Neuropsychological profile of Mild Cognitive Impairment with Lewy body disease

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Abstract

Objective: Efforts are being made to identify dementia with Lewy bodies (DLB), the second commonest cause of neurodegenerative dementia after Alzheimer's disease (AD), in the Mild Cognitive Impairment (MCI) phase, during which intervention on the disease processes would likely be most successful. Few studies have targeted this group and the cognitive profile of MCI with Lewy bodies (MCI-LB) is therefore unclear. The present study aims to elucidate the neuropsychology of MCI-LB relative to MCI due to AD (MCI-AD) and healthy controls.

Methods: In addition to age-matched controls (*n* = 31), participants with MCI and symptoms suggestive of LB disease were recruited from local clinics. Baseline assessment of all subjects included clinical examination, imaging (^{123}iodine-metaiodobenzylguanidine [MIBG], dopamine transporter imaging [DaTscan]), and comprehensive neuropsychological assessments. Simple and Choice Reaction Time (SRT and CRT) and a Continuous Performance Test-AX (CPT-AX) were also administered to measure intraindividual variability (IIV) in attention using ex-Gaussian modelling of reaction times. MCI patients were diagnosed firstly following National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for MCI. Participants with demonstrable cognitive impairment but no clinical symptoms or biomarkers for DLB were considered MCI-AD (*n* = 18). Within MCI-LB (*n* = 44), individuals with two or more consensus criteria for the diagnostic features or biomarkers of DLB (McKeith et al., 2017) were considered "Probable" MCI-LB (*n* = 30). White matter integrity was quantified using diffusion tensor imaging (DTI) and tract-based spatial statistics.

Results: While both groups are impaired relative to controls, MCI-LB Probable performed worse than MCI-AD on processing speed (Digit Symbol Substitution Test [DSST, *p* = .011]), executive function (Verbal Fluency [FAS], *p* = .027) and visuospatial function (pareidolia task, *p* = .010; Visual Patterns Test, *p* = .019) tests. In contrast, MCI-AD scored significantly lower than MCI-LB Probable on tests of verbal learning and memory (Rey Auditory Verbal Learning Test short, *p* = .047, and long delay, *p* = .025, and retroactive interference, *p* = .029). DSST was the best predictor of group allocation using a stepwise discriminant analysis, $F(2,76) = 36.89$, $p < .001$, and 92.6% of MCI-LB Probable scored at or below the 16th percentile of control DSST scores. Using hierarchical linear regression, a control-informed processing speed composite fully explained group-associated variance in the visuospatial composite, RAVLT learning and RAVLT short delay recall. In contrast, FAS explained only 25.0% of group variance in the visuospatial composite and is not significantly correlated with RAVLT short delay (*p* = .132). MCI-LB Probable showed increased IIV using ex-Gaussian *tau* in CRT (*p* = .021, *d* = 1.12) and CPT-AX (*p* = .007, *d* =0.80) relative to controls, while MCI-AD differed significantly from controls in SRT *tau* (*p* = .002, *d* = 0.93). No difference between groups was found in white mater integrity, although the DSST showed substantial correlation with fractional anisotropy in the sample as a whole.

Conclusions: The present study succeeded in demonstrating that the cognitive dysfunction typical of advanced DLB and AD is observable in the MCI phase of clinically-defined MCI-LB and MCI-AD, respectively. MCI-LB showed visuospatial, attentional and processing speed impairments. Processing speed emerged as particularly important to MCI-LB neuropsychology, suggesting a processing speed, rather than executive, mediated model of decline in MCI-LB. MCI-AD, in contrast, shows verbal learning and memory impairment. Future work should pursue this promising evidence of subtle, aetiologically-specific differences in cognition in MCI.

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The ^{123}I-MIBG Scintigraphy Utility as a Biomarker for Prodromal Dementia with Lewy Bodies (SUPErB) study is a large, multifaceted study. I (the author) selected the neuropsychological battery with the support of my supervisors. I personally took consent and medical history for all participants and administered, scored, and analysed all of the neuropsychological tests; however, in a few, rare occasions, illness or double-booking necessitated that another trained researcher administered tasks on my behalf. Programming of the computerised tasks was adapted for the study by myself with guidance from Dr Michael Firbank, Dr Rachel Moss and Dr Andreas Finkelmeyer. The groups were created based on clinical and imaging assessments completed and interpreted by other members of the SUPErB team. These are described further in Chapter 3. Dr Michael Firbank created and oversaw the magnetic resonance imaging protocol and acquisition was done by trained medical imaging staff at the Newcastle Magnetic Resonance Imaging Centre (see Chapter 9).

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Abbreviations

ACE-R: Addenbrooke's Cognitive Examination-Revised

AD: Alzheimer's disease

ADNI: Alzheimer's Disease Neuroimaging Initiative

ANCOVA: analysis of covariance

ANOVA: analysis of variance

APOE: apolipoprotein E

CAF: Clinical Assessment of Fluctuations Scale

CDR: Clinical Dementia Rating Scale

CPT: Continuous Performance Task

CRT: choice reaction time

CSF: cerebrospinal fluid

CT: computed tomography

DaTSCAN: dopamine transporter imaging

DCFS: Dementia Cognitive Fluctuations Scale

DLB: Dementia with Lewy bodies

DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5

DSST: Digit Symbol Substitution Test

EEG: electroencephalogram

EFA: exploratory factor analysis

ES: effect size

FDG-PET: fluorodeoxyglucose positron tomography

FSL: Functional Magnetic Resonance Imaging of the Brain software library

GDS: Geriatric Depression Scale

HC: healthy controls

HLR: hierarchical linear regression

HMR: heart-to-mediastinum ratio

IADL: Lawton Instrumental Activities of Daily Living Scale

ID: Inhibitory Deficit

IIV: intra-individual variability

JOLO: Benton's Judgement of Line Orientation Task

KMO: Kaiser-Mayer-Olkin

LB: Lewy body

LBD: Lewy body dementias

MCAR: Little's Missing Completely at Random Test

MCI: Mild Cognitive Impairment

MCI-LB: Mild Cognitive Impairment with Lewy bodies

MDS: Movement Disorder Society

MIBG: ^{123}iodine-metaiodobenzylguanidine

MMSE: Mini-Mental State Examination

MRI: magnetic resonance imaging

MTCF: Modified Taylor Complex Figure

NART: National Adult Reading Test

NE-DeNDRoN: North-East Local Research Network of the Dementias & Neurodegenerative Diseases Research Network

NEVHI: North East Visual Hallucinations Interview

NIA-AA: National Institute on Aging-Alzheimer's Association

NICE: National Institute for Health and Clinical Excellence

NPI-D: Neuropsychiatric Inventory with Caregiver Distress Scale

PCA: principal components analysis

PD: Parkinson's disease

PD-MCI: Parkinson's disease with Mild Cognitive Impairment

PDD: Parkinson's disease dementia

PET: positron emission tomography

PIB: Pittsburgh Compound B

RAVLT: Rey Auditory Verbal Learning Test

RBD: Rapid Eye Movement Sleep Behavior Disorder

ROC: receiver operating characteristic

ROCF: Rey-Osterrieth complex figure

ROI: regions of interest

REM: Rapid eye movement

SD: standard deviations

SPECT: single-photon emission computed tomography

SPSS: Statistical Package for the Social Sciences

SRT: simple reaction time

UPDRS: Unified Parkinson's Disease Rating Scale

VOSP: Visual Object and Space Perception Battery

VPT: Visual Patterns Task

WAIS: Weschler Intelligence Scales

Chapter One: Introduction to Lewy body disease

1.1 Introduction

The prevalence of dementia, defined as “a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities” (McKeith et al., 2017, p. 2), is anticipated to reach 131 million worldwide by 2050 (Prince, Comas-Herrera, Knapp, Guerchet, & Karagiannidou, 2016). In 2016, this was estimated to equate to a worldwide cost of 818 billion USD (Prince et al., 2016). Indeed, dementia poses a critical economic, medical and scientific challenge to society. Dementia with Lewy bodies (DLB) is the second most common cause of dementia following Alzheimer’s disease (AD) (Donaghy & McKeith, 2014; Perry et al., 1990). A recent review by Vann Jones and O'Brien (2014) found DLB represented 7.5% and 4.2% of diagnosed dementias in secondary care and community studies, respectively. However, epidemiological studies are limited and it is believed that 50% of DLB remains undiagnosed (Palmqvist, Hansson, Minthon, & Londos, 2009), making accurate estimation problematic, although Vann Jones and O'Brien (2014) note that use of the (then most recent) 2005 revised Third DLB International Consensus Criteria was successful in significantly increasing the proportion of DLB diagnoses. Brain bank studies report much higher rates of Lewy body (LB) disease, with DLB occurring in up to a quarter of such cases (McKeith et al., 2017).

