafa, you had confidence in me to let me pursue what I wanted and when my thesis took a turn that was outside of your area of expertise, you were still there to give me guidance and support when I needed it. Thank you to Professor Glenda Halliday for your invaluable input for my publications.

I would also like to thank all the members past and present of the Parkinson's Disease Research Clinic. It is a pleasure to work in a team of friendly people with broad range of expertise and are willing to help each other and hold each other up. Specifically, Elie, you are the most intelligent and busiest person I know. Even so, you would make time to discuss different theories or help me understand the plethora of medical terms I learnt during my candidature. Kaylena, your passion, and enthusiasm helped me push forward while your knowledge helped me overcome obstacles. I was privileged to be able to work alongside two accomplished early career researchers and I look forward to collaborating in the future. A huge thank you to Deb, who was there when I needed to talk to a friend. Marilia my wingman, I couldn't have completed this thesis without the experience from Deb and yourself in clinic, engaging with patients and deciphering doctor speak. Tash, Belle, and Josh for helping me keep the social side of the clinic (and my sanity) alive with our weekly Jackbox sessions during lock downs. Dee for giving me an excuse to get away from my computer to meet up and talk about non-PhD topics.

To my Western Sydney University PhD colleagues that took part in our shenanigans, you all saved my sanity by lifting my head up to see the outside world. And when that world fell apart, keeping in touch with Zoom for Friyay drinks and games. El you are one of the kindest, selfless people I know, you showed me what true strength is and your friendship kept me going. You also kept me on my toes as my pranking nemesis. Thank you to Brooke for the fortnightly-after-work drinks, it was usually the high point of my week. Amy, another wonderful person in my life that made the office much more fun to be in and whose friendship also got me through dark times.

I would also like to acknowledge the support from my friends and family back home. While is has been difficult being unable to return home for the past couple of years, you have all still been supportive and given me encouragement during this long

journey. I would also like to acknowledge and the love, support, and encouragement from Melanie, you stuck with me during the first half of this odyssey and tried to give me as much support as you could during the second half. Carolyn and Harry for reminding me how much on an accomplishment this thesis was and distracting me during the long examination period.

Statement of Authentication

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Joseph R Phillips

Table of Contents

Publications

Publications that make up this thesis:

Chapter Two:

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (2019). Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia With Lewy Bodies. *J Geriatr Psychiatry Neurol*, 891988719882093. https://doi.org/10.1177/0891988719882093

Chapter Three:

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (In Review). An adaptive measure of visuospatial impairment in Dementia with Lewy Bodies. *Movement Disorders Clinical Practice*.

Chapter Four:

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (2021). Evaluating a novel behavioral paradigm for visual hallucinations in Dementia with Lewy bodies. *Aging Brain*, *1*, 100011. https://doi.org/https://doi.org/10.1016/j.nbas.2021.100011

Publications during candidature:

Matar, E., Phillips, J. R., Ehgoetz Martens, K. A., Halliday, G. M., & Lewis, S. J. G. (2019b). Impaired Color Discrimination-A Specific Marker of Hallucinations in Lewy Body Disorders. *J Geriatr Psychiatry Neurol*, *32*(5), 257-264. https://doi.org/10.1177/0891988719845501

Ehgoetz Martens, K. A., Matar, E., Hall, J. M., Phillips, J., Szeto, J. Y. Y., Gouelle, A., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2019). Subtle gait and balance impairments occur in idiopathic rapid eye movement sleep behavior disorder. *Mov Disord*, *34*(9), 1374-1380. https://doi.org/10.1002/mds.27780

Ehgoetz Martens, K. A., Matar, E., Shine, J. M., Phillips, J. R., Georgiades, M. J., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2020). The Neural Signature of Impaired Dual-Tasking in Idiopathic Rapid Eye Movement Sleep Behavior Disorder Patients. *Mov Disord*, *35*(9), 1596-1606. https://doi.org/10.1002/mds.28114

Bailey, P. E., Ebner, N. C., Moustafa, A. A., Phillips, J. R., Leon, T., & Weidemann, G. (2020). The weight of advice in older age. *Decision*. https://doi.org/10.1037/dec0000138

Crouse, J. J., Phillips, J. R., Jahanshahi, M., & Moustafa, A. A. (2016). Postural instability and falls in Parkinson's disease. *Rev Neurosci*. https://doi.org/10.1515/revneuro-2016-0002

Hall, J. M., O'Callaghan, C., Muller, A. J., Ehgoetz Martens, K. A., Phillips, J. R., Moustafa, A. A., Lewis, S. J. G., & Shine, J. M. (2019). Changes in structural network topology correlate with severity of hallucinatory behavior in Parkinson's disease. *Netw Neurosci*, *3*(2), 521-538. https://doi.org/10.1162/netn_a_00078

Hall, J. M., O'Callaghan, C., Shine, J. M., Muller, A. J., Phillips, J. R., Walton, C. C., Lewis, S. J., & Moustafa, A. A. (2016). Dysfunction in attentional processing in patients with Parkinson's disease and visual hallucinations. *J Neural Transm (Vienna)*, *123*(5), 503-507. https://doi.org/10.1007/s00702-016-1528-3

Matar, E., Phillips, J., Martens, K. E., Halliday, G., & Lewis, S. (2019a). Differential temporal processing across Lewy body disorders and relation to cognitive fluctuations. Movement Disorders,

Moustafa, A. A., Chakravarthy, S., Phillips, J. R., Crouse, J. J., Gupta, A., Frank, M. J., Hall, J. M., & Jahanshahi, M. (2016a). Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: behavioral and neural studies. *Rev Neurosci*. https://doi.org/10.1515/revneuro-2015-0070

Moustafa, A. A., Chakravarthy, S., Phillips, J. R., Gupta, A., Keri, S., Polner, B., Frank, M. J., & Jahanshahi, M. (2016b). Motor symptoms in Parkinson's disease: A unified framework. *Neuroscience & Biobehavioral Reviews*, *68*, 727-740. https://doi.org/https://doi.org/10.1016/j.neubiorev.2016.07.010

Moustafa, A. A., Phillips, J., Kéri, S., Misiak, B., & Frydecka, D. (2016c). On the Complexity of Brain Disorders: A Symptom-Based Approach [Perspective]. *Frontiers in Computational Neuroscience, 10*. https://doi.org/10.3389/fncom.2016.00016

Phillips, J. R., Eissa, A. M., Hewedi, D. H., Jahanshahi, M., El-Gamal, M., Keri, S., & Moustafa, A. A. (2016). Neural substrates and potential treatments for levodopa-induced dyskinesias in Parkinson's disease. *Rev Neurosci*, *27*(7), 729-738. https://doi.org/10.1515/revneuro-2016-0009

Tables and Figures

Abbreviations

5HT	Serotonin
ACh	Acetylcholine
AChEIs	Acetylcholinesterase Inhibitors
AD	Alzheimer's disease
APOE	apolipoprotein E
BOLD	Blood oxygen level dependent
BPP	Bistable Percept Paradigm
CAF	Clinical Assessment of Fluctuations
CDT	Clock Drawing Task
CF	Cognitive fluctuations
CI	Cingulate Island
COWAT	Controlled Oral Word Association Test
CSF	cerebrospinal fluid
DA	Dopamine
DAN	Dorsal attentional network
DAT	DA transporters
DBS	Deep brain stimulation
DJ-7	Parkinson's protein 7
DLB	Dementia with Lewy Bodies
DMN	Default mode network
DTi	Diffusion tensor imaging
EEG	Electroencephalography
EMG	Electromyography
FIRDA	Frontal intermittent rhythmic delta activity
fMRI	Functional MRI
FTD	Frontotemporal dementia

GBA	glucocerebrosidase
Glu	Glutamate
HC	Healthy control
HMR	heart-mediastinum ratio
IMR	Immunomagnetic reduction assay
LB	Lewy bodies
LBD	Lewy body dementia
LC	Locus coeruleus
LRRK2	leucine-rich repeat kinase 2
MCI	Mild cognitive impairment
MCI-LB	Prodromal DLB
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MFQ	Mayo Fluctuations Questionnaire
MIBG	Meta-iodobenzylguanidine myocardial scintigraphy
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Mental Rotation
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
NBM	Nucleus of Basalis of Meynert
NE	Norepinephrine
NfL	Neurofilament light chains
NPI	Neuropsychiatric Inventory
ODF	One Day Fluctuation
OSA	Obstructive sleep apnoea
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PET	photon emission tomography

PsycH-Q	Psychosis and Hallucinations Questionnaire
pTau	Phosphorated Tau
QoL	Quality of life
RAVLT	Rey Adult Verbal Learning Task
RBD	REM Sleep Behaviour Disorder
RBDSQ	RBD Screening Questionnaire
RCF	Rey Complex Figure
REM	Rapid eye movement
rsfMRI	Resting state fMRI
RSWA	REM sleep without atonia
RT-QuIC	real-time quaking-induced conversion
SART	Sustained Attention Response Task
SCOPA-PC	Scale for Outcomes in Parkinson's Disease – Psychiatric Complications
SNCA	α-synuclein encoding gene
SPECT	single photon emission computed tomography
STD	sublaterodorsal tegmental nucleus
STN	sub-thalamic nucleus
TMT	Trials Making Task
VAN	Ventral attentional network
VH	Visual hallucinations
VOSP	Visual Object and Space Perception battery
vPSG	Video polysomnography
5HT	Serotonin

Abstract

Dementia with Lewy bodies (DLB) is a neurodegenerative disease and a common cause of dementia in the elderly. The primary pathology of DLB is the mis-folding of the α-synuclein protein, classifying DLB as a synucleinopathy. However, concomitant pathologies are commonly found in post-mortem examination of DLB patients that may complicate diagnosis. Furthermore, DLB is a relatively new disease, first discovered in 1976, while the first official diagnostic criteria released in 1996. Consequently, the diagnostic criteria for DLB have evolved as more is learnt about the clinical and neuropathological profile. Synucleinopathies are also known to be heterogeneous, with no single symptom or biomarker present in *all* DLB cases. Instead, combinations of common symptoms lead to a diagnosis of *probable* DLB. Two of the most prominent and debilitating symptoms of DLB are visual hallucinations and cognitive fluctuations. Visual hallucinations (VH) in DLB patients are typically vivid, well-formed percepts and are a major cause of patient and caregiver stress as well as a risk factor for the patient being placed into professional care. Cognitive fluctuations (CF) involve a cycling change in attention and alertness and may occur on a daily or monthly basis, while drops in awareness may last seconds or hours. Currently, the only tools to measure cognitive fluctuations or visual hallucinations are scales or questionnaires that rely on responses from the patient or informant. Furthermore, severity of the symptom is then ranked on an arbitrary ranking system. While this method has advantages in a clinical setting, the subjective nature of the scales combined with the ranking of scores results in a loss of sensitivity. In a research setting, especially imaging or clinical trials, objective measures that are sensitive to changes in symptom severity are highly valued. This allows researchers to assess the relationship between behavioural and fMRI data and clinicians to observe subtle changes in severity. Furthermore, the measures need to be easy to conduct as patients are often severely impaired.

The aim of this thesis is to test cognitive function using three paradigms that are novel to DLB patients: Sustained Attention Response Task (SART), the Mental Rotation (MR) task and the Bistable Percept Paradigm (BPP). Chapter Two tests the SART as a measure of sustained attention within the DLB cohort and compares performance with clinical measures of CF. Findings suggest that the number of misses in the SART are correlated with measure of CF, supporting future use of the SART as an indicator of CF severity. Chapter Three compares DLB performance in the MR task with healthy controls. Findings from this chapter suggest that the MR is accessible to DLB patients, as well as providing a good measure of visuospatial impairment. Furthermore, the difficulty of the MR task can be adapted to match the ability of DLB patients, making a more sensitive measure. Chapter Four investigates the BPP as a measure of VH severity in DLB patients. This study found that the number of

misperceptions made was correlated with measures of VH. Additionally, DLB patients were found to miss many percepts when presented with multi percept images. This indicated that misses in the BPP may tap into attention or saccadic impairments present in DLB patients. Chapter Five focused on patients that have a high-risk of developing DLB, referred to as prodromal DLB. These high-risk patients were given the SART, MR and BPP tasks to compare their performance with performance of DLB patients in Chapters Two – Four. Prodromal DLB patients performed at the same level as cognitively normal isolated REM sleep behaviour disorder (iRBD) patients for the SART. However, there is a trend suggesting that the prodromal DLB patients may be poorer at the MR and BPP tasks but did not make significance due to small sample sizes. The findings from Chapter Five also highlight that a revision is needed for the recently proposed prodromal DLB criteria. Overall, this thesis provided the groundwork needed before these three tasks can be utilised in a clinical or research setting. Moreover, as each task was accessible to DLB patients and provided a measure associated with VH or CF, they may prove useful for future neuroimaging/neuropsychological studies. Indeed, the SART is currently part of a neuropsychological battery used in a drug trial (NCT04739423). I here argue that the remaining tasks will also prove to be useful and provide much needed insight to this devastating disease.

Chapter One

1. An overview of dementia with Lewy bodies.

1.1.   Overview of Chapter

During the early stages of the dementia with Lewy bodies (DLB), separating patients with DLB from Parkinson's disease (PD), PD with dementia (PDD) or Alzheimer's disease (AD) patients has been a problem for many clinicians. Difficulty arises due to the overlap of shared symptoms between DLB, PD, PDD and AD and comorbidity of pathology often present in DLB patients. The purpose of this chapter is to review the current knowledge on DLB and to compare with similar findings in PD, PDD or AD to demonstrate the amount of overlap between DLB and PD, PDD and AD. This will begin with a general overview of DLB (section 1.2), highlighting the main features of DLB, the challenges and the impact DLB has on patients and caregivers. Neuropathology that underlies DLB is then reviewed (section 1.3), beginning with α-synuclein and how this protein leads to DLB and how α-synuclein interrupts neurotransmitters systems. This is followed with an extensive review of current biomarkers of DLB (section 1.4) which will include findings from imaging studies, neurochemicals, electroencephalography (EEG) and biopsies. Genetic risk factors will then be covered (section 1.6), outlining the genes that are associated higher risk of developing DLB, that are also shared with PD or AD. The review will then focus on the main symptoms of DLB (section 1.7) and the common methods used to measure DLB symptoms (section 1.8). The final section of this chapter will review current pharmacological and non-pharma logical interventions for DLB, highlighting the problems with current treatments and the need for improved clinical trials using the SART, MR and BPP introduced in Chapters 2 - 4.

1.2.   Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a common neurodegenerative disease that is characterised pathologically by the presence of Lewy body (LB) inclusions, which are composed of abnormally configured α-synuclein protein. Dementia with Lewy

bodies is characterised by a precipitous decline in cognition; Van der Beek et al. (2022) demonstrate a significant annual decline in the Mini Mental State Exam (MMSE) as well as an increase in psychotic symptoms each year following diseases onset. Given its primary pathology, DLB is regarded as a synucleinopathy: a cluster of neurodegenerative diseases that also have LB pathology. Although, concomitant pathologies (e.g., amyloid, tau and cerebrovascular; Chin et al., 2019; Matej et al., 2019; McKeith et al., 2005) are commonly found in DLB patients at post-mortem that may influence the clinical phenotype (Sarro et al., 2016; van der Zande et al., 2020b) and have significant implications for future therapeutic strategies (McKeith et al., 2017).

The prevalence of DLB varies considerably across studies. When focusing on patients diagnosed with dementia, studies have found that 4 – 5% have DLB (Kane et al., 2018; Vann Jones & O'Brien, 2014). While other studies suggest that DLB is responsible for 15-20% of dementia cases (Aarsland et al., 2008; Jellinger & Attems, 2011). The large variance across the studies is likely due to the evolving diagnostic criteria for DLB (McKeith et al., 2017; McKeith et al., 2005; McKeith et al., 1996), as well as the use of different diagnostic techniques (inspection of case notes, autopsy reports or literature reviews) and equipment available (clinical interview or single photon emission computed tomography [SPECT] scans; Kamagata et al., 2017; Kasanuki et al., 2017b).

In most cases, the prognosis of DLP patients is bleak (Aarsland 2016). This poor prognosis is often driven by a delayed diagnosis due to presentation of seemingly disparate range of symptoms. These symptoms may include a decline in cognition, the presence of parkinsonian symptoms (e.g., tremor, slowness), sleep disturbances (dream enactment) and psychiatric/ophthalmologic features such as visual hallucinations (Surendranathan et al., 2020). However, neurodegenerative Lewy body pathology is a slow process, which is likely to have begun many years before a clinical presentation. Indeed, on detailed questioning many patients will have experienced anosmia or sleep disorders before their first clinic visit (Donaghy et al., 2015; Ferman et al., 2011; Fujishiro et al., 2015; Postuma et al., 2019). The disease course of DLB

varies across patients, with the life expectancy from diagnosis quoted as varying between 2 and 10 years across studies (Mueller et al., 2017; Mueller et al., 2019; Price et al., 2017).

Cognitive decline is the essential core feature of DLB (McKeith et al., 2017) and is more rapid than most neurodegenerative dementias with DLB patients averaging a loss of 4 points per year on the Mini Mental State Examination (MMSE; Rongve et al., 2016). This is compared to 1.75 points lost per year in Parkinson's Disease (PD) patients with dementia (PDD) and 3 points per year in Alzheimer's disease (AD; Mueller et al., 2017). Quality of life (QoL) in DLB patients is also very low (Bostrom et al., 2007a), which is due not only to the rapid cognitive decline, but also to other core features of DLB (see Section 1.5). Indeed, the presence of cognitive fluctuations and the emergence of visual hallucinations (VH) can cause significant distress, as well as hospitalisation (Lee et al., 2018a). Burden on the caregivers attending to patients with DLB is also higher than what is experienced by caregivers of patients with other dementias. This is thought to be due to several factors including the following: lower selfcare, increased aggression and neuropsychiatric symptoms from the patient, decrease in responsiveness from patient, as well as poor sleep due to the patient being less settled overnight (Rigby et al., 2019; Rigby et al., 2021). The economic costs of DLB are also high (DLB: US$ 52,200, AD: US$ 17,800 per annum; Bostrom et al. 2007a) due to the increased levels of full-time care required and the higher rates of hospitalisation arising from psychotic symptoms (visual hallucinations and/or delusions), episodes of delirium, injury due to falling and aspiration pneumonia (Bostrom et al., 2007b).

Currently, there are no treatments available to slow down the aggregation of LB and neuronal loss (Jellinger, 2018; Korczyn & Hassin-Baer, 2015), while symptomatic treatments typically involve off-label interventions with unclear efficacy (Querfurth et al., 2000; Rolinski et al., 2012; Sabbagh et al., 2005; Wang et al., 2015; Wild et al., 2003; see section 1.7). Furthermore, treatments that do counteract neurochemical imbalances that drive symptoms are short lived due to the rapid progression of DLB,

while some treatments can trigger severe adverse reactions (Ballard et al., 2005; McKeith et al., 1992a).

1.3.   Neuropathology in Dementia with Lewy Bodies

The hallmark feature of DLB are the insoluble LB that form within neuronal bodies, resulting in neuronal death. This section will discuss theories regarding how LB are formed from α-synuclein and how LB may result in neuronal apoptosis. This effect of LB on neurotransmitter systems in DLB will then be discussed and compared with neurotransmitter impairments observed in PD, PDD and AD.

1.3.1. Proteinopathy and Lewy Bodies

The main histological feature of DLB is the presence intra-cytoplasmic inclusions of α-synuclein protein referred to as LB that form within neurons throughout the nigrostriatal, limbic, and neocortical regions (Burton et al., 2002; Collerton et al., 2003; Morra & Donovick, 2014; Nakatsuka et al., 2013). Lewy bodies consist mostly of α-synuclein proteins that have become misfolded from their wild-type configuration (Burré et al., 2018; Spillantini et al., 1997). During their maturation, Lewy bodies may attract other components, such that a mature LB often contains microtubule associated proteins (Jensen et al., 2000), various lipids (Araki et al., 2015) and hundreds of other substances (Leverenz et al., 2007; Shahmoradian et al., 2019). Whilst the main function of α-synuclein is largely unknown, it is found in high concentrations around the synapse of neurons suggesting it is involved with vesicle trafficking between neurons (Maroteaux et al., 1988). The reason behind why α-synuclein begins to mutate is unknown but may relate to impaired protein degradation, genetic disposition, or the inclusion of a toxic element (Fares et al., 2021). Furthermore, why the formation of LB is associated with neuronal death is also unknown. Flavin and colleagues (Flavin et al., 2017) observed that in vitro, LB's can trigger the rupture of surrounding vesicles and the subsequent disruption of neuron transmission may trigger apoptosis. It has

also been reported that Lewy bodies can attract surrounding organelles, such as mitochondria, thus removing them from their supporting roles in the neuron, which results in wider dysfunction and neuronal death (Fares et al., 2021; Volpicelli-Daley et al., 2011). The pattern of neuronal death is also associated with deficits across a range of major neurotransmitter systems.

1.3.2. Neurotransmitter deficits in Dementia with Lewy Bodies

1.3.2.1. *Dopaminergic pathways*

In PD, the primary synucleinopathy affects the nigrostriatal tract with a significant loss of dopaminergic neurons in the substantia nigra, which leads to depletion of this neurotransmitter across the striatum (Aquino et al., 2014; Pagano et al., 2016). Similar degeneration has also been observed in DLB patients (Huang et al., 2015) with SPECT and [18F]DOPA positron emission tomography (PET) studies showing significant dopamine (DA) loss across the striatum (Caminiti et al., 2017; O'Brien et al., 2004; Walker et al., 1999; Walker et al., 2004; Walker et al., 2002). However, whilst the majority of DLB patients have significant degeneration across their dopamine pathways, this is not universal with 25% having normal DA imaging (McKeith et al., 2007b) and where identified, dopaminergic losses are typically not as severe as those observed in PD and PDD patients (Kasanuki et al., 2017a; O'Brien et al., 2004; Walker et al., 2004). This heterogeneity of DA involvement would also explain inconsistencies in the presence of motor symptoms of DLB, as well as the ineffectiveness of DA treatments in a proportion of DLB patients (McKeith et al. 2017).

1.3.2.2. *Cholinergic pathways*

Impairments in the cholinergic (Acetylcholine - ACh) system have been associated with AD and PDD with evidence from imaging studies (Halliday et al., 2014; Mega, 2000) and clinical response to acetylcholinesterase inhibitors, which help improve levels of neurotransmission. Furthermore, it has been noted that in the early stages of DLB, these deficits may be more severe than those found in AD patients with similar

disease duration (Marcone et al., 2012; Samuel et al., 1997; Tiraboschi et al., 2002; Tiraboschi et al., 2000). Using PET with tracers sensitive to ACh has shown reduced levels in the cingulate, hippocampus, insula, thalamus and fornices (Kanel et al., 2020), as well as parietal (Mazère et al., 2017), frontal and occipital regions (Klein et al., 2010). These areas have roles in alertness, visuospatial processes, visual attention, apathy, and motor symptoms.

The Nucleus of Basalis of Meynert (NBM) represents the brain's primary cholinergic pathway with connections spreading throughout cortical regions (Mesulam & Geula, 1988). Previous imaging studies in DLB have demonstrated decreased activation (Mazère et al., 2017) and connectivity (Caminiti et al., 2017) of the NBM and neuropathological studies have also confirmed significant neuronal losses (Grothe et al., 2014; Schumacher et al., 2020b). Furthermore, previous clinical trials have also confirmed that cholinesterase inhibitors are useful in the treatment of cognitive impairments in DLB (McKeith et al., 2004). Evidence suggests that the ACh system is impaired in DLB patients and is a likely driver of cognitive impairment observed in these patients.

1.3.2.3.   *Serotonin pathways*

The dorsal raphe nuclei are the main source of central serotonin (5HT) and project throughout the mid brain and cortical areas (Okaty et al., 2019; Walker & Tadi, 2021). In DLB, LB pathology has been found in the dorsal raphe, which can be linked to a reduction in serotonergic neurons (Seidel et al., 2015) resulting in a decrease of 5HT neurons (Benarroch et al., 2007). Similarly, a range of neuroimaging studies have demonstrated disrupted 5HT activity in the hypothalamus (Joling et al., 2019) and striatal areas (Joling et al., 2018; Roselli et al., 2010).

Serotonin is linked clinically to affective symptoms such as depression (Dell'Osso et al., 2016). Interestingly, previous studies in DLB patients with depression have found a relative preservation of 5HT re-uptake transporters in the parietal area, compared to patients without depression (Ballard et al., 2002a; Sharp et al., 2008). This

finding appears counterintuitive as in depression without DLB, 5HT levels are typically lower than in non-depressed individuals. However, there have been mixed findings regarding the role of these transporters on depression within dementia populations (Berardelli et al., 2019) and a number of other studies have highlighted a role for serotonergic processes across cognition and psychosis (Ballanger et al., 2010; Halliday et al., 2014; Meltzer et al., 2010).

1.3.2.4.   Norepinephrine pathways

The locus coeruleus (LC) is the main source of norepinephrine (NE) for the brain (Benarroch, 2009). Norepinephrine interacts with other neurotransmitters (DA, ACh, 5HT) by modulating the sensitivity of neurons, making them more or less likely to fire an action potential (Briand et al., 2007; Vermeirön & De Deyn, 2017). The LC has projections throughout the brain, suggesting that impairment in this system would present with symptoms across a broad range of domains (Briand et al., 2007). Indeed, NE has been implicated in alertness, attention, and spatial navigation (Benarroch, 2009; Dayan & Yu, 2006), as well as learning (Cartford et al., 2004) and the autonomic nervous system (Coon et al., 2020). Furthermore, NE dysfunction has also been associated with neuropsychiatric symptoms experienced in dementia patients (Hansen, 2021). With many of these symptoms matching the DLB profile, it would be expected that the NE system is compromised in this cohort.

The integrity of the LC has been measured with immunostaining at post-mortem in patients with DLB and has consistently shown a profound reduction in NE neurons compared to findings in PDD and AD (Brunnström et al., 2011; Haglund et al., 2016; Szot et al., 2006; Tilley et al., 2021). In addition, cerebrospinal fluid (CSF) has also been used to measure the level of 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), a metabolite of NE. Again, these findings have shown that compared to AD patients, levels of MHGP are significantly reduced in DLB, further indicating the loss of the neurotransmitter NE (Herbert et al., 2014; Janssens et al., 2018). An appreciation of this NE loss does potentially offer some pharmacological treatments targeting this

neurotransmitter system, which may have far reaching consequences across cognitive, psychiatric, and autonomic features, although robust clinical trials are awaited.

1.3.2.5.   *Glutamate pathways*

Glutamate (Glu) is an excitatory neurotransmitter that has an important role in learning and memory (McEntee & Crook, 1993). Furthermore, elevated levels of glutamate have been shown to be neurotoxic and may drive neuronal death (Lau & Tymianski, 2010). There have been mixed findings regarding Glu activity in DLB, which in part reflects the difficulties in the tools for probing this system so almost all Glu studies on DLB have been performed at post-mortem. Some work in DLB has demonstrated elevated levels of mitochondrial branched-chain aminotransferase, which is known to increase the concentration of glutamate, especially in the frontal cortical region (Ashby et al., 2017; Hull et al., 2015). An increase in Glu was also found by Truder and colleagues (2021) who reported that the presence of oligomeric α-synuclein encouraged the release of Glu possibly through astrocytes.

By contrast, there have also been several studies suggesting that reduced Glu activity may also underpin some of the symptoms experienced in DLB. For example, glutamate reduction has been observed in the pulvinar nuclei of the thalamus (Erskine et al., 2018), possibly resulting in the loss of synchronicity seen in DLB brains, which is a feature of cognitive fluctuations (CF; Franciotti et al., 2020). Furthermore, Glu receptor reduction has also been noted in the frontal regions, correlating with advancing levels of disease (Albasanz et al., 2005).

Recent observations testing caffeine and theanine in healthy controls suggest that whilst Glu may have differential effects depending on the specific brain region, this approach may lead to improved attention and overall cognition (Kahathuduwa et al., 2017). Indeed, pre-clinical rodent DLB model studies evaluating Ceftriaxone's ability to increase glutamate transporter 1 expression and glutamate reuptake have demonstrated cognitive improvements (Ho et al., 2019), but patient studies are lacking.

There is no single neurotransmitter that presents itself as the main driver of DLB. While DA loss is the defining feature of PD (Kalia & Lang 2015), and ACh in patients with AD (Ballard et al 2011); patients with DLB may have impairment across several neurotransmitter systems while having other transmitter systems intact. The heterogeneity of neurotransmitter impairment across DLB patients is a likely cause to the variance in symptoms observed patients, adding to the difficulty of not only diagnosing DLB, but also in providing effective treatments.

1.4. Neuroimaging observations in Dementia with Lewy Bodies

1.4.1. Magnetic Resonance Imaging (MRI)

1.4.1.1. Structural Imaging

Given the degree of cortical and subcortical atrophy that occurs in DLB, many studies have assessed the role of volumetric MRI as a biomarker in DLB. Compared to healthy controls, DLB patients display significant grey matter loss throughout the frontal, temporal, insular, and occipital cortices (Beyer et al., 2007; Burton et al., 2002). However, temporal lobe atrophy is not as severe in DLB when compared to patients with PDD, AD, or those DLB patients with concurrent AD, (Beyer et al., 2007; Burton et al., 2002; Chabran et al., 2020; Colloby et al., 2020; Harper et al., 2016; Oppedal et al., 2019; Tam et al., 2005; van der Zande et al., 2018b). Hippocampal volume is also relatively preserved in DLB compared to AD (Burton et al., 2002; Chow et al., 2012; Kantarci et al., 2012; Mak et al., 2016), while hippocampal volume reduction in DLB is likely due to presence of AD pathology (Burton et al., 2009).

Changes in the substantia nigra have also been proposed as an imaging biomarker that can differentiate DLB from AD (Kamagata et al., 2017), but unfortunately not DLB from PD (Shams et al., 2017). Subcortical grey matter loss has also been observed in DLB patients with a reduced size of the substantia innominata, which was correlated with cognitive impairment (Colloby et al., 2017). In addition, impairments in executive function have been traced to atrophy in the left pulvinar nuclei (Tak et al.,

2020) and the entorhinal cortex (Elder et al., 2017). In relation to specific clinical features, prominent atrophy in the medial frontal gyri, insula, caudate nucleus, striatum, and insula (Pezzoli et al., 2019) have been noted in those DLB patients with visual hallucinations, which presumably reflects the role of these areas in visual attention.

Diffusion tensor imaging (DTi) uses the behaviour of water surrounding axons to visualise the integrity of white matter tracts. Whilst DLB and PDD patients have very similar clinical profiles, more severe degradation in the temporal lobe and cingulate, as well as the visual fibres that extend to the occipital cortex is seen in those with DLB (Lee et al., 2010; Watson et al., 2012). Similarly, DLB patients also have significant changes in the white matter tracts of the precuneus (Firbank et al., 2007), a region that plays a role in visuospatial imagery and insight (Cavanna & Trimble, 2006). Degraded visual pathways appear to be a common feature in DLB patients and may explain the high prevalence of VH in this cohort (Delli Pizzi et al., 2014; Kantarci et al., 2010; Zorzi et al., 2021). Reviewing other clinical features, white matter tracts in the right postcentral gyrus of the temporal lobe, the thalamus and pons have been correlated with motor impairments in DLB (Firbank et al., 2011; Watson et al., 2012), whereas DTi changes from the thalamus to frontal regions appear to play a role in cognitive fluctuations in DLB (Delli Pizzi et al., 2015).

1.4.1.2. *Functional Imaging*

Functional MRI (fMRI) is reliant on the Blood Oxygen Level Dependent (BOLD) signal. The BOLD signal measures the change in the proportion of oxygenated blood in tissue and is correlated with the activation of that region, although this does not indicate whether the processes are excitatory or inhibitory. Functional MRI can measure changes in the BOLD signal over time, which is then analysed several ways depending on the hypothesis being tested. Resting state fMRI (rsfMRI) is used to measure connections between regions while the participant is alert but resting. This technique is useful with mapping networks throughout the brain, as well as studying

how different regions might interact. The analysis of connectivity may involve "Seeding", where a particular region of interest is selected, and other brain regions are explored to see if their activity is correlated, anti-correlated or unrelated to the primary region of interest (Smitha et al., 2017). In event related fMRI, imaging of the brain is studied during a task. By synchronising the imaging sequences with aspects of the task, researchers can observe changes in BOLD signal in relation to the processes being performed. For example, by scanning PD patients while they performed a VH inducing task, researchers were able to determine the role of the attentional networks during VH in PD patients (Shine et al., 2015c).

1.4.1.2.1. *Connectivity*

Data from rsfMRI shows that dementia patients have less connections between regions compared to healthy controls (HC). Schumacher and colleagues (2019a) identified three states of connectivity that HC and dementia patients alternate between: The first state involves strong connections between motor and visual networks; state two had less connections between networks, but stronger within network connections; while the third state had more connectivity between the visual, saliency and default mode network (DMN) networks than the second state. Healthy controls alternate between these states, while spending more time in the first state. However, dementia patients appear to spend less time in the first state and more time in the second state, thus reducing communication between networks (Fiorenzato et al., 2019; Schumacher et al., 2019a; Wang et al., 2007). Furthermore, the more time patients spent in the second connectivity state, the more severe their impairment was found to be (Fiorenzato et al., 2019). Indeed, CF in DLB patients are more severe when there is less communication between regions (Peraza et al., 2015). As CFs are not as prevalent in PDD or AD, this suggests that while general dementia may be driven by the segregation of the main networks, there are likely disease specific impairments to particular networks (Chabran et al., 2018).

Compared to HC, AD patients appear to have reduced connectivity between the hippocampal, frontal, and parietal regions (Allen et al., 2007; Passamonti et al., 2019), while DLB hippocampal connectivity was matched with HC (Kenny et al., 2012). This preservation of hippocampal connectivity in DLB may be aligned with why memory in DLB patients is not as impaired as AD patients. The DMN has been implemented in VH within α-synucleinopathies, however there are mixed findings regarding the connectivity of this network in PD and DLB patients. In PDD patients, there are reduced connections within the DMN, which have been associated with dementia severity (Wolters et al., 2019). Regarding DLB patients, some studies have found reduction in DMN connectivity compared to AD (Lowther et al., 2014), whilst others have found DMN connectivity to match HC (Peraza et al., 2014; Schumacher et al., 2018), and lower connectivity in AD compared to HC (Passamonti et al., 2019). This discrepancy may reflect several factors from different acquisition and analysis techniques to patient characteristics. Additionally, it could also be due to intermittent decoupling of the DMN, which has been observed in PD patients with VH (Shine et al., 2015a; see section 1.5.3).

1.4.1.2.2. *Event related fMRI*

Dementia with Lewy bodies patients have also been imaged while performing various tasks. Using fMRI, activation patterns of DLB, AD and HC were compared while performing the Attentional Network Task (Firbank et al., 2016a). The two patient groups have higher activation of the fronto-parieto-occipital network than the HC group, while the DLB group had more pronounced deactivations of their DMN than the AD and HC groups. The authors hypothesised that this could be due to the DLB patients reallocating resources away from the DMN to accommodate degradation of other attentional networks (Firbank et al., 2016a). This is in line with current theories linking impaired attentional networks to VH in synuclein diseases (Shine et al., 2014a). Visual hallucinations have also been investigated with fMRI.

While observing various checkerboard designs, DLB patients demonstrated reduced activation throughout their occipital lobe, but especially in the V5 region (Taylor et al., 2012). However, the reduced activation did not differ between patients that did experience VH and those who did not. This may be due to VH being a complex symptom that reaches beyond the visual system and the temporal resolution of event related fMRI.

1.4.2. Positron Emission Tomography (PET)

Fluorodeoxyglucose F 18([18F]FDG) PET has proved useful in neurology as a means to observe and measure glucose metabolism in the brain. Brain regions with degeneration or reduced activity show less metabolism making this a useful tool to identify impairment and assist in diagnosis. In DLB, [18F]FDG PET has revealed hypometabolism throughout the medial temporal lobe, posterior cingulate gyrus and occipital lobe (Imamura et al., 1999; Sarro et al., 2016; Whitwell et al., 2017). Indeed, [18F]FDG PET has also been applied to differentiate DLB from AD patients and whilst both diseases have very similar profiles, DLB patients can show preserved metabolism in the amygdala (Pillai et al., 2019), as well as the "cingulate island sign", which is characterised by preservation of metabolic activity in the posterior cingulate region relative to the precuneus and cuneus (Gjerum et al., 2020; Pillai et al., 2019). Previously, Lim and colleagues (2009) investigated the strength of the Cingulate Island (CI) imaging biomarker in isolation as an indicator of DLB, and reported a sensitivity of 83%, and a specificity of 100%. However, these findings should be regarded with some caution due to the small sample size studied (14 DLB; 10 AD). Further efforts to identify the veracity of [18F]FDG PET markers have not proved robust. For example, O'Brien and colleagues (2014) attempted to combine metabolism across the occipital, medial temporal lobes with the CI marker to differentiate DLB from HC and AD patients. Although these markers were excellent at separating clinical from non-clinical patients, they performed poorly in differentiating DLB from AD patients. In a more recent study, Iizuka and colleagues (2020) looked at [18F]FDG

PET in the left parahippocampus, right parietal cortex, vermis, and cuneus in an effort to differentiate DLB from AD patients. This combination of features was found to have a sensitivity score of 94% and a specificity score of 82% in 50 DLB and 50 AD cases. However, these cases also lacked post-mortem verification of the diagnosis.

A number of studies have also explored whether regional hypometabolism on [^{18}F]FDG PET can be linked to specific symptoms in DLB. Indeed, preservation of the Cingulate Island was correlated with better cognition and less pathology at post-mortem (Graff-Radford et al., 2020; Graff-Radford et al., 2014), as well as lower VH scores (Iizuka & Kameyama, 2016) and occipital hypometabolism has also been linked to VH in DLB (Firbank et al., 2016b; Nagahama et al., 2010), especially in the occipitotemporal junction, an area that is responsible for visual association processes (Perneczky et al., 2008). Hallucinations have also been linked to hypometabolism in the premotor area, basal ganglia and cerebellum (Miyazawa et al., 2010). As this hypometabolism was not correlated to MMSE or parkinsonism, this finding may suggest that these areas play a specific role in hallucinations and are not a sign of more general disease severity.

To address [^{18}F]FDG PET's inability to differentiate AD from DLB patients ligands that target other transmitter mechanisms have also been studied. Once such mechanism are vesicular monoamine type 2 transporters (VMAT2). These transporters are responsible for pumping monoamine neurotransmitters such as DA, NE and 5-HT (Lin, et al. 2013). In healthy controls high up take of the VMAT2 tracer 18F-9-fluoropropyl-(+)-dihydrotetrabenzazine (18F-FP-(+)-DTBZ) was observed in regions rich in DA (i.e. striatum, nucleus accumbens, hypothalamus, substantia nigra and raphe nuclei) (Lin, et al. 2013). In PD patients, VMAT2 tracer uptake was significantly lower (40 - 80%) in the posterior and anterior putamen, and caudate nucleus compared to HC (Hsiao, et al. 2022; Okamura, et al. 2010). Furthermore, adding VMAT2 PET scans also increased diagnostic accuracy for early and later stages of PD (Alexander, et al. 2017). However, while VMAT2 may have utility in identifying PD and DLB patients from AD (Villemagne, et al. 2012); VMAT2 behaviour is similar

in both PD and DLB patients (Siderowf, et al. 2014). Another promising ligand is 18F-Fluorodopa, which is sensitive to nigrostriatal DA denervation (Sinha, Firbank & O'Brien 2012). However, while it is able to differentiate between DLB and PD patients (Hu et al. 2000), it has not proven useful when separating PD from DLB patients (Klein et al. 2010)

Through the use of specific ligands, PET also offers a greater understanding of the neuropathology underpinning DLB. Obviously, as a synucleinopathy, it would be ideal to use PET to measure the distribution and progression of α-synuclein. However, currently there are no available tracers that can reliably bind to α-synuclein given its intra-cellular distribution, although efforts to develop reliable ligands are ongoing (Korat et al., 2021).

As commented on above, amyloid-β pathology is common in DLB patients at post-mortem (Fodero-Tavoletti et al., 2007; Irwin et al., 2017; Walker et al., 2015a). In addition, a number of studies utilising PET ligands to bind amyloid deposits (e.g. Pittsburg B[PiB], Ikonomovic et al., 2008; florbetapir [corrected] F^{18}, Wong et al., 2010; and florbetaben F^{18}, Barthel et al., 2011) have helped to study neurodegeneration in DLB (Klunk et al., 2004). Comparing PiB between DLB and AD patients, Kantarci and colleagues (2020) found higher levels in AD patients with an 80% sensitivity and 86% specificity to differentiate patients with AD and combined AD with LB pathology from patients with just LB pathology. However, the disease duration in this study was not reported and AD patients had severe cognitive impairment compared to the DLB group, suggesting that the AD patients were likely to be at the later stages of their disease compared to DLB patients. Studying amyloid pathology across the synucleinopathies has provided some clinical insights with some authors reporting that amyloid build up is higher in DLB compared to both PD and PDD in the prefrontal, parietotemporal, occipital and primary visual cortex, striatum and cingulate regions (Claassen et al., 2011; Edison et al., 2008). Furthermore, amyloid load was correlated with cognitive impairment (Kalaitzakis et al., 2011; Maetzler et al., 2009). In contrast, another study could find no significant difference in amyloid

burden across PD, PDD and DLB (Shirvan et al., 2019). It should be acknowledged that some of the inconsistencies seen across these studies are likely due to low or unbalanced sample sizes and inconsistent measures of cognition and diagnostic methods.

Significantly, amyloid comorbidity has also been linked to cognitive decline in the synucleinopathies, with higher levels being correlated with poorer cognition, as well as a more accelerated rate of decline (Brooks, 2009; Gomperts et al., 2016b). However, the presence and amount of amyloid is unlikely to affect the nature of impairment with similar cognitive profiles being demonstrated across groups (Brooks, 2009). However, it should be appreciated that many studies appear to have employed very general measures of cognition (i.e. MMSE; Abdelnour et al., 2020; Edison et al., 2008; Gomperts et al., 2012; Maetzler et al., 2009; van Steenoven et al., 2019; Walker et al., 2015a) making it difficult to determine, which domains are impaired.

Hyper-phosphorylated tau protein in the form of intracellular neurofibrillary tangles is also commonly present in the neuropathology of DLB. One recent study has highlighted that tau concentrations in DLB, mirror the accumulation of amyloid-β (Lee et al., 2018b). Interestingly, this Alzheimer-type pathology appears more abundant in the sensorimotor and visual regions compared to that which is typically seen in AD patients (Kantarci et al., 2017), suggesting that α-synuclein pathology may increase the susceptibility of these areas to developing AD pathology. Indeed, Lee and colleagues have found that different strains of α-synuclein can seed tau fibrillization in rats (Lee et al., 2018b).

Some studies have investigated whether PET imaging of tau may represent a useful tool to separate DLB from AD. Tau pathology is synonymous with AD, but it is also common DLB patients (Chin et al., 2020; Ferman et al., 2020; McKeith et al., 2017; Sarro et al., 2016). Indeed, high levels of Tau in DLB patients may lead to a misdiagnosis of AD (Merdes et al., 2003), implying that diagnosis should not rely solely on imaging biomarkers. In addition to its diagnostic potential, tau-PET has also been offering insights regarding the basis for some of the common symptoms

observed in DLB. For example, greater cognitive impairment has been found in DLB patients with higher tau levels in the inferior temporal gyrus and precuneus (Gomperts et al., 2016a). Increased tau in the parietal regions has also been linked to poor executive function in DLB patients, whereas lower tau deposition in the substantia nigra may unexpectedly be related to more severe motor symptoms (Smith et al., 2018), although the sample size was potentially too low (DLB cases, n < 10) to generalise these findings.

Neuroinflammation can also be traced and measured with PET using the [11C]-PK11195 tracer that indicates the presence of microglia, a sign of inflammation (Bartels et al., 2010). This is useful in α-synucleinopathies where neuroinflammation may be activated by α-synuclein, leading to neuronal loss (Surendranathan et al., 2015). Indeed, PET studies measuring neuroinflammation within synucleinopathies have shown inflammation in the substantia nigra and putamen in PD and DLB patients (Iannaccone et al., 2013), while DLB patients had further inflammation across several cortical regions (frontal lateral, parietal lateral, temporal lateral, temporal pole, precuneus, occipital medial, occipital lateral, anterior cingulate, posterior cingulate; Iannaccone et al., 2013; Mak et al., 2019). Furthermore, the level of these neuroinflammation PET markers has also correlated with poorer cognition (Surendranathan et al., 2018).

1.4.3. Single photon emission computed tomography (SPECT)

Single photon emission computed tomography is relatively less expensive and more accessible than PET scanning. However, the resolution of SPECT is much lower than PET and the number of ligands more restricted with much of the work focusing on brain metabolism and the dopaminergic neurotransmitter system.

Cerebral blood flow can be measured with SPECT by using ^{99}mTc-HMPAO(^{99}mTc-hexamethylpropyleneamine oxime), a gamma-emitting tracer that allows for the level of regional brain activity to be derived. This blood flow marker of hypometabolism

has been used to compare DLB and AD, with DLB patients having poorer blood flow in the occipital lobe and AD having lower blood flow in the medial temporal region (Lobotesis et al., 2001). The sensitivity and specificity for this discrimination has been calculated as being 65% and 71% respectively (Pasquier et al., 2002), which is clearly not suitable for diagnostic purposes. Whilst SPECT has shown some utility in differentiating AD from DLB patients, it is quite unable to differentiate DLB from PDD cases (Yousaf et al., 2019).

In addition to its role in diagnosis, SPECT imaging has also been used to explore a variety of symptoms in DLB. Comparing DLB and PDD patients has revealed that regardless of disease group, patients with reduced blood flow in the midline posterior cingulate region have less severe VH (O'Brien et al., 2005) and other work has reported that hypometabolism in the bilateral anterior cingulate cortex, left orbitofrontal cortex, right parahippocampal gyrus, right inferior temporal cortex, and left cuneus can be correlated with the severity of VH (Heitz et al., 2015). Furthermore, CF, one of the core features of DLB, have been associated with increased thalamic and decreased occipital blood flow on SPECT in DLB patients (O'Brien et al., 2005).

Using ^{123}I-FP-CIT(N-omega-fluoropropyl-2 beta-carbomethoxy-3 beta-(4-iodophenyl)nortropane), a tracer with affinity for DA transporters (DAT), can be used to investigate the integrity of DA receptors as a surrogate measure of nigrostriatal degeneration (DATscan). Pronounced DA receptor loss in the nigrostriatal projection is common in patients with PD and DLB (Kramberger et al., 2010; Lobotesis et al., 2001; Pardini et al., 2020; Taylor et al., 2007; Walker et al., 2002), whereas the nigrostriatal tract is well preserved throughout the course of AD (Nobili et al., 2017).

Correlating dopaminergic loss on DATscan with the symptoms of DLB has yielded mixed findings. Whilst motor symptoms in DLB patients have been correlated with nigrostriatal loss (Siepel et al., 2016), no such relationship has been found with cognitive symptoms. However, Roselli and colleagues (2009) did find a relationship between nigrostriatal loss and the severity of VH, and Kasanuki and colleagues (2017b) also found that the extent of degeneration was correlated with the presence of

anosmia and RBD. These findings suggest that DATscan may offer some utility for understanding the extended symptoms of DLB.

Using DATscan may prove useful for detecting prodromal cases of DLB (Kasanuki et al., 2017b), where the integrity of the striatal region is compromised early. Indeed, Thomas and colleagues (2019) found that DAT SPECT scanning had a 54% sensitivity and 89% specificity in prodromal DLB and AD cases. The relatively low sensitivity presumably reflects the fact that whilst striatal dopamine uptake is correlated with DA receptor loss, it does not reflect the presence of Lewy Bodies (Colloby et al., 2012).

There are some patients who display clinical features of DLB but have normal DATscans (O'Brien et al., 2009) and in contrast, others who do not have clinical features of DLB but can have abnormal scans and longitudinal follow up is recommended in the context of clinical suspicion (Siepel et al., 2013). Re-imaging patients with a clinical diagnosis of DLB but normal baseline DATscans showed that at 1.5 years, most (5 out of 7) had gone on to develop an abnormal scan (van der Zande et al., 2016). Reasons for the separation of clinical features and neuroimaging findings may include inaccurate clinical diagnosis in scan positive patients (O'Brien et al., 2009) or possible progression of Lewy Body formation that does not follow a traditional Braak pathway with cortical areas being impacted before the striatum (Siepel et al., 2013; van der Zande et al., 2016).

The sensitivity and specificity of the DATscan does increase as the disease progresses to approximately 80% and 90%, respectively (McKeith et al., 2007b; Thomas et al., 2017). This level of diagnostic accuracy combined with its relatively lower costs and higher availability compared to PET, has led to SPECT scans becoming a useful tool in the diagnosis of DLB, proving helpful in distinguishing DLB from AD (McKeith et al., 2007a; Walker et al., 2002; Walker et al., 2015b). For this reason, DATscan in conjunction with clinical assessment has been incorporated as an indicative biomarker into the most recent diagnostic criteria for DLB (McKeith et al., 2017). ^{123}I-FP-CIT can also be used to measure degradation in 5HT regions and

compared to healthy controls, DLB patients have severely reduced 5HT transporter in the hypothalamus (Joling et al., 2019; Roselli et al., 2010). Unfortunately, little work has looked at comparing 5HT preservation between AD and DLB using SPECT to this point.

1.4.4. Meta-iodobenzylguanidine(MIBG) Myocardial Scintigraphy

Meta-iodobenzylguanidine(MIBG) myocardial scintigraphy is a similar technique to PET(1.2.2) and SPECT(1.2.3) imaging as it involves an isotope tracer [123]Iodine(^{123}I-MIBG) and a camera sensitive to gamma radiation to measure tracer behaviour and present a 2D image for reporting. ^{123}I-MIBG behaves like norepinephrine and is received by postsynaptic epinephrine receptors. In myocardial scintigraphy this behaviour is exploited to measure the integrity of epinephrine receptors in the heart. The most common measure used in MIBG is the heart-mediastinum ratio (HMR). This is calculated by comparing ^{123}I-MIBG uptake in the cardiac region with a control area of interest (ROI) in the chest (Orimo et al., 2016). However, inconsistency in how the HMR is measured has caused mixed results (Roberts et al., 2019), requiring caution when interpreting HMR values.

Patients with DLB are known to have a degraded norepinephrine system (see section 1.1.2.4). This can be seen in MIBG scans as low uptake of ^{123}I-MIBG in the heart and may be the cause of autonomic symptoms in DLB such as orthostatic, supine, and/or postprandial hypotension (Kobayashi et al., 2009; Oka et al., 2020). The HMR has shown significant promise and has been added as an indicative biomarker for the diagnosis of DLB (McKeith et al., 2017). Indeed, many studies have found significantly lower HMR ratios in DLB patients compared to AD patients, with an average sensitivity of 85% (71 – 100%), specificity of 91% (75% - 100%; Abbasi et al., 2017; Kane et al., 2019; Nihashi et al., 2020; Slaets et al., 2015; Treglia & Cason, 2012; Wada-Isoe et al., 2007).

Multiple system atrophy patients have preserved cardio norepinephrine systems and have a HMR score comparable to HC (Goldstein et al., 2008; Kikuchi et al., 2011). This feature has given MIBG high sensitivity in separating PD patients from MSA (Alves Do Rego et al., 2018). However, there are few studies comparing other synucleinopathies, but one study reported DLB as having a lower HMR than PD (Oka et al., 2020), it should be noted however, that both PD and DLB had very low HMR ratios. Some studies have tried to combine the HMR biomarker with SPECT and DATscan to improve their diagnostic effectiveness with mixed results. Sakamoto and colleagues (2014) found that combining the HMR ratio with SPECT of the parietal region did not improve diagnostic accuracy and that HMR combined with DATscan reduced the sensitivity and specificity performance. In contrast, Shimizu and colleagues (2016) improved diagnostic accuracy by combining MIBG results with DATscan findings.

Few studies have investigated the relationship between abnormal myocardial scintigraphy and specific DLB symptoms. Slaets and colleagues (2015) found that lower HMR ratios were correlated with the presence of more core symptoms, whereas Oka and colleagues (2020) did not find any relationship between the HMR and the degree of cognitive impairment. Shimizu and colleagues (2015) did note that REM Sleep Behaviour Disorder (RBD), an early risk factor for synucleinopathies, appeared to be more common in patients with low HMR. Indeed, in a mild cognitive impairment (MCI) with LB (MCI-LB) group, patients who had RBD were more likely to have a low HMR and the patients with a low HMR were more likely to progress towards clinical DLB (Fujishiro et al., 2021).

Overall, MIBG appears to be a promising biomarker but is differentially affected across the synucleinopathies. Furthermore, a low HMR may also be present in patients with heart conditions. Indeed, patients with heart failure or myocardial injury from ischemic event will also present with low HMR (Carrió et al., 2010; Iqbal et al., 2018), requiring a thorough medical history to ensure accurate diagnosis. Until

more consistent methods are adopted across all laboratories and clinics, HMR values should be used diagnostically with caution.

1.5. Other biomarkers in Dementia with Lewy Bodies

1.5.1. Neurochemical biomarkers

Biofluids that are likely to have the most relevance in DLB are blood and CSF, as they have both had contact with the brain to varying degrees. Whilst extracting blood is less invasive and less expensive than a lumbar puncture, it is likely that CSF may provide a more accurate representation of which neurochemicals are being impacted in the brain.

1.5.1.1. *Plasma*

Recently phosphorated forms of tau (pTau) have been identified as a potentially useful biomarker in the plasma of AD patients. Indeed, levels of Tau isoforms 217 and 181 have been found to not only correlate with CSF pTau levels (Barthélemy et al., 2020; Hall et al., 2021), but also predict cortical levels of amyloid-β pathology (Janelidze et al., 2021; Mielke et al., 2018) and cognitive impairment (Fossati et al., 2019). With tau also being present in DLB patients, pTau markers used in AD may also be applicable in the DLB cohort. However, whilst these markers could be used to differentiate DLB from PD, it would be potentially less useful at separating DLB from AD. With the improvement of laboratory techniques and reagents, recent studies have broken down plasma from DLB patients to identify possible biomarkers that could aid diagnosis. The main features of DLB blood that separate the disease from healthy controls and PDD are the presence of elevated proteins related to metabolic and vascular dysfunction (O'Bryant et al., 2019), neuroinflammation (Usenko et al., 2020) and oxidative stress (Kume et al., 2012). However, as these are also present in a wide range of diseases and illness, they typically have a low specificity for identifying DLB. Focusing on extracellular vesicles responsible for intercellular communication, immunomodulation, and inflammation; Gámez-Valero

and colleagues (2019) identified gelosine, a protein believed to encourage the aggregation of α-synuclein and amyloid-β in DLB patients. However, this was also present in AD patients, limiting this marker's ability to separate DLB from AD patients. Immunomagnetic reduction assay (IMR) has recently been employed as an indirect means to detect α-synuclein in plasma. This involves adding iron-infused antibodies that are sensitive to amino acid residues of α-synuclein. The magnetic susceptibility can then be measured and used as a reference for α-synuclein levels (Chang et al., 2019). This technique has shown a high sensitivity (99%) and specificity (92%) at differentiating PD patients from HC (Chang et al., 2019). α-synuclein levels using this method may also predict motor impairment, but not cognition (Lin et al., 2019). Few studies have used IMR to differentiate synucleinopathy diseases, but one study did not find a difference in α-synuclein levels when comparing PD with DLB, frontal temporal dementia with parkinsonism, progressive supranuclear palsy and cortical basal disease (Lin et al., 2018). However, as the diseases were all grouped together, individual differences cannot be determined.

1.5.1.2. *Cerebrospinal Fluid*

In DLB and PD, there are mixed findings regarding levels of α-synuclein as a diagnostic tool in the CSF. Studies have found lower α-synuclein CSF levels in DLB and PD patients compared to AD patients (Mollenhauer et al., 2011; Parnetti et al., 2011), which has been attributed to the potential accumulation of α-synuclein in the form of Lewy bodies at the neuronal level, removing it from the CSF (Al-Nimer et al., 2014). However, other studies did not observe differences in CSF α-synuclein between DLB and HC (Llorens et al., 2016), or AD patients (Chaudhry et al., 2020). Furthermore, Bousiges and colleagues (2020) did find that AD patients had a higher α-synuclein concentration in their CSF but adding α-synuclein concentration in the CSF to a diagnostic model with AD markers did not improve the model's accuracy. Indeed, several studies have also found that ratios of different amyloid-β peptides appear to be the most accurate approach for separating DLB from AD (Chaudhry et

al., 2020; Parnetti et al., 2019), but with limited sensitivity (78%) and specificity (67%; Mulugeta et al., 2011). Recently, a real-time quaking-induced conversion (RT-QuIC) assay has been utilised in the detection of α-synuclein in CSF (Fairfoul et al., 2016). Initial studies have found this technique to be highly sensitive (93 – 95%) and have high specificity (96 – 100%) at differentiating synucleinopathies from non-synucleinopathies (Bongianni et al., 2019; Fairfoul et al., 2016; Groveman et al., 2018). However, this technique is not as sensitive when differentiating leucine-rich repeat kinase 2 (LRRK2)-PD (n= 15) from LRRK2-HC (n = 16) with 40% sensitivity, 81% specificity (Garrido et al., 2019). To enhance the accuracy of RT-QuIC, it can be combined with molecule florescence microscope, giving precise quantities of α-synuclein present in CSF (Bhumkar et al., 2021). Currently RT-QuIC is restricted to use with CSF, however current work is being undertaken to optimise the assay for use within other biofluids such as plasma (Bargar et al., 2021; Metrick et al., 2019).

Concentrations of CSF phosphorated tau 181(p-tau181) have also shown mixed results in differential diagnosis, with an accuracy of 87.8% for separating DLB from HC patients (Llorens et al., 2016), and 73% sensitivity and 90% specificity at separating DLB from AD patients (van Harten et al., 2011). However, this finding has not been consistent across studies. For example, p-tau181 alone has been unable to separate DLB and AD patients (Goossens et al., 2017) or DLB from HC, PD and PDD patients (Gmitterová et al., 2020). The accuracy of p-tau measurements could be increased when it was considered as a ratio to non-phosphorated tau with 60% and 70% sensitivity and specificity, respectively (Gmitterová et al., 2020).

Neurofilament light chains (NfL) have also been studied as a potential means to improve diagnostic accuracy. Neurofilament light chains are a marker of neuronal and axonal damage (Yilmaz et al., 2017). Dementia with Lewy body patients appear to have higher NfL levels than PD and HC (Canaslan et al., 2021). However, measuring NfL does not appear to improve diagnostic accuracy with moderate to low accuracy when discriminating DLB from HC (Zerr et al., 2018), or PD (Canaslan et al., 2021). When measured from plasma, this diagnostic accuracy may increase, with

prodromal and clinical DLB patients having higher concentrations compared to HC (Pilotto et al., 2021). Furthermore, NfL may also predict disease severity and rate of progression (Pilotto et al., 2021), which could be helpful for prognostication and future disease modifying trials. Overall, due to the current inconsistencies across neurochemical biomarkers, more research is needed before these techniques are implemented clinically.

1.5.1.3. *Saliva*

Saliva is another target that has shown promise for the early detection of α-synuclein. Unlike skin and colonic biopsies, saliva is much more accessible, less invasive and has a lower chance of being contaminated by blood. It has been reported that α-synuclein concentrations in saliva are similar to CSF, where HC generally have higher concentrations than PD (Al-Nimer et al., 2014; Vivacqua et al., 2016). This has been attributed to α-synuclein aggregating to form LB in synucleinopathy, thus reducing the amount found in bodily fluids. However, some studies have failed to detect a difference in α-synuclein between PD and HC (Devic et al., 2011; Fernández-Espejo et al., 2021), and although one other study did find a difference, this had a very low sensitivity (56%) in separating PD from HC (Chahine et al., 2020). The Parkinson's protein 7 (DJ-7) was also higher in PD patients than HC, even when there was no difference between α-synuclein levels (Devic et al., 2011). But there was no association between DJ-7 concentration and symptom severity, suggesting a more complex relation between saliva DJ-7 and PD symptoms. Oligomers of α-synuclein, which play a large role in the formation of LB are also higher in PD patients than HC, with saliva concentrations increasing with disease duration and being associated with poor cognition (Vivacqua et al., 2016). Thus, whilst saliva may be a promising biomarker for early synucleinopathies, more research is needed especially in DLB where data is severely lacking.

1.5.2. Electroencephalography (EEG)

Electroencephalography (EEG) is a relatively inexpensive and non-invasive technique to measure electrical changes across the cortex. The main finding regarding DLB patients is a generalised slowing of their dominant wave frequency (Law et al., 2020). Indeed, this feature has been compared with AD patients, with DLB patients not only demonstrating a slower dominant frequency, but that this activity fluctuates more than in AD (Bonanni et al., 2016; Pascarelli et al., 2020). These patterns have also been found in prodromal DLB (Schumacher et al., 2020a), with more abnormal EEG scans predicting a shorter interval until the patients converts to clinical DLB (van der Zande et al., 2020a).

Comparing DLB EEG patterns with PD has demonstrated mixed results with Bonnani and colleagues (2008) finding that overall, DLB patients had slower dominant frequency and higher variability than PD patients. However, this variability appears to have been driven by the presence of CF, and it was shown that PDD patients with CF had similar patterns to DLB patients (Bonanni et al., 2008). Furthermore, other studies have found that PD and PDD patients have a similar dominant frequency to that seen in DLB (Massa et al., 2020; Stylianou et al., 2018).

Interestingly, EEG slowing in DLB has been correlated with atrophy of the Nucleus Basalis of Maynert, the main source of ACh in the brain (Schumacher et al., 2020b). This would suggest that patients with AD, who have a more pronounced ACh deficit, would have similar EEG readings to DLB. However, van der Zande and colleagues (2018a) compared DLB patients with concurrent AD pathology to patients without AD pathology and found that the profile was unchanged in patients with both α-synuclein and AD pathology. This suggests that this EEG slowing may be caused more specifically by α-synuclein rather than AD pathology.

Using various algorithms, neural networks and connectivity can also be measured using EEG. Comparing DLB to AD patients, DLB patients have been shown to have poorer connectivity between cortical hubs (van der Zande et al., 2018a). Indeed, DLB patients have also been shown to have fewer hubs than HC and AD patients, with inefficient connections between them (van Dellen et al., 2015). This observation echoes

MRI findings that demonstrate DLB patients have isolated hubs with poorer connections (Peraza et al., 2015). One reason for this could be due to random sprouting of the connections observed in DLB brains (Peraza et al., 2018), creating an incohesive network system. The primary network connections that are impaired are between the frontal region with the parietal and occipital lobes (Aoki et al., 2019; Dauwan et al., 2016), which may explain some of the attentional and visuoperceptive symptoms experienced by DLB patients. Taking a different approach to investigate connectivity in DLB, Schumacher and colleagues (2019b) focused on microstates (set topographical patterns that the brain switches between every ~80 – 120 ms) in DLB compared to AD patients and HC. Interestingly, DLB patients appeared to have similar variations in their microstates to HC, with both groups having more than AD. However, DLB patients appeared to spend more time within each microstate than the other two groups. The authors theorised that this may be driving some of the slower cognition observed in this cohort.

Some of the symptoms in DLB have also been linked to EEG patterns. Overall, poor cognition has been linked to abnormal EEG patterns (Barber et al., 2000). Specifically, CF have been correlated to EEG slowing as well as dominant frequency variability (Stylianou et al., 2018). Furthermore, slow microstate transitions have also been linked to CF (Schumacher et al., 2019b). Visual hallucinations are more severe in patients with higher proportions of delta waves in their parietal area (Pascarelli et al., 2020). Additionally, thalamocortical dysrhythmia is also observed in DLB (Franciotti et al., 2020). This phenomenon causes theta bursts throughout the cortex, that in turn could lead to VH through a decoupling of the DMN (Onofrj et al., 2019).

As a tool to differentiate DLB from AD, findings are also mixed. Using the "Grand Total EEG" score, a scale that rates qualitative measures (i.e. speed of background frequency, spread of abnormalities) to give a score (2 [normal] – 31 [very abnormal]), produced a sensitivity score of approximately 75% and specificity of 80% (Lee et al., 2015; Roks et al., 2008). Frontal intermittent rhythmic delta activity (FIRDA) has also shown promise as a complimentary tool to differentiate DLB from AD. It appears to

be present in 30% of DLB patients and in less than 7% of AD patients (Calzetti et al., 2002; Dauwan et al., 2018; Roks et al., 2008). Perhaps, more surprisingly, FIRDA has been reported in less than 5% of PDD patients (Zinno et al., 2021). Applying connectivity models that are characteristic of AD patients, Colloby and colleagues (2016) also had showed modest utility as diagnostic tool, with a 77% accuracy rate for identifying DLB patients amongst AD patients. The most accurate measures to separate DLB from AD patients appears to be using frequency prevalence, dominant frequency, and variations with the dominant frequency, which provided a sensitivity score of 92% and specificity score of 83% (Stylianou et al., 2018), these measures were 90% accurate at classifying DLB from AD (Bonanni et al., 2016).

While EEG studies have been fruitful in providing patterns of activity and network stability, there are a lot of inconsistencies between studies resulting in contradicting findings. This is likely due to the different methods used to define patient groups, measuring techniques, as well as different methods and algorithms used to analyse and interpret data. However, using the core measures of frequency power, EEG appears to be a good technique that could assist the diagnosis of DLB and was added to the most recent diagnostic criteria.

1.5.3. Biopsy

With the high prevalence of autonomic dysfunction in α-synucleinopathies, researchers have also been searching for α-synuclein throughout the body. As these biopsies are still relatively new, most studies have focused on the utility of each one at differentiating PD from HC, with few studies attempting to distinguish synucleinopathies from each other.

1.5.3.1. Skin

Skin biopsies are a relatively non-invasive method to test for the spread of α-synuclein throughout the peripheral systems. Early studies yielded modest findings, with 70% of PD and PDD patients showing immunoreactive responses to α-synuclein in their skin nerves, while only 40% of DLB patients showed signs of α-synuclein

(Ikemura et al., 2008). These low numbers could be due to the retrospective nature of the study, which used samples up to 10 years old, or the use of unrefined lab techniques and assays which have since improved. Recent studies have utilised RT-QuIC to analyse skin nerves from biopsies from cadavers and found 89% sensitivity and 96% specificity in distinguishing confirmed Lewy body dementia (LBD) cases from non-LBD cases (Wang et al., 2020). While intra vitam samples ranged from 89-95% and 96-100% sensitivity and specificity respectively, at separating PD patients from HC (Mammana et al., 2021; Wang et al., 2020). Dementia with Lewy body patients also appear to have higher concentrations of dermal α-synuclein than PD patients (Donadio et al., 2018). Furthermore, concentrations were associated with severity of autonomic dysfunction in this cohort (Donadio et al., 2017).

1.5.3.2. Colon

Gastroenterological complications are also common in synucleinopathies (Sakakibara et al., 2019; Stocchi & Torti, 2017), making the colon a promising area to detect α-synuclein. Findings regarding the relationship between colonic α-synuclein and synucleinopathies are mixed with early studies concluding that the presence of α-synuclein in the colon was only present in PD patients, and not HC or patients with non-PD gastroenterological conditions (Lebouvier et al., 2008; Pouclet et al., 2012; Shannon et al., 2012b). Furthermore, the presence of colonic α-synuclein also predated motor symptoms by up to eight years and was paired with early autonomic symptoms (Hilton et al., 2013; Shannon et al., 2012a). Conversely, several studies have also found no difference between patient groups or HC samples, detecting α-synuclein in portions of PD patients as well as HC (Chung et al., 2016; Gold et al., 2013; Visanji et al., 2015). Indeed, in a systematic review, Malek and colleagues (2014) found a lot of variances in sensitivity across studies, reporting values from 42-90%, while specificity was 100%. Low sample sizes and inconsistencies in sample collection, storage and analysis likely drive the discrepancy between findings (Beach et al., 2016). Until a gold

standard method of sample analysis is agreed upon, evidence from colonic biopsy should be interpreted with caution and in conjunction with other diagnostic methods.

1.5.3.3. *Salivary glands*

The salivary glands have also been investigated as a target for detecting α-synuclein pathology in PD patients (Cersósimo et al., 2009). Furthermore, biopsy of the parotid gland in an RBD patient was shown to contain α-synuclein pathology (Fernández-Arcos et al., 2018), suggesting that α-synuclein pathology may be present during the prodromal stages of synucleinopathies. Indeed, this patient later transitioned to PD (Fernández-Arcos et al., 2018). However, in larger samples there have been mixed findings. Whilst some studies have found α-synuclein pathology in all of their PD patients and most of their DLB patients (Del Tredici et al., 2010; Ma et al., 2019), other studies have reported positive findings in approximately half of their PD and DLB patients (Iranzo et al., 2018; Shin et al., 2019). Thus, whilst these findings look promising as a potential biomarker for α-synucleinopathies, interpretation should be made with caution due to very small sample sizes. Large studies are needed before α-synuclein pathology in the salivary glands can be regarded as a reliable biomarker for synucleinopathies.

1.6. Genetics

Thus far, most research on synucleinopathies that has been reported in this thesis has focused on idiopathic, or incidental cases. While most cases of synucleinopathy do occur without a clear cause, there are several genes that have been identified as strong risk factors for developing an α-synuclein (Jellinger, 2018). The study of these genes in synucleinopathies can provide researchers with a better understanding of dysfunctional mechanisms that may be driving aspects of the disease. For example, the high prevalence of synucleinopathies in Gaucher's disease patients who survive into later life has led researchers to identify glucocerebrosidase (GBA) mutations as strong genetic risk factor for DLB and PD (Goker-Alpan et al., 2004; Mazzulli et al.,

2011; Tayebi et al., 2001; Tayebi et al., 2003). This has also led researchers to focus on glucocerebrosidase and its role in synucleinopathies.