1.2 Clinical diagnosis of DLB

Clinical diagnosis of DLB is challenging. Recently, the DLB Consortium has published updated recommendations on clinical and pathological diagnosis of the disease, which reflect levels of uncertainty in such diagnoses (McKeith et al., 2017). The revised consensus criteria stipulates that a diagnosis of “probable DLB” requires cognitive impairment plus two or more “core clinical features” or one “core clinical feature” with one positive indicative biomarker (McKeith et al., 2017, see Table 1 on p. 2). Core features are: recurrent and detailed visual hallucinations, one or more cardinal features of spontaneous parkinsonism, REM sleep behaviour disorder, and pronounced fluctuations in attention and arousal. The update retained a list of features supportive of DLB (such as severe neuroleptic sensitivity, repeated falls or syncope, severe autonomic dysfunction, non-visual hallucinations, and other

Table 1. Revised clinical and biomarker criteria for the diagnosis of dementia with Lewy bodies (adapted from McKeith et al., 2017).

Clinical Features	*Core*	Fluctuating cognition with pronounced variations in attention and alertness Recurrent visual hallucinations that are typically well formed and detailed REM sleep behaviour disorder, which may precede cognitive decline One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity
	Supportive	Severe sensitivity to antipsychotic agents Postural instability Repeated falls Syncope or other transient episodes of unresponsiveness Severe autonomic dysfunction (e.g. constipation, orthostatic hypotension, urinary incontinence) Hypersomnia Hyposmia Hallucinations in other modalities Systematized delusions Apathy, anxiety, and depression
Biomarkers	*Indicative*	Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy. Polysomnographic confirmation of REM sleep without atonia.
	Supportive	Relative preservation of medial temporal lobe structures on CT/MRI scan. Generalized low uptake on SPECT/PET perfusion/ metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging. Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range.

psychiatric symptoms), but these are not used formally in diagnosis. Alternatively, “possible DLB” can be used for patients with dementia demonstrating only one feature of DLB, either a core clinical feature or indicative biomarker. A possible DLB diagnosis is more uncertain: patients are equally likely to be diagnosed with probable DLB or non-DLB dementia at follow up (O'Brien et al., 2009).

1.3 DLB pathophysiology

LB disease is characterised by the presence of intracellular aggregates of ubiquinated alpha-synuclein, Lewy bodies and Lewy neurites. Alpha-synuclein is a 140 amino acid protein concentrated within the presynaptic terminals of dopaminergic neurons where it is thought to maintain synaptic vesicles required for

neurotransmission (Cheng, Vivacqua, & Yu, 2011; Engelender, 2008; Forno, 1996). While LB disease is associated with loss of dopaminergic neurons, dopamine itself may also bind to alpha-synuclein to facilitate the formation of Lewy body protofibrils (Eriksen, Dawson, Dickson, & Petrucelli, 2003; Overk & Masliah, 2014). At autopsy, 20-35% of dementia patients will have Lewy bodies in the neocortex, while they are not typically found in the brains of healthy late-life adults (Hansen et al., 1990; Perry et al., 1990). Wakisaka et al. (2003), however, showed that Lewy body presence is associated with advancing age in a community-based study while clinic-based estimates show even higher proportions of Lewy bodies regardless of the extent of cognitive impairment.

Neuropathologically, DLB is characterised by the loss of dopaminergic neurons of the substantia nigra and cholinergic neurons of the nucleus basalis (Mayo & Bordelon, 2014). Overall, it is generally accepted that the areas particularly vulnerable to Lewy body pathology are brainstem nuclei, such as the substantia nigra and the dorsal motor nucleus of the vagal nerve, the olfactory bulb and peripheral autonomic nervous system (Donaghy & McKeith, 2014). Staging based on the Braak system of Parkinson's disease (PD) neuropathology was initially developed with a brainstem to cortex progression (Braak et al., 2003). However, this has not proved reliable in DLB, with studies showing many DLB cases as unclassifiable using this staging model (Beach et al., 2009; Zaccai, Brayne, McKeith, Matthews, & Ince, 2008). More recent evidence points to the presence of alpha-synuclein pathology in the peripheral nervous system, even in early, mild cases of LB disease (Beach et al., 2010; Wang, Gibbons, Lafo, & Freeman, 2013). Thus, the pathology of alpha-synucleinopathy in DLB is not currently well understood nor predictable; this is in contrast to AD, which has a highly predictable progression, beginning in the transentorhinal cortex.

1.4 Lewy body (LB) dementias and diagnostic overlap

LB disease manifests clinically as a spectrum of phenotypes: PD, PD dementia (PDD), and DLB (Aarsland, 2016; Sengupta et al., 2015). The latter two syndromes are referred to as the Lewy body dementias (LBDs) and are believed to differ clinically due to different loci of early degeneration (Aarsland, 2016).

DLB is diagnosed when dementia presents either before or concurrently with motor symptoms, while PDD refers to dementia presenting in the context of well-

established PD. This distinction has been arbitrarily set at one year of PD before cognitive decline for PDD and DLB is diagnosed if features of PD are present within a year or later than the cognitive decline ('the one year rule') (McKeith et al., 2017; Petrova, Mehrabian-Spasova, Aarsland, Raycheva, & Traykov, 2015). PD increases one's risk of developing dementia and over three quarters of PD patients that survive for 10 years or more will develop PDD (Aarsland, Zaccai, & Brayne, 2005; Kramberger et al., 2015; Mosimann et al., 2004), with a cumulative frequency of 83% in 20-year PD survivors (Hely, Reid, Adena, Halliday, & Morris, 2008). While cohort studies suggest cognitive impairment in PD is not solely a late-stage issue, it is not always detected in patients nor reported as a presenting condition, suggestive of the problematic diagnostics of synucleinopathies (Aarsland, 2016; Aarsland et al., 2008; reviewed in Goldman, Williams-Gray, Barker, Duda, & Galvin, 2014a).

Indeed, there is appreciable overlap in the clinical presentation of DLB and PDD, including physical symptoms such as orthostatic dizziness, increased salivation, hyposmia, constipation and parkinsonism (Donaghy, O'Brien, & Thomas, 2014). In cases of early, pronounced cognitive impairment, it can be unclear whether a PDD or DLB diagnosis is more appropriate (Aarsland, 2016). Mosimann et al. (2004), for example, found no difference between the patient groups in terms of Unified PD Rating Scale (UPDRS) motor scores, dementia duration, or impairment in activities of daily living. In both DLB and PDD, REM Behaviour Sleep Disorder (RBD) and fluctuations of attention are commonly reported, and both categories of patients may respond well to cholinergic therapy (Burn & McKeith, 2003; Thomas et al., 2006). The third report of the DLB Consortium in 2005 concluded that, "no major differences between DLB and PDD have been found in any variable examined including cognitive profile, attentional performance, neuropsychiatric features, sleep disorders, autonomic dysfunction, type and severity of parkinsonism, neuroleptic sensitivity, and responsiveness to cholinesterase inhibitors" (McKeith et al., 2005, p. 1865). Post-mortem diagnosis is unhelpful in differentiating PDD and DLB (Mayo & Bordelon, 2014). As such, there is controversy regarding the validity of the temporal distinction between the conditions, and whether there are indeed any variables that differ significantly. In light of the current emphasis on early diagnosis, in which symptoms such as parkinsonism and cognitive impairment will be especially mild, Donaghy and McKeith (2014) argue that "the distinction between DLB and PDD is unlikely to be useful or practicable at this stage and a general classification of 'prodromal LB disease' may be more appropriate." This perspective is adopted in

Chapter 2, in which a structured review of the literature includes not only MCI due to LB disease but also early PD and MCI-PD in order to best capture the populations relevant to DLB.

1.5 Risk factors and genetics

Males are at a higher risk for DLB than females (Nelson et al., 2010), though other evidence does not confirm this (Vann Jones & O'Brien, 2014) or suggests only a slight male predominance (McKeith, Fairbairn, Perry, Thompson, & Perry, 1992). DLB often appears at an older age of onset (60 to 90 years) than AD with early reported symptoms including disturbed sleep, anxiety, hallucinations, constipation and parkinsonism, usually bilateral symmetric limb rigidity or bradykinesia (Mayo & Bordelon, 2014). Hypertension and hyperlipidaemia have been identified as potential risk factors (Gardner, Valcour, & Yaffe, 2013).

A recent comprehensive study by Guerreiro et al. (2018) investigated genetic variability in DLB. Results implicated three primary genes. Firstly, apolipoprotein ε4 (APOE ε4), well-established as the main genetic risk factor for AD, was found to have the strongest association with DLB (Guerreiro et al., 2018). The second strongest association occurred at the SNCA locus, which encodes the alpha-synuclein protein (Guerreiro et al., 2018). Moreover, Guerreiro et al. (2018) replicated their group's earlier findings that different SNCA haplotypes are associated with increased DLB and PD risk (Bras et al., 2014). The authors tentatively suggest that this differential gene expression may be responsible for the different localization of pathology in the two conditions (Bras et al., 2014; Guerreiro et al., 2018; Halliday, Hely, Reid, & Morris, 2008). An effect size similar to that of APOE was found with GBA. GBA showed the only significant association with DLB risk in a genome-wide burden-based analysis (Guerreiro et al., 2018). GBA1, the most common currently identified PD-associated gene, is estimated at 3.5% versus 2.9% in PDD and 0.4% in the general population (Mata et al., 2008). Overall, Guerreiro et al. (2018) quantify DLB's heritability at 36%.