1.6.1. Glucocerebrosidase (GBA)

Probably, the most important genetic contribution to DLB relates to mutations in the GBA gene, which are also common in PD (Blauwendraat et al., 2020; Sidransky & Lopez, 2012; Sidransky et al., 2009). Defective GBA has been found to be the driving cause of Gaucher's disease (Do et al., 2019). Gaucher's disease is a hereditary disease that affects lipid storage through the lysosome system, driven by GBA mutations (Aflaki et al., 2017). Early studies of Gaucher's disease noted the high prevalence of PD within this cohort (Tayebi et al., 2003), as well as close proximity familial members (Goker-Alpan et al., 2004). This phenomenon directed focus towards identifying potential genes that cross over both diseases and to study how they interact (Tayebi et al., 2001). The mechanism behind the interaction between GBA and α-synuclein is still unclear, although there are several theories. Glucocerebrosidase is involved in the lysosomal system, so mutations to this enzyme would impair the metabolism of glycolipids and in turn promote the conversion of α-synuclein to its toxic insoluble form (Blandini et al., 2019; Rongve et al., 2019). It is also theorised that there is a bidirectional interaction between GBA and α-synuclein, where the build-up of α-synuclein interrupts the lysosomal system, which in turn promotes further α-synuclein to be formed (Mazzulli et al., 2011). These theories have been supported with low GBA lysosome activity in striatal and substantia nigra regions in PD and DLB patients (Chiasserini et al., 2015), as well as decreased concentration of GBA in the CSF of DLB patients (Parnetti et al., 2009). Furthermore, decreased concentrations of GBA in the substantia nigra of PD patients has been correlated with increase concentrations of α-synuclein (Gündner et al., 2019). Focusing on a group of Ashkenazi Jews (a population notorious for their susceptibility to synucleinopathies and other inherited conditions; Aharon-Peretz et al., 2004), one third of the DLB patients had GBA mutations (Shiner et al., 2016). In a large multi-centre study,

patients from around the world people with GBA mutations were more likely to develop DLB than PD (Nalls et al., 2013). Not surprisingly, GBA mutation carriers are also more likely to develop DLB than AD (Clark et al., 2009). Furthermore, patients with GBA mutations appear to have younger onset and poorer prognosis than non-carriers (Blauwendraat et al., 2020; Bregman et al., 2019; Lerche et al., 2019; Nalls et al., 2013; Parnetti et al., 2009; Setó-Salvia et al., 2012; Shiner et al., 2016; Shiner et al., 2021).

1.6.2. Synuclein encoding gene (SNCA)

The role of α-synuclein encoding gene (SNCA) mutations has also been explored with some findings supporting the presence of SNCA mutations within a group of familial DLB patients (Zarranz et al., 2004). However, other reports have found that the presence SNCA mutations reduced the chance of developing DLB (Guerreiro et al., 2018). Similar patterns of findings are also present in the β-synuclein encoding gene (SNCB) mutations. By investigating SNCB in PDD and DLB patients, Gámez-Valero and colleagues (2018) found several mutations that were unique to the DLB group. However, Ohtaki and colleagues (2004) did not find any mutations to the SNCB gene that were consistent across there DLB group. Differences in these findings likely represent advancements in techniques and technology involved in genetic analysis.

1.6.3. Leucine-rich repeat kinase 2(LRRK2)

As Dementia with Lewy bodies and PD share synuclein pathology, they also share many of the same genetic mutations that increase the risk of developing LB. Mutations in the LRRK2 gene are the most common mutation in familial PD disease (Ross et al., 2006; Zimprich et al., 2004). Mutations to the LRRK2 gene have been shown to interfere with mitochondrial dynamics, which results in oxidative stress on the neuron leading to neuronal death (Singh et al., 2019). Mutations in this gene have been linked with non-motor symptoms in PD, such as cognitive impairment, anxiety, and orthostatic hypotension, but not motor symptoms (Kalia et al., 2015). However, Heckman and colleagues investigated the genetic profile of 400 DLB patients and did

not find any common mutations in the LRRK2 gene to support its role in DLB (Heckman et al., 2016).

1.6.4. Apolipoprotein-E

Mutations in the genes that are common in AD are also present in DLB and PDD. The apolipoprotein E (APOE) ε4 allele has been found to exacerbate the aggregation of α-synuclein within DLB and PDD populations while having no effect on amyloidβ presence. Additionally, mutations to the butyrylcholinesterase are also found in AD and DLB and result in decreased levels of cortical ACh (Josviak et al., 2017). Additionally, the presence of APOE in DLB patients is also associated with less severe symptoms related to α-synuclein (i.e. RBD and Parkinsonism; Ferreira et al., 2020) and higher memory impairments (Mirza et al., 2019). Thus, increasing the overlap of DLB and AD clinical profiles, which increases the risk of misdiagnosis.

To date, no gene has been found that is unique to DLB patients. Not surprisingly, genes that have been responsible in PD and AD have also found to interact with symptomology of DLB patients. These genetic mutations can cause symptoms that mirror those in PD or AD, further complicating accurate diagnosis of DLB. Furthermore, genetic mutations are not present in all DLB patients, so genes are not the sole cause of DLB. They do appear make the individual more predisposed not only developing DLB, but also having more severe symptoms than idiopathic DLB patients.

1.7. Core symptoms

1.7.1. Cognitive Decline

The essential feature of DLB is dementia, which is defined as a progressive decline in cognition that interferes with occupational or social functioning, as well as daily activities (McKeith et al., 2017). The rate of decline varies across the cognitive domains and whilst non-amnestic domains decline at a faster rate in DLB patients (Smirnov et al., 2020), findings regarding amnestic domains in DLB compared to AD are less clear.

Most studies have demonstrated that compared to patients with AD, there is a relative preservation of memory (Bussè et al., 2017; Economou et al., 2016; van de Beek et al., 2020; Westervelt et al., 2016). However, amnestic deficits do occur in DLB and memory decline has been repeatedly demonstrated in comparison to age matched controls (Calderon et al., 2001; Kemp et al., 2017; Petrova et al., 2016). Studies have found that non-verbal memory in DLB is impaired (Lambon Ralph et al., 2001), which may be due to the visuospatial demands of these tasks given that impairments to this domain are common in DLB (Kemp et al., 2017; McLaughlin et al., 2012). In contrast, there have been mixed findings regarding verbal memory impairments in DLB. Whilst there are findings to suggest that AD patients have poorer verbal memory than DLB (Kawai et al., 2013), others have failed to demonstrate any difference on the performance of verbal memory tasks between DLB and AD (Bussè et al., 2017; Calil et al., 2021; Hamilton et al., 2004; Simard et al., 2002). Such inconsistencies may reflect the heterogeneity of DLB, the presence of comorbid Alzheimer-type pathology or the specific verbal memory tests that were evaluated.

Non-amnestic deficits have been more consistent across DLB studies. For example, performance on visuospatial tasks have typically revealed more impairments in DLB compared to age matched controls (Pal et al., 2016) and AD patients (Johnson et al., 2005; Mosimann et al., 2004). However, it has been more difficult to discriminate visuospatial performance between DLB and PDD patients (Mosimann et al., 2004). Impaired executive function is also a characteristic finding when comparing healthy age matched controls to DLB patients (Aldridge et al., 2018; Bradshaw et al., 2006; Petrova et al., 2016). However, the findings are less clear cut when comparing executive performance between DLB and AD patients. Whilst greater impairments have been reported in DLB (Bradshaw et al., 2006; Nagahama et al., 2017), these findings have not been universal with some studies failing to show a difference between DLB and AD (Firbank et al., 2016a). Again, these inconsistencies are likely to reflect the varying degrees of comorbid AD pathology in DLB. It is also common for DLB patients to have language processing impairments, with prodromal

and early-stage patients performing worse than healthy controls (Kemp et al., 2017; Petrova et al., 2016). However, there are mixed findings when comparing language performance between DLB and AD (Ferman et al., 2006; Smits et al., 2015; Westervelt et al., 2016).

1.7.2. Rapid eye movement (REM) sleep behaviour disorder

Rapid eye movement (REM) sleep behaviour disorder is characterised by dream enactment and the loss of skeletal atonia (muscle paralysis) during the REM stage of sleep (Postuma et al., 2015a). This loss of atonia releases motor movements that are normally suppressed during REM cycles, which results in the dream enactment that is reported clinically. Dream enactment movements can range from minor jerks to complex behaviours (e.g. walking motion, grabbing, talking; Nepozitek et al., 2021). These movements may result in the patient falling from bed or causing injury to themselves or their bed partner. Such patients often report experiencing very vivid nightmares (Dauvilliers et al., 2018), although only a small percentage report making motor movements to reflect this (Nepozitek et al., 2021). The risk of injury to patients and their bed partners, as well the potential for disturbing dream content makes RBD a distressing symptom that can lead to significant concerns.

The pathophysiology underlying RBD is not fully understood but some interest has focused on the sublaterodorsal tegmental nucleus (STD; Peever et al., 2014), which is located rostrally to the locus coeruleus in the brain stem (Torontali et al., 2019). Experimental lesions in animal models to discrete areas within this nucleus have been shown to induce REM sleep without atonia and alter the length and number of REM periods during sleep (Boissard et al., 2002; Lu et al., 2006). In a model of early PD, mice had been genetically altered to include SNCA with an A53T mutation, a common polymorphism identified in familial PD, while also maintaining their natural α-synuclein production (Taguchi et al., 2020). In these mice, LB have been observed in the STD nucleus that also had RBD symptoms (Taguchi et al., 2020). This suggests

that the STD may be a site of LB aggregation early in synucleinopathies. Indeed, RBD patients also have decreased DAT uptake in the caudate compared to HC (Iranzo et al., 2017), which decreases to eventually match PD patients with RBD (Bauckneht et al., 2018; Heller et al., 2017), implying a link between RBD and synucleinopathies. Moreover, autopsies of RBD patients who have not transitioned to PD or DLB ante-mortem have shown widespread LB pathology (Boeve et al., 2007; Iranzo et al., 2013). Furthermore, α-synuclein pathology has also been detected in skin biopsies of RBD patients who did not meet diagnostic criteria for a synucleinopathy (Al-Qassabi et al., 2021).

Rapid eye movement sleep behaviour disorder is highly prevalent in DLB and has recently been included as a core symptom of DLB (McKeith et al., 2017). Indeed, in cases confirmed at autopsy, RBD was present in 74% of the clinical profiles (Ferman et al., 2011), compared to 3-15% of AD patients (Galbiati et al., 2018; Park et al., 2020). Furthermore, patients with RBD have a higher chance of progressing to a synucleinopathy than non-RBD individuals (Postuma et al., 2019). Indeed, between 39 - 87% of RBD patients progress to a synucleinopathy over the course of 13 years (Fereshtehnejad et al., 2017; Schenck et al., 2013). To capture RBD patients who are likely to transition to a clinical form of synucleinopathy, prodromal stages of DLB and PD have been classified. The criteria for prodromal DLB (MCI-LB) mirror those of DLB; however, the threshold for cognitive impairment has been reduced to match criteria for MCI (i.e. objective impairment in one domain, patients' independence is not affected). Patients with MCI-LB also have at least one DLB core feature, but in a mild form (McKeith et al., 2020). Indeed, RBD patients with autonomic dysfunction, minor hallucinations or misperception errors also had lower scores on general cognition tests (Montreal Cognitive Assessment; MoCA) and were more likely to transition to DLB within 1 – 3 years (Honeycutt et al., 2020; Postuma et al., 2013; Sumi et al., 2021). Additionally, 74% of patients with RBD meet Movement Disorder Society's (MDS) criteria for probable prodromal PD (Barber et al., 2017). With such a high rate of RBD patients progressing to a degenerative synucleinopathy, RBD

patients are an ideal population to study for markers that foreshadow PD or DLB. However, differentiating between these two diseases during very early stages is difficult. Following a cohort of 55 RBD patients until transition, researchers identified motor, cognition, and autonomic impairments that deteriorated leading to transition (Fereshtehnejad et al., 2019). From this cohort, half transitioned to PD, while almost half transitioned to DLB with a minority developing a multiple systems atrophy (MSA). Predictors of DLB transition were a *sharper* decline in cognition, impaired colour vision and more severe orthostatic hypotension. Whilst presence of constipation and hyposmia were the predictors of PD (Fereshtehnejad et al., 2019). Findings from this study highlight that none of the core symptoms of PD separated prodromal PD from MCI-LB patients, while a more rapid decline in cognition was the only core feature to differentiate DLB from PD. Furthermore, separation of these two diseases during prodromal stages cannot rely on the presence, even in mild form, of their defining characteristics and more sensitive testing is needed separate them.

1.7.3. Hallucinations

Hallucinations are defined as percepts that are not attached to any object (O'Brien et al., 2020). Illusions, while like hallucinations, are the instances where a percept has been either mistaken or distorted to look like something else. While these perceptual abnormalities can occur in all modalities (visual, aural, tactile, gustatory, and olfactory) the most common form in DLB and synucleinopathies are visual. Patients may experience illusions that include misperceptions, where an object is perceived as something that it is not (e.g. mistaking a garden hose for a snake; Shine et al., 2012); hallucinations of presence (ou de presence), the strong sensation that someone is nearby; or hallucinations passage (ou de passage), the brief movement of a person or animal in the peripheral visual field (Friedman, 2013); and VH, a percept in the absence of corresponding external stimuli. The latter will be the focus of this section.

Visual hallucinations may also be present in non-clinical populations. Charles Bonnet syndrome is the presence of VH in otherwise healthy individuals, typically

caused by damage to the ocular or visual pathways (Pang, 2016). This syndrome is more prevalent in individuals with visual impairments or lesions to the visual pathways (Pang, 2016). Indeed, many studies have found that individuals with poor visual acuity are more likely to experience VH, regardless of age, cognition, or comorbid conditions (Gordon, 2016; Marmamula et al., 2020; Scott et al., 2001; Urwyler et al., 2014). A similar pattern has been found in PD patients, with poorer visual acuity in patients that experienced VH (Matsui et al., 2006). In Healthy individuals specific visual impairments have also been linked to VH. Poor contrast sensitivity has been found to be a risk factor of VH (Jackson et al., 2007). Patients with PD are also known to have poor contrast sensitivity, likely caused by LB pathology in the retina or visual pathways (Ortuño-Lizarán et al., 2018; Visser et al., 2020; Weil et al., 2016). Indeed, PD patients with poor contrast sensitivity are also more likely to experience VH (Visser et al., 2020).

In synucleinopathies, VH are frequently considered along a spectrum of severity. At the mild end of the spectrum are misperceptions. While misperceptions are illusions, they are included in this spectrum as they are likely to precede the presence of VH in their different forms. Further along the spectrum, patients start to report shadowy shapes or figures. These then begin to take form to become complex hallucinations (O'Brien et al., 2020) and can take the form of animals or people (Ferman et al., 2013; Gomperts, 2016). At the most severe end of the scale hallucinations become more vivid and can be accompanied by delusions (false beliefs). This is often distressing for the patient and caregiver and commonly leads to the patient being admitted into a full-time care facility. While there are few studies on visual impairments in DLB patients, one recent study found that in DLB patients poor colour discrimination was strongly associated with VH (Matar et al., 2019a), also linked to LB pathology in the visual pathway. There are multiple theories behind the causes of VH within clinical populations, with many of them including poor visual input combined with poor awareness and attention (Arnulf et al., 2000; Ballanger et al., 2010; Barnes et al., 2003; Diederich et al., 1998; Diederich et al., 2005; Gordon, 2016;

Hamilton et al., 2012; Jackson et al., 2007; Koerts et al., 2010; Matar et al., 2019a; Matsui et al., 2006; Muller et al., 2014; Shine et al., 2014a; Shine et al., 2015c; Shine et al., 2014b).

Due to the high comorbidity of VH and RBD in PD patients, early theories surmised that VH were the product of impaired sleep cycles (Arnulf et al., 2000). Driving this model was the temporal proximity between occurrence of VH and REM cycles, which led researchers to believe that VH were the product of dream imagery that occurs during RBD stages of sleep intruding into waking states (Arnulf et al., 2000). However, a 24-hr sleep study monitored PD patients with VH and noted that while VH did appear around REM transitions, they also occurred during fully attentive, wakeful states of patients (Manni et al., 2002). This suggests that while dream intrusion may explain some VH, there are likely other mechanisms that also increase the risk of VH within this population. Additionally, imaging studies have shown intact brainstems in some PD patients with VH (Goetz et al., 2014; Ibarretxe-Bilbao et al., 2010) but hypometabolism in the cortical areas.

Hallucinations in schizophrenia are believed to be due to confusion of the source of a stimulus, leading to internal representations thought to be external stimuli (e.g. internal voices believed to be coming from a higher power; Mondino et al., 2019). The reality monitoring deficit is supported in PD with patients that experience VH performing poorly on source memory tests compared to non-VH PD patients (Barnes et al., 2003). Furthermore, performance was worsened when VH patients had to switch between internal and external sources of stimuli (Barnes et al., 2003). However, impaired source memory does not explain complexities of the hallucination content, suggesting additional areas are likely involved (Muller et al., 2014).

The activation, input, and modulation model of VH combines aspects from the dream intrusion and reality monitoring deficit models combining REM, external stimuli with the addition of visual impairment and cognition (Diederich et al., 2005). This model is based on Hobson's states of consciousness that includes three main dimensions that influence consciousness: Activation, Input, and Modulation. Activation refers to the activation of information processes, at the high state the

individual is alert and awake, while the low state would represent non-REM sleep. Input refers to the gating of internal and external stimuli, at high levels (open) information is exchanged between internal and external sources (during alert, wakeful states) while at low levels information is restricted to internal sources only (during REM and non-REM stages of sleep). The input dimension also relies on internal stimuli and a mechanism that controls the gating of internal/external stimuli. Modulation controls the interaction of activation and input over time. During alert, wakeful states the activation of attention, logical thinking and other frontal functions are enhanced. During REM states, hyper-associative cognition and production of visual imagery are facilitated (Hobson et al., 2000). In PD, impairment in the input dimension is believed to be the driving cause of VH (Diederich et al., 2005). Here, an imbalance between external and internal input occurs. This could be due to visual impairments or poor lighting of the environment. This causes the input gating system to rely on internal stimuli to complete ambiguous external stimuli, leading to VH (Diederich et al., 2005). According to this model, impairment to the ponto-geniculo-occipital system which modulates internal stimuli as well as being involved in the processing of external stimuli (Diederich et al., 2005). However, imaging studies have also linked abnormalities to the frontal, and parietal cortices, and thalamus (Esmaeeli et al., 2019; Onofrj et al., 2019; Pezzoli et al., 2019; Pezzoli et al., 2021).

The perception and attention deficit model focusses on attention due to many VH occurring at the centre of visual attention and how it interacts with visual perception to recreate and process a visual scene. This model is based on scene perception models that propose that the perception of a scene is subjective, and the construction of the visualisation is driven by both top-down (attention, goals, mnemonics) and bottom-up processes (sensory) (Collerton et al., 2005). During construction, objects are represented by top-down processes (i.e. what we expect to see in this space) that compete with bottom-up processes (perceptual stimuli), to be placed in conscious awareness. Visual hallucinations occur when objects from top-down processes which are inconsistent with the bottom-up percepts are incorrectly placed into conscious

awareness. This could be due to a hyperactive attention system or visual impairment (Collerton et al., 2005). This model relies on the ventral visual stream, which has been shown to be impaired in hallucinators (Ramírez-Ruiz et al., 2008). However, both the ventral and dorsal visual streams have been shown to be impaired in PD patients with VH (Boecker et al., 2007), suggesting more involvement of the attentional networks.

A more recently developed theory focuses on the attentional networks (Shine et al., 2011). These networks consist of the dorsal attentional network (DAN), the ventral attentional network (VAN) and the default mode network (DMN). The DAN is responsible for directed or goal driven attention (Fox et al., 2006). It contains the intraparietal sulcus and the frontal eye field regions (Vossel et al., 2014). The former being responsible for top-down influence over attention (Hwang et al., 2020) whereas the latter controls saccadic eye movements (Vernet et al., 2014), highlighting the influence the DAN has on the visual network (Shine et al., 2015c). The VAN is involved in exogenous attention that are driven by stimuli (Fox et al., 2006) and includes regions such as the temporoparietal junction, an area involved in awareness and attention (Chang et al., 2013; Wilterson et al., 2021), and the ventral frontal cortex, which has been linked to feature based attention (Bichot et al., 2019). The DMN is known as a task negative network, which is activate during rest (awake and alert, but not attending to any particular stimuli) and is responsible for introspective thought and mind wandering, as well as playing a role in episodic memory retrieval. The main regions of the DMN are the posterior cingulate cortex, precuneus and medial frontal cortex (Hu et al., 2017). These areas have lowered activity during active tasks, while increased activity during rest periods (Cavanna & Trimble, 2006), as well as being involved in preparation of attentional shifts (Small et al., 2003).

The attentional network model of VH consists of two components: the impairment of the goal directed DAN and the uncoupling of the DMN (Shine et al., 2011). The uncoupling of the DMN causes abnormal communication between the DMN and VAN, allowing the DMN to influence what the VAN perceives resulting in misperceptions or VH (Shine et al., 2015c). Moreover, during misperceptions

connectivity between the DMN and the visual network also increases (Shine et al., 2015c). While the DAN would normally filter out incorrect perceptions, degradation of this network removes this filtration system (Shine et al., 2011). This model has been evaluated empirically using fMRI and EEG in PD patients with VH (Piarulli et al., 2021; Shine et al., 2015c). Shine and colleagues (2012) employed the Bistable Percept Paradigm (BPP; see section 1.5.3) as a measure of VH. In this paradigm participants are presented with ambiguous images, of which half have multiple perceptual interpretations while the other half only have one. Participants are then required to identify if there are one or more main percepts in each image. Misperceptions occurred when incorrect percepts were described for either image type, while misses were defined as percepts that were missed by the participant (Shine et al., 2012). Parkinson's patients underwent fMRI while completing the BPP, focusing on activity of their attentional networks. Abnormal connectivity was found that was specific for PD patients with VH, this was characterised by a decrease in VAN activity during correct and misperceived images. Misperceptions were also paired with a large increase in activity in the DMN network and an increase in connectivity between the DMN and visual network (Shine et al., 2015a).

Dementia with Lewy body patients have shown impairment in the dorsolateral prefrontal cortex (Ye et al., 2019), posterior parietal cortex (Crutch et al., 2012), and frontal eye fields (Ishii, 2020), areas that are involved in the DAN (Ishii, 2020), suggesting that the DAN network would also be impaired in DLB. The decoupling of the DMN may be caused by thalamocortical dysrhythmia with pathological bursts of theta wave activity originating from the thalamus (Onofrj et al., 2019). As a main conduit of information travelling throughout subcortical and cortical regions (Esmaeeli et al., 2019), the theta bursts ripple throughout the cortex, specifically the frontal areas. These bursts of theta waves are believed to have an inhibitory effect on the frontal attention networks, allowing the DMN to decouple and potentially become unfiltered (Onofrj et al., 2019). As discussed in section 1.3.1.3, DLB patients have also shown low ACh uptake and metabolism in the thalamus (Kanel et al., 2020; Kanemoto

et al., 2020), as well as a shift towards slower theta waves (Bonanni et al., 2015; Franciotti et al., 2020). This pathology in DLB patients, combined with impairments in the temporoparietal junction, would suggest that the attentional networks are affected in the same way in DLB as in PD patients with VH. Moreover, hypometabolism in the occipital cortex is common in DLB (Prosser et al., 2017), and has been linked to a disconnection between the visual network and higher order visual processing regions (Iaccarino et al., 2018). Indeed, VH severity and frequency in DLB patients has been shown to correlate with degeneration of the occipital cortex (Firbank et al., 2016b; Iaccarino et al., 2018; Pezzoli et al., 2021), further supporting the attentional network theory of VH and potentially explaining the main drivers of VH in DLB patients. An empirical study using the BPP to investigate the mechanisms behind VH in DLB forms the basis of Chapter Four of this thesis.

Visual hallucinations are very common in DLB, affecting 30 – 70% of patients (Jellinger, 2018), compared to 19 - 40% of PD patients (Eversfield & Orton, 2018), and just 13% in AD patients (Zhao et al., 2016). This high prevalence in DLB has resulted in VH being a core feature of DLB in the official diagnostic criteria (McKeith et al., 2017). The presence of VH also signals a poor prognosis for DLB patients (Bostrom et al., 2007a). Severity and frequency of VH are often paired with poorer cognition, as well as other neuropsychiatric symptoms (depression, anxiety, apathy). They are also the main causes of carer stress (Svendsboe et al., 2016), as well as a strong predictor of the patient being admitted into institutionalised care (Rongve et al., 2014). Therefore, the impact of VH clinically emphasises the need for more accurate detection, as well as improved treatments.

1.7.4. Cognitive Fluctuations

Cognitive fluctuations are characterised by a cycling change between high and low cognition and alertness that affects responsiveness, speech, memory, and behaviour (McKeith et al., 1992b). These CF are associated with poor cognition, especially in the domains of attention, working memory and executive function

(Ballard et al., 2002b; Bliwise et al., 2014). Whilst CF have been a core symptom of DLB since the first iteration of diagnostic criteria, little is known about their underlying pathophysiology. However, a recent framework has been proposed that emphasises that the dysfunction underlying the phenomenon is occurring across a distributed neural system, operating at a network-level that ordinarily controls the transition between conscious and unconscious brain states (Matar et al., 2019b). The duration of these episodes may be from seconds, minutes or even longer in rare cases. Their frequency can also vary from multiple times in the same day to every few months. During a cognitive fluctuation, a patient's behaviour could be likened to that which is observed during partial seizures. However, unlike what occurs in a seizure, patients can often be roused by salient stimuli such as calling their name (Matar et al., 2019b).

Electroencephalography has been used to identify the neurophysiological abnormalities occurring in DLB patients with CF. Walker and colleagues (2000b) observed a slowing in wave frequency in the frontal and parietal regions during the resting state of a DLB patient with severe CF. A similar pattern has also been recorded in a larger cohort, with EEG slowing and dominant frequency variation being correlated with CF severity within DLB patients (Stylianou et al., 2018). Theta activity in the frontal region has also been linked to behavioural inhibition (Huster et al., 2013), suggesting that the unresponsive component of CF could be the result of an overactive inhibition system. Electroencephalography disturbance is not restricted to the frontal and parietal regions. Focusing on whole-brain dynamics in DLB, Schumacher and colleagues (2019b) found that DLB patients have fewer microstate transitions compared to HC and AD patients. Furthermore, the length of time spent within a single state was also correlated with CF. While this may explain the overall cognitive slowing experienced by DLB patients, it is unclear how this slowing specifically leads to fluctuations of cognition. In addition, the duration of the microstate was also correlated with functional activity between the cortex, basal ganglia, and thalamus (Schumacher et al., 2019b), suggesting that the thalamus, which is a major source of

theta wave activity may play a key role in CF. It has been suggested that thalamic impairments in DLB may be due to a depletion in ACh levels (Kanel et al., 2020; Kanemoto et al., 2020), secondary to neurodegeneration of the nucleus basalis of Meynert. Indeed, a loss of volume within this region has been correlated with the severity of CF (Colloby et al., 2017; Kim et al., 2011). Furthermore, pharmacological interventions targeting AChEI have also been shown to reduce the severity of CF within DLB patients (Kazui et al., 2017; Onofrj et al., 2003).

The prevalence of CF in DLB is very high, with approximately $80 - 90\%$ of patients reporting fluctuations (Lee et al., 2012). This compares to just 20% of AD patients (Onofri et al., 2015) and 29% of PDD patients (Ballard et al., 2002b), making CF a potentially useful feature for differentiating between these diseases. Furthermore, the quality of CF seems to be different in AD compared to DLB, wherein they may be triggered by environmental factors and tend to impact more significantly on memory function (Bradshaw et al., 2004). Conversely, the CF observed in DLB patients are typically spontaneous and appear to be internally driven with characteristic impairments in attention and alertness (Bradshaw et al., 2004). These differences might reflect differential neural underpinnings for the CF experienced in DLB and AD presumably in relation to their distinct neuropathology.

To date, no link between disease severity and CF severity has been found (Ferman et al., 2004) and there is no evidence that their presence is associated with a more aggressive disease progression (Kramberger et al., 2017). Additionally, DLB patients who present with CF during the early stages of their disease do not experience more severe CF than those who develop them in later stages (Graff-Radford et al., 2017) and CF do not necessarily predict cognitive performance with no significant differences recorded on MMSE between patients with and without this symptom (Cagnin et al., 2013). However, DLB patients with CF do perform more poorly on specific tests of attention (Ballard et al., 2002b; Cagnin et al., 2013).

1.7.5. Parkinsonism

Parkinsonism is defined as the presence of bradykinesia and either rest tremor and/or rigidity (Postuma et al., 2015b). Unlike the diagnostic criteria for PD (Postuma et al., 2015b), the diagnostic criteria for DLB require the presence of just one of these features and do not demand the more stringent features of bradykinesia with decrement, tremor occurring predominantly at rest or rigidity in association with cogwheeling (McKeith et al., 2017). Parkinsonian features occur in up to 85% of DLB patients over the course of their disease (Jellinger & Korczyn, 2018) with bradykinesia appearing as the most frequent finding, compared to tremor (Onofrj et al., 2013). The presence of parkinsonism does not predict prognosis in DLB but may have a negative effect on their quality of life and activities of daily living (Bostrom et al., 2007a; Lee et al., 2018a). To date, there are no studies investigating motor symptoms on quality of life in DLB.

Parkinsonian signs are much less common in other dementias, for example being present in <10% of Vascular Dementia (Al-Harrasi et al., 2021) and 13% of AD patients (Scarmeas et al., 2005). The pathology driving parkinsonism in DLB mirrors that which is observed in PD with loss of dopaminergic neurons predominantly in the nigrostriatal projection, which can be measured with DAT scanning as described above (section 1.4.3; McKeith et al., 2007b).

1.8. Measuring Core Features in DLB

1.8.1. Cognitive Decline

The Mini Mental State Examination (MMSE, Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) represent common measures of general cognition and whilst both tests may be appropriate for testing patients with dementia, it is well recognised that the MMSE has a low sensitivity for differentiating between different dementia subtypes (Arevalo-Rodriguez et al., 2015) compared to the MoCA (Martini et al., 2020). Comparing the two scales, the MoCA has been shown to have fewer ceiling and floor effects than the MMSE, whilst the MMSE appears to be

more stable across timepoints (Biundo et al., 2016). However, it should be emphasised that the current consensus would be that neither test should be used as the sole diagnostic tool for DLB (Arevalo-Rodriguez et al., 2015). Indeed, many studies have highlighted the role of testing specific cognitive domains in DLB, both in clinical and research settings, to detect and measure more specific and subtle impairments.

There are numerous cognitive tests designed to target specific domains. This section, however, will only focus on the paradigms commonly used with DLB patients to measure executive function, attention, visuospatial ability, memory, and language. Compared to other disorders and dementias, there are few studies that have applied these tests on a DLB population, let alone compared results between DLB and other dementias. Furthermore, many standard cognitive tests are not designed to be used with severely demented populations such as DLB patients, while tests that are used often yield very high variance within the DLB cohort. These two features make it challenging to obtain consistent results from DLB populations and highlight the need for new tests that are practicable for use in DLB patients.

1.8.1.1. *Executive function and Attention*

Executive function and attention can be severely impaired in DLB patients and thus consideration needs to be given to the limitations when selecting an appropriate task.

One common task designed to measure processing speed, inhibition, as well as task switching is the Stroop task (Stroop, 1935). Processing speed is measured in the first two sections with patients required to read a matrix of words and then name colours presented in another matrix. Dementia with Lewy body patients are usually able to complete the first two sections of the Stroop task, although at a slower speed than HC (Pezzoli et al., 2019), demonstrating a slower processing speed. The first two sections of the Stroop produce worse performance amongst DLB than AD and frontotemporal dementia (FTD) patients (Breitve et al., 2018; Johns et al., 2009; Park et

al., 2011). The second two sections of the Stroop require patients to identify the text colour of mismatched colour words, and then to switch between stating the word or the colour of the word. These measure inhibition and task switching, respectively. Dementia with Lewy bodies patients are severely impaired at these Stoop sections (Petrova et al., 2016). Furthermore, DLB patients with mild cognitive impairment performed at a similar level to patients with more severe cognitive impairment (MMSE < 20), suggesting a floor effect with this cohort. This floor effect may also be evident through the absence of difference between AD and DLB (Breitve et al., 2018). However, this could be disease specific as FTD patients performed better than DLB (Johns et al., 2009). Although, studies have also found the Stroop sections designed to measure inhibition and task switching too difficult for DLB patients to complete or have avoided the later sections altogether (Martini et al., 2020; Park et al., 2011; Petrova et al., 2016), highlighting the need for tasks that are suitable for more severely demented populations.

The Trail Making Test (TMT; Reitan & Wolfson, 1985) requires patients to connect numbered dots with lines in numerical order. There are two parts: part A only contains numbers and relies on visuospatial ability; whilst part B included numbers and letters, requiring patients to alternate between them. Part B also relies on inhibitory control, task switching and working memory (Sánchez-Cubillo et al., 2009). Dementia with Lewy body patients perform poorly on the TMT-A compared to PDD (Mondon et al., 2007) and AD (Breitve et al., 2018) and whilst the task switching in TMT-B may be helpful for probing this domain, many DLB patients are unable complete the test (Breitve et al., 2018; Breitve et al., 2014; Martini et al., 2020).

The Digit Span task requires patients to repeat a string of numbers read to them by the researcher that get incrementally longer (Wechsler, 2008). Performance can be reported for forward and backwards digit spans, or as a combined score. High scores are associated with good working memory and attention. Dementia with Lewy body patients are able to complete this task, demonstrating a similar digit span to PDD patients (Howard et al., 2021; Petrova et al., 2015), but lower than HC (Gnanalingham

et al., 1997; Warden et al., 2016; Yoon et al., 2014). However, focusing on backward digit span, patients with DLB were more impaired than PDD (Petrova et al., 2015), but this was not replicated in a recent study (Howard et al., 2021). Inconsistent findings also appear when comparing DLB with AD patients. One early study found that DLB and AD had similar forward digit spans, while DLB had poorer backward digit span (Calderon et al., 2001). This finding was also supported with a retrospective autopsy study of a dementia cohort finding that patients with only LB pathology had poorer digit span than patients with either AD pathology, or both LB and AD pathology (Kraybill et al., 2005). Unfortunately, the only composite score was reported, restricting further analysis to determine if this was driven by forward or backward digit span scores. More recently, although using only the backward digit span, Howard and colleagues (2021) did not find a difference between AD and DLB patients. Backward digit spans for DLB in the aforementioned studies was also very short (1 – 3), suggesting that this could be a floor effect for this cohort. Indeed, Martini and colleagues found that the majority of their DLB sample were unable to complete the backward digit span due to the difficulty level (Martini et al., 2020).

1.8.1.2. *Language*

The verbal fluency task requires the patient to state as many words as they can that begin with a particular letter (the Controlled Oral Word Association Test - COWAT) or fit a specific category (e.g. animals) within a set time. Performance is measured from the number of words made and as well as the number of errors/repetitions. Verbal fluency targets working memory, as well as language (Lezak et al., 2012). Dementia with Lewy body patients are able to complete this task and have poor verbal fluency when compared with HC (Ferman et al., 2006; Petrova et al., 2016; Wajman et al., 2019). Unfortunately, task performance becomes inconsistent when comparing DLB with other clinical groups.

During prodromal stages of disease, DLB and PD patients perform at similar levels, but prodromal DLB patients perform worse with the category condition (Yoon

et al., 2014). Moreover, Génier Marchand and colleagues (2018) found that prodromal DLB patients had lower fluency up to six years before diagnosis. Comparing task performance across dementias, DLB demonstrates variable results with some groups reporting poorer performance at the verbal fluency task than PDD patients (Martini et al., 2020), whereas others did not find a difference between DLB and PDD (Park et al., 2011). However, this non-significant finding may have been due to low statistical power from a small sample of DLB (n = 10) as their finding was trending towards significance (p = 0.07). Performance on the verbal fluency task also had mixed results at separating DLB from AD patients. During early stages, MCI-LB patients have been found to have poorer fluency than patients with MCI and AD pathology (Cagnin et al., 2015). However, this was not found in a recent study, with both prodromal groups performing at the same level (Hamilton et al., 2021b). In clinical populations, older studies have found DLB to perform poorer than AD (Ferman et al., 2006; Lambon Ralph et al., 2001), but more recently, Wajman and colleagues (2019) did not find any difference between AD and DLB groups. These conflicting findings are likely due to inconsistencies task methods, with Wajman and colleagues (2019) only using a category rule (animals) whilst others reported results on the COWAT for the letters F, A and S. No difference in fluency was found between DLB and FTD (Johns et al., 2009), perhaps reflecting similarities in impairment to frontal regions in these two groups.

1.8.1.3. *Memory*

There are hundreds of tests designed to measure specific domains in memory (i.e. episodic, semantic, procedural). Additionally, they can target verbal domains (i.e. recollection of word lists, vignettes) or non-verbal (i.e. tapping blocks in a particular order, recalling a visual scene). In this section, DLB ability will be compared with other types of dementia across verbal and non-verbal tasks among various memory domains.

Verbal memory tasks typically involve the participant listening to a list of words or a story and then after a set delay, they are required to recall as many words or as much of the story as possible. The Rey Adult Verbal Learning Task (RAVLT) is commonly used to test word recall. This task is similar to a basic word list recall task; however, the list is repeated several times with recall times spread out across the testing to cover a range of delays. Compared with controls, DLB patients typically have poorer performance in the RAVLT (Caso et al., 2021; Ferman et al., 2006). When comparing prodromal AD and DLB, the RAVLT is not able to differentiate between the two diseases (Hamilton et al., 2021b). However, in clinical DLB and AD, DLB is often found to have poorer performance than AD (Caso et al., 2021; Ferman et al., 2006). Although, in a basic word recall task, DLB have been shown to perform at the same level as AD (Kawai et al., 2013; Salmon et al., 2015). This suggests that DLB patients may benefit from a shorter verbal memory task, possibly due to increased attentional demand of longer tasks. The Logical Memory task is another verbal task, in which participants are read a story and are required to recall as much as they can either immediately or after a delay. This task appears appropriate for DLB patients who perform poorer than HC (Calderon et al., 2001), while better than AD (Calderon et al., 2001; Kawai et al., 2013; Oda et al., 2009)

Non-verbal memory tasks often present the patient with images, shapes, or patterns, with patients then required to recall or recognise the image or shape or pattern immediately or after a delay. These tests appear to be good at separating DLB from AD, with studies agreeing that DLB patients have worse non-verbal memory than AD patients (Nervi et al., 2008; Noe et al., 2004; Salmon et al., 2015). However, there are mixed findings between DLB and PDD performance with some work showing no difference in performance between these groups (Noe et al., 2004), whilst another found worse performance in DLB compared to PDD (Sanchez-Castaneda et al., 2009).

1.8.1.4.   Visuospatial

Visuospatial tasks require the manipulation or recreation or judgement of visual stimuli. The Visual Object and Space Perception battery (VOSP) is a battery of tasks designed to measure impairment in object and space perception. Tasks require patients to complete incomplete letters, name objects from silhouettes and compare the positions of objects (Warrington, 1991). During prodromal stages of DLB, it appears that the VOSP is unable to differentiate MCI-LB from HC (Kemp et al., 2017), however it can separate clinical DLB from HC, with DLB patients having poorer performance (Pal et al., 2016). Additionally, some of the VOSP components have shown differences between DLB and AD patients (Calderon et al., 2001). These findings suggest that while the VOSP may be useful at distinguishing clinical populations, it may not be sensitive enough to differentiate prodromal patients.

The Block Design task requires patients to replicate set patterns using blocks with various shapes printed on them (Kohs, 1920). Studies have found DLB and AD patients performing at a similar level (Hamilton et al., 2008; Johnson et al., 2005), suggesting that this task may be too difficult to separate between these two cohorts. The Clock Drawing Task requires patients to draw an analogue clock that is displaying a specific time. Compared with HC, DLB patients are very impaired with this task (Gnanalingham et al., 1997; Ota et al., 2015). However, there are mixed findings when comparing AD patients with DLB (Cahn-Weiner et al., 2003; Gnanalingham et al., 1997; Ota et al., 2015). The copy condition of the Rey Complex Figure task requires patients to replicate a complicated shape with smaller shapes and patterns within it. Comparing prodromal patients, MCI-LB have been shown to perform poorer than MCI-PD (Yoon et al., 2014). Findings are mixed when comparing DLB with PDD patients, with DLB patients performing poorer than PDD in a recent study (Martini et al., 2020), but no difference being found between the two in previous studies (Mondon et al., 2007; Park et al., 2011). This difference may be due to the small number of DLB patients of the earlier studies (n = 10) compared with a larger sample in the recent study (n = 18). The Benton Judgement of Line Orientation is another task that has been applied to compare DLB and AD patients, with mixed findings. When

completed, it appears that DLB patients are impaired at this task (Ota et al., 2015; Simard et al., 2003). However, a recent study has also reported that this task is too difficult with most of their DLB patients unable to complete it (Martini et al., 2020).

A reoccurring theme with cognitive testing is an inconsistency in findings across studies. This could be due to tests not being sensitive enough to measure subtle impairment in prodromal patients or small differences between DLB and AD. Regardless, current tasks may need to be altered or new tasks introduced to ensure accurate measurements of cognitive impairments within the DLB cohort.

1.8.2. Rapid Eye Movement Sleep Behaviour Disorder

The gold standard for the diagnosis of RBD is using video polysomnography (vPSG). While this test involves many different measures to detect a broad range of sleep disturbances (Qian et al., 2021), the most relevant measures for RBD are from the EEG, Electromyography (EMG), and video recording, as well as excluding the confound of severe sleep apnea. Cycles of REM are detected with the EEG, while body movement is detected with EMG and video analysis. The current international classification of sleep disorders lists two requirements for the diagnosis of RBD: (1) the repeated presence of behaviour or vocalisations during REM as measured by vPSG, or an informant (typically bed partner); (2) evidence of REM sleep without atonia (RSWA) from vPSG (Sateia, 2014). Additionally, muscle activity during REM cycles is scored for frequency and severity (St Louis & Boeve, 2017). However, the presence of any muscle activity during REM supports the loss of atonia and allows for the diagnosis of RBD in the right clinical context. While vPSG provides a confident diagnosis of RBD, it has very limited accessibility to the general population. With expensive setup and maintenance costs, vPSG is only available in health centres specialised in sleep disorders or select hospitals. Furthermore, measuring a condition during "normal" sleep can be difficult when requiring the patient to sleep in a laboratory environment, whilst wired for the different measures required. Ideally,

testing should be as unintrusive as possible, and be undertaken in an environment comfortable and familiar to the patient. This is even more imperative when testing patients with dementia. There are currently trials underway investigating the use of a home PSG device. If these trials prove successful, it will make the diagnosis of RBD much easier (Hof Zum Berge et al., 2020).

Currently, without access to a PSG test, only probable RBD can be diagnosed. This can be done via clinical interview where the patient is probed to identify dream features (if they are vivid and negative; for review see Matar & Lewis, 2017), and if they experience any dream enactment (Dauvilliers et al., 2018). Alternatively, the RBD Screening Questionnaire (RBDSQ; Stiasny-Kolster et al., 2007) or Mayo Sleep Questionnaire (Boeve et al. 2013) can be used to detect RBD symptoms. These questionnaires ask if the patient is aware of enacting their dreams and the nature of their dreams. The RBDSQ it has high sensitivity (Stiasny-Kolster et al., 2007) the reliability of this tool has been reported to be low (Stefani et al., 2017). Conversely the MSQ has shown promise in correctly identifying RBD patients (Boeve et al. 2013; Bolitho et al. 2014). Variance across the questionnaires and clinical interview may be due to the self-report format, potentially allowing for recall bias or the denial or ignorance of symptoms, especially if they are mild. For these reasons, clinical interview, MSQ and the RBDSQ are preferred to be completed with a bed partner or relevant informant present (Gilat et al., 2020).

1.8.3. Hallucinations

Hallucinations in DLB patients are typically vivid and well-formed (McKeith et al., 2017). This feature allows for many hallucinations in DLB to be detected during a clinical interview or self-report questionnaire. During interviews, some studies may just ask the patient if they experience VH as a direct question (Gama et al., 2015; Heitz et al., 2015). The North East Visual Hallucination Interview is a semi-structured that probes for visual perception errors (i.e. VH or misperceptions) and queries if the

participnat has experienced any VH or "other visual experiences" (Mosimann et al. 2008). These interviews, however, leave the definition of VH to the researcher, as well as the interpretation of the response. To provide some consistency across studies, VH can also be probed as part of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2004). Scoring of this item ranges from "no hallucinations experienced" (0) to "vivid hallucinations without insight" (3). While most patients can answer this question, it does depend on a level of insight from the patient, or if the caregiver identified this symptom. The Scale for Outcomes in Parkinson's Disease – Psychiatric Complications (SCOPA-PC; Visser et al., 2007) also includes an item that targets hallucinations, however like the MDS-UPDRS, it reduces the presence and characteristics of hallucinations to a generic four-point scale. The Neuropsychiatric Inventory (NPI) is another measure that is commonly used in synucleinopathy research (Cummings, 1997). This is a comprehensive scale with more than 80 items, which cover 12 different domains of neuropsychiatric symptoms (e.g. apathy, anxiety, irritability), with seven items for hallucinations. The NPI has been used in DLB populations where it has been able to differentiate DLB from AD patients, but with a low sensitivity (Suárez-González et al., 2014). This could be due to the NPI having been originally designed to detect neuropsychiatric symptoms in AD before DLB was formally recognised as a separate disease. This scale has also been used to separate MCI patients with LB characteristics from MCI patients with a more AD phenotype. Whilst the LB with MCI patients scored higher overall on this scale, the authors did not indicate which domains were driving this difference (Donaghy et al., 2020).

The Psychosis and Hallucinations Questionnaire (PsycHQ; Shine et al., 2015b) is a recently developed scale that was designed to not only probe for hallucinations in PD patients, but to also measure symptoms that often present with VH in this cohort. A strength of the PsycHQ is that it probes for the broad spectrum of hallucinations,

across all modalities. While it has been validated in PD, it has yet to be validated in a DLB cohort.

The Pareidolia task is a computerised tasked designed to measure misperceptions in the form of pareidolias (i.e., seeing objects in unrelated stimuli; Uchiyama et al., 2012). Dementia with Lewy body patients appear to identify more pareidolias than AD patients (Inagawa et al., 2020; Uchiyama et al., 2012), however the accuracy of separating these two diseases is varied with 73 – 100% sensitivity, and 62 – 88% specificity (Inagawa et al., 2020; Uchiyama et al., 2012). This task has also been tested with RBD patients, with higher pareidolia scores predicting transition to DLB (Honeycutt et al., 2020) but there was poor sensitivity at separating MCI-LB patients from HC (sensitivity = 41%; specificity = 91%) or MCI-AD patients (sensitivity = 27%; specificity = 89%; Hamilton et al., 2021a). Furthermore, while misperceptions can involve any type of object or living thing, the Pareidolia task only captures the misperception of faces, potentially missing other misperceptions that are not faces.

Chapter Four of this thesis evaluates the BPP in DLB patients for the first time. The BPP is a novel behavioural task that was originally designed to measure visual hallucinatory phenomenon in PD (Shine et al., 2012). The BPP provides an objective score that could be used by researchers and clinicians to measure and track changes in VH with disease progression and potentially in the context of a treatment intervention. A further strength of the BPP is that it can also measure misperceptions, which are less severe phenomena that are experienced by PDD and DLB patients, and it well recognised that patients with misperceptions are more likely to experience VH (Shine et al., 2012). This paradigm is also able to be administered in the context of fMRI, allowing researchers to investigate brain activation patterns that are associated with misperceptions and VH (Shine et al., 2015a; Shine et al., 2015c).

1.8.4. Cognitive fluctuations

Cognitive fluctuations are possibly the most difficult DLB symptom to diagnose (Matar et al., 2019b) and are difficult to measure reliably. Currently, fluctuations are identified during a clinical interview where a patient or their caregiver are asked if the patient has had periods of confusion, low alertness, or inattention. The severity of these episodes may be gauged by probing their frequency and duration, as well as functional performance during the period. There are validated scales designed to measure the severity of CF in DLB patients, such as the Clinical Assessment of Fluctuations (CAF) and the One Day Fluctuation Assessment Scale (ODFAS; Walker et al., 2000a), as well as the Mayo Fluctuations Questionnaire (MFQ; Ferman et al., 2004).

The CAF measures symptoms that have occurred over the preceding month and consists of four items. The first 'yes' or 'no' item identifies the presence of any periods of lowered cognition; the second item identifies if these periods fluctuate over time, whilst the last two items measure the duration and frequency of any impaired cycles. The main criticism of this scale is that the clinician needs to have expert knowledge in CF to decide if various behaviours would indicate a CF (e.g. if the patient is quiet while remembering a word or event; Ferman et al., 2004). Furthermore, the scale does not distinguish any characteristics of the fluctuation episodes. As discussed above this would be useful to measure as the CF in DLB patients are often qualitatively different to those observed in AD (Bradshaw et al., 2004).

The ODFAS measures impairments in different domains that are known to be impaired in patients with CF (e.g. communication, disorganised thinking, drowsiness; Walker et al., 2000a) and these features are each scored on a three-point scale. The main issue with the ODFAS is that it only covers the current day of testing. Obviously, as CF may appear daily or monthly, it would need to be administered on a 'typical' day with fluctuations to appropriately capture these symptoms. The CAF has been used to differentiate between DLB, AD and vascular dementia patients with high (>80%) sensitivity and specificity (Walker et al., 2000b). The CAF scale has also been used in conjunction with the ODFAS to compare DLB and AD patients

(Bradshaw et al., 2004). The DLB patients scored much higher on the CAF and the ODFAS than AD, however AD patients also scored higher on the ODFAS than the CAF. This is likely due to the ODFAS having only one section that addresses fluctuations. This implies that patients with non-fluctuating dementia may score highly on the remaining items, bringing the specificity of the ODFAS as a measure of CF into question.

The MFQ consists of four items targeting drowsiness, daytime sleep, staring into space for extended periods of time and disorganised thoughts (Ferman et al., 2004). If an item is present in the patient, they are given one point. Thus, the maximum score is four, whilst a score of at least three is needed to suggest presence of CF (Galvin et al., 2021). Whilst this scale has some items that describe episodes of CF (e.g. staring into space), it focuses more on the symptoms that may accompany CF. The Mayo Fluctuation scale has been used to compare DLB and AD profiles, with DLB patients scoring higher on each domain than AD patients (Galvin et al., 2021). However, this may just be targeting features that are more common in DLB than AD, regardless of CF themselves.

The above scales and interviews have demonstrated their utility in differentiating DLB from other dementias. However, as these scales are also based on responses from either the patient or caregiver, there is potential for recall bias or denial of symptoms. Furthermore, as the scales appear to group many aspects of CF within one item, which is then reduced to a score ranging from 0 – 4, it may not be sensitive enough to detect mild instances of fluctuations or subtle changes to fluctuations, which would be very useful when assessing the effectiveness of an intervention. Chapter Two will introduce the Sustained Attention Response Task (SART) to DLB patients (Phillips et al., 2019). The SART is a simple computerised task that requires patients to maintain their attention during a mundane activity. In this chapter performance on the task is compared with CF severity as measured by the CAF and CF features as measured with the ODFAS, as well as measures of DLB core features (Parkinsonism, RBD and cognitive decline).

1.8.5. Parkinsonism

Parkinsonian features may be the reason why many DLB patients first seek medical advice. Currently, the gold standard for objectively measuring Parkinsonian features is by using the MDS-UPDRS. While this scale covers many aspects of PD, the third section is dedicated to motor symptoms (Goetz et al., 2008). These assessments measure multiple aspects of physical performance on a five-point scale. In comparative studies across dementias, PDD patients score higher than DLB, followed by AD patients (Smirnov et al., 2020). Whilst the MDS-UPDRS is a comprehensive measurement tool, it requires highly trained clinicians to perform it correctly. Furthermore, as symptom severity is based on subjective judgements from the clinician, ratings are prone to inconsistency across clinicians (Evers et al., 2019). Additionally, the reduction of symptom severity to a five-point scale reduces the sensitivity of the overall test, as well as reducing potential variance that could be utilised when using the scale in a research setting.

Applying technology designed to measure movement may provide a more accurate report of parkinsonism in DLB and PD patients. Gait analysis mats allow the precise measurement of a kinematic features such as stride length, speed, rhythm, and step variability. Furthermore, these features can be measured during normal walking or walking under cognitive load (subtracting 1s or 7s starting from 100). Merory and colleagues (2007) compared DLB with AD patients and HC, finding that both dementias had smaller stride length and slower pace than HC. However, there were no significant differences between DLB and AD (Merory et al., 2007). However, under high cognitive load, RBD patients have demonstrated subtle abnormalities in their gait compared to HC (Ehgoetz Martens et al., 2019). Unfortunately, it was not known whether these patients were more likely to progress to PD or DLB. However, abnormal gait may not be unique to synucleinopathies as it has also found to be a risk factor for AD and VaD (Beauchet et al., 2016). Although this study focused on

dementias, it did not include PDD or DLB, making a comparison from its findings difficult.

Advances in personal and portable technologies has made actigraphy analysis much more accessible. Indeed, using portable accelerometers, PDD patients have been shown to have slower step times with more variability than AD patients, whilst differences between DLB and AD patients were trending towards significance (Mc Ardle et al., 2020). Accelerometers have also been utilised, taking advantage of their mobility to measure gait during natural activities (Mc Ardle et al., 2021). While this study found DLB patients having larger step length variability, this was only during walks within the laboratory. When in a natural environment, patients only displayed gait impairments during short walks (< 10s; Mc Ardle et al., 2021). Motion capture technology has also been utilised to analyse the upper limb movements in DLB patients (Fadda et al., 2019) and it was found that movement in these patients was impacted by parkinsonism, as well as executive impairment (Fadda et al., 2019). Overall, the clinical assessment of motor impairment in DLB may benefit from objective measuring devices.

1.9. Current treatments

1.9.1. Pharmacological

1.9.1.1. Disease Modifying

Currently, there are several potential pharmacological interventions that target synuclein pathology and mechanisms that influence LB formation (section 1.1.2) (Dong et al., 2019; Pope et al., 2021; Yang et al., 2021). Unfortunately, these are still in their infancy, requiring more research before they can be prescribed. Therefore, current pharmacological approaches target symptom relief and have typically been originally developed for patients with other conditions such as PD, AD, mood, and psychiatric disorders. This is not ideal as underlying mechanisms in DLB are different to what is seen in these other diseases (Panza et al., 2021) and typically results in poor

outcomes for DLB patients. Additionally, care is required as treating one symptom may exacerbate another symptom (Stinton et al., 2015).

1.9.1.2.   *Cognition*

Pharmacological treatments for cognitive impairment in DLB have been drawn from treatment plans in AD and primarily target depleted ACh. The main acetylcholinesterase inhibitors (AChEI) that are prescribed in DLB patients are rivastigmine and donepezil. While both have been reported to improve cognition in DLB patients, donepezil has fewer adverse side effects (Ikeda et al., 2015; McKeith et al., 2000; Mori et al., 2012; Stinton et al., 2015). Galantamine has also been used in DLB patients, while it did not improve cognition it did appear to alleviate neuropsychiatric symptoms (Edwards et al., 2007). Memantine, a N-methyl-D-aspartate (NMDA) agonist, has been reported as giving general improvements in DLB, but not specifically improving cognition (Wang et al., 2015). However, many of these clinical trials have relied on general measures of cognition (i.e. MMSE) as their main outcome, which as discussed in section 1.6.1 may not be sensitive to subtle changes in domains within DLB. These trials would therefore benefit from employing tasks that produce quantifiable measures, allowing an accurate assessment of the intervention.

1.9.1.3.   *Neuropsychiatric*

The main pharmacological intervention prescribed for RBD is clonazepam (Ferri et al., 2017). However, as a benzodiazepine, DLB patients prescribed this drug need to be carefully monitored given negative impacts on cognition, balance, and obstructive sleep apnoea (OSA) (Aurora et al., 2010). Melatonin, an alternative to clonazepam, is a naturally occurring hormone within humans making it is generally well tolerated. However, effectiveness at reducing RBD behaviours is mixed. Some studies have found melatonin to have modest effects on RBD behaviour (Kunz & Bes, 1999; Kunz & Mahlberg, 2010; Takeuchi et al., 2001), but not for all patients (Boeve et al., 2003). While a recent study did not find any improvements from melatonin in PD

patients with RBD (Gilat et al., 2020). Recently, nelotanserin, a serotonin reverse agonist, has also been found ineffective with RBD symptoms (Stefani et al., 2021).

The treatment of hallucinations is complicated, with some VH induced from treatments for cognition, mood, or parkinsonism (Stinton et al., 2015). Furthermore, older treatments for psychosis in DLB utilised antipsychotics with fatal side effects occurring rarely (McKeith et al., 2005). More recently, atypical antipsychotics have reduced this risk but are still associated with increased cardiovascular deaths in this population (Weintraub et al., 2016), although this needs to be balanced against more the individualised risks of non-treatment (Malaty et al., 2016). Clozapine is probably the most effective treatment for psychosis in DLB given findings in similar PD populations (The Parkinson's Study Group, 1999; Pollak et al., 2004; The French Clozapine Parkinson Study Group, 1999), but its use is restricted by the monitoring required to avoid agranulocytosis and other common side effects including sedation, hypotension, and delirium (Stinton et al., 2015). This shortcoming has probably led to the more widespread use of Quetiapine despite its lack of robust effect in clinical trials (Morgante et al., 2004; Weintraub et al., 2011). There are also reports of AChEIs being effective at treating hallucinations (Henriksen et al., 2006) and their safety profile is typically more acceptable. Probably, the most robust evidence in the field for the treatment of psychosis has come over the last decade using Pimavanserin, a 5-HT2A receptor inverse agonist/antagonist (Cummings et al., 2014; Tariot et al., 2021). However, this agent is not widely available and there have been some mixed concerns regarding its safety profile in post-surveillance monitoring (Brown et al., 2021; Hwang et al., 2021; Moreno et al., 2018).

Parkinsonism symptoms are treated using similar protocols to those used in PD. Levodopa is the most common treatment; however, doses need to be kept low as to avoid causing/exacerbating neuropsychiatric symptoms (Hershey & Coleman-Jackson, 2019). Dopamine agonists pramipexole and ropinirole may also be used in DLB, however agonists have a higher chance to elicit neuropsychiatric symptoms so are typically avoided (Fernandez et al., 2003). Zonisamide, an anticonvulsant that acts

on the dopamine system via opioid receptors, has been approved in Japan (Murata et al., 2020) and still undergoing trials in Europe with plans for it to be used in conjunction with levodopa to reduce adverse side effects (Panza et al., 2021).

1.9.2. Non-pharmacological

Deep brain stimulation (DBS) of the sub-thalamic nucleus (STN) is a common treatment for drug resistant motor symptoms in PD. The effects of DBS on cognition are unknown, with one review reporting that STN DBS reduced verbal learning and executive function in patients, while WM was improved (Halpern et al., 2009). A more recent review concluded that DBS of the STN had beneficial improvements on neuropsychiatric symptoms including VH and apathy, improvement in general cognition and improvement of parasympathetic symptoms (Hogg et al., 2017). However, with the small sample sizes, and potential variations in electrode placement or pathways taken to reach the target locations, these findings should be taken with caution.

Deep Brain Stimulation is not commonly used with DLB patients; however recently DBS of the Nucleus of Basalis of Meynert (NBM), a main source of ACh (section 1.1.2.2) has been trialed. Six DLB patients underwent the procedure with one experiencing adverse post-op complications. Three of the remaining five reported an improvement with neuropsychiatric symptoms with no other benefits (Gratwicke et al., 2020). Additionally, connectivity patterns concerning the DMN and parietotemporal junction changed with stimulation. In an identical trial, no benefits were cited with some patients deteriorating in general cognition after the surgery, while stimulation impaired verbal fluency (Maltête et al., 2021). Although the two trials have reported opposing outcomes, there is potential with NBM DBS. However, more research is needed to identify the most beneficial region for stimulation. Moreover, the main outcomes for both trials were based on scales (e.g. MMSE, NPI, MDS-UPDRS), while utilising behavioural tasks such as the SART (Chapter 2), BPP

(Chapter 3) or Mental Rotation (MR; Chapter 4) would potentially increase the sensitivity allowing the detection of less subtle effects of stimulation.

A number of other non-pharmacological therapies such as physical therapy, art and music therapy, occupational therapy, psychological therapy and electroconvulsive therapy have been tested in the treatment of DLB. However, most involve very small sample sizes and anecdotal reports of improvement (Connors et al., 2018). More controlled studies with larger sample sizes are needed before any conclusions can be made about the effectiveness of these alternative treatments.

1.9.3. Future directions

As mentioned in section 1.9.1.1, multiple potential pharmacological treatments are in the development stage that target the formation of LB in synuclein diseases. Dong et al. (2019) are testing cyclic tetrapyrroles, which have been shown to affect the aggregation of prion proteins, which have behaviour analogous to α-synuclein. Their initial findings suggest that the mechanisms that drive aggregation of the prion proteins are similar to those for α-synuclein (Dong et al. 2019). This suggest that may be able to interrupt the aggregation of α-synuclein, blocking the formation of LB. Taking a different approach, Yang et al. (2021) are developing safe vehicles to transport antisense oligonucleotides (ASO), peptides that have been shown to inhibit the formation of α-synuclein (Zharikov et al. 2017). While they have found a suitable transport, it has yet to advance past testing on rodents.

1.10. Summary

Dementia with Lewy bodies is one of the common causes of dementia in the older population. This disease has crippling effects on the patient, the highest rate of caregiver stress, high hospitalisation rates and a higher burden on society than other dementias (Espinosa et al., 2020; Mueller et al., 2018; Rongve et al., 2014). Given that DLB is a neurodegenerative disease, it would be best diagnosed as early as possible,

which requires an accurate clinical profile. The clinical profile of DLB is very similar to AD and significantly overlaps with that of PDD, making an accurate diagnosis difficult. This task is even more difficult during the prodromal stage where neuronal damage is limited, and cognition is relatively preserved. Currently, diagnostic methods are reliant on clinical interviews or scales. As discussed in section 1.6, these methods may not be sensitive enough to separate DLB from other dementias, especially in their prodromal stage. Suggesting a need for objective measures that are sensitive to subtle difference between diseases.

Section 1.5 discusses common cognitive measures that have been used to test and compare cognitive impairment within domains that DLB typically shows deficits. However, findings are inconsistent, which may be due to tasks that are too difficult, or not sensitive enough to differentiate between diseases. The aim of this thesis is to introduce novel tasks that have the potential to produce quantifiable measures of three symptoms that are synonymous with DLB, namely VH, visuospatial impairment and CF. The main focus of this thesis will present four studies in which I was leading the design, and analysis of the data, while also being heavily involved in the collection of data with two colleagues.

Chapter Two will look at the SART and how it is related to CFs. The SART presents patients with a series of numbers and requires the same button press for each number, except for the number "3", where they are required to withhold their response. The strength of the SART lies in the constant responding that patients are required to do. This allows for lapses in attention or alertness, which characterise CF in DLB, to be recorded and quantified.

Chapter Three will introduce MR as a means of measuring visuospatial impairments in DLB. The MR task requires patients to compare two 3-dimensional shapes to decide if they are identical, or if one is a mirror image of the other. At the simplest condition, both shapes are pointed in the same direction which requires a direct comparison to make an accurate response. While the more difficult conditions see one of the shapes rotated on a set number of degrees. To make an accurate

response during these conditions the patient is required to internally visualise the shape and then rotate their visualisation of the shape. One of the strengths of this paradigm is that task difficulty is scalable, ranging from 0 ° to 180°.

Chapter Four will then focus on the BPP, one of the few behavioural tasks that has been validated to measure VH in synucleinopathy patients. Furthermore, the BPP has been used with functional imaging to provide insight to the underlying mechanisms behind this crippling symptom. The BPP is tested on a DLB cohort to see if it is accessible to these patients, and to see if it can also measure VH in DLB patients, as it does in PD patients.

Chapter Five reports a study that assessed patients with isolated RBD (iRBD) who form part of an ongoing, longitudinal prospective study being conducted at the Brain and Mind Centre. This Chapter highlights how the recently proposed research criteria for making the diagnosis of prodromal DLB might be best implemented in patients who have mild cognitive impairment (the essential feature of prodromal DLB) with at least one core clinical feature (dream enactment – RBD) and one objective biomarker (polysomnographically confirmed REM Sleep Without Atonia - RSWA). This study also evaluates whether the SART, MR and BPP tasks described in this thesis might have any utility in differentiating patients meeting the proposed research criteria for prodromal DLB from those at risk of synucleinopathy who have iRBD and no significant cognitive impairment. Furthermore, this Chapter evaluates the baseline performance on the SART, MR and BPP of those iRBD patients who transitioned to DLB or PD in the period of this research thesis.

Finally, in Discussion, I will summarise the findings of these research papers and highlight the future directions that need to be pursued. During the course of my candidature I also co-authored several papers that compliment the topics of this thesis. The first paper investigated the subtle features of gait disturbance within an iRBD cohort compared to age matched Healthy Controls (HC). Here we recruited iRBD patients with confirmed RSWA via vPSG and had them walk on a pressure sensitive mat whilst performing various tasks (Ehgoetz Martens et al., 2019) and found that

during normal paced walking the two groups had similar gait patterns. However, during a dual task walk, the HC group widened their stride width, perhaps to maximise stability during cognitive load, a behaviour that was absent in iRBD patients who instead varied their width during cognitive load. This finding was further investigated in the follow-up paper that utilised a validated Virtual Reality gait paradigm in combination with event related fMRI to investigate the neural correlates during dual task walking in iRBD (Ehgoetz Martens et al., 2020). This study found that as cognitive load increased, HC maintained high connectivity between the frontoparietal and motor networks. Conversely, in iRBD patients this connectivity decreased with increasing cognitive load, suggesting that this network is impaired in iRBD patients, resulting in the use of compensatory strategies. The third published paper focuses on VH in the DLB cohort and how they are related to colour discrimination vision (Matar et al., 2019a). The findings demonstrated that DLB patients had poorer colour discrimination compared with aged match HC and that the degree of colour discrimination impairment was associated with the severity and frequency of VH within DLB patients. This finding supports the involvement of low-level visual networks in the complex VH experienced by DLB patients.

It is believed that through the introduction of the SART, MR and BPP researchers will be provided with additional tools that are much needed to measure some of the key features in DLB. These tasks are already being found to be valuable for accurately quantifying the effects of different interventions in clinical trials and may prove invaluable in future neuroimaging/neurophysiological studies to better understand the neural correlates underpinning clinical symptoms. It is hoped that these fresh insights will lead to the improved future diagnosis and management of patients impacted by DLB.

1.11. References

Aarsland, D., Rongve, A., Nore, S. P., Skogseth, R., Skulstad, S., Ehrt, U., Hoprekstad, D., & Ballard, C. (2008). Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord*, *26*(5), 445-452. https://doi.org/10.1159/000165917

Aarsland, D. (2016). Cognitive impairment in Parkinson's disease and dementia with Lewy bodies. Parkinsonism Relat Disord, 22 Suppl 1, S144-148. https://doi.org/10.1016/j.parkreldis.2015.09.034

Abbasi, M., Ghalandari, N., Farzanefar, S., Aghamollaii, V., Ahmadi, M., Ganji, M., Afarideh, M., Loloee, S., Naseri, M., & Tafakhori, A. (2017). Potential diagnostic value of (131)I-MIBG myocardial scintigraphy in discrimination between Alzheimer disease and dementia with Lewy bodies. *Clin Neurol Neurosurg*, *163*, 163-166. https://doi.org/10.1016/j.clineuro.2017.10.024

Abdelnour, C., Ferreira, D., Oppedal, K., Cavallin, L., Bousiges, O., Wahlund, L. O., Hort, J., Nedelska, Z., Padovani, A., Pilotto, A., Bonanni, L., Kramberger, M. G., Boada, M., Westman, E., Pagonabarraga, J., Kulisevsky, J., Blanc, F., & Aarsland, D. (2020). The combined effect of amyloid-β and tau biomarkers on brain atrophy in dementia with Lewy bodies. *NeuroImage. Clinical*, *27*, 102333. https://doi.org/10.1016/j.nicl.2020.102333

Aflaki, E., Westbroek, W., & Sidransky, E. (2017). The Complicated Relationship between Gaucher Disease and Parkinsonism: Insights from a Rare Disease. *Neuron*, *93*(4), 737-746. https://doi.org/10.1016/j.neuron.2017.01.018

Aharon-Peretz, J., Rosenbaum, H., & Gershoni-Baruch, R. (2004). Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med, 351(19), 1972-1977. https://doi.org/10.1056/NEJMoa033277

Al-Harrasi, A. M., Iqbal, E., Tsamakis, K., Lasek, J., Gadelrab, R., Soysal, P., Kohlhoff, E., Tsiptsios, D., Rizos, E., Perera, G., Aarsland, D., Stewart, R., & Mueller, C. (2021). Motor signs in Alzheimer's disease and vascular dementia: Detection

through natural language processing, co-morbid features and relationship to adverse outcomes. *Exp Gerontol*, *146*, 111223. https://doi.org/10.1016/j.exger.2020.111223

Al-Nimer, M. S., Mshatat, S. F., & Abdulla, H. I. (2014). Saliva α-Synuclein and A High Extinction Coefficient Protein: A Novel Approach in Assessment Biomarkers of Parkinson's Disease. *N Am J Med Sci*, *6*(12), 633-637. https://doi.org/10.4103/1947-2714.147980

Al-Qassabi, A., Tsao, T. S., Racolta, A., Kremer, T., Cañamero, M., Belousov, A., Santana, M. A., Beck, R. C., Zhang, H., Meridew, J., Pugh, J., Lian, F., Robida, M. D., Ritter, M., Czech, C., Beach, T. G., Pestic-Dragovich, L., Taylor, K. I., Zago, W., Tang, L., Dziadek, S., & Postuma, R. B. (2021). Immunohistochemical Detection of Synuclein Pathology in Skin in Idiopathic Rapid Eye Movement Sleep Behavior Disorder and Parkinsonism. *Mov Disord*, *36*(4), 895-904. https://doi.org/10.1002/mds.28399

Albasanz, J. L., Dalfó, E., Ferrer, I., & Martín, M. (2005). Impaired metabotropic glutamate receptor/phospholipase C signaling pathway in the cerebral cortex in Alzheimer's disease and dementia with Lewy bodies correlates with stage of Alzheimer's-disease-related changes. *Neurobiol Dis*, *20*(3), 685-693. https://doi.org/10.1016/j.nbd.2005.05.001

Aldridge, G. M., Birnschein, A., Denburg, N. L., & Narayanan, N. S. (2018). Parkinson's Disease Dementia and Dementia with Lewy Bodies Have Similar Neuropsychological Profiles. *Front Neurol*, *9*, 123. https://doi.org/10.3389/fneur.2018.00123

Allen, G., Barnard, H., McColl, R., Hester, A. L., Fields, J. A., Weiner, M. F., Ringe, W. K., Lipton, A. M., Brooker, M., McDonald, E., Rubin, C. D., & Cullum, C. M. (2007). Reduced hippocampal functional connectivity in Alzheimer disease. *Arch Neurol*, *64*(10), 1482-1487. https://doi.org/10.1001/archneur.64.10.1482

Alexander, P. K., Lie, Y., Jones, G., Sivaratnam, C., Bozinvski, S., Mulligan, R. S., Young, K., Villemagne, V. L., & Rowe, C. C. (2017). Management Impact of

Imaging Brain Vesicular Monoamine Transporter Type 2 in Clinically Uncertain Parkinsonian Syndrome with (18)F-AV133 and PET. J Nucl Med, 58(11), 1815-1820. https://doi.org/10.2967/jnumed.116.189019

Alves Do Rego, C., Namer, I. J., Marcel, C., Lefebvre, F., Lagha-Boukbiza, O., Renaud, M., Tranchant, C., & Anheim, M. (2018). Prospective study of relevance of (123)I-MIBG myocardial scintigraphy and clonidine GH test to distinguish Parkinson's disease and multiple system atrophy. *J Neurol*, *265*(9), 2033-2039. https://doi.org/10.1007/s00415-018-8941-5

Aoki, Y., Kazui, H., Pascal-Marqui, R. D., Ishii, R., Yoshiyama, K., Kanemoto, H., Suzuki, Y., Sato, S., Hata, M., Canuet, L., Iwase, M., & Ikeda, M. (2019). EEG Resting-State Networks in Dementia with Lewy Bodies Associated with Clinical Symptoms. *Neuropsychobiology*, *77*(4), 206-218. https://doi.org/10.1159/000495620

Aquino, D., Contarino, V., Albanese, A., Minati, L., Farina, L., Grisoli, M., Romita, L., Elia, A. E., Bruzzone, M. G., & Chiapparini, L. (2014). Substantia nigra in Parkinson's disease: a multimodal MRI comparison between early and advanced stages of the disease. *Neurol Sci*, *35*(5), 753-758. https://doi.org/10.1007/s10072-013-1595-2

Araki, K., Yagi, N., Ikemoto, Y., Yagi, H., Choong, C. J., Hayakawa, H., Beck, G., Sumi, H., Fujimura, H., Moriwaki, T., Nagai, Y., Goto, Y., & Mochizuki, H. (2015). Synchrotron FTIR micro-spectroscopy for structural analysis of Lewy bodies in the brain of Parkinson's disease patients. *Sci Rep*, *5*, 17625. https://doi.org/10.1038/srep17625

Arevalo-Rodriguez, I., Smailagic, N., Roqué, I. F. M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O. L., Bonfill Cosp, X., & Cullum, S. (2015). Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*, *2015*(3), Cd010783. https://doi.org/10.1002/14651858.CD010783.pub2

Arnulf, I., Bonnet, A. M., Damier, P., Bejjani, B. P., Seilhean, D., Derenne, J. P., & Agid, Y. (2000). Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology*, *55*(2), 281-288. https://doi.org/10.1212/wnl.55.2.281

Ashby, E. L., Kierzkowska, M., Hull, J., Kehoe, P. G., Hutson, S. M., & Conway, M. E. (2017). Altered Expression of Human Mitochondrial Branched Chain Aminotransferase in Dementia with Lewy Bodies and Vascular Dementia. *Neurochem Res*, *42*(1), 306-319. https://doi.org/10.1007/s11064-016-1855-7

Aurora, R. N., Zak, R. S., Maganti, R. K., Auerbach, S. H., Casey, K. R., Chowdhuri, S., Karippot, A., Ramar, K., Kristo, D. A., & Morgenthaler, T. I. (2010). Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med*, *6*(1), 85-95.