1.6 Prevalence and prognosis

Although, as discussed above, there is a dearth of well-designed epidemiological studies, LB dementia is generally accepted to be responsible for 15% of dementia cases with PDD and DLB contributing about equally to that figure (Aarsland, 2016), although brain bank reports are higher. A recent study of the

prevalence of LB dementia in two regions of England suggests that both DLB and PDD are under-diagnosed (Kane et al., 2018). Specifically, significantly fewer dementia cases were reported as DLB in East Anglia (3.3%) than in the North East (5.6%), the latter of which is a hub of LB dementia research and medical training, though those local diagnostic rates remain lower than expected (Kane et al., 2018). The percentage of total clinical dementia cases due to DLB was lower than figures prevously reported by both meta-analyses (4.2-7.5%; Vann Jones & O'Brien, 2014) and neuropathological studies (15-20%; Aarsland, Ballard, McKeith, Perry, & Larsen, 2001; Jellinger & Attems, 2011). Kane et al. (2018) similarly found lower prevalence of PDD in their case study than had previously been reported in systematic review (3.6% of all dementia cases; Aarsland et al., 2005).

Various studies report a more aggressive disease course in LBDs than AD in terms of mortality (Collerton, Burn, McKeith, & O'Brien, 2003), hospitalisation rate (Mueller et al., 2018), cognition (Olichney et al., 1998) and resource requirements (Boström et al., 2009; Williams, Xiong, Morris, & Galvin, 2006). A recent study by Price et al. (2017), one of the largest clinical cohorts of DLB published to date, showed significantly faster decline from first presentation to death in DLB versus AD. This relationship was independent of age, sex, physical comorbidities and antipsychotic use (Price et al., 2017). However, a systematic review by (Breitve et al., 2014) did not support faster rates of cognitive decline.

1.7 Imaging and biomarkers in DLB

Lewy bodies were first described pathologically by Fritz Heinrich Lewy in 1912 in the brainstem of PD patients (Lewy, 1912). Advances in *in vivo* imaging technology since have shed further light on brain status and cognitive correlates in DLB. Biomarkers that are used in dementia/ cognitive decline investigations either identify tissue pathology (biochemical) or tissue damage (i.e. consequential neuronal injury)(Albert et al., 2011). The addition of biomarkers to the Consortium Consensus criteria aims to aid clinicians in assigning diagnostic certainty (probable or possible) to a DLB diagnosis. The imaging biomarkers are validated for use in later disease states, however, and their utility early in the disease process is less clear.

In the current DLB diagnostic criteria biomarkers are termed “indicative” or “supportive” (McKeith et al., 2017). Indicative biomarkers in DLB are: reduced dopamine transporter (DaTSCAN) uptake in basal ganglia using single-photon emission computed tomography (SPECT) or positron emission tomography (PET),

reduced uptake in ^{123}iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, and confirmation of REM sleep without atonia (REM sleep behaviour disorder) by polysomnography. Indicative biomarkers cannot diagnose probable DLB in isolation. However, if one or more is present in combination with one or more core clinical features a probable DLB diagnosis is given. Possible DLB is diagnosed if there are one or more positive indicative biomarkers only.

Supportive biomarkers are those that can assist in evaluation of a patient and are associated with DLB, but lack diagnostic specificity (McKeith et al., 2017). They include: preservation of medial temporal lobe (particularly hippocampus) on computed tomography (CT) or magnetic resonance imaging (MRI); generalized low uptake, reduced occipital activity, or the posterior cingulate island sign on SPECT/ PET perfusion or metabolism; prominent posterior slow-wave activity with fluctuations on electroencephalogram (EEG); amyloid-beta (Aβ) PET imaging; and other biomarkers such as cerebrospinal fluid (CSF), blood or genetic screens. In particular, using fluorodeoxyglucose positron tomography (FDG-PET), reduced perfusion may be observed in the occipital lobe and the primary visual cortex, with one study reporting a 61% decrease in occipital metabolism (Mosconi et al., 2008).

The most commonly-used imaging and biomarkers techniques in the investigation of suspected LB disease, and utilised in the study entitled ^{123}I-MIBG Scintigraphy Utility as a Biomarker for Prodromal Dementia with Lewy Bodies (SUPErB; see Chapter 3), are briefly presented below.

Dopamine Transporter Imaging

As discussed, LB diseases are associated with a loss of dopaminergic transporters associated with nigrostriatal degeneration (Piggott et al., 1999). Dopamine transporter imaging (DaTscan) utilizes a dopamine transporter radioligand to assess loss of these neurons. It is licensed for use in the differentiation of AD and DLB and listed in the National Institute for Health and Clinical Excellence's (NICE) guidelines for use in doubtful DLB cases. Along with MIBG and EEG, DaTscan imaging is now included in the consensus diagnostic criteria as a indicative biomarker of DLB for its diagnostic accuracy in advanced DLB (McKeith et al., 2017). However, both DLB and PDD are associated with low DaTSCAN uptake within the basal ganglia and, as such, it cannot differentiate between DLB, PDD or PD (Walker, 2007). DaTSCAN has high sensitivity (78%) and specificity (90%) for the differentiation of probable DLB from AD (McKeith et al., 2007; Papathanasiou,

Boutsiadis, Dickson, & Bomanji, 2012). In MCI with LB disease (MCI-LB), Thomas et al. (2018) reported lower sensitivity (54.2%) but high specificity (90.0% in detecting clinically-diagnosed possible or probable MCI-LB.

MIBG myocardial scintigraphy

Recent studies indicate that the cardiac sympathetic plexus may show LB disease pathology very early in the disease process, possibly prior to cerebral involvement or clinical symptoms (Orimo, Takahashi, et al., 2007; Orimo, Uchihara, et al., 2007). MIBG imaging is used to identify this alpha-synuclein pathology in the nervous system by showing reduced cardiac MIBG uptake. It has shown potential for greater specificity in discriminating DLB from AD and frontotemporal dementia than DaTscan (Tiraboschi et al., 2016), as well as for identifying prodromal DLB (Fujishiro et al., 2013; Yoon, Lee, Yong, Moon, & Lee, 2014). Komatsu et al. (2018) recently reported follow up results of sensitivity/ specificity values of 0.77/0.94 in distinguishing probable DLB versus probable AD. This is an improvement in sensitivity from their baseline report of 68.9%, regardless of using an automated or visual assessment (Yoshita et al., 2015). Sensitivity and specificity were higher (77.4% and 93.8%, respectively) when considering only mild dementia (MMSE ≥ 22) (Yoshita et al., 2015).

Amyloid imaging

In AD, amyloid positron emission tomography (PET) is used to detect the presence of amyloid pathology *in vivo*. Amyloid-positive DLB patients may indicate concomitant AD pathology, while “pure” DLB cases will be associated with an average lower abnormal cortical uptake (Aarsland, 2016). The presence of amyloid deposition in DLB requires direct investigation using PET imaging, as it has not been shown to correlate with clinical or neuropsychological measures (Donaghy, Firbank, et al., 2018). Findings by Donaghy, Firbank, et al. (2018) suggest that there is little evidence of an AD-like clinical profile in amyloid-positive DLB patients, but AD-like medial temporal lobe abnormalities are more likely in those patients.

MRI Imaging

Using MRI, DLB typically shows generalized cortical atrophy and preserved hippocampal volume (Barber, Ballard, McKeith, Gholkar, & O’brien, 2000; Barber et al., 1999; Chow et al., 2012). AD, conversely, is strongly associated with

hippocampal atrophy (Albert et al., 2011; Whitwell et al., 2007). However, atrophy may also be observed in DLB cases, likely due to comorbid AD pathology (Nedelska et al., 2015). As such, MRI hippocampal imaging is listed as a *supportive* positive biomarker for DLB.

Electroencephalogram

Non-invasive EEG recordings are used to quantify changes in electro-cortical activity in a variety of conditions including neurodegenerative dementias. Alterations are believed to reflect neuronal/ synaptic dysfunction. EEG has shown DLB to be associated with abnormalities relative to both healthy controls and AD (Bonanni et al., 2008; Roks, Korf, Van der Flier, Scheltens, & Stam, 2007). At resting state, increases in posterior slow-wave activity are observed and shown to relate to clinical phenotype such as the severity of cognitive fluctuations (Bonanni et al., 2008; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). In terms of early diagnosis, such alterations may be visible in the Mild Cognitive Impairment (MCI) stage (Bonanni et al., 2015) and may thus serve as an early biomarker.