Ballanger, B., Strafella, A. P., van Eimeren, T., Zurowski, M., Rusjan, P. M., Houle, S., & Fox, S. H. (2010). Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol*, *67*(4), 416-421. https://doi.org/10.1001/archneurol.2010.35

Ballard, C., Johnson, M., Piggott, M., Perry, R., O'Brien, J., Rowan, E., Perry, E., Lantos, P., Cairns, N., & Holmes, C. (2002a). A positive association between 5HT re-uptake binding sites and depression in dementia with Lewy bodies. *J Affect Disord*, *69*(1-3), 219-223. https://doi.org/10.1016/s0165-0327(00)00375-x

Ballard, C. G., Aarsland, D., McKeith, I., O'Brien, J., Gray, A., Cormack, F., Burn, D., Cassidy, T., Starfeldt, R., Larsen, J. P., Brown, R., & Tovee, M. (2002b). Fluctuations in attention: PD dementia vs DLB with parkinsonism. *Neurology*, *59*(11), 1714-1720. http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCLBCANPIF00/fs047/ovft/live/gv031/00006114/00006114-200212100-00011.pdf

Ballard, C. G., Perry, R. H., McKeith, I. G., & Perry, E. K. (2005). Neuroleptics are associated with more severe tangle pathology in dementia with Lewy bodies. *Int J Geriatr Psychiatry*, *20*(9), 872-875. https://doi.org/10.1002/gps.1378

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. Lancet, 377(9770), 1019-1031. https://doi.org/10.1016/s0140-6736(10)61349-9

Barber, P. A., Varma, A. R., Lloyd, J. J., Haworth, B., Snowden, J. S., & Neary, D. (2000). The electroencephalogram in dementia with Lewy bodies. *Acta Neurol Scand*, *101*(1), 53-56. https://onlinelibrary.wiley.com/doi/abs/10.1034/j.1600-0404.2000.00006.x?sid=nlm%3Apubmed

Barber, T. R., Lawton, M., Rolinski, M., Evetts, S., Baig, F., Ruffmann, C., Gornall, A., Klein, J. C., Lo, C., Dennis, G., Bandmann, O., Quinnell, T., Zaiwalla, Z., Ben-Shlomo, Y., & Hu, M. T. M. (2017). Prodromal Parkinsonism and Neurodegenerative Risk Stratification in REM Sleep Behavior Disorder. *Sleep*, *40*(8). https://doi.org/10.1093/sleep/zsx071

Bargar, C., Wang, W., Gunzler, S. A., LeFevre, A., Wang, Z., Lerner, A. J., Singh, N., Tatsuoka, C., Appleby, B., Zhu, X., Xu, R., Haroutunian, V., Zou, W. Q., Ma, J., & Chen, S. G. (2021). Streamlined alpha-synuclein RT-QuIC assay for various biospecimens in Parkinson's disease and dementia with Lewy bodies. *Acta Neuropathol Commun*, *9*(1), 62. https://doi.org/10.1186/s40478-021-01175-w

Barnes, J., Boubert, L., Harris, J., Lee, A., & David, A. S. (2003). Reality monitoring and visual hallucinations in Parkinson's disease. *Neuropsychologia, 41*(5), 565-574. https://doi.org/10.1016/s0028-3932(02)00182-3

Bartels, A. L., Willemsen, A. T., Doorduin, J., de Vries, E. F., Dierckx, R. A., & Leenders, K. L. (2010). [11C]-PK11195 PET: quantification of neuroinflammation and a monitor of anti-inflammatory treatment in Parkinson's disease? *Parkinsonism Relat Disord*, *16*(1), 57-59. https://doi.org/10.1016/j.parkreldis.2009.05.005

Barthel, H., Gertz, H. J., Dresel, S., Peters, O., Bartenstein, P., Buerger, K., Hiemeyer, F., Wittemer-Rump, S. M., Seibyl, J., Reininger, C., & Sabri, O. (2011). Cerebral amyloid-β PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol*, *10*(5), 424-435. https://doi.org/10.1016/s1474-4422(11)70077-1

Barthélemy, N. R., Horie, K., Sato, C., & Bateman, R. J. (2020). Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med, 217*(11). https://doi.org/10.1084/jem.20200861

Bauckneht, M., Chincarini, A., De Carli, F., Terzaghi, M., Morbelli, S., Nobili, F., & Arnaldi, D. (2018). Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: A systematic review and meta-analysis. *Sleep Med Rev, 41*, 266-274. https://doi.org/10.1016/j.smrv.2018.04.001

Beach, T. G., Corbillé, A. G., Letournel, F., Kordower, J. H., Kremer, T., Munoz, D. G., Intorcia, A., Hentz, J., Adler, C. H., Sue, L. I., Walker, J., Serrano, G., & Derkinderen, P. (2016). Multicenter Assessment of Immunohistochemical Methods for Pathological Alpha-Synuclein in Sigmoid Colon of Autopsied Parkinson's Disease and Control Subjects. *J Parkinsons Dis, 6*(4), 761-770. https://doi.org/10.3233/jpd-160888

Beauchet, O., Annweiler, C., Callisaya, M. L., De Cock, A. M., Helbostad, J. L., Kressig, R. W., Srikanth, V., Steinmetz, J. P., Blumen, H. M., Verghese, J., & Allali, G. (2016). Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis. *J Am Med Dir Assoc, 17*(6), 482-490. https://doi.org/10.1016/j.jamda.2015.12.092

Benarroch, E. E. (2009). The locus ceruleus norepinephrine system: functional organization and potential clinical significance. *Neurology, 73*(20), 1699-1704. https://doi.org/10.1212/WNL.0b013e3181c2937c

Benarroch, E. E., Schmeichel, A. M., Sandroni, P., Parisi, J. E., & Low, P. A. (2007). Rostral raphe involvement in Lewy body dementia and multiple system atrophy. *Acta Neuropathol, 114*(3), 213-220. https://doi.org/10.1007/s00401-007-0260-3

Berardelli, I., Belvisi, D., Pasquini, M., Fabbrini, A., Petrini, F., & Fabbrini, G. (2019). Treatment of psychiatric disturbances in hypokinetic movement disorders. *Expert Rev Neurother, 19*(10), 965-981. https://doi.org/10.1080/14737175.2019.1636648

Beyer, M. K., Larsen, J. P., & Aarsland, D. (2007). Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. *Neurology*, *69*(8), 747-754. https://doi.org/10.1212/01.wnl.0000269666.62598.1c

Bhumkar, A., Magnan, C., Lau, D., Jun, E. S. W., Dzamko, N., Gambin, Y., & Sierecki, E. (2021). Single-Molecule Counting Coupled to Rapid Amplification Enables Detection of α-Synuclein Aggregates in Cerebrospinal Fluid of Parkinson's Disease Patients. *Angew Chem Int Ed Engl*, *60*(21), 11874-11883. https://doi.org/10.1002/anie.202014898

Bichot, N. P., Xu, R., Ghadooshahy, A., Williams, M. L., & Desimone, R. (2019). The role of prefrontal cortex in the control of feature attention in area V4. *Nature communications*, *10*(1), 5727. https://doi.org/10.1038/s41467-019-13761-7

Biundo, R., Weis, L., Bostantjopoulou, S., Stefanova, E., Falup-Pecurariu, C., Kramberger, M. G., Geurtsen, G. J., Antonini, A., Weintraub, D., & Aarsland, D. (2016). MMSE and MoCA in Parkinson's disease and dementia with Lewy bodies: a multicenter 1-year follow-up study. *J Neural Transm (Vienna)*, *123*(4), 431-438. https://doi.org/10.1007/s00702-016-1517-6

Blandini, F., Cilia, R., Cerri, S., Pezzoli, G., Schapira, A. H. V., Mullin, S., & Lanciego, J. L. (2019). Glucocerebrosidase mutations and synucleinopathies: Toward a model of precision medicine. *Mov Disord*, *34*(1), 9-21. https://doi.org/10.1002/mds.27583

Blauwendraat, C., Reed, X., Krohn, L., Heilbron, K., Bandres-Ciga, S., Tan, M., Gibbs, J. R., Hernandez, D. G., Kumaran, R., Langston, R., Bonet-Ponce, L., Alcalay, R. N., Hassin-Baer, S., Greenbaum, L., Iwaki, H., Leonard, H. L., Grenn, F. P., Ruskey, J. A., Sabir, M., Ahmed, S., Makarious, M. B., Pihlstrøm, L., Toft, M., van Hilten, J. J., Marinus, J., Schulte, C., Brockmann, K., Sharma, M., Siitonen, A., Majamaa, K., Eerola-Rautio, J., Tienari, P. J., Pantelyat, A., Hillis, A. E., Dawson, T. M., Rosenthal, L. S., Albert, M. S., Resnick, S. M., Ferrucci, L., Morris, C. M., Pletnikova, O., Troncoso, J., Grosset, D., Lesage, S., Corvol, J. C., Brice, A., Noyce, A. J., Masliah, E., Wood, N., Hardy, J., Shulman, L. M.,

Jankovic, J., Shulman, J. M., Heutink, P., Gasser, T., Cannon, P., Scholz, S. W., Morris, H., Cookson, M. R., Nalls, M. A., Gan-Or, Z., & Singleton, A. B. (2020). Genetic modifiers of risk and age at onset in GBA associated Parkinson's disease and Lewy body dementia. *Brain*, *143*(1), 234-248. https://doi.org/10.1093/brain/awz350

Bliwise, D. L., Scullin, M. K., & Trotti, L. M. (2014). Fluctuations in cognition and alertness vary independently in dementia with Lewy bodies. *Mov Disord*, *29*(1), 83-89. https://doi.org/10.1002/mds.25707

Boecker, H., Ceballos-Baumann, A. O., Volk, D., Conrad, B., Forstl, H., & Haussermann, P. (2007). Metabolic alterations in patients with Parkinson disease and visual hallucinations. *Arch Neurol*, *64*(7), 984-988. https://doi.org/10.1001/archneur.64.7.984

Boeve, B. F., Molano, J. R., Ferman, T. J., Lin, S. C., Bieniek, K., Tippmann-Peikert, M., Boot, B., St Louis, E. K., Knopman, D. S., Petersen, R. C., & Silber, M. H. (2013). Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. J Clin Sleep Med, 9(5), 475-480. https://doi.org/10.5664/jcsm.2670

Boeve, B. F., Dickson, D. W., Olson, E. J., Shepard, J. W., Silber, M. H., Ferman, T. J., Ahlskog, J. E., & Benarroch, E. E. (2007). Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med*, *8*(1), 60-64. https://doi.org/10.1016/j.sleep.2006.08.017

Boeve, B. F., Silber, M. H., & Ferman, T. J. (2003). Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med*, *4*(4), 281-284. https://doi.org/10.1016/s1389-9457(03)00072-8

Boissard, R., Gervasoni, D., Schmidt, M. H., Barbagli, B., Fort, P., & Luppi, P. H. (2002). The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur J Neurosci*, *16*(10), 1959-1973. https://doi.org/10.1046/j.1460-9568.2002.02257.x

Bolitho, S. J., Naismith, S. L., Terpening, Z., Grunstein, R. R., Melehan, K., Yee, B. J., Coeytaux, A., Gilat, M., & Lewis, S. J. (2014). Investigating rapid eye movement sleep without atonia in Parkinson's disease using the rapid eye movement sleep behavior disorder screening questionnaire. Mov Disord, 29(6), 736-742. https://doi.org/10.1002/mds.25832

Bonanni, L., Franciotti, R., Nobili, F., Kramberger, M. G., Taylor, J. P., Garcia-Ptacek, S., Falasca, N. W., Fama, F., Cromarty, R., Onofrj, M., & Aarsland, D. (2016). EEG Markers of Dementia with Lewy Bodies: A Multicenter Cohort Study. *J Alzheimers Dis*, *54*(4), 1649-1657. https://doi.org/10.3233/jad-160435

Bonanni, L., Perfetti, B., Bifolchetti, S., Taylor, J. P., Franciotti, R., Parnetti, L., Thomas, A., & Onofrj, M. (2015). Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. *Neurobiol Aging*, *36*(1), 434-445. https://doi.org/10.1016/j.neurobiolaging.2014.07.009

Bonanni, L., Thomas, A., Tiraboschi, P., Perfetti, B., Varanese, S., & Onofrj, M. (2008). EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. *Brain*, *131*(3), 690. https://doi.org/10.1093/brain/awm322

Bongianni, M., Ladogana, A., Capaldi, S., Klotz, S., Baiardi, S., Cagnin, A., Perra, D., Fiorini, M., Poleggi, A., Legname, G., Cattaruzza, T., Janes, F., Tabaton, M., Ghetti, B., Monaco, S., Kovacs, G. G., Parchi, P., Pocchiari, M., & Zanusso, G. (2019). α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies. *Ann Clin Transl Neurol*, *6*(10), 2120-2126. https://doi.org/10.1002/acn3.50897

Bostrom, F., Jonsson, L., Minthon, L., & Londos, E. (2007a). Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*, *21*(2), 150-154. https://doi.org/10.1097/WAD.0b013e318065c4a9

Bostrom, F., Jonsson, L., Minthon, L., & Londos, E. (2007b). Patients with Lewy body dementia use more resources than those with Alzheimer's disease. *Int J Geriatr Psychiatry*, *22*(8), 713-719. https://doi.org/10.1002/gps.1738

Bousiges, O., Philippi, N., Lavaux, T., Perret-Liaudet, A., Lachmann, I., Schaeffer-Agalède, C., Anthony, P., Botzung, A., Rauch, L., Jung, B., de Sousa, P. L., Demuynck, C., Martin-Hunyadi, C., Cretin, B., & Blanc, F. (2020). Differential diagnostic value of total alpha-synuclein assay in the cerebrospinal fluid between Alzheimer's disease and dementia with Lewy bodies from the prodromal stage. *Alzheimers Res Ther*, *12*(1), 120. https://doi.org/10.1186/s13195-020-00684-5

Bradshaw, J., Saling, M., Hopwood, M., Anderson, V., & Brodtmann, A. (2004). Fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease is qualitatively distinct. *J Neurol Neurosurg Psychiatry*, *75*(3), 382-387. https://doi.org/10.1136/jnnp.2002.002576

Bradshaw, J. M., Saling, M., Anderson, V., Hopwood, M., & Brodtmann, A. (2006). Higher cortical deficits influence attentional processing in dementia with Lewy bodies, relative to patients with dementia of the Alzheimer's type and controls. *J Neurol Neurosurg Psychiatry*, *77*(10), 1129-1135. https://doi.org/10.1136/jnnp.2006.090183

Bregman, N., Kavé, G., Mirelman, A., Thaler, A., Gana Weisz, M., Bar-Shira, A., Orr-Urtreger, A., Giladi, N., & Shiner, T. (2019). Distinguishing Dementia With Lewy Bodies From Alzheimer Disease: What is the Influence of the GBA Genotype in Ashkenazi Jews? *Alzheimer Dis Assoc Disord*, *33*(3), 279-281. https://doi.org/10.1097/wad.0000000000000283

Breitve, M. H., Chwiszczuk, L. J., Bronnick, K., Hynninen, M. J., Auestad, B. H., Aarsland, D., & Rongve, A. (2018). A Longitudinal Study of Neurocognition in Dementia with Lewy Bodies Compared to Alzheimer's Disease. *Front Neurol*, *9*, 124. https://doi.org/10.3389/fneur.2018.00124

Breitve, M. H., Chwiszczuk, L. J., Hynninen, M. J., Rongve, A., Brønnick, K., Janvin, C., & Aarsland, D. (2014). A systematic review of cognitive decline in dementia with Lewy bodies versus Alzheimer's disease. *Alzheimers Res Ther*, *6*(5-8), 53. https://doi.org/10.1186/s13195-014-0053-6

Briand, L. A., Gritton, H., Howe, W. M., Young, D. A., & Sarter, M. (2007). Modulators in concert for cognition: modulator interactions in the prefrontal cortex. *Prog Neurobiol*, *83*(2), 69-91. https://doi.org/10.1016/j.pneurobio.2007.06.007

Brooks, D. J. (2009). Imaging amyloid in Parkinson's disease dementia and dementia with Lewy bodies with positron emission tomography. *Mov Disord*, *24 Suppl 2*, S742-747. https://doi.org/10.1002/mds.22581

Brown, J. D., Cicali, B., Henriksen, C., Malaty, I., Okun, M. S., & Armstrong, M. J. (2021). Comparative pharmacovigilance assessment of mortality with pimavanserin in Parkinson disease-related psychosis. *J Manag Care Spec Pharm*, *27*(6), 785-790. https://doi.org/10.18553/jmcp.2021.27.6.785

Brunnström, H., Friberg, N., Lindberg, E., & Englund, E. (2011). Differential degeneration of the locus coeruleus in dementia subtypes. *Clin Neuropathol*, *30*(3), 104-110. https://doi.org/10.5414/npp30104

Burré, J., Sharma, M., & Südhof, T. C. (2018). Cell Biology and Pathophysiology of α-Synuclein. *Cold Spring Harb Perspect Med*, *8*(3). https://doi.org/10.1101/cshperspect.a024091

Burton, E. J., Barber, R., Mukaetova-Ladinska, E. B., Robson, J., Perry, R. H., Jaros, E., Kalaria, R. N., & O'Brien, J. T. (2009). Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. *Brain*, *132*(Pt 1), 195-203. https://doi.org/10.1093/brain/awn298

Burton, E. J., Karas, G., Paling, S. M., Barber, R., Williams, E. D., Ballard, C. G., McKeith, I. G., Scheltens, P., Barkhof, F., & O'Brien, J. T. (2002). Patterns of

cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. *Neuroimage, 17*(2), 618-630.

Bussè, C., Anselmi, P., Pompanin, S., Zorzi, G., Fragiacomo, F., Camporese, G., Di Bernardo, G. A., Semenza, C., Caffarra, P., & Cagnin, A. (2017). Specific Verbal Memory Measures May Distinguish Alzheimer's Disease from Dementia with Lewy Bodies. *J Alzheimers Dis, 59*(3), 1009-1015. https://doi.org/10.3233/jad-170154

Cagnin, A., Bussè, C., Gardini, S., Jelcic, N., Guzzo, C., Gnoato, F., Mitolo, M., Ermani, M., & Caffarra, P. (2015). Clinical and Cognitive Phenotype of Mild Cognitive Impairment Evolving to Dementia with Lewy Bodies. *Dement Geriatr Cogn Dis Extra, 5*(3), 442-449. https://doi.org/10.1159/000441184

Cagnin, A., Gnoato, F., Jelcic, N., Favaretto, S., Zarantonello, G., Ermani, M., & Dam, M. (2013). Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry, 84*(5), 505-510. https://doi.org/10.1136/jnnp-2012-304095

Cahn-Weiner, D. A., Williams, K., Grace, J., Tremont, G., Westervelt, H., & Stern, R. A. (2003). Discrimination of dementia with lewy bodies from Alzheimer disease and Parkinson disease using the clock drawing test. *Cogn Behav Neurol, 16*(2), 85-92. https://doi.org/10.1097/00146965-200306000-00001

Calderon, J., Perry, R. J., Erzinclioglu, S. W., Berrios, G. E., Dening, T. R., & Hodges, J. R. (2001). Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 70*(2), 157-164. https://doi.org/10.1136/jnnp.70.2.157

Calil, V., Silveira de Souza, A., Sudo, F. K., Santiago-Bravo, G., Assunção, N., Drummond, C., Rodrigues, F., Soares, R., Oliveira, N., Teldeschi, A., Bernardes, G., Lima, G., Lima, C., Lima, M. A., & Mattos, P. (2021). Anosognosia for memory in dementia with Lewy bodies compared with Alzheimer's disease. *Int J Geriatr Psychiatry, 36*(7), 1059-1064. https://doi.org/10.1002/gps.5521

Calzetti, S., Bortone, E., Negrotti, A., Zinno, L., & Mancia, D. (2002). Frontal intermittent rhythmic delta activity (FIRDA) in patients with dementia with Lewy bodies: a diagnostic tool? *Neurol Sci*, *23 Suppl 2*, S65-66. https://doi.org/10.1007/s100720200072

Caminiti, S. P., Tettamanti, M., Sala, A., Presotto, L., Iannaccone, S., Cappa, S. F., Magnani, G., & Perani, D. (2017). Metabolic connectomics targeting brain pathology in dementia with Lewy bodies. *J Cereb Blood Flow Metab*, *37*(4), 1311-1325. https://doi.org/10.1177/0271678x16654497

Canaslan, S., Schmitz, M., Villar-Piqué, A., Maass, F., Gmitterová, K., Varges, D., Lingor, P., Llorens, F., Hermann, P., & Zerr, I. (2021). Detection of Cerebrospinal Fluid Neurofilament Light Chain as a Marker for Alpha-Synucleinopathies. *Front Aging Neurosci*, *13*, 717930. https://doi.org/10.3389/fnagi.2021.717930

Carrió, I., Cowie, M. R., Yamazaki, J., Udelson, J., & Camici, P. G. (2010). Cardiac sympathetic imaging with mIBG in heart failure. *JACC Cardiovasc Imaging*, *3*(1), 92-100. https://doi.org/10.1016/j.jcmg.2009.07.014

Cartford, M. C., Gould, T., & Bickford, P. C. (2004). A central role for norepinephrine in the modulation of cerebellar learning tasks. *Behav Cogn Neurosci Rev*, *3*(2), 131-138. https://doi.org/10.1177/1534582304270783

Caso, F., Agosta, F., Scamarcia, P. G., Basaia, S., Canu, E., Magnani, G., Volontè, M. A., & Filippi, M. (2021). A multiparametric MRI study of structural brain damage in dementia with lewy bodies: A comparison with Alzheimer's disease. *Parkinsonism Relat Disord*, *91*, 154-161. https://doi.org/https://doi.org/10.1016/j.parkreldis.2021.09.025

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, *129*(Pt 3), 564-583. https://doi.org/10.1093/brain/awl004

Cersósimo, M. G., Tumilasci, O. R., Raina, G. B., Benarroch, E. E., Cardoso, E. M., Micheli, F., & Pazo, J. H. (2009). Hyposialorrhea as an early manifestation of

Parkinson disease. *Autonomic Neuroscience*, *150*(1), 150-151. https://doi.org/https://doi.org/10.1016/j.autneu.2009.04.004

Chabran, E., Noblet, V., Loureiro de Sousa, P., Demuynck, C., Philippi, N., Mutter, C., Anthony, P., Martin-Hunyadi, C., Cretin, B., & Blanc, F. (2020). Changes in gray matter volume and functional connectivity in dementia with Lewy bodies compared to Alzheimer's disease and normal aging: implications for fluctuations. *Alzheimers Res Ther*, *12*(1), 9. https://doi.org/10.1186/s13195-019-0575-z

Chabran, E., Roquet, D., Gounot, D., Sourty, M., Armspach, J. P., & Blanc, F. (2018). Functional Disconnectivity during Inter-Task Resting State in Dementia with Lewy Bodies. *Dement Geriatr Cogn Disord*, *45*(1-2), 105-120. https://doi.org/10.1159/000486780

Chahine, L. M., Beach, T. G., Brumm, M. C., Adler, C. H., Coffey, C. S., Mosovsky, S., Caspell-Garcia, C., Serrano, G. E., Munoz, D. G., White, C. L., 3rd, Crary, J. F., Jennings, D., Taylor, P., Foroud, T., Arnedo, V., Kopil, C. M., Riley, L., Dave, K. D., & Mollenhauer, B. (2020). In vivo distribution of α-synuclein in multiple tissues and biofluids in Parkinson disease. *Neurology*, *95*(9), e1267-e1284. https://doi.org/10.1212/wnl.0000000000010404

Chang, C. F., Hsu, T. Y., Tseng, P., Liang, W. K., Tzeng, O. J., Hung, D. L., & Juan, C. H. (2013). Right temporoparietal junction and attentional reorienting. *Hum Brain Mapp*, *34*(4), 869-877. https://doi.org/10.1002/hbm.21476

Chang, C. W., Yang, S. Y., Yang, C. C., Chang, C. W., & Wu, Y. R. (2019). Plasma and Serum Alpha-Synuclein as a Biomarker of Diagnosis in Patients With Parkinson's Disease. *Front Neurol*, *10*, 1388. https://doi.org/10.3389/fneur.2019.01388

Chaudhry, A., Houlden, H., & Rizig, M. (2020). Novel fluid biomarkers to differentiate frontotemporal dementia and dementia with Lewy bodies from Alzheimer's disease: A systematic review. *J Neurol Sci*, *415*, 116886. https://doi.org/10.1016/j.jns.2020.116886

Chiasserini, D., Paciotti, S., Eusebi, P., Persichetti, E., Tasegian, A., Kurzawa-Akanbi, M., Chinnery, P. F., Morris, C. M., Calabresi, P., Parnetti, L., & Beccari, T. (2015). Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies. *Mol Neurodegener*, *10*, 15. https://doi.org/10.1186/s13024-015-0010-2

Chin, K. S., Teodorczuk, A., & Watson, R. (2019). Dementia with Lewy bodies: Challenges in the diagnosis and management. *Australian & New Zealand Journal of Psychiatry*, 0004867419835029. https://doi.org/10.1177/0004867419835029

Chin, K. S., Yassi, N., Churilov, L., Masters, C. L., & Watson, R. (2020). Prevalence and clinical associations of tau in Lewy body dementias: A systematic review and meta-analysis. *Parkinsonism Relat Disord*, *80*, 184-193. https://doi.org/10.1016/j.parkreldis.2020.09.030

Chow, N., Aarsland, D., Honarpisheh, H., Beyer, M. K., Somme, J. H., Elashoff, D., Rongve, A., Tysnes, O. B., Thompson, P. M., & Apostolova, L. G. (2012). Comparing hippocampal atrophy in Alzheimer's dementia and dementia with lewy bodies. *Dement Geriatr Cogn Disord*, *34*(1), 44-50. https://doi.org/10.1159/000339727

Chung, S. J., Kim, J., Lee, H. J., Ryu, H. S., Kim, K., Lee, J. H., Jung, K. W., Kim, M. J., Kim, M. J., Kim, Y. J., Yun, S. C., Lee, J. Y., Hong, S. M., & Myung, S. J. (2016). Alpha-synuclein in gastric and colonic mucosa in Parkinson's disease: Limited role as a biomarker. *Mov Disord*, *31*(2), 241-249. https://doi.org/10.1002/mds.26473

Claassen, D. O., Lowe, V. J., Peller, P. J., Petersen, R. C., & Josephs, K. A. (2011). Amyloid and glucose imaging in dementia with Lewy bodies and multiple systems atrophy. *Parkinsonism Relat Disord*, *17*(3), 160-165. https://doi.org/10.1016/j.parkreldis.2010.12.006

Clark, L. N., Kartsaklis, L. A., Wolf Gilbert, R., Dorado, B., Ross, B. M., Kisselev, S., Verbitsky, M., Mejia-Santana, H., Cote, L. J., Andrews, H., Vonsattel, J. P., Fahn, S., Mayeux, R., Honig, L. S., & Marder, K. (2009). Association of

glucocerebrosidase mutations with dementia with lewy bodies. *Arch Neurol*, *66*(5), 578-583. https://doi.org/10.1001/archneurol.2009.54

Collerton, D., Burn, D., McKeith, I., & O'Brien, J. (2003). Systematic Review and Meta-Analysis Show that Dementia with Lewy Bodies Is a Visual-Perceptual and Attentional-Executive Dementia. *Dementia and Geriatric Cognitive Disorders*, *16*(4), 229-237. http://www.karger.com/DOI/10.1159/000072807

Collerton, D., Perry, E., & McKeith, I. (2005). Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. *Behav Brain Sci*, *28*(6), 737-757; discussion 757-794. https://doi.org/10.1017/s0140525x05000130

Colloby, S. J., Cromarty, R. A., Peraza, L. R., Johnsen, K., Jóhannesson, G., Bonanni, L., Onofrj, M., Barber, R., O'Brien, J. T., & Taylor, J. P. (2016). Multimodal EEG-MRI in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. *J Psychiatr Res*, *78*, 48-55. https://doi.org/10.1016/j.jpsychires.2016.03.010

Colloby, S. J., Elder, G. J., Rabee, R., O'Brien, J. T., & Taylor, J. P. (2017). Structural grey matter changes in the substantia innominata in Alzheimer's disease and dementia with Lewy bodies: a DARTEL-VBM study. *Int J Geriatr Psychiatry*, *32*(6), 615-623. https://doi.org/10.1002/gps.4500

Colloby, S. J., McParland, S., O'Brien, J. T., & Attems, J. (2012). Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. *Brain*, *135*(Pt 9), 2798-2808. https://doi.org/10.1093/brain/aws211

Colloby, S. J., Watson, R., Blamire, A. M., O'Brien, J. T., & Taylor, J. P. (2020). Cortical thinning in dementia with Lewy bodies and Parkinson disease dementia. *Aust N Z J Psychiatry*, *54*(6), 633-643. https://doi.org/10.1177/0004867419885165

Connors, M. H., Quinto, L., McKeith, I., Brodaty, H., Allan, L., Bamford, C., Thomas, A., Taylor, J. P., & O'Brien, J. T. (2018). Non-pharmacological interventions for Lewy body dementia: a systematic review. *Psychol Med*, *48*(11), 1749-1758. https://doi.org/10.1017/s0033291717003257

Coon, E. A., Mandrekar, J. N., Berini, S. E., Benarroch, E. E., Sandroni, P., Low, P. A., & Singer, W. (2020). Predicting phenoconversion in pure autonomic failure. *Neurology*, *95*(7), e889-e897. https://doi.org/10.1212/wnl.0000000000010002

Crutch, S. J., Lehmann, M., Schott, J. M., Rabinovici, G. D., Rossor, M. N., & Fox, N. C. (2012). Posterior cortical atrophy. *Lancet Neurol*, *11*(2), 170-178. https://doi.org/10.1016/s1474-4422(11)70289-7

Cummings, J., Isaacson, S., Mills, R., Williams, H., Chi-Burris, K., Corbett, A., Dhall, R., & Ballard, C. (2014). Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*, *383*(9916), 533-540. https://doi.org/10.1016/S0140-6736(13)62106-6

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*, *48*(5 Suppl 6), S10-16.

Dauvilliers, Y., Schenck, C. H., Postuma, R. B., Iranzo, A., Luppi, P. H., Plazzi, G., Montplaisir, J., & Boeve, B. (2018). REM sleep behaviour disorder. *Nat Rev Dis Primers*, *4*(1), 19. https://doi.org/10.1038/s41572-018-0016-5

Dauwan, M., Linszen, M. M. J., Lemstra, A. W., Scheltens, P., Stam, C. J., & Sommer, I. E. (2018). EEG-based neurophysiological indicators of hallucinations in Alzheimer's disease: Comparison with dementia with Lewy bodies. *Neurobiol Aging*, *67*, 75-83. https://doi.org/10.1016/j.neurobiolaging.2018.03.013

Dauwan, M., van Dellen, E., van Boxtel, L., van Straaten, E. C. W., de Waal, H., Lemstra, A. W., Gouw, A. A., van der Flier, W. M., Scheltens, P., Sommer, I. E., & Stam, C. J. (2016). EEG-directed connectivity from posterior brain regions is decreased in dementia with Lewy bodies: a comparison with Alzheimer's disease and controls. *Neurobiol Aging*, *41*, 122-129. https://doi.org/10.1016/j.neurobiolaging.2016.02.017

Dayan, P., & Yu, A. J. (2006). Phasic norepinephrine: a neural interrupt signal for unexpected events. *Network*, *17*(4), 335-350. https://doi.org/10.1080/09548980601004024

Del Tredici, K., Hawkes, C. H., Ghebremedhin, E., & Braak, H. (2010). Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. *Acta Neuropathol*, *119*(6), 703-713. https://doi.org/10.1007/s00401-010-0665-2

Dell'Osso, L., Carmassi, C., Mucci, F., & Marazziti, D. (2016). Depression, Serotonin and Tryptophan. *Curr Pharm Des*, *22*(8), 949-954. https://doi.org/10.2174/1381612822666151214104826

Delli Pizzi, S., Franciotti, R., Taylor, J. P., Thomas, A., Tartaro, A., Onofrj, M., & Bonanni, L. (2015). Thalamic Involvement in Fluctuating Cognition in Dementia with Lewy Bodies: Magnetic Resonance Evidences. *Cereb Cortex*, *25*(10), 3682-3689. https://doi.org/10.1093/cercor/bhu220

Delli Pizzi, S., Maruotti, V., Taylor, J. P., Franciotti, R., Caulo, M., Tartaro, A., Thomas, A., Onofrj, M., & Bonanni, L. (2014). Relevance of subcortical visual pathways disruption to visual symptoms in dementia with Lewy bodies. *Cortex*, *59*, 12-21. https://doi.org/10.1016/j.cortex.2014.07.003

Devic, I., Hwang, H., Edgar, J. S., Izutsu, K., Presland, R., Pan, C., Goodlett, D. R., Wang, Y., Armaly, J., Tumas, V., Zabetian, C. P., Leverenz, J. B., Shi, M., & Zhang, J. (2011). Salivary α-synuclein and DJ-1: potential biomarkers for Parkinson's disease. *Brain*, *134*(Pt 7), e178. https://doi.org/10.1093/brain/awr015

Diederich, N. J., Goetz, C. G., Raman, R., Pappert, E. J., Leurgans, S., & Piery, V. (1998). Poor visual discrimination and visual hallucinations in Parkinson's disease. *Clin Neuropharmacol, 21*(5), 289-295.

Diederich, N. J., Goetz, C. G., & Stebbins, G. T. (2005). Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: focused review and a new integrative model. *Mov Disord*, *20*(2), 130-140. https://doi.org/10.1002/mds.20308

Do, J., McKinney, C., Sharma, P., & Sidransky, E. (2019). Glucocerebrosidase and its relevance to Parkinson disease. *Mol Neurodegener*, *14*(1), 36. https://doi.org/10.1186/s13024-019-0336-2

Donadio, V., Incensi, A., El-Agnaf, O., Rizzo, G., Vaikath, N., Del Sorbo, F., Scaglione, C., Capellari, S., Elia, A., Stanzani Maserati, M., Pantieri, R., & Liguori, R. (2018). Skin α-synuclein deposits differ in clinical variants of synucleinopathy: an in vivo study. *Sci Rep*, *8*(1), 14246. https://doi.org/10.1038/s41598-018-32588-8

Donadio, V., Incensi, A., Rizzo, G., Capellari, S., Pantieri, R., Stanzani Maserati, M., Devigili, G., Eleopra, R., Defazio, G., Montini, F., Baruzzi, A., & Liguori, R. (2017). A new potential biomarker for dementia with Lewy bodies: Skin nerve α-synuclein deposits. *Neurology*, *89*(4), 318-326. https://doi.org/10.1212/wnl.0000000000004146

Donaghy, P. C., Ciafone, J., Durcan, R., Hamilton, C. A., Barker, S., Lloyd, J., Firbank, M., Allan, L. M., O'Brien, J. T., Taylor, J. P., & Thomas, A. J. (2020). Mild cognitive impairment with Lewy bodies: neuropsychiatric supportive symptoms and cognitive profile. *Psychol Med*, 1-9. https://doi.org/10.1017/s0033291720002901

Donaghy, P. C., O'Brien, J. T., & Thomas, A. J. (2015). Prodromal dementia with Lewy bodies. *Psychol Med*, *45*(2), 259-268. https://doi.org/10.1017/s0033291714000816

Dong, C., Garen, C. R., Mercier, P., Petersen, N. O., & Woodside, M. T. (2019). Characterizing the inhibition of α-synuclein oligomerization by a pharmacological chaperone that prevents prion formation by the protein PrP. *Protein Sci*, *28*(9), 1690-1702. https://doi.org/10.1002/pro.3684

Economou, A., Routsis, C., & Papageorgiou, S. G. (2016). Episodic Memory in Alzheimer Disease, Frontotemporal Dementia, and Dementia With Lewy Bodies/Parkinson Disease Dementia: Disentangling Retrieval From Consolidation. *Alzheimer Dis Assoc Disord*, *30*(1), 47-52. https://doi.org/10.1097/wad.0000000000000089

Edison, P., Rowe, C. C., Rinne, J. O., Ng, S., Ahmed, I., Kemppainen, N., Villemagne, V. L., O'Keefe, G., Någren, K., Chaudhury, K. R., Masters, C. L., & Brooks, D. J. (2008). Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *J Neurol Neurosurg Psychiatry*, *79*(12), 1331-1338. https://doi.org/10.1136/jnnp.2007.127878

Edwards, K., Royall, D., Hershey, L., Lichter, D., Hake, A., Farlow, M., Pasquier, F., & Johnson, S. (2007). Efficacy and safety of galantamine in patients with dementia with Lewy bodies: a 24-week open-label study. *Dement Geriatr Cogn Disord*, *23*(6), 401-405. https://doi.org/10.1159/000101512

Ehgoetz Martens, K. A., Matar, E., Hall, J. M., Phillips, J., Szeto, J. Y. Y., Gouelle, A., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2019). Subtle gait and balance impairments occur in idiopathic rapid eye movement sleep behavior disorder. *Mov Disord*, *34*(9), 1374-1380. https://doi.org/10.1002/mds.27780

Ehgoetz Martens, K. A., Matar, E., Shine, J. M., Phillips, J. R., Georgiades, M. J., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2020). The Neural Signature of Impaired Dual-Tasking in Idiopathic Rapid Eye Movement Sleep Behavior Disorder Patients. *Mov Disord*, 35(9), 1596-1606. https://doi.org/10.1002/mds.28114

Elder, G. J., Mactier, K., Colloby, S. J., Watson, R., Blamire, A. M., O'Brien, J. T., & Taylor, J. P. (2017). The influence of hippocampal atrophy on the cognitive phenotype of dementia with Lewy bodies. *Int J Geriatr Psychiatry*, *32*(11), 1182-1189. https://doi.org/10.1002/gps.4719

Erskine, D., Ding, J., Thomas, A. J., Kaganovich, A., Khundakar, A. A., Hanson, P. S., Taylor, J. P., McKeith, I. G., Attems, J., Cookson, M. R., & Morris, C. M. (2018). Molecular changes in the absence of severe pathology in the pulvinar in dementia with Lewy bodies. *Mov Disord*, *33*(6), 982-991. https://doi.org/10.1002/mds.27333

Esmaeeli, S., Murphy, K., Swords, G. M., Ibrahim, B. A., Brown, J. W., & Llano, D. A. (2019). Visual hallucinations, thalamocortical physiology and Lewy body disease: A review. *Neurosci Biobehav Rev, 103*, 337-351. https://doi.org/10.1016/j.neubiorev.2019.06.006

Espinosa, R., Davis, M., Johnson, S., Cline, S., & Weintraub, D. (2020). Direct Medical Costs of Dementia With Lewy Bodies by Disease Complexity. *J Am Med Dir Assoc, 21*(11), 1696-1704.e1695. https://doi.org/10.1016/j.jamda.2020.06.006

Evers, L. J. W., Krijthe, J. H., Meinders, M. J., Bloem, B. R., & Heskes, T. M. (2019). Measuring Parkinson's disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Mov Disord, 34*(10), 1480-1487. https://doi.org/10.1002/mds.27790

Eversfield, C. L., & Orton, L. D. (2018). Auditory and visual hallucination prevalence in Parkinson's disease and dementia with Lewy bodies: a systematic review and meta-analysis. *Psychol Med*, 1-12. https://doi.org/10.1017/s0033291718003161

Fadda, L., Corona, F., Floris, G., Mascia, M. M., Cossa, B., Ercoli, T., Pau, M., & Defazio, G. (2019). Upper limb movements in dementia with Lewy body: a quantitative analysis. *Exp Brain Res, 237*(8), 2105-2110. https://doi.org/10.1007/s00221-019-05575-2

Fairfoul, G., McGuire, L. I., Pal, S., Ironside, J. W., Neumann, J., Christie, S., Joachim, C., Esiri, M., Evetts, S. G., Rolinski, M., Baig, F., Ruffmann, C., Wade-Martins, R., Hu, M. T., Parkkinen, L., & Green, A. J. (2016). Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies. *Ann Clin Transl Neurol, 3*(10), 812-818. https://doi.org/10.1002/acn3.338

Fares, M. B., Jagannath, S., & Lashuel, H. A. (2021). Reverse engineering Lewy bodies: how far have we come and how far can we go? *Nat Rev Neurosci, 22*(2), 111-131. https://doi.org/10.1038/s41583-020-00416-6

Fereshtehnejad, S. M., Montplaisir, J. Y., Pelletier, A., Gagnon, J. F., Berg, D., & Postuma, R. B. (2017). Validation of the MDS research criteria for prodromal

Parkinson's disease: Longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. *Mov Disord*, *32*(6), 865-873. https://doi.org/10.1002/mds.26989

Fereshtehnejad, S. M., Yao, C., Pelletier, A., Montplaisir, J. Y., Gagnon, J. F., & Postuma, R. B. (2019). Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. *Brain*, *142*(7), 2051-2067. https://doi.org/10.1093/brain/awz111

Ferman, T. J., Aoki, N., Boeve, B. F., Aakre, J. A., Kantarci, K., Graff-Radford, J., Parisi, J. E., Van Gerpen, J. A., Graff-Radford, N. R., Uitti, R. J., Pedraza, O., Murray, M. E., Wszolek, Z. K., Reichard, R. R., Fields, J. A., Ross, O. A., Knopman, D. S., Petersen, R. C., & Dickson, D. W. (2020). Subtypes of dementia with Lewy bodies are associated with α-synuclein and tau distribution. *Neurology*, *95*(2), e155-e165. https://doi.org/10.1212/wnl.0000000000009763

Ferman, T. J., Arvanitakis, Z., Fujishiro, H., Duara, R., Parfitt, F., Purdy, M., Waters, C., Barker, W., Graff-Radford, N. R., & Dickson, D. W. (2013). Pathology and temporal onset of visual hallucinations, misperceptions and family misidentification distinguishes dementia with Lewy bodies from Alzheimer's disease. *Parkinsonism Relat Disord*, *19*(2), 227-231. https://doi.org/10.1016/j.parkreldis.2012.10.013

Ferman, T. J., Boeve, B. F., Smith, G. E., Lin, S. C., Silber, M. H., Pedraza, O., Wszolek, Z., Graff-Radford, N. R., Uitti, R., Van Gerpen, J., Pao, W., Knopman, D., Pankratz, V. S., Kantarci, K., Boot, B., Parisi, J. E., Dugger, B. N., Fujishiro, H., Petersen, R. C., & Dickson, D. W. (2011). Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology*, *77*(9), 875-882. https://doi.org/10.1212/WNL.0b013e31822c9148

Ferman, T. J., Smith, G. E., Boeve, B. F., Graff-Radford, N. R., Lucas, J. A., Knopman, D. S., Petersen, R. C., Ivnik, R. J., Wszolek, Z., Uitti, R., & Dickson, D. W. (2006). Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. *Clin Neuropsychol*, *20*(4), 623-636. https://doi.org/10.1080/13854040500376831

Ferman, T. J., Smith, G. E., Boeve, B. F., Ivnik, R. J., Petersen, R. C., Knopman, D., Graff-Radford, N., Parisi, J., & Dickson, D. W. (2004). DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. *Neurology*, *62*(2), 181-187. https://doi.org/10.1212/WNL.62.2.181

Fernández-Arcos, A., Vilaseca, I., Aldecoa, I., Serradell, M., Tolosa, E., Santamaría, J., Gelpi, E., & Iranzo, A. (2018). Alpha-synuclein aggregates in the parotid gland of idiopathic REM sleep behavior disorder. *Sleep Med*, *52*, 14-17. https://doi.org/10.1016/j.sleep.2018.08.003

Fernández-Espejo, E., Rodríguez de Fonseca, F., Suárez, J., Tolosa, E., Vilas, D., Aldecoa, I., Berenguer, J., & Damas-Hermoso, F. (2021). Native α-Synuclein, 3-Nitrotyrosine Proteins, and Patterns of Nitro-α-Synuclein-Immunoreactive Inclusions in Saliva and Submandibulary Gland in Parkinson's Disease. *Antioxidants (Basel)*, *10*(5). https://doi.org/10.3390/antiox10050715

Fernandez, H. H., Wu, C. K., & Ott, B. R. (2003). Pharmacotherapy of dementia with Lewy bodies. *Expert Opin Pharmacother*, *4*(11), 2027-2037. https://doi.org/10.1517/14656566.4.11.2027

Ferreira, D., Przybelski, S. A., Lesnick, T. G., Lemstra, A. W., Londos, E., Blanc, F., Nedelska, Z., Schwarz, C. G., Graff-Radford, J., Senjem, M. L., Fields, J. A., Knopman, D. S., Savica, R., Ferman, T. J., Graff-Radford, N. R., Lowe, V. J., Jack, C. R., Jr., Petersen, R. C., Mollenhauer, B., Garcia-Ptacek, S., Abdelnour, C., Hort, J., Bonanni, L., Oppedal, K., Kramberger, M. G., Boeve, B. F., Aarsland, D., Westman, E., & Kantarci, K. (2020). β-Amyloid and tau biomarkers and clinical phenotype in dementia with Lewy bodies. *Neurology*, *95*(24), e3257-e3268. https://doi.org/10.1212/wnl.0000000000010943

Ferri, R., Rundo, F., Silvani, A., Zucconi, M., Bruni, O., Ferini-Strambi, L., Plazzi, G., & Manconi, M. (2017). REM Sleep EEG Instability in REM Sleep Behavior Disorder and Clonazepam Effects. *Sleep*, *40*(8). https://doi.org/10.1093/sleep/zsx080

Fiorenzato, E., Strafella, A. P., Kim, J., Schifano, R., Weis, L., Antonini, A., & Biundo, R. (2019). Dynamic functional connectivity changes associated with dementia in Parkinson's disease. *Brain*, *142*(9), 2860-2872. https://doi.org/10.1093/brain/awz192

Firbank, M., Kobeleva, X., Cherry, G., Killen, A., Gallagher, P., Burn, D. J., Thomas, A. J., O'Brien, J. T., & Taylor, J. P. (2016a). Neural correlates of attention-executive dysfunction in lewy body dementia and Alzheimer's disease. *Hum Brain Mapp*, *37*(3), 1254-1270. https://doi.org/10.1002/hbm.23100

Firbank, M. J., Blamire, A. M., Krishnan, M. S., Teodorczuk, A., English, P., Gholkar, A., Harrison, R. M., & O'Brien, J. T. (2007). Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease. *Psychiatry Res*, *155*(2), 135-145. https://doi.org/10.1016/j.pscychresns.2007.01.001

Firbank, M. J., Blamire, A. M., Teodorczuk, A., Teper, E., Mitra, D., & O'Brien, J. T. (2011). Diffusion tensor imaging in Alzheimer's disease and dementia with Lewy bodies. *Psychiatry Res*, *194*(2), 176-183. https://doi.org/10.1016/j.pscychresns.2011.08.002

Firbank, M. J., Lloyd, J., & O'Brien, J. T. (2016b). The relationship between hallucinations and FDG-PET in dementia with Lewy bodies. *Brain Imaging and Behavior*, *10*(3), 636-639. https://doi.org/10.1007/s11682-015-9434-0

Flavin, W. P., Bousset, L., Green, Z. C., Chu, Y., Skarpathiotis, S., Chaney, M. J., Kordower, J. H., Melki, R., & Campbell, E. M. (2017). Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol*, *134*(4), 629-653. https://doi.org/10.1007/s00401-017-1722-x

Fodero-Tavoletti, M. T., Smith, D. P., McLean, C. A., Adlard, P. A., Barnham, K. J., Foster, L. E., Leone, L., Perez, K., Cortés, M., Culvenor, J. G., Li, Q. X., Laughton, K. M., Rowe, C. C., Masters, C. L., Cappai, R., & Villemagne, V. L. (2007). In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. *J Neurosci*, *27*(39), 10365-10371. https://doi.org/10.1523/jneurosci.0630-07.2007

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, *12*(3), 189-198.

Fossati, S., Ramos Cejudo, J., Debure, L., Pirraglia, E., Sone, J. Y., Li, Y., Chen, J., Butler, T., Zetterberg, H., Blennow, K., & de Leon, M. J. (2019). Plasma tau complements CSF tau and P-tau in the diagnosis of Alzheimer's disease. *Alzheimers Dement (Amst)*, *11*, 483-492. https://doi.org/10.1016/j.dadm.2019.05.001

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A*, *103*(26), 10046-10051. https://doi.org/10.1073/pnas.0604187103

Franciotti, R., Pilotto, A., Moretti, D. V., Falasca, N. W., Arnaldi, D., Taylor, J. P., Nobili, F., Kramberger, M., Ptacek, S. G., Padovani, A., Aarlsand, D., Onofrj, M., & Bonanni, L. (2020). Anterior EEG slowing in dementia with Lewy bodies: a multicenter European cohort study. *Neurobiol Aging*, *93*, 55-60. https://doi.org/10.1016/j.neurobiolaging.2020.04.023

French Clozapine Parkinson Study Group, The (1999). Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. *Lancet*, *353*(9169), 2041-2042.

Friedman, J. H. (2013). Parkinson disease psychosis: Update. *Behav Neurol*, *27*(4), 469-477. https://doi.org/10.3233/ben-129016

Fujishiro, H., Nakamura, S., Sato, K., & Iseki, E. (2015). Prodromal dementia with Lewy bodies. *Geriatr Gerontol Int*, *15*(7), 817-826. https://doi.org/10.1111/ggi.12466

Fujishiro, H., Ota, K., Yamagata, M., Ito, T., Hieda, S., Suga, H., Fukui, T., & Nagahama, Y. (2021). Early diagnosis of prodromal dementia with Lewy bodies using clinical history of probable REM sleep behaviour disorder and cardiac

(123) I-MIBG scintigraphy in memory clinics. *Psychogeriatrics*, 21(3), 288-295. https://doi.org/10.1111/psyg.12662

Galbiati, A., Carli, G., Hensley, M., & Ferini-Strambi, L. (2018). REM Sleep Behavior Disorder and Alzheimer's Disease: Definitely No Relationship? *J Alzheimers Dis*, *63*(1), 1-11. https://doi.org/10.3233/jad-171164

Galvin, J. E., Chrisphonte, S., Cohen, I., Greenfield, K. K., Kleiman, M. J., Moore, C., Riccio, M. L., Rosenfeld, A., Shkolnik, N., Walker, M., Chang, L. C., & Tolea, M. I. (2021). Characterization of dementia with Lewy bodies (DLB) and mild cognitive impairment using the Lewy body dementia module (LBD-MOD). *Alzheimers Dement*, *17*(10), 1675-1686. https://doi.org/10.1002/alz.12334

Gama, R. L., de Bruin, V. M., de Bruin, P. F., Tavora, D. G., Lopes, E. M., Jorge, I. F., Bittencourt, L. R., & Tufik, S. (2015). Risk factors for visual hallucinations in patients with Parkinson's disease. *Neurol Res*, *37*(2), 112-116. https://doi.org/10.1179/1743132814y.0000000418

Gámez-Valero, A., Campdelacreu, J., Reñé, R., Beyer, K., & Borràs, F. E. (2019). Comprehensive proteomic profiling of plasma-derived Extracellular Vesicles from dementia with Lewy Bodies patients. *Sci Rep*, *9*(1), 13282. https://doi.org/10.1038/s41598-019-49668-y

Gámez-Valero, A., Canet-Pons, J., Urbizu, A., Anillo, A., Santos, C., Ariza, A., & Beyer, K. (2018). INDEL Length and Haplotypes in the β-Synuclein Gene: A Key to Differentiate Dementia with Lewy Bodies? *J Alzheimers Dis*, *65*(1), 207-219. https://doi.org/10.3233/jad-180074

Garrido, A., Fairfoul, G., Tolosa, E. S., Martí, M. J., & Green, A. (2019). α-synuclein RT-QuIC in cerebrospinal fluid of LRRK2-linked Parkinson's disease. *Ann Clin Transl Neurol*, *6*(6), 1024-1032. https://doi.org/10.1002/acn3.772

Génier Marchand, D., Postuma, R. B., Escudier, F., De Roy, J., Pelletier, A., Montplaisir, J., & Gagnon, J. F. (2018). How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. *Ann Neurol*, *83*(5), 1016-1026. https://doi.org/10.1002/ana.25239

Gilat, M., Coeytaux Jackson, A., Marshall, N. S., Hammond, D., Mullins, A. E., Hall, J. M., Fang, B. A. M., Yee, B. J., Wong, K. K. H., Grunstein, R. R., & Lewis, S. J. G. (2020). Melatonin for rapid eye movement sleep behavior disorder in Parkinson's disease: A randomised controlled trial. *Mov Disord*, *35*(2), 344-349. https://doi.org/10.1002/mds.27886

Gjerum, L., Frederiksen, K. S., Henriksen, O. M., Law, I., Anderberg, L., Andersen, B. B., Bjerregaard, E., Hejl, A. M., Høgh, P., & Hasselbalch, S. G. (2020). A visual rating scale for cingulate island sign on 18F-FDG-PET to differentiate dementia with Lewy bodies and Alzheimer's disease. *J Neurol Sci*, *410*, 116645. https://doi.org/10.1016/j.jns.2019.116645

Gmitterová, K., Gawinecka, J., Llorens, F., Varges, D., Valkovič, P., & Zerr, I. (2020). Cerebrospinal fluid markers analysis in the differential diagnosis of dementia with Lewy bodies and Parkinson's disease dementia. *Eur Arch Psychiatry Clin Neurosci*, *270*(4), 461-470. https://doi.org/10.1007/s00406-018-0928-9

Gnanalingham, K. K., Byrne, E. J., Thornton, A., Sambrook, M. A., & Bannister, P. (1997). Motor and cognitive function in Lewy body dementia: comparison with Alzheimer's and Parkinson's diseases. *J Neurol Neurosurg Psychiatry*, *62*(3), 243-252. https://doi.org/10.1136/jnnp.62.3.243

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, C., Giladi, N., Holloway, R. G., Moore, C. G., Wenning, G. K., Yahr, M. D., & Seidl, L. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord*, *19*(9), 1020-1028. https://doi.org/10.1002/mds.20213

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation

and clinimetric testing results. *Mov Disord*, *23*(15), 2129-2170. https://doi.org/10.1002/mds.22340

Goetz, C. G., Vaughan, C. L., Goldman, J. G., & Stebbins, G. T. (2014). I finally see what you see: Parkinson's disease visual hallucinations captured with functional neuroimaging. *Mov Disord*, *29*(1), 115-117. https://doi.org/10.1002/mds.25554

Goker-Alpan, O., Schiffmann, R., LaMarca, M. E., Nussbaum, R. L., McInerney-Leo, A., & Sidransky, E. (2004). Parkinsonism among Gaucher disease carriers. *J Med Genet*, *41*(12), 937-940. https://doi.org/10.1136/jmg.2004.024455

Gold, A., Turkalp, Z. T., & Munoz, D. G. (2013). Enteric alpha-synuclein expression is increased in Parkinson's disease but not Alzheimer's disease. *Movement Disorders*, *28*(2), 237-241. https://doi.org/10.1002/mds.25298

Goldstein, D. S., Holmes, C., Bentho, O., Sato, T., Moak, J., Sharabi, Y., Imrich, R., Conant, S., & Eldadah, B. A. (2008). Biomarkers to detect central dopamine deficiency and distinguish Parkinson disease from multiple system atrophy. *Parkinsonism Relat Disord*, *14*(8), 600-607. https://doi.org/10.1016/j.parkreldis.2008.01.010

Gomperts, S. N. (2016). Lewy Body Dementias: Dementia With Lewy Bodies and Parkinson Disease Dementia. *Continuum (Minneap Minn)*, *22*(2 Dementia), 435-463. https://doi.org/10.1212/con.0000000000000309

Gomperts, S. N., Locascio, J. J., Makaretz, S. J., Schultz, A., Caso, C., Vasdev, N., Sperling, R., Growdon, J. H., Dickerson, B. C., & Johnson, K. (2016a). Tau Positron Emission Tomographic Imaging in the Lewy Body Diseases. *JAMA Neurol*, *73*(11), 1334-1341. https://doi.org/10.1001/jamaneurol.2016.3338

Gomperts, S. N., Locascio, J. J., Marquie, M., Santarlasci, A. L., Rentz, D. M., Maye, J., Johnson, K. A., & Growdon, J. H. (2012). Brain amyloid and cognition in Lewy body diseases. *Mov Disord*, *27*(8), 965-973. https://doi.org/10.1002/mds.25048

Gomperts, S. N., Marquie, M., Locascio, J. J., Bayer, S., Johnson, K. A., & Growdon, J. H. (2016b). PET Radioligands Reveal the Basis of Dementia in Parkinson's

Disease and Dementia with Lewy Bodies. *Neurodegener Dis*, *16*(1-2), 118-124. https://doi.org/10.1159/000441421

Goossens, J., Bjerke, M., Struyfs, H., Niemantsverdriet, E., Somers, C., Van den Bossche, T., Van Mossevelde, S., De Vil, B., Sieben, A., Martin, J. J., Cras, P., Goeman, J., De Deyn, P. P., Van Broeckhoven, C., van der Zee, J., & Engelborghs, S. (2017). No added diagnostic value of non-phosphorylated tau fraction (p-tau(rel)) in CSF as a biomarker for differential dementia diagnosis. *Alzheimers Res Ther*, *9*(1), 49. https://doi.org/10.1186/s13195-017-0275-5

Gordon, K. D. (2016). Prevalence of visual hallucinations in a national low vision client population. *Can J Ophthalmol*, *51*(1), 3-6. https://doi.org/10.1016/j.jcjo.2015.10.006

Graff-Radford, J., Aakre, J., Savica, R., Boeve, B., Kremers, W. K., Ferman, T. J., Jones, D. T., Kantarci, K., Knopman, D. S., Dickson, D. W., Kukull, W. A., & Petersen, R. C. (2017). Duration and Pathologic Correlates of Lewy Body Disease. *JAMA Neurol*, *74*(3), 310-315. https://doi.org/10.1001/jamaneurol.2016.4926

Graff-Radford, J., Lesnick, T. G., Savica, R., Chen, Q., Ferman, T. J., Przybelski, S. A., Jones, D. T., Senjem, M. L., Gunter, J. L., Kremers, W. K., Jack, C. R., Jr., Lowe, V. J., Petersen, R. C., Knopman, D. S., Boeve, B. F., Murray, M. E., Dickson, D. W., & Kantarci, K. (2020). (18)F-fluorodeoxyglucose positron emission tomography in dementia with Lewy bodies. *Brain Commun*, *2*(1), fcaa040. https://doi.org/10.1093/braincomms/fcaa040

Graff-Radford, J., Murray, M. E., Lowe, V. J., Boeve, B. F., Ferman, T. J., Przybelski, S. A., Lesnick, T. G., Senjem, M. L., Gunter, J. L., Smith, G. E., Knopman, D. S., Jack, C. R., Jr., Dickson, D. W., Petersen, R. C., & Kantarci, K. (2014). Dementia with Lewy bodies: basis of cingulate island sign. *Neurology*, *83*(9), 801-809. https://doi.org/10.1212/wnl.0000000000000734

Gratwicke, J., Zrinzo, L., Kahan, J., Peters, A., Brechany, U., McNichol, A., Beigi, M., Akram, H., Hyam, J., Oswal, A., Day, B., Mancini, L., Thornton, J., Yousry, T., Crutch, S. J., Taylor, J. P., McKeith, I., Rochester, L., Schott, J. M., Limousin, P.,

Burn, D., Rossor, M. N., Hariz, M., Jahanshahi, M., & Foltynie, T. (2020). Bilateral nucleus basalis of Meynert deep brain stimulation for dementia with Lewy bodies: A randomised clinical trial. *Brain Stimul, 13*(4), 1031-1039. https://doi.org/10.1016/j.brs.2020.04.010

Grothe, M. J., Schuster, C., Bauer, F., Heinsen, H., Prudlo, J., & Teipel, S. J. (2014). Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. *J Neurol, 261*(10), 1939-1948. https://doi.org/10.1007/s00415-014-7439-z

Groveman, B. R., Orrù, C. D., Hughson, A. G., Raymond, L. D., Zanusso, G., Ghetti, B., Campbell, K. J., Safar, J., Galasko, D., & Caughey, B. (2018). Rapid and ultra-sensitive quantitation of disease-associated α-synuclein seeds in brain and cerebrospinal fluid by αSyn RT-QuIC. *Acta Neuropathol Commun, 6*(1), 7. https://doi.org/10.1186/s40478-018-0508-2

Guerreiro, R., Ross, O. A., Kun-Rodrigues, C., Hernandez, D. G., Orme, T., Eicher, J. D., Shepherd, C. E., Parkkinen, L., Darwent, L., Heckman, M. G., Scholz, S. W., Troncoso, J. C., Pletnikova, O., Ansorge, O., Clarimon, J., Lleo, A., Morenas-Rodriguez, E., Clark, L., Honig, L. S., Marder, K., Lemstra, A., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Barber, I., Braae, A., Brown, K., Morgan, K., Troakes, C., Al-Sarraj, S., Lashley, T., Holton, J., Compta, Y., Van Deerlin, V., Serrano, G. E., Beach, T. G., Lesage, S., Galasko, D., Masliah, E., Santana, I., Pastor, P., Diez-Fairen, M., Aguilar, M., Tienari, P. J., Myllykangas, L., Oinas, M., Revesz, T., Lees, A., Boeve, B. F., Petersen, R. C., Ferman, T. J., Escott-Price, V., Graff-Radford, N., Cairns, N. J., Morris, J. C., Pickering-Brown, S., Mann, D., Halliday, G. M., Hardy, J., Trojanowski, J. Q., Dickson, D. W., Singleton, A., Stone, D. J., & Bras, J. (2018). Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol, 17*(1), 64-74. https://doi.org/10.1016/s1474-4422(17)30400-3

Gündner, A. L., Duran-Pacheco, G., Zimmermann, S., Ruf, I., Moors, T., Baumann, K., Jagasia, R., van de Berg, W. D. J., & Kremer, T. (2019). Path mediation analysis

reveals GBA impacts Lewy body disease status by increasing α-synuclein levels. *Neurobiol Dis*, *121*, 205-213. https://doi.org/10.1016/j.nbd.2018.09.015

Haglund, M., Friberg, N., Danielsson, E. J., Norrman, J., & Englund, E. (2016). A methodological study of locus coeruleus degeneration in dementing disorders. *Clin Neuropathol*, *35*(5), 287-294. https://doi.org/10.5414/np300930

Hall, S., Janelidze, S., Londos, E., Leuzy, A., Stomrud, E., Dage, J. L., & Hansson, O. (2021). Plasma Phospho-Tau Identifies Alzheimer's Co-Pathology in Patients with Lewy Body Disease. *Mov Disord*, *36*(3), 767-771. https://doi.org/10.1002/mds.28370

Halliday, G. M., Leverenz, J. B., Schneider, J. S., & Adler, C. H. (2014). The neurobiological basis of cognitive impairment in Parkinson's disease. *Mov Disord*, *29*(5), 634-650. https://doi.org/10.1002/mds.25857

Halpern, C. H., Rick, J. H., Danish, S. F., Grossman, M., & Baltuch, G. H. (2009). Cognition following bilateral deep brain stimulation surgery of the subthalamic nucleus for Parkinson's disease. *Int J Geriatr Psychiatry*, *24*(5), 443-451. https://doi.org/10.1002/gps.2149

Hamilton, C. A., Matthews, F. E., Allan, L. M., Barker, S., Ciafone, J., Donaghy, P. C., Durcan, R., Firbank, M. J., Lawley, S., O'Brien, J. T., Roberts, G., Taylor, J. P., & Thomas, A. J. (2021a). Utility of the pareidolia test in mild cognitive impairment with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*, *36*(9), 1407-1414. https://doi.org/10.1002/gps.5546

Hamilton, C. A., Matthews, F. E., Donaghy, P. C., Taylor, J. P., O'Brien, J. T., Barnett, N., Olsen, K., Lloyd, J., Petrides, G., McKeith, I. G., & Thomas, A. J. (2021b). Cognitive Decline in Mild Cognitive Impairment With Lewy Bodies or Alzheimer Disease: A Prospective Cohort Study. *Am J Geriatr Psychiatry*, *29*(3), 272-284. https://doi.org/10.1016/j.jagp.2020.07.018

Hamilton, J. M., Landy, K. M., Salmon, D. P., Hansen, L. A., Masliah, E., & Galasko, D. (2012). Early visuospatial deficits predict the occurrence of visual

hallucinations in autopsy-confirmed dementia with Lewy bodies. *Am J Geriatr Psychiatry*, *20*(9), 773-781. https://doi.org/10.1097/JGP.0b013e31823033bc

Hamilton, J. M., Salmon, D. P., Galasko, D., Delis, D. C., Hansen, L. A., Masliah, E., Thomas, R. G., & Thal, L. J. (2004). A comparison of episodic memory deficits in neuropathologically-confirmed Dementia with Lewy bodies and Alzheimer's disease. *J Int Neuropsychol Soc*, *10*(5), 689-697. https://doi.org/10.1017/s1355617704105043

Hamilton, J. M., Salmon, D. P., Galasko, D., Raman, R., Emond, J., Hansen, L. A., Masliah, E., & Thal, L. J. (2008). Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies. *Neuropsychology*, *22*(6), 729-737. https://doi.org/10.1037/a0012949

Hansen, N. (2021). Locus Coeruleus Malfunction Is Linked to Psychopathology in Prodromal Dementia With Lewy Bodies. *Front Aging Neurosci*, *13*, 641101. https://doi.org/10.3389/fnagi.2021.641101

Harper, L., Fumagalli, G. G., Barkhof, F., Scheltens, P., O'Brien, J. T., Bouwman, F., Burton, E. J., Rohrer, J. D., Fox, N. C., Ridgway, G. R., & Schott, J. M. (2016). MRI visual rating scales in the diagnosis of dementia: evaluation in 184 post-mortem confirmed cases. *Brain*, *139*(Pt 4), 1211-1225. https://doi.org/10.1093/brain/aww005

Heckman, M. G., Soto-Ortolaza, A. I., Contreras, M. Y. S., Murray, M. E., Pedraza, O., Diehl, N. N., Walton, R., Labbé, C., Lorenzo-Betancor, O., Uitti, R. J., van Gerpen, J., Ertekin-Taner, N., Smith, G. E., Kantarci, K., Savica, R., Jones, D. T., Graff-Radford, J., Knopman, D. S., Lowe, V. J., Jack, C. R., Jr., Petersen, R. C., Parisi, J. E., Rademakers, R., Wszolek, Z. K., Graff-Radford, N. R., Ferman, T. J., Dickson, D. W., Boeve, B. F., & Ross, O. A. (2016). LRRK2 variation and dementia with Lewy bodies. *Parkinsonism Relat Disord*, *31*, 98-103. https://doi.org/10.1016/j.parkreldis.2016.07.015

Heitz, C., Noblet, V., Cretin, B., Philippi, N., Kremer, L., Stackfleth, M., Hubele, F., Armspach, J. P., Namer, I., & Blanc, F. (2015). Neural correlates of visual

hallucinations in dementia with Lewy bodies. *Alzheimers Res Ther*, *7*(1), 6. https://doi.org/10.1186/s13195-014-0091-0

Heller, J., Brcina, N., Dogan, I., Holtbernd, F., Romanzetti, S., Schulz, J. B., Schiefer, J., & Reetz, K. (2017). Brain imaging findings in idiopathic REM sleep behavior disorder (RBD) – A systematic review on potential biomarkers for neurodegeneration. *Sleep Medicine Reviews*, *34*, 23-33. https://doi.org/https://doi.org/10.1016/j.smrv.2016.06.006

Henriksen, A. L., St Dennis, C., Setter, S. M., & Tran, J. T. (2006). Dementia with lewy bodies: therapeutic opportunities and pitfalls. *Consult Pharm*, *21*(7), 563-575. https://doi.org/10.4140/tcp.n.2006.563