CSF biomarkers

Decreased CSF Aβ, which in AD is believed to reflect the increased deposition occurring in the brain, and increased tau levels are not observed in DLB (Aarsland, 2016). However, there is evidence that the proportion of biomarkers in the CSF may delineate dementia subtypes. For example, a relative decrease in CSF Aβ-42 and increase in tau may distinguish between DLB and PD (Kaerst et al., 2014). Increased tau may be associated with decreased longevity in DLB patients (reviewed in Mayo & Bordelon, 2014).The recent consensus reports notes that understanding of the interactions between Aβ, alpha-synuclein and tau is increasingly important (Guo et al., 2013; McKeith et al., 2017).

Mixed pathologies

Findings in LBD generally reflects a divergence from AD in most biomarkers, although mixed-pathology cases may display greater overlap (Aarsland, 2016; Compta et al., 2011; Kehagia, Barker, & Robbins, 2012). While the preceding sections attempt to summarize the typical pattern of DLB, LB pathology will not occur in isolation. Coexisting pathologies, especially Aβ and hyperphosphorylated tau (typically associated with AD) and cerebrovascular disease, are present in a large

proportion of synucleinopathy patients (Kehagia et al., 2012). These abnormalities exert their own influence on cognition and function, while also further promoting LB pathology and disrupting downstream activities (Irwin, Lee, & Trojanowski, 2013; Sengupta et al., 2015). In particular, DLB has been shown to be associated with greater amounts of co-occurring amyloid and tau pathology than PDD (Jellinger & Attems, 2011). For example, a systematic review of amyloid imaging in LBD revealed that 68% of DLB cases were positive for amyloid using Pittsburgh Compound B (PIB) (Petrou et al., 2015). In contrast, half this number of PDD patients (34%) and only 5% of PD patients in the Mild Cognitive Impairment (MCI) stage were PIB positive (Petrou et al., 2015). Tarawneh and Galvin (2007) report that 80% of individuals with a DLB diagnosis show AD neuropathology sufficient for a mixed dementia diagnosis. The phenomenon of multiple pathologies in many people with dementia makes attempts to delineate a clear, etiologically-orientated neuropsychological profile challenging. In particular, the role of tau and the possible synergistic interactions of concurrent AD and DLB pathology require elucidation in future work.

1.8 Mild Cognitive Impairment

Dementia syndrome was long believed to represent widespread and advanced pathology (Donaghy & McKeith, 2014). However, there is increasing evidence that synaptic dysfunction occurs in the prefibrillar oligomeric stage and that the actual amount of cortical LB pathology does not necessarily correlate with clinical dementia severity (Donaghy & McKeith, 2014; Paleologou et al., 2009). It follows that the current criteria for DLB is likely only fulfilled after the underlying disease processes are too advanced to intervene with dementia. Accordingly, there is great interest in early and specific MCI diagnosis. Such would (1) create an essential window of opportunity for intervention potential pharmacological intervention, including identification of suitable clinical trial participants, and (2) improve disease management in the clinical setting (Donaghy & McKeith, 2014). For example, earlier identification of DLB would allow patients to access treatment for other related symptoms of the condition (e.g. motor, dysautonomia and other non-psychiatric symptoms) (Pink, O'Brien, Robinson, & Longson, 2018). Similarly, the cognitive fluctuations characteristic of DLB are often misdiagnosed as delirium and inappropriately treated with antipsychotics, despite the severe neuroleptic intolerance experienced by up to 50% of DLB (McKeith et al., 1992) and clinicians are cautioned against their use in DLB (McKeith et al., 2017).

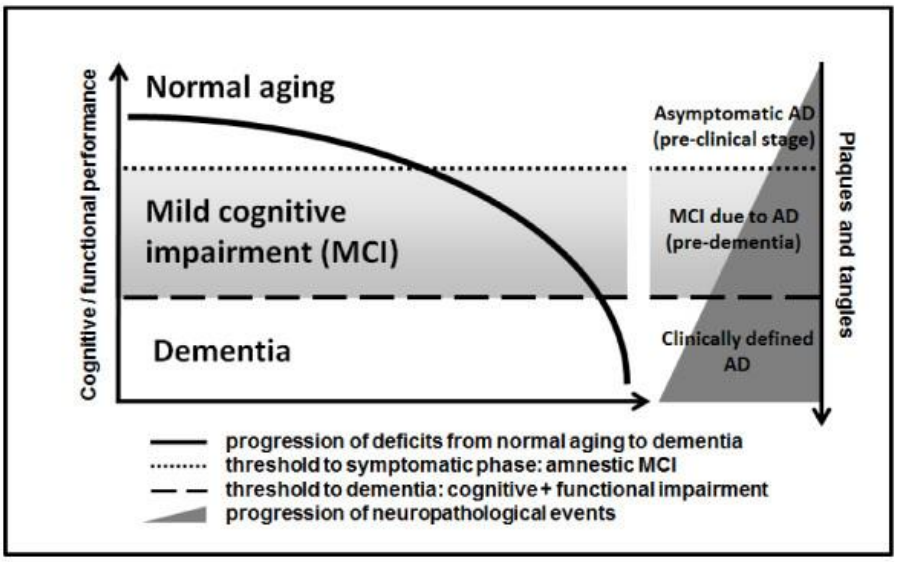

Figure 1. Trajectory of decline in Alzheimer's disease (Forlenza, et al., 2010).

The concept of Mild Cognitive Impairment (MCI) was introduced in the 1990s by Flicker et al. (1991) and Petersen (1995) and is characterized by impaired cognitive abilities that are less severe than in dementia yet more pronounced than expected in normal ageing (Arnáiz & Almkvist, 2003; Donaghy & McKeith, 2014). MCI is generally conceptualized as an intermediate stage preceding dementia, in which activities of daily living are preserved (Albert et al., 2011). Dementia, on the other hand, is associated with significant functional declines and an inability to live independently (Aarsland, 2016). Figure 1 illustrates the trajectory of such a decline in the context of AD.

The original criteria for the identification of MCI, which is often still used, was based on neuropsychological assessment and subsequent classification by MCI subtype (Flicker, Ferris, & Reisberg, 1991; Petersen et al., 1999). Subtypes were used to reflect MCI heterogeneity and firstly differentiated based on an amnestic or non-amnestic manifestation, depending on the degree of memory dysfunction (Donaghy & McKeith, 2014). As defined, the amnestic subtype associated with a high rate of progression to AD, while non-amnestic MCI patients with deficits in other domains were more likely to convert to DLB, vascular or frontotemporal dementias (Ferman et al., 2011). The amnestic and nonamnestic MCI subtypes are further differentiated based on whether other domains are impacted, i.e. single or multiple domain (Petersen et al., 2001). However, what constitutes a "deficit" in a given domain differs, in both this amnestic/ nonamnestic MCI classification system as well as later-evolved clinical approaches.

While development of the concept of MCI supported a proliferation of studies targeting the prodromal stages of dementia since the 1990s, most of the focus has been in MCI later diagnosed as AD (MCI-AD) and prodromal AD (pAD). To date, analogous MCI due to LB disease (MCI-LB) criteria have not been standardized and validated. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5; American Psychiatric Association, 2013)(DSM-5) has proposed 'mild neurocognitive disorder due to Lewy bodies' (roughly equivalent to MCI-LB). Absent from these criteria, however, are biomarkers or symptoms to assist in differentiation from pAD. DLB core and suggestive features, like visual hallucinations, REM Behaviour Sleep Disorder, and autonomic dysfunction, have been shown to be effective in accurate early discrimination between pAD and pDLB (Blanc et al., 2015; Donaghy, O'Brien, & Thomas, 2015; Thomas, Blanc, Donaghy, & Bousiges, 2015). Although preliminary and requiring replication, this work suggests that LB disease in the pre-dementia, MCI stage can be identified clinically. Clinical diagnosis of MCI-LB is also advantageous in allowing consideration of the cognitive profile of the diagnostic group. A neuropsychological approach has alternatively been used in the context of PD with MCI (PD-MCI) by the Movement Disorder Society (MDS). MDS criteria diagnosis PD-MCI at either Level 1 or 2, measuring cognition ideally in five domains by at least two tasks each. This is intended to capture the breadth of each domain and identify all impaired individuals (relative to normative data). However, the use of such a large battery of tests will also increase the likelihood of reaching significance on at least one measure and the inclusion of false positives. Furthermore, the use of such neuropsychological criteria precludes consideration of cognitive function in more detail. Significant impairments are guaranteed between groups at the level stipulated by the criteria (typically between 1 and 2 SDs). While it would be reasonable to hypothesize that neuropsychological impairment in MCI-LB will occur in the domain impacted in advanced DLB (i.e. executive functions, visuospatial ability), this remains an assumption that requires empirical support.

Taken together, there is therefore a clear unmet need to understand the neuropsychological profile which is associated with MCI-LB. Criteria should utilize the emergent evidence of reliable biomarkers of early DLB. To this end, MCI-LB can be clinically diagnosed using the symptoms and biomarkers from the consensus criteria for DLB in conjunction with the National Institute on Aging-Alzheimer's Association (NIA-AA) research criteria for mild cognitive impairment (Albert et al., 2011), as operationalised successfully in Donaghy, O'Brien, Colloby, et al. (2015) and Blanc et

al. (2015). Of course, the criteria may not be purely clinical: cut-offs using global scores can aid in omitting dementia and cognitively normal cases, while allowing for potential heterogeneous neuropsychological presentation.

Chapter Two: The neuropsychology of MCI-LB

2.1 Rationale for a review of the neuropsychological profile of MCI-LB

In addition to the prominent clinical features that can interfere with psychological processes, such as visual hallucinations and cognitive fluctuations, cognitive impairment per se is a hallmark of LBD. While DLB in particular has experienced increased visibility the past decade, there remains a paucity of research on the neuropsychology of DLB when compared to the AD evidence base. In a meta-analytic review, Collerton et al. (2003) found only 21 controlled-comparison studies of the cognitive performance of patients with DLB, for example. To the author's knowledge, no more recent structured reviews have been published. More recent narrative reviews, moreover, have typically contrasted cognition in DLB with PD or AD and do not include controls (Aarsland, 2016; Gross, Siderowf, & Hurtig, 2008; Metzler-Baddeley, 2007). While AD is associated with an amnestic cognitive profile, advanced PDD and DLB typically show similar impairments of the executive function, visuospatial and memory domains (Aarsland, 2016). However, some differences between LBD groups have been reported. In particular, DLB may perform more poorly than PDD on tasks with high executive or attentional demands (Downes et al., 1998; Gnanalingham, Byrne, Thornton, Sambrook, & Bannister, 1997; Mondon et al., 2007).

As concluded in Chapter One, there is increasing interest in the MCI phase of disease, which precedes dementia. Cognitive impairment is observable in MCI, but individuals are generally able to function independently. The neurocognitive profile of clinically-diagnosed MCI-LB is unclear, although it is anticipated to be related to that of advanced DLB. In MCI that will progress to DLB and PDD, memory and language are believed to be less impaired than in prodromal AD, in line with advanced AD's amnestic cognitive profile. MCI-LB individuals, who are more likely to convert to DLB, are expected to show impairments in the executive, attentional, and visuospatial domains (Aarsland, 2016). A recent longitudinal study of 266 patients by Breitve et al. (2018) suggests that MCI-LB patients experience a steeper cognitive decline than MCI-AD, but only on one task (Trail Making Test A [Trails A]) from a battery of neuropsychological tests. Higher executive function scores at baseline were associated with slower overall decline to severe dementia or death; however, this did not differ by aetiology, in contrast to previous studies showing executive impairment conferring greater risk of decline in AD (Buccione et al., 2007; Marra, Silveri, &

Gainotti, 2000). Neuropsychological profiles in MCI can range broadly, are subject to disease progression, and could be impacted by mixed pathologies (Goldman et al., 2014a; Mosimann et al., 2004). Methodological issues, including disregard of cognitive models (see Chapter 6), the use of a wide range of tasks across different studies, questionable validity and reliability of such tasks, use of nonspecific MCI classification, and the still-evolving MCI diagnostic criteria, likely also add to contradictions in the MCI literature (Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Smith & Bondi, 2013).

As presented in Chapter One, PDD and DLB are differentially diagnosed based on the timeline of cognitive impairment onset. However, PD cohort studies suggest cognitive impairment is not solely a late-stage issue and may not always be detected or reported at presentation (reviewed in Aarsland et al., 2008; Goldman, Weis, Stebbins, Bernard, & Goetz, 2012). Thus, validity of this approach of differentiating PDD and DLB diagnoses remains debated. Based on the neuropathological and phenotypic overlap of PDD and DLB and the dearth of MCI-LB-specific research, understanding of the neuropsychological profile of MCI-LB should be informed by research in earliest PD and PD-MCI. To this end, a systematic review was performed by the author in MCI-DLB, earliest PD, and PD-MCI in order to gain a broader understanding of cognition in early synucleinopathies. Relevant findings are discussed below.

2.2 Methods: semi-structured review

The semi-structured review targeted studies in early LBD. In addition to prodromal DLB, the primary target of the present study, PD-MCI and “early PD” were of interest to the review. As discussed previously, there is considerable overlap between conditions. Inclusion of both “early PD” and “PD-MCI” studies allowed fuller consideration of earliest presentations of PD. PD-MCI studies tend to utilize MDS diagnostic criteria for MCI, which is based on neuropsychological performance. Thus, evaluation of the cognitive profiles of MDS-defined PD-MCI patients guarantees deficits of a certain magnitude based on the a priori determined diagnostic criteria. While “early PD” is clearly a vaguer patient category, its inclusion in the review serves to capture recently-diagnosed, *de novo*, and earliest disease-stage PD patients, and is less likely to be impacted by the circularity of MDS-MCI criteria. These patients are typical of first clinical presentation. Although it must be done

cautiously, comparison of early PD with PD-MCI also offers insight into disease temporal progression.

The outcome of interest was cognitive impairment, measured using standardised tests and organized by the author into domains. The key terms of the database search were “Lewy bodies,” “neuropsychology,” and “MCI” or “early.” Synonyms were created for each term and exploded with medical subject headings in the databases where appropriate to capture relevant papers. Databases searched were Medline (from 1946), Embase (from 1988), Psychinfo (from 1987), PubMed, ProQuest, Scopus (from 1987) and ScienceDirect (from 1987). Results were limited to human studies in peer-reviewed English language journals. Reviews, meta-analyses, abstracts, case studies, commentaries, discussion papers, editorials and conference proceedings were excluded. As the focus of the review was on the neuropsychological pattern in early LBD articles that were primarily imaging or eye tracking studies were removed. Articles with titles related to animal testing (‘rodents,’ ‘rats,’ ‘mouse,’ ‘monkey’) were excluded using separate key terms. References were exported to EndNote. The author performed the initial title screen for relevant articles after duplicates were removed both by using EndNote’s duplicate search function and during the title review. After the initial title screen, titles and abstracts were reviewed by two reviewers independently (the author, Bethany Little). A review of the full text occurred if it was not clear from the title or abstract whether the study met the review criteria described below. Any conflicts between reviewers were flagged for re-review, which resulted in agreement for inclusion versus exclusion.

Inclusion and exclusion criteria

Studies were included if they measured at least one domain of cognition using an established neuropsychological task. Tasks and outcome measures were considered established if they were published in at least ten peer-reviewed journal articles. Composite scores of standardised tasks were accepted, for example the “Power of Attention” in Peraza et al. (2017) and “Working Memory Index” in Yu et al. (2012). Articles were excluded if they only measured cognition globally (for e.g. Mini-Mental State Exam [MMSE; Tombaugh , 1992], Montreal Cognitive Assessment [MoCA; Nasreddine, 2005]), used only subtests from such global measures as a proxy for domain scores, or only provided domain-level composite score data. However, authors were contacted for the individual test scores whenever possible. Measures of intelligence were not included.

Studies were included if a group of healthy controls (HCs) was tested for comparison. However, only three studies in MCI-LB remained after applying other inclusion and exclusion criteria; therefore, although two of these three studies utilized MCI subtypes as comparison groups (see below), they were retained for qualitative review. Studies that considered the prevalence of deficits based on published normative data rather than a control group were excluded. Where studies included both HCs and a second clinical group, only comparisons with the HC groups were extracted. Only the baseline data were extracted in the case of longitudinal studies. Studies were excluded if PD diagnostic criteria was unclear, insufficient or not based on clinical assessment. Studies that used unspecified MCI classification criteria, MCI subtypes, or ten or fewer patient participants were excluded.

Data review, extraction and synthesis

From each study, the following variables for each established cognitive outcome measure were extracted: first author, year of publication, country of publication, participant numbers, participant age means and standard deviations (SD), PD diagnostic criteria, MCI criteria (where applicable), disease duration, and outcome measure mean and SD (see Appendix A). The direction of effect sizes (ES) was reversed as appropriate to reflect deficits as negative ES, for example number of errors. Data was entered into an Excel ES calculator that is freely distributed online by the Centre for Evaluation and Monitoring (CEM; Coe, R, retrieved from http://www.cem.org/effect-size-calculator). The calculator produces a bias-corrected ES and 95% confidence interval to estimate the difference between the two means in terms of the pooled estimate of SD. It is bias-corrected based on a factor provided by Hedges and Olkin (1985). ES and confidence intervals were plotted by domain (verbal learning and memory, visuospatial learning and memory, working memory, and executive function) and organized by number of participants. Separate graphs were constructed for closer comparison of equivalent tasks (see Appendix B). When there were at least five studies using the same task in a patient group, summary ES and 95% total confidence intervals were calculated using Cochrane Reviews' Review Manager (RevMan; The Nordic Cochrane Centre, 2014) fixed effect model and inverse variance. Due to different testing parameters and scoring across studies (i.e. *z*-scores), the summary ES were calculated as the standardized mean difference to avoid overestimation of the overall difference. RevMan calculates standardized mean

difference ES as Hedges' adjusted *g*, which is very similar to Cohen's *d,* but includes an adjustment for small sample bias (Deeks & Higgins, 2010).