Herbert, M. K., Aerts, M. B., Kuiperij, H. B., Claassen, J., Spies, P. E., Esselink, R. A. J., Bloem, B. R., & Verbeek, M. M. (2014). Addition of MHPG to Alzheimer's disease biomarkers improves differentiation of dementia with Lewy bodies from Alzheimer's disease but not other dementias. *Alzheimers Dement*, *10*(4), 448-455.e442. https://doi.org/10.1016/j.jalz.2013.05.1775

Hershey, L. A., & Coleman-Jackson, R. (2019). Pharmacological Management of Dementia with Lewy Bodies. *Drugs Aging*, *36*(4), 309-319. https://doi.org/10.1007/s40266-018-00636-7

Hilton, D., Stephens, M., Kirk, L., Edwards, P., Potter, R., Zajicek, J., Broughton, E., Hagan, H., & Carroll, C. (2013). Accumulation of α-synuclein in the bowel of patients in the pre-clinical phase of Parkinson's disease. *Acta Neuropathol*, *127*(2), 235-241. https://doi.org/10.1007/s00401-013-1214-6

Ho, Y. J., Shen, M. S., Tai, C. H., Li, H. H., Chen, J. H., Liao, W. C., Chiu, P. Y., Lee, I. Y., Lin, C. L., & Hung, C. S. (2019). Use of Ceftriaxone in Treating Cognitive and Neuronal Deficits Associated With Dementia With Lewy Bodies. *Front Neurosci*, *13*, 507. https://doi.org/10.3389/fnins.2019.00507

Hobson, J. A., Pace-Schott, E. F., & Stickgold, R. (2000). Dreaming and the brain: toward a cognitive neuroscience of conscious states. *Behav Brain Sci*, *23*(6), 793-842; discussion 904-1121. https://doi.org/10.1017/s0140525x00003976

Hof Zum Berge, A., Kellmann, M., Kallweit, U., Mir, S., Gieselmann, A., Meyer, T., Ferrauti, A., Pfeiffer, M., & Kölling, S. (2020). Portable PSG for sleep stage monitoring in sports: Assessment of SOMNOwatch plus EEG. *Eur J Sport Sci*, *20*(6), 713-721. https://doi.org/10.1080/17461391.2019.1659421

Hogg, E., Wertheimer, J., Graner, S., & Tagliati, M. (2017). Deep Brain Stimulation and Nonmotor Symptoms. *Int Rev Neurobiol*, *134*, 1045-1089. https://doi.org/10.1016/bs.irn.2017.05.022

Honeycutt, L., Gagnon, J. F., Pelletier, A., De Roy, J., Montplaisir, J. Y., & Postuma, R. B. (2020). Pareidolias and cognition in isolated REM sleep behavior disorder. *Parkinsonism Relat Disord*, *75*, 76-79. https://doi.org/10.1016/j.parkreldis.2020.05.017

Howard, E., Irwin, D. J., Rascovsky, K., Nevler, N., Shellikeri, S., Tropea, T. F., Spindler, M., Deik, A., Chen-Plotkin, A., Siderowf, A., Dahodwala, N., Weintraub, D., Shaw, L. M., Trojanowski, J. Q., Vaishnavi, S. N., Wolk, D. A., Mechanic-Hamilton, D., Morley, J. F., Duda, J. E., Grossman, M., & Cousins, K. A. Q. (2021). Cognitive Profile and Markers of Alzheimer Disease-Type Pathology in Patients With Lewy Body Dementias. *Neurology*, *96*(14), e1855-e1864. https://doi.org/10.1212/wnl.0000000000011699

Hsiao, I. T., Chang, Y. T., Weng, Y. H., Hsu, S. W., Lin, K. J., Lu, C. S., & Chang, C. C. (2022). Comparisons of vesicular monoamine transporter type 2 signals in Parkinson's disease and parkinsonism secondary to carbon monoxide poisoning. Neurotoxicology, 88, 178-186. https://doi.org/10.1016/j.neuro.2021.11.004

Hu, M. L., Zong, X. F., Mann, J. J., Zheng, J. J., Liao, Y. H., Li, Z. C., He, Y., Chen, X. G., & Tang, J. S. (2017). A Review of the Functional and Anatomical Default Mode Network in Schizophrenia. *Neurosci Bull*, *33*(1), 73-84. https://doi.org/10.1007/s12264-016-0090-1

Hu, X. S., Okamura, N., Arai, H., Higuchi, M., Matsui, T., Tashiro, M., Shinkawa, M., Itoh, M., Ido, T., & Sasaki, H. (2000). 18F-fluorodopa PET study of striatal

dopamine uptake in the diagnosis of dementia with Lewy bodies. Neurology, 55(10), 1575-1577. https://doi.org/10.1212/wnl.55.10.1575

Huang, S. H., Chang, C. C., Lui, C. C., Chen, N. C., Lee, C. C., Wang, P. W., & Jiang, C. F. (2015). Cortical metabolic and nigrostriatal abnormalities associated with clinical stage-specific dementia with Lewy bodies. *Clin Nucl Med*, *40*(1), 26-31. https://doi.org/10.1097/rlu.0000000000000620

Hull, J., Patel, V. B., Hutson, S. M., & Conway, M. E. (2015). New insights into the role of the branched-chain aminotransferase proteins in the human brain. *J Neurosci Res*, *93*(7), 987-998. https://doi.org/10.1002/jnr.23558

Huster, R. J., Enriquez-Geppert, S., Lavallee, C. F., Falkenstein, M., & Herrmann, C. S. (2013). Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. *Int J Psychophysiol*, *87*(3), 217-233. https://doi.org/10.1016/j.ijpsycho.2012.08.001

Hwang, K., Shine, J. M., Cellier, D., & D'Esposito, M. (2020). The Human Intraparietal Sulcus Modulates Task-Evoked Functional Connectivity. *Cereb Cortex*, *30*(3), 875-887. https://doi.org/10.1093/cercor/bhz133

Hwang, Y. J., Alexander, G. C., An, H., Moore, T. J., & Mehta, H. B. (2021). Risk of Hospitalization and Death Associated With Pimavanserin Use in Older Adults With Parkinson Disease. *Neurology*, *97*(13), e1266-e1275. https://doi.org/10.1212/WNL.0000000000012601

Iaccarino, L., Sala, A., Caminiti, S. P., Santangelo, R., Iannaccone, S., Magnani, G., & Perani, D. (2018). The brain metabolic signature of visual hallucinations in dementia with Lewy bodies. *Cortex*, *108*, 13-24. https://doi.org/10.1016/j.cortex.2018.06.014

Iannaccone, S., Cerami, C., Alessio, M., Garibotto, V., Panzacchi, A., Olivieri, S., Gelsomino, G., Moresco, R. M., & Perani, D. (2013). In vivo microglia activation in very early dementia with Lewy bodies, comparison with Parkinson's disease. *Parkinsonism Relat Disord*, *19*(1), 47-52. https://doi.org/10.1016/j.parkreldis.2012.07.002

Ibarretxe-Bilbao, N., Ramirez-Ruiz, B., Junque, C., Marti, M. J., Valldeoriola, F., Bargallo, N., Juanes, S., & Tolosa, E. (2010). Differential progression of brain atrophy in Parkinson's disease with and without visual hallucinations. *J Neurol Neurosurg Psychiatry*, *81*(6), 650-657. https://doi.org/10.1136/jnnp.2009.179655

Iizuka, T., & Kameyama, M. (2016). Cingulate island sign on FDG-PET is associated with medial temporal lobe atrophy in dementia with Lewy bodies. *Ann Nucl Med*, *30*(6), 421-429. https://doi.org/10.1007/s12149-016-1076-9

Iizuka, T., & Kameyama, M. (2020). Spatial metabolic profiles to discriminate dementia with Lewy bodies from Alzheimer disease. *J Neurol*, *267*(7), 1960-1969. https://doi.org/10.1007/s00415-020-09790-8

Ikeda, M., Mori, E., Matsuo, K., Nakagawa, M., & Kosaka, K. (2015). Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial. *Alzheimers Res Ther*, *7*(1), 4. https://doi.org/10.1186/s13195-014-0083-0

Ikemura, M., Saito, Y., Sengoku, R., Sakiyama, Y., Hatsuta, H., Kanemaru, K., Sawabe, M., Arai, T., Ito, G., Iwatsubo, T., Fukayama, M., & Murayama, S. (2008). Lewy body pathology involves cutaneous nerves. *J Neuropathol Exp Neurol*, *67*(10), 945-953. https://doi.org/10.1097/NEN.0b013e318186de48

Ikonomovic, M. D., Klunk, W. E., Abrahamson, E. E., Mathis, C. A., Price, J. C., Tsopelas, N. D., Lopresti, B. J., Ziolko, S., Bi, W., Paljug, W. R., Debnath, M. L., Hope, C. E., Isanski, B. A., Hamilton, R. L., & DeKosky, S. T. (2008). Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain*, *131*(Pt 6), 1630-1645. https://doi.org/10.1093/brain/awn016

Imamura, T., Ishii, K., Hirono, N., Hashimoto, M., Tanimukai, S., Kazuai, H., Hanihara, T., Sasaki, M., & Mori, E. (1999). Visual hallucinations and regional cerebral metabolism in dementia with Lewy bodies (DLB). *Neuroreport*, *10*(9), 1903-1907. https://doi.org/10.1097/00001756-199906230-00020

Inagawa, Y., Kanetaka, H., Tsugawa, A., Sakurai, S., Serisawa, S., Shimizu, S., Sakurai, H., & Hanyu, H. (2020). Efficacy of Olfactory and Pareidolia Tests Compared With That of Indicative Biomarkers in Diagnosis of Dementia With Lewy Bodies. *Front Neurol, 11*, 540291. https://doi.org/10.3389/fneur.2020.540291

Iqbal, B., Currie, G., & Kiat, H. (2018). Regional Cardiac Sympathetic Nervous System Evaluation Using 123I-mIBG SPECT in Patients with Heart Failure. *J Med Imaging Radiat Sci, 49*(4), 397-405. https://doi.org/10.1016/j.jmir.2018.05.001

Iranzo, A., Borrego, S., Vilaseca, I., Martí, C., Serradell, M., Sánchez-Valle, R., Kovacs, G. G., Valldeoriola, F., Gaig, C., Santamaria, J., Tolosa, E., & Gelpi, E. (2018). α-Synuclein aggregates in labial salivary glands of idiopathic rapid eye movement sleep behavior disorder. *Sleep, 41*(8). https://doi.org/10.1093/sleep/zsy101

Iranzo, A., Stefani, A., Serradell, M., Martí, M. J., Lomeña, F., Mahlknecht, P., Stockner, H., Gaig, C., Fernández-Arcos, A., Poewe, W., Tolosa, E., Högl, B., & Santamaria, J. (2017). Characterization of patients with longstanding idiopathic REM sleep behavior disorder. *Neurology, 89*(3), 242-248. https://doi.org/10.1212/wnl.0000000000004121

Iranzo, A., Tolosa, E., Gelpi, E., Molinuevo, J. L., Valldeoriola, F., Serradell, M., Sanchez-Valle, R., Vilaseca, I., Lomeña, F., Vilas, D., Lladó, A., Gaig, C., & Santamaria, J. (2013). Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *The Lancet Neurology, 12*(5), 443-453. https://doi.org/http://dx.doi.org/10.1016/S1474-4422(13)70056-5

Irwin, D. J., Grossman, M., Weintraub, D., Hurtig, H. I., Duda, J. E., Xie, S. X., Lee, E. B., Van Deerlin, V. M., Lopez, O. L., Kofler, J. K., Nelson, P. T., Jicha, G. A., Woltjer, R., Quinn, J. F., Kaye, J., Leverenz, J. B., Tsuang, D., Longfellow, K., Yearout, D., Kukull, W., Keene, C. D., Montine, T. J., Zabetian, C. P., & Trojanowski, J. Q. (2017). Neuropathological and genetic correlates of survival

and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol*, *16*(1), 55-65. https://doi.org/10.1016/s1474-4422(16)30291-5

Ishii, K. (2020). Diagnostic imaging of dementia with Lewy bodies, frontotemporal lobar degeneration, and normal pressure hydrocephalus. *Jpn J Radiol*, *38*(1), 64-76. https://doi.org/10.1007/s11604-019-00881-9

Jackson, M. L., Bassett, K., Nirmalan, P. V., & Sayre, E. C. (2007). Contrast sensitivity and visual hallucinations in patients referred to a low vision rehabilitation clinic. *Br J Ophthalmol*, *91*(3), 296-298. https://doi.org/10.1136/bjo.2006.104604

Janelidze, S., Berron, D., Smith, R., Strandberg, O., Proctor, N. K., Dage, J. L., Stomrud, E., Palmqvist, S., Mattsson-Carlgren, N., & Hansson, O. (2021). Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease. *JAMA Neurol*, *78*(2), 149-156. https://doi.org/10.1001/jamaneurol.2020.4201

Janssens, J., Vermeiren, Y., Fransen, E., Aerts, T., Van Dam, D., Engelborghs, S., & De Deyn, P. P. (2018). Cerebrospinal fluid and serum MHPG improve Alzheimer's disease versus dementia with Lewy bodies differential diagnosis. *Alzheimers Dement (Amst)*, *10*, 172-181. https://doi.org/10.1016/j.dadm.2018.01.002

Jellinger, K. A. (2018). Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)*, *125*(4), 615-650. https://doi.org/10.1007/s00702-017-1821-9

Jellinger, K. A., & Attems, J. (2011). Prevalence and pathology of dementia with Lewy bodies in the oldest old: a comparison with other dementing disorders. *Dement Geriatr Cogn Disord*, *31*(4), 309-316. https://doi.org/10.1159/000327360

Jellinger, K. A., & Korczyn, A. D. (2018). Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Med*, *16*(1), 34. https://doi.org/10.1186/s12916-018-1016-8

Jensen, P. H., Islam, K., Kenney, J., Nielsen, M. S., Power, J., & Gai, W. P. (2000). Microtubule-associated protein 1B is a component of cortical Lewy bodies and

binds alpha-synuclein filaments. *J Biol Chem*, *275*(28), 21500-21507. https://doi.org/10.1074/jbc.M000099200

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., Ska, B., Gilbert, B., Inglis, G., Panisset, M., de Boysson, C., & Chertkow, H. (2009). Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*, *23*(6), 765-777. https://doi.org/10.1037/a0016792

Johnson, D. K., Morris, J. C., & Galvin, J. E. (2005). Verbal and visuospatial deficits in dementia with Lewy bodies. *Neurology*, *65*(8), 1232-1238. https://doi.org/10.1212/01.wnl.0000180964.60708.c2

Joling, M., Vriend, C., Raijmakers, P., van der Zande, J. J., Lemstra, A. W., Berendse, H. W., Booij, J., & van den Heuvel, O. A. (2019). Striatal DAT and extrastriatal SERT binding in early-stage Parkinson's disease and dementia with Lewy bodies, compared with healthy controls: An (123)I-FP-CIT SPECT study. *NeuroImage. Clinical*, *22*, 101755. https://doi.org/10.1016/j.nicl.2019.101755

Joling, M., Vriend, C., van der Zande, J. J., Lemstra, A. W., van den Heuvel, O. A., Booij, J., & Berendse, H. W. (2018). Lower (123)I-FP-CIT binding to the striatal dopamine transporter, but not to the extrastriatal serotonin transporter, in Parkinson's disease compared with dementia with Lewy bodies. *NeuroImage. Clinical*, *19*, 130-136. https://doi.org/10.1016/j.nicl.2018.04.009

Josviak, N. D., Batistela, M. S., Souza, R. K. M., Wegner, N. R., Bono, G. F., Sulzbach, C. D., Simão-Silva, D. P., Piovezan, M. R., Souza, R. L. R., & Furtado-Alle, L. (2017). Plasma butyrylcholinesterase activity: a possible biomarker for differential diagnosis between Alzheimer's disease and dementia with Lewy bodies? *Int J Neurosci*, *127*(12), 1082-1086. https://doi.org/10.1080/00207454.2017.1329203

Kahathuduwa, C. N., Dassanayake, T. L., Amarakoon, A. M. T., & Weerasinghe, V. S. (2017). Acute effects of theanine, caffeine and theanine-caffeine combination on attention. *Nutr Neurosci*, *20*(6), 369-377. https://doi.org/10.1080/1028415x.2016.1144845

Kalaitzakis, M. E., Walls, A. J., Pearce, R. K., & Gentleman, S. M. (2011). Striatal Aβ peptide deposition mirrors dementia and differentiates DLB and PDD from other parkinsonian syndromes. *Neurobiol Dis*, *41*(2), 377-384. https://doi.org/10.1016/j.nbd.2010.10.005

Kalia, L. V., Lang, A. E., Hazrati, L. N., Fujioka, S., Wszolek, Z. K., Dickson, D. W., Ross, O. A., Van Deerlin, V. M., Trojanowski, J. Q., Hurtig, H. I., Alcalay, R. N., Marder, K. S., Clark, L. N., Gaig, C., Tolosa, E., Ruiz-Martínez, J., Marti-Masso, J. F., Ferrer, I., López de Munain, A., Goldman, S. M., Schüle, B., Langston, J. W., Aasly, J. O., Giordana, M. T., Bonifati, V., Puschmann, A., Canesi, M., Pezzoli, G., Maues De Paula, A., Hasegawa, K., Duyckaerts, C., Brice, A., Stoessl, A. J., & Marras, C. (2015). Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. *JAMA Neurol*, *72*(1), 100-105. https://doi.org/10.1001/jamaneurol.2014.2704

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. Lancet, 386(9996), 896-912. https://doi.org/10.1016/s0140-6736(14)61393-3

Kamagata, K., Nakatsuka, T., Sakakibara, R., Tsuyusaki, Y., Takamura, T., Sato, K., Suzuki, M., Hori, M., Kumamaru, K. K., Inaoka, T., Aoki, S., & Terada, H. (2017). Diagnostic imaging of dementia with Lewy bodies by susceptibility-weighted imaging of nigrosomes versus striatal dopamine transporter single-photon emission computed tomography: a retrospective observational study. *Neuroradiology*, *59*(1), 89-98. https://doi.org/10.1007/s00234-016-1773-z

Kane, J. P. M., Roberts, G., Petrides, G. S., Lloyd, J. J., O'Brien, J. T., & Thomas, A. J. (2019). (123)I-MIBG scintigraphy utility and cut-off value in a clinically representative dementia cohort. *Parkinsonism Relat Disord*, *62*, 79-84. https://doi.org/10.1016/j.parkreldis.2019.01.024

Kane, J. P. M., Surendranathan, A., Bentley, A., Barker, S. A. H., Taylor, J.-P., Thomas, A. J., Allan, L. M., McNally, R. J., James, P. W., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2018). Clinical prevalence of Lewy body dementia. *Alzheimers Res Ther*, *10*(1), 19. https://doi.org/10.1186/s13195-018-0350-6

Kanel, P., Müller, M., van der Zee, S., Sanchez-Catasus, C. A., Koeppe, R. A., Frey, K. A., & Bohnen, N. I. (2020). Topography of Cholinergic Changes in Dementia With Lewy Bodies and Key Neural Network Hubs. *J Neuropsychiatry Clin Neurosci*, *32*(4), 370-375. https://doi.org/10.1176/appi.neuropsych.19070165

Kanemoto, H., Kazui, H., Adachi, H., Yoshiyama, K., Wada, T., Nomura, K. T., Shimosegawa, E., & Ikeda, M. (2020). Thalamic pulvinar metabolism, sleep disturbances, and hallucinations in dementia with Lewy bodies: Positron emission tomography and actigraphy study. *Int J Geriatr Psychiatry*, *35*(8), 934-943. https://doi.org/10.1002/gps.5315

Kantarci, K., Avula, R., Senjem, M. L., Samikoglu, A. R., Zhang, B., Weigand, S. D., Przybelski, S. A., Edmonson, H. A., Vemuri, P., Knopman, D. S., Ferman, T. J., Boeve, B. F., Petersen, R. C., & Jack, C. R., Jr. (2010). Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology*, *74*(22), 1814-1821. https://doi.org/10.1212/WNL.0b013e3181e0f7cf

Kantarci, K., Ferman, T. J., Boeve, B. F., Weigand, S. D., Przybelski, S., Vemuri, P., Murray, M. E., Senjem, M. L., Smith, G. E., Knopman, D. S., Petersen, R. C., Jack, C. R., Jr., Parisi, J. E., & Dickson, D. W. (2012). Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies. *Neurology*, *79*(6), 553-560. https://doi.org/10.1212/WNL.0b013e31826357a5

Kantarci, K., Lowe, V. J., Boeve, B. F., Senjem, M. L., Tosakulwong, N., Lesnick, T. G., Spychalla, A. J., Gunter, J. L., Fields, J. A., Graff-Radford, J., Ferman, T. J., Jones, D. T., Murray, M. E., Knopman, D. S., Jack, C. R., Jr., & Petersen, R. C. (2017). AV-1451 tau and β-amyloid positron emission tomography imaging in dementia with Lewy bodies. *Ann Neurol*, *81*(1), 58-67. https://doi.org/10.1002/ana.24825

Kantarci, K., Lowe, V. J., Chen, Q., Przybelski, S. A., Lesnick, T. G., Schwarz, C. G., Senjem, M. L., Gunter, J. L., Jack, C. R., Jr., Graff-Radford, J., Jones, D. T., Knopman, D. S., Graff-Radford, N., Ferman, T. J., Parisi, J. E., Dickson, D. W., Petersen, R. C., Boeve, B. F., & Murray, M. E. (2020). β-Amyloid PET and

neuropathology in dementia with Lewy bodies. *Neurology*, *94*(3), e282-e291. https://doi.org/10.1212/wnl.0000000000008818

Kasanuki, K., Heckman, M. G., Diehl, N. N., Murray, M. E., Koga, S., Soto, A., Ross, O. A., & Dickson, D. W. (2017a). Regional analysis and genetic association of nigrostriatal degeneration in Lewy body disease. *Mov Disord*, *32*(11), 1584-1593. https://doi.org/10.1002/mds.27184

Kasanuki, K., Iseki, E., Ota, K., Kondo, D., Ichimiya, Y., Sato, K., & Arai, H. (2017b). (123)I-FP-CIT SPECT findings and its clinical relevance in prodromal dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging*, *44*(3), 358-365. https://doi.org/10.1007/s00259-016-3466-6

Kawai, Y., Miura, R., Tsujimoto, M., Sakurai, T., Yamaoka, A., Takeda, A., Arahata, Y., Washimi, Y., Kachi, T., & Toba, K. (2013). Neuropsychological differentiation between Alzheimer's disease and dementia with Lewy bodies in a memory clinic. *Psychogeriatrics*, *13*(3), 157-163. https://doi.org/10.1111/psyg.12019

Kazui, H., Adachi, H., Kanemoto, H., Yoshiyama, K., Wada, T., Tokumasu Nomura, K., Tanaka, T., & Ikeda, M. (2017). Effects of donepezil on sleep disturbances in patients with dementia with Lewy bodies: An open-label study with actigraphy. *Psychiatry Res*, *251*, 312-318. https://doi.org/10.1016/j.psychres.2017.02.039

Kemp, J., Philippi, N., Phillipps, C., Demuynck, C., Albasser, T., Martin-Hunyadi, C., Schmidt-Mutter, C., Cretin, B., & Blanc, F. (2017). Cognitive profile in prodromal dementia with Lewy bodies. *Alzheimers Res Ther*, *9*(1), 19. https://doi.org/10.1186/s13195-017-0242-1

Kenny, E. R., Blamire, A. M., Firbank, M. J., & O'Brien, J. T. (2012). Functional connectivity in cortical regions in dementia with Lewy bodies and Alzheimer's disease. *Brain*, *135*(Pt 2), 569-581. https://doi.org/10.1093/brain/awr327

Kikuchi, A., Baba, T., Hasegawa, T., Sugeno, N., Konno, M., & Takeda, A. (2011). Differentiating Parkinson's disease from multiple system atrophy by [123I] meta-iodobenzylguanidine myocardial scintigraphy and olfactory test.

Parkinsonism Relat Disord, *17*(9), 698-700. https://doi.org/10.1016/j.parkreldis.2011.07.011

Kim, H. J., Lee, J. E., Shin, S. J., Sohn, Y. H., & Lee, P. H. (2011). Analysis of the substantia innominata volume in patients with Parkinson's disease with dementia, dementia with lewy bodies, and Alzheimer's disease. *J Mov Disord*, *4*(2), 68-72. https://doi.org/10.14802/jmd.11014

Klein, J. C., Eggers, C., Kalbe, E., Weisenbach, S., Hohmann, C., Vollmar, S., Baudrexel, S., Diederich, N. J., Heiss, W. D., & Hilker, R. (2010). Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology*, *74*(11), 885-892. https://doi.org/10.1212/WNL.0b013e3181d55f61

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., Bergström, M., Savitcheva, I., Huang, G. F., Estrada, S., Ausén, B., Debnath, M. L., Barletta, J., Price, J. C., Sandell, J., Lopresti, B. J., Wall, A., Koivisto, P., Antoni, G., Mathis, C. A., & Långström, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*, *55*(3), 306-319. https://doi.org/10.1002/ana.20009

Kobayashi, S., Tateno, M., Morii, H., Utsumi, K., & Saito, T. (2009). Decreased cardiac MIBG uptake, its correlation with clinical symptoms in dementia with Lewy bodies. *Psychiatry Res*, *174*(1), 76-80. https://doi.org/10.1016/j.pscychresns.2009.02.006

Koerts, J., Borg, M. A. J. P., Meppelink, A. M., Leenders, K. L., van Beilen, M., & van Laar, T. (2010). Attentional and perceptual impairments in Parkinson's disease with visual hallucinations. *Parkinsonism Relat Disord*, *16*(4), 270-274. https://doi.org/https://doi.org/10.1016/j.parkreldis.2010.01.003

Kohs, S. C. (1920). The Block-Design Tests. *Journal of Experimental Psychology*, *3*(5), 357-376. https://doi.org/10.1037/h0074466

Korat, Š., Bidesi, N. S. R., Bonanno, F., Di Nanni, A., Hoàng, A. N. N., Herfert, K., Maurer, A., Battisti, U. M., Bowden, G. D., Thonon, D., Vugts, D., Windhorst, A. D., & Herth, M. M. (2021). Alpha-Synuclein PET Tracer Development-An

Overview about Current Efforts. *Pharmaceuticals (Basel)*, *14*(9). https://doi.org/10.3390/ph14090847

Korczyn, A. D., & Hassin-Baer, S. (2015). Can the disease course in Parkinson's disease be slowed? *BMC Med*, *13*, 295. https://doi.org/10.1186/s12916-015-0534-x

Kramberger, M. G., Auestad, B., Garcia-Ptacek, S., Abdelnour, C., Olmo, J. G., Walker, Z., Lemstra, A. W., Londos, E., Blanc, F., Bonanni, L., McKeith, I., Winblad, B., de Jong, F. J., Nobili, F., Stefanova, E., Petrova, M., Falup-Pecurariu, C., Rektorova, I., Bostantjopoulou, S., Biundo, R., Weintraub, D., & Aarsland, D. (2017). Long-Term Cognitive Decline in Dementia with Lewy Bodies in a Large Multicenter, International Cohort. *J Alzheimers Dis*, *57*(3), 787-795. https://doi.org/10.3233/jad-161109

Kramberger, M. G., Stukovnik, V., Cus, A., Repovs, G., Tomse, P., Meglic, N. P., Garasević, Z., Jensterle, J., & Pirtosek, Z. (2010). Parkinson's disease dementia: clinical correlates of brain spect perfusion and treatment. *Psychiatr Danub*, *22*(3), 446-449.

Kraybill, M. L., Larson, E. B., Tsuang, D. W., Teri, L., McCormick, W. C., Bowen, J. D., Kukull, W. A., Leverenz, J. B., & Cherrier, M. M. (2005). Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology*, *64*(12), 2069-2073. https://doi.org/10.1212/01.Wnl.0000165987.89198.65

Kume, K., Kikukawa, M., Hanyu, H., Takata, Y., Umahara, T., Sakurai, H., Kanetaka, H., Ohyashiki, K., Ohyashiki, J. H., & Iwamoto, T. (2012). Telomere length shortening in patients with dementia with Lewy bodies. *Eur J Neurol*, *19*(6), 905-910. https://doi.org/10.1111/j.1468-1331.2011.03655.x

Kunz, D., & Bes, F. (1999). Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov Disord*, *14*(3), 507-511. https://doi.org/10.1002/1531-8257(199905)14:3<507::aid-mds1021>3.0.co;2-8

Kunz, D., & Mahlberg, R. (2010). A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res*, *19*(4), 591-596. https://doi.org/10.1111/j.1365-2869.2010.00848.x

Lambon Ralph, M. A., Powell, J., Howard, D., Whitworth, A. B., Garrard, P., & Hodges, J. R. (2001). Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review. *J Neurol Neurosurg Psychiatry*, *70*(2), 149-156. https://doi.org/10.1136/jnnp.70.2.149

Lau, A., & Tymianski, M. (2010). Glutamate receptors, neurotoxicity and neurodegeneration. *Pflugers Arch*, *460*(2), 525-542. https://doi.org/10.1007/s00424-010-0809-1

Law, Z. K., Todd, C., Mehraram, R., Schumacher, J., Baker, M. R., LeBeau, F. E. N., Yarnall, A., Onofrj, M., Bonanni, L., Thomas, A., & Taylor, J. P. (2020). The Role of EEG in the Diagnosis, Prognosis and Clinical Correlations of Dementia with Lewy Bodies-A Systematic Review. *Diagnostics (Basel)*, *10*(9). https://doi.org/10.3390/diagnostics10090616

Lebouvier, T., Chaumette, T., Damier, P., Coron, E., Touchefeu, Y., Vrignaud, S., Naveilhan, P., Galmiche, J. P., Bruley des Varannes, S., Derkinderen, P., & Neunlist, M. (2008). Pathological lesions in colonic biopsies during Parkinson's disease. *Gut*, *57*(12), 1741-1743. https://doi.org/10.1136/gut.2008.162503

Lee, C. Y., Cheng, S. J., Lin, H. C., Liao, Y. L., & Chen, P. H. (2018a). Quality of Life in Patients with Dementia with Lewy Bodies. *Behav Neurol*, *2018*, 8320901. https://doi.org/10.1155/2018/8320901

Lee, D. R., Taylor, J. P., & Thomas, A. J. (2012). Assessment of cognitive fluctuation in dementia: a systematic review of the literature. *Int J Geriatr Psychiatry*, *27*(10), 989-998. https://doi.org/10.1002/gps.2823

Lee, H., Brekelmans, G. J. F., & Roks, G. (2015). The EEG as a diagnostic tool in distinguishing between dementia with Lewy bodies and Alzheimer's disease.

Clinical Neurophysiology, *126*(9), 1735-1739. https://doi.org/10.1016/j.clinph.2014.11.021

Lee, J. E., Park, H. J., Park, B., Song, S. K., Sohn, Y. H., Lee, J. D., & Lee, P. H. (2010). A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*, *81*(3), 320-326. https://doi.org/10.1136/jnnp.2009.184747

Lee, S. H., Cho, H., Choi, J. Y., Lee, J. H., Ryu, Y. H., Lee, M. S., & Lyoo, C. H. (2018b). Distinct patterns of amyloid-dependent tau accumulation in Lewy body diseases. *Mov Disord*, *33*(2), 262-272. https://doi.org/10.1002/mds.27252

Lerche, S., Machetanz, G., Wurster, I., Roeben, B., Zimmermann, M., Pilotto, A., Preische, O., Stransky, E., Deuschle, C., Hauser, A. K., Schulte, C., Lachmann, I., Waniek, K., Gasser, T., Berg, D., Maetzler, W., & Brockmann, K. (2019). Dementia with lewy bodies: GBA1 mutations are associated with cerebrospinal fluid alpha-synuclein profile. *Mov Disord*, *34*(7), 1069-1073. https://doi.org/10.1002/mds.27731

Leverenz, J. B., Umar, I., Wang, Q., Montine, T. J., McMillan, P. J., Tsuang, D. W., Jin, J., Pan, C., Shin, J., Zhu, D., & Zhang, J. (2007). Proteomic identification of novel proteins in cortical lewy bodies. *Brain Pathol*, *17*(2), 139-145. https://doi.org/10.1111/j.1750-3639.2007.00048.x

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed. ed.). New York : Oxford University Press.

Lim, S. M., Katsifis, A., Villemagne, V. L., Best, R., Jones, G., Saling, M., Bradshaw, J., Merory, J., Woodward, M., Hopwood, M., & Rowe, C. C. (2009). The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. *J Nucl Med*, *50*(10), 1638-1645. https://doi.org/10.2967/jnumed.109.065870

Lin, C. H., Liu, H. C., Yang, S. Y., Yang, K. C., Wu, C. C., & Chiu, M. J. (2019). Plasma pS129-α-Synuclein Is a Surrogate Biofluid Marker of Motor Severity and

Progression in Parkinson's Disease. *J Clin Med*, *8*(10). https://doi.org/10.3390/jcm8101601

Lin, C. H., Yang, S. Y., Horng, H. E., Yang, C. C., Chieh, J. J., Chen, H. H., Liu, B. H., & Chiu, M. J. (2018). Plasma Biomarkers Differentiate Parkinson's Disease From Atypical Parkinsonism Syndromes. *Front Aging Neurosci*, *10*, 123. https://doi.org/10.3389/fnagi.2018.00123

Lin, K. J., Weng, Y. H., Hsieh, C. J., Lin, W. Y., Wey, S. P., Kung, M. P., Yen, T. C., Lu, C. S., & Hsiao, I. T. (2013). Brain imaging of vesicular monoamine transporter type 2 in healthy aging subjects by 18F-FP-(+)-DTBZ PET. PLoS One, 8(9), e75952. https://doi.org/10.1371/journal.pone.0075952

Llorens, F., Schmitz, M., Varges, D., Kruse, N., Gotzmann, N., Gmitterová, K., Mollenhauer, B., & Zerr, I. (2016). Cerebrospinal α-synuclein in α-synuclein aggregation disorders: tau/α-synuclein ratio as potential biomarker for dementia with Lewy bodies. *J Neurol*, *263*(11), 2271-2277. https://doi.org/10.1007/s00415-016-8259-0

Lobotesis, K., Fenwick, J. D., Phipps, A., Ryman, A., Swann, A., Ballard, C., McKeith, I. G., & O'Brien, J. T. (2001). Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. *Neurology*, *56*(5), 643-649. https://doi.org/10.1212/wnl.56.5.643

Lowther, E. R., O'Brien, J. T., Firbank, M. J., & Blamire, A. M. (2014). Lewy body compared with Alzheimer dementia is associated with decreased functional connectivity in resting state networks. *Psychiatry Res*, *223*(3), 192-201. https://doi.org/10.1016/j.pscychresns.2014.06.004

Lu, J., Sherman, D., Devor, M., & Saper, C. B. (2006). A putative flip-flop switch for control of REM sleep. *Nature*, *441*(7093), 589-594. https://doi.org/10.1038/nature04767

Ma, L. Y., Gao, L. Y., Li, X., Ma, H. Z., & Feng, T. (2019). Nitrated alpha-synuclein in minor salivary gland biopsies in Parkinson's disease. *Neurosci Lett*, *704*, 45-49. https://doi.org/10.1016/j.neulet.2019.03.054

Maetzler, W., Liepelt, I., Reimold, M., Reischl, G., Solbach, C., Becker, C., Schulte, C., Leyhe, T., Keller, S., Melms, A., Gasser, T., & Berg, D. (2009). Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. *Neurobiol Dis*, *34*(1), 107-112. https://doi.org/10.1016/j.nbd.2008.12.008

Mak, E., Su, L., Williams, G. B., Watson, R., Firbank, M., Blamire, A., & O'Brien, J. (2016). Differential Atrophy of Hippocampal Subfields: A Comparative Study of Dementia with Lewy Bodies and Alzheimer Disease. *Am J Geriatr Psychiatry*, *24*(2), 136-143. https://doi.org/10.1016/j.jagp.2015.06.006

Mak, E., Surendranathan, A., Nicastro, N., Aigbirhio, F., Rowe, J., & O'Brien, J. (2019). Imaging Tau, Neuroinflammation, and Aβ in Dementia With Lewy Bodies: A Deep-Phenotyping Case Report. *Mov Disord Clin Pract*, *6*(1), 77-80. https://doi.org/10.1002/mdc3.12689

Malaty, I. A., Okun, M. S., & Jaffee, M. (2016). The Danger of Not Treating Parkinson Disease Psychosis. *JAMA Neurol*, *73*(9), 1156. https://doi.org/10.1001/jamaneurol.2016.2280

Malek, N., Swallow, D., Grosset, K. A., Anichtchik, O., Spillantini, M., & Grosset, D. G. (2014). Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease - a systematic review. *Acta Neurol Scand*, *130*(2), 59-72. https://doi.org/10.1111/ane.12247

Maltête, D., Wallon, D., Bourilhon, J., Lefaucheur, R., Danaila, T., Thobois, S., Defebvre, L., Dujardin, K., Houeto, J. L., Godefroy, O., Krystkowiak, P., Martinaud, O., Gillibert, A., Chastan, M., Vera, P., Hannequin, D., Welter, M. L., & Derrey, S. (2021). Nucleus Basalis of Meynert Stimulation for Lewy Body Dementia: A Phase I Randomized Clinical Trial. *Neurology*, *96*(5), e684-e697. https://doi.org/10.1212/wnl.0000000000011227

Mammana, A., Baiardi, S., Quadalti, C., Rossi, M., Donadio, V., Capellari, S., Liguori, R., & Parchi, P. (2021). RT-QuIC Detection of Pathological α-Synuclein in Skin Punches of Patients with Lewy Body Disease. *Mov Disord*, *36*(9), 2173-2177. https://doi.org/10.1002/mds.28651

Manni, R., Pacchetti, C., Terzaghi, M., Sartori, I., Mancini, F., & Nappi, G. (2002). Hallucinations and sleep-wake cycle in PD: a 24-hour continuous polysomnographic study. *Neurology*, *59*(12), 1979-1981. https://doi.org/10.1212/01.wnl.0000038351.32678.4a

Marcone, A., Garibotto, V., Moresco, R. M., Florea, I., Panzacchi, A., Carpinelli, A., Virta, J. R., Tettamanti, M., Borroni, B., Padovani, A., Bertoldo, A., Herholz, K., Rinne, J. O., Cappa, S. F., & Perani, D. (2012). [11C]-MP4A PET cholinergic measurements in amnestic mild cognitive impairment, probable Alzheimer's disease, and dementia with Lewy bodies: a Bayesian method and voxel-based analysis. *J Alzheimers Dis*, *31*(2), 387-399. https://doi.org/10.3233/jad-2012-111748

Marmamula, S., Sumalini, R., Reddy, T. K., Brahmanandam, S. M., & Satgunam, P. (2020). Prevalence of visual hallucinations. *Clin Exp Optom*, *103*(6), 865-869. https://doi.org/10.1111/cxo.13015

Maroteaux, L., Campanelli, J. T., & Scheller, R. H. (1988). Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *J Neurosci*, *8*(8), 2804-2815. https://doi.org/10.1523/jneurosci.08-08-02804.1988

Martini, A., Weis, L., Schifano, R., Pistonesi, F., Fiorenzato, E., Antonini, A., & Biundo, R. (2020). Differences in cognitive profiles between Lewy body and Parkinson's disease dementia. *J Neural Transm (Vienna)*, *127*(3), 323-330. https://doi.org/10.1007/s00702-019-02129-2

Massa, F., Meli, R., Grazzini, M., Famà, F., De Carli, F., Filippi, L., Arnaldi, D., Pardini, M., Morbelli, S., & Nobili, F. (2020). Utility of quantitative EEG in early Lewy body disease. *Parkinsonism Relat Disord*, *75*, 70-75. https://doi.org/10.1016/j.parkreldis.2020.05.007

Matar, E., & Lewis, S. J. (2017). REM sleep behaviour disorder: not just a bad dream. *Med J Aust*, *207*(6), 262-268. https://doi.org/10.5694/mja17.00321

Matar, E., Phillips, J. R., Ehgoetz Martens, K. A., Halliday, G. M., & Lewis, S. J. G. (2019a). Impaired Color Discrimination-A Specific Marker of Hallucinations in

Lewy Body Disorders. *J Geriatr Psychiatry Neurol*, *32*(5), 257-264. https://doi.org/10.1177/0891988719845501

Matar, E., Shine, J. M., Halliday, G. M., & Lewis, S. J. G. (2019b). Cognitive fluctuations in lewy body dementia - towards a pathophysiological framework. *Brain*.

Matej, R., Tesar, A., & Rusina, R. (2019). Alzheimer's disease and other neurodegenerative dementias in comorbidity: A clinical and neuropathological overview. *Clin Biochem*, *73*, 26-31. https://doi.org/10.1016/j.clinbiochem.2019.08.005

Matsui, H., Udaka, F., Tamura, A., Oda, M., Kubori, T., Nishinaka, K., & Kameyama, M. (2006). Impaired visual acuity as a risk factor for visual hallucinations in Parkinson's disease. *J Geriatr Psychiatry Neurol*, *19*(1), 36-40. https://doi.org/10.1177/0891988705284739

Mazère, J., Lamare, F., Allard, M., Fernandez, P., & Mayo, W. (2017). 123I-Iodobenzovesamicol SPECT Imaging of Cholinergic Systems in Dementia with Lewy Bodies. *J Nucl Med*, *58*(1), 123-128. https://doi.org/10.2967/jnumed.116.176180

Mazzulli, J. R., Xu, Y. H., Sun, Y., Knight, A. L., McLean, P. J., Caldwell, G. A., Sidransky, E., Grabowski, G. A., & Krainc, D. (2011). Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell*, *146*(1), 37-52. https://doi.org/10.1016/j.cell.2011.06.001

Mc Ardle, R., Del Din, S., Donaghy, P., Galna, B., Thomas, A. J., & Rochester, L. (2021). The Impact of Environment on Gait Assessment: Considerations from Real-World Gait Analysis in Dementia Subtypes. *Sensors (Basel)*, *21*(3). https://doi.org/10.3390/s21030813

Mc Ardle, R., Del Din, S., Galna, B., Thomas, A., & Rochester, L. (2020). Differentiating dementia disease subtypes with gait analysis: feasibility of wearable sensors? *Gait Posture*, *76*, 372-376. https://doi.org/10.1016/j.gaitpost.2019.12.028

McEntee, W. J., & Crook, T. H. (1993). Glutamate: its role in learning, memory, and the aging brain. *Psychopharmacology (Berl)*, *111*(4), 391-401. https://doi.org/10.1007/bf02253527

McKeith, I., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., Cicin-Sain, A., Ferrara, R., & Spiegel, R. (2000). Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*, *356*(9247), 2031-2036. https://doi.org/10.1016/s0140-6736(00)03399-7

McKeith, I., O'Brien, J., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Padovani, A., Giubbini, R., Bonuccelli, U., Volterrani, D., Holmes, C., Kemp, P., Tabet, N., Meyer, I., & Reininger, C. (2007a). Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol*, *6*(4), 305-313. https://doi.org/10.1016/s1474-4422(07)70057-1

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/wnl.0000000000004058

McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'Brien, J. T., Feldman, H., Cummings, J., Duda, J. E., Lippa, C., Perry, E. K., Aarsland, D., Arai, H., Ballard,

C. G., Boeve, B., Burn, D. J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C. G., Gomez-Tortosa, E., Halliday, G., Hansen, L. A., Hardy, J., Iwatsubo, T., Kalaria, R. N., Kaufer, D., Kenny, R. A., Korczyn, A., Kosaka, K., Lee, V. M., Lees, A., Litvan, I., Londos, E., Lopez, O. L., Minoshima, S., Mizuno, Y., Molina, J. A., Mukaetova-Ladinska, E. B., Pasquier, F., Perry, R. H., Schulz, J. B., Trojanowski, J. Q., & Yamada, M. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*, *65*(12), 1863-1872. https://doi.org/10.1212/01.wnl.0000187889.17253.b1

McKeith, I. G., Fairbairn, A., Perry, R., Thompson, P., & Perry, E. (1992a). Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *Bmj*, *305*(6855), 673-678. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1882909/pdf/bmj00092-0017.pdf

McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., Kantarci, K., Muscio, C., O'Brien, J. T., Postuma, R. B., Aarsland, D., Ballard, C., Bonanni, L., Donaghy, P., Emre, M., Galvin, J. E., Galasko, D., Goldman, J. G., Gomperts, S. N., Honig, L. S., Ikeda, M., Leverenz, J. B., Lewis, S. J. G., Marder, K. S., Masellis, M., Salmon, D. P., Taylor, J. P., Tsuang, D. W., Walker, Z., & Tiraboschi, P. (2020). Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology*, *94*(17), 743-755. https://doi.org/10.1212/wnl.0000000000009323

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A., & Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*, *47*(5), 1113-1124.

http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCOBNHDBOM00/fs047/ovft/live/g
v024/00006114/00006114-199611000-00001.pdf

McKeith, I. G., Mintzer, J., Aarsland, D., Burn, D., Chiu, H., Cohen-Mansfield, J.,
Dickson, D., Dubois, B., Duda, J. E., Feldman, H., Gauthier, S., Halliday, G.,
Lawlor, B., Lippa, C., Lopez, O. L., Carlos Machado, J., O'Brien, J., Playfer, J., &
Reid, W. (2004). Dementia with Lewy bodies. *Lancet Neurol*, *3*(1), 19-28.

McKeith, I. G., O'Brien, J., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Padovani, A.,
Giubbini, R., Bonuccelli, U., Volterrani, D., Holmes, C., Kemp, P., Tabet, N.,
Meyer, I., & Reininger, C. (2007b). Sensitivity and specificity of dopamine
transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a
phase III, multicentre study. *Lancet Neurol*, *6*(4), 305-313.
https://doi.org/10.1016/s1474-4422(07)70057-1

McKeith, I. G., Perry, R. H., Fairbairn, A. F., Jabeen, S., & Perry, E. K. (1992b).
Operational criteria for senile dementia of Lewy body type (SDLT). *Psychol
Med*, *22*(4), 911-922. https://doi.org/10.1017/s0033291700038484

McLaughlin, N. C., Chang, A. C., & Malloy, P. (2012). Verbal and nonverbal learning
and recall in dementia with lewy bodies and Alzheimer's disease. *Appl
Neuropsychol Adult*, *19*(2), 86-89. https://doi.org/10.1080/09084282.2011.643944

Mega, M. S. (2000). The cholinergic deficit in Alzheimer's disease: impact on cognition,
behaviour and function. *Int J Neuropsychopharmacol*, *3*(7), 3-12.
https://doi.org/10.1017/s1461145700001942

Meltzer, H. Y., Mills, R., Revell, S., Williams, H., Johnson, A., Bahr, D., & Friedman, J.
H. (2010). Pimavanserin, a serotonin(2A) receptor inverse agonist, for the
treatment of parkinson's disease psychosis. *Neuropsychopharmacology*, *35*(4),
881-892. https://doi.org/10.1038/npp.2009.176

Merdes, A. R., Hansen, L. A., Jeste, D. V., Galasko, D., Hofstetter, C. R., Ho, G. J., Thal,
L. J., & Corey-Bloom, J. (2003). Influence of Alzheimer pathology on clinical
diagnostic accuracy in dementia with Lewy bodies. *Neurology*, *60*(10), 1586-
1590. https://doi.org/10.1212/01.wnl.0000065889.42856.f2

Merory, J. R., Wittwer, J. E., Rowe, C. C., & Webster, K. E. (2007). Quantitative gait analysis in patients with dementia with Lewy bodies and Alzheimer's disease. *Gait Posture*, *26*(3), 414-419. https://doi.org/10.1016/j.gaitpost.2006.10.006

Mesulam, M. M., & Geula, C. (1988). Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. *J Comp Neurol*, *275*(2), 216-240. https://doi.org/10.1002/cne.902750205

Metrick, M. A., 2nd, do Carmo Ferreira, N., Saijo, E., Hughson, A. G., Kraus, A., Orrú, C., Miller, M. W., Zanusso, G., Ghetti, B., Vendruscolo, M., & Caughey, B. (2019). Million-fold sensitivity enhancement in proteopathic seed amplification assays for biospecimens by Hofmeister ion comparisons. *Proc Natl Acad Sci U S A*, *116*(46), 23029-23039. https://doi.org/10.1073/pnas.1909322116

Mielke, M. M., Hagen, C. E., Xu, J., Chai, X., Vemuri, P., Lowe, V. J., Airey, D. C., Knopman, D. S., Roberts, R. O., Machulda, M. M., Jack, C. R., Jr., Petersen, R. C., & Dage, J. L. (2018). Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement*, *14*(8), 989-997. https://doi.org/10.1016/j.jalz.2018.02.013

Mirza, S. S., Saeed, U., Knight, J., Ramirez, J., Stuss, D. T., Keith, J., Nestor, S. M., Yu, D., Swardfager, W., Rogaeva, E., St George Hyslop, P., Black, S. E., & Masellis, M. (2019). APOE ε4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. *Neurology*, *93*(19), e1807-e1819. https://doi.org/10.1212/wnl.0000000000008377

Miyazawa, N., Shinohara, T., Nagasaka, T., & Hayashi, M. (2010). Hypermetabolism in patients with dementia with Lewy bodies. *Clin Nucl Med*, *35*(7), 490-493. https://doi.org/10.1097/RLU.0b013e3181e05dbc

Mollenhauer, B., Locascio, J. J., Schulz-Schaeffer, W., Sixel-Doring, F., Trenkwalder, C., & Schlossmacher, M. G. (2011). alpha-Synuclein and tau concentrations in

cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. *Lancet Neurol*, *10*(3), 230-240. https://doi.org/10.1016/s1474-4422(11)70014-x

Mondino, M., Dondé, C., Lavallé, L., Haesebaert, F., & Brunelin, J. (2019). Reality-monitoring deficits and visual hallucinations in schizophrenia. *Eur Psychiatry*, *62*, 10-14. https://doi.org/10.1016/j.eurpsy.2019.08.010

Mondon, K., Gochard, A., Marqué, A., Armand, A., Beauchamp, D., Prunier, C., Jacobi, D., de Toffol, B., Autret, A., Camus, V., & Hommet, C. (2007). Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia. *J Neurol Neurosurg Psychiatry*, *78*(7), 738-741. https://doi.org/10.1136/jnnp.2006.104257

Moreno, G. M., Gandhi, R., Lessig, S. L., Wright, B., Litvan, I., & Nahab, F. B. (2018). Mortality in patients with Parkinson disease psychosis receiving pimavanserin and quetiapine. *Neurology*, *91*(17), 797-799. https://doi.org/10.1212/WNL.0000000000006396

Morgante, L., Epifanio, A., Spina, E., Zappia, M., Di Rosa, A. E., Marconi, R., Basile, G., Di Raimondo, G., La Spina, P., & Quattrone, A. (2004). Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol*, *27*(4), 153-156. https://doi.org/10.1097/01.wnf.0000136891.17006.ec

Mori, E., Ikeda, M., & Kosaka, K. (2012). Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol*, *72*(1), 41-52. https://doi.org/10.1002/ana.23557

Morra, L. F., & Donovick, P. J. (2014). Clinical presentation and differential diagnosis of dementia with Lewy bodies: a review. *Int J Geriatr Psychiatry*, *29*(6), 569-576. https://doi.org/10.1002/gps.4039

Mosimann, U. P., Collerton, D., Dudley, R., Meyer, T. D., Graham, G., Dean, J. L., Bearn, D., Killen, A., Dickinson, L., Clarke, M. P., & McKeith, I. G. (2008). A semi-structured interview to assess visual hallucinations in older people. Int J Geriatr Psychiatry, 23(7), 712-718. https://doi.org/10.1002/gps.1965

Mosimann, U. P., Mather, G., Wesnes, K. A., O'Brien, J. T., Burn, D. J., & McKeith, I. G. (2004). Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology*, *63*(11), 2091-2096. https://doi.org/10.1212/01.wnl.0000145764.70698.4e

Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). The prognosis of dementia with Lewy bodies. *Lancet Neurol*, *16*(5), 390-398. https://doi.org/10.1016/s1474-4422(17)30074-1

Mueller, C., Perera, G., Rajkumar, A. P., Bhattarai, M., Price, A., O'Brien, J. T., Ballard, C., Stewart, R., & Aarsland, D. (2018). Hospitalization in people with dementia with Lewy bodies: Frequency, duration, and cost implications. *Alzheimers Dement (Amst)*, *10*, 143-152. https://doi.org/10.1016/j.dadm.2017.12.001

Mueller, C., Soysal, P., Rongve, A., Isik, A. T., Thompson, T., Maggi, S., Smith, L., Basso, C., Stewart, R., Ballard, C., O'Brien, J. T., Aarsland, D., Stubbs, B., & Veronese, N. (2019). Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. *Ageing Res Rev*, *50*, 72-80. https://doi.org/10.1016/j.arr.2019.01.005

Muller, A. J., Shine, J. M., Halliday, G. M., & Lewis, S. J. (2014). Visual hallucinations in Parkinson's disease: theoretical models. *Mov Disord*, *29*(13), 1591-1598. https://doi.org/10.1002/mds.26004

Mulugeta, E., Londos, E., Ballard, C., Alves, G., Zetterberg, H., Blennow, K., Skogseth, R., Minthon, L., & Aarsland, D. (2011). CSF amyloid β38 as a novel diagnostic marker for dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*, *82*(2), 160-164. https://doi.org/10.1136/jnnp.2009.199398

Murata, M., Odawara, T., Hasegawa, K., Kajiwara, R., Takeuchi, H., Tagawa, M., & Kosaka, K. (2020). Effect of zonisamide on parkinsonism in patients with dementia with Lewy bodies: A phase 3 randomized clinical trial. *Parkinsonism Relat Disord*, *76*, 91-97. https://doi.org/10.1016/j.parkreldis.2019.12.005

Nagahama, Y., Okina, T., & Suzuki, N. (2017). Neuropsychological Differences Related to Age in Dementia with Lewy Bodies. *Dement Geriatr Cogn Dis Extra*, *7*(2), 188-194. https://doi.org/10.1159/000477296

Nagahama, Y., Okina, T., Suzuki, N., & Matsuda, M. (2010). Neural correlates of psychotic symptoms in dementia with Lewy bodies. *Brain*, *133*(Pt 2), 557-567. https://doi.org/10.1093/brain/awp295

Nakatsuka, T., Imabayashi, E., Matsuda, H., Sakakibara, R., Inaoka, T., & Terada, H. (2013). Discrimination of dementia with Lewy bodies from Alzheimer's disease using voxel-based morphometry of white matter by statistical parametric mapping 8 plus diffeomorphic anatomic registration through exponentiated Lie algebra. *Neuroradiology*, *55*(5), 559-566. https://doi.org/10.1007/s00234-013-1138-9

Nalls, M. A., Duran, R., Lopez, G., Kurzawa-Akanbi, M., McKeith, I. G., Chinnery, P. F., Morris, C. M., Theuns, J., Crosiers, D., Cras, P., Engelborghs, S., De Deyn, P. P., Van Broeckhoven, C., Mann, D. M., Snowden, J., Pickering-Brown, S., Halliwell, N., Davidson, Y., Gibbons, L., Harris, J., Sheerin, U. M., Bras, J., Hardy, J., Clark, L., Marder, K., Honig, L. S., Berg, D., Maetzler, W., Brockmann, K., Gasser, T., Novellino, F., Quattrone, A., Annesi, G., De Marco, E. V., Rogaeva, E., Masellis, M., Black, S. E., Bilbao, J. M., Foroud, T., Ghetti, B., Nichols, W. C., Pankratz, N., Halliday, G., Lesage, S., Klebe, S., Durr, A., Duyckaerts, C., Brice, A., Giasson, B. I., Trojanowski, J. Q., Hurtig, H. I., Tayebi, N., Landazabal, C., Knight, M. A., Keller, M., Singleton, A. B., Wolfsberg, T. G., & Sidransky, E. (2013). A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. *JAMA Neurol*, *70*(6), 727-735. https://doi.org/10.1001/jamaneurol.2013.1925

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, *53*(4), 695-699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nepozitek, J., Unalp, C., Dostalova, S., Dusek, P., Kemlink, D., Prihodova, I., Ibarburu Lorenzo, Y. L. V., Trnka, J., Zogala, D., Bezdicek, O., Nikolai, T., Perinova, P., Dall'Antonia, I., Ruzicka, E., & Sonka, K. (2021). Systematic video-analysis of motor events during REM sleep in idiopathic REM sleep behavior disorder, follow-up and DAT-SPECT. *Sleep Med*, *83*, 132-144. https://doi.org/10.1016/j.sleep.2021.04.033

Nervi, A., Reitz, C., Tang, M. X., Santana, V., Piriz, A., Reyes-Dumeyer, D., Lantigua, R., Medrano, M., Jiménez-Velázquez, I. Z., Lee, J. H., & Mayeux, R. (2008). Comparison of clinical manifestations in Alzheimer disease and dementia with Lewy bodies. *Arch Neurol*, *65*(12), 1634-1639. https://doi.org/10.1001/archneur.65.12.1634

Nihashi, T., Ito, K., & Terasawa, T. (2020). Diagnostic accuracy of DAT-SPECT and MIBG scintigraphy for dementia with Lewy bodies: an updated systematic review and Bayesian latent class model meta-analysis. *Eur J Nucl Med Mol Imaging*, *47*(8), 1984-1997. https://doi.org/10.1007/s00259-019-04480-8

Nobili, A., Latagliata, E. C., Viscomi, M. T., Cavallucci, V., Cutuli, D., Giacovazzo, G., Krashia, P., Rizzo, F. R., Marino, R., Federici, M., De Bartolo, P., Aversa, D., Dell'Acqua, M. C., Cordella, A., Sancandi, M., Keller, F., Petrosini, L., Puglisi-Allegra, S., Mercuri, N. B., Coccurello, R., Berretta, N., & D'Amelio, M. (2017). Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. *Nature communications*, *8*, 14727. https://doi.org/10.1038/ncomms14727

Noe, E., Marder, K., Bell, K. L., Jacobs, D. M., Manly, J. J., & Stern, Y. (2004). Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. *Mov Disord*, *19*(1), 60-67. https://doi.org/10.1002/mds.10633

O'Brien, J., Taylor, J. P., Ballard, C., Barker, R. A., Bradley, C., Burns, A., Collerton, D., Dave, S., Dudley, R., Francis, P., Gibbons, A., Harris, K., Lawrence, V., Leroi, I., McKeith, I., Michaelides, M., Naik, C., O'Callaghan, C., Olsen, K., Onofrj, M.,

Pinto, R., Russell, G., Swann, P., Thomas, A., Urwyler, P., Weil, R. S., & Ffytche, D. (2020). Visual hallucinations in neurological and ophthalmological disease: pathophysiology and management. *J Neurol Neurosurg Psychiatry*, *91*(5), 512-519. https://doi.org/10.1136/jnnp-2019-322702

O'Brien, J. T., Colloby, S., Fenwick, J., Williams, E. D., Firbank, M., Burn, D., Aarsland, D., & McKeith, I. G. (2004). Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. *Arch Neurol*, *61*(6), 919-925. https://doi.org/10.1001/archneur.61.6.919

O'Brien, J. T., Firbank, M. J., Davison, C., Barnett, N., Bamford, C., Donaldson, C., Olsen, K., Herholz, K., Williams, D., & Lloyd, J. (2014). 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med*, *55*(12), 1959-1965. https://doi.org/10.2967/jnumed.114.143347

O'Brien, J. T., Firbank, M. J., Mosimann, U. P., Burn, D. J., & McKeith, I. G. (2005). Change in perfusion, hallucinations and fluctuations in consciousness in dementia with Lewy bodies. *Psychiatry Res*, *139*(2), 79-88. https://doi.org/10.1016/j.pscychresns.2005.04.002

O'Brien, J. T., McKeith, I. G., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Marquardt, M., & Reininger, C. (2009). Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. *Br J Psychiatry*, *194*(1), 34-39. https://doi.org/10.1192/bjp.bp.108.052050

O'Bryant, S. E., Ferman, T. J., Zhang, F., Hall, J., Pedraza, O., Wszolek, Z. K., Como, T., Julovich, D., Mattevada, S., Johnson, L. A., Edwards, M., Hall, J., & Graff-Radford, N. R. (2019). A proteomic signature for dementia with Lewy bodies. *Alzheimers Dement (Amst)*, *11*, 270-276. https://doi.org/10.1016/j.dadm.2019.01.006

Oda, H., Yamamoto, Y., & Maeda, K. (2009). The neuropsychological profile in dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*, *24*(2), 125-131. https://doi.org/10.1002/gps.2078

Ohtake, H., Limprasert, P., Fan, Y., Onodera, O., Kakita, A., Takahashi, H., Bonner, L. T., Tsuang, D. W., Murray, I. V., Lee, V. M., Trojanowski, J. Q., Ishikawa, A., Idezuka, J., Murata, M., Toda, T., Bird, T. D., Leverenz, J. B., Tsuji, S., & La Spada, A. R. (2004). Beta-synuclein gene alterations in dementia with Lewy bodies. *Neurology*, *63*(5), 805-811. https://doi.org/10.1212/01.wnl.0000139870.14385.3c

Oka, H., Umehara, T., Nakahara, A., & Matsuno, H. (2020). Comparisons of cardiovascular dysautonomia and cognitive impairment between de novo Parkinson's disease and de novo dementia with Lewy bodies. *BMC Neurol*, *20*(1), 350. https://doi.org/10.1186/s12883-020-01928-5

Okamura, N., Villemagne, V. L., Drago, J., Pejoska, S., Dhamija, R. K., Mulligan, R. S., Ellis, J. R., Ackermann, U., O'Keefe, G., Jones, G., Kung, H. F., Pontecorvo, M. J., Skovronsky, D., & Rowe, C. C. (2010). In vivo measurement of vesicular monoamine transporter type 2 density in Parkinson disease with (18)F-AV-133. J Nucl Med, 51(2), 223-228. https://doi.org/10.2967/jnumed.109.070094

Okaty, B. W., Commons, K. G., & Dymecki, S. M. (2019). Embracing diversity in the 5-HT neuronal system. *Nature Reviews Neuroscience*, *20*(7), 397-424. https://doi.org/10.1038/s41583-019-0151-3

Onofri, E., Mercuri, M., Donato, G., & Ricci, S. (2015). Cognitive fluctuations in connection to dysgraphia: a comparison of Alzheimer's disease with dementia Lewy bodies. *Clin Interv Aging*, *10*, 625-633. https://doi.org/10.2147/cia.S79679

Onofrj, M., Espay, A. J., Bonanni, L., Delli Pizzi, S., & Sensi, S. L. (2019). Hallucinations, somatic-functional disorders of PD-DLB as expressions of thalamic dysfunction. *Mov Disord*, *34*(8), 1100-1111. https://doi.org/10.1002/mds.27781

Onofrj, M., Thomas, A., Iacono, D., Luciano, A. L., & Di Iorio, A. (2003). The effects of a cholinesterase inhibitor are prominent in patients with fluctuating cognition: a part 3 study of the main mechanism of cholinesterase inhibitors in dementia. *Clin Neuropharmacol*, *26*(5), 239-251. https://doi.org/10.1097/00002826-200309000-00008

Onofrj, M., Varanese, S., Bonanni, L., Taylor, J. P., Antonini, A., Valente, E. M., Petrucci, S., Stocchi, F., Thomas, A., & Perfetti, B. (2013). Cohort study of prevalence and phenomenology of tremor in dementia with Lewy bodies. *J Neurol*, *260*(7), 1731-1742. https://doi.org/10.1007/s00415-013-6853-y

Oppedal, K., Ferreira, D., Cavallin, L., Lemstra, A. W., Ten Kate, M., Padovani, A., Rektorova, I., Bonanni, L., Wahlund, L. O., Engedal, K., Nobili, F., Kramberger, M., Taylor, J. P., Hort, J., Snædal, J., Blanc, F., Walker, Z., Antonini, A., Westman, E., & Aarsland, D. (2019). A signature pattern of cortical atrophy in dementia with Lewy bodies: A study on 333 patients from the European DLB consortium. *Alzheimers Dement*, *15*(3), 400-409. https://doi.org/10.1016/j.jalz.2018.09.011

Orimo, S., Yogo, M., Nakamura, T., Suzuki, M., & Watanabe, H. (2016). (123)I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy in α-synucleinopathies. *Ageing Res Rev*, *30*, 122-133. https://doi.org/10.1016/j.arr.2016.01.001

Ortuño-Lizarán, I., Beach, T. G., Serrano, G. E., Walker, D. G., Adler, C. H., & Cuenca, N. (2018). Phosphorylated α-synuclein in the retina is a biomarker of Parkinson's disease pathology severity. *Mov Disord*, *33*(8), 1315-1324. https://doi.org/10.1002/mds.27392

Ota, K., Murayama, N., Kasanuki, K., Kondo, D., Fujishiro, H., Arai, H., Sato, K., & Iseki, E. (2015). Visuoperceptual assessments for differentiating dementia with Lewy bodies and Alzheimer's disease: illusory contours and other neuropsychological examinations. *Arch Clin Neuropsychol*, *30*(3), 256-263. https://doi.org/10.1093/arclin/acv016

Pagano, G., Niccolini, F., & Politis, M. (2016). Imaging in Parkinson's disease. *Clinical Medicine*, *16*(4), 371-375. https://doi.org/10.7861/clinmedicine.16-4-371

Pal, A., Biswas, A., Pandit, A., Roy, A., Guin, D., Gangopadhyay, G., & Senapati, A. K. (2016). Study of visuospatial skill in patients with dementia. *Ann Indian Acad Neurol*, *19*(1), 83-88. https://doi.org/10.4103/0972-2327.168636

Pang, L. (2016). Hallucinations Experienced by Visually Impaired: Charles Bonnet Syndrome. *Optom Vis Sci*, *93*(12), 1466-1478. https://doi.org/10.1097/opx.0000000000000959

Panza, F., Lozupone, M., Watling, M., & Imbimbo, B. P. (2021). Pharmacological management of dementia with Lewy bodies with a focus on zonisamide for treating parkinsonism. *Expert Opin Pharmacother*, *22*(3), 325-337. https://doi.org/10.1080/14656566.2020.1828350

Pardini, M., Nobili, F., Arnaldi, D., Morbelli, S., Bauckneht, M., Rissotto, R., Serrati, C., Serafini, G., Lapucci, C., Ghio, L., Amore, M., Massucco, D., Sassos, D., Bonzano, L., Mancardi, G. L., & Roccatagliata, L. (2020). (123)I-FP-CIT SPECT validation of nigro-putaminal MRI tractography in dementia with Lewy bodies. *Eur Radiol Exp*, *4*(1), 27. https://doi.org/10.1186/s41747-020-00153-6

Park, J., Suh, S. W., Kim, G. E., Lee, S., Kim, J. S., Kim, H. S., Byun, S., Bae, J. B., Kim, J. H., Kim, S. E., Han, J. W., & Kim, K. W. (2020). Smaller pineal gland is associated with rapid eye movement sleep behavior disorder in Alzheimer's disease. *Alzheimers Res Ther*, *12*(1), 157. https://doi.org/10.1186/s13195-020-00725-z

Park, K. W., Kim, H. S., Cheon, S. M., Cha, J. K., Kim, S. H., & Kim, J. W. (2011). Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. *J Clin Neurol*, *7*(1), 19-24. https://doi.org/10.3988/jcn.2011.7.1.19

Parkinson's Study Group (1999). Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med*, *340*(10), 757-763. https://doi.org/10.1056/nejm199903113401003

Parnetti, L., Balducci, C., Pierguidi, L., De Carlo, C., Peducci, M., D'Amore, C., Padiglioni, C., Mastrocola, S., Persichetti, E., Paciotti, S., Bellomo, G., Tambasco, N., Rossi, A., Beccari, T., & Calabresi, P. (2009). Cerebrospinal fluid beta-glucocerebrosidase activity is reduced in Dementia with Lewy Bodies. *Neurobiol Dis*, *34*(3), 484-486. https://doi.org/10.1016/j.nbd.2009.03.002

Parnetti, L., Chiasserini, D., Bellomo, G., Giannandrea, D., De Carlo, C., Qureshi, M. M., Ardah, M. T., Varghese, S., Bonanni, L., Borroni, B., Tambasco, N., Eusebi, P., Rossi, A., Onofrj, M., Padovani, A., Calabresi, P., & El-Agnaf, O. (2011). Cerebrospinal fluid Tau/alpha-synuclein ratio in Parkinson's disease and degenerative dementias. *Mov Disord*, *26*(8), 1428-1435. https://doi.org/10.1002/mds.23670

Parnetti, L., Paciotti, S., Farotti, L., Bellomo, G., Sepe, F. N., & Eusebi, P. (2019). Parkinson's and Lewy body dementia CSF biomarkers. *Clin Chim Acta*, *495*, 318-325. https://doi.org/10.1016/j.cca.2019.04.078

Pascarelli, M. T., Del Percio, C., De Pandis, M. F., Ferri, R., Lizio, R., Noce, G., Lopez, S., Rizzo, M., Soricelli, A., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Salvetti, M., Cipollini, V., Franciotti, R., Onofri, M., Fuhr, P., Gschwandtner, U., Ransmayr, G., Aarsland, D., Parnetti, L., Farotti, L., Marizzoni, M., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Yener, G., Emek-Savaş, D. D., Triggiani, A. I., Paul Taylor, J., McKeith, I., Stocchi, F., Vacca, L., Hampel, H., Frisoni, G. B., Bonanni, L., & Babiloni, C. (2020). Abnormalities of resting-state EEG in patients with prodromal and overt dementia with Lewy bodies: Relation to clinical symptoms. *Clin Neurophysiol*, *131*(11), 2716-2731. https://doi.org/10.1016/j.clinph.2020.09.004

Pasquier, J., Michel, B. F., Brenot-Rossi, I., Hassan-Sebbag, N., Sauvan, R., & Gastaut, J. L. (2002). Value of (99m)Tc-ECD SPET for the diagnosis of dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging*, *29*(10), 1342-1348. https://doi.org/10.1007/s00259-002-0919-x

Passamonti, L., Tsvetanov, K. A., Jones, P. S., Bevan-Jones, W. R., Arnold, R., Borchert, R. J., Mak, E., Su, L., O'Brien, J. T., & Rowe, J. B. (2019). Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance. *J Neurosci*, *39*(36), 7218-7226. https://doi.org/10.1523/jneurosci.2574-18.2019

Peever, J., Luppi, P. H., & Montplaisir, J. (2014). Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci*, *37*(5), 279-288. https://doi.org/10.1016/j.tins.2014.02.009

Peraza, L. R., Cromarty, R., Kobeleva, X., Firbank, M. J., Killen, A., Graziadio, S., Thomas, A. J., O'Brien, J. T., & Taylor, J. P. (2018). Electroencephalographic derived network differences in Lewy body dementia compared to Alzheimer's disease patients. *Sci Rep*, *8*(1), 4637. https://doi.org/10.1038/s41598-018-22984-5

Peraza, L. R., Kaiser, M., Firbank, M., Graziadio, S., Bonanni, L., Onofrj, M., Colloby, S. J., Blamire, A., O'Brien, J., & Taylor, J.-P. (2014). fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. *NeuroImage. Clinical*, *4*, 558-565. https://doi.org/10.1016/j.nicl.2014.03.013

Peraza, L. R., Taylor, J. P., & Kaiser, M. (2015). Divergent brain functional network alterations in dementia with Lewy bodies and Alzheimer's disease. *Neurobiol Aging*, *36*(9), 2458-2467. https://doi.org/10.1016/j.neurobiolaging.2015.05.015

Perneczky, R., Drzezga, A., Boecker, H., Förstl, H., Kurz, A., & Häussermann, P. (2008). Cerebral metabolic dysfunction in patients with dementia with Lewy bodies and visual hallucinations. *Dement Geriatr Cogn Disord*, *25*(6), 531-538. https://doi.org/10.1159/000132084

Petrova, M., Mehrabian-Spasova, S., Aarsland, D., Raycheva, M., & Traykov, L. (2015). Clinical and Neuropsychological Differences between Mild Parkinson's Disease Dementia and Dementia with Lewy Bodies. *Dement Geriatr Cogn Dis Extra*, *5*(2), 212-220. https://doi.org/10.1159/000375363

Petrova, M., Pavlova, R., Zhelev, Y., Mehrabian, S., Raycheva, M., & Traykov, L. (2016). Investigation of neuropsychological characteristics of very mild and mild dementia with Lewy bodies. *J Clin Exp Neuropsychol*, *38*(3), 354-360. https://doi.org/10.1080/13803395.2015.1117058

Pezzoli, S., Cagnin, A., Antonini, A., & Venneri, A. (2019). Frontal and subcortical contribution to visual hallucinations in dementia with Lewy bodies and

Parkinson's disease. *Postgrad Med*, *131*(7), 509-522. https://doi.org/10.1080/00325481.2019.1656515

Pezzoli, S., Sánchez-Valle, R., Solanes, A., Kempton, M. J., Bandmann, O., Shin, J. I., Cagnin, A., Goldman, J. G., Merkitch, D., Firbank, M. J., Taylor, J. P., Pagonabarraga, J., Kulisevsky, J., Blanc, F., Verdolini, N., Venneri, A., & Radua, J. (2021). Neuroanatomical and cognitive correlates of visual hallucinations in Parkinson's disease and dementia with Lewy bodies: Voxel-based morphometry and neuropsychological meta-analysis. *Neurosci Biobehav Rev*, *128*, 367-382. https://doi.org/10.1016/j.neubiorev.2021.06.030

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Halliday, G. M., Moustafa, A. A., & Lewis, S. J. G. (2019). Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia With Lewy Bodies. *J Geriatr Psychiatry Neurol*, 891988719882093. https://doi.org/10.1177/0891988719882093

Piarulli, A., Annen, J., Kupers, R., Laureys, S., & Martial, C. (2021). High-Density EEG in a Charles Bonnet Syndrome Patient during and without Visual Hallucinations: A Case-Report Study. *Cells*, *10*(8). https://doi.org/10.3390/cells10081991

Pillai, J. A., Wu, G., Tousi, B., Larvie, M., Léger, G. C., & Leverenz, J. B. (2019). Amygdala sign, a FDG-PET signature of dementia with Lewy Bodies. *Parkinsonism Relat Disord*, *64*, 300-303. https://doi.org/10.1016/j.parkreldis.2019.03.005

Pilotto, A., Imarisio, A., Carrarini, C., Russo, M., Masciocchi, S., Gipponi, S., Cottini, E., Aarsland, D., Zetterberg, H., Ashton, N. J., Hye, A., Bonanni, L., & Padovani, A. (2021). Plasma Neurofilament Light Chain Predicts Cognitive Progression in Prodromal and Clinical Dementia with Lewy Bodies. *J Alzheimers Dis*, *82*(3), 913-919. https://doi.org/10.3233/jad-210342

Pollak, P., Tison, F., Rascol, O., Destée, A., Péré, J. J., Senard, J. M., Durif, F., & Bourdeix, I. (2004). Clozapine in drug induced psychosis in Parkinson's disease:

a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry*, *75*(5), 689-695. https://doi.org/10.1136/jnnp.2003.029868

Pope, E. D., Cordes, L., Shi, J., Mari, Z., Decourt, B., & Sabbagh, M. N. (2021). Dementia with Lewy bodies: emerging drug targets and therapeutics. *Expert Opin Investig Drugs*, *30*(6), 603-609. https://doi.org/10.1080/13543784.2021.1916913

Postuma, R. B., Adler, C. H., Dugger, B. N., Hentz, J. G., Shill, H. A., Driver-Dunckley, E., Sabbagh, M. N., Jacobson, S. A., Belden, C. M., Sue, L. I., Serrano, G., & Beach, T. G. (2015a). REM sleep behavior disorder and neuropathology in Parkinson's disease. *Mov Disord*, *30*(10), 1413-1417. https://doi.org/10.1002/mds.26347

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015b). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*, *30*(12), 1591-1601. https://doi.org/10.1002/mds.26424

Postuma, R. B., Gagnon, J. F., Pelletier, A., & Montplaisir, J. (2013). Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. *Mov Disord*, *28*(5), 597-604. https://doi.org/10.1002/mds.25445

Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., Oertel, W. H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K. Y., Kunz, D., Dauvilliers, Y., Provini, F., Lewis, S. J., Buskova, J., Pavlova, M., Heidbreder, A., Montplaisir, J. Y., Santamaria, J., Barber, T. R., Stefani, A., St Louis, E. K., Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J. F., Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M., Mahlknecht, P., Holzknecht, E., Boeve, A. R., Teigen, L. N., Toscano, G., Mayer, G., Morbelli, S., Dawson, B., & Pelletier, A. (2019). Risk and predictors of

dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*, *142*(3), 744-759. https://doi.org/10.1093/brain/awz030

Pouclet, H., Lebouvier, T., Coron, E., Des Varannes, S. B., Neunlist, M., & Derkinderen, P. (2012). A comparison between colonic submucosa and mucosa to detect Lewy pathology in Parkinson's disease. *Neurogastroenterol Motil*, *24*(4), e202-205. https://doi.org/10.1111/j.1365-2982.2012.01887.x

Price, A., Farooq, R., Yuan, J. M., Menon, V. B., Cardinal, R. N., & O'Brien, J. T. (2017). Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. *BMJ Open*, *7*(11), e017504. https://doi.org/10.1136/bmjopen-2017-017504

Prosser, A. M. J., Tossici-Bolt, L., & Kipps, C. M. (2017). Occipital lobe and posterior cingulate perfusion in the prediction of dementia with Lewy body pathology in a clinical sample. *Nucl Med Commun*, *38*(12), 1029-1035. https://doi.org/10.1097/mnm.0000000000000750

Qian, X., Qiu, Y., He, Q., Lu, Y., Lin, H., Xu, F., Zhu, F., Liu, Z., Li, X., Cao, Y., & Shuai, J. (2021). A Review of Methods for Sleep Arousal Detection Using Polysomnographic Signals. *Brain Sci*, *11*(10). https://doi.org/10.3390/brainsci11101274

Querfurth, H. W., Allam, G. J., Geffroy, M. A., Schiff, H. B., & Kaplan, R. F. (2000). Acetylcholinesterase inhibition in dementia with Lewy bodies: results of a prospective pilot trial. *Dement Geriatr Cogn Disord*, *11*(6), 314-321. https://doi.org/10.1159/000017260

Ramírez-Ruiz, B., Martí, M. J., Tolosa, E., Falcón, C., Bargalló, N., Valldeoriola, F., & Junqué, C. (2008). Brain response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study. *Mov Disord*, *23*(16), 2335-2343. https://doi.org/10.1002/mds.22258

Reitan, R., & Wolfson, D. (1985). The Halstead-Reitan Neuropsychological Test Battery: Therapy and Clinical Interpretation (1985). *Tucson, AZ: Neuropsychological Press*.