2.3 Results

Early and MCI due to PD

Due to the high number of studies yielded, results in PD-MCI and early PD were considered quantitatively, summarized in Table 2. These analyses emphasize that there are significant deficits in PD-MCI and early-PD relative to HCs. Overall, the highest proportion of deficits was observed in the visuospatial domain, which was particularly poor in PD-MCI (measured by figure copying tasks). One of the largest differences between PD-MCI and controls was in Benton's Judgement of Line Orientation task (JOLO; Benton, Hamsher, Varney, & Spreen, 1983), while the effect in early PD was small. JOLO, unlike many other visuospatial tasks, requires minimal motor skill and is free of practice effects (Montse, Pere, Carme, Francesc, & Eduardo, 2001). Such tasks may be particularly useful in tracking cognitive decline in the progression of both PD and DLB. Similarly, in the verbal domain, studies in PD-MCI reported verbal learning and memory deficits more frequently than those in early-PD. About three quarters of the outcome variables in EF and verbal domains showed significant impairment, as opposed to only half of working memory variables.

Table 2 Summary of impairments in early Parkinson's disease (PD) and Parkinson's disease with Mild Cognition Impairment (PD-MCI) across neuropsychological domains.

Group	Number of papers retained	Patient group			Control group		Domain	Proportion of studies with at least one impaired variable relative to controls	Proportion of outcome variables impaired relative to controls
		n	Age Mean (SD)	Disease duration Mean (SD)	*n*	Age Mean (SD)			
Early-PD	10	568	64.3 (6.0)	21.3 (6.9)	564	64.1 (5.8)	Executive function	88.9% (8/9)	61% (22/36)
							WM/Attention	77.8% (7/9)	47% (14/30)
							Visuospatial L&M	100% (5/5)	76% (13/17)
							Visuospatial WM	33.3% (1/3)	75% (1/6)
							Verbal L&M	100.0% (6/6)	64% (16/25)
PD-MCI	13	530	65.0 (3.9)	54.0 (36.0)	840	64.4 (2.8)	Executive function	100% (13/13)	89% (39/44
							WM/Attention	88.9% (8/9)	68% (21/31)
							Visuospatial L&M	88.9% (8/9)	91% (30/33)
							Visuospatial WM	75.0% (3/4)	67% (4/6)
							Verbal L&M	100% (11/11)	88% (30/34)
Both groups combined	23	1098	64.7 (4.2)	39.8 (27.0)	1404	64.3 (3.5)	Executive function	95.5% (21/22)	76% (61/80)
							WM/Attention	83.3% (15/18)	57% (35/61)
							Visuospatial L&M	92.9% (13/14)	86% (43/50)
							Visuospatial WM	57.1% (4/7)	42% (5/12)
							Verbal L&M	100.0% (17/17)	78% (46/59)

SD = standard deviation; PD = Parkinson's Disease; MCI = Mild Cognitive Impairment; WM = working memory, L&M = learning and memory.

PD-MCI-associated deficits in figure copying were more pronounced than in recall, although both had large effect sizes. Conversely, visuospatial recognition is much less impaired (Song, Kim, Jeong, Song, & Lee, 2008) and was not shown to be impaired in early-PD (Elgh et al., 2009). Recognition memory for word list stimuli seems similarly intact in PD-MCI, in contrast to deficits in both immediate and delayed recall conditions. This pattern of dysfunction in both the visuospatial and verbal domains in PD-MCI suggests impaired retrieval and relatively intact encoding and storage mechanisms (Shin, Park, Park, Seol, & Kwon, 2006). This supports the established retrieval deficit hypothesis of memory impairment in PD (Tröster & Fields, 1995; Whittington, Podd, & Kan, 2000) which argues that the cause of memory impairment is inability to retrieve material on demand rather than encoding or retention ability (Mahurin, Feher, Nance, Levy, & Pirozzolo, 1993). However, there has been increasing scrutiny of this hypothesis and evidence of recognition impairment in some PD patients without dementia (Higginson, Wheelock, Carroll, & Sigvardt, 2005; Whittington et al., 2000). Whittington (2000) found impairment in recognition in PD participants without dementia, but not in newly diagnosed PD patients, and Bronnick, Alves, Aarsland, Tysnes, and Larsen (2011) found that early-PD patients performed poorly on free recall, cued recall and recognition memory. Bronnick et al. (2011) attribute this impairment to encoding failure due to poor executive function, rather than to impaired retrieval. Indeed, PD participants used fewer semantic clustering strategies to enhance their recall, and both strategy and executive function explained significant variance in learning. Earlier, Gershberg and Shimamura (1995) and Hirst and Volpe (1988) had demonstrated that frontal lobe lesion patients were unable to capitalize on the potential semantic organization present in word lists. My review similarly shows PD is associated with larger executive function deficits in semantic than phonemic verbal fluency.

Thus, it is likely that the prominent executive function impairments in early-PD at least partly explain poorer performance on tasks of greater complexity, regardless of domain. For example, early-PD patients with shorter disease durations demonstrated intact working memory capacity but performance declines if updating or set-shifting components are added (e.g., Digit Backwards and Trails B). PD-MCI conversely, show impairment in both purer working memory tasks and the executive-weighted variants. PD-MCI and early-PD groups were of similar ages but PD-MCI, as expected, report longer disease duration than early-PD (approximately 54 months versus 21 months). The divergence between groups could thus be taken as a proxy

for advancement of PD, and much of the review's interpretation of the neuropsychological results proceeded under this assumption. Therefore, increased executive dysfunction as early-PD progresses to PD-MCI may explain why working memory capacity is more compromised in PD-MCI than early-PD. Similarly, impairment was found on only 41% of visuospatial working memory measures despite a high proportion of visuospatial learning and memory tasks showing deficits in early-PD and PD-MCI. Why then is visuoconstructional ability impaired but not visuospatial working memory? Figure copying such as the Rey-Osterrieth complex figure (ROCF) is a complex task that requires executive functions such as sustained attention, planning and organization (Shin et al., 2006), in addition to the visuospatial perception and processing that is required in visuospatial working memory tasks like Corsi blocks. Methodologically, this emphasizes the importance of locating the executive processes within tasks with face validity in other domains. However, even simple working memory tasks such as Digits Forward could be argued to be influenced by executive control ("chunking", for example.). This issue could thus relate more to the debate regarding multicomponent versus unitary models of working memory (Cowan, 1999; Engle, Tuholski, Laughlin, & Conway, 1999) than to a salient difference in the patient population.

Taken together, PD-MCI and early-PD show deficits in visuospatial, executive and verbal tasks. However, these results should be interpreted with caution due to issues of circularity. Hierarchical linear regression modelling can be pursued in future studies to help determine the potential mediating role of executive function.

MCI-LB

The search strategy did not yield any studies in MCI-LB that met full inclusion criteria, notably use of control group. The three studies measuring cognition in MCI-LB compared function with MCI-AD. One study had only nine participants (Jicha et al., 2010). All three studies measured cognition globally using MMSE and found no significant difference between MCI-LB and MCI-AD. Domain-level function was assessed in all as executive function, working memory/ attention and verbal learning and memory. Cagnin, Bussè, Gardini, et al. (2015) also assessed visuospatial function. The studies together provide 43 outcome measures from 22 tasks across 5 total domains. Only eleven of the extracted outcome variables in MCI-LB showed significant differences between groups after bias-correction. Yoon, Kim, Moon, Yong, and Hong (2015) only showed impairment in executive function (Stroop Colour test;

ES: -0.73). Cagnin, Bussè, Gardini, et al. (2015) reported poorer performance in MCI-LB in working memory (Trail Making Test A), visuospatial and visuoconstructive ability [Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991), ROCF copy], and executive function (Verbal Fluency, Digit Span Backwards). Magnitude of these deficits ranged from medium (-0.57, Object Decision Visuospatial Test of VOSP) to large (-0.97, Digit Span Backwards). Jicha et al. (2010) also reported a phonemic Verbal Fluency impairment, but this failed to remain significant after bias correction, likely due to small sample size. The remaining nine outcome measures of Jicha et al. (2010), including semantic Verbal Fluency, did not differ significantly between groups.

These findings from the semi-structured review thus provide only limited, and at times contradictory evidence, for differentiation between MCI-LB and MCI-AD based on a small number of studies. Two studies (Cagnin, Bussè, Gardini, et al., 2015; Yoon et al., 2015) show worse performance in MCI-LB in some, but not all, tasks of visuospatial, working memory, and executive function. Half of the variables extracted across the three papers differ between groups, but most came from one study (Cagnin et al., 2015). The findings of Cagnin, Bussè, Gardini, et al. (2015) are further surprising given high global cognitive scores (MMSE) as an inclusion criterion. Their retrospective design may have introduced selection bias or an overestimation of deficits. The findings and other evidence of impairment in DLB are discussed further by domain below.

Executive function and attention

Deficits in these domains are common in neurodegenerative dementias overall and, along with visuospatial ability, are the most typically impaired domains in advanced LBD (Collerton et al., 2003). All three of the retained MCI-LB studies in the review provide evidence for executive dysfunction at the MCI stage. It was the only domain significantly impacted in Yoon et al. (2015), with a medium-large effect size, and Cagnin, Bussè, Gardini, et al. (2015) report poorer performance than MCI-AD in Verbal Fluency and Digit Span Backwards with large effect sizes. However, the executive measures in Jicha et al. (2010) did not reach significance with bias-correction. These findings are in line with other work (not retained through the search strategy) demonstrating attentional and executive impairments in the MCI phase of DLB as well (Kemp et al., 2017; Molano et al., 2009; Sadiq, Whitfield, & Walker, 2015). Prominent executive function impairments also emerged within the retained

PD literature, both in PD-MCI and “early PD.” Early PD patients perform poorly on tasks with executive weighting, regardless of which domain they appear to target (working memory, processing speed, visuospatial and verbal learning), and despite general intact performance on simpler tasks in those domains (Trail Making Test A, Rey Auditory Verbal Learning Test [RAVLT]).

Indeed, executive and attentional dysfunction may have specific relevancy to LBD (Ballard et al., 2002). Attentional difficulties observed in DLB, PD and PDD are similar and more pronounced than in AD (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Ballard et al., 2002), and may thus be expected to be demonstrable in the MCI phase. Both PD and DLB have been argued as “dysexecutive syndromes” (p. 81, Kehagia, 2013), with executive dysfunction likely one of the earliest-occurring cognitive symptoms (Collerton et al., 2003; Foltynie, Brayne, Robbins, & Barker, 2004; Muslimović, Post, Speelman, & Schmand, 2005). Kehagia et al. (2012), in a review of their laboratory’s findings over two decades, concludes that executive deficits in the MCI stage are present in 50% of PD patients and are comparable to those observed in frontal lobe-damaged patients. These deficits are associated with impaired activities of daily living and goal-directed behaviour, which can have important consequences for patient quality of life and caregiver burden (Bronnick et al., 2006; Lee, McKeith, Mosimann, Ghosh-Nodyal, & Thomas, 2013). Executive and attentional impairment is also implicated in the aetiology of LBD cognitive fluctuations and hallucinations (Firbank et al., 2016; Shine, Halliday, Naismith, & Lewis, 2011).

Donaghy, Taylor, et al. (2018) recently published study on the LewyPro study, a forerunner and pilot to SUPErB with similar patient classifications. This showed MCI-LB performed significantly worse than MCI-AD in attention and visuospatial function (Donaghy, Taylor, et al., 2018), in line with the divergent profiles of the advanced dementias (Metzler-Baddeley, 2007). One commonly-used measure of executive function is FAS, and Donaghy, Taylor, et al. (2018) demonstrate that MCI-LB performs worse on both the category and letter fluency variants relative to MCI-AD. FAS, however, also depends on intact verbal function (Shao, Janse, Visser, & Meyer, 2014). Donaghy, Taylor, et al. (2018) notes that because MCI-LB performed no worse on measures of language function than MCI-AD (ACE-R, Graded Naming Test), the difference in FAS performance can be said to be strictly related to executive dysfunction in MCI-LB, rather than any verbal ability that might be required by the test, such as confrontational naming.

Visuospatial domain

Of the three retained MCI-LB studies in the review, only Cagnin, Bussè, Gardini, et al. (2015) assessed visuospatial ability, with small to medium effect sizes on visuoconstructive and visuoperceptual tasks. Larger magnitudes of deficit might have been expected, given that visuospatial difficulty is a well-documented feature of impairment in DLB (McKeith et al., 1996). Tiraboschi et al. (2006), for example, found visuospatial dysfunction to be present in 74% of neuropathologically-confirmed DLB cases and lack of impairment to be the best negative predictor of DLB at autopsy. Such dysfunction is also suggested to occur early in disease and to precede memory impairment (Alescio-Lautier et al., 2007; Hort et al., 2007) and associated with greater frequency of visual hallucinations in both PDD and DLB (Sanchez-Castaneda et al., 2010). Visuospatial impairment has been shown to predict greater functional decline in DLB, for example as measured by nursing home admission rate, falls incidence and quality of life (Aarsland, Larsen, Tandberg, & Laake, 2000; Kudo, Imamura, Sato, & Endo, 2009). Hamilton et al. (2008) used autopsy-verified DLB cases to demonstrate that steeper cognitive decline and more severe visual hallucinations was predicted by baseline visuoconstructive skills using the WISC-R Block Design and Clock Drawing Test-Copy. Visuospatial function has also been linked to decreased activities of daily living at follow-up in DLB, but not in AD (Wood, Neumiller, Setter, & Dobbins, 2010). As opposed to executive and attentional domains, visuospatial declines are less typical in normal aging, suggesting that the large deficits seen in LBD are more directly linked to the disease process (Klencklen, Després, & Dufour, 2012). These findings of early and substantial visuospatial difficulties in DLB suggest that deficits in this domain may be the most apparent at the MCI stage (McKeith et al., 1996). Results from the structured review indicate the visuospatial ability is particularly poor in PD-MCI, but less so in early PD, which may be said to represent an earlier disease state. It thus remains unclear whether visuospatial deficits will be the most salient cognitive deficit in MCI-LB as in established DLB. Results from the LewyPro study, in which MCI-LB Probable showed lower scores on the ACE-Visuospatial subtest and an angle discrimination test, indicate that deficits are indeed present (Donaghy, Taylor, et al., 2018).

Verbal Memory and Learning

While Cagnin, Bussè, Gardini, et al. (2015) and Yoon et al. (2015) show deficits in MCI-LB versus MCI-AD in the domains of working memory, executive function and visuospatial function, MCI-LBs performed significantly better than MCI-AD on verbal learning and memory tasks in all three studies. Verbal learning and memory appears preserved in MCI-LB relative to MCI-AD, in line with the pronounced memory encoding deficits of AD (Lange et al., 2002; Martin, Brouwers, Cox, & Fedio, 1985). However, without the use of HCs, it cannot be concluded whether the verbal domain is intact or simply less impaired compared with MCI-AD. Results in PD from the structured review stress the relevancy of verbal impairment to early PD. Patients performed significantly worse than controls in 78% of the verbal domain variables, with PD-MCI showing a higher proportion than early-PD. Each study that tested verbal learning and memory reported at least one significant difference between groups. However, 7 of the 17 studies reporting a deficit in one outcome measure also reported at least one other without a significant difference, highlighting the potential equivocality in using large neuropsychological batteries. Recognition in both the visuospatial and verbal domains in PD-MCI seems intact, while recall is not. As discussed above, this suggests impaired retrieval and relatively intact encoding and storage mechanisms, supporting the established retrieval deficit hypothesis of memory impairment in PD.

Thus, evidence from the review is equivocal. The MCI-LB studies do not indicate poor verbal performance, while there is substantial evidence within the early PD/ PD-MCI literature. Similar to the three retained MCI-LB studies, Donaghy, Taylor, et al. (2018) found MCI-LB performance to exceed MCI-AD in memory. However, 40% of the MCI-LB group scored greater than 2 SD below the mean in RAVLT delayed recall. Indeed, Ferman et al. (2013); Yoon et al. (2015) and Kemp et al. (2017) note that a substantial proportion of DLB cases will have an amnestic MCI profile, despite non-amnestic MCI being more likely to convert to DLB (Ferman et al., 2013). Some studies have shown that DLB patients may demonstrate early memory and language deficits. Auning et al. (2011), for example, used caregiver report to argue that memory impairment was the most common presenting symptom of DLB (57%); that it is much more reported in AD (99% caregiver report) perhaps lends credence to this methodology. However, caregiver reporting is notoriously influenced by bias, especially in retrospective accounts (Caviness et al., 2007; Noe et al., 2004). Noe et al. (2004), for example, found objective measurement in PDD conflicted with

subjective reports by caregivers of memory impairment as the earliest symptom. The use of control groups in the present study is therefore based on the need to clarify how MCI patients objectively perform relative to age-matched controls, as well as the differential profiles of MCI-LB and MCI-AD.

As discussed above, PD participants may fail to capitalize on their semantic knowledge or use of semantic clustering strategies as frequently. These are essentially executive functions, but may present as verbal memory dysfunction without careful consideration of task demands. The present study aims to consider whether domain-general executive functions can explain any measurable memory impairment.