Rigby, T., Ashwill, R. T., Johnson, D. K., & Galvin, J. E. (2019). Differences in the Experience of Caregiving Between Spouse and Adult Child Caregivers in Dementia With Lewy Bodies. *Innov Aging*, *3*(3), igz027. https://doi.org/10.1093/geroni/igz027

Rigby, T., Johnson, D. K., Taylor, A., & Galvin, J. E. (2021). Comparison of the Caregiving Experience of Grief, Burden, and Quality of Life in Dementia with Lewy Bodies, Alzheimer's Disease, and Parkinson's Disease Dementia. *J Alzheimers Dis*, *80*(1), 421-432. https://doi.org/10.3233/jad-201326

Roberts, G., Kane, J. P. M., Lloyd, J. J., Petrides, G. S., Howe, K., O'Brien, J. T., & Thomas, A. J. (2019). A comparison of visual and semiquantitative analysis methods for planar cardiac 123I-MIBG scintigraphy in dementia with Lewy bodies. *Nucl Med Commun*, *40*(7), 734-743. https://doi.org/10.1097/mnm.0000000000001024

Roks, G., Korf, E. S., van der Flier, W. M., Scheltens, P., & Stam, C. J. (2008). The use of EEG in the diagnosis of dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*, *79*(4), 377-380. https://doi.org/10.1136/jnnp.2007.125385

Rolinski, M., Fox, C., Maidment, I., & McShane, R. (2012). Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev*(3), Cd006504. https://doi.org/10.1002/14651858.CD006504.pub2

Rongve, A., Soennesyn, H., Skogseth, R., Oesterhus, R., Hortobágyi, T., Ballard, C., Auestad, B. H., & Aarsland, D. (2016). Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. *BMJ Open*, *6*(2), e010357. https://doi.org/10.1136/bmjopen-2015-010357

Rongve, A., Vossius, C., Nore, S., Testad, I., & Aarsland, D. (2014). Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *Int J Geriatr Psychiatry*, *29*(4), 392-398. https://doi.org/10.1002/gps.4015

Rongve, A., Witoelar, A., Ruiz, A., Athanasiu, L., Abdelnour, C., Clarimon, J., Heilmann-Heimbach, S., Hernández, I., Moreno-Grau, S., de Rojas, I., Morenas-Rodríguez, E., Fladby, T., Sando, S. B., Bråthen, G., Blanc, F., Bousiges, O., Lemstra, A. W., van Steenoven, I., Londos, E., Almdahl, I. S., Pålhaugen, L., Eriksen, J. A., Djurovic, S., Stordal, E., Saltvedt, I., Ulstein, I. D., Bettella, F., Desikan, R. S., Idland, A. V., Toft, M., Pihlstrøm, L., Snaedal, J., Tárraga, L., Boada, M., Lleó, A., Stefánsson, H., Stefánsson, K., Ramírez, A., Aarsland, D., & Andreassen, O. A. (2019). GBA and APOE ε4 associate with sporadic dementia with Lewy bodies in European genome wide association study. *Sci Rep, 9*(1), 7013. https://doi.org/10.1038/s41598-019-43458-2

Roselli, F., Pisciotta, N. M., Pennelli, M., Aniello, M. S., Gigante, A., De Caro, M. F., Ferrannini, E., Tartaglione, B., Niccoli-Asabella, A., Defazio, G., Livrea, P., & Rubini, G. (2010). Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. *Mov Disord, 25*(12), 1853-1859. https://doi.org/10.1002/mds.23179

Roselli, F., Pisciotta, N. M., Perneczky, R., Pennelli, M., Aniello, M. S., De Caro, M. F., Ferrannini, E., Tartaglione, B., Defazio, G., Rubini, G., & Livrea, P. (2009). Severity of neuropsychiatric symptoms and dopamine transporter levels in dementia with Lewy bodies: a 123I-FP-CIT SPECT study. *Mov Disord, 24*(14), 2097-2103. https://doi.org/10.1002/mds.22702

Ross, O. A., Toft, M., Whittle, A. J., Johnson, J. L., Papapetropoulos, S., Mash, D. C., Litvan, I., Gordon, M. F., Wszolek, Z. K., Farrer, M. J., & Dickson, D. W. (2006). Lrrk2 and Lewy body disease. *Ann Neurol, 59*(2), 388-393. https://doi.org/10.1002/ana.20731

Sabbagh, M. N., Hake, A. M., Ahmed, S., & Farlow, M. R. (2005). The use of memantine in dementia with Lewy bodies. *J Alzheimers Dis, 7*(4), 285-289. https://doi.org/10.3233/jad-2005-7403

Sakakibara, R., Doi, H., & Fukudo, S. (2019). Lewy body constipation. *J Anus Rectum Colon, 3*(1), 10-17. https://doi.org/10.23922/jarc.2018-022

Sakamoto, F., Shiraishi, S., Yoshida, M., Tomiguchi, S., Hirai, T., Namimoto, T., Hashimoto, M., Ikeda, M., Uetani, H., & Yamashita, Y. (2014). Diagnosis of dementia with Lewy bodies: diagnostic performance of combined ^{123}I-IMP brain perfusion SPECT and ^{123}I-MIBG myocardial scintigraphy. *Ann Nucl Med*, *28*(3), 203-211. https://doi.org/10.1007/s12149-013-0796-3

Salmon, D. P., Heindel, W. C., Hamilton, J. M., Vincent Filoteo, J., Cidambi, V., Hansen, L. A., Masliah, E., & Galasko, D. (2015). Recognition memory span in autopsy-confirmed Dementia with Lewy Bodies and Alzheimer's Disease. *Neuropsychologia*, *75*, 548-555. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2015.07.014

Samuel, W., Alford, M., Hofstetter, C. R., & Hansen, L. (1997). Dementia with Lewy bodies versus pure Alzheimer disease: differences in cognition, neuropathology, cholinergic dysfunction, and synapse density. *J Neuropathol Exp Neurol*, *56*(5), 499-508. https://doi.org/10.1097/00005072-199705000-00006

Sanchez-Castaneda, C., Rene, R., Ramirez-Ruiz, B., Campdelacreu, J., Gascon, J., Falcon, C., Calopa, M., Jauma, S., Juncadella, M., & Junque, C. (2009). Correlations between gray matter reductions and cognitive deficits in dementia with Lewy Bodies and Parkinson's disease with dementia. *Mov Disord*, *24*(12), 1740-1746. https://doi.org/10.1002/mds.22488

Sánchez-Cubillo, I., Periáñez, J. A., Adrover-Roig, D., Rodríguez-Sánchez, J. M., Ríos-Lago, M., Tirapu, J., & Barceló, F. (2009). Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc*, *15*(3), 438-450. https://doi.org/10.1017/s1355617709090626

Sarro, L., Senjem, M. L., Lundt, E. S., Przybelski, S. A., Lesnick, T. G., Graff-Radford, J., Boeve, B. F., Lowe, V. J., Ferman, T. J., Knopman, D. S., Comi, G., Filippi, M., Petersen, R. C., Jack, C. R., Jr., & Kantarci, K. (2016). Amyloid-β deposition and regional grey matter atrophy rates in dementia with Lewy bodies. *Brain*, *139*(Pt 10), 2740-2750. https://doi.org/10.1093/brain/aww193

Sateia, M. J. (2014). International classification of sleep disorders-third edition: highlights and modifications. *Chest*, *146*(5), 1387-1394. https://doi.org/10.1378/chest.14-0970

Scarmeas, N., Albert, M., Brandt, J., Blacker, D., Hadjigeorgiou, G., Papadimitriou, A., Dubois, B., Sarazin, M., Wegesin, D., Marder, K., Bell, K., Honig, L., & Stern, Y. (2005). Motor signs predict poor outcomes in Alzheimer disease. *Neurology*, *64*(10), 1696-1703. https://doi.org/10.1212/01.Wnl.0000162054.15428.E9

Schenck, C. H., Boeve, B. F., & Mahowald, M. W. (2013). Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*, *14*(8), 744-748. https://doi.org/10.1016/j.sleep.2012.10.009

Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., O'Brien, J. T., Blamire, A. M., & Taylor, J. P. (2018). Functional connectivity in dementia with Lewy bodies: A within- and between-network analysis. *Hum Brain Mapp*, *39*(3), 1118-1129. https://doi.org/10.1002/hbm.23901

Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., O'Brien, J. T., Blamire, A. M., & Taylor, J. P. (2019a). Dynamic functional connectivity changes in dementia with Lewy bodies and Alzheimer's disease. *NeuroImage. Clinical*, *22*, 101812. https://doi.org/10.1016/j.nicl.2019.101812

Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., O'Brien, J. T., Blamire, A. M., & Taylor, J. P. (2019b). Dysfunctional brain dynamics and their origin in Lewy body dementia. *Brain*, *142*(6), 1767-1782. https://doi.org/10.1093/brain/awz069

Schumacher, J., Taylor, J. P., Hamilton, C. A., Firbank, M., Cromarty, R. A., Donaghy, P. C., Roberts, G., Allan, L., Lloyd, J., Durcan, R., Barnett, N., O'Brien, J. T., & Thomas, A. J. (2020a). Quantitative EEG as a biomarker in mild cognitive impairment with Lewy bodies. *Alzheimers Res Ther*, *12*(1), 82. https://doi.org/10.1186/s13195-020-00650-1

Schumacher, J., Thomas, A. J., Peraza, L. R., Firbank, M., Cromarty, R., Hamilton, C. A., Donaghy, P. C., O'Brien, J. T., & Taylor, J. P. (2020b). EEG alpha reactivity and cholinergic system integrity in Lewy body dementia and Alzheimer's disease. *Alzheimers Res Ther*, *12*(1), 46. https://doi.org/10.1186/s13195-020-00613-6

Scott, I. U., Schein, O. D., Feuer, W. J., & Folstein, M. F. (2001). Visual hallucinations in patients with retinal disease. *Am J Ophthalmol*, *131*(5), 590-598. https://doi.org/10.1016/s0002-9394(01)00833-9

Seidel, K., Mahlke, J., Siswanto, S., Kruger, R., Heinsen, H., Auburger, G., Bouzrou, M., Grinberg, L. T., Wicht, H., Korf, H. W., den Dunnen, W., & Rub, U. (2015). The brainstem pathologies of Parkinson's disease and dementia with Lewy bodies. *Brain Pathol*, *25*(2), 121-135. https://doi.org/10.1111/bpa.12168

Setó-Salvia, N., Pagonabarraga, J., Houlden, H., Pascual-Sedano, B., Dols-Icardo, O., Tucci, A., Paisán-Ruiz, C., Campolongo, A., Antón-Aguirre, S., Martín, I., Muñoz, L., Bufill, E., Vilageliu, L., Grinberg, D., Cozar, M., Blesa, R., Lleó, A., Hardy, J., Kulisevsky, J., & Clarimón, J. (2012). Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. *Mov Disord*, *27*(3), 393-399. https://doi.org/10.1002/mds.24045

Shahmoradian, S. H., Lewis, A. J., Genoud, C., Hench, J., Moors, T. E., Navarro, P. P., Castaño-Díez, D., Schweighauser, G., Graff-Meyer, A., Goldie, K. N., Sütterlin, R., Huisman, E., Ingrassia, A., Gier, Y., Rozemuller, A. J. M., Wang, J., Paepe, A., Erny, J., Staempfli, A., Hoernschemeyer, J., Großerüschkamp, F., Niedieker, D., El-Mashtoly, S. F., Quadri, M., Van, I. W. F. J., Bonifati, V., Gerwert, K., Bohrmann, B., Frank, S., Britschgi, M., Stahlberg, H., Van de Berg, W. D. J., & Lauer, M. E. (2019). Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes. *Nat Neurosci*, *22*(7), 1099-1109. https://doi.org/10.1038/s41593-019-0423-2

Shams, S., Fällmar, D., Schwarz, S., Wahlund, L. O., van Westen, D., Hansson, O., Larsson, E. M., & Haller, S. (2017). MRI of the Swallow Tail Sign: A Useful

Marker in the Diagnosis of Lewy Body Dementia? *AJNR Am J Neuroradiol, 38*(9), 1737-1741. https://doi.org/10.3174/ajnr.A5274

Shannon, K. M., Keshavarzian, A., Dodiya, H. B., Jakate, S., & Kordower, J. H. (2012a). Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? Evidence from 3 cases. *Mov Disord, 27*(6), 716-719. https://doi.org/10.1002/mds.25020

Shannon, K. M., Keshavarzian, A., Mutlu, E., Dodiya, H. B., Daian, D., Jaglin, J. A., & Kordower, J. H. (2012b). Alpha-synuclein in colonic submucosa in early untreated Parkinson's disease. *Mov Disord, 27*(6), 709-715. https://doi.org/10.1002/mds.23838

Sharp, S. I., Ballard, C. G., Ziabreva, I., Piggott, M. A., Perry, R. H., Perry, E. K., Aarsland, D., Ehrt, U., Larsen, J. P., & Francis, P. T. (2008). Cortical serotonin 1A receptor levels are associated with depression in patients with dementia with Lewy bodies and Parkinson's disease dementia. *Dement Geriatr Cogn Disord, 26*(4), 330-338. https://doi.org/10.1159/000161058

Shimizu, S., Hirao, K., Kanetaka, H., Namioka, N., Hatanaka, H., Hirose, D., Fukasawa, R., Umahara, T., Sakurai, H., & Hanyu, H. (2016). Utility of the combination of DAT SPECT and MIBG myocardial scintigraphy in differentiating dementia with Lewy bodies from Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 43*(1), 184-192. https://doi.org/10.1007/s00259-015-3146-y

Shin, J., Park, S. H., Shin, C., Kim, J. H., Yun, T. J., Kim, H. J., & Jeon, B. (2019). Submandibular gland is a suitable site for alpha synuclein pathology in Parkinson disease. *Parkinsonism Relat Disord, 58*, 35-39. https://doi.org/10.1016/j.parkreldis.2018.04.019

Shine, J. M., Halliday, G. H., Carlos, M., Naismith, S. L., & Lewis, S. J. (2012). Investigating visual misperceptions in Parkinson's disease: a novel behavioral paradigm. *Mov Disord, 27*(4), 500-505. https://doi.org/10.1002/mds.24900

Shine, J. M., Halliday, G. M., Gilat, M., Matar, E., Bolitho, S. J., Carlos, M., Naismith, S. L., & Lewis, S. J. (2014a). The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Hum Brain Mapp*, *35*(5), 2206-2219. https://doi.org/10.1002/hbm.22321

Shine, J. M., Halliday, G. M., Naismith, S. L., & Lewis, S. J. (2011). Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? *Mov Disord*, *26*(12), 2154-2159. https://doi.org/10.1002/mds.23896

Shine, J. M., Keogh, R., O'Callaghan, C., Muller, A. J., Lewis, S. J., & Pearson, J. (2015a). Imagine that: elevated sensory strength of mental imagery in individuals with Parkinson's disease and visual hallucinations. *Proc Biol Sci*, *282*(1798), 20142047. https://doi.org/10.1098/rspb.2014.2047

Shine, J. M., Mills, J. M. Z., Qiu, J., O'Callaghan, C., Terpening, Z., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2015b). Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease. *Movement Disorders Clinical Practice*, *2*(2), 175-181.

Shine, J. M., Muller, A. J., O'Callaghan, C., Hornberger, M., Halliday, G. M., & Lewis, S. J. (2015c). Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. *NPJ Parkinsons Dis*, *1*, 15003. https://doi.org/10.1038/npjparkd.2015.3

Shine, J. M., O'Callaghan, C., Halliday, G. M., & Lewis, S. J. (2014b). Tricks of the mind: Visual hallucinations as disorders of attention. *Prog Neurobiol*, *116*, 58-65. https://doi.org/10.1016/j.pneurobio.2014.01.004

Shiner, T., Mirelman, A., Gana Weisz, M., Bar-Shira, A., Ash, E., Cialic, R., Nevler, N., Gurevich, T., Bregman, N., Orr-Utreger, A., & Giladi, N. (2016). High Frequency of GBA Gene Mutations in Dementia With Lewy Bodies Among Ashkenazi Jews. *JAMA Neurol*, *73*(12), 1448-1453. https://doi.org/10.1001/jamaneurol.2016.1593

Shiner, T., Mirelman, A., Rosenblum, Y., Kavé, G., Weisz, M. G., Bar-Shira, A., Goldstein, O., Thaler, A., Gurevich, T., Orr-Urtreger, A., Giladi, N., & Bregman, N. (2021). The Effect of GBA Mutations and APOE Polymorphisms on Dementia with Lewy Bodies in Ashkenazi Jews. *J Alzheimers Dis*, *80*(3), 1221-1229. https://doi.org/10.3233/jad-201295

Shirvan, J., Clement, N., Ye, R., Katz, S., Schultz, A., Johnson, K. A., Gomez-Isla, T., Frosch, M., Growdon, J. H., & Gomperts, S. N. (2019). Neuropathologic correlates of amyloid and dopamine transporter imaging in Lewy body disease. *Neurology*, *93*(5), e476-e484. https://doi.org/10.1212/wnl.0000000000007855

Siderowf, A., Pontecorvo, M. J., Shill, H. A., Mintun, M. A., Arora, A., Joshi, A. D., Lu, M., Adler, C. H., Galasko, D., Liebsack, C., Skovronsky, D. M., & Sabbagh, M. N. (2014). PET imaging of amyloid with Florbetapir F 18 and PET imaging of dopamine degeneration with 18F-AV-133 (florbenazine) in patients with Alzheimer's disease and Lewy body disorders. BMC Neurol, 14, 79. https://doi.org/10.1186/1471-2377-14-79

Sidransky, E., & Lopez, G. (2012). The link between the GBA gene and parkinsonism. *Lancet Neurol*, *11*(11), 986-998. https://doi.org/10.1016/s1474-4422(12)70190-4

Sidransky, E., Nalls, M. A., Aasly, J. O., Aharon-Peretz, J., Annesi, G., Barbosa, E. R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., Chen, C. M., Clark, L. N., Condroyer, C., De Marco, E. V., Dürr, A., Eblan, M. J., Fahn, S., Farrer, M. J., Fung, H. C., Gan-Or, Z., Gasser, T., Gershoni-Baruch, R., Giladi, N., Griffith, A., Gurevich, T., Januario, C., Kropp, P., Lang, A. E., Lee-Chen, G. J., Lesage, S., Marder, K., Mata, I. F., Mirelman, A., Mitsui, J., Mizuta, I., Nicoletti, G., Oliveira, C., Ottman, R., Orr-Urtreger, A., Pereira, L. V., Quattrone, A., Rogaeva, E., Rolfs, A., Rosenbaum, H., Rozenberg, R., Samii, A., Samaddar, T., Schulte, C., Sharma, M., Singleton, A., Spitz, M., Tan, E. K., Tayebi, N., Toda, T., Troiano, A. R., Tsuji, S., Wittstock, M., Wolfsberg, T. G., Wu, Y. R., Zabetian, C. P., Zhao, Y., & Ziegler, S. G. (2009). Multicenter analysis of glucocerebrosidase mutations in

Parkinson's disease. *N Engl J Med*, *361*(17), 1651-1661. https://doi.org/10.1056/NEJMoa0901281

Siepel, F. J., Dalen, I., Grüner, R., Booij, J., Brønnick, K. S., Buter, T. C., & Aarsland, D. (2016). Loss of Dopamine Transporter Binding and Clinical Symptoms in Dementia With Lewy Bodies. *Mov Disord*, *31*(1), 118-125. https://doi.org/10.1002/mds.26327

Siepel, F. J., Rongve, A., Buter, T. C., Beyer, M. K., Ballard, C. G., Booij, J., & Aarsland, D. (2013). (123I)FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study. *BMJ Open*, *3*(4). https://doi.org/10.1136/bmjopen-2013-002642

Simard, M., van Reekum, R., & Myran, D. (2003). Visuospatial impairment in dementia with Lewy bodies and Alzheimer's disease: a process analysis approach. *Int J Geriatr Psychiatry*, *18*(5), 387-391. https://doi.org/10.1002/gps.839

Simard, M., van Reekum, R., Myran, D., Panisset, M., Cohen, T., Freedman, M., Black, S., & Suvajac, B. (2002). Differential memory impairment in dementia with Lewy bodies and Alzheimer's disease. *Brain Cogn*, *49*(2), 244-249.

Singh, A., Zhi, L., & Zhang, H. (2019). LRRK2 and mitochondria: Recent advances and current views. *Brain Res*, *1702*, 96-104. https://doi.org/10.1016/j.brainres.2018.06.010

Sinha, N., Firbank, M., & O'Brien, J. T. (2012). Biomarkers in dementia with Lewy bodies: a review. Int J Geriatr Psychiatry, 27(5), 443-453. https://doi.org/10.1002/gps.2749

Slaets, S., Van Acker, F., Versijpt, J., Hauth, L., Goeman, J., Martin, J. J., De Deyn, P. P., & Engelborghs, S. (2015). Diagnostic value of MIBG cardiac scintigraphy for differential dementia diagnosis. *Int J Geriatr Psychiatry*, *30*(8), 864-869. https://doi.org/10.1002/gps.4229

Small, D. M., Gitelman, D. R., Gregory, M. D., Nobre, A. C., Parrish, T. B., & Mesulam, M. M. (2003). The posterior cingulate and medial prefrontal cortex mediate the

anticipatory allocation of spatial attention. *Neuroimage, 18*(3), 633-641. https://doi.org/10.1016/s1053-8119(02)00012-5

Smirnov, D. S., Galasko, D., Edland, S. D., Filoteo, J. V., Hansen, L. A., & Salmon, D. P. (2020). Cognitive decline profiles differ in Parkinson disease dementia and dementia with Lewy bodies. *Neurology, 94*(20), e2076-e2087. https://doi.org/10.1212/wnl.0000000000009434

Smith, R., Schöll, M., Londos, E., Ohlsson, T., & Hansson, O. (2018). (18)F-AV-1451 in Parkinson's Disease with and without dementia and in Dementia with Lewy Bodies. *Sci Rep, 8*(1), 4717. https://doi.org/10.1038/s41598-018-23041-x

Smitha, K. A., Akhil Raja, K., Arun, K. M., Rajesh, P. G., Thomas, B., Kapilamoorthy, T. R., & Kesavadas, C. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *Neuroradiol J, 30*(4), 305-317. https://doi.org/10.1177/1971400917697342

Smits, L. L., van Harten, A. C., Pijnenburg, Y. A., Koedam, E. L., Bouwman, F. H., Sistermans, N., Reuling, I. E., Prins, N. D., Lemstra, A. W., Scheltens, P., & van der Flier, W. M. (2015). Trajectories of cognitive decline in different types of dementia. *Psychol Med, 45*(5), 1051-1059. https://doi.org/10.1017/s0033291714002153

Spillantini, M. G., Schmidt, M. L., Lee, V. M. Y., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). α-Synuclein in Lewy bodies. *Nature, 388*(6645), 839-840. https://doi.org/10.1038/42166

St Louis, E. K., & Boeve, B. F. (2017). REM Sleep Behavior Disorder: Diagnosis, Clinical Implications, and Future Directions. *Mayo Clin Proc, 92*(11), 1723-1736. https://doi.org/10.1016/j.mayocp.2017.09.007

Stefani, A., Mahlknecht, P., Seppi, K., Nocker, M., Mair, K. J., Hotter, A., Stockner, H., Willeit, J., Kiechl, S., Rungger, G., Gasperi, A., Poewe, W., & Högl, B. (2017). Consistency of "Probable RBD" Diagnosis with the RBD Screening Questionnaire: A Follow-up Study. *Mov Disord Clin Pract, 4*(3), 403-405. https://doi.org/10.1002/mdc3.12448

Stefani, A., Santamaria, J., Iranzo, A., Hackner, H., Schenck, C. H., & Högl, B. (2021). Nelotanserin as symptomatic treatment for rapid eye movement sleep behavior disorder: a double-blind randomized study using video analysis in patients with dementia with Lewy bodies or Parkinson's disease dementia. *Sleep Med*, *81*, 180-187. https://doi.org/10.1016/j.sleep.2021.02.038

Stiasny-Kolster, K., Mayer, G., Schafer, S., Moller, J. C., Heinzel-Gutenbrunner, M., & Oertel, W. H. (2007). The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. *Mov Disord*, *22*(16), 2386-2393. https://doi.org/10.1002/mds.21740

Stinton, C., McKeith, I., Taylor, J. P., Lafortune, L., Mioshi, E., Mak, E., Cambridge, V., Mason, J., Thomas, A., & O'Brien, J. T. (2015). Pharmacological Management of Lewy Body Dementia: A Systematic Review and Meta-Analysis. *Am J Psychiatry*, *172*(8), 731-742. https://doi.org/10.1176/appi.ajp.2015.14121582

Stocchi, F., & Torti, M. (2017). Constipation in Parkinson's Disease. *Int Rev Neurobiol*, *134*, 811-826. https://doi.org/10.1016/bs.irn.2017.06.003

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Pyschology*, *11*, 643-662. https://doi.org/10.1037/h0054651

Stylianou, M., Murphy, N., Peraza, L. R., Graziadio, S., Cromarty, R., Killen, A., O' Brien, J. T., Thomas, A. J., LeBeau, F. E. N., & Taylor, J.-P. (2018). Quantitative electroencephalography as a marker of cognitive fluctuations in dementia with Lewy bodies and an aid to differential diagnosis. *Clinical Neurophysiology*, *129*(6), 1209-1220. https://doi.org/10.1016/j.clinph.2018.03.013

Suárez-González, A., Serrano-Pozo, A., Arroyo-Anlló, E. M., Franco-Macías, E., Polo, J., García-Solís, D., & Gil-Néciga, E. (2014). Utility of neuropsychiatric tools in the differential diagnosis of dementia with Lewy bodies and Alzheimer's disease: quantitative and qualitative findings. *Int Psychogeriatr*, *26*(3), 453-461. https://doi.org/10.1017/s1041610213002068

Sumi, Y., Ubara, A., Ozeki, Y., & Kadotani, H. (2021). Minor hallucinations in isolated rapid eye movement sleep behavior disorder indicative of early

phenoconversion: A preliminary study. *Acta Neurol Scand*. https://doi.org/10.1111/ane.13555

Surendranathan, A., Kane, J. P. M., Bentley, A., Barker, S. A. H., Taylor, J. P., Thomas, A. J., Allan, L. M., McNally, R. J., James, P. W., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2020). Clinical diagnosis of Lewy body dementia. *BJPsych Open*, *6*(4), e61. https://doi.org/10.1192/bjo.2020.44

Surendranathan, A., Rowe, J. B., & O'Brien, J. T. (2015). Neuroinflammation in Lewy body dementia. *Parkinsonism Relat Disord*, *21*(12), 1398-1406. https://doi.org/10.1016/j.parkreldis.2015.10.009

Surendranathan, A., Su, L., Mak, E., Passamonti, L., Hong, Y. T., Arnold, R., Vázquez Rodríguez, P., Bevan-Jones, W. R., Brain, S. A. E., Fryer, T. D., Aigbirhio, F. I., Rowe, J. B., & O'Brien, J. T. (2018). Early microglial activation and peripheral inflammation in dementia with Lewy bodies. *Brain*, *141*(12), 3415-3427. https://doi.org/10.1093/brain/awy265

Svendsboe, E., Terum, T., Testad, I., Aarsland, D., Ulstein, I., Corbett, A., & Rongve, A. (2016). Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*, *31*(9), 1075-1083. https://doi.org/10.1002/gps.4433

Szot, P., White, S. S., Greenup, J. L., Leverenz, J. B., Peskind, E. R., & Raskind, M. A. (2006). Compensatory changes in the noradrenergic nervous system in the locus ceruleus and hippocampus of postmortem subjects with Alzheimer's disease and dementia with Lewy bodies. *J Neurosci*, *26*(2), 467-478. https://doi.org/10.1523/jneurosci.4265-05.2006

Taguchi, T., Ikuno, M., Hondo, M., Parajuli, L. K., Taguchi, K., Ueda, J., Sawamura, M., Okuda, S., Nakanishi, E., Hara, J., Uemura, N., Hatanaka, Y., Ayaki, T., Matsuzawa, S., Tanaka, M., El-Agnaf, O. M. A., Koike, M., Yanagisawa, M., Uemura, M. T., Yamakado, H., & Takahashi, R. (2020). α-Synuclein BAC transgenic mice exhibit RBD-like behaviour and hyposmia: a prodromal

Parkinson's disease model. *Brain*, *143*(1), 249-265. https://doi.org/10.1093/brain/awz380

Tak, K., Lee, S., Choi, E., Suh, S. W., Oh, D. J., Moon, W., Kim, H. S., Byun, S., Bae, J. B., Han, J. W., Kim, J. H., & Kim, K. W. (2020). Magnetic Resonance Imaging Texture of Medial Pulvinar in Dementia with Lewy Bodies. *Dement Geriatr Cogn Disord*, *49*(1), 8-15. https://doi.org/10.1159/000506798

Takeuchi, N., Uchimura, N., Hashizume, Y., Mukai, M., Etoh, Y., Yamamoto, K., Kotorii, T., Ohshima, H., Ohshima, M., & Maeda, H. (2001). Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci*, *55*(3), 267-269. https://doi.org/10.1046/j.1440-1819.2001.00854.x

Tam, C. W., Burton, E. J., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2005). Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. *Neurology*, *64*(5), 861-865. https://doi.org/10.1212/01.Wnl.0000153070.82309.D4

Tariot, P. N., Cummings, J. L., Soto-Martin, M. E., Ballard, C., Erten-Lyons, D., Sultzer, D. L., Devanand, D. P., Weintraub, D., McEvoy, B., Youakim, J. M., Stankovic, S., & Foff, E. P. (2021). Trial of Pimavanserin in Dementia-Related Psychosis. *N Engl J Med*, *385*(4), 309-319. https://doi.org/10.1056/NEJMoa2034634

Tayebi, N., Callahan, M., Madike, V., Stubblefield, B. K., Orvisky, E., Krasnewich, D., Fillano, J. J., & Sidransky, E. (2001). Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. *Mol Genet Metab*, *73*(4), 313-321. https://doi.org/10.1006/mgme.2001.3201

Tayebi, N., Walker, J., Stubblefield, B., Orvisky, E., LaMarca, M. E., Wong, K., Rosenbaum, H., Schiffmann, R., Bembi, B., & Sidransky, E. (2003). Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? *Mol Genet Metab*, *79*(2), 104-109. https://doi.org/10.1016/s1096-7192(03)00071-4

Taylor, J. P., Colloby, S. J., McKeith, I. G., Burn, D. J., Williams, D., Patterson, J., & O'Brien, J. T. (2007). Cholinesterase inhibitor use does not significantly

influence the ability of 123I-FP-CIT imaging to distinguish Alzheimer's disease from dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*, *78*(10), 1069-1071. https://doi.org/10.1136/jnnp.2006.111666

Taylor, J. P., Firbank, M. J., He, J., Barnett, N., Pearce, S., Livingstone, A., Vuong, Q., McKeith, I. G., & O'Brien, J. T. (2012). Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study. *Br J Psychiatry*, *200*(6), 491-498. https://doi.org/10.1192/bjp.bp.111.099432

Thomas, A. J., Attems, J., Colloby, S. J., O'Brien, J. T., McKeith, I., Walker, R., Lee, L., Burn, D., Lett, D. J., & Walker, Z. (2017). Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. *Neurology*, *88*(3), 276-283. https://doi.org/10.1212/wnl.0000000000003512

Thomas, A. J., Donaghy, P., Roberts, G., Colloby, S. J., Barnett, N. A., Petrides, G., Lloyd, J., Olsen, K., Taylor, J. P., McKeith, I., & O'Brien, J. T. (2019). Diagnostic accuracy of dopaminergic imaging in prodromal dementia with Lewy bodies. *Psychol Med*, *49*(3), 396-402. https://doi.org/10.1017/s0033291718000995

Tilley, B. S., Patel, S. R., Goldfinger, M. H., Pearce, R. K. B., & Gentleman, S. M. (2021). Locus Coeruleus Pathology Indicates a Continuum of Lewy Body Dementia. *J Parkinsons Dis*. https://doi.org/10.3233/jpd-212748

Tiraboschi, P., Hansen, L. A., Alford, M., Merdes, M. D., Masliah, E., Thal, L. J., & Cory-Bloom, J. (2002). Early and widespread cholinergic losses differentiate dementia with lewy bodies from alzheimer disease. *Arch Gen Psychiatry*, *59*(10), 946-951. https://doi.org/10.1001/archpsyc.59.10.946

Tiraboschi, P., Hansen, L. A., Alford, M., Sabbagh, M. N., Schoos, B., Masliah, E., Thal, L. J., & Corey-Bloom, J. (2000). Cholinergic dysfunction in diseases with Lewy bodies. *Neurology*, *54*(2), 407-411. https://doi.org/10.1212/wnl.54.2.407

Torontali, Z. A., Fraigne, J. J., Sanghera, P., Horner, R., & Peever, J. (2019). The Sublaterodorsal Tegmental Nucleus Functions to Couple Brain State and Motor Activity during REM Sleep and Wakefulness. *Curr Biol*, *29*(22), 3803-3813.e3805. https://doi.org/10.1016/j.cub.2019.09.026

Treglia, G., & Cason, E. (2012). Diagnostic performance of myocardial innervation imaging using MIBG scintigraphy in differential diagnosis between dementia with lewy bodies and other dementias: a systematic review and a meta-analysis. *J Neuroimaging*, *22*(2), 111-117. https://doi.org/10.1111/j.1552-6569.2010.00532.x

Trudler, D., Sanz-Blasco, S., Eisele, Y. S., Ghatak, S., Bodhinathan, K., Akhtar, M. W., Lynch, W. P., Piña-Crespo, J. C., Talantova, M., Kelly, J. W., & Lipton, S. A. (2021). α-Synuclein Oligomers Induce Glutamate Release from Astrocytes and Excessive Extrasynaptic NMDAR Activity in Neurons, Thus Contributing to Synapse Loss. *J Neurosci*, *41*(10), 2264-2273. https://doi.org/10.1523/jneurosci.1871-20.2020

Uchiyama, M., Nishio, Y., Yokoi, K., Hirayama, K., Imamura, T., Shimomura, T., & Mori, E. (2012). Pareidolias: complex visual illusions in dementia with Lewy bodies. *Brain*, *135*(Pt 8), 2458-2469. https://doi.org/10.1093/brain/aws126

Urwyler, P., Nef, T., Killen, A., Collerton, D., Thomas, A., Burn, D., McKeith, I., & Mosimann, U. P. (2014). Visual complaints and visual hallucinations in Parkinson's disease. *Parkinsonism Relat Disord*, *20*(3), 318-322. https://doi.org/10.1016/j.parkreldis.2013.12.009

Usenko, T. S., Nikolaev, M. A., Miliukhina, I. V., Bezrukova, A. I., Senkevich, K. A., Gomzyakova, N. A., Beltceva, Y. A., Zalutskaya, N. M., Gracheva, E. V., Timofeeva, A. A., Petrova, O. A., Semenov, A. V., Lubimova, N. E., Totolyan, A. A., & Pchelina, S. N. (2020). Plasma cytokine profile in synucleinophaties with dementia. *J Clin Neurosci*, *78*, 323-326. https://doi.org/10.1016/j.jocn.2020.04.058

van de Beek, M., van Steenoven, I., van der Zande, J. J., Barkhof, F., Teunissen, C. E., van der Flier, W. M., & Lemstra, A. W. (2020). Prodromal Dementia With Lewy Bodies: Clinical Characterization and Predictors of Progression. *Mov Disord*, *35*(5), 859-867. https://doi.org/10.1002/mds.27997

van de Beek, M., van Unnik, A., van Steenoven, I., van der Zande, J., Barkhof, F., Teunissen, C. E., van der Flier, W., & Lemstra, A. W. (2022). Disease progression in dementia with Lewy bodies: A longitudinal study on clinical symptoms, quality of life and functional impairment. Int J Geriatr Psychiatry, 37(12). https://doi.org/10.1002/gps.5839

van Dellen, E., de Waal, H., van der Flier, W. M., Lemstra, A. W., Slooter, A. J., Smits, L. L., van Straaten, E. C., Stam, C. J., & Scheltens, P. (2015). Loss of EEG Network Efficiency Is Related to Cognitive Impairment in Dementia With Lewy Bodies. *Mov Disord*, *30*(13), 1785-1793. https://doi.org/10.1002/mds.26309

van der Zande, J. J., Booij, J., Scheltens, P., Raijmakers, P. G., & Lemstra, A. W. (2016). [(123)]FP-CIT SPECT scans initially rated as normal became abnormal over time in patients with probable dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging*, *43*(6), 1060-1066. https://doi.org/10.1007/s00259-016-3312-x

van der Zande, J. J., Gouw, A. A., van Steenoven, I., Scheltens, P., Stam, C. J., & Lemstra, A. W. (2018a). EEG Characteristics of Dementia With Lewy Bodies, Alzheimer's Disease and Mixed Pathology. *Front Aging Neurosci*, *10*, 190. https://doi.org/10.3389/fnagi.2018.00190

van der Zande, J. J., Gouw, A. A., van Steenoven, I., van de Beek, M., Scheltens, P., Stam, C. J., & Lemstra, A. W. (2020a). Diagnostic and prognostic value of EEG in prodromal dementia with Lewy bodies. *Neurology*, *95*(6), e662-e670. https://doi.org/10.1212/wnl.0000000000009977

van der Zande, J. J., Joling, M., Happach, I. G., Vriend, C., Scheltens, P., Booij, J., & Lemstra, A. W. (2020b). Serotonergic deficits in dementia with Lewy bodies with concomitant Alzheimer's disease pathology: An (123)I-FP-CIT SPECT study. *NeuroImage. Clinical*, *25*, 102062. https://doi.org/10.1016/j.nicl.2019.102062

van der Zande, J. J., Steenwijk, M. D., Ten Kate, M., Wattjes, M. P., Scheltens, P., & Lemstra, A. W. (2018b). Gray matter atrophy in dementia with Lewy bodies

with and without concomitant Alzheimer's disease pathology. *Neurobiol Aging*, *71*, 171-178. https://doi.org/10.1016/j.neurobiolaging.2018.07.005

van Harten, A. C., Kester, M. I., Visser, P. J., Blankenstein, M. A., Pijnenburg, Y. A., van der Flier, W. M., & Scheltens, P. (2011). Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. *Clin Chem Lab Med*, *49*(3), 353-366. https://doi.org/10.1515/cclm.2011.086

van Steenoven, I., van der Flier, W. M., Scheltens, P., Teunissen, C. E., & Lemstra, A. W. (2019). Amyloid-β peptides in cerebrospinal fluid of patients with dementia with Lewy bodies. *Alzheimers Res Ther*, *11*(1), 83. https://doi.org/10.1186/s13195-019-0537-5

Vann Jones, S. A., & O'Brien, J. T. (2014). The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med*, *44*(4), 673-683. https://doi.org/10.1017/s0033291713000494

Vermeiren, Y., & De Deyn, P. P. (2017). Targeting the norepinephrinergic system in Parkinson's disease and related disorders: The locus coeruleus story. *Neurochem Int*, *102*, 22-32. https://doi.org/10.1016/j.neuint.2016.11.009

Vernet, M., Quentin, R., Chanes, L., Mitsumasu, A., & Valero-Cabré, A. (2014). Frontal eye field, where art thou? Anatomy, function, and non-invasive manipulation of frontal regions involved in eye movements and associated cognitive operations. *Front Integr Neurosci*, *8*, 66. https://doi.org/10.3389/fnint.2014.00066

Villemagne, V. L., Okamura, N., Pejoska, S., Drago, J., Mulligan, R. S., Chételat, G., O'Keefe, G., Jones, G., Kung, H. F., Pontecorvo, M., Masters, C. L., Skovronsky, D. M., & Rowe, C. C. (2012). Differential diagnosis in Alzheimer's disease and dementia with Lewy bodies via VMAT2 and amyloid imaging. Neurodegener Dis, 10(1-4), 161-165. https://doi.org/10.1159/000334535

Visanji, N. P., Marras, C., Kern, D. S., Al Dakheel, A., Gao, A., Liu, L. W., Lang, A. E., & Hazrati, L. N. (2015). Colonic mucosal a-synuclein lacks specificity as a biomarker for Parkinson disease. *Neurology*, *84*(6), 609-616. https://doi.org/10.1212/wnl.0000000000001240

Visser, F., Apostolov, V. I., Vlaar, A. M. M., Twisk, J. W. R., Weinstein, H. C., & Berendse, H. W. (2020). Visual hallucinations in Parkinson's disease are associated with thinning of the inner retina. *Sci Rep*, *10*(1), 21110. https://doi.org/10.1038/s41598-020-77833-1

Visser, M., Verbaan, D., van Rooden, S. M., Stiggelbout, A. M., Marinus, J., & van Hilten, J. J. (2007). Assessment of psychiatric complications in Parkinson's disease: The SCOPA-PC. *Mov Disord*, *22*(15), 2221-2228. https://doi.org/10.1002/mds.21696

Vivacqua, G., Latorre, A., Suppa, A., Nardi, M., Pietracupa, S., Mancinelli, R., Fabbrini, G., Colosimo, C., Gaudio, E., & Berardelli, A. (2016). Abnormal Salivary Total and Oligomeric Alpha-Synuclein in Parkinson's Disease. *PLoS One*, *11*(3), e0151156. https://doi.org/10.1371/journal.pone.0151156

Volpicelli-Daley, L. A., Luk, K. C., Patel, T. P., Tanik, S. A., Riddle, D. M., Stieber, A., Meaney, D. F., Trojanowski, J. Q., & Lee, V. M. (2011). Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron*, *72*(1), 57-71. https://doi.org/10.1016/j.neuron.2011.08.033

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. *Neuroscientist*, *20*(2), 150-159. https://doi.org/10.1177/1073858413494269

Wada-Isoe, K., Kitayama, M., Nakaso, K., & Nakashima, K. (2007). Diagnostic markers for diagnosing dementia with Lewy bodies: CSF and MIBG cardiac scintigraphy study. *J Neurol Sci*, *260*(1-2), 33-37. https://doi.org/10.1016/j.jns.2007.03.016

Wajman, J. R., Cecchini, M. A., Bertolucci, P. H. F., & Mansur, L. L. (2019). Quanti-qualitative components of the semantic verbal fluency test in cognitively healthy controls, mild cognitive impairment, and dementia subtypes. *Appl Neuropsychol Adult*, *26*(6), 533-542. https://doi.org/10.1080/23279095.2018.1465426

Walker, E. P., & Tadi, P. (2021). Neuroanatomy, Nucleus Raphe. In *StatPearls*. StatPearls Publishing.

Walker, L., McAleese, K. E., Thomas, A. J., Johnson, M., Martin-Ruiz, C., Parker, C., Colloby, S. J., Jellinger, K., & Attems, J. (2015a). Neuropathologically mixed Alzheimer's and Lewy body disease: burden of pathological protein aggregates differs between clinical phenotypes. *Acta Neuropathol*, *129*(5), 729-748. https://doi.org/10.1007/s00401-015-1406-3

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000a). The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale: Two methods to assess fluctuating confusion in dementia. *British Journal of Psychiatry*, *177*(3), 252-256. https://doi.org/10.1192/bjp.177.3.252

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000b). Quantifying fluctuation in dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. *Neurology*, *54*(8), 1616-1625. https://doi.org/10.1212/wnl.54.8.1616

Walker, Z., Costa, D. C., Ince, P., McKeith, I. G., & Katona, C. L. (1999). In-vivo demonstration of dopaminergic degeneration in dementia with Lewy bodies. *Lancet*, *354*(9179), 646-647. https://doi.org/10.1016/s0140-6736(99)01178-2

Walker, Z., Costa, D. C., Walker, R. W., Lee, L., Livingston, G., Jaros, E., Perry, R., McKeith, I., & Katona, C. L. (2004). Striatal dopamine transporter in dementia with Lewy bodies and Parkinson disease: a comparison. *Neurology*, *62*(9), 1568-1572. https://doi.org/10.1212/01.wnl.0000123248.39847.1d

Walker, Z., Costa, D. C., Walker, R. W., Shaw, K., Gacinovic, S., Stevens, T., Livingston, G., Ince, P., McKeith, I. G., & Katona, C. L. (2002). Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. *J Neurol Neurosurg Psychiatry*, *73*(2), 134-140. https://doi.org/10.1136/jnnp.73.2.134

Walker, Z., Moreno, E., Thomas, A., Inglis, F., Tabet, N., Rainer, M., Pizzolato, G., & Padovani, A. (2015b). Clinical usefulness of dopamine transporter SPECT imaging with 123I-FP-CIT in patients with possible dementia with Lewy bodies: randomised study. *Br J Psychiatry*, *206*(2), 145-152. https://doi.org/10.1192/bjp.bp.114.148643

Wang, H. F., Yu, J. T., Tang, S. W., Jiang, T., Tan, C. C., Meng, X. F., Wang, C., Tan, M. S., & Tan, L. (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry*, *86*(2), 135-143. https://doi.org/10.1136/jnnp-2014-307659

Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., Li, K., & Jiang, T. (2007). Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Hum Brain Mapp*, *28*(10), 967-978. https://doi.org/10.1002/hbm.20324

Wang, Z., Becker, K., Donadio, V., Siedlak, S., Yuan, J., Rezaee, M., Incensi, A., Kuzkina, A., Orrú, C. D., Tatsuoka, C., Liguori, R., Gunzler, S. A., Caughey, B., Jimenez-Capdeville, M. E., Zhu, X., Doppler, K., Cui, L., Chen, S. G., Ma, J., & Zou, W. Q. (2020). Skin α-Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease. *JAMA Neurol*, *78*(1), 1-11. https://doi.org/10.1001/jamaneurol.2020.3311

Warden, C., Hwang, J., Marshall, A., Fenesy, M., & Poston, K. L. (2016). The effects of dopamine on digit span in Parkinson's disease. *J Clin Mov Disord*, *3*, 5. https://doi.org/10.1186/s40734-016-0033-z

Warrington, E. K., James, M. (1991). *The Visual Object and Space Perception Battery*. Thames Valley Test Company.

Watson, R., Blamire, A. M., Colloby, S. J., Wood, J. S., Barber, R., He, J., & O'Brien, J. T. (2012). Characterizing dementia with Lewy bodies by means of diffusion tensor imaging. *Neurology*, *79*(9), 906-914. https://doi.org/10.1212/WNL.0b013e318266fc51

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition: Administration and scoring manual*. NCS Pearson.

Weil, R. S., Schrag, A. E., Warren, J. D., Crutch, S. J., Lees, A. J., & Morris, H. R. (2016). Visual dysfunction in Parkinson's disease. *Brain*, *139*(11), 2827-2843. https://doi.org/10.1093/brain/aww175

Weintraub, D., Chen, P., Ignacio, R. V., Mamikonyan, E., & Kales, H. C. (2011). Patterns and Trends in Antipsychotic Prescribing for Parkinson Disease Psychosis. *Archives of neurology (Chicago)*, *68*(7), 899-904. https://doi.org/10.1001/archneurol.2011.139

Weintraub, D., Chiang, C., Kim, H. M., Wilkinson, J., Marras, C., Stanislawski, B., Mamikonyan, E., & Kales, H. C. (2016). Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease. *JAMA Neurol*, *73*(5), 535-541. https://doi.org/10.1001/jamaneurol.2016.0031

Westervelt, H. J., Bruce, J. M., & Faust, M. A. (2016). Distinguishing Alzheimer's disease and dementia with Lewy bodies using cognitive and olfactory measures. *Neuropsychology*, *30*(3), 304-311. https://doi.org/10.1037/neu0000230

Whitwell, J. L., Graff-Radford, J., Singh, T. D., Drubach, D. A., Senjem, M. L., Spychalla, A. J., Tosakulwong, N., Lowe, V. J., & Josephs, K. A. (2017). (18)F-FDG PET in Posterior Cortical Atrophy and Dementia with Lewy Bodies. *J Nucl Med*, *58*(4), 632-638. https://doi.org/10.2967/jnumed.116.179903

Wild, R., Pettit, T., & Burns, A. (2003). Cholinesterase inhibitors for dementia with Lewy bodies. *Cochrane Database Syst Rev*, *2003*(3), Cd003672. https://doi.org/10.1002/14651858.Cd003672

Wilterson, A. I., Nastase, S. A., Bio, B. J., Guterstam, A., & Graziano, M. S. A. (2021). Attention, awareness, and the right temporoparietal junction. *Proc Natl Acad Sci U S A*, *118*(25). https://doi.org/10.1073/pnas.2026099118

Wolters, A. F., van de Weijer, S. C. F., Leentjens, A. F. G., Duits, A. A., Jacobs, H. I. L., & Kuijf, M. L. (2019). Resting-state fMRI in Parkinson's disease patients with

cognitive impairment: A meta-analysis. *Parkinsonism Relat Disord*, *62*, 16-27. https://doi.org/10.1016/j.parkreldis.2018.12.016

Wong, D. F., Rosenberg, P. B., Zhou, Y., Kumar, A., Raymont, V., Ravert, H. T., Dannals, R. F., Nandi, A., Brasić, J. R., Ye, W., Hilton, J., Lyketsos, C., Kung, H. F., Joshi, A. D., Skovronsky, D. M., & Pontecorvo, M. J. (2010). In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *J Nucl Med*, *51*(6), 913-920. https://doi.org/10.2967/jnumed.109.069088

Yang, J., Luo, S., Zhang, J., Yu, T., Fu, Z., Zheng, Y., Xu, X., Liu, C., Fan, M., & Zhang, Z. (2021). Exosome-mediated delivery of antisense oligonucleotides targeting α-synuclein ameliorates the pathology in a mouse model of Parkinson's disease. *Neurobiol Dis*, *148*, 105218. https://doi.org/10.1016/j.nbd.2020.105218

Ye, B. S., Lee, S., Yoo, H., Chung, S. J., Lee, Y. H., Choi, Y., Lee, P. H., Sohn, Y. H., & Yun, M. (2019). Distinguishing between dementia with Lewy bodies and Alzheimer's disease using metabolic patterns. *Neurobiol Aging*. https://doi.org/10.1016/j.neurobiolaging.2019.10.020

Yilmaz, A., Blennow, K., Hagberg, L., Nilsson, S., Price, R. W., Schouten, J., Spudich, S., Underwood, J., Zetterberg, H., & Gisslén, M. (2017). Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV-negative controls. *Expert Rev Mol Diagn*, *17*(8), 761-770. https://doi.org/10.1080/14737159.2017.1341313

Yoon, J. H., Lee, J. E., Yong, S. W., Moon, S. Y., & Lee, P. H. (2014). The mild cognitive impairment stage of dementia with Lewy bodies and Parkinson disease: a comparison of cognitive profiles. *Alzheimer Dis Assoc Disord*, *28*(2), 151-155. https://doi.org/10.1097/wad.0000000000000007

Yousaf, T., Dervenoulas, G., Valkimadi, P. E., & Politis, M. (2019). Neuroimaging in Lewy body dementia. *J Neurol*, *266*(1), 1-26. https://doi.org/10.1007/s00415-018-8892-x

Zarranz, J. J., Alegre, J., Gomez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Munoz, D. G., & de Yebenes, J. G. (2004). The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol*, *55*(2), 164-173. https://doi.org/10.1002/ana.10795

Zerr, I., Schmitz, M., Karch, A., Villar-Piqué, A., Kanata, E., Golanska, E., Díaz-Lucena, D., Karsanidou, A., Hermann, P., Knipper, T., Goebel, S., Varges, D., Sklaviadis, T., Sikorska, B., Liberski, P. P., Santana, I., Ferrer, I., Zetterberg, H., Blennow, K., Calero, O., Calero, M., Ladogana, A., Sánchez-Valle, R., Baldeiras, I., & Llorens, F. (2018). Cerebrospinal fluid neurofilament light levels in neurodegenerative dementia: Evaluation of diagnostic accuracy in the differential diagnosis of prion diseases. *Alzheimers Dement*, *14*(6), 751-763. https://doi.org/10.1016/j.jalz.2017.12.008

Zhao, Q. F., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., Xu, W., Li, J. Q., Wang, J., Lai, T. J., & Yu, J. T. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*, *190*, 264-271. https://doi.org/10.1016/j.jad.2015.09.069

Zharikov, A., Bai, Q., De Miranda, B. R., Van Laar, A., Greenamyre, J. T., & Burton, E. A. (2019). Long-term RNAi knockdown of α-synuclein in the adult rat substantia nigra without neurodegeneration. Neurobiol Dis, 125, 146-153. https://doi.org/https://doi.org/10.1016/j.nbd.2019.01.004

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R. J., Calne, D. B., Stoessl, A. J., Pfeiffer, R. F., Patenge, N., Carbajal, I. C., Vieregge, P., Asmus, F., Müller-Myhsok, B., Dickson, D. W., Meitinger, T., Strom, T. M., Wszolek, Z. K., & Gasser, T. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron*, *44*(4), 601-607. https://doi.org/10.1016/j.neuron.2004.11.005

Zinno, L., Negrotti, A., Falzoi, C., Messa, G., Goldoni, M., & Calzetti, S. (2021). Generalized Rhythmic Delta Activity Frontally Predominant Differentiates

Dementia With Lewy Bodies From Alzheimer's Disease and Parkinson's Disease Dementia: A Conventional Electroencephalography Visual Analysis. *Clin EEG Neurosci*, 1550059421997147. https://doi.org/10.1177/1550059421997147

Zorzi, G., Thiebaut de Schotten, M., Manara, R., Bussè, C., Corbetta, M., & Cagnin, A. (2021). White matter abnormalities of right hemisphere attention networks contribute to visual hallucinations in dementia with Lewy bodies. *Cortex*, *139*, 86-98. https://doi.org/10.1016/j.cortex.2021.03.007

Chapter Two

2.   **Evaluating the Sustained Attention Response Task to quantify Cognitive Fluctuations in Dementia with Lewy Bodies**

This study was published in the Journal of Geriatric Psychiatry and Neurology:

2.1. Abstract

Cognitive fluctuations (CF) are a core diagnostic feature of Dementia with Lewy Bodies (DLB). Detection of CF are still mostly based on subjective reports from the patient or informant, more quantitative measures are likely to improve the accuracy of diagnosis of DLB. The purpose of the current study was to test whether performance on the Sustained Attention Response Task (SART) could distinguish those DLB patients with and without CF. Twenty-four DLB patients were tested on the SART and performance was related to scores on the Clinical Assessment of Fluctuations (CAF) and One Day Fluctuations Assessment Scale (ODFAS). The number of 'Misses' made was a significant predictor of their fluctuation severity, attentional performance, disorganized thinking and language production ratings on the ODFAS. However, measures on the SART did not correlate with measures on the CAF scale. In conclusion, these findings suggest that SART is a feasible measure of sustained attention in this population and has clinical and diagnostic relevance to the measurement of CF, particularly those aspects measured by the ODFAS.

Key Words: Dementia with Lewy Bodies; attention; cognition; Sustained Attention Response Task

2.2. Introduction

Dementia is characterized by a decrease in cognitive ability that negatively impacts everyday functioning (Chertkow et al., 2013). Dementia with Lewy bodies (DLB) is a neurodegenerative disease that accounts for 5% of dementia worldwide (Kane et al., 2018). One of the most difficult clinical challenges has been dissociating DLB from other forms of dementia, especially Alzheimer's disease (AD), thus highlighting the need for improved diagnostic tools (McKeith et al., 2016).

The recently revised diagnostic guidelines for DLB specify four core clinical features: the presence of visual hallucinations, REM sleep behavior disorder (RBD), spontaneous parkinsonism and cognitive fluctuations (CF; McKeith et al., 2017). The presence of any two of these core features, in the context of a dementing illness, allows for the diagnosis of probable DLB. Despite early recognition of its diagnostic importance, CF remains one of the most challenging of DLB features to elicit reliably in clinical practice.

Cognitive fluctuations are characterized by varying levels of cognitive ability, attention or arousal (McKeith et al., 1996). While CF are present in up to 90% of DLB, they are much less frequent in AD (20%) and Vascular Dementia (35-50%; Lee et al., 2014). Patients with CF may alternate from holding a lucid conversation, to being in a state of delirium (Gore et al., 2015). Such episodes vary widely in their duration and frequency, such that they may last for a minute or several hours and may occur monthly or multiple times per day (Walker et al., 2000b). Importantly, in AD populations, it has been found that patients with CF perform more poorly on neuropsychological tests than patients who do not fluctuate (Escandon et al., 2010) suggesting an overall cognitive impairment that is not confined to the more impaired phases of performance.

Unfortunately, CF have proven to be difficult to accurately identify (Luis et al., 1999; Mega et al., 1996; Van Dyk et al., 2016) and currently their identification is derived from structured clinical interviews that can be supported using instruments

like the Clinical Assessment of Fluctuation scale (CAF) and the One Day Fluctuation Assessment Scale (ODFAS; Walker et al., 2000a). The CAF measures the frequency and duration of episodes of impaired alertness or concentration and confusion over the period of the preceding month. In contrast, the ODFAS relates to CF symptoms over the last 24 hours. It focuses on seven components affiliated with fluctuations, namely falls, fluctuations, drowsiness, attention, disorganized thinking, level of consciousness and communication, which are not solely focused on cognition (Walker et al., 2000a). A more recent scale is the Dementia Cognitive Fluctuation scale combine aspects from both the CAF and ODFAS and focuses of four aspects of CF: Changes in function, daytime drowsiness, daytime sleep, and levels of consciousness %; Lee et al., 2014). While these scales have improved the sensitivity for detecting CF, they still rely on either self-report from the patient, their informants or by observations made directly by the clinician, all of which remain subjective. Therefore, introducing a behavioral task to quantify CF could improve the sensitivity of measuring this symptom and potentially offer an objective, easy-to-use clinical tool that could overcome issues of interrater reliability.

The Sustained Attention Response Task (SART; Robertson et al., 1997) is a simple and ecologically valid task designed to measure failures in sustained attention (Smilek et al., 2010). The SART is based on the Go/No-Go paradigm with a high ratio of go to no-go trials (9:1; Robertson et al., 1997). During the SART, participants are briefly presented with a number (1 – 9) and are required to press a button as quickly as possible if the number is not the number "3". The main measures of the SART are response times (RT) and errors, identified as are either False Alarms or Misses. False Alarms indicate errors in inhibition (i.e., a key was pressed when a "3" was presented; Carter et al., 2013). A Miss is interpreted as lapses of attention (i.e., no response is made for non-target numbers; Robertson et al., 1997). Short RT also suggests that participants have fallen into rhythmic responding and have stopped attending to the stimuli.

The SART has been used in several clinical populations including traumatic brain injury (Richard et al., 2018; Robertson et al., 1997; Whyte et al., 2006), depression (Farrin et al., 2003; Naim-Feil et al., 2016), schizophrenia (Seok et al., 2012), Huntington's disease (Hart et al., 2015) and AD (Gyurkovics et al., 2018; Huntley et al., 2017) but not DLB. The simple nature of the SART requires a low cognitive load making it accessible by DLB patients, who are characterized with moderate cognitive impairment. The high number of go trials should make the task sensitive to drops in attention that would be experienced during a CF. These features that should make the SART an ideal tool for detecting CF in DLB patients. However, to date the SART has not been previously assessed for its ability to assess CF in any population, or with a DLB cohort.

Given that the SART has not been tested previously for identifying CF, this study took an exploratory approach to evaluate whether DLB patients could complete the task and then explored its effectiveness at detecting CF in this population. It was expected that DLB patients who scored highly on the CF or ODFAS may also have more Misses when performing the SART than patients who had low CF scores. We also predicted that given the SART represented a snapshot of performance on the day of testing, it may have stronger correlations with the ODFAS than the CAF, which considers more retrospective patient and informant accounts, with less emphasis on attention. Whilst traditionally short RT on the SART have been indicative of low attention, we proposed that this may not be the case with our parkinsonian DLB patients who are prone to slow response times due to bradyphrenia and parkinsonism. Thus, we expected that higher standard deviations in response time (RTSD) would more closely mimic fluctuations in attention and would be more likely correlated with CAF and ODFAS measures.

2.3. Methods

2.3.1. Participants

Twenty-four patients meeting diagnostic criteria for probable DLB (McKeith et al., 2017) were recruited through the Parkinson's Disease Research Clinic at the Brain and Mind Centre, University of Sydney, Australia. This clinic specializes in Lewy body diseases, and is not limited to patients with Parkinson disease, or parkinsonian features. Patients were also recruited through the community and neurology clinics in the wider Sydney region. Informed written consent was provided by each patient and the study was approved by the Human Research Ethics Committee at Sydney University. Demographics and diagnostic characteristics are presented in Table 1. Eighteen patients were taking cholinesterase inhibitors. Four patients were excluded from the study due to fatigue or equipment failure. The excluded patients did not differ in fluctuation scores or demographic characteristics from the patients who completed the task. Parkinsonism was assessed using section three of the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008), global cognitive impairment was assessed using Mini Mental State Exam (MMSE; Folstein et al., 1975) and Rapid Eye Movement Sleep Behavior Disorder (RBD) was confirmed with polysomnography using the SINBAR protocol (Frauscher et al., 2008; Iranzo et al., 2011).

2.3.2. Apparatus/Procedure

The SART was run on a 15" laptop using E-Prime 2.10 (Psychology Software Tools, 2013). The SART presented a fixation cross for 900 ms followed by a random number between 1 – 9 for 750 ms. Note that stimuli were shown at a slower rate than in the original SART (250ms; Robertson et al., 1997), as the original version was too fast for this clinical population. The participants were instructed to press the "spacebar" each time they saw any number (i.e., 'go' trial), except for when the number '3' was presented (i.e. 'no-go' trial; Figure 2.1). The original paradigm used a 9:1 ratio of go to no-go trials. Due to time restraints during session the length was reduced from 225 trials to 180 trials. In order to maintain a high number of 'no-go'

trials the ration was reduced to 5:1 go to no-go trials. This ratio will still result in a high error rate (Wilson et al., 2016). There were 130 'go' trials and 50 'no-go' trials. The font size of the number displayed was also varied, ranging between 48 pt to 120 pt. This was to ensure that participants were processing the numbers and not using unique graphical features of the number three. A *hit* was defined as a correct button press for a 'go' trial; a *correct rejection* was the absence of a button press for a 'no-go' trial; while the absence of a response for a 'go' trial was labelled as a *Miss*; and a response for the 'no-go' trial was labelled as a *False Alarm*. Once the participant indicated that they understood what they were required to do, they would then begin a practice session. Following a successful completion of the practice session, the main task would begin and last for six minutes. Average and standard deviation of the response time, number of Misses (when no response was made for a 'go' trial) and number of False Alarms (when a response was made for a 'no-go' trial) were recorded as a measure of task performance. As this was a go/no-go task, response times and accuracy were correlated to ensure there was no speed/accuracy trade off in our sample.
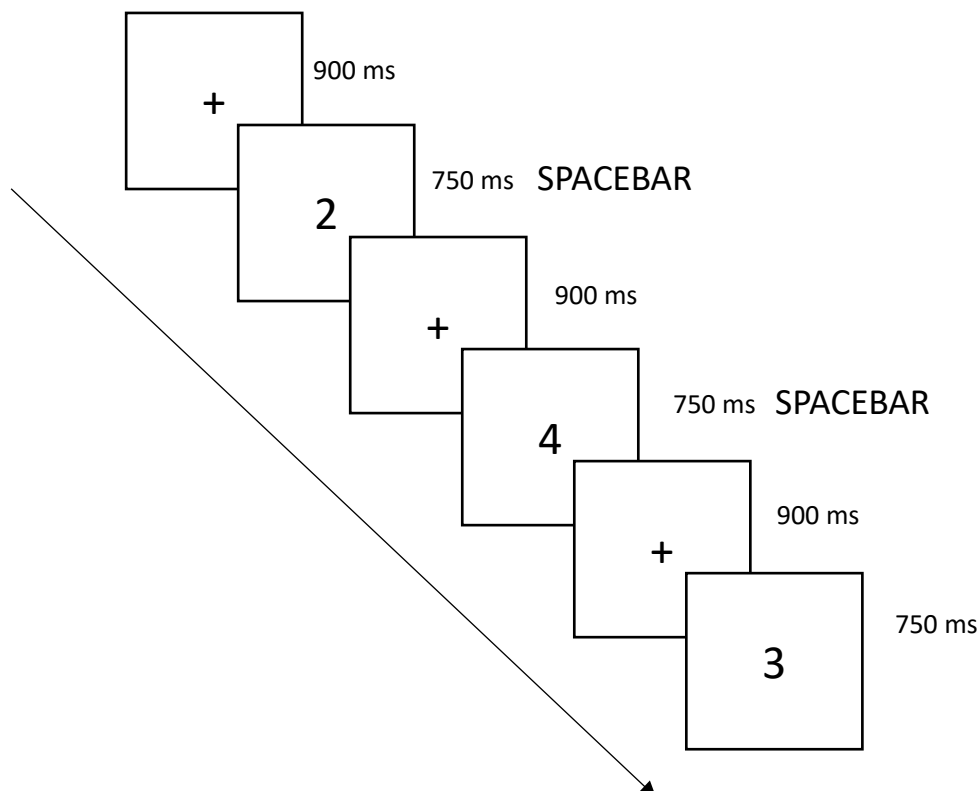
Figure 2.1: Sustained Attention Response

Cognitive fluctuations were identified and measured using the CAF and ODFAS (Walker et al., 2000a) during a semi-structured clinical interview by a trained clinician (E.M.). The CAF includes two items, the first probes for fluctuations in alertness and concentration while the second focuses on confusion. Positive responses to either of these items then require the clinician to score the frequency and duration of the fluctuations which are multiplied together to give a severity score ranging from 0 – 16 with a score of 16 indicating a constant state of confusion. The ODFAS uses seven items to measure fluctuating cognition (occurrence of falls, fluctuation, drowsiness, attention, disorganized thoughts, altered level of consciousness and communication) during the 24 hours before the assessment. Scores range from 0 – 21, with a score of 21 taken to indicate a high degree of confusion associated with fluctuations if present. Twelve patients scored higher than 5 in the CAF, indicating clinical CF (Walker et al., 2000a).

The remaining three core features of DLB were measured using the Rapid Eye Movement Behaviour Disorder scale for RBD (RBDSQ; Stiasny-Kolster et al., 2007); Section III from the MDS-UPDRS for parkinsonism; MDS-UPDRS Section I Item 2 for hallucinations and the depression subscale from the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

2.3.3. Statistical Analysis

All statistical analyses were performed using SPSS 25 (IBM, 2017), with an alpha set to 0.05. Correlations were calculated using Spearman's Rho due to the data not meeting normality. Backward stepwise multiple regressions were used to determine how well the SART variables predicted the CF measures.

2.4. Results

2.4.1. Overall SART performance

Overall, performance in the SART was high; cognitive impairment according to the MMSE did not appear to impede patient's ability to complete the SART. Patients had a mean accuracy of 87.3% (SD = 8.5%). Regarding errors, there were 11.7 (SD = 9.14) Misses and 8.35 (SD = 6.49) False Alarms. The average response time for correct responses was 584.23 ms (SD = 106.90 ms) and 743.86 ms (SD = 359.40) for False Alarms.

2.4.2. Relationship between clinical measures and SART

Age, disease duration, years of education, MMSE, daily dopamine equivalent, section III (motor examination) of the MDS-UPDRS and RBDSQ scores were not significantly correlated with the number of Misses, False Alarms, or the average response time of the SART. The depression subscale from the HADS and the visual hallucination item in MDS-UPDRS did correlate with SART measures (Table 2.1) and were therefore included in the regression analysis below. An initial analysis on the relationship between the SART measures and the CF scales revealed that the number of Misses correlated with the ODFAS ($r_s(18) = 0.55$, $p < 0.05$; figure 2.2), but not the CAF ($r_s(18) = 0.29$, $p = 0.211$).

2.4.3. Relationship between SART and cognitive fluctuations

A stepwise multiple regression was used to identify which elements of the SART were predictive of fluctuation measures from the CAF and ODFAS. Using a backward stepwise method, the number of Misses ($\beta = 0.61$) was the only measure that significantly predicted ODFAS scores (R = 0.614, R^2 = 0.37, Adj. R^2 = 0.34, F(1,17) = 10.11, $p < 0.01$). As the ODFAS contains different items that measure different aspects of CF, each item was also correlated with Misses to identify which features of CF were driving the relationship (Table 2.2). To account for family wise error, Sidak correction was applied, reducing the alpha to 0.006. With the stricter alpha level, the only correlation that maintained significance was with disorganized thinking ($r_s(18) = .62$, $p < 0.006$). The remaining correlations between Misses and the ODFAS sections fell out

of significance (severity of fluctuations $r_s(18) = 0.48$, $p = 0.03$, attention $r_s(18) = 0.49$, $p = 0.03$, and language production $r_s(18) = 0.53$, $p = 0.016$). Additionally, RTSD correlated with language production ($r_s(18) = 0.61$, $p < 0.006$), while a correlation with attention did not meet the stringent alpha level ($r_s(18) = 0.46$, $p < 0.05$). Notably, none of the SART measures were significant predictors of the CAF and thus none were retained for the model (Adj. $R^2 = 0.04$, $F(1,18) = 1.79$, $p = 0.20$).

		Correlation (Spearman's Rho)			
	Mean (SD)	Misses	False Alarms	Average RT	SD RT
Age (years)	74.2(6.6)	.12	-.25	.36	.17
Disease Duration (years)	1.9(1.4)	.04	-.28	.12	-.15
Years of Education	12(0.4)	-.10	.03	-.07	-.28
MMSE	22.5(5.9)	-.42	-.29	-.41	-.40
MDS-UPDRS-III	35.33(13.71)	.12	.08	-.09	-.02
RBD	6.26(3.93)	-.24	-.37	-.34	-.23
MDS-UPDRS-VH	0.26(0.22)	**.59***	.36	.47	**.48***
HADS-D	7.19(4.83)	**.69***	.08	.29	.33

Table 2.1: Participant demographics: * = p < 0.05; MMSE = Mini Mental State Exam; RT = Response Time, MDS-UPDRSIII = Movement Disorder Society – Unified Parkinson's Disease Rating Scale Section III; VH = visual hallucination as measured from the MDS-UPDRS; HADS-D = Hospital Anxiety and Depression Scale – Depression.
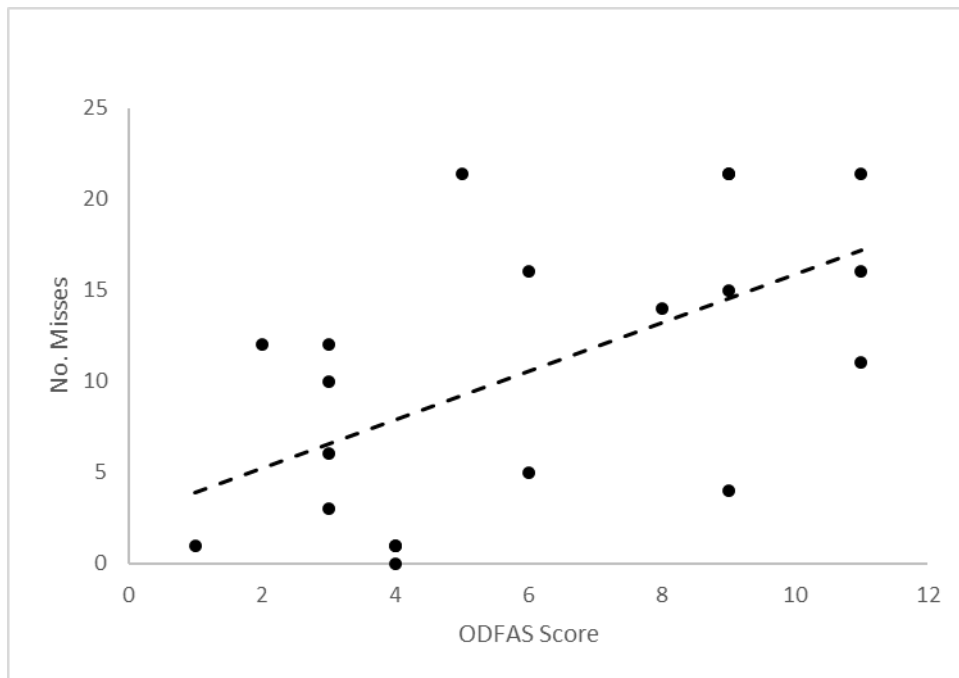
Figure 2.2: Correlation between the number of misses made and ODFAS scores Spearman's correlation = 0.55. ODFAS = One Day Fluctuation Assessment Scale.

	Total Misses	Total False Alarm	Average RT	RT SD
Mean (S.D.)	11.7 (9.14)	8.35 (6.49)	584.22 (106.94)	254.56 (107.71)
Range (min, max)	0, 30	0, 26	397.43, 786.48	77.19, 398.29
Correlations:				
CAF	.29	.09	.09	-.06
ODFAS Total	**.55***	.20	.31	.33
Fluctuations	.53*	.29	.27	.37
Drowsiness	.22	-.05	-.02	-.07

Attention	.49*	.41*	.35	.46*
Disorganised thoughts	**.62****	.22	.50*	.34
Altered consciousness	.20	.08	.10	.06
Communication				
Comprehension	.24	.12	.02	.28
Production	.53*	.33	.53*	**.64****

*Table 2.2: SART Performance and Correlations: * = p < .05; ** p < .006. Response times are in milliseconds. Correlations are Spearman's Rho.*

2.4.4. Speed-accuracy trade-off

Overall, response accuracy was high (M = 87.12%; SD = 8.34%). Potential speed-accuracy trade-off was measured by correlating SART accuracy (percentage of trials where responses were correctly made or withheld) with average response time. There was a negative correlation of $r_s(19) = -0.634$, $p < 0.001$ suggesting that the more accurate participants were also faster at responding. This does not reflect a speed accuracy trade-off but more likely reflected overall disease severity and suggests that the more severe DLB patients were less accurate and slower to respond, whereas the less severe patients were more accurate and faster to respond.

2.5.   Discussion

The current study aimed to test the viability of using the SART to objectively detect CF in a DLB population. Overall, DLB patients recruited for this study had

high response accuracy, supporting the feasibility of using the SART in this population. Cognitive fluctuations as measured by the ODFAS were best predicted by the number of Misses made in the SART.

While the SART was able to predict ODFAS scores, it was unable to predict CAF scores. The relationship between SART measures and the ODFAS but not the CAF could be due to the different approaches each scale takes to measuring CF. Whilst the CAF probes for periods of impaired alertness or concentration and periods of confusion, measuring the severity as frequency and duration of the fluctuation, the ODFAS focuses on specific symptoms that are likely to be experienced during the impaired cycle of CF testing the change in impairment from the highest point to the lowest point of CF. This dimension of severity may therefore represent what the SART is sensitive to. It also brings into question the existence of different CF phenotypes and potentially heterogeneous underlying pathology that causes CFs to vary in duration, frequency and level of impairment across individuals. The lack of relationship between SART and CAF scores is not in agreement with previous work by Walker, Ayre, Cummings, et al. (Walker et al., 2000a) who found that DLB patients who scored high on the CAF also exhibited more variance in their response time for a Choice Reaction Task (CRT) and a Digit Vigilance Task (DVT). One potential reason for the discrepancy in outcomes could be due to the response nature of the task. The CRT requires the participant to make an active choice between two response buttons for each trial, while the SART requires participants to make a single response for most of the trials. The choice aspect of the CRT may be more sensitive to impairments in CFs that are occurring over the preceding month. The DVT has participants withholding responses for most trials and responding less frequently to a target stimulus. It could be that the periods of response absent trials are more sensitive to CFs rather than when responses are required. Alternatively, there could also have been discrepancies between patients studied by Walker, Ayre, Cummings, et al. (Walker et al., 2000a) and the present study given the recent revision of the diagnostic criteria for DLB. Overall,

these results support two of the study's hypotheses predicting that patients with high CF scores would exhibit more Misses in the SART task and these Misses would be more correlated with ODFAS rather than CAF scores. It was also hypothesized that RTSD would predict CF scores. However, this was not supported as RTSD failed to be a predictor of CF scores.

Using a linear regression, the number of Misses during the SART was a significant predictor of ODFAS scores, verifying its use as an objective CF measure. When the items of the ODFAS were separated and correlated with the number of Misses made during the SART, there were four sections that had medium to strong correlations. These were fluctuation severity, attention, communication production and disorganized thoughts. Of interest, the strongest relationship that maintained significance after the application of stricter statistical constraints was between Misses and disorganized thinking. The relationship between Misses and disorganized thinking may relate to pathology in the self-referential network, which has been proposed to be disrupted in individuals with disorganized thinking (Lagioia et al., 2010)[34]. This network is also part of the default mode network (DMN; Sheline et al., 2009; Shine et al., 2011), which has been implicated in internal thought processes (Danckert & Merrifield, 2018) and the evolution of visual hallucinations in patients with Parkinson's disease (Shine et al., 2015)[38]. The activation of the DMN has also been positively correlated with errors made in a CRT (Bonnelle et al., 2011). However, the impact of the DMN using standard fMRI methods is debated (Chabran et al., 2018; Franciotti et al., 2013; Galvin et al., 2011; Onofrj et al., 2019; Peraza et al., 2014; Schumacher et al., 2018) while a recent article by Schumacher and colleagues (Schumacher et al., 2019) further implicated a role for the DMN with potential EEG markers of fluctuations.

The number of Misses was also strongly correlated with depression scores on the HADS and visual hallucinations ratings as measured by the MDS-UPDRS. The correlation with depression is not surprising as attention is impaired during low mood

(Smallwood & O'Connor, 2011). However, depression scores from our DLB cohort were in the mild to moderate range, suggesting that patients' moods were not so low as to affect their motivation to complete the task. We found that the SART measures had medium strength correlations with the attention item of the ODFAS, although this significance was not maintained after a Sidak correction. While this is perhaps counterintuitive given that the SART is an attentional task, the original (Robertson et al., 1997) study evaluating the SART in patients with traumatic brain injury indicated that whereas response times were the best measure of attention, the observation of short response times indicated that responses had become more automatic and that attention had drifted. In our present study of patients with DLB, response time had the smallest correlation with the ODFAS attention item and Misses had the highest correlation. One reason for this could be due to alterations in the cholinergic system in DLB patients. This system is heavily involved in alertness and attention (Harris & Thiele, 2011). Indeed, neuronal depletion in the basalis of Meynert had been observed in DLB patients (Kasanuki et al., 2018). This region has also been implicated in sustained attention in rhesus monkeys (Liu et al., 2018), inferring that impairment will reduce sustained attention, resulting in higher misses.

While Misses made in the SART were able to predict scores on the ODFAS there are some limitations that need to be highlighted in these findings in relation to the way different items on the scale are scored. For example, on the ODFAS, fluctuation severity and language production items involve a three-point system, whereas the attention and disorganized thinking items are both binary responses. Therefore, in order to thoroughly test the relationship between the SART and these domains, the inclusion of neuropsychological tests designed to measure these domains would be required in future studies. It is important to recognize that there is no current gold-standard associated with measuring fluctuations and that although currently the most widely used method is via self and carer-reporting, there are limitations and inherent biases associated with this (Matar et al., 2019). Future assessments will be targeted to

establish convergent validity with other proposed objective measures such as EEG (Bonanni et al., 2015; Bonanni et al., 2008) and fMRI (Peraza et al., 2014).

Additionally, there may be different phenotypes of CF present in our DLB sample. As postulated by Matar and colleagues (Matar et al., 2019), there may be multiple types of CFs that DLB patients experience. The first type consists of infrequent instances, but they have a long duration of impairment. The second type are more frequent and short duration of impairment. Due to the high frequency, the latter would be more likely recognized by the ODFAS, while the CAF would detect both types. This would suggest that the attention deficits noted in our sample may only be characteristic of the DLB patients who experience high frequency, short fluctuations. Further, the current study had a relatively small sample size, suggesting some caution with interpreting the results.

Overall, the SART demonstrated utility as an objective testing tool within our DLB population. The SART was not a strong predictor of CAF scores, suggesting that CF are not solely a problem of sustained attention but encompass other delirium symptoms that are recalled more accurately over the preceding month. However, the number of Misses made on the SART was able to predict scores on the ODFAS relating to the severity of CF. The Misses were driven by the disorganized thinking, fluctuation severity, attention, and language production components of the ODFAS. The SART also proved to be a relatively simple attention task for our DLB patients with a high completion rate.

Taken together, there is potential for the SART to be a useful objective measure of CF. Given its simplicity and feasibility to implement in a clinical setting, it certainly warrants further research into the relationship between the SART and other measures of CF in DLB. It may also have further utility in objectively measuring the acute period of a fluctuation, which could be potentially incorporated into future clinical trials targeting this devastating symptom.

2.6. References

Bonanni, L., Perfetti, B., Bifolchetti, S., Taylor, J. P., Franciotti, R., Parnetti, L., Thomas, A., & Onofrj, M. (2015). Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging, 36(1), 434-445. https://doi.org/10.1016/j.neurobiolaging.2014.07.009

Bonanni, L., Thomas, A., Tiraboschi, P., Perfetti, B., Varanese, S., & Onofrj, M. (2008). EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain, 131(3), 690. https://doi.org/10.1093/brain/awm322

Bonnelle, V., Leech, R., Kinnunen, K. M., Ham, T. E., Beckmann, C. F., De Boissezon, X., Greenwood, R. J., & Sharp, D. J. (2011). Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. J Neurosci, 31(38), 13442-13451. https://doi.org/10.1523/jneurosci.1163-11.2011

Carter, L., Russell, P. N., & Helton, W. S. (2013). Target predictability, sustained attention, and response inhibition. Brain Cogn, 82(1), 35-42. https://doi.org/10.1016/j.bandc.2013.02.002

Chabran, E., Roquet, D., Gounot, D., Sourty, M., Armspach, J. P., & Blanc, F. (2018). Functional Disconnectivity during Inter-Task Resting State in Dementia with Lewy Bodies. Dement Geriatr Cogn Disord, 45(1-2), 105-120. https://doi.org/10.1159/000486780

Chertkow, H., Feldman, H. H., Jacova, C., & Massoud, F. (2013). Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. Alzheimers Res Ther, 5(Suppl 1), S2-S2. https://doi.org/10.1186/alzrt198

Danckert, J., & Merrifield, C. (2018). Boredom, sustained attention and the default mode network. Exp Brain Res, 236(9), 2507-2518. https://doi.org/10.1007/s00221-016-4617-5

Escandon, A., Al-Hammadi, N., & Galvin, J. E. (2010). Effect of cognitive fluctuation on neuropsychological performance in aging and dementia. Neurology, 74(3), 210-217. https://doi.org/10.1212/WNL.0b013e3181ca017d

Farrin, L., Hull, L., Unwin, C., Wykes, T., & David, A. (2003). Effects of depressed mood on objective and subjective measures of attention. J Neuropsychiatry Clin Neurosci, 15(1), 98-104. https://doi.org/10.1176/jnp.15.1.98

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12(3), 189-198.

Franciotti, R., Falasca, N. W., Bonanni, L., Anzellotti, F., Maruotti, V., Comani, S., Thomas, A., Tartaro, A., Taylor, J. P., & Onofrj, M. (2013). Default network is not hypoactive in dementia with fluctuating cognition: an Alzheimer disease/dementia with Lewy bodies comparison. Neurobiol Aging, 34(4), 1148-1158. https://doi.org/10.1016/j.neurobiolaging.2012.09.015

Frauscher, B., Iranzo, A., Hogl, B., Casanova-Molla, J., Salamero, M., Gschliesser, V., Tolosa, E., Poewe, W., & Santamaria, J. (2008). Quantification of electromyographic activity during REM sleep in multiple muscles in REM sleep behavior disorder. Sleep, 31(5), 724-731. https://doi.org/10.1093/sleep/31.5.724

Galvin, J. E., Price, J. L., Yan, Z., Morris, J. C., & Sheline, Y. I. (2011). Resting bold fMRI differentiates dementia with Lewy bodies vs Alzheimer disease. Neurology, 76(21), 1797-1803. https://doi.org/10.1212/WNL.0b013e31821ccc83

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the

Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord, 23(15), 2129-2170. https://doi.org/10.1002/mds.22340

Gore, R. L., Vardy, E. R., & O'Brien, J. T. (2015). Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? J Neurol Neurosurg Psychiatry, 86(1), 50-59. https://doi.org/10.1136/jnnp-2013-306389

Gyurkovics, M., Balota, D. A., & Jackson, J. D. (2018). Mind-wandering in healthy aging and early stage Alzheimer's disease. Neuropsychology, 32(1), 89-101. https://doi.org/10.1037/neu0000385

Harris, K. D., & Thiele, A. (2011). Cortical state and attention. Nat Rev Neurosci, 12(9), 509-523. https://doi.org/10.1038/nrn3084

Hart, E. P., Dumas, E. M., van Zwet, E. W., van der Hiele, K., Jurgens, C. K., Middelkoop, H. A., van Dijk, J. G., & Roos, R. A. (2015). Longitudinal pilot-study of Sustained Attention to Response Task and P300 in manifest and pre-manifest Huntington's disease. J Neuropsychol, 9(1), 10-20. https://doi.org/10.1111/jnp.12031

Huntley, J. D., Hampshire, A., Bor, D., Owen, A. M., & Howard, R. J. (2017). The importance of sustained attention in early Alzheimer's disease. Int J Geriatr Psychiatry, 32(8), 860-867. https://doi.org/10.1002/gps.4537

IBM. (2017). IBM SPSS Statistics. In (Version 25) IBM.

Iranzo, A., Frauscher, B., Santos, H., Gschliesser, V., Ratti, L., Falkenstetter, T., Sturner, C., Salamero, M., Tolosa, E., Poewe, W., Santamaria, J., & Hogl, B. (2011). Usefulness of the SINBAR electromyographic montage to detect the motor and vocal manifestations occurring in REM sleep behavior disorder. Sleep Med, 12(3), 284-288. https://doi.org/10.1016/j.sleep.2010.04.021

Kane, J. P. M., Surendranathan, A., Bentley, A., Barker, S. A. H., Taylor, J.-P., Thomas, A. J., Allan, L. M., McNally, R. J., James, P. W., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2018). Clinical prevalence of Lewy body dementia. Alzheimers Res Ther, 10(1), 19. https://doi.org/10.1186/s13195-018-0350-6

Kasanuki, K., Ferman, T. J., Murray, M. E., Heckman, M. G., Pedraza, O., Hanna Al-Shaikh, F. S., Mishima, T., Diehl, N. N., van Gerpen, J. A., Uitti, R. J., Wszolek, Z. K., Graff-Radford, N. R., & Dickson, D. W. (2018). Daytime sleepiness in dementia with Lewy bodies is associated with neuronal depletion of the nucleus basalis of Meynert. Parkinsonism Relat Disord, 50, 99-103. https://doi.org/10.1016/j.parkreldis.2018.02.003

Lagioia, A., Van De Ville, D., Debbané, M., Lazeyras, F., & Eliez, S. (2010). Adolescent resting state networks and their associations with schizotypal trait expression. Front Syst Neurosci, 4, 35. https://doi.org/10.3389/fnsys.2010.00035

Lee, D. R., McKeith, I., Mosimann, U., Ghosh-Nodial, A., Grayson, L., Wilson, B., & Thomas, A. J. (2014). The dementia cognitive fluctuation scale, a new psychometric test for clinicians to identify cognitive fluctuations in people with dementia. Am J Geriatr Psychiatry, 22(9), 926-935. https://doi.org/10.1016/j.jagp.2013.01.072

Liu, R., Crawford, J., Callahan, P. M., Terry, A. V., Constantinidis, C., & Blake, D. T. (2018). Intermittent stimulation in the nucleus basalis of meynert improves sustained attention in rhesus monkeys. Neuropharmacology, 137, 202-210. https://doi.org/10.1016/j.neuropharm.2018.04.026

Luis, C. A., Barker, W. W., Gajaraj, K., Harwood, D., Petersen, R., Kashuba, A., Waters, C., Jimison, P., Pearl, G., Petito, C., Dickson, D., & Duara, R. (1999). Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. Int J Geriatr Psychiatry, 14(7), 526-533. https://doi.org/10.1002/(sici)1099-1166(199907)14:7<526::aid-gps965>3.0.co;2-0

Matar, E., Shine, J. M., Halliday, G. M., & Lewis, S. J. G. (2019). Cognitive fluctuations in lewy body dementia - towards a pathophysiological framework. Brain.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro,

H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology, 89(1), 88-100. https://doi.org/10.1212/wnl.0000000000004058

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A., & Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology, 47(5), 1113-1124. http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCOBNHDBOM00/fs047/ovft/live/gv024/00006114/00006114-199611000-00001.pdf

McKeith, I. G., Taylor, J. P., Thomas, A., Donaghy, P., & Kane, J. (2016). Revisiting DLB Diagnosis: A Consideration of Prodromal DLB and of the Diagnostic Overlap With Alzheimer Disease. J Geriatr Psychiatry Neurol, 29(5), 249-253. https://doi.org/10.1177/0891988716656083

Mega, M. S., Masterman, D. L., Benson, D. F., Vinters, H. V., Tomiyasu, U., Craig, A. H., Foti, D. J., Kaufer, D., Scharre, D. W., Fairbanks, L., & Cummings, J. L. (1996). Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. Neurology, 47(6), 1403-1409. https://doi.org/10.1212/wnl.47.6.1403

Naim-Feil, J., Bradshaw, J. L., Sheppard, D. M., Rosenberg, O., Levkovitz, Y., Dannon, P., Fitzgerald, P. B., Isserles, M., & Zangen, A. (2016). Neuromodulation of Attentional Control in Major Depression: A Pilot DeepTMS Study. Neural Plast, 2016, 5760141. https://doi.org/10.1155/2016/5760141

Onofrj, M., Espay, A. J., Bonanni, L., Delli Pizzi, S., & Sensi, S. L. (2019). Hallucinations, somatic-functional disorders of PD-DLB as expressions of thalamic dysfunction. Mov Disord, 34(8), 1100-1111. https://doi.org/10.1002/mds.27781

Peraza, L. R., Kaiser, M., Firbank, M., Graziadio, S., Bonanni, L., Onofrj, M., Colloby, S. J., Blamire, A., O'Brien, J., & Taylor, J.-P. (2014). fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. NeuroImage. Clinical, 4, 558-565. https://doi.org/10.1016/j.nicl.2014.03.013

Psychology Software Tools, I. (2013). E-Prime 2.0. In Psychology Software Tools, Inc.

Richard, N. M., O'Connor, C., Dey, A., Robertson, I. H., & Levine, B. (2018). External modulation of the sustained attention network in traumatic brain injury. Neuropsychology, 32(5), 541-553. https://doi.org/10.1037/neu0000442

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia, 35(6), 747-758. https://doi.org/10.1016/S0028-3932(97)00015-8

Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., O'Brien, J. T., Blamire, A. M., & Taylor, J. P. (2018). Functional connectivity in dementia with Lewy bodies: A within- and between-network analysis. Hum Brain Mapp, 39(3), 1118-1129. https://doi.org/10.1002/hbm.23901

Schumacher, J., Peraza, L. R., Firbank, M., Thomas, A. J., Kaiser, M., Gallagher, P., O'Brien, J. T., Blamire, A. M., & Taylor, J. P. (2019). Dysfunctional brain dynamics and their origin in Lewy body dementia. Brain, 142(6), 1767-1782. https://doi.org/10.1093/brain/awz069

Seok, J. H., Park, H. J., Lee, J. D., Kim, H. S., Chun, J. W., Son, S. J., Oh, M. K., Ku, J., Lee, H., & Kim, J. J. (2012). Regional cerebral blood flow changes and

performance deficit during a sustained attention task in schizophrenia: (15) O-water positron emission tomography. Psychiatry Clin Neurosci, 66(7), 564-572. https://doi.org/10.1111/j.1440-1819.2012.02407.x

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., Mintun, M. A., Wang, S., Coalson, R. S., & Raichle, M. E. (2009). The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences of the United States of America, 106(6), 1942-1947. https://doi.org/10.1073/pnas.0812686106

Shine, J. M., Halliday, G. M., Naismith, S. L., & Lewis, S. J. (2011). Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? Mov Disord, 26(12), 2154-2159. https://doi.org/10.1002/mds.23896

Shine, J. M., Muller, A. J., O'Callaghan, C., Hornberger, M., Halliday, G. M., & Lewis, S. J. (2015). Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. NPJ Parkinsons Dis, 1, 15003. https://doi.org/10.1038/npjparkd.2015.3

Smallwood, J., & O'Connor, R. C. (2011). Imprisoned by the past: unhappy moods lead to a retrospective bias to mind wandering. Cogn Emot, 25(8), 1481-1490. https://doi.org/10.1080/02699931.2010.545263

Smilek, D., Carriere, J. S., & Cheyne, J. A. (2010). Failures of sustained attention in life, lab, and brain: ecological validity of the SART. Neuropsychologia, 48(9), 2564-2570. https://doi.org/10.1016/j.neuropsychologia.2010.05.002

Stiasny-Kolster, K., Mayer, G., Schafer, S., Moller, J. C., Heinzel-Gutenbrunner, M., & Oertel, W. H. (2007). The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. Mov Disord, 22(16), 2386-2393. https://doi.org/10.1002/mds.21740

Van Dyk, K., Towns, S., Tatarina, O., Yeung, P., Dorrejo, J., Zahodne, L. B., & Stern, Y. (2016). Assessing Fluctuating Cognition in Dementia Diagnosis:Interrater

Reliability of the Clinician Assessment of Fluctuation. American Journal of Alzheimer's Disease & Other Dementias, 31(2), 137-143. https://doi.org/10.1177/1533317515603359

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000a). The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale: Two methods to assess fluctuating confusion in dementia. British Journal of Psychiatry, 177(3), 252-256. https://doi.org/10.1192/bjp.177.3.252

Walker, M. P., Ayre, G. A., Perry, E. K., Wesnes, K., McKeith, I. G., Tovee, M., Edwardson, J. A., & Ballard, C. G. (2000b). Quantification and characterization of fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord, 11(6), 327-335. https://doi.org/17262

Whyte, J., Grieb-Neff, P., Gantz, C., & Polansky, M. (2006). Measuring sustained attention after traumatic brain injury: differences in key findings from the sustained attention to response task (SART). Neuropsychologia, 44(10), 2007-2014. https://doi.org/10.1016/j.neuropsychologia.2006.02.012

Wilson, K. M., Finkbeiner, K. M., de Joux, N. R., Russell, P. N., & Helton, W. S. (2016). Go-stimuli proportion influences response strategy in a sustained attention to response task. Exp Brain Res, 234(10), 2989-2998. https://doi.org/10.1007/s00221-016-4701-x

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. Acta Psychiatr Scand, 67(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Chapter Three

3. **An adaptive measure of visuospatial impairment in Dementia with Lewy Bodies**

3.1. Abstract

Background: Dementia with Lewy bodies (DLB) is a common cause of dementia with poor prognosis and high hospitalisation rates. DLB is frequently misdiagnosed, with clinical features that overlap significantly with other diseases including Parkinson's disease (PD). Clinical instruments that discriminate and track the progression of cognitive impairment in DLB are needed.

Objectives: The current study was designed to assess the utility of a mental rotation (MR) task for assessing visuospatial impairments in early DLB. *Methods*: Accuracy of 22 DLB patients, 22 PD patients and 22 age-matched healthy controls in the MR task were compared at comparing shapes with 0°, 45° and 90° rotations.

Results: Healthy controls and PD patients performed at similar levels while the DLB group were significantly impaired. Further, impairment in the visuospatial and executive function measures correlated with MR poor outcomes.

Conclusion: These findings support the MR task as an objective measure of visuospatial impairment with the ability to adjust difficulty to suit impairments in a DLB population. This would be a useful tool within clinical trials.

3.2. Introduction

Dementia with Lewy Bodies (DLB) is the second most common cause of neurodegenerative dementia in the elderly, accounting for up to 5-20% of dementia cases (Aarsland et al., 2008; Jellinger & Attems, 2011; Kane et al., 2018; Vann Jones & O'Brien, 2014). This neurodegenerative disease is characterised by an aggressive decline that significantly impacts on everyday activities (Chertkow et al., 2013) with a poor prognosis that frequently requires hospitalisation or full-time care (Mueller et al., 2017). Whilst diagnostic criteria have been established to facilitate an earlier and more accurate diagnosis by recognising four core features (parkinsonism, cognitive fluctuations, visual hallucinations, and dream enactment; McKeith et al., 2017), many patients remain undiagnosed or misdiagnosed (Kane et al., 2018; Vann Jones & O'Brien, 2014). The frequent presence of parkinsonism will usually help the clinician in differentiating DLB from Alzheimer's Disease (AD) but given that even at the time of first diagnosis, around a third of Parkinson's Disease (PD) patients are known to have Mild Cognitive Impairment (MCI; Foltynie et al., 2004). Indeed, differentiating these two synucleinopathies from each other can prove challenging. Thus, there is an immediate need to find convenient approaches to assist in the recognition of such cases.

Whilst the cognitive decline observed in DLB may encompass a broad range of domains, the most significant impairments occur across executive (McKeith et al., 2007) and visuospatial function (Kemp et al., 2017; Smirnov et al., 2020). Indeed, it has been reported that even during the prodromal (classified as MCI with two of the core diagnostic features) and early stages of the disease, DLB patients have more visuospatial impairments than PD patients with a similar disease duration (Génier Marchand et al., 2018), as well as prodromal and early AD patients (van de Beek et al., 2020). Therefore, this differential impairment of visuoperceptive abilities may represent a suitable neuropsychometric target that could be utilised to differentiate

early DLB cases from other conditions with similar initial clinical profiles, such as PD and AD.

A range of tests investigating visuospatial ability have been employed in patients with DLB, but these results have lacked consistency. This may be due to the heterogeneity of the disease or the nature of other disease features such as cognitive fluctuations, which are common in DLB and would clearly impact upon the performance of many tasks. The Visual Object and Space Perception battery (VOSP) was originally designed to help differentiate DLB patients with a disease duration of at least 12 months from AD patients (Calderon et al., 2001). The task requires subjects to complete a series of trials designed to measure an individual's spatial and object perception (Quental et al., 2013). The VOSP consists of nine simple tasks that involve the identification of obscure shapes and silhouettes by matching numbers to locations (Warrington, 1991). However, applying the VOSP to prodromal DLB patients has produced mixed results. Van de Beek and colleagues (van de Beek et al., 2020) found more impairment in prodromal DLB patients compared to prodromal AD patients, however Kemp and colleagues (2017) were unable to separate prodromal DLB patients from either AD or healthy controls using the VOSP. This suggest that the VOSP may not be sensitive enough to discriminate between neurodegenerative conditions.

The Benton Line Orientation Judgement task is a 30-item task that also measures visuospatial ability by having patients compare and match line orientations. Compared to AD, patients with DLB have shown greater deficits on this task (Simard et al., 2003) but a more recent study has found that most DLB patients are unable to complete this task and thus it may prove unsuitable for general use (Martini et al., 2020). The Rey-Osterrieth Complex Figure copy (ROCF) is another popular test to measure visuospatial abilities in healthy and clinical populations (Meyers & Meyers, 1995). In persons with dementia, it has been shown to differentiate AD from PD patients with mixed results (Freeman, 1999; Freeman et al., 2000; Grossi et al., 2011), perhaps due to absence of control for the duration and severity of disease. The ROCF

has also been used to differentiate DLB from PDD patients (Martini et al., 2020) but such findings have not been universal (Mondon et al., 2007).

Previously, the Mental Rotation task has been utilised in AD (Adduri & Marotta, 2009; Bird et al., 2010; Flicker et al., 1988), PD (Lee et al., 1998), Huntington's disease (Lineweaver et al., 2005), and traumatic brain injury (Oostra et al., 2012) to evaluate an individual's ability to internally visualise and manipulate three dimensional (3D) objects (Shepard & Metzler, 1971). Participants are presented pairs of shapes and are required to determine if the shapes are identical or mirror images of each other (Shepard & Metzler, 1971). One shape is rotated on its y-axis, which then requires the participant to visualise and rotate the shape to determine if it is the same or a mirror image of its pair. The amount of rotation has been shown to be correlated with greater cognitive load and subsequently higher difficulty as the rotation approaches 180° (Bourrelier et al., 2015). This feature of the Mental Rotation task allows the difficulty to be adjusted to be more accessible to patients with differing degrees of visuospatial impairment.

Variations of the Mental Rotation task have already been tested with non-demented PD patients. Duncombe and colleagues (1994) tested PD patients rotating 2D stick figures on the z-axis and found that they performed as well as healthy controls. Employing a similar paradigm but replacing the figures with faces, Adduri and Marotta (2009) found impairments in AD patients that worsened as the degree of rotation increased. However, the extent of dementia was not controlled for, and the impaired domains were not specified. To date, Mental Rotation tasks have not been utilised in DLB but would appear to hold some utility in assessing visuospatial performance.

The aim of the current study was to assess a novel version of the Mental Rotation task, which incorporated 3D shapes with varying degrees of rotation on the y-axis, to detect differences across DLB and PD patients with matched disease durations, as well as age matched healthy controls. We predicted that performance by the two patient groups would be more impaired than in the healthy controls, and that the DLB group

would have significantly poorer accuracy than the PD group. Furthermore, it was anticipated that performance across attentional and visuospatial domains would be correlated with performance on the Mental Rotation task, as opposed to memory deficits.

3.3.   Methods

3.3.1. Participants

Groups were matched on age, years of education and within the patient groups, disease duration. This resulted in a sample of 22 healthy controls, 22 DLB patients and 22 PD patients. Participants were recruited through the ForeFront Parkinson's Disease Research Clinic (University of Sydney). Informed consent was provided by each patient and the study was approved by the Human Research Ethics Committee at Sydney University. All patients underwent neurological assessment including the Movement Disorder Society Unified Parkinson's Disease Rating Scale for motor features (MDS-UPDRS section III) and a comprehensive neuropsychological battery for cognitive impairments. PD patients were diagnosed using the Movement Disorder Society diagnostic criteria (Postuma et al., 2015), DLB patients were diagnosed using according to the fourth diagnostic consensus criteria (McKeith et al., 2017). Healthy controls were recruited generally as spouses, caregivers, or close relatives and screened for underlying conditions via a clinical interview. Participants were excluded if they less than 6/12 corrected vision or were unable to perform the task, this resulted in the exclusion of no participants. Patients were tested whilst taking their normal medications, with 17 DLB patients taking cholinesterase inhibitors (AChEI) and six DLB patients taking dopaminergic medications.

Procedure 3.3.2

3.3.1.1.   *Mental Rotation Task*

The Mental Rotation (MR) task was adapted from Shepard and Metzler (1971) using E-Prime 2.10(Psychology Software Tools, 2013), which was presented on a 15" laptop. Pairs of shapes that were constructed from 10 cubes and contained two 90°

bends (figure 1) were presented in front of the patient at a comfortable distance. Each shape was either an exact copy of its paired shape (figure 3.1a), or a mirror image (figure 3.1b). Participants were required to indicate if shapes within each pair were the same by pressing a key labelled "Same" or if they were a mirror image by pressing key labelled "Mirror". Each pair was presented until a response was made or after 30 seconds the trial would timeout, which was scored as incorrect. The researcher would also prompt for an answer during trials to make sure the participant was still performing the task to avoid the potential confound of cognitive fluctuations. The initial Shepard and Metzler (Shepard & Metzler, 1971) study presented the pairs with different ranges of rotation on the y-axis from 0 – 180°. However, the current study only used three rotations 0°, 45° and 90°. These rotations proved simple enough for the cognitively impaired sample, whilst still providing enough variance for analysis. Before the test trials, participants were briefed on how to differentiate *same* pairs from *mirror* pairs and given practice examples to complete to ensure they knew how to correctly complete the task. Each rotation condition was presented 18 times in random order. The total number of trials was 54, with a break after 28 trials to minimise fatigue. The average run time was 20 minutes. The main measure of the MR task for the current study was mean accuracy and correct response time (RT) for each rotation condition. Changes in accuracy between difficulties 0° - 45° and 0° - 90° were also calculated to measure potential cost of increasing the rotation between the pairs by 45° or 90°. The minimum score was 50% as this would represent random chance.
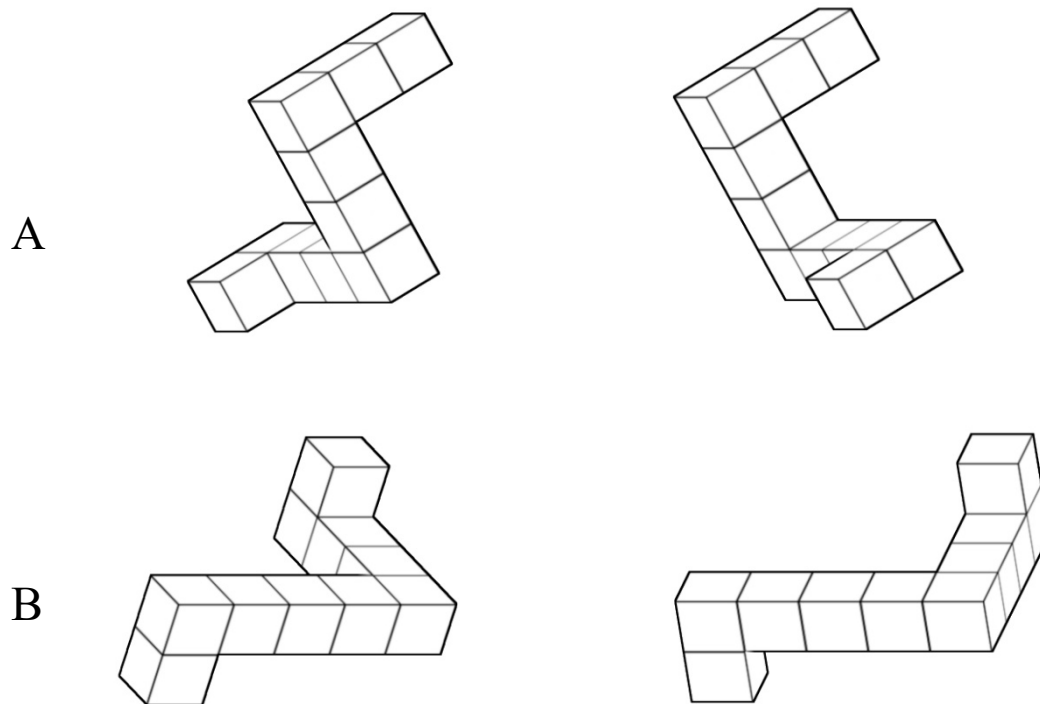
Figure 3.1: A) a pair of mirror image shapes with 0° rotation. B) a pair of identical shape with 45° rotation

3.3.1.2.   *Clinical Measures*

General level of cognitive impairment was measured using the Mini Mental State Examination (MMSE; Folstein et al., 1975). Visual hallucinations were measured using the item 1.2 from MDS-UPDRS, which rates the severity of hallucinations as part of a clinical interview. Severity is scored on a 5-point Likert scale ranging from 0 ("*no hallucinations or psychotic behaviour*") to 4 ("*Patient has delusions and paranoid behaviour*"). Hallucinations were also measured using the Psychosis and Hallucinations Questionnaire (PsycH-Q). The PsycH-Q consists of two main subscales, *Hallucinations and Psychosis* and *Hallucination Phenotypes.* The first subscale probes the severity of hallucinations (e.g. "*over the last month how often did you…*" "*feel like there is something lurking in the corner of your vision*" or "*see people or things that aren't there*"). Other modalities of hallucinations are also identified (i.e. auditory, tactile, olfactory, and gustatory), along with features of psychosis (i.e. disordered thoughts or presence of delusion). The second subscale measures symptoms that commonly co-occur with

hallucinations (i.e. attention difficulties, vivid dreams, and enactment of dreams). Frequency of hallucinatory behaviours and features are measure on a 5-point Likert scale ranging from 0 ("*never*") to 4 ("*daily*"). The PsycH-Q has been validated in a non-demented PD population (Shine et al., 2015a; Shine et al., 2015b). Cognitive fluctuations were also measured using the One Day Fluctuation scale (Walker et al., 2000). This scale measures the prevalence of symptoms associated with fluctuations as observed by a caregiver. Symptoms included impaired attention, communication, drowsiness, disorganised thinking, consciousness, falls and fluctuations of impairment (Walker et al., 2000). Scores range from 0 (no fluctuations) to 21 (severe fluctuations).

3.3.1.3. *Neuropsychological Battery*

Neuropsychological tests included the copy component of the Rey Complex Figure task (RCF; Meyers & Meyers, 1995), Trail-making task parts A and B (Reitan, 1958), digit span (Wechsler, 2008), Stroop test (Strauss, 2006), Controlled Oral Word Association Test (Benton, 1969) and the clock drawing component of the MoCA. Additionally, memory impairment was measured using the Digit span forward and Logical Memory task (Wechsler, 2009)

3.3.2. Statistics

Demographics were compared across the groups using Kruskal-Wallis and Mann-Whitney U tests. Performance of the MR task was analysed using a 3 (HC, PD, DLB) x 3 (0°, 45°, 90°) factorial, mixed repeated measures ANOVA. Due to deviations from normal distribution, potential correlations between MR performance and selected neuropsychological tests were analysed using Spearman correlations. A receiver operator characteristic (ROC) curve was also calculated to determine the accuracy the MR task as at identifying DLB patients from PD and HC patients.

3.4. Results

3.4.1. Demographics

Demographic differences are listed in Table 3.1. All groups were matched on age, years of education and the two patient groups were matched on their disease duration. There were many more females in the HC group compared to the patient groups due to the higher incidence of DLB and PD in males and the use of spousal controls. Parkinson's disease patients were on a higher Dopamine Dose Equivalent (DDE; M = 730, SD 210) than the DLB group (M = 152, SD 246). As anticipated, the groups differed on the MMSE score with DLB (M = 22.2, SD = 6.2), having the poorer performance than HC (M = 29.3, SD = 0.91) and PD (M = 28.7, SD = 1.36) groups. While no difference between MMSE scores for the HC and PD group.

	HC	PD	DLB
N	22	22	22
Age	73.6(5.9)	71.2(3.6)	74.3(6.0)
Gender (males)	9	16	20
Years of education	14.0(3.4)	13.6(3.3)	12.4(3.5)
Disease Duration	n/a	1.18(0.85)	0.45(1.10)
MMSE	29.3(0.91)	28.7(1.36)	22.2(6.2)[a,b]
DDE	n/a	273(210)	152(244)[a]
Hallucinators	n/a	3	15
RBD	n/a	12	21
MDS-UPDRS III	n/a	21.2(8.10)	32.8(14.4)

Table 3.1: Clinical and demographic characteristics of patient populations means (SD). HC = Healthy controls; PD = Parkinson's disease; DLB = Dementia with Lewy bodies; MMSE = Mini Mental State Examination; DDE - Daily Dopamine Equivalent; a = DLB ≠ PD, p < 0.01; b = DLB ≠ HC, p < 0.01

3.4.2. Performance on Mental Rotation

Differences in accuracy between groups and across difficulty levels in the Mental Rotation task was analysed using a mixed repeated measures ANOVA (Table 3.2). The assumption of sphericity was not met, and a Huynh-Feldt correction was used. Additionally, homogeneity of variance was not met, so a Games-Howell correction was used for pairwise comparisons. The interaction of task difficulty and diagnosis was not significant $F(3.47, 109.29) = 0.77$, $p = 0.53$, $\eta^2 = 0.02$. However, there was a significant effect of rotation $F(1.74,109.29) = 52.82$, $p < 0.001$, $\eta^2 = 0.46$. Pairwise comparisons using Sidak correction showed that participants had the most difficulty on the 90° ($p < 0.001$), followed by the 45° ($p < 0.001$) rotation difficulty. There was also an effect of diagnosis, $F(2, 63) = 10.13$, $p < 0.001$, $\eta^2 = 0.24$. Adjusting the alpha to 0.017 for pairwise comparisons, it was found that this effect was driven by the DLB group having a lower accuracy than the HC and PD groups ($p < 0.001$, $p = 0.007$, respectively). There was no significant difference between the HC and PD groups. No difference was found between DLB patients who were taking AChEI and DLB patients not on AChEIs for any of the MR difficulty levels. Changes in accuracy between 0° and 45° were not different between groups, $F(2, 63) = 0.44$, $p = 0.65$ $\eta^2 = 0.01$, nor were they between the 0° and 90° conditions $F(2,63) = 0.25$, $p = 0.8$, $\eta^2 = 0.01$. Receiver operator analysis revealed that total accuracy scores on the MR were 80% accurate at distinguishing DLB patients from HC and PD groups. Setting an accuracy threshold of 80% provides a sensitivity and specificity score of 86% and 47% respectively. Response time was also compared using a mixed measures ANOVA. There was a significant interaction between diagnosis and difficulty $F(4,114) = 5.61$, $p < 0.001$, $\eta = 0.16$. To analyse this interaction further, simple effects were measured using a repeated measures ANOVA for each individual patient group. The effect of difficulty was only significant in the HC group ($F(2,42) = 3.74$, $p < 0.001$, $\eta^2 = 0.4$) as PD and DLB groups were not significant after correcting for multiple comparisons ($p = 0.07$ & $p = 0.03$, respectively). Using pairwise comparison with Sidak correction, the

HC group were significantly quicker at responding for the 0° condition compared with the 45° condition.

3.4.3. Neuropsychological measures

3.4.3.1. *Clinical measures:*

Spearman correlations were performed within the DLB group across the three difficulty levels of the MR task (Table 3.3). No correlation was found between MMSE scores and MR performance across any of these difficulties. Negative correlations were found between the 90° and the PsycH-Q ($r_s(19) = -0.43$, $p = 0.05$) and the 45° trials were trending towards significance ($p = 0.06$). Within the PsycH-Q, the 45° difficulty was negatively correlated with the Hallucination and Psychosis subscale while the 90° difficulty was trending towards significance ($r_s(19) = -0.43$, $p = 0.05$, $r_s(19) = -0.39$, $p = 0.07$, respectively). Accuracy for each difficulty correlated with the Hallucination Phenotype scale ($r_s(19) = -0.50$, $p = 0.02$; $r_s(19) = -0.45$, $p = 0.04$; $r_s(19) = -0.45$, $p = 0.04$, respectively). Furthermore, each difficulty also had strong negative correlations with the visual hallucinations (VH) item of the MDS-UPDRS scale ($r_s(20) = -0.50$, $p = 0.02$; $r_s(19) = -0.69$, $p < 0.001$; $r_s(20) = -0.52$, $p = 0.01$, respectively). Cognitive fluctuations as measured by the ODF were also negatively correlated with accuracy for the 0° and 45° difficulties ($r_s(16) = -0.53$, $p = 0.02$; $r_s(16) = -0.51$, $p = 0.03$, respectively) while the overall accuracy of the MR correlated with the ODF ($r_s(16) = -0.56$, $p = 0.02$).

	0°	45°	90°	0 − 45°	0 − 90°
Accuracy(%)					
HC	89.6(12.4)	79.6(16.5)	72.2(14.0)	-10.1(9.5)	-17.5(14.8)
PD	84.6(15.2)	71.0(18.1)	70.4(17.0)	-13.8(10.7)	-14.3(12.4)
DLB	70.6(22.2)[a]	59.4(15.8)[a]	55.1(10.8)[a]	-11.3(17.1)	-15.6(19.6)
RT (ms)					
HC	4896.99	6250.27	7176.14[c]	1353.28	2279.15
	(2256.98)	(2722.86)	(3186.59)	(2167.24)	(2150.84)
PD	4810.72	5660.21	5162.92	848.76	275.04
	(1801.68)	(2616.62)	(2617.06)	(1530.98)	(1683.06)[b]
DLB	6202.17	7130.58	6040.89	928.41	-161.28
	(2904.05)	(3985.40)	(3178.23)	(2014.17)	(1450.59)[b]

Table 3.2: Mean (SD) Accuracy (%) and RT (ms) for Mental Rotation Task and change of accuracy and RT between difficulties. RT = Response time; HC = Healthy controls; PD = Parkinson's disease; DLB = Dementia with Lewy bodies; a = DLB < PD & HC, p < 0.001; b = < HC, p < 0.001.

Cognitive performance across the groups was compared (Table 3.3). As expected, the DLB group performed poorly with most measures. Dementia with Lewy body patients' performance on the MR task was correlated against measures of visuospatial, executive function and memory impairments (Table 3.4). Significant correlations indicated that the MR task was reliant on visuospatial and executive domains and conversely, there were no correlations between memory and MR performance.

	HC	PD	DLB
Visuospatial			
Clock Drawing	10.00(0.00)	9.68(0.57)[a]	6.85(3.15)[a,b]
RCF – Copy (z-score)	0.40(0.10)	0.34(0.78)	-1.00(2.08)[a]
RCF - Immediate (z-score)	0.65(0.65)	0.17(0.95)	-1.10(0.89)[a,b]
RCF - 20 min delay (z-score)	0.74(0.61)	0.09(0.79)	-1.07(1.03)[a,b]
Trails-A (z-score)	0.73(0.72)	-0.07(0.89)[a]	-3.17(4.09)[a,b]
Executive Function[c]			
Backward Digit Span	7.35(1.83)	7.18(1.53)	4.77(2.79)[a,b]
Verbal Fluency (animals; z-score)	0.79(1.00)	0.61(1.20)	-1.04(1.10)[a,b]
Verbal Fluency (letter F; z-score)	0.60(0.92)	0.56(1.09)	-0.64(1.03)[a,b]
Memory			
Digit span forward	10.35(1.53)	11.36(1.92)	9.10(2.39) [b]
LM - Immediate Recall	12.10(3.24)	9.59(2.97)[a]	5.19(3.28)[a,b]
LM - Delayed Recall	12.52(2.20)	10.23(2.88)[a]	6.40(3.28)[a,b]

Table 3.3: Group differences in cognitive measures. RCF = Rey Complex Figure; LM = Logical Memory; a = < HC; b = < DLB; c = Stroop and Trials B were excluded due to low completion numbers. p = 0.017

| | N | Degrees of rotation (r_s) | | |
		0°	45°	90°
Clinical				
MMSE	21	0.34	0.19	0.15
PsycH-Q - Total	22	-0.39	-0.42	-0.43
Hallucinations and Psychosis	22	-0.26	**-0.43[a]**	-0.35
Hallucination Phenotype	**22**	**-0.50[a]**	**-0.45[a]**	**-0.45[a]**
VH – UPDRS	**22**	**-0.50[b]**	**-0.69[c]**	**-0.52[b]**
One Day Fluctuations Scale	**18**	**-0.53[a]**	**-0.51[a]**	-0.29
MDSUPDRS Section III	22	0.16	-0.04	-0.12
Visuospatial				
Clock Drawing	**21**	0.46[a]	0.50[a]	0.55[a]
RCF - Copy	**15**	0.74[b]	0.79[b]	0.48
RCF - Immediate	15	0.38	0.44	0.51
RCF - 20 min delay	14	0.37	0.50	0.56[a]
Trails-A	18	0.24	0.50[a]	0.54[a]
Executive Function[d]				
Backward Digit Span	**22**	0.47[a]	0.39	0.43[a]
Verbal Fluency (animals)	**21**	0.22	0.18	0.15
Verbal Fluency (letter F)	**21**	0.16	0.07	-0.15
Memory				
Digit span forward	21	0.27	0.33	0.20
LM - Immediate Recall	21	0.29	0.10	0.04
LM - Delayed Recall	20	0.34	0.03	0.05

Table 3.4: Clinical and cognitive Spearman correlations with Mental Rotation accuracy. MMSE = Mini Mental State Examination; PsycH-Q = Psychosis and Hallucinations Questionnaire; MDSUPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; VH = Visual Hallucinations; RCF = Rey Complex Figure; LM = Logical Memory; a = p < 0.05; b = p < 0.01; c = p < 0.001; d = Stroop and Trials B were excluded due to low completion numbers

3.5. Discussion

The current study aimed to test the MR task as a potential tool to assist the differentiation of early DLB from patients with PD. In addition, it was hypothesized that the MR task may provide a sensitive measure of visuospatial impairment that could be used in symptomatic trials for such patients.

Despite being matched for age, education, and disease duration, DLB patients had significantly worse performance than PD patients on the MR task with poorer accuracy when the level of difficulty (degree of rotation) was increased. Similar patterns were seen between DLB patients and Controls.

Importantly, DLB patients were able understand and engage with the task across all levels of cognitive impairment. Performance accuracy was near chance for the 90° difficulty level, indicating that the limits of performance for DLB patients on the MR task lie between 0 to 90°, although future studies would be required to determine the most sensitive range. With the current rotational degrees, the MR had an 80% accuracy of separating DLB from the other two groups. Additionally, with an accuracy threshold set to 80% the MR had high sensitivity, but low specificity. With the potential limit of the DLB ability at 90° of rotation, decreasing this rotation may increase the specificity without significantly decreasing the sensitivity.

As predicted MR performance in DLB was correlated with measures of visuospatial ability and executive function. For example, clock drawing was related to performance on the 45 and 90° conditions of the MR, which probably reflects the fact that patients would rely on internally visualising the stimulus before successfully drawing a clock or comparing the shapes presented in the MR task (Pezzoli et al.,

2021). Working memory, as measured with backward digit span, also correlated with accuracy on the MR task. This is in line with previous research supporting the role of executive function in the manipulation of internally visualised stimuli (Mazhari & Moghadas Tabrizi, 2014). However, there was no difference in the cost of increasing the rotation between the groups. This was also supported with non-significant interaction between groups and task difficulty. This could suggest that working memory is not a strong driver of the results. Alternatively, the lack of effect here could be due to the DLB group performing poorly at 45° and near chance for 90°, or low power due to a small sample size. Interestingly, deficits in memory as measured by recall and delayed recall were also not correlated with MR accuracy, suggesting a memory component may be involved in the visualisation and rotation of the object. Perhaps because of a lower reliance on this domain.

Within the DLB cohort, MR performance also appeared to be linked to visuoperceptive symptoms as patients who experienced more frequent and/or severe visual hallucinations were less accurate with the MR task. This is consistent with previous work that has linked poor performance on other visuospatial tests with presence of VH in DLB patients (Rosenblum et al., 2021). In addition, a high occurrence of cognitive fluctuations was also associated with poor MR performance. The basis of this observation is less clear, as patients with severe fluctuations have also been shown to perform poorly on attentional tasks (Phillips et al., 2019). Thus, it may be that patients with poor attention or concentration might struggle to perform MR.

The findings of this study suggest that DLB patients can complete the MR task when the degrees of rotation are not too great, given that their ability to visualise and manipulate objects is impaired but they were able to simply match stimuli at 0°. Thus, one advantage of the MR paradigm in future studies would be that the difficulty of the task may be manipulated and individualised to a patient's own performance. Thus, future symptomatic or disease modifying trials could optimise the sensitivity of the MR task to an individual patient's performance at baseline and then measure their response to an intervention ensuring that they were sensitive enough to measure and

track effects. In addition, the MR task could be made increasingly difficult to probe subtle visuospatial impairment that might be present in proposed prodromal DLB cohorts (McKeith et al., 2020). Indeed, in patients with isolated REM Sleep behaviour disorder (a prodromal stage of Lewy body diseases), the MR task may be a useful tool to distinguish those patients who may phenoconvert to DLB instead of PD (Postuma et al., 2019).

Previous studies have demonstrated that non-cognitively impaired individuals may employ strategies to assist them with mental rotation tasks. These strategies appear to improve accuracy and response time, (Berneiser et al., 2018; Nagashima et al., 2019) as well allowing participants to better adapt to changes in stimuli(Zhao & Sala, 2018). While the current study did not focus on potential strategies that patients may have used during the MR task, it would be interesting to see if a cognitively impaired group would be able to employ such strategies and if these strategies would benefit their performance.

When interpreting the findings of this study there are several limitations that should be acknowledged. The first is that there was no comparison with an AD group, which would have been more ideal given that the cognitive profiles of DLB and AD may be similar with many professionals misdiagnosing DLB patients with AD and vice versa. Interestingly, our findings did not identify any correlation between MR performance and memory impairment, which is the most prominently affected domain in patients with AD (especially early in the disease course) and so we would hypothesize that MR may be more sensitive in patients with DLB than AD. Additionally, few studies have looked at the sensitivity of visuospatial tests for differentiating between these two cohorts. Using the revised Addenbrooke's Cognitive Examination, which consist of memory measures as well as measures of executive function, attention and visuospatial ability, accuracy of differentiating between DLB and AD was vastly improved when emphasis was placed on the non-amnestic scores (Prats-Sedano et al., 2021). This highlights the utility of using non-amnestic measures to differentiate between the two diseases. Indeed, Ota and

colleagues (2015) found that using a battery of visuospatial tests had a high sensitivity, but low specificity at separating DLB from AD. This suggests that while visuospatial tests are very useful in differential diagnosis, more tasks may be needed to improve the overall specificity. Further research is needed to investigate differences in performance between DLB and AD patients, and if the diagnostic accuracy can be improved through adjustments to the degrees of rotation. The second potential limitation of this study was that the majority (17/22) of the DLB patients were treated with a cholinesterase inhibitor to improve cognition (Wesnes et al., 2002). However, there was no difference in MR performance between those patients with and without AChEI treatment and one might anticipate that if anything, being on this therapy might have reduced our ability to detect an effect, which was not the case. The third limitation of the current study was its small sample size of DLB patients. However, this is a well-phenotyped cohort of DLB patients diagnosed using the most recent criteria (McKeith et al., 2017) and the numbers tested were comparable with similar previous behavioural studies (Bliwise et al., 2014; Johns et al., 2009; Park et al., 2011). Finally, it should be highlighted that many of the DLB patients tested were performing at chance for the 90° condition. This would have created a ceiling effect, thus reducing the amount of variance potentially leading to type II errors for these correlations. Future research would benefit from decreasing the maximum degrees of rotation, whilst also having more increments to identify the rotation where DLB patients begin to fail.

In summary, we identified that the MR task may be a sensitive tool for distinguishing DLB from early PD patients, with performance appearing to be correlated selectively with visuospatial, attention and working memory deficits but not long-term memory. The ability of even quite severely impaired DLB patients to engage with this task suggests that its use should be explored in future clinical trials evaluating visuospatial impairment, where task difficulty could be matched to individual baseline performance.

3.6. References

Aarsland, D., Rongve, A., Nore, S. P., Skogseth, R., Skulstad, S., Ehrt, U., Hoprekstad, D., & Ballard, C. (2008). Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord*, *26*(5), 445-452. https://doi.org/10.1159/000165917

Adduri, C. A., & Marotta, J. J. (2009). Mental rotation of faces in healthy aging and Alzheimer's disease. *PLoS One*, 4(7), e6120. https://doi.org/10.1371/journal.pone.0006120

Benton, A. L. (1969). Development of a multilingual aphasia battery. Progress and problems. *J Neurol Sci*, *9*(1), 39-48.

Berneiser, J., Jahn, G., Grothe, M., & Lotze, M. (2018). From visual to motor strategies: Training in mental rotation of hands. *Neuroimage*, *167*, 247-255. https://doi.org/10.1016/j.neuroimage.2016.06.014

Bird, C. M., Chan, D., Hartley, T., Pijnenburg, Y. A., Rossor, M. N., & Burgess, N. (2010). Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus*, *20*(10), 1154-1169. https://doi.org/10.1002/hipo.20715

Bliwise, D. L., Scullin, M. K., & Trotti, L. M. (2014). Fluctuations in cognition and alertness vary independently in dementia with Lewy bodies. *Mov Disord*, *29*(1), 83-89. https://doi.org/10.1002/mds.25707

Bourrelier, J., Kubicki, A., Rouaud, O., Crognier, L., & Mourey, F. (2015). Mental Rotation as an Indicator of Motor Representation in Patients with Mild Cognitive Impairment. *Front Aging Neurosci*, *7*, 238. https://doi.org/10.3389/fnagi.2015.00238

Calderon, J., Perry, R. J., Erzinclioglu, S. W., Berrios, G. E., Dening, T. R., & Hodges, J. R. (2001). Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *J*

Neurol Neurosurg Psychiatry, *70*(2), 157-164. https://doi.org/10.1136/jnnp.70.2.157

Chertkow, H., Feldman, H. H., Jacova, C., & Massoud, F. (2013). Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimers Res Ther*, *5*(Suppl 1), S2-S2. https://doi.org/10.1186/alzrt198

Duncombe, M. E., Bradshaw, J. L., Iansek, R., & Phillips, J. G. (1994). Parkinsonian patients without dementia or depression do not suffer from bradyphrenia as indexed by performance in mental rotation tasks with and without advance information. *Neuropsychologia, 32*(11), 1383-1396. https://doi.org/10.1016/0028-3932(94)00071-9

Flicker, C., Ferris, S. H., Crook, T., Reisberg, B., & Bartus, R. T. (1988). Equivalent spatial-rotation deficits in normal aging and Alzheimer's disease. *J Clin Exp Neuropsychol*, *10*(4), 387-399. https://doi.org/10.1080/01688638808408247

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, *12*(3), 189-198.

Foltynie, T., Brayne, C. E., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain*, *127*(Pt 3), 550-560. https://doi.org/10.1093/brain/awh067

Freeman, R. Q. (1999). *Visuoconstructional performance of Alzheimer's, Vascular and Parkinson's disease patients on the Rey-Osterrieth complex figure*. Drexel University.

Freeman, R. Q., Giovannetti, T., Lamar, M., Cloud, B. S., Stern, R. A., Kaplan, E., & Libon, D. J. (2000). Visuoconstructional problems in dementia: contribution of executive systems functions. *Neuropsychology*, *14*(3), 415-426. https://doi.org/10.1037//0894-4105.14.3.415

Génier Marchand, D., Postuma, R. B., Escudier, F., De Roy, J., Pelletier, A., Montplaisir, J., & Gagnon, J. F. (2018). How does dementia with Lewy bodies start?

prodromal cognitive changes in REM sleep behavior disorder. *Ann Neurol*, *83*(5), 1016-1026. https://doi.org/10.1002/ana.25239

Grossi, D., Carotenuto, A., Trojano, L., Manzo, V., & Fasanaro, A. M. (2011). Do frontal dysfunctions play a role in visual hallucinations in Alzheimer's disease as in Parkinson's disease? a comparative study. *Psychology & Neuroscience, 4*, 385-389.

Jellinger, K. A., & Attems, J. (2011). Prevalence and pathology of dementia with Lewy bodies in the oldest old: a comparison with other dementing disorders. *Dement Geriatr Cogn Disord*, *31*(4), 309-316. https://doi.org/10.1159/000327360

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., Ska, B., Gilbert, B., Inglis, G., Panisset, M., de Boysson, C., & Chertkow, H. (2009). Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*, *23*(6), 765-777. https://doi.org/10.1037/a0016792

Kane, J. P. M., Surendranathan, A., Bentley, A., Barker, S. A. H., Taylor, J.-P., Thomas, A. J., Allan, L. M., McNally, R. J., James, P. W., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2018). Clinical prevalence of Lewy body dementia. *Alzheimers Res Ther*, *10*(1), 19. https://doi.org/10.1186/s13195-018-0350-6

Kemp, J., Philippi, N., Phillipps, C., Demuynck, C., Albasser, T., Martin-Hunyadi, C., Schmidt-Mutter, C., Cretin, B., & Blanc, F. (2017). Cognitive profile in prodromal dementia with Lewy bodies. *Alzheimers Res Ther*, *9*(1), 19. https://doi.org/10.1186/s13195-017-0242-1

Lee, A. C., Harris, J. P., & Calvert, J. E. (1998). Impairments of mental rotation in Parkinson's disease. *Neuropsychologia*, *36*(1), 109-114. https://doi.org/10.1016/S0028-3932(97)00017-1

Lineweaver, T. T., Salmon, D. P., Bondi, M. W., & Corey-Bloom, J. (2005). Differential effects of Alzheimer's disease and Huntington's disease on the performance of mental rotation. *J Int Neuropsychol Soc*, *11*(1), 30-39. https://doi.org/10.1017/s1355617705050034

Martini, A., Weis, L., Schifano, R., Pistonesi, F., Fiorenzato, E., Antonini, A., & Biundo, R. (2020). Differences in cognitive profiles between Lewy body and Parkinson's

disease dementia. *J Neural Transm (Vienna)*, *127*(3), 323-330. https://doi.org/10.1007/s00702-019-02129-2

Mazhari, S., & Moghadas Tabrizi, Y. (2014). Abnormalities of mental rotation of hands associated with speed of information processing and executive function in chronic schizophrenic patients. *Psychiatry Clin Neurosci*, *68*(6), 410-417. https://doi.org/10.1111/pcn.12148

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/WNL.0000000000004058

McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., Kantarci, K., Muscio, C., O'Brien, J. T., Postuma, R. B., Aarsland, D., Ballard, C., Bonanni, L., Donaghy, P., Emre, M., Galvin, J. E., Galasko, D., Goldman, J. G., Gomperts, S. N., Honig, L. S., Ikeda, M., Leverenz, J. B., Lewis, S. J. G., Marder, K. S., Masellis, M., Salmon, D. P., Taylor, J. P., Tsuang, D. W., Walker, Z., Tiraboschi, P., & prodromal, D. L. B. D. S. G. (2020). Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology*, *94*(17), 743-755. https://doi.org/10.1212/WNL.0000000000009323

McKeith, I. G., O'Brien, J., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Padovani, A., Giubbini, R., Bonuccelli, U., Volterrani, D., Holmes, C., Kemp, P., Tabet, N., Meyer, I., & Reininger, C. (2007). Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol*, *6*(4), 305-313. https://doi.org/10.1016/s1474-4422(07)70057-1

Meyers, J., & Meyers, K. (1995). Rey Complex Figure Test and Recognition Trial. In *Psychological Assessment Resources*.

Mondon, K., Gochard, A., Marque, A., Armand, A., Beauchamp, D., Prunier, C., Jacobi, D., de Toffol, B., Autret, A., Camus, V., & Hommet, C. (2007). Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia. *J Neurol Neurosurg Psychiatry*, *78*(7), 738-741. https://doi.org/10.1136/jnnp.2006.104257

Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). The prognosis of dementia with Lewy bodies. *Lancet Neurol, 16*(5), 390-398. https://doi.org/10.1016/s1474-4422(17)30074-1

Nagashima, I., Takeda, K., Shimoda, N., Harada, Y., & Mochizuki, H. (2019). Variation in Performance Strategies of a Hand Mental Rotation Task on Elderly. *Front Hum Neurosci*, *13*, 252. https://doi.org/10.3389/fnhum.2019.00252

Oostra, K. M., Vereecke, A., Jones, K., Vanderstraeten, G., & Vingerhoets, G. (2012). Motor imagery ability in patients with traumatic brain injury. *Arch Phys Med Rehabil*, *93*(5), 828-833. https://doi.org/10.1016/j.apmr.2011.11.018

Ota, K., Murayama, N., Kasanuki, K., Kondo, D., Fujishiro, H., Arai, H., Sato, K., & Iseki, E. (2015). Visuoperceptual assessments for differentiating dementia with Lewy bodies and Alzheimer's disease: illusory contours and other neuropsychological examinations. *Arch Clin Neuropsychol*, *30*(3), 256-263. https://doi.org/10.1093/arclin/acv016

Park, K. W., Kim, H. S., Cheon, S. M., Cha, J. K., Kim, S. H., & Kim, J. W. (2011). Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's

Disease Dementia: A Comparison of Cognitive Profiles. *J Clin Neurol*, *7*(1), 19-24. https://doi.org/10.3988/jcn.2011.7.1.19

Pezzoli, S., Cagnin, A., Bussè, C., Zorzi, G., Fragiacomo, F., Bandmann, O., & Venneri, A. (2021). Cognitive correlates and baseline predictors of future development of visual hallucinations in dementia with Lewy bodies. *Cortex*, *142*, 74-83. https://doi.org/10.1016/j.cortex.2021.05.018

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (2019). Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia With Lewy Bodies. *J Geriatr Psychiatry Neurol*, 891988719882093. https://doi.org/10.1177/0891988719882093

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*, *30*(12), 1591-1601. https://doi.org/10.1002/mds.26424

Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., Oertel, W. H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K. Y., Kunz, D., Dauvilliers, Y., Provini, F., Lewis, S. J., Buskova, J., Pavlova, M., Heidbreder, A., Montplaisir, J. Y., Santamaria, J., Barber, T. R., Stefani, A., St Louis, E. K., Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J. F., Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M., Mahlknecht, P., Holzknecht, E., Boeve, A. R., Teigen, L. N., Toscano, G., Mayer, G., Morbelli, S., Dawson, B., & Pelletier, A. (2019). Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*, *142*(3), 744-759. https://doi.org/10.1093/brain/awz030

Prats-Sedano, M. A., Savulich, G., Surendranathan, A., Donaghy, P. C., Thomas, A. J., Rowe, J. B., Su, L., & O'Brien, J. T. (2021). The revised Addenbrooke's Cognitive

Examination can facilitate differentiation of dementia with Lewy bodies from Alzheimer's disease. *Int J Geriatr Psychiatry*, *36*(6), 831-838. https://doi.org/10.1002/gps.5483

Psychology Software Tools, I. (2013). *E-Prime 2.0.* In Psychology Software Tools, Inc.

Quental, N., Brucki, S., & Bueno, O. (2013). Visuospatial Function in Early Alzheimer's Disease—The Use of the Visual Object and Space Perception (VOSP) Battery. *PLoS One*, *8*(7). https://doi.org/http://dx.doi.org/10.1371/journal.pone.0068398

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*, *8*(3), 271-276.

Rosenblum, Y., Bregman, N., Giladi, N., Mirelman, A., & Shiner, T. (2021). Associations between visual hallucinations and impaired visuo-spatial abilities in dementia with Lewy bodies. *Neuropsychology*, *35*(3), 276-284. https://doi.org/10.1037/neu0000728

Shepard, R. N., & Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science*, *171*(3972), 701-703.

Shine, J. M., Mills, J. M. Z., Qiu, J., O'Callaghan, C., Terpening, Z., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2015a). Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease. *Movement Disorders Clinical Practice*, *2*(2), 175-181.

Shine, J. M., Muller, A. J., O'Callaghan, C., Hornberger, M., Halliday, G. M., & Lewis, S. J. (2015b). Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. *NPJ Parkinsons Dis*, *1*, 15003. https://doi.org/10.1038/npjparkd.2015.3

Simard, M., van Reekum, R., & Myran, D. (2003). Visuospatial impairment in dementia with Lewy bodies and Alzheimer's disease: a process analysis approach. *Int J Geriatr Psychiatry*, *18*(5), 387-391. https://doi.org/10.1002/gps.839

Smirnov, D. S., Galasko, D., Edland, S. D., Filoteo, J. V., Hansen, L. A., & Salmon, D. P. (2020). Cognitive decline profiles differ in Parkinson disease dementia and

dementia with Lewy bodies. *Neurology*, *94*(20), e2076-e2087. https://doi.org/10.1212/wnl.0000000000009434

Strauss, E. (2006). *A compendium of neuropsychological tests : administration, norms, and commentary* (3rd ed. ed.). New York : Oxford University Press.

van de Beek, M., van Steenoven, I., van der Zande, J. J., Barkhof, F., Teunissen, C. E., van der Flier, W. M., & Lemstra, A. W. (2020). Prodromal Dementia With Lewy Bodies: Clinical Characterization and Predictors of Progression. *Mov Disord*, *35*(5), 859-867. https://doi.org/10.1002/mds.27997

Vann Jones, S. A., & O'Brien, J. T. (2014). The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med*, *44*(4), 673-683. https://doi.org/10.1017/s0033291713000494

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000). The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale: Two methods to assess fluctuating confusion in dementia. *British Journal of Psychiatry*, *177*(3), 252-256. https://doi.org/10.1192/bjp.177.3.252

Warrington, E. K., James, M. (1991). *The Visual Object and Space Perception Battery*. Thames Valley Test Company.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition: Administration and scoring manual*. NCS Pearson.

Wechsler, D. (2009). *The Wechsler memory scale - fourth edition (WMS-IV)*. Pearson Assessment.

Wesnes, K. A., McKeith, I. G., Ferrara, R., Emre, M., Del Ser, T., Spano, P. F., Cicin-Sain, A., Anand, R., & Spiegel, R. (2002). Effects of rivastigmine on cognitive function in dementia with lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. *Dement Geriatr Cogn Disord*, *13*(3), 183-192. https://doi.org/48651

Zhao, B., & Sala, S. D. (2018). Different representations and strategies in mental rotation. *Q J Exp Psychol (Hove)*, *71*(7), 1574-1583. https://doi.org/10.1080/17470218.2017.1342670

Chapter Four

4. **Evaluating a novel behavioral paradigm for visual hallucinations in Dementia with Lewy Bodies**

This study was published in Aging Brain:

4.1. Abstract

The aim of this study was to evaluate the utility of the Bistable Percept Paradigm (BPP), a computerised behavioural task that has previously been utilised for the assessment of visual hallucinations in Parkinson's Disease, in a Dementia with Lewy bodies (DLB) cohort. DLB patients demonstrated poorer performance than healthy controls (HC) on the BPP with significantly more misperceptions and a greater failure to detect bistable percepts correctly compared to HC. Further, the number of misperceptions was also correlated with the severity of hallucinations. The findings from this study demonstrate that the BPP is a viable tool to measure misperceptions in DLB patients.

Key words: Dementia with Lewy Bodies; visual hallucinations; misperceptions.

4.2. Introduction

Dementia with Lewy Bodies (DLB) is a neurodegenerative disease with a similar dementia profile to Parkinson's disease with dementia (PDD) and some overlap with the clinical features of Parkinson's disease (PD; Jellinger, 2018). Indeed both DLB and PDD are characterised by the abnormal deposition of α-synuclein in the brain, typically accompanied by less severe Alzheimer-type pathology (Maetzler et al., 2010). Although often under- and misdiagnosed, DLB is the second most common pathologically confirmed cause of dementia (Hogan et al., 2016; Kane et al. 2018) after Alzheimer's Dementia (AD). Importantly, DLB patients are reported to experience a more rapid cognitive decline than that found in AD (Mueller et al., 2017), as well as having fewer treatment options (Arnaoutoglou et al., 2019), which results in a lower quality of life (Mueller et al., 2017) and higher mortality rate (Price et al., 2017). Additionally, the high burden of neuropsychiatric symptoms, including visual hallucinations (VH), results in higher levels of caregiver stress (Svendsboe et al., 2016) and earlier admission into full-time care facilities (Rongve et al., 2014).

The diagnosis of probable DLB requires that the patient presents with dementia that is associated with at least two of the following core symptoms: REM sleep behavior disorder (RBD), cognitive fluctuations, spontaneous parkinsonism or VH (McKeith et al. 2017). Previous studies have suggested that 60-80% of DLB patients have VH (Chiu et al., 2018; Eversfield & Orton, 2018; McKeith et al., 2017; Onofrj et al., 2013), although work utilizing the most recent diagnostic criteria in newly diagnosed patients identified that only 44% experienced well-formed VH with 15% reporting visual misperceptions. It has been proposed that VH in Lewy Body diseases (DLB, PD and PDD) tend to follow a path of increasing severity (Ffytche et al., 2017), where initially patients experience misperceptions or feelings of presence before seeing poorly formed shapes, which often progress into well-formed images of objects,

animals or people with advancing disease. With this progression there is commonly an increasing lack of insight, which can make management even more challenging.

Current methods for detecting VH in DLB involve self-report scales and semi-structured clinical interviews, which may prove over reliant on a patient's insight or the observations made by their caregivers. Additionally, patients may resist reporting VH due to the stigma attached to them (Mosimann et al., 2008). Many scales and interviews reduce the complexities of VH to one or two items and there are limitations to using continuous and categorical scales given that patients may experience variable levels of phenomena. Therefore, utilising a behavioral task that is sensitive to the presence of VH would help to minimize some of these issues and provide an objective measurement. However, inducing VH in a clinical setting is difficult and traditional methods, such as flickering stimuli, have been found to be ineffective in PD populations (Zarkali et al., 2019).

There are two tasks that have been recently used to measure misperceptions in patients with Lewy body diseases (DLB and PD): the Pareidolia test and the Bistable Percept Paradigm (BPP). The Pareidolia test is designed to measure an individual's susceptibility to pareidolias - a variation of misperceptions where people see faces in non-facial stimuli (Uchiyama et al., 2012). In a RBD population, patients who made more errors in the pareidolia test were also more likely to transition to DLB (Honeycutt et al., 2020). Dementia with Lewy body patients also make more pareidolia errors than AD patients (Inagawa et al., 2020; Mamiya et al., 2016); which was also associated with VH measures from the neuropsychiatric inventory questionnaire (NPI; Mamiya et al. 2016). Whilst these studies demonstrate the utility of a behavioral task for detecting VH in DLB, the Pareidolia test does not capture other visual misperceptions or when a patient fails to correctly identify all of the elements in a scene.

The other testing paradigm sensitive to misperceptions in Lewy body diseases is the BPP (Shine et al., 2012). This computerized task presents participants with a series of monostable (Figure 1a) and bistable percepts (Figure 1b) to which they have to respond via a button press, allowing for the generation of an error score (Shine et al., 2012; Shine et al., 2014a). The BPP has been used with PD populations to compare patients with and without VH with performance being correlated with the severity of the hallucinatory phenomenon (Shine et al., 2012). Furthermore, the BPP has been used in combination with functional MRI (Shine et al. 2014, Shine et al. 2015) to highlight the role played by the attentional networks in the pathophysiology underlying VH (Shine et al., 2011; Shine et al., 2014b).

The current study was designed to investigate the feasibility of using the BPP in patients with DLB. We hypothesised that patients with DLB would demonstrate more misperceptions and have greater impairments in the recognition of bistable percepts compared to healthy controls in keeping with PD patients with VH. We also anticipated that these objective measures would be correlated with rating scales measuring hallucinatory phenomena. The identification of a robust objective measure for VH in DLB would be invaluable for future research and clinical trials.

4.3. Methods

4.3.1. Participants

The study included 23 patients diagnosed with probable DLB according to consensus criteria outlined by the fourth report of the DLB Consortium (McKeith et al., 2017) and 20 healthy age-matched controls. Participants with less than 6/12 corrected vision were excluded from the study. DLB patients were taking their normal medications during testing; 18 were on cholinesterase inhibitors (CHEI), 10 were on dopamine agonists, six were on serotonin reuptake inhibitors (SSRI), two were on

benzodiazepines, one was taking atypical antipsychotics and another patient was taking monoamine oxidase type B inhibitor. Two DLB patients had glaucoma during the testing. All patients were assessed on their regular medication and recruited through the PD Research Clinic at the Brain and Mind Centre, University of Sydney, Australia. The study was approved by the Sydney University Human Research Ethics Committee. All patients provided written consent before undertaking any testing.

4.3.2. Apparatus/Procedure

The BPP was administered on a 15" laptop using E-Prime (Psychology Software Tools, 2013) and the details of the task have been previously reported elsewhere (Shine et al., 2012). In brief, participants were instructed to verbally indicate whether each image was a *single image* (stable; see image 4.1a) or a *hidden image* (bi-stable; see image 4.1b) and respond with the appropriate button response. They were also required to give a brief description of the image to ensure that they correctly perceived the image and so that any incorrect button responses could be addressed. Responses to a single image were scored as correct if the participant correctly classified and identified the image. Hidden images were scored as correct if the participant classified the image as a hidden image and correctly identified the two components to the image. Misperceptions were scored if the participant described a feature that did not exist for either single or bistable images (e.g. describing a face in the grass of Figure 4.1a); even if they correctly classified the image. Misses were scored when the participant failed to identify the presence of a bistable percept. The BPP produces three main measures: the number of misses, the number of misperceptions and an error score which is calculated by averaging the percentage of misses with the percentage of misperceptions. An error score above 11% suggest impairment in the BPP task (Shine et al., 2012).

Figure 4.2: Stable (a) and bistable (b) images used in the BPP

Visual hallucinations were measured using item 1.2 from the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS; Goetz et al. 2008) and the Psychosis and Hallucinations Questionnaire (PsycH-Q; Shine et al. 2015). The MDS-UPDRS is a semi-structured clinical interview performed by a clinician. Item 1.2 on the MDS-UPDRS rates the severity of VH on a five-point Likert scale ranging from 0 (*"no hallucinations or psychotic behaviour"*) to 4 (*"Patient has delusions and paranoia"*). The PsycH-Q is a self-report questionnaire that consists of subscales. The first of these subscales (Hallucinations and Psychosis), probes the severity of visual hallucinations (e.g. "over the last month how often did you"… "feel like there is something lurking in the corner of your vision" or "see people or things that aren't there"), as well as seeking to identify other hallucinatory phenomena (i.e. auditory, tactile, olfactory and gustatory) and any features of psychosis (e.g. occurrence of disordered thoughts or presence of delusion). The second subscale (Hallucination Phenotypes) measures the occurrence of symptoms that often co-occur in patients with hallucinations (e.g. difficulties with attention or symptoms of dream enactment - RBD). Occurrences are measured using a Likert scale ranging from 0 (never) to 4 (daily). It has been validated

in a non-demented PD population (Shine et al. 2015). General cognitive impairment was measured using the Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975). Cognitive fluctuations were measured using the Clinical Assessment of Fluctuations (CAF) scale (Walker et al., 2000). Attention impairment was measured with the Trails Making Test (TMT) A and B (Reitan, 1958) while set shifting was measured as the difference between the TMT_A and TMT_B (TMT_{B-A}; Naismith et al. 2010). Times were standardized and scores below -1.5 were considered as impaired (Lezak et al., 2012). Visuospatial ability was measured using the copy component of the Rey Complex Figure (Meyers & Meyers, 1995) as well as the clock drawing component of the MMSE (Folstein et al., 1975). The Rey Complex Figure was scored using the (Meyers & Meyers, 1995) method. Scores were standardised with scores below -1.5 considered as impaired (Martini et al., 2020). Clock drawing performance was scored as outlined in Kitabayashi et al. (2001).

4.3.3. Statistical Analysis

Analysis was performed using SSPS 26 (IBM, 2019). The data was not normally distributed, requiring non-parametric tests to compare groups. Demographic information and BPP error scores were compared across the two groups (DLB vs HC) using Mann-Whitney U. The relationship between PsycH-Q, the MDS-UPDRS VH item and BPP scores were evaluated using Spearman's correlations.

4.4. Results

4.4.1. Demographics

Demographic data are presented in Table 4.1. The two groups did not differ in age ($\chi^2(43) = -1.40$, $p = 0.16$, $r^2 = 0.05$) or years of education ($\chi^2(43) = -1.39$, $p = 0.17$, $r^2 = 0.05$). The DLB group had a median MMSE score within the mild impairment range (mean = 21.70, min = 8, max = 29) and as expected were significantly worse than the HC group (mean = 29.26, min = 27, max = 30; $\chi^2(43) = -4.84$, $p < 0.001$, $r^2 = 0.57$). The DLB group

contained more males than the HC group ($\chi^2(43) = -3.26$, $p < 0.01$, $r^2 = 0.28$), reflecting the typical gender prevalence of the condition.

Measure	HC	DLB
N	20	23
Age yr	69.95(73)	73.91(75)
Hoehn and Yahr, stage		1.62(2)
Years of Education, yr	12.95(15)	11.36(12)
MMSE	29.22(30)*	21.69(22)*
Rey Complex Figure Copy (z-score)	0.39(0.43)	-1.57(-0.39)**
Clock	9.9(10)	7.09(8)***
TMT$_A$ (s)	29.90(27.81)	104.41(72.11)***
MDSUPDRS 1.2	0	1.8(2)***
PsycH-Q total	3(4)	16.95**
Hallucinations and Psychosis	0.29(0)	7.59(6)**
Hallucination Phenotype	2.71(2)	11.09(12)**

*Table 4.1: Demographics. Note All values are means (median); Comparisons made using Mann Whitney U; * = p < 0.05, ** = P < 0.01, *** p < 0.001; HC = Healthy controls; DLB = Dementia with Lewy bodies; MMSE = Mini Mental State Exam; TMT$_A$ = Trails Making Test A; MDSUPDRS = Movement Disorder Society Unified Parkinson Disease Rating Scale; PsycH-Q = Psychosis and Hallucinations Questionnaire*

4.4.2. Dementia with Lewy Body Clinical Profile

Cognitive fluctuations were present in 13 patients as indicated by CAF scores of five or greater. Eight patients were unable to complete the copy portion of the Rey Complex Figure due to fatigue or low tolerance for the exercise. Of the remaining 14 patients seven patients scored below -1.5 SD, indicating impairment. Twenty two patients were able to complete the clock drawing component of the MMSE. Eight patients displayed impairment (score < 8), five of these had severe impairment (score

< 3). Five patients were unable to complete the TMT$_A$ task. From the remaining 18 patients, 12 had a score below 1.5 SD, indicating impairment. Seven patients were able to complete the TMT$_B$, five refused to attempt the task while 11 patients took longer than the 300s time limit and were therefore given a score of 300 s (Table 4.2).

Using the MDSUPRS and the Hallucinations and Psychosis subscale of the PsycH-Q as measure of VH; 20 patients indicated that they experienced visual misperceptions or hallucinations on either scale, while three patients scored 0 in both measures.

Domain (test)	No. impaired	No. non-impaired	Unable to complete
Cognitive Fluctuations (CAF)	13	10	0
Visuospatial impairment (RCF, copy & Clock drawing)	12	11	0
Visual hallucinations (MDSUPDRS & PsycH-Q)	20	3	0
Attention (TMT$_A$)	12	6	5

Table 4.2: Clinical characteristics of the DLB patients. Note: CAF = Clinical Assessment of Fluctuations; RCF = Rey Complex Figure; MDSUPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; PsycH-Q = Psychosis and Hallucinations Questionnaire; TMT$_A$ = Trails Making Test A.

4.4.3. BPP Performance

Performance is presented in Table 4.3. The DLB group had a higher BPP error rate than the HC group (m = 9.25%, SD = 4.45%; $\chi^2(43)$ = -4.02, p < 0.001). The DLB group also had more misperceptions ($\chi^2(43)$ = -3.09, p = 0.011, r^2 = 0.22) and misses ($\chi^2(43)$ = -2.53, p = 0.002, r^2 = 0.15) than the HC group (Figure 4.2). The number of misperceptions or misses was not correlated with MMSE scores ($r_s(20)$ = -0.026, p = 0.91; $r_s(20)$ = -0.22,

p = 0.33 respectively). The effect of medications on BPP performance were also analysed. Patients on SSRIs had more misses than patients not on SSRIs ($\chi^2(23)$ = -2.27, p = 0.02, r^2 = -0.47) but they did not experience greater misperceptions. No significant effects on BPP measures in those patients taking CHEIs or on dopamine agonists were found, nor any correlations between CHEI dose and BPP measures. No correlations were found between cognitive fluctuations, MMSE, visuospatial or attention impairment (Table 4.4) Analysis was also repeated with the exclusion of two DLB patients with glaucoma. Excluding these patients did not change the findings of the study.

	HC	DLB	DLBVH	DLBnonVH
N	20	23	20	3
BPP error rate	9.25%(8.75%)	17.66%(16.25%)	17.69%(15.63%)	17.50%(17.50%)
Misperceptions	1.95(1.73)	5.83(4.73)	6.10(5)	1.33(2)
Misses	5.45(2.84)	8.52(4.47)	8.05(9)	12.67(14)

Table 4.3: Mean (median) BPP scores across the two groups. Note: Due to imbalance group size, comparative statistics was not performed.
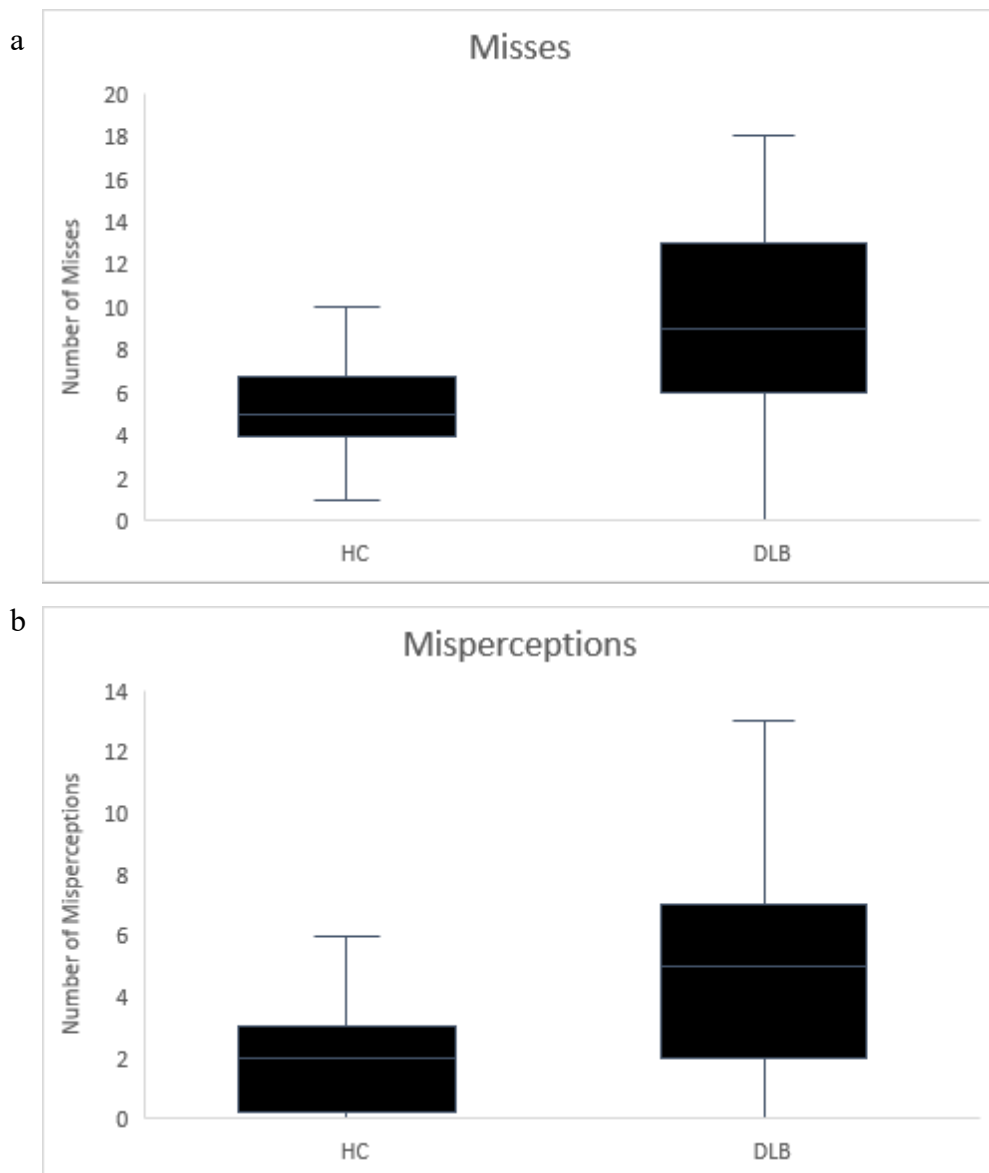
Figure 4.2: Box plots illustrating the differences between healthy controls (HC) and dementia with Lewy bodies (DLB) for misses (a) and misperceptions (b) in the BPP.

|	N	Misperceptions (r_s)	Misses (r_s)	Error Rate (r_s)
MDSUPDRS	22	0.20	0.13	0.18

	N			
PsycH-Q: Total	22	-0.03	-0.26	-0.25
Hallucinations and Psychosis	22	0.32	-0.06	0.16
Visual Misperception	22	0.44*	-0.20	0.25
Sensory Misperceptions	22	0.05	0.01	0.08
Disordered Thought	22	-0.10	0.20	-0.09
Hallucinations Phenotype	22	-0.01	-0.13	-0.20
Attention Dysfunction	22	0.10	-0.03	-0.4
Sleep Impairment	22	0.17	0.09	0.03
MMSE	23	-0.11	-0.31	-0.09
Clinical Assessment of Fluctuations	23	0.20	0.18	0.24
Rey Complex Figure – Copy	16	-0.44	-0.17	-0.27
Clock Drawing	22	-0.13	-0.18	-0.06
TMT$_A$	18	0.29	-0.10	0.15
TMT$_B$	18	0.32	-0.14	-0.06
TMT$_{B-A}$	18	0.08	-0.27	-0.18

Table 4.4: Spearman correlations between between cogntive and visual hallucination measures and BPP for DLB patients. Note: MDSUPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale, MMSE = Mini Mental State Exam, TMT = Trails Making Test * = p < 0.05

4.4.4. BPP and Visual Hallucinations

Separating DLB patients into those who experience VH vs. patients who do not (nonVH) produced two uneven groups (20 VH vs 3 nonVH). This disparity between group size makes comparative analysis unreliable and were therefore not performed. However, upon inspection of the means for each group patients who experienced VH also appeared to have more misperceptions in the BPP than the nonVH patients (m = 6.10 vs 1.33, respectively). Further, nonVH patients appeared to perform in a similar

manner to the HC (m = 1.33 vs 1.95, respectively). Conversely, patients who did VH patients appear to have performed less misses than the VH sample (mean 8.05 vs. 12.67, respectively). Due to skewed group sizes Spearman correlations were used to further investigate the relationship between VH and BPP performance. A significant correlation was found between the Visual Misperception sub-scale from the PsycH-Q and the number of misperceptions recorded by the BPP ($r_s(20) = 0.45$, p = 0.042). However, no relationships were found between the number of misses or misperceptions and the Attention subscale, the Hallucination and Psychosis scales or the total PsycH-Q scores (Table 4.4). No significant relationship was found between the VH item of the MDS-UPDRS and the number of misperceptions ($r_s(20) = 0.20$, p = 0.36) or misses ($r_s(20) = 0.13$, p = 0.56), potentially reflecting the low variance possible with this five point rating scale. The DLB group was then split between patients on SSRIs and those that are not. This resulted in a similar outcome, allowing for the smaller sample size.

4.5. Discussion

The current study aimed to investigate the feasibility of using the BPP in a DLB population to measure VH. One of the concerns relating to any behavioural task in patients with DLB relates to the ability of such patients to understand, engage with and tolerate the testing session. Whilst the DLB group was slower in completing the BPP, no patient took longer than 35 minutes. Furthermore, the ability to identify over 80% of the stimuli correctly would suggest that DLB patients understood and were fully engaged with the testing, despite having impaired performance. However, DLB patients still demonstrated significantly more misperceptions and misses than the HC group. Further, the absence of a correlation between MMSE and BPP performance supports the potential of the BBP in a cognitively impaired population as an objective measure of VH. Furthermore, there was a positive correlation between the number of misperceptions made in the BPP task and the misperception sub-scale of the PsycH-

Q. Whilst the current study did not find a correlation between BPP scores and the MDS-UPDRS item rating VH, this likely reflects the limited sensitivity of the MDS-UPDRS (Aynsworth et al., 2017).

Previous work by Shine et al. (2012) reported a relationship between TMT$_{B-A}$ scores and BPP error in both PD patients and healthy controls. The current study did not find this relationship within our DLB cohort. This is likely due to poor performance by the DLB group in the TMT$_B$ task, which exhibited a ceiling effect. This further iterates the need for cognitive tasks that are accessible by patients burdened with dementia.

The higher completion rate for the BPP compared to the TMT$_B$ combined with the relationship between BPP scores and TMT$_{B-A}$ performance as found in previous research [40] further supports the utility of the BPP as a clinical tool in the DLB population.

Our results also demonstrated that misses were not correlated with misperceptions, suggesting that they may represent related but distinct disturbances. It is known that DLB patients demonstrate reduced activity in the frontal eye fields (Nagahama et al., 2008), which may result in fewer saccades resulting in poor scene construction and could have contributed to missing hidden components, such as the bistable percept. Additionally, misses may be being driven by poor attentional switching, which is also observed in DLB patients (Marchand et al., 2016; Petrova et al., 2016). This is further supported with the low number of DLB patients able to complete the TMT$_B$ Whilst not universal, the findings from a wide range of diverse neuroimaging approaches including volumetry (e.g. Heitz et al. 2015, Nagahama et al. 2020), diffusion tensor imaging (e.g. Hall et al. 2019, delli Pizzi et al. 2014, Kantarci et al. 2010), and metabolic FDG-PET (Iaccarino et al., 2018; Imamura et al., 1999; Taylor et al., 2012), have emphasised a key role for disturbances across higher order visual processing and integration in the pathophysiology of VH in DLB. Further work using more objective measures of VH in association with neuroimaging and controlling for comorbidities, such as the degree of cognitive impairment across attentional and visuospatial domains, would clarify the neural dysfunction underlying VH in DLB.

The current study had some limitations that need to be considered when interpreting the results. The small sample size is clearly a factor that might have impacted our findings, although it should be highlighted that the DLB patients were diagnosed using the most recent criteria (McKeith et al., 2017) and that participant numbers are comparable with other previously published behavioural studies (Bliwise et al., 2014; Johns et al., 2009; Park et al., 2011). Patients were tested on their regular medication including SSRIs, CHEIs and dopamine agonists. The more significant performance deficits of those patients taking SSRIs may reflect either a drug effect or the fact that such patients might have increased mood and sleep disturbances, which themselves may be associated with impaired attention. Whilst no significant effects on BPP measures in those patients taking CHEIs or on dopamine agonists were found, the low number of medicated patients mean that this finding should be regarded with caution. Future studies could consider excluding patients on such medications or attempting to control for their effects. Additionally, a small number of patients were also prescribed other medications such as atypical antipsychotics, monoamine oxidase B inhibitors and benzodiazepines. However, removing these cases did not seem to impact the main findings. The current study focused on VH in DLB patients. Whilst this did provide a performance profile for the BPP in DLB, future work in other neurodegenerative diseases, such as Alzheimer's are now of vital importance especially if the paradigm could help differentiate DLB from AD. Due to the BPP being a novel task for VH in DLB further investigation into the test-retest reliability of the BPP is also needed, preferably in a larger cohort. Finally, our sample consisted of patients who may not represent the full spectrum of DLB severity. Ideally, the BPP should now be assessed in patients with more advanced disease and even potentially those meeting the recently published research criteria for prodromal DLB (McKeith et al., 2020). If the BPP could identify early deficits, then it may be useful as a biomarker for the transition from prodromal DLB to those reaching a formal diagnosis.

The current work demonstrates that the BPP can be employed in DLB patients to objectively measure misperceptions and hallucinatory phenomena. Utilising the BPP could provide researchers and clinicians with a useful tool to elucidate the pathophysiology underpinning VH in DLB through functional neuroimaging and electrophysiological studies, as well as providing an outcome measure for future clinical trials of this undertreated symptom.

4.6. References

Arnaoutoglou, N. A., O'Brien, J. T., & Underwood, B. R. (2019). Dementia with Lewy bodies - from scientific knowledge to clinical insights. *Nat Rev Neurol*, *15*(2), 103-112. https://doi.org/10.1038/s41582-018-0107-7

Aynsworth, C., Collerton, D., & Dudley, R. (2017). Measures of visual hallucinations: Review and recommendations. *Clinical Psychology Review*, *57*, 164-182. https://doi.org/https://doi.org/10.1016/j.cpr.2017.05.001

Bliwise, D. L., Scullin, M. K., & Trotti, L. M. (2014). Fluctuations in cognition and alertness vary independently in dementia with Lewy bodies. *Mov Disord*, *29*(1), 83-89. https://doi.org/10.1002/mds.25707

Chiu, P. Y., Teng, P. R., Wei, C. Y., Wang, C. W., & Tsai, C. T. (2018). Gender difference in the association and presentation of visual hallucinations in dementia with Lewy bodies: a cross-sectional study. *Int J Geriatr Psychiatry*, *33*(1), 193-199. https://doi.org/10.1002/gps.4706

Delli Pizzi, S., Maruotti, V., Taylor, J. P., Franciotti, R., Caulo, M., Tartaro, A., Thomas, A., Onofrj, M., & Bonanni, L. (2014). Relevance of subcortical visual pathways disruption to visual symptoms in dementia with Lewy bodies. *Cortex*, *59*, 12-21. https://doi.org/10.1016/j.cortex.2014.07.003

Eversfield, C. L., & Orton, L. D. (2018). Auditory and visual hallucination prevalence in Parkinson's disease and dementia with Lewy bodies: a systematic review and meta-analysis. *Psychol Med*, 1-12. https://doi.org/10.1017/s0033291718003161

Ffytche, D. H., Creese, B., Politis, M., Chaudhuri, K. R., Weintraub, D., Ballard, C., & Aarsland, D. (2017). The psychosis spectrum in Parkinson disease. *Nat Rev Neurol*, *13*(2), 81-95. https://doi.org/10.1038/nrneurol.2016.200

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, *12*(3), 189-198.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*, *23*(15), 2129-2170. https://doi.org/10.1002/mds.22340

Hall, J. M., O'Callaghan, C., Muller, A. J., Ehgoetz Martens, K. A., Phillips, J. R., Moustafa, A. A., Lewis, S. J. G., & Shine, J. M. (2019). Changes in structural network topology correlate with severity of hallucinatory behavior in Parkinson's disease. *Netw Neurosci*, *3*(2), 521-538. https://doi.org/10.1162/netn_a_00078

Heitz, C., Noblet, V., Cretin, B., Philippi, N., Kremer, L., Stackfleth, M., Hubele, F., Armspach, J. P., Namer, I., & Blanc, F. (2015). Neural correlates of visual hallucinations in dementia with Lewy bodies. *Alzheimers Res Ther*, *7*(1), 6. https://doi.org/10.1186/s13195-014-0091-0

Honeycutt, L., Gagnon, J. F., Pelletier, A., De Roy, J., Montplaisir, J. Y., & Postuma, R. B. (2020). Pareidolias and cognition in isolated REM sleep behavior disorder. *Parkinsonism Relat Disord*, *75*, 76-79. https://doi.org/10.1016/j.parkreldis.2020.05.017

Iaccarino, L., Sala, A., Caminiti, S. P., Santangelo, R., Iannaccone, S., Magnani, G., & Perani, D. (2018). The brain metabolic signature of visual hallucinations in dementia with Lewy bodies. *Cortex*, *108*, 13-24. https://doi.org/10.1016/j.cortex.2018.06.014

IBM. (2019). *IBM SPSS Statistics*. In (Version 26) IBM.

Imamura, T., Ishii, K., Hirono, N., Hashimoto, M., Tanimukai, S., Kazuai, H., Hanihara, T., Sasaki, M., & Mori, E. (1999). Visual hallucinations and regional

cerebral metabolism in dementia with Lewy bodies (DLB). *Neuroreport, 10*(9), 1903-1907. https://doi.org/10.1097/00001756-199906230-00020

Inagawa, Y., Kanetaka, H., Tsugawa, A., Sakurai, S., Serisawa, S., Shimizu, S., Sakurai, H., & Hanyu, H. (2020). Efficacy of Olfactory and Pareidolia Tests Compared With That of Indicative Biomarkers in Diagnosis of Dementia With Lewy Bodies. *Front Neurol, 11*, 540291. https://doi.org/10.3389/fneur.2020.540291

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., Ska, B., Gilbert, B., Inglis, G., Panisset, M., de Boysson, C., & Chertkow, H. (2009). Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology, 23*(6), 765-777. https://doi.org/10.1037/a0016792

Kantarci, K., Avula, R., Senjem, M. L., Samikoglu, A. R., Zhang, B., Weigand, S. D., Przybelski, S. A., Edmonson, H. A., Vemuri, P., Knopman, D. S., Ferman, T. J., Boeve, B. F., Petersen, R. C., & Jack, C. R., Jr. (2010). Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology, 74*(22), 1814-1821. https://doi.org/10.1212/WNL.0b013e3181e0f7cf

Kitabayashi, Y., Ueda, H., Narumoto, J., Nakamura, K., Kita, H., & Fukui, K. (2001). Qualitative analyses of clock drawings in Alzheimer's disease and vascular dementia. *Psychiatry Clin Neurosci, 55*(5), 485-491. https://doi.org/10.1046/j.1440-1819.2001.00894.x

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed. ed.). New York : Oxford University Press.

Maetzler, W., Stoycheva, V., Schmid, B., Schulte, C., Hauser, A. K., Brockmann, K., Melms, A., Gasser, T., & Berg, D. (2010). Neprilysin activity in cerebrospinal fluid is associated with dementia and amyloid-beta42 levels in Lewy body disease. *J Alzheimers Dis, 22*(3), 933-938. https://doi.org/10.3233/JAD-2010-101197

Mamiya, Y., Nishio, Y., Watanabe, H., Yokoi, K., Uchiyama, M., Baba, T., Iizuka, O., Kanno, S., Kamimura, N., Kazui, H., Hashimoto, M., Ikeda, M., Takeshita, C., Shimomura, T., & Mori, E. (2016). The Pareidolia Test: A Simple

Neuropsychological Test Measuring Visual Hallucination-Like Illusions. *PLoS One*, *11*(5), e0154713. https://doi.org/10.1371/journal.pone.0154713

Marchand, D. G., Montplaisir, J., Postuma, R. B., Rahayel, S., & Gagnon, J. F. (2016). Detecting the cognitive prodrome of dementia with Lewy bodies: A prospective study of REM sleep behavior disorder. *Sleep*.

Martini, A., Weis, L., Schifano, R., Pistonesi, F., Fiorenzato, E., Antonini, A., & Biundo, R. (2020). Differences in cognitive profiles between Lewy body and Parkinson's disease dementia. *J Neural Transm (Vienna)*, *127*(3), 323-330. https://doi.org/10.1007/s00702-019-02129-2

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/WNL.0000000000004058

McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., Kantarci, K., Muscio, C., O'Brien, J. T., Postuma, R. B., Aarsland, D., Ballard, C., Bonanni, L., Donaghy, P., Emre, M., Galvin, J. E., Galasko, D., Goldman, J. G., Gomperts, S. N., Honig, L. S., Ikeda, M., Leverenz, J. B., Lewis, S. J. G., Marder, K. S., Masellis, M., Salmon, D. P., Taylor, J. P., Tsuang, D. W., Walker, Z., & Tiraboschi, P. (2020). Research criteria for the diagnosis of prodromal dementia

with Lewy bodies. *Neurology*, *94*(17), 743-755. https://doi.org/10.1212/wnl.0000000000009323

Meyers, J., & Meyers, K. (1995). Rey Complex Figure Test and Recognition Trial. In *Psychological Assessment Resources*.

Mosimann, U. P., Collerton, D., Dudley, R., Meyer, T. D., Graham, G., Dean, J. L., Bearn, D., Killen, A., Dickinson, L., Clarke, M. P., & McKeith, I. G. (2008). A semi-structured interview to assess visual hallucinations in older people. *Int J Geriatr Psychiatry*, *23*(7), 712-718. https://doi.org/10.1002/gps.1965

Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). The prognosis of dementia with Lewy bodies. *Lancet Neurol*, *16*(5), 390-398. https://doi.org/10.1016/s1474-4422(17)30074-1

Nagahama, Y., Okina, T., Suzuki, N., & Matsuda, M. (2008). Cerebral substrates related to impaired performance in the clock-drawing test in dementia with Lewy bodies. *Dement Geriatr Cogn Disord*, *25*(6), 524-530. https://doi.org/10.1159/000131665

Nagahama, Y., Okina, T., Suzuki, N., & Matsuda, M. (2010). Neural correlates of psychotic symptoms in dementia with Lewy bodies. *Brain*, *133*(Pt 2), 557-567. https://doi.org/10.1093/brain/awp295

Naismith, S. L., Shine, J. M., & Lewis, S. J. (2010). The specific contributions of set-shifting to freezing of gait in Parkinson's disease. *Mov Disord*, *25*(8), 1000-1004. https://doi.org/10.1002/mds.23005

Onofrj, M., Taylor, J. P., Monaco, D., Franciotti, R., Anzellotti, F., Bonanni, L., Onofrj, V., & Thomas, A. (2013). Visual hallucinations in PD and Lewy body dementias: old and new hypotheses. *Behav Neurol*, *27*(4), 479-493. https://doi.org/10.3233/ben-129022

Park, K. W., Kim, H. S., Cheon, S. M., Cha, J. K., Kim, S. H., & Kim, J. W. (2011). Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. *J Clin Neurol*, *7*(1), 19-24. https://doi.org/10.3988/jcn.2011.7.1.19

Petrova, M., Pavlova, R., Zhelev, Y., Mehrabian, S., Raycheva, M., & Traykov, L. (2016). Investigation of neuropsychological characteristics of very mild and mild dementia with Lewy bodies. *J Clin Exp Neuropsychol*, *38*(3), 354-360. https://doi.org/10.1080/13803395.2015.1117058

Price, A., Farooq, R., Yuan, J. M., Menon, V. B., Cardinal, R. N., & O'Brien, J. T. (2017). Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. *BMJ Open*, *7*(11), e017504. https://doi.org/10.1136/bmjopen-2017-017504

Psychology Software Tools, I. (2013). *E-Prime 2.0*. In Psychology Software Tools, Inc.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*, *8*(3), 271-276.

Rongve, A., Vossius, C., Nore, S., Testad, I., & Aarsland, D. (2014). Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. *Int J Geriatr Psychiatry*, *29*(4), 392-398. https://doi.org/10.1002/gps.4015

Shine, J. M., Halliday, G. H., Carlos, M., Naismith, S. L., & Lewis, S. J. (2012). Investigating visual misperceptions in Parkinson's disease: a novel behavioral paradigm. *Mov Disord*, *27*(4), 500-505. https://doi.org/10.1002/mds.24900

Shine, J. M., Halliday, G. M., Gilat, M., Matar, E., Bolitho, S. J., Carlos, M., Naismith, S. L., & Lewis, S. J. (2014a). The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Hum Brain Mapp*, *35*(5), 2206-2219. https://doi.org/10.1002/hbm.22321

Shine, J. M., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2011). Visual Misperceptions and Hallucinations in Parkinson's Disease: Dysfunction of Attentional Control Networks? *Mov Disord*, *26*(12), 2154-2159.

Shine, J. M., Mills, J. M. Z., Qiu, J., O'Callaghan, C., Terpening, Z., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2015a). Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease. *Movement Disorders Clinical Practice*, *2*(2), 175-181.

Shine, J. M., Muller, A. J., O'Callaghan, C., Hornberger, M., Halliday, G. M., & Lewis, S. J. (2015b). Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. *NPJ Parkinsons Dis*, *1*, 15003. https://doi.org/10.1038/npjparkd.2015.3

Shine, J. M., O'Callaghan, C., Halliday, G. M., & Lewis, S. J. (2014b). Tricks of the mind: Visual hallucinations as disorders of attention. *Prog Neurobiol*, *116*, 58-65. https://doi.org/10.1016/j.pneurobio.2014.01.004

Svendsboe, E., Terum, T., Testad, I., Aarsland, D., Ulstein, I., Corbett, A., & Rongve, A. (2016). Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*, *31*(9), 1075-1083. https://doi.org/10.1002/gps.4433

Taylor, J. P., Firbank, M. J., He, J., Barnett, N., Pearce, S., Livingstone, A., Vuong, Q., McKeith, I. G., & O'Brien, J. T. (2012). Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study. *Br J Psychiatry*, *200*(6), 491-498. https://doi.org/10.1192/bjp.bp.111.099432

Uchiyama, M., Nishio, Y., Yokoi, K., Hirayama, K., Imamura, T., Shimomura, T., & Mori, E. (2012). Pareidolias: complex visual illusions in dementia with Lewy bodies. *Brain*, *135*(Pt 8), 2458-2469. https://doi.org/10.1093/brain/aws126

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000). The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale: Two methods to assess fluctuating confusion in dementia. *British Journal of Psychiatry*, *177*(3), 252-256. https://doi.org/10.1192/bjp.177.3.252

Zarkali, A., Lees, A. J., & Weil, R. S. (2019). Flickering Stimuli Do Not Reliably Induce Visual Hallucinations in Parkinson's Disease. *J Parkinsons Dis*, *9*(3), 631-635. https://doi.org/10.3233/jpd-191635

Chapter Five

5. Exploring the utility of novel tasks in prodromal Dementia with Lewy Bodies

Phillips JR, Matar E, Ehgoetz Martens KA, Moustafa AA, Halliday GM, Lewis SJG. Exploring the Sensitivity of Prodromal Dementia with Lewy Bodies Research Criteria. Brain Sci. 2022 Nov 22;12(12):1594. doi: 10.3390/brainsci12121594. PMID: 36552054; PMCID: PMC9775171.

5.1. Abstract

Dementia with Lewy bodies (DLB) is an insidious neurodegenerative disease that has a prodromal period where symptoms begin to be recognised but do not yet meet clinical requirements for DLB. Recently, criteria for prodromal DLB have been put forward to aid the classification and research of this ambiguous cohort of patients. However, these criteria allow for isolated REM sleep behaviour disorder (iRBD) patients with REM sleep without atonia (RSWA) as confirmed with vPSG and MCI to be classified as *probable* prodromal DLB. This double counting of iRBD characteristics may reduce the specificity of these criteria. To address the double counting, the current study classified a cohort of iRBD patients as *probable* prodromal DLB only in the presence of an additional core feature or biomarker. Thirty-four iRBD patient were classified as cognitively normal (iRBD-CN) and 13 iRBD patients were classified as MCI. From the MCI patients, one presented with parkinsonism and was classified as *probable* MCI-LB while the remaining 12 were *possible* MCI-LB. All patients performed three tasks (Sustained Attention Response Task; SART, Mental Rotation; MR and Bistable Percept Paradigm; BPP) that have been found to be sensitive to core DLB symptoms. Findings indicate that on the MR task there was a trend for higher overall accuracy amongst iRBD patients than MCI-LB patients (p = 0.06). MCI-LB patients also performed more misses in the BPP while both groups performed at the same level for the SART. However, due to a low number of patients, these findings should be interpreted with caution. Additionally, the *probable* MCI-LB patient had poorer performance with the MR and BPP tasks compared to the iRBD-CN and *possible* MCI-LB patients. This supports the need for more stringent criteria of prodromal DLB that does not allow the double

counting of RBD as a biomarker and a clinical feature. This will allow for a more accurate assessment of the risk factors for DLB.

5.2. Introduction

Neurodegenerative synucleinopathies follow a relentless trajectory associated with increases in pathology, neuronal loss, and symptom severity. However, the initial stages of these conditions are not typically perceived by patients until the pathology results in more obvious clinical symptoms that trigger them to seek medical advice. Over the past couple of decades, more information has emerged about this prodromal phase in Dementia with Lewy Bodies (DLB) and the clinical characteristics that might allow earlier, and potentially even pre-clinical diagnosis.

Genetic testing represents one mechanism for identifying those people who are at risk for developing DLB, but as stated in Chapter One, the majority of DLB cases cannot be traced to a single causative gene and whilst the presence of a *GBA1* mutation has been identified as a clear risk factor (Leonard et al., 2020; section 1.4.1), most DLB cases do not carry this mutation (Guerreiro et al., 2018). However, increasing evidence has demonstrated that the emergence of isolated REM Sleep Behaviour Disorder (iRBD) represents the strongest predictor for synucleinopathy. These studies have highlighted that over 80% of iRBD patients go on to develop PD or DLB in roughly equal proportions (with a much smaller number developing Multiple System Atrophy) when followed for over a decade (Iranzo et al., 2013; Schenck et al., 2013).

A recent international, multi-centre study evaluating over 1,300 iRBD patients reported a conversion rate to synucleinopathy of 6.3% per year, with 73.5% of cases having converted at 12 years following an initial diagnosis (Postuma et al., 2019). This study also confirmed a number of clinical features that predicted earlier conversion including abnormal motor testing (especially on objective measures), Mild Cognitive Impairment (MCI), anosmia, impairment on colour vision discrimination, erectile dysfunction, constipation, abnormal dopamine imaging (e.g., DATscan), and the

neurophysiological correlate of RBD, namely REM Sleep without Atonia (RSWA; Postuma et al., 2019). However, it should also be noted that 27% of patients who had negative results on these assessments, still transitioned to either DLB or PD after 8 years. This study also found that cognitive impairment was the only feature that differentiated those iRBD patients who were more likely to transition to DLB rather than PD (Postuma et al., 2019).

Given these insights, diagnostic criteria for prodromal DLB have been proposed for use in research settings (McKeith et al., 2020). These prodromal DLB guidelines formally identify three specific at-risk patient groups - namely those with an MCI-onset, Delirium-onset or Psychiatric-onset presentation. Due to the absence of any detailed, prospective phenotype data these guidelines offer only limited advice regarding the Delirium/Psychiatric-onset prodromes. However, a characterisation of the MCI-onset sub-group is more aligned with the established clinical criteria for DLB. In line with the requirement for dementia in DLB, the MCI-onset prodromal DLB (MCI-LB) requires the presence of MCI, defined as exhibiting cognitive impairment, across at least one cognitive domain that does not interfere with the patient's ability to complete everyday activities (American Psychiatry Association, 2013). This effectively identifies those patients that fall between having normal cognition and clinical dementia (Petersen, 2004). Furthermore, the MCI-LB research criteria also include cognitive fluctuations (CF), spontaneous visual hallucinations (VH), RBD and parkinsonian motor impairments, which must not fulfill existing diagnostic criteria to achieve a diagnosis of PD (Postuma et al., 2015). The criteria also include three objective biomarkers: abnormal DATscan, RSWA as confirmed by video polysomnography (vPSG) and an abnormal iodine-123 meta-iodobenzylguanidine (MIBG) scan (McKeith et al., 2020). Additionally, prodromal DLB can fall into two categories: probable and possible MCI-LB. Probable MCI-LB requires either the presence of two or more core clinical features or one core feature and one or more

objective biomarkers. A research diagnosis of possible MCI-LB requires only one core feature or the presence of only one or more biomarker (McKeith et al., 2020).

Whilst the proposed research criteria provide a means to classify this difficult population, the definition of probable MCI-LB may present some problems with specificity. Firstly, to be confident about the diagnosis of RBD requires confirmation on (ideally video) polysomnography (vPSG; Dauvilliers et al., 2018), which usually manifests with the neurophysiological appearance of RSWA (Sateia, 2014). This implies that the presence of RBD confirmed on vPSG equates to probable MCI-LB rather than specifying that the supporting objective biomarker should be orthogonal to the clinical core feature. For example, having an abnormal MIBG scan in an MCI case with RBD may carry more significance than an MCI case with clinical RBD and PSG confirmed RSWA. It should also be recognised that MCI has a high prevalence within the iRBD population (35%; Szeto et al., 2017). Moreover, 89% of these iRBD patients with MCI have a cognitive profile that would also be consistent with the proposed criteria for prodromal PD (Berg et al., 2015).

Clearly, further studies are needed to confirm the utility of the proposed MCI-LB criteria and one approach would be to determine if behavioural paradigms that have been validated in DLB patients would show any predictive capability in prodromal cases. As outlined in Chapters Two, Three and Four, recent work has shown that the Sustained Attention Response Task (SART; Phillips et al., 2019), the Mental Rotation (MR) test and the Bistable Percept Paradigm (BPP; Phillips et al., 2021) do show impairments in patients with DLB. Therefore, the current study sought to evaluate these novel behavioural assessments in a cohort of iRBD patients undergoing detailed longitudinal assessment at the ForeFront Parkinson's Disease Research Clinic at the Brain and Mind Centre, University of Sydney. These patients were also enrolled in a study of gait kinematics to assess parkinsonian features (Ehgoetz Martens et al., 2019), as well as a neuroimaging study utilising a validated Virtual Reality gait paradigm in

combination with fMRI to identify any neural correlates of motor disturbance in this at-risk population (Ehgoetz Martens et al., 2020).

It was predicted that the iRBD patients enrolled in this study would include both those with MCI, as well as those who were cognitively intact. All iRBD patients had their diagnosis confirmed on vPSG, which demonstrated neurophysiological RSWA. Thus, using the research criteria for MCI-LB, those iRBD patients with MCI satisfied a diagnosis of at least *possible* prodromal DLB, noting that their supportive biomarker was not orthogonal to the core feature of RBD. Therefore, this study sought to explore two related questions. Firstly, whether those patients with prodromal DLB (iRBD with MCI) were impaired on the SART, MR or BPP compared to iRBD patients with no cognitive impairment. Secondly, whether any individual MCI-LB patient that transitioned to DLB during their period of follow up had baseline results on SART, MR or BPP testing that might indicate any potential for the use of such testing as a predictive biomarker for transition.

5.3. Methods

5.3.1. Participants

A total of 47 iRBD participants were recruited from the ForeFront Parkinson's Disease Research Clinic at the Brain and Mind Centre, University of Sydney where they form part of an ongoing, prospective longitudinal study that aims to review patients every 12 months. Unfortunately, the COVID-19 pandemic impacted upon this longitudinal review, but efforts to confirm whether subjects had remained clinically stable or had transitioned to a synucleinopathy were pursued via several avenues including in person outpatient clinical review and via telehealth. The study was approved by the Human Research Ethics Committee at the University of Sydney, and all participants provided written informed consent. A diagnosis of iRBD was confirmed prior to recruitment according to the International Classification of Sleep

Disorders, 3rd Edition (Sateia, 2014), where the electromyographic recordings demonstrating REM Sleep Without Atonia (RSWA) on vPSG were recorded utilising the SINBAR protocol (Frauscher et al., 2008; Iranzo et al., 2011). Whilst full (research focused) follow-up assessments would typically occur every 12 months (or sooner depending on the emergence of symptoms), the impact of the COVID-19 pandemic meant that many patients were seen for clinical purposes in person or via telehealth. The restricted access and health concerns resulting from the pandemic, resulted in a range of follow-up intervals stretching out to 41 months. At their follow-up assessment, patients were classified as transitioned if they satisfied the MDS criteria for PD (Postuma et al., 2015), or the International DLB Consortium criteria for DLB (McKeith et al., 2017).

5.3.2. Clinical assessments

All clinical assessments were undertaken by a qualified clinician. All participants were assessed for the presence of other neurodegenerative, neurological, psychiatric, or general medical conditions that would impact on their diagnosis/assessment and in addition underwent a semi-structured interview, which screened for salient prodromal core features of cognitive fluctuations (CF) and visual hallucinations (VH). Visual hallucinations were also objectively assessed using item 1.2 from the MDS-UPDRS, which uses a five-point Likert scale ranging from 0 ("no hallucinations or psychotic behaviour") to 4 ("Patient has delusions and paranoia"; Goetz et al., 2008), as well as the PsycH-Q, a self-report questionnaire that measures the characteristics of hallucinations in addition to the severity of these symptoms (Shine et al., 2015). The core feature of parkinsonism was objectively measured using the MDS-UPDRS III (Goetz et al., 2008) and a trained Movement Disorders Neurologist evaluated whether they met clinical criteria for a diagnosis of PD evaluating features such as bradykinesia with decrement, rigidity with cogwheeling and the nature of any tremor. The RBD screening questionnaire (RBDQ) was used to help quantify the degree of dream

enactment experienced (Stiasny-Kolster et al., 2007). Given their highlighted role in predicting synucleinopathy, colour discrimination and contrast sensitivity were assessed using the Farnsworth-Munsell Color Test (Farnsworth, 1957) and Pelli-Robson chart (Pelli & Bex, 2013), respectively, whilst olfaction was measured using Sniffin Sticks testing (Hummel et al., 1997).

Participants were tested on a cognitive battery including: the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) as a measure of global cognition; Memory was assessed using the Logical Memory 1 and 2 tasks from the Wechsler Memory Scale-Revised (Wechsler, 2009) and Rey Adult Verbal Learning task (Bean, 2011); Executive function was assessed using the forward and backward Digit Span (Lezak et al., 2012) task to measure working memory (Stroop, 1935); visuospatial ability was assessed with the TMT-A (Stroop, 1935), copying a wire cube and the clock drawing task (Sunderland et al., 1989); attention was assessed with the TMT-B (Stroop, 1935) and parts 3 and 4 of the Stroop (Stroop, 1935); language was assessed the with the COWAT word fluency for the letters (F, A, S) and categorical fluency for naming animals (Lezak et al., 2012). More specifically, a diagnosis of mild cognitive impairment was defined according to the International Working Group on MCI criteria (Petersen, 2004; Winblad et al., 2004), which specifies a complaint of cognitive impairment from the patient or informant, which is supported by impairment in two cognitive domains (Litvan et al., 2012). Impairment within a cognitive domain was determined by isolating components of the MoCA for each cognitive domain and applying impairment thresholds as outlined in Szeto et al. (2020): Memory was assessed with the word recall component, where less than three recalled words indicated impaired memory. Executive function was assessed with digit span backwards where a score of zero was rated as impaired. Visuospatial impairment was assessed with the cube copy item, where a score of zero indicated impairment. Impairment within the attention domain was assessed using "serial 7s" with a score less than three correct subtractions representing impairment. Language was assessed with the verbal fluency task, where less than 12 words generated in 60 s was scored

as impaired.   Based on these assessments the iRBD patients were then grouped into patients who were cognitively normal (iRBD-CN) and patients with MCI who were regarded by definition as having at least *possible* prodromal DLB. *Probable* prodromal DLB was assessed according to proposed research criteria (McKeith et al., 2020), wherein such patients were required to have at least one additional core feature from cognitive fluctuations (CF), visual hallucinations (VH) and/or parkinsonism that did not meet diagnostic criteria for PD. Other biomarkers (DATscan, MIBG) were not available in these patients.

5.3.3. Novel Tasks for assessing Prodromal DLB

The SART is a task of attention to probe the core feature of cognitive fluctuations (CF). The SART presents the patient with a series of numbers between 1-9. Patients are required to press a button when any number is presented but withhold their response when the number "3" is displayed (for full description see Phillips et al. 2019). The number of missed responses and variance in response time (RTSD) have been shown to correlate with CF in DLB patients (Phillips et al., 2019).

The MR task is designed to measure visuospatial impairment. Patients are presented with pairs of shapes and required to indicate if the shapes are identical, or a mirror image of each other. Trials may involve shapes facing the same direction, or one shape is rotated either to 45° or 90° (see Chapter 3 for a full description). Accuracy is the main outcome of the MR, with the lowest accuracy limited to 50%, representing chance performance. Accuracy on the MR task has been shown to be correlated with VH and visuospatial ability in DLB patients (Chapter 3).

The BPP was used to provide an objective measure of VH. In this task, patients are presented with ambiguous images that contain either one (single image) or two percepts (hidden or bistable). Patients are then required to indicate if there are one or two percepts in each image being displayed. Percepts that were misidentified were labelled as misperceptions, while percepts that were not identified were labelled as

misses (Shine et al., 2012; for a full description, see Phillips et al. 2021). The BPP has been shown to correlate with VH in patients with PD (Shine et al., 2012) and DLB (Phillips et al., 2021).

5.3.4. Statistics

Statistical analysis was performed using SPSS 26 (IBM, 2019). Demographic measures across the iRBD-CN and MCI-LB were not normally distributed as demonstrated from the Shapiro-Wilks normality test. This resulted in group comparisons to be made using Mann-Whitney U tests. Furthermore, the number of misses, false alarms, and the standard deviation of response time from the SART and accuracy performing the MR task were not normally distribution and again between group comparisons were performed with a Mann-Whitney U test. Further analysis to control for years of education. was performed with an Analysis of Covariance (ANCOVA). This covariate was chosen as it is known to be correlated with cognitive test scores in older adults. The low number of iRBD patients completing the BPP restricted any between group comparisons. Due to the low number of patients who transitioned to DLB or PD, baseline performance on the SART, MR and BPP were simply rank ordered across all participants to assess whether these individuals showed any impairments that might have been indicative of their likelihood for transition. The most impaired score of each measure was ranked "1".

5.4. Results

5.4.1. Demographics

Demographic data are presented in Table 1. Mild Cognitive Impairment was detected in 13 of the 47 iRBD patients. Within these 13 patients, clinical interview failed to detect any CF or VH. Across all of the iRBD patients, the MDS-UPDRS III scores ranged from 0 to 18 but none satisfied clinical criteria for a diagnosis of PD. However, one iRBD patient with MCI also demonstrated clinical parkinsonism having

unilateral bradykinesia with decrement. Thus, 12 of the 13 patients in the MCI-LB group were stratified as having *possible* prodromal DLB, with only one having PSG confirmed RBD, along with clinical parkinsonism who was defined as meeting research criteria for *probable* prodromal DLB by virtue of having two core clinical features (RBD and parkinsonism) and one biomarker (RSWA). For group comparisons, all MCI-LB patients (12 *possible* and 1 *probable*) were combined into one group. The iRBD-CN and MCI-LB groups were matched for age and RBD symptom duration. However, MCI-LB patients had fewer years of education than the iRBD across the groups that conducted each of the SART (χ^2(N = 31) = -2.39, p = 0.02, r^2 = 0.18), MR (χ^2(N = 46) = -2.36, p < 0.01, r^2 = 0.12) and BPP (χ^2(N = 23) = -3.00, p < 0.01, r^2 = 0.39).

Over the period of follow up (range 17-45 months), six iRBD patients have undergone full follow-up assessment, 20 patients had a clinical only based follow-up (5 of the 20 patients were telehealth). Twenty-one patients were unable to attend follow-up appointments due to COVID restrictions, change of contact details or refused to continue testing. From the follow-ups, two iRBD patients had transitioned with one iRBD-CN patient being diagnosed with PD (33 months from their baseline visit), while one MCI-LB with *probable* prodromal DLB transitioned to DLB (28 months from their baseline visit; Table 2).

	iRBD-CN mean (SD)	MCI-LB mean (SD)
Total N	34	13

Sustained Attention Response Task

N	20	11
Age	68.5(7.9)	70.2(9.3)
Gender m(%)	17(85%)	8(61%)
Disease Duration	1.8(2.8)	2.9(4.2)
Years of Education	15.2(2.2)	12.9(2.7)[a]
MoCA	27.6(2.0)	23.6(2.5)[a]
MDS-UPDRS III	9.8(7.1)	8.1(5.3)
Misses	1.8(4.1)	1.3(1.5)
False Alarms	2.9(3.3)	3.2(3.1)
RTSD	107.33(80.21)	92.80(28.97)

Mental Rotation

N	34	12
Age	67.9(6.9)	70.1(8.9)
Gender	19(55.9%)	9(75%)
Duration	2.8(5.4)	2.7(4.1)
Years of Education	15.1(2.7)	12.9(2.6)[a]
MoCA	27.9(1.7)	23.3(2.7)[a]
MDS-UPDRS III	9.5(6.5)	8.9(5.8)
0°	94.9%(9.1%)	86.0%(13.6%)
45°	87.5%(11.6%)	77.6%(15.4%)
90°	79.4%(14.4%)	67.2%(16.3%)
Total	87.3%(10.2%)	77.0%(12.9%)

Bistable Percept Paradigm

N	19	4
Age	67.6(8.9)	67.2(7.0)
Gender m(%)	17(83.5%)	3(75%)
Duration	1.5(2.7)	0.5(0.57)
Years of Education	15.3(2.2)	10(1.6)[a]
MoCA	27.1(2.6)	24.3(2.6)[a]
MDS-UPDRS III	9.5(7.1)	7.3(3.8)
Misses	4.9(2.3)	8.8(4.0)
Misperceptions	2.4(2.2)	1.25(1.3)
Error Score	9.1%(3.7%)	12.6%(4.4%)

Table 1 – Demographic and task performance. iRBD-CN = cognitive normal iRBD; MCI-Pos = Possible prodromal DLB; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; RTSD = Response time standard deviation; Age, disease duration and years of education are presented in years. [a] = p < 0.05

	DLB (rank)	PD (rank)	iRBD-CN mean(SD)	MCI-LB Mean(SD)
Total N	1	1	43	12
Age	84	68	69.3(7.4)	70.5(7.7)
Gender m(%)	Male	Male	36(83.7%)	12(100%)
Disease Duration	-	-	3.2(5.0)	2.7(3.8)
Years to transition	7	5	-	-
Years of Education	17	13	14.5(3.2)	12.3(2.7)
MoCA	23	28	26.8(4.5)	23.5(2.3)

MDS-UPDRS III	9	12	9.9(8.2)	9.5(6.6)
SART				
Misses	0(13)	0(13)	1.8(4.2)	1.4(1.5)
False Alarms	0(27)	0(27)	3.3(3.5)	3.5(3.0)
RTSD	111.6(9)	56.3 (29)	110.0(90.9)	90.9(29.8)
Mental Rotation				
0°	72.0%(4)	89.0%(9)	95.0%(9.2%)	87.3%(13.5%)
45°	61.0%(2)	61.0%(2)	88.3%(10.7%)	79.1%(15.2%)
90°	78.0%(21)	72.0%(19)	80.0%(14.6%)	66.2%(16.7%)
Total	70.4%(7)	74.1%(10)	87.7%(10.1%)	77.6%(13.4%)
BPP				
Misses	11(2)	6(7)	4.5(1.9)	8.6(4.0)
Misperceptions	0(18)	0(18)	2.6(2.1)	1.3(1.3)
Error	13.8%(2)	7.5%(7)	9.0%(3.7%)	12.5%(4.5%)

Table 2 – Baseline demographic and task performance between transition and stable iRBD patients. PD = Parkinson's disease; DLB = Dementia with Lewy bodies; iRBD-CN = cognitive normal iRBD; MCI-Pos = Possible prodromal DLB; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; SART = Sustained Attention Response Task; RTSD = Response time standard deviation; BPP = Bistable Percept Paradigm; Age, disease duration, year to transition and years of education are presented in years.

5.4.2. Task Performance

5.4.2.1.   *Sustained Attention Response Task*

The iRBD-CN with MCI-LB groups had similar performance on the SART with no difference between misses (χ^2(N = 31) = -1.65, *p* = 0.16, r^2 = 0.09), false alarms (χ^2(N = 31) = -0.59, *p* = 0.58, r^2 = 0.01) or variance in response time (χ^2(N = 31) = -0.78, *p* = 0.45, r^2 = 0.02; see Table 1). No further analysis was performed.

5.4.2.2.   *Mental Rotation*

The iRBD-CN group had higher accuracy at the 0°, 45°, 90° conditions compared to the MCI-LB group (0°: χ^2(N = 46) = -2.74, *p* = 0.01, r^2 = 0.16; 45°: χ^2(N = 46) = -2.11, *p* = 0.04, r^2 = 0.10; 90°: χ^2(N = 46) = -2.26, *p* = 0.03, r^2 = 0.10) and this was also reflected in the overall accuracy (χ^2(N = 46) = -2.39, *p* = 0.02, r^2 = 0.12). However, this group effect was removed across each condition after controlling for years of education with an ANCOVA (0°: F(1, 43) = 2.67, *p* = 0.11, η^2 = 0.06, β = 0.36; 45°: F(1, 43) = 2.78, *p* = 0.10, η^2 = 0.06, β = 0.37; 90°: F(1, 43) = 2.61, *p* = 0.11, η^2 = 0.06, β = 0.35). Whilst not significant, the accuracy on the MR did appear to be trending towards a significant difference (F(1, 43) = 3.64, *p* = 0.06, η^2 = 0.09, β = 0.46) between the groups despite controlling for years of education, which might reflect an under-powered study.

5.4.2.3.   *Bistable Percept Paradigm*

The group sizes for the BPP task were very unbalanced with only four MCI-LB participants tested (see Table 1) and whilst there was a significant difference with MCI-LB patients missing more percepts than iRBD-CN, (χ^2(N = 23) = -2.47, *p* = 0.01, r^2 = 0.26), there were no differences between misperceptions (χ^2(N = 23) = -1.44, *p* = 0.15, r^2 = 0.09) or the BPP error rate (χ^2(N = 23) = -1.73, *p* = 0.08, r^2 = 0.13). The groups were also unmatched for years of education, however a small sample size restricted further analysis of this effect.

5.4.3. Transitioned Patients

During the period of the study, two patients transitioned, one to DLB and one to PD. The transitioned DLB patient (JE) was male, 84 years old and diagnosed with iRBD 7 years prior to their DLB diagnosis (see Table 2). On their first assessment JE scored poorly on the MoCA (23/30), indicating moderate cognitive impairment, but were not demented. At that assessment, there were no CF or VH and whilst JE had parkinsonism (bradykinesia with decrement), they did not satisfy diagnostic criteria for PD. Thus, at their baseline assessment JE satisfied the research criteria for *probable* MCI-LB and transitioned to DLB after a further 28 months. JE performed well on the SART with no false alarms or misses and across the 31 patients tested they had the ninth highest RTSD. JE's accuracy was varied on the MR task. Out of the 46 patients tested, JE had the fourth poorest score of 72% at 0° rotation, the second lowest score of 61% at 45°, but at 90° they performed relatively well scoring 78%, which was ranked 21st poorest. Overall, using MR, JE had an accuracy of 70.4%, which was the seventh lowest accuracy and lower than the mean accuracies of the iRBD-CN and MCI-LB groups. Their performance on the BPP was also significantly impaired with the second highest number of misses, although JE had no misperceptions.

The patient who transitioned to PD (HM) was a 65-year-old male who was diagnosed with iRBD for 5 years prior to their clinical diagnosis. HM scored well on the MoCA (28/30) and did not meet criteria for MCI (see Table 2). HM also performed well on the SART with no misses or false alarms and had a consistent response time. For the MR task HM performed well at 0°, but poorly for the 45° condition with the second lowest accuracy out of the 46 patients. HM had moderate performance on the 90° condition scoring 72.0% and had the tenth lowest accuracy overall of 74.1%. HM's BPP score was within the normal range with an error score of 7.5%, which is below the threshold reported for impairment (11%; Shine et al., 2012). Clinically, HM had mild parkinsonism that did not reach diagnostic criteria for PD at baseline assessment with only mild bradykinesia.

5.5. Discussion

The aim of the current study was to test the performance of prodromal DLB patients on the SART, MR and BPP and to capture the baseline performance on these tasks of patients that later transitioned to DLB (or PD). The data revealed no striking performance differences between patients with iRBD-CN and MCI-LB, but the study was impacted by low sample sizes, partly as a result of the restriction imposed by the COVID-19 pandemic. However, this study did highlight the value of classifying possible versus probable prodromal DLB using orthogonal clinical and objective biomarker measures. Of the 16 patients with PSG confirmed iRBD who demonstrated MCI, only one had an additional core clinical feature that allowed them to be classified as having *probable* prodromal DLB and it was this individual patient who transitioned to DLB.

No significant differences were observed between the iRBD-CN and MCI-LB groups on measures of the SART with a generally low number of misses and false alarms, along with having a consistent response time. These findings support a previous study that correlated SART performance to CF severity in DLB patients (Phillips et al., 2019). As CF was not reported within this iRBD cohort, it perhaps was only to be expected that both groups would perform similarly. Findings from the current study also support previous work indicating that performance on the SART is not affected by the degree of global cognitive impairment in DLB (Phillips et al., 2019).

Attentional impairment is a characteristic finding in DLB, and some previous studies have identified this in MCI-LB patients using digit span, TMT part B, and the Stroop test (Génier Marchand et al., 2018; Hemminghyth et al., 2020; Kemp et al., 2017; van de Beek et al., 2020). These conflicting findings may be due to previous studies investigated MCI-LB patients that were diagnosed by combining MCI, DLB or PDD criteria (Hemminghyth et al., 2020; Kemp et al., 2017) or by retrospectively assigning a diagnosis depending on the individual's clinical transition (Génier Marchand et al., 2018). These studies also reported higher frequencies of CF, VH and parkinsonism,

suggesting a more severe population than tested in the current study. Furthermore, tasks used by previous studies may rely on a different mechanism than that SART, such as attentional switching or shifting. Indeed, the tasks used by previous studies required shorter attention spans than the SART, suggesting different mechanisms are required to sustain attention compared to those that rely on short bursts of attention.

An initial analysis highlighted lower accuracy on the MR task amongst the MCI-LB participants, but this effect may have been driven by years of education. However, the group effect was trending towards significant for overall accuracy ($F(1, 43) = 3.64$, $p = 0.06$, $\eta^2 = 0.09$, $\beta = 0.46$) and the low beta value indicates that this comparison was underpowered. Thus, a larger sample size is required to further evaluate this potential relationship. Previous findings have suggested that the MR task is reliant on visuospatial ability in DLB patients (See Chapter 3), which might suggest that visuospatial impairment occurs very early in DLB, before other core features emerge. An interesting additional observation was the number of patients that had low accuracy at the 0° condition from both groups. This condition involves a straight comparison of two relatively simple shapes, and it was surprising that six of the iRBD-CN patients were somewhat impaired (>90%). However, performance on the MR has been found to be unrelated to the level of cognitive impairment *per se* (See Chapter 3), suggesting that performance at the 0° condition may reflect a selective, sub-clinical visuospatial impairment in both groups.

Whilst the MCI-LB group performed more poorly on the BPP than the iRBD-CN group, this result should be interpreted with caution due to the small sample size and the difference in years of education between the groups with more education in the iRBD-CN patients. It should also be noted that previous studies have found the BPP to be correlated with self-reported VH in PD (Shine et al., 2012) and DLB (Phillips et al., 2021), whereas the iRBD patients in the current study had no reports of these phenomena. However, a higher number of misses by MCI-LB patients would be in keeping with previous work that reported DLB patients had more misses than misperceptions on the BPP (Phillips et al., 2021), a finding that may reflect impaired

attentional switching or reduced saccadic processes in DLB patients (Phillips et al., 2021).

In the current study, two patients who were assessed at baseline transitioned to a clinical synucleinopathy at follow up over a minimum period of 28 months. At their baseline assessment the patient transitioning to DLB was the only participant classified as meeting criteria for *probable* prodromal DLB by the presence of two core clinical features (RBD and parkinsonism), as well as RSWA on their PSG. However, they did not endorse cognitive fluctuations or visual hallucinations at this visit. In keeping with the absence of cognitive fluctuations, they performed relatively well on the SART but their performance on the MR task was variable with poor performance at the 0 and 45° conditions but reasonable performance on the 90° trials. Finally, performance on the BPP of the patient who transitioned from probable prodromal DLB to DLB resembled what has been reported in previous work in DLB patients who experience VH where subjects have a higher rate of trials where they fail to identify 'hidden' percepts (Phillips et al., 2021). The variable pattern of performance across the SART, MR and BPP in this individual who transitioned to DLB highlights the heterogeneity that exists not only across patients with DLB but also within individuals who may have a differential pattern of impairments across attention and visuoperceptive function. In contrast, the patient who transitioned to PD was younger (only 68 years of age) at baseline with a five-year history of iRBD and did not have MCI. They performed very well at the SART and did not reach the threshold to suggest impairment on the BPP. Their performance on the MR was mixed suggesting potentially selective visuospatial impairment.

Finally, the approach taken here stipulated that individuals with MCI and PSG confirmed RBD should be regarded as meeting a diagnosis for only *possible* prodromal DLB, which was the situation for 13 participants. Only one patient had MCI with PSG confirmed RBD, also had a second core feature (parkinsonism), which resulted in their classification as *probable* prodromal DLB. Significantly, this was the only patient who transitioned to DLB emphasising the importance of employing orthogonal clinical

core features and objective biomarkers. The currently proposed research criteria for MCI-LB do not specify that the combination of clinically reported RBD (one core feature) confirmed by RSWA (one objective biomarker) should be insufficient to meet a diagnosis of *probable* prodromal DLB. The results presented here would support the need for more stringent criteria to allow a more accurate stratification of the risk of developing DLB.

There are several significant limitations in the current study. The first relates to the small number of patients that had transitioned during the follow up period which averaged at 31 months. The transition rate of iRBD patients into either PD or DLB has been reported as being around 6% per annum (Postuma et al., 2019) and 35% at five years (Iranzo et al., 2013), but results have varied from 6% to 10% per annum across studies (Arnaldi et al., 2021; Iranzo et al., 2006; Miyamoto et al., 2020; Postuma et al., 2019). From the current cohort of 47 patients, this would have predicted 7-12 patients over the period evaluated. Unfortunately, not all patients were able to attend a full in person follow-up due to COVID-19 restrictions, meaning that some subtle features that might have permitted a clinical diagnosis may have gone undetected. In addition, 21 patients declined or could not conduct a follow-up assessment, which might reasonably have included at least some of those who had transitioned to PD or DLB.

Due to the cognitive battery applied, a more detailed classification of MCI was not attempted. However, the current study did identify patients with two or more domain impairments as MCI where the domains were taken from relevant sections of the MoCA with thresholds drawn from previously published work (Szeto et al., 2017) noting that a diagnosis of MCI cannot be made using MoCA alone (Petersen et al., 2009). This method of defining MCI patients reflects the current MCI guidelines that suggest test scores that are 1 – 1.5 standard deviations below healthy, age matched controls to be considered as impaired (Petersen, 2004). Previous studies have found that MCI patients with only amnestic impairments are more likely to transition to AD, whereas MCI patients with multiple domain impairments or only non-amnestic domains are more likely to transition to DLB (Petersen, 2004). Making this distinction

in the current study may have yielded stronger effects if MCI with only amnestic impairments were excluded. However, it should be emphasised that the presence of RBD is extremely rare in AD (Boeve et al., 2013). This suggest that if patients within the current cohort were to transition, it would likely be to a synucleinopathy.

Performance on the MR task was also an area that might need to be explored further in future studies. It should be noted that five patients with iRBD-CN performed the 90° condition near chance, suggesting that this task may have been too difficult with participants either giving up or exhibiting a floor phenomenon. Therefore, the sensitivity of this task needs to be questioned and future studies should consider using a dynamic design that adjusts difficulty depending on performance. The outcome of this would thus provide a maximum rotation calculated for each patient. This maximum would be lower for impaired patients and higher for cognitively normal patients making the task more sensitive, which would be useful when investigating groups with heterogenous performance. Future studies investigating the cognitive characteristics of iRBD patients on the SART, MR and BPP would also clearly benefit from a longitudinal design to monitor the patients until they transitioned.

In summary, the current study demonstrated the potential utility of the SART, MR and BPP as tools in the assessment of patients with prodromal DLB. However, more work with larger cohorts and longitudinal assessment is required to confirm the utility of these measures. Furthermore, the findings presented here emphasise the need for a more stringent deployment of the recently proposed research criteria for prodromal DLB that would insist on orthogonal measures of core clinical features and objective biomarkers to stratify prodromal DLB between possible and probable status by avoiding the circularity of recognising both RBD symptoms and positive RSWA on vPSG.

5.6. References

Arnaldi, D., Chincarini, A., Hu, M. T., Sonka, K., Boeve, B., Miyamoto, T., Puligheddu, M., De Cock, V. C., Terzaghi, M., Plazzi, G., Tachibana, N., Morbelli, S., Rolinski, M., Dusek, P., Lowe, V., Miyamoto, M., Figorilli, M., Verbizier, D., Bossert, I., Antelmi, E., Meli, R., Barber, T. R., Trnka, J., Miyagawa, T., Serra, A., Pizza, F., Bauckneht, M., Bradley, K. M., Zogala, D., McGowan, D. R., Jordan, L., Manni, R., & Nobili, F. (2021). Dopaminergic imaging and clinical predictors for phenoconversion of REM sleep behaviour disorder. *Brain*, *144*(1), 278-287. https://doi.org/10.1093/brain/awaa365

American Psychiatry Association (2013). *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). Arlington, VA : American Psychiatric Association.

Bean, J. (2011). Rey Auditory Verbal Learning Test, Rey AVLT. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 2174-2175). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1153

Berg, D., Postuma, R. B., Adler, C. H., Bloem, B. R., Chan, P., Dubois, B., Gasser, T., Goetz, C. G., Halliday, G., Joseph, L., Lang, A. E., Liepelt-Scarfone, I., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C. W., Poewe, W., Stern, M., & Deuschl, G. (2015). MDS research criteria for prodromal Parkinson's disease. *Mov Disord*, *30*(12), 1600-1611. https://doi.org/10.1002/mds.26431

Boeve, B. F., Silber, M. H., Ferman, T. J., Lin, S. C., Benarroch, E. E., Schmeichel, A. M., Ahlskog, J. E., Caselli, R. J., Jacobson, S., Sabbagh, M., Adler, C., Woodruff, B., Beach, T. G., Iranzo, A., Gelpi, E., Santamaria, J., Tolosa, E., Singer, C., Mash, D. C., Luca, C., Arnulf, I., Duyckaerts, C., Schenck, C. H., Mahowald, M. W., Dauvilliers, Y., Graff-Radford, N. R., Wszolek, Z. K., Parisi, J. E., Dugger, B., Murray, M. E., & Dickson, D. W. (2013). Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a

coexisting neurologic disorder. *Sleep Med*, *14*(8), 754-762. https://doi.org/10.1016/j.sleep.2012.10.015

Dauvilliers, Y., Schenck, C. H., Postuma, R. B., Iranzo, A., Luppi, P. H., Plazzi, G., Montplaisir, J., & Boeve, B. (2018). REM sleep behaviour disorder. *Nat Rev Dis Primers*, *4*(1), 19. https://doi.org/10.1038/s41572-018-0016-5

Ehgoetz Martens, K. A., Matar, E., Hall, J. M., Phillips, J., Szeto, J. Y. Y., Gouelle, A., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2019). Subtle gait and balance impairments occur in idiopathic rapid eye movement sleep behavior disorder. *Mov Disord*, *34*(9), 1374-1380. https://doi.org/10.1002/mds.27780

Ehgoetz Martens, K. A., Matar, E., Shine, J. M., Phillips, J. R., Georgiades, M. J., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2020). The Neural Signature of Impaired Dual-Tasking in Idiopathic Rapid Eye Movement Sleep Behavior Disorder Patients. *Mov Disord*, *35*(9), 1596-1606. https://doi.org/10.1002/mds.28114

Farnsworth, D. (1957). *The Farnsworth-Munsell 100-hue test for examination of color discrimination*. Munsell Color Co.

Frauscher, B., Iranzo, A., Hogl, B., Casanova-Molla, J., Salamero, M., Gschliesser, V., Tolosa, E., Poewe, W., & Santamaria, J. (2008). Quantification of electromyographic activity during REM sleep in multiple muscles in REM sleep behavior disorder. *Sleep*, *31*(5), 724-731. https://doi.org/10.1093/sleep/31.5.724

Génier Marchand, D., Postuma, R. B., Escudier, F., De Roy, J., Pelletier, A., Montplaisir, J., & Gagnon, J. F. (2018). How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. *Ann Neurol*, *83*(5), 1016-1026. https://doi.org/10.1002/ana.25239

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R.,

Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*, *23*(15), 2129-2170. https://doi.org/10.1002/mds.22340

Guerreiro, R., Ross, O. A., Kun-Rodrigues, C., Hernandez, D. G., Orme, T., Eicher, J. D., Shepherd, C. E., Parkkinen, L., Darwent, L., Heckman, M. G., Scholz, S. W., Troncoso, J. C., Pletnikova, O., Ansorge, O., Clarimon, J., Lleo, A., Morenas-Rodriguez, E., Clark, L., Honig, L. S., Marder, K., Lemstra, A., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Barber, I., Braae, A., Brown, K., Morgan, K., Troakes, C., Al-Sarraj, S., Lashley, T., Holton, J., Compta, Y., Van Deerlin, V., Serrano, G. E., Beach, T. G., Lesage, S., Galasko, D., Masliah, E., Santana, I., Pastor, P., Diez-Fairen, M., Aguilar, M., Tienari, P. J., Myllykangas, L., Oinas, M., Revesz, T., Lees, A., Boeve, B. F., Petersen, R. C., Ferman, T. J., Escott-Price, V., Graff-Radford, N., Cairns, N. J., Morris, J. C., Pickering-Brown, S., Mann, D., Halliday, G. M., Hardy, J., Trojanowski, J. Q., Dickson, D. W., Singleton, A., Stone, D. J., & Bras, J. (2018). Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. *Lancet Neurol*, *17*(1), 64-74. https://doi.org/10.1016/S1474-4422(17)30400-3

Hemminghyth, M. S., Chwiszczuk, L. J., Rongve, A., & Breitve, M. H. (2020). The Cognitive Profile of Mild Cognitive Impairment Due to Dementia With Lewy Bodies-An Updated Review. *Front Aging Neurosci*, *12*, 597579. https://doi.org/10.3389/fnagi.2020.597579

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses*, *22*(1), 39-52. http://chemse.oxfordjournals.org/content/22/1/39.full.pdf

IBM. (2019). IBM SPSS Statistics. In (Version 26) IBM.

Iranzo, A., Frauscher, B., Santos, H., Gschliesser, V., Ratti, L., Falkenstetter, T., Sturner, C., Salamero, M., Tolosa, E., Poewe, W., Santamaria, J., & Hogl, B. (2011). Usefulness of the SINBAR electromyographic montage to detect the motor and vocal manifestations occurring in REM sleep behavior disorder. *Sleep Med*, *12*(3), 284-288. https://doi.org/10.1016/j.sleep.2010.04.021

Iranzo, A., Molinuevo, J. L., Santamaría, J., Serradell, M., Martí, M. J., Valldeoriola, F., & Tolosa, E. (2006). Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*, *5*(7), 572-577. https://doi.org/10.1016/s1474-4422(06)70476-8

Iranzo, A., Tolosa, E., Gelpi, E., Molinuevo, J. L., Valldeoriola, F., Serradell, M., Sanchez-Valle, R., Vilaseca, I., Lomena, F., Vilas, D., Llado, A., Gaig, C., & Santamaria, J. (2013a). Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol*, *12*(5), 443-453. https://doi.org/10.1016/S1474-4422(13)70056-5

Kemp, J., Philippi, N., Phillipps, C., Demuynck, C., Albasser, T., Martin-Hunyadi, C., Schmidt-Mutter, C., Cretin, B., & Blanc, F. (2017). Cognitive profile in prodromal dementia with Lewy bodies. *Alzheimers Res Ther*, *9*(1), 19. https://doi.org/10.1186/s13195-017-0242-1

Leonard, H., Blauwendraat, C., Krohn, L., Faghri, F., Iwaki, H., Ferguson, G., Day-Williams, A. G., Stone, D. J., Singleton, A. B., Nalls, M. A., Gan-Or, Z., & International Parkinson's Disease Genomic, C. (2020). Genetic variability and potential effects on clinical trial outcomes: perspectives in Parkinson's disease. *J Med Genet*, *57*(5), 331-338. https://doi.org/10.1136/jmedgenet-2019-106283

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed. ed.). New York : Oxford University Press.

Litvan, I., Goldman, J. G., Troster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., Mollenhauer, B., Adler, C. H., Marder, K., Williams-Gray, C. H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M. C., Burn, D. J., Barker, R. A., & Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord*, *27*(3), 349-356. https://doi.org/10.1002/mds.24893

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/wnl.0000000000004058

McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., Kantarci, K., Muscio, C., O'Brien, J. T., Postuma, R. B., Aarsland, D., Ballard, C., Bonanni, L., Donaghy, P., Emre, M., Galvin, J. E., Galasko, D., Goldman, J. G., Gomperts, S. N., Honig, L. S., Ikeda, M., Leverenz, J. B., Lewis, S. J. G., Marder, K. S., Masellis, M., Salmon, D. P., Taylor, J. P., Tsuang, D. W., Walker, Z., & Tiraboschi, P. (2020). Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology*, *94*(17), 743-755. https://doi.org/10.1212/wnl.0000000000009323

Miyamoto, M., Miyamoto, T., Saitou, J., & Sato, T. (2020). Longitudinal study of striatal aromatic l-amino acid decarboxylase activity in patients with idiopathic rapid eye movement sleep behavior disorder. *Sleep Med*, *68*, 50-56. https://doi.org/10.1016/j.sleep.2019.09.013

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, *53*(4), 695-699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Pelli, D. G., & Bex, P. (2013). Measuring contrast sensitivity. *Vision Res*, *90*, 10-14. https://doi.org/10.1016/j.visres.2013.04.015

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J Intern Med*, *256*(3), 183-194. https://doi.org/10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., Smith, G. E., & Jack, C. R., Jr. (2009). Mild cognitive impairment: ten years later. *Arch Neurol*, *66*(12), 1447-1455. https://doi.org/10.1001/archneurol.2009.266

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (2019). Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia With Lewy Bodies. *J Geriatr Psychiatry Neurol*, 891988719882093. https://doi.org/10.1177/0891988719882093

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (2021). Evaluating a novel behavioral paradigm for visual hallucinations in Dementia with Lewy bodies. *Aging Brain*, *1*, 100011. https://doi.org/https://doi.org/10.1016/j.nbas.2021.100011

Phillips, J. R., Matar, E., Ehgoetz Martens, K. A., Moustafa, A. A., Halliday, G. M., & Lewis, S. J. G. (In Review). An adaptive measure of visuospatial impairment in Dementia with Lewy Bodies. *Movement Disorders Clinical Practice*.

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J.,
Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois,
B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical
diagnostic criteria for Parkinson's disease. *Mov Disord*, *30*(12), 1591-1601.
https://doi.org/10.1002/mds.26424

Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., Oertel, W. H.,
Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V.,
Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K. Y., Kunz, D.,
Dauvilliers, Y., Provini, F., Lewis, S. J., Buskova, J., Pavlova, M., Heidbreder,
A., Montplaisir, J. Y., Santamaria, J., Barber, T. R., Stefani, A., St Louis, E. K.,
Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-
Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J. F.,
Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M.,
Mahlknecht, P., Holzknecht, E., Boeve, A. R., Teigen, L. N., Toscano, G., Mayer,
G., Morbelli, S., Dawson, B., & Pelletier, A. (2019b). Risk and predictors of
dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a
multicentre study. *Brain*, *142*(3), 744-759. https://doi.org/10.1093/brain/awz030

Sateia, M. J. (2014). International classification of sleep disorders-third edition:
highlights and modifications. *Chest*, *146*(5), 1387-1394.
https://doi.org/10.1378/chest.14-0970

Schenck, C. H., Boeve, B. F., & Mahowald, M. W. (2013). Delayed emergence of a
parkinsonian disorder or dementia in 81% of older men initially diagnosed
with idiopathic rapid eye movement sleep behavior disorder: a 16-year update
on a previously reported series. *Sleep Med*, *14*(8), 744-748.
https://doi.org/10.1016/j.sleep.2012.10.009

Shine, J. M., Halliday, G. H., Carlos, M., Naismith, S. L., & Lewis, S. J. (2012). Investigating visual misperceptions in Parkinson's disease: a novel behavioral paradigm. *Mov Disord*, *27*(4), 500-505. https://doi.org/10.1002/mds.24900

Shine, J. M., Mills, J. M. Z., Qiu, J., O'Callaghan, C., Terpening, Z., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2015). Validation of the Psychosis and Hallucinations Questionnaire in Non-demented Patients with Parkinson's Disease. *Movement Disorders Clinical Practice*, *2*(2), 175-181.

Stiasny-Kolster, K., Mayer, G., Schafer, S., Moller, J. C., Heinzel-Gutenbrunner, M., & Oertel, W. H. (2007). The REM sleep behavior disorder screening questionnaire- -a new diagnostic instrument. *Mov Disord*, *22*(16), 2386-2393. https://doi.org/10.1002/mds.21740 [doi]

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Pyschology*, *11*, 643-662. https://doi.org/10.1037/h0054651

Sunderland, T., Hill, J. L., Mellow, A. M., Lawlor, B. A., Gundersheimer, J., Newhouse, P. A., & Grafman, J. H. (1989). Clock drawing in Alzheimer's disease. A novel measure of dementia severity. *J Am Geriatr Soc*, *37*(8), 725-729. https://doi.org/10.1111/j.1532-5415.1989.tb02233.x

Szeto, J. Y. Y., Halliday, G. M., Naismith, S. L., & Lewis, S. J. G. (2017). Exploring the Phenotype in Mild Cognitive Impairment to Aid the Prediction of Those at Risk of Transitioning to Parkinson Disease and Dementia With Lewy Bodies. *J Geriatr Psychiatry Neurol*, *30*(4), 196-205. https://doi.org/10.1177/0891988717711451

Szeto, J. Y. Y., Walton, C. C., Rizos, A., Martinez-Martin, P., Halliday, G. M., Naismith, S. L., Chaudhuri, K. R., & Lewis, S. J. G. (2020). Dementia in long-term Parkinson's disease patients: a multicentre retrospective study. *NPJ Parkinsons Dis*, *6*, 2. https://doi.org/10.1038/s41531-019-0106-4

van de Beek, M., van Steenoven, I., van der Zande, J. J., Barkhof, F., Teunissen, C. E., van der Flier, W. M., & Lemstra, A. W. (2020). Prodromal Dementia With Lewy Bodies: Clinical Characterization and Predictors of Progression. *Mov Disord*, *35*(5), 859-867. https://doi.org/10.1002/mds.27997

Wechsler, D. (2009). *The Wechsler memory scale - fourth edition (WMS-IV)*. Pearson Assessment.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., & Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*, *256*(3), 240-246. https://doi.org/10.1111/j.1365-2796.2004.01380.x

Chapter Six

6. Thesis discussion and conclusions

6.1. Overview of thesis

The main aim of this thesis was to introduce novel behavioural tasks that can accurately and sensitively assess core symptoms of DLB to identify those who are at risk of developing DLB, enhance our understanding of DLB progression and ultimately to use in the evaluation of future treatments for DBL. Dementia with Lewy Bodies was only identified relatively recently (McKeith et al., 1992) and the diagnostic criteria have been updated periodically as more has been learnt through research (McKeith et al., 2017; McKeith et al., 2005; McKeith et al., 2020; McKeith et al., 1996). However, as has been consistently highlighted throughout this thesis, DLB overlaps clinically with other neurodegenerative conditions, principally Alzheimer's Dementia and Parkinson's Disease, limiting the utility of many of the available behavioural tests that have been explored.

Autopsy series have reported that a high proportion of DLB patients have concomitant AD pathology and vice versa (Fodero-Tavoletti et al., 2007; Irwin et al., 2017; Walker et al., 2015). Therefore, it is not surprising that a proportion of DLB patients will present with AD symptoms, which delays and complicates the accurate diagnosis of DLB. In addition, early DLB may also mimic PD and the debate as to whether they truly represent different entities continues (Boeve et al., 2016; McKeith et al., 2017; Postuma et al., 2015). Given this spectrum of overlapping clinical profiles across DLB, AD and PD more sensitive measures are needed that could assist with diagnosis and in particular, the assessment and monitoring of specific clinical features of DLB. It is also acknowledged throughout this thesis that further studies assessing the paradigms presented here will now need to be tested in other patient cohorts including AD and PDD. However, it was vital to initially establish the potential utility of these tasks in more limited populations before embarking on such a significant undertaking.

The widespread application of behavioural and cognitive paradigms in the DLB field has been met with numerous challenges. Clearly, one of the major features in

DLB is that of rapid cognitive decline, resulting in a severely impaired cohort (Jellinger, 2018). Thus, many of the tasks trialed previously that have been of some use in other dementia cohorts have often resulted in ceiling effects or have been deemed too difficult for DLB patients to complete (Martini et al., 2020; Park et al., 2013; Petrova et al., 2016). Indeed, in Chapters Two and Three of the current thesis, the initial versions of the tasks were modified in preliminary testing by slowing down stimulus delivery or by reducing task difficulty to accommodate DLB patients, without compromising the measures of the task.

It is widely appreciated that DLB is a heterogeneous disease where symptom severity can vary greatly across individual patients and in addition, even within patients who are prone to cognitive fluctuations, cycling from periods of relatively preserved cognition and alertness to low levels that may result in the subject being untestable. This accessibility of the task and the impact of cognitive fluctuations has resulted in mixed findings and made difficult the interpretation of results when comparing DLB with PDD and/or AD (section 1.6). Fluctuation of cognition combined with the heterogeneity of DLB have necessitated the development of novel cognitive tasks that are accessible to DLB patients and can be adaptable to impairments across the cohort.

Currently, three of the four core features of DLB, namely cognitive fluctuations (CF), Visual Hallucinations (VH) and parkinsonian symptoms are measured either by a rating scale or clinical interview. These approaches have three main disadvantages: (1) they rely on responses from either the patient or an informant and whilst these responses are assumed to be accurate, they are reliant on the respondent (patient/caregiver) being aware of the symptoms, as well as a willingness to disclose the often stigmatising symptoms (de Medeiros et al., 2010); (2) responses gathered from scales and clinical interviews are subjective and prone to bias from either the respondent and/or the clinician; and , (3) scales typically measure the severity of a symptom by applying it to an arbitrary Likert scale, which ranks severity that might represent a practical approach in the clinical setting, but for research and clinical trials

a more objective measure of severity applied along a continuous scale would be more desirable. Increasing the sensitivity of any measure would allow subtle differences to be observed and perhaps more importantly in the context of an intervention, changes in the severity of the response to be recorded.

To address this need for cognitive and behavioural paradigms that are sensitive and adaptable for DLB patients, whilst also providing measures that are suitable for research and clinical trials, the current thesis evaluated three tasks namely, the SART, MR and BPP. The objective was to test whether these three paradigms were accessible to patients with DLB and represented valid objective measures of specific symptoms. It was anticipated that if found to be useful, further testing of these paradigms could be directed to other dementia groups (e.g., AD and PDD) and larger sample sizes with longitudinal follow-up. In addition, it was hoped that any utility of the SART, MR or BPP could be implemented directly into research. To this end, the SART as described in Chapter Two, has been incorporated as a Secondary Outcome measure in a clinical trial evaluating a beta-agonist in patients with DLB (NCT04739423).

It was also argued that if the paradigms introduced in this thesis offered any utility in DLB, there may also be a role for them in the assessment of patients with prodromal DLB. Thus, this thesis also presents data from testing conducted in patients with isolated RBD (iRBD) who form part of an ongoing, longitudinal study. Clearly, iRBD represents an 'at risk' state for developing a synucleinopathy and the presence of Mild Cognitive Impairment (MCI) in such individuals has been linked to the greater likelihood of transitioning to DLB (Postuma et al., 2019). Furthermore, the combination of MCI and RBD would be regarded within the framework of the recently proposed research criteria as representing a diagnosis of prodromal DLB (MCI-LB; McKeith et al., 2020). Therefore, this thesis also offers guidance on how the proposed research criteria for prodromal DLB should be best implemented in these at-risk patients, as well as evaluating the potential utility of the SART, MR and BPP.

6.2.   Summary of Key Findings

6.2.1.   Chapter Two: Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia with Lewy Bodies

The aim of Chapter Two was to present a novel task that could be used in DLB patients to detect and objectively measure the severity of CF. Currently, the only means for detecting and measuring CFs is via clinical interview and using scales such as the Clinical Assessment of Fluctuations (CAF) or One Day Fluctuation (ODF) scale. While these scales are commonly used in clinical and research settings, they lose sensitivity by using ordinal scales, whilst also relying on subjective responses. These issues are potentially exacerbated further by the definitions that are included in the tool. For example, the fluctuation item of the ODF scale contains "…he/she *seemed* to be confused…" and "…he/she *seemed* to improve…" (Walker et al., 2000, p. 255). While the purpose of this ambiguous wording would be to make the question more accessible to a non-trained informant, without a concrete definition, the response is reliant on what behaviour the respondent thinks reflect confusion. This is then interpreted by the clinician who may add their own bias to the respondent's definition of confusion. This design may be acceptable in a clinical setting where the presence of CF and a severity ranking may be all that is needed. However, in a research or clinical trial setting, where the severity of CF is being monitored or its neural correlate being explored with neuroimaging/neurophysiology, an objective measure is needed.

Currently, there are few behavioural tasks to measure attention that have been used within DLB. The Choice Reaction (CRT) and Digit Vigilance tasks (DVT) have been used in DLB with CF (Walker et al., 2000). However, the CRT requires patients to make a choice response, which may be stimulating enough to prevent CF, whereas the DVT requires participants to only make a response when they see a target number, potentially missing short periods of fluctuation that may occur during the non-response time. Indeed, this phenomenon was evident in the SART findings presented

here, with patients who indicated frequent fluctuations also missing more responses than patients who fluctuate less frequently.

The SART was introduced to this population to reduce bias and produce a quantifiable measure of CF severity. The original version of the SART presented stimuli for 250ms (Robertson et al., 1997), however this was deemed too brief for an older population with dementia and was increased to 750ms. Even though this presentation period is considerably longer than the original paradigm, it was still able to produce errors and was more accessible to cognitively impaired patients. A quantifiable, objective measure of CF that is accessible to DLB patients make the SART an ideal tool to use in interventional studies as an outcome that can be accurately measured. Furthermore, during a clinical assessment, the SART could also be utilised as a brief, real time gauge of CF. This would provide confidence in the outcomes of other neuropsychological tests administered in a testing session. For example, if a clinician was concerned that a patient performed poorly on a task due to the presence of an active CF, the SART could be measured and repeated to confirm an actual improvement before re-testing the participant in a clinical trial. Furthermore, the objective nature of the SART make it an ideal instrument to be combined with EEG or fMRI studies to investigate the neural correlates of CF (Matar et al., 2019).

The first main finding from the study presented in Chapter Two was that the SART was accessible to DLB patients. This was demonstrated with high accuracy from DLB patients. This is an important finding, as DLB patients are often too severely impaired for objective testing where they can struggle to engage with a task that is too complicated or too long (section 1.6.1). Furthermore, measures on the SART were not correlated with MMSE, which could support its use across other dementia populations.

The second finding from Chapter Two was that the number of misses made had a medium strength, positive correlation with the ODF scale. Thus, the higher patients scored on the ODF, the greater the number of misses they made on the SART. When dissecting the ODF, patients who indicated more fluctuations, poorer attention and

greater disorganised thoughts produced a greater number of misses. Interestingly, no association was found between the CAF and SART measures. This is likely due to the CAF measuring the presence of CF over the last 30 days, whilst the SART provides a real time measure of attentional impairment. This real time measurement is highly desirable in research as it allows for the combination of the SART with other time-locked modalities such as EEG and fMRI, potentially offering further insights into the mechanisms underlying CF.

6.2.2. Chapter Three: An adaptive measure of visuospatial impairment in Dementia with Lewy Bodies

Chapter Three focused on visuospatial impairment, where the MR task was introduced to DLB patients to investigate visuospatial impairment, whilst also offering different levels of difficulty, so as to reduce the chance of floor or ceiling effects that have been previously reported when using other available paradigms (Martini et al., 2020). Such dimensions would make the MR task suitable in DLB research for evaluating longitudinal progression and potentially sensitive to detect the response to interventions with patients serving as their own internal controls where their performance could be 'normalised' to their own baseline.

Again, the primary finding from this Chapter was the accessibility of the MR task across DLB patients. Initial versions of the MR involved 0°, 90° and 180° rotations, however these proved too difficult for this clinical population. This led to the current version with 0°, 45° and 90°, which whilst easier for patients was still difficult enough to provide variance in performance. Whilst at the 0°, 45° and 90° of rotation conditions, the HC and early PD groups performed at the same level, the DLB group had significantly lower accuracy. However, at the 0° rotation condition, the DLB group performed well above chance and not at ceiling, suggesting that they were engaged and able to complete the simplest difficulty level of the task. Even when a mental rotation was required for the 45° condition, although accuracy fell across all

groups, performance by the DLB participants remained above chance. However, performance by the DLB patients decreased to chance with the 90° rotation condition, implying that this level of rotation was too difficult for DLB patients and achieved an unhelpful floor effect.

The second finding from Chapter Three was that performance on the MR task was correlated with measures of VH and orthogonal tests of visuospatial ability including the Clock Drawing Task (CDT), the copy condition of Rey Complex Figure (RCF) and the TMT part A, further supporting the validity of using this paradigm in future studies of DLB. There is an established literature reporting that visuospatial impairment is a key finding in DLB (and PD) patients who experience VH (Revie et al., 2020; Rosenblum et al., 2021; Specketer et al., 2019). Furthermore, within the DLB group, accuracy on the MR task was also correlated with measures of VH from both the MDS-UPDRS part I and the PsycH-Q.

One strength of the MR paradigm is that it could be easily adjusted to match the ability of the DLB cohort that is being tested by adjusting the difficulty across 0°, 45° and 90° trials to obviate floor and ceiling effects that would allow a more sensitive measure of visuospatial ability. Furthermore, other common visuospatial tasks such as the CDT, RCF and TMT tasks require complex motor responses (i.e., drawing) that would make combining their performance with time-locked research approaches such as EEG and fMRI less practical compared to the MR task that requires only a single key press for each trial. Thus, in future research combining the MR task with EEG or fMRI, each trial could be broken down into the components of comparing the shapes, then creating a visual representation and manipulating that representation. Thus, researchers would potentially be able to identify regions involved in each of these processes separately, offering further insights into the neural correlates of visuospatial processing. Such an approach could obviously be applied not only to DLB but also in other disease populations and in HC.

Finally, accuracy on the MR task was not correlated with performance on memory testing or the MMSE, as a global measure of cognition. This suggests that performance

on the MR task does not rely on memory, and it is anticipated that in future testing, AD patients with similar levels of dementia, would be less impaired than DLB, potentially allowing this paradigm to differentiate accurately between these two diseases.

6.2.3. Chapter Four: Evaluating a novel behavioural paradigm for visual hallucinations in Dementia with Lewy Bodies

Chapter Four focused on VH in DLB given that there are few paradigms that can detect and objectively measure the severity of VH and none that measure misperceptions or the failure to detect visual information from a scene. Currently, researchers typically utilise scales to measure VH severity that rely on reports from the patient or informant and are scored using an arbitrary Likert scale. While this may be useful in the clinical setting, more objective, continuous measures that provide a sensitive measure of change would be more desirable for research and in clinical trials.

The Bistable Percept Paradigm (BPP) creates an optimal environment for misperceptions by presenting ambiguous images with one or two percepts that requires the participant to indicate how many percepts they see. The BPP has been validated in PD, with patients that experience VH having more misperceptions than non-VH patients (Shine et al., 2012). This sensitivity to VH and the simplicity of the task make it ideal for testing within the DLB cohort who frequently experience this core symptom but often deny it due to the related stigma (Mosimann et al., 2008).

The primary outcome of Chapter Four found that the BPP was accessible to DLB patients as they were able accurately identify over 80% of the images, although they were slower to complete the task compared to HC. As expected, DLB patients recorded more misperceptions and 'misses' where they failed to appreciate a second percept than the HC group. It is not clear whether such failures in perception reflect hypoactivation in the frontal eye fields in DLB (Nagahama et al., 2008), potentially reducing the number of saccades and reducing the amount of information extracted

from each scene, or if alternatively, it could be driven by impaired attentional switching, which has been demonstrated in PD patients with VH (Crescentini et al., 2012; Mandal & Khan, 2021; Shine et al., 2015b). Now that the BPP has been validated in DLB, it is possible to see how it could be combined with saccadometry and/or fMRI to provide some greater insights into the roles of these mechanisms.

Secondly, performance on the BPP correlated with the misperception components of the PsycH-Q, although not the MDS-UPDRS part I measure of VH, which may simply reflect the limited sensitivity of this measure (Aynsworth et al., 2017). Having an objective measure of a symptom that can be correlated with measures obtained through clinical interview would again be useful for future longitudinal research and interventional studies. Additionally, performance on the BPP was not correlated with the MMSE, supporting the study of this task in other cognitively impaired cohorts, such as AD.

6.2.4. Chapter Five Evaluating novel paradigms in prodromal Dementia with Lewy Bodies

Chapter Five introduced a group of isolated RBD (iRBD) patients who were recruited as part of an ongoing longitudinal program of research recognising that such patients are at high risk for the development of synucleinopathies and that the presence of MCI represents a predictor for DLB (Postuma et al., 2019). This study was performed at a crucial time given the recent proposal of research criteria for the diagnosis of prodromal DLB (McKeith et al., 2020). Previous studies attempting to investigate prodromal DLB have adopted a variety of approaches such as mixing and matching diagnostic criteria (Bussè et al., 2018; Kemp et al., 2017) or assigning patients retrospectively, dependent on their transition (Génier Marchand et al., 2018; van der Zande et al., 2020). The recent research criteria seek to avoid this level of ambiguity and have proposed the existence of three prodromal DLB sub-groups characterised by an MCI-onset, Delirium-onset and Psychiatric-onset phenotype. In this

framework, MCI-onset DLB requires the presence of MCI as an essential feature and the diagnosis of prodromal DLB can be supported by the presence of core clinical features (CF, VH, RBD or parkinsonism) and proposed biomarkers (abnormal DATscan, abnormal cardiac MIBG, REM Sleep without Atonia (RSWA) on polysomnography (PSG)). Furthermore, the criteria stratify cases as *possible* or *probable* prodromal DLB of MCI-LB type by the identification of more than one core clinical feature and/or the presence of a proposed biomarker. Thus, patients with MCI who report the presence of RBD fulfill the criteria for MCI-LB, a sub-type of prodromal DLB. However, to avoid the circularity of designating all MCI patients with PSG confirmed RBD as *probable* prodromal DLB, Chapter Five required orthogonal measures of core clinical features and potential biomarkers or the presence of more than one core feature to denote a case as being *probable* prodromal DLB. Utilising this approach, only one patient fulfilled research criteria for *probable* prodromal DLB and significantly, they transitioned to DLB 28 months after their baseline assessment, whereas 13 *possible* prodromal DLB cases remained clinically stable. A further patient with iRBD who had no MCI when tested, transitioned after 33 months to PD. These findings call for a more stringent application of the research criteria for prodromal DLB in future studies so as to avoid the over-classification of *probable* MCI-LB.

In addition to this evaluation of the research criteria for prodromal DLB, Chapter Five evaluated whether the SART, MR and BPP could differentiate between patients with MCI-LB and those iRBD patients who were cognitively intact. This study also investigated whether performance on these novel paradigms could aid in predicting any patient who transitioned to DLB. The initial group analysis suggested that MCI-LB patients had poorer performance on the MR and BPP than cognitively normal iRBD patients but this finding lost its statistical significance when years of education was controlled for. However, the overall accuracy on the MR task was trending towards significance (p = 0.06) and may have been significant with more statistical power.

These non-significant trends on the MR and BPP were further supported by inspecting the performance of the only *probable* prodromal DLB patient in the study

who later transitioned to DLB. This patient showed poor accuracy on the MR task and missed a high number of percepts in the BPP task. These findings highlight the potential of the MR and BPP tasks for identifying mild impairments within prodromal patients. However, further testing with larger samples is needed to confirm this.

6.3. Limitations of the current work

The aim of the current thesis was to evaluate novel tasks in DLB patients to assess their accessibility and gauge whether they could be valid measures of relevant core symptoms in DLB. Whilst these aims were largely accomplished, there are some limitations to consider when interpreting the findings of this thesis.

6.3.1. Comparisons across dementias

The first limitation emphasised here is absence of alternative dementia cohorts. In a clinical environment, the immediate priority is often towards providing an accurate diagnosis. Obviously, whilst considered arbitrary by many, the *12-month rule* that differentiates DLB from PDD based on remaining cognitively intact for at least a year following the diagnosis of PD has proven useful in the clinical setting (Boeve et al., 2016). Thus, this thesis attempted to include PD patients in the earlier stages of disease (<5y) to confirm the utility of the paradigms in discriminating patients with the earlier stages of DLB. As highlighted throughout this thesis, the clinical similarities between DLB and PDD, along with their broadly similar pattern of cognitive impairments would make it unlikely that any form of behavioural testing would be useful for accurately differentiating such cases (for review see (Gomperts, 2016; Jellinger, 2018; Jellinger & Korczyn, 2018)). However, the ability to investigate specific clinical features (e.g., cognitive fluctuations, visuospatial function, and visual hallucinations) with objective measures that are accessible in patients with moderate levels of dementia is seen as an important advance of the work presented here.

Obviously, it can also be difficult to separate DLB from AD, especially during early stages where additional tools would be invaluable. Unfortunately, after initially confirming the utility of the paradigms in DLB, reaching out to memory clinics for AD patients or using a community-based recruitment approaches became untenable during the global COVID-19 pandemic. However, performance on none of the tasks assessed in this thesis (SART, MR and BPP), demonstrated strong correlations with tests of memory or the MMSE as a global cognitive measure. Thus, given the existing literature that suggests cognitive fluctuations (Escandon et al., 2010; Mainland et al., 2017), visuospatial impairments (Breitve et al., 2018; Yoon et al., 2015) and visual hallucinations (Zhao et al., 2016) are less frequent and severe in AD, we would propose that future studies should evaluate these comparisons between DLB and AD using the paradigms reported here to determine their ability to discriminate between these diseases.

6.3.2. Small sample sizes

In keeping with much of the published literature in DLB, each of the studies presented in this thesis had small sample sizes, which were further impacted when DLB patients were unable to complete complimentary cognitive tasks to allow greater correlations (i.e., RCF, TMT part B). Clearly, small sample sizes result in less statistical power, and this could have been one of the explanations where expected findings did not reach significance. This was demonstrated in Chapter Four where it was expected that a significant correlation would exist between misperceptions and the TMT part B, based on previous work in PD patients with VH (Shine et al., 2012) but the results demonstrated only a non-significant correlation (p = 0.18).

Small sample sizes are not uncommon when testing clinical populations (Bliwise et al., 2014; Johns et al., 2009; Knuffman et al., 2001; Park et al., 2011; Tilley et al., 2021; Zarkali et al., 2019) and this is emphasised in challenging conditions like DLB with severe neuropsychiatric and physical symptoms. However, it should be appreciated

that the DLB and PD patients involved in the studies presented were diagnosed using the latest diagnostic criteria (McKeith et al., 2017; Postuma et al., 2015) and that the iRBD patients were confirmed using video PSG following the International Classification of Sleep Disorders (ICSD-3). Thus, whilst sample sizes were small, the patients included had undergone detailed phenotyping and form part of an ongoing longitudinal population, which is ultimately linked with a clinicopathological program of brain donation.

6.3.3. Cross sectional vs longitudinal

Each study in the current thesis used a cross sectional design. While this design was sufficient to provide a comparison between patient groups, or correlate task performance with DLB symptoms, cross sectional design does have several limitations. The main limitation is that it only provides performance from one point in time. This makes it difficult to make any inferences from the data provided, especially when studying a degenerative disease. A longitudinal design would obtain the most accurate picture of performance across the SART, MR and BPP in DLB patients. Ideally, regular testing during iRBD or the prodromal stages of DLB through to later stages of DLB would provide rich data that could be plotted against disease and symptom progression. This would provide researchers with further insights into the involvement of different neural systems and their impact on specific symptoms.

Cross sectional studies also compare mean or median performance of patient groups to determine any difference in symptoms or task performance. This can be problematic in α-synucleinopathy research due to the heterogeneity within each disease, as well as within individuals. As outlined in Chapter One, DLB involves a broad range of pathology that affects many different systems. Moreover, not all DLB patients follow the same pattern of neurodegeneration or are limited to one clinical profile. By grouping these patients together, individual variability is typically lost. The loss of variability could potentially be addressed by employing a longitudinal

design, where individual patients can be their own control, allowing for changes in performance to be mapped across disease progression, or treatment/intervention schedule. Furthermore, longitudinal design would also allow some individual variance to be controlled for.

Repeated testing would also provide a measure of the reliability for the SART, MR and BPP within DLB patients. This would be especially useful when testing DLB patients as many of them experience CF, that may impact performance. However, a longitudinal design may also introduce confounding variables such as potential learning effects. This could be accentuated in settings such as a clinical trial, where repeat testing typically occurs over shorter periods. The BPP would be most at-risk task described in this thesis with a limited battery of mono-/bistable images. Learning may also take place on the MR task where this would likely manifest as the development of strategies to make the task easier as has been reported elsewhere (Berneiser et al., 2018; Nagashima et al., 2019; Zhao & Sala, 2018). While this could be difficult to control for completely, changes to the plain of rotation or shapes may make it difficult for patients to apply techniques to subsequent MR tasks. Similarly, a strategy of varying task difficulty to attain a level that might be varied continuously across the degrees of rotation could be useful. Repeated testing may have the opposite effect on SART performance where the task is designed to be unstimulating so as to encourage fluctuations. Thus, repeated performance would remove novelty from the task making it potentially more monotonous and more likely to provoke CF.

6.4. Future directions

6.4.1. Larger, diverse cohorts

Having demonstrated that the SART, MR and BPP appear to be accessible in early DLB patients, it is now vital to confirm their validity across research and clinical settings. Initial studies should employ larger sample sizes and include other dementia cohorts as highlighted above. Larger sample sizes would provide more statistical

power, allowing potentially underpowered effects in the current thesis to reach significance. Larger samples combined with the inclusion of AD and PDD patients could potentially demonstrate the ability of the SART, MR and BPP to separate DLB from other dementia populations, which could be of great benefit to future research and clinical trials. There is also a growing appreciation that research teams working in DLB will need to collaborate more closely across the world and it is anticipated that combined testing across these settings could provide a pathway forward (D'Antonio et al., 2021).

6.4.2. Longitudinal design

Future studies applying the SART, MR and BPP to a RBD cohort may also benefit from a longitudinal over a cross-sectional design. Longitudinal design would allow individual patients to provide their own baseline to be compared against. This design is ideal for clinical testing of an intervention as it would provide an objective measure of the effect of any intervention. Repeated testing would allow psychometrics of the three tasks to be measured, and where required, improved. Individual differences could also be controlled for, providing accurate and in-depth models of DLB progression and individual changes could be further analysed to identify specific patterns of progression that could represent different phenotypes of DLB (Matar et al., 2019). Finally, more work could be conducted in other prodromal DLB groups such as the Delirium- and Psychiatric-onset phenotypes.

6.4.3. Applying tasks in clinical trials

Currently, clinical trials targeting cognitive fluctuations and visual hallucinations in DLB patients would rely on self/informant-reported scales to test the efficacy of the intervention. Given that these tools reduce the severity of such symptoms to simple ranked Likert scales, they are potentially insensitive to subtle changes in the outcome. By contrast, the SART, MR and BPP can objectively quantify changes in impairment

on a continuous scale, thus allowing subtle changes in the target symptom to be more accurately monitored. Indeed, as a result of the work published in this thesis the version of the SART presented here is currently being utilised as a measure of cognitive fluctuations in DLB patients enrolled in a clinical trial (NCT04739423). Furthermore, there are plans to evaluate to the neural correlates of VH and visuospatial processing in DLB by utilising the BPP and MR tasks having confirmed in this thesis that DLB patients are able to complete these tasks

6.4.4. Applying tasks in imaging studies

There are few paradigms that can provide real time feedback in demented patients like those potentially offered by the SART, MR and BPP as described here. Indeed, the BPP has previously been utilised with fMRI and EEG in PD patients to investigate the neural correlates of visual hallucinations in PD (Muller et al., 2021; Shine et al., 2015a; Shine et al., 2015b). Furthermore, the SART has been used in conjunction with EEG in different patient and HC populations (Hart et al., 2015; Ko et al., 2017; McMackin et al., 2021; Meghdadi et al., 2021). Future studies could replicate these studies with a DLB cohort to ascertain whether VH are also driven by changes to the attentional network. Similarly, combining the SART and MR tasks with EEG and fMRI could prove valuable in future studies investigating the neural correlates underlying cognitive fluctuations and visuospatial impairments in DLB.

6.4.5. Further task specific directions

Studies looking to enhance the MR task could dynamically alter the degrees of rotation in response to correct or incorrect responses from individual patients to identify the maximum rotation where the subject is able to perform. This would involve decreasing the rotation when an error is made and increasing with a correct response. This version would have several advantages as it would make the task more accessible. As reported in Chapter Five, several cognitively normal or mildly

impaired iRBD patients were unable to complete the higher rotations. This was also observed in a high proportion of DLB patients in Chapter Three. A dynamic difficulty would adjust to individuals, making it more accessible and sensitive. This approach may also shorten the task, which would make it more practical to administer with an outcome score measured in degrees that could be related to visuospatial ability.

Future studies could also further investigate the relationship between visuospatial impairment and VH by investigating the activation of the frontal eye fields with combined fMRI and saccadometry during the MR and BPP. This approach would provide valuable insights into how visuospatial impairment interacts with the attentional networks and how this may be disrupted and lead to visual hallucinations.

6.5. Concluding remarks

Dementia with Lewy body patients are notoriously difficult to test due to severe cognitive impairment, fluctuating attention, neuropsychiatric and motor symptoms. This thesis introduced new tasks to use with DLB patients that were accessible and measured cognitive fluctuations, visuospatial impairment, and visual hallucinations. It is proposed that the versions of the SART, MR, and BPP described here can produce objective measures with minimum effects from bias. Furthermore, the measures from these tasks are continuous and quantifiable allowing for subtle changes in the severity of these features to be observed. Thus, it would appear that the SART, MR and BPP may prove useful in clinical research and interventional trials that can offer objective measures of severity and potentially identify responses to future interventions across the spectrum of disease ranging from prodromal to established disease. Furthermore, the behavioural design of the tasks should make them valuable tools for greater understanding the neurobiology underpinning symptoms in DLB. The findings from this thesis are thus intended to provide the foundation for future studies and it is hoped that this will improve the management of patients impacted by DLB.

~fin~

6.6. References

Aynsworth, C., Collerton, D., & Dudley, R. (2017). Measures of visual hallucinations: Review and recommendations. *Clinical Psychology Review*, *57*, 164-182. https://doi.org/https://doi.org/10.1016/j.cpr.2017.05.001

Berneiser, J., Jahn, G., Grothe, M., & Lotze, M. (2018). From visual to motor strategies: Training in mental rotation of hands. *Neuroimage*, *167*, 247-255. https://doi.org/10.1016/j.neuroimage.2016.06.014

Bliwise, D. L., Scullin, M. K., & Trotti, L. M. (2014). Fluctuations in cognition and alertness vary independently in dementia with Lewy bodies. *Mov Disord*, *29*(1), 83-89. https://doi.org/10.1002/mds.25707

Boeve, B. F., Dickson, D. W., Duda, J. E., Ferman, T. J., Galasko, D. R., Galvin, J. E., Goldman, J. G., Growdon, J. H., Hurtig, H. I., Kaufer, D. I., Kantarci, K., Leverenz, J. B., Lippa, C. F., Lopez, O. L., McKeith, I. G., Singleton, A. B., Taylor, A., Tsuang, D., Weintraub, D., & Zabetian, C. P. (2016). Arguing against the proposed definition changes of PD. *Mov Disord*, *31*(11), 1619-1622. https://doi.org/10.1002/mds.26721

Breitve, M. H., Chwiszczuk, L. J., Bronnick, K., Hynninen, M. J., Auestad, B. H., Aarsland, D., & Rongve, A. (2018). A Longitudinal Study of Neurocognition in Dementia with Lewy Bodies Compared to Alzheimer's Disease. *Front Neurol*, *9*, 124. https://doi.org/10.3389/fneur.2018.00124

Bussè, C., Caffarra, P., Rossi, A., Zorzi, G., Fragiacomo, F., Camporese, G., Pompanin, S., Di Bernardo, G. A., & Cagnin, A. (2018). Testing Hippocampal Memory in Prodromal Dementia with Lewy Bodies. *J Alzheimers Dis*, *64*(2), 349-353. https://doi.org/10.3233/jad-180166

Crescentini, C., Mondolo, F., Biasutti, E., & Shallice, T. (2012). Preserved and impaired task-switching abilities in non-demented patients with Parkinson's disease. *J Neuropsychol*, *6*(1), 94-118. https://doi.org/10.1111/j.1748-6653.2011.02018.x

D'Antonio, F., Kane, J. P. M., Ibañez, A., Lewis, S. J. G., Camicioli, R., Wang, H., Yu, Y., Zhang, J., Ji, Y., Borda, M. G., Kandadai, R. M., Babiloni, C., Bonanni, L., Ikeda, M., Boeve, B. F., Leverenz, J. B., & Aarsland, D. (2021). Dementia with Lewy bodies research consortia: A global perspective from the ISTAART Lewy Body Dementias Professional Interest Area working group. *Alzheimers Dement (Amst)*, *13*(1), e12235. https://doi.org/10.1002/dad2.12235

de Medeiros, K., Robert, P., Gauthier, S., Stella, F., Politis, A., Leoutsakos, J., Taragano, F., Kremer, J., Brugnolo, A., Porsteinsson, A. P., Geda, Y. E., Brodaty, H., Gazdag, G., Cummings, J., & Lyketsos, C. (2010). The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. *Int Psychogeriatr*, *22*(6), 984-994. https://doi.org/10.1017/s1041610210000876

Escandon, A., Al-Hammadi, N., & Galvin, J. E. (2010). Effect of cognitive fluctuation on neuropsychological performance in aging and dementia. *Neurology*, *74*(3), 210-217. https://doi.org/10.1212/WNL.0b013e3181ca017d

Fodero-Tavoletti, M. T., Smith, D. P., McLean, C. A., Adlard, P. A., Barnham, K. J., Foster, L. E., Leone, L., Perez, K., Cortés, M., Culvenor, J. G., Li, Q. X., Laughton, K. M., Rowe, C. C., Masters, C. L., Cappai, R., & Villemagne, V. L. (2007). In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. *J Neurosci*, *27*(39), 10365-10371. https://doi.org/10.1523/jneurosci.0630-07.2007

Génier Marchand, D., Postuma, R. B., Escudier, F., De Roy, J., Pelletier, A., Montplaisir, J., & Gagnon, J. F. (2018). How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. *Ann Neurol*, *83*(5), 1016-1026. https://doi.org/10.1002/ana.25239

Gomperts, S. N. (2016). Lewy Body Dementias: Dementia With Lewy Bodies and Parkinson Disease Dementia. *Continuum (Minneap Minn)*, *22*(2 Dementia), 435-463. https://doi.org/10.1212/con.0000000000000309

Hart, E. P., Dumas, E. M., van Zwet, E. W., van der Hiele, K., Jurgens, C. K., Middelkoop, H. A., van Dijk, J. G., & Roos, R. A. (2015). Longitudinal pilot-study of Sustained Attention to Response Task and P300 in manifest and pre-manifest Huntington's disease. *J Neuropsychol*, *9*(1), 10-20. https://doi.org/10.1111/jnp.12031

Irwin, D. J., Grossman, M., Weintraub, D., Hurtig, H. I., Duda, J. E., Xie, S. X., Lee, E. B., Van Deerlin, V. M., Lopez, O. L., Kofler, J. K., Nelson, P. T., Jicha, G. A., Woltjer, R., Quinn, J. F., Kaye, J., Leverenz, J. B., Tsuang, D., Longfellow, K., Yearout, D., Kukull, W., Keene, C. D., Montine, T. J., Zabetian, C. P., & Trojanowski, J. Q. (2017). Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. *Lancet Neurol*, *16*(1), 55-65. https://doi.org/10.1016/s1474-4422(16)30291-5

Jellinger, K. A. (2018). Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)*, *125*(4), 615-650. https://doi.org/10.1007/s00702-017-1821-9

Jellinger, K. A., & Korczyn, A. D. (2018). Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Med*, *16*(1), 34. https://doi.org/10.1186/s12916-018-1016-8

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., Ska, B., Gilbert, B., Inglis, G., Panisset, M., de Boysson, C., & Chertkow, H. (2009). Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*, *23*(6), 765-777. https://doi.org/10.1037/a0016792

Kemp, J., Philippi, N., Phillipps, C., Demuynck, C., Albasser, T., Martin-Hunyadi, C., Schmidt-Mutter, C., Cretin, B., & Blanc, F. (2017). Cognitive profile in

prodromal dementia with Lewy bodies. *Alzheimers Res Ther*, *9*(1), 19. https://doi.org/10.1186/s13195-017-0242-1

Knuffman, J., Mohsin, F., Feder, J., & Grossberg, G. T. (2001). Differentiating between lewy body dementia and Alzheimer's disease: a retrospective brain bank study. *J Am Med Dir Assoc*, *2*(4), 146-148.

Ko, L. W., Komarov, O., Hairston, W. D., Jung, T. P., & Lin, C. T. (2017). Sustained Attention in Real Classroom Settings: An EEG Study. *Front Hum Neurosci*, *11*, 388. https://doi.org/10.3389/fnhum.2017.00388

Mainland, B. J., Herrmann, N., Mallya, S., Fiocco, A. J., Sin, G.-L., Shulman, K. I., & Ornstein, T. J. (2017). Cognitive Fluctuations and Cognitive Test Performance Among Institutionalized Persons With Dementia. *American Journal of Alzheimer's Disease & Other Dementias®*, *32*(7), 393-400. https://doi.org/10.1177/1533317517718954

Mandal, M., & Khan, A. (2021). Attention switching deficit in patients of Parkinson's disease who experience freezing of gait. *Appl Neuropsychol Adult*, 1-12. https://doi.org/10.1080/23279095.2021.1951268

Martini, A., Weis, L., Schifano, R., Pistonesi, F., Fiorenzato, E., Antonini, A., & Biundo, R. (2020). Differences in cognitive profiles between Lewy body and Parkinson's disease dementia. *J Neural Transm (Vienna)*, *127*(3), 323-330. https://doi.org/10.1007/s00702-019-02129-2

Matar, E., Shine, J. M., Halliday, G. M., & Lewis, S. J. G. (2019). Cognitive fluctuations in lewy body dementia - towards a pathophysiological framework. *Brain*.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C. G., Bayston, A., Beach, T. G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J. E., El-Agnaf, O., Feldman, H., Ferman, T. J., Ffytche, D., Fujishiro,

H., Galasko, D., Goldman, J. G., Gomperts, S. N., Graff-Radford, N. R., Honig, L. S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V. M. Y., Leverenz, J. B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T. J., Moreno, E., Mori, E., Murray, M., O'Brien, J. T., Orimo, S., Postuma, R. B., Ramaswamy, S., Ross, O. A., Salmon, D. P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J. B., Trojanowski, J. Q., Tsuang, D., Walker, Z., Yamada, M., & Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/wnl.0000000000004058

McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'Brien, J. T., Feldman, H., Cummings, J., Duda, J. E., Lippa, C., Perry, E. K., Aarsland, D., Arai, H., Ballard, C. G., Boeve, B., Burn, D. J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C. G., Gomez-Tortosa, E., Halliday, G., Hansen, L. A., Hardy, J., Iwatsubo, T., Kalaria, R. N., Kaufer, D., Kenny, R. A., Korczyn, A., Kosaka, K., Lee, V. M., Lees, A., Litvan, I., Londos, E., Lopez, O. L., Minoshima, S., Mizuno, Y., Molina, J. A., Mukaetova-Ladinska, E. B., Pasquier, F., Perry, R. H., Schulz, J. B., Trojanowski, J. Q., & Yamada, M. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*, *65*(12), 1863-1872. https://doi.org/10.1212/01.wnl.0000187889.17253.b1

McKeith, I. G., Fairbairn, A., Perry, R., Thompson, P., & Perry, E. (1992). Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *Bmj, 305*(6855), 673-678. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1882909/pdf/bmj00092-0017.pdf

McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., Kantarci, K., Muscio, C., O'Brien, J. T., Postuma, R. B., Aarsland, D., Ballard, C.,

Bonanni, L., Donaghy, P., Emre, M., Galvin, J. E., Galasko, D., Goldman, J. G., Gomperts, S. N., Honig, L. S., Ikeda, M., Leverenz, J. B., Lewis, S. J. G., Marder, K. S., Masellis, M., Salmon, D. P., Taylor, J. P., Tsuang, D. W., Walker, Z., & Tiraboschi, P. (2020). Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology*, *94*(17), 743-755. https://doi.org/10.1212/wnl.0000000000009323

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A., & Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*, *47*(5), 1113-1124. http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCOBNHDBOM00/fs047/ovft/live/g v024/00006114/00006114-199611000-00001.pdf

McMackin, R., Dukic, S., Costello, E., Pinto-Grau, M., Keenan, O., Fasano, A., Buxo, T., Heverin, M., Reilly, R., Pender, N., Hardiman, O., & Nasseroleslami, B. (2021). Sustained attention to response task-related beta oscillations relate to performance and provide a functional biomarker in ALS. *J Neural Eng*, *18*(2). https://doi.org/10.1088/1741-2552/abd829

Meghdadi, A. H., Berka, C., Richard, C., Rupp, G., Smith, S., Stevanović Karić, M., McShea, K., Sones, E., Marinković, K., & Marcotte, T. (2021). EEG event related potentials in sustained, focused and divided attention tasks: Potential biomarkers for cognitive impairment in HIV patients. *Clin Neurophysiol*, *132*(2), 598-611. https://doi.org/10.1016/j.clinph.2020.11.026

Mosimann, U. P., Collerton, D., Dudley, R., Meyer, T. D., Graham, G., Dean, J. L., Bearn, D., Killen, A., Dickinson, L., Clarke, M. P., & McKeith, I. G. (2008). A

semi-structured interview to assess visual hallucinations in older people. *Int J Geriatr Psychiatry*, *23*(7), 712-718. https://doi.org/10.1002/gps.1965

Muller, A. J., Shine, J. M., Rolle, C. E., Chitty, K., Hall, J. M., Halliday, G. M., Hermens, D. F., Lewis, S. J. G., & O'Callaghan, C. (2021). Anterior-posterior electrophysiological activity characterizes Parkinsonian visual misperceptions. *Neurol Clin Neurosci*, *9*, 312-318. https://doi.org/https://doi.org/10.1111/ncn3.12508

Nagahama, Y., Okina, T., Suzuki, N., & Matsuda, M. (2008). Cerebral substrates related to impaired performance in the clock-drawing test in dementia with Lewy bodies. *Dement Geriatr Cogn Disord*, *25*(6), 524-530. https://doi.org/10.1159/000131665

Nagashima, I., Takeda, K., Shimoda, N., Harada, Y., & Mochizuki, H. (2019). Variation in Performance Strategies of a Hand Mental Rotation Task on Elderly. *Front Hum Neurosci*, *13*, 252. https://doi.org/10.3389/fnhum.2019.00252

Park, H. K., Kim, J. S., Im, K. C., Kim, M. J., Lee, J. H., Lee, M. C., Kim, J., & Chung, S. J. (2013). Visual hallucinations and cognitive impairment in Parkinson's disease. *Can J Neurol Sci*, *40*(5), 657-662. https://doi.org/10.1017/s0317167100014888

Park, K. W., Kim, H. S., Cheon, S. M., Cha, J. K., Kim, S. H., & Kim, J. W. (2011). Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. *J Clin Neurol*, *7*(1), 19-24. https://doi.org/10.3988/jcn.2011.7.1.19

Petrova, M., Pavlova, R., Zhelev, Y., Mehrabian, S., Raycheva, M., & Traykov, L. (2016). Investigation of neuropsychological characteristics of very mild and mild dementia with Lewy bodies. *J Clin Exp Neuropsychol*, *38*(3), 354-360. https://doi.org/10.1080/13803395.2015.1117058

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*, *30*(12), 1591-1601. https://doi.org/10.1002/mds.26424

Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., Oertel, W. H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K. Y., Kunz, D., Dauvilliers, Y., Provini, F., Lewis, S. J., Buskova, J., Pavlova, M., Heidbreder, A., Montplaisir, J. Y., Santamaria, J., Barber, T. R., Stefani, A., St Louis, E. K., Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J. F., Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M., Mahlknecht, P., Holzknecht, E., Boeve, A. R., Teigen, L. N., Toscano, G., Mayer, G., Morbelli, S., Dawson, B., & Pelletier, A. (2019). Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*, *142*(3), 744-759. https://doi.org/10.1093/brain/awz030

Revie, L., Hamilton, C. A., Ciafone, J., Donaghy, P. C., Thomas, A., & Metzler-Baddeley, C. (2020). Visuo-Perceptual and Decision-Making Contributions to Visual Hallucinations in Mild Cognitive Impairment in Lewy Body Disease: Insights from a Drift Diffusion Analysis. *Brain Sci*, *10*(8). https://doi.org/10.3390/brainsci10080540

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*, *35*(6), 747-758. https://doi.org/10.1016/S0028-3932(97)00015-8

Rosenblum, Y., Bregman, N., Giladi, N., Mirelman, A., & Shiner, T. (2021). Associations between visual hallucinations and impaired visuo-spatial abilities in dementia with Lewy bodies. *Neuropsychology*, *35*(3), 276-284. https://doi.org/10.1037/neu0000728

Shine, J. M., Halliday, G. H., Carlos, M., Naismith, S. L., & Lewis, S. J. (2012). Investigating visual misperceptions in Parkinson's disease: a novel behavioral paradigm. *Mov Disord*, *27*(4), 500-505. https://doi.org/10.1002/mds.24900

Shine, J. M., Keogh, R., O'Callaghan, C., Muller, A. J., Lewis, S. J., & Pearson, J. (2015a). Imagine that: elevated sensory strength of mental imagery in individuals with Parkinson's disease and visual hallucinations. *Proc Biol Sci*, *282*(1798), 20142047. https://doi.org/10.1098/rspb.2014.2047

Shine, J. M., Muller, A. J., O'Callaghan, C., Hornberger, M., Halliday, G. M., & Lewis, S. J. (2015b). Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. *NPJ Parkinsons Dis*, *1*, 15003. https://doi.org/10.1038/npjparkd.2015.3

Specketer, K., Zabetian, C. P., Edwards, K. L., Tian, L., Quinn, J. F., Peterson-Hiller, A. L., Chung, K. A., Hu, S. C., Montine, T. J., & Cholerton, B. A. (2019). Visuospatial functioning is associated with sleep disturbance and hallucinations in nondemented patients with Parkinson's disease. *J Clin Exp Neuropsychol*, *41*(8), 803-813. https://doi.org/10.1080/13803395.2019.1623180

Tilley, B. S., Patel, S. R., Goldfinger, M. H., Pearce, R. K. B., & Gentleman, S. M. (2021). Locus Coeruleus Pathology Indicates a Continuum of Lewy Body Dementia. *J Parkinsons Dis*. https://doi.org/10.3233/jpd-212748

van der Zande, J. J., Gouw, A. A., van Steenoven, I., van de Beek, M., Scheltens, P., Stam, C. J., & Lemstra, A. W. (2020). Diagnostic and prognostic value of EEG in

prodromal dementia with Lewy bodies. *Neurology*, *95*(6), e662-e670. https://doi.org/10.1212/wnl.0000000000009977

Walker, L., McAleese, K. E., Thomas, A. J., Johnson, M., Martin-Ruiz, C., Parker, C., Colloby, S. J., Jellinger, K., & Attems, J. (2015). Neuropathologically mixed Alzheimer's and Lewy body disease: burden of pathological protein aggregates differs between clinical phenotypes. *Acta Neuropathol*, *129*(5), 729-748. https://doi.org/10.1007/s00401-015-1406-3

Walker, M. P., Ayre, G. A., Cummings, J. L., Wesnes, K., McKeith, I. G., O'Brien, J. T., & Ballard, C. G. (2000). The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale: Two methods to assess fluctuating confusion in dementia. *British Journal of Psychiatry*, *177*(3), 252-256. https://doi.org/10.1192/bjp.177.3.252

Yoon, J. H., Kim, M., Moon, S. Y., Yong, S. W., & Hong, J. M. (2015). Olfactory function and neuropsychological profile to differentiate dementia with Lewy bodies from Alzheimer's disease in patients with mild cognitive impairment: A 5-year follow-up study. *J Neurol Sci*, *355*(1-2), 174-179. https://doi.org/10.1016/j.jns.2015.06.013

Zarkali, A., Lees, A. J., & Weil, R. S. (2019). Flickering Stimuli Do Not Reliably Induce Visual Hallucinations in Parkinson's Disease. *J Parkinsons Dis*, *9*(3), 631-635. https://doi.org/10.3233/jpd-191635

Zhao, B., & Sala, S. D. (2018). Different representations and strategies in mental rotation. *Q J Exp Psychol (Hove)*, *71*(7), 1574-1583. https://doi.org/10.1080/17470218.2017.1342670

Zhao, Q. F., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., Xu, W., Li, J. Q., Wang, J., Lai, T. J., & Yu, J. T. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*, *190*, 264-271. https://doi.org/10.1016/j.jad.2015.09.069