2.4 Importance of clinical characterization of patient groups

As mentioned above, early PD and PD-MCI could be interpreted as representing earlier and later forms of PD with advancing cognitive impairment. However, a crucial limitation to this interpretation is the potential for circularity due to the neuropsychological characterisation of MCI.[1] In the PD-MCI group, all but one study (Anderson, Simpson, Channon, Samuel, & Brown, 2013) defined groups on neuropsychological criteria. Most followed MDS criteria, developed in order to provide clarity in the diagnosis of MCI, which is an understandable endeavour given the complicated overlap between LBDs. However, these criteria also ensure significant impairments are observed between groups. For example, one of largest overall differences found in the present study was in Benton's JOLO, with PD-MCI performing on average more than two *SD*s worse than HCs, and a more moderate deficit in early-PD (g=-0.36). This could represent real divergence between early-PD and PD-MCI, the latter of which have longer disease durations and are more likely to develop dementia than a cognitively intact early PD patient (Janvin, Larsen, Aarsland, & Hugdahl, 2006). Indeed, many of the standardized mean differences computed in the present review are between 1 and 2 *SD*s. However, this is perhaps more assuredly evidence of circularity rather than a demonstration of PD-associated impairment.

[1] MCI is frequently diagnosed based on neuropsychological cut-offs relative to normative data. For example, PD-MCI criteria by Litvan et al. (2012) stipulates impairment of 1-2 SDs in two tests in a single domain or one test in two domains. However, MCI-LB can be diagnosed clinically following consensus criteria guidelines. These criteria do include a cut-off for global function (MMSE, for example), but do not depend on neuropsychological cut-offs by domain. When using clinical criteria, a more nuanced investigation of cognitive impairment in MCI-LB may be possible.

Methodological decisions regarding what level of deficit constitutes "impairment" also has critical implications to a study's results. Dalrymple-Alford et al. (2011), for example, found that while only 14% of a PD sample was considered PD-MCI when defined as two *SD*s below normative scores in at least two tests in a domain, this number increases to 89% if considered at 1 *SD* or more. In the latter scenario, 70% of clinically-defined HCs were also identified as MCI. Similarly, Brooks, Iverson, Holdnack, and Feldman (2008) found 30.8% of healthy older adults meet Petersen et al.'s (2001) criterion for MCI. These findings pointedly question the utility of such a cut-off. MDS criteria stipulates that cognition should ideally be measured in five domains by at least two tasks. This is intended to capture the breadth of each domain and identify all impaired individuals, but also increases the likelihood of reaching significance on at least one measure. Few studies correct for multiple comparisons. Such a large amount of neuropsychological testing can also become unwieldy to report in entirety and encourages selection biases in presenting only significant results. Thus, choosing a battery poses a problem: decreasing the breadth may omit relevant individuals, but increased breadth often leads to contradictory findings within domains. The use of composite domain scores may help to overcome this methodological challenge (Crane et al., 2012; Gibbons et al., 2012) but a neuropsychological definition of MCI in research remains problematic. Alternatively, defining MCI clinically (e.g. by measuring independent function and daily activities, input from family members, neurological examination, or biomarker tests) achieves a less biased sample of participants when investigating neuropsychological impairment.

2.5 Overall aims of the PhD

While advances in neuroimaging and other methods of identifying biomarkers *in vivo* are greatly accelerating diagnostics in the MCI stage, neuropsychological measurement remains a critical tool in neurodegeneration research and clinical practice (Smith & Bondi, 2013). The criteria for defining MCI-LB clinically has only recently been established and its associated cognitive phenotype is unclear. Moreover, the previous work that suggests MCI-LB will consistently show a dysexecutive profile is troubled by the use of a wide range of tasks across different studies, questionable validity and reliability of such tasks, and the use of inconsistent MCI diagnostics (Rasquin et al., 2005; Smith & Bondi, 2013). This PhD therefore firstly aims to define the neuropsychological profile of clinically defined MCI-LB

relative to both healthy controls and MCI-AD. The following chapters will attempt to clarify neuropsychological function using these clearly and clinically-defined MCI groups. Secondly, the PhD will use a cognitive psychological framework to consider whether domain-general resources are responsible for the higher-order deficits commonly associated with DLB, particularly visuospatial dysfunction. Because of the large comprehensive battery utilised in the study, Principal Components Analysis (PCA) will be employed as data reduction technique before moving into these multivariate analyses. There is a dearth of data in this novel MCI-LB population; therefore, few specific hypotheses are offered. However, given the existing literature in DLB, it is hypothesized that MCI-LB will be associated with deficits in visuospatial function, executive function and attention, relative to both controls and MCI-AD. MCI-AD, conversely, is expected to demonstrate a mildly amnestic profile with impaired verbal learning and memory skills. Following these initial empirical chapters, a cognitive psychological approach and advanced modelling techniques will be employed to expand on the initial findings in greater detail. Introduced in detail in Chapters 6-8, these research questions include whether there is a hierarchy of deficits in MCI-LB and if intraindividual variability in reaction time performance differs between groups. Finally, an exploratory chapter (Chapter 9) will tentatively consider how the neuropsychological processes that emerge in the earlier chapters may relate to the MCI-LB phenotype more broadly, using measures of severity of cognitive fluctuations (a major clinical symptom) and white matter integrity in the brain.

Chapter Three: Description of the SUPErB study cohort

3.1 Introduction to SUPErB

Chapter one and two presented background literature on DLB and current understanding of the neuropsychology of MCI-LB. The structured literature review highlighted the minimal existing empirical evidence in MCI-LB and reviewed findings in other forms of early LB disease (MCI-PD and early PD). In addition to the lack of existing studies in the population, the issue of circularity when defining MCI-LB based on neuropsychological cut-offs was introduced. Clinical identification of MCI-LB is possible following consensus criteria guidelines. While these criteria benefit from use of thresholds of global function to ensure participants are sufficiently cognitively intact to warrant an MCI diagnosis, they do not depend on neuropsychological cut-offs by domain. Therefore, use of clinical criteria can allow for a more nuanced investigation of cognitive impairment in MCI-LB. The ^{123}I-MIBG Scintigraphy Utility as a Biomarker for Prodromal Dementia with Lewy Bodies (SUPErB) study was designed to address these and other issues in MCI-LB. The current chapter aims to outline the SUPErB study, including recruitment, biomarker testing, and the diagnostic process, and present the overall aims of the present PhD. The cohort will be described in the present chapter terms of clinical and biomarker presentation, global cognitive scores, and demographics. Subsequent chapters will contain detailed information on the empirical results of the neuropsychological testing.

MCI-LB Possible patients

MCI-LB will be diagnosed following the most recent consensus criteria on DLB (McKeith et al., 2017) in conjunction with NIA-AA clinical diagnosis of MCI (Albert et al., 2011), as described further in section 3.4.3. In this scenario, two MCI-LB diagnostic categories are created. MCI-LB Possible requires clinical MCI criteria are met and the presence of one core clinical symptom of DLB or one positive indicative biomarkers (DaTSCAN or MIBG). MCI-LB Probable is a stricter diagnosis, requiring two clinical symptoms or one clinical symptom and a positive biomarker. Therefore, the MCI-LB Probable group, by definition, will be more assuredly showing cognitive decline due to LB disease. As discussed above (section 1.7.7), neuropathological research shows that at autopsy many dementia patients show concomitant brain pathologies typical of AD and DLB. For example, studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) report that only a quarter of clinical AD cases

have pure AD brain pathology at autopsy (Cairns et al., 2015). Mixed-pathology individuals are particularly difficult to diagnosis clinically (Merdes et al., 2003), and would be likely to be included in the MCI-LB Possible group, rather than MCI-AD or MCI-LB Probable, due to positive biomarker results. For example, a patient with amnestic cognition and absent DLB clinical symptoms, like hallucinations and parkinsonism, may show abnormal MIBG or DaTSCAN results suggesting latent LB disease. This would lead to a diagnosis of MCI-LB Possible in the present study. In contrast, a MCI-LB Probable diagnosis requires more evidence that decline is due to purer LB disease. As such, basic information on the clinical profile of MCI-LB Possible will be presented in the current chapter, but the neuropsychological comparisons in the subsequent chapters will focus primarily on MCI-LB Probable. This allows greater confidence that scores in the MCI-LB Probable group relate to LB pathology specifically and that inferences can be more safely drawn when comparing the group to MCI-AD and controls.

MCI-AD and controls

The present study also utilises control and MCI-AD groups. The control group was recruited to be matched to the MCI patients overall on age and sex. Healthy controls have normal cognitive function and undergo all imaging and neuropsychological components of the study. This allows for optimal comparison with the MCI group rather than depending on normative data. Neuropsychological tasks can be subject to biases such as order effects. Moreover, many of the tasks have subtle differences in administration. For example, the RAVLT is regularly administered with Long Delay recall conditions of between 15 and 30 minutes. The use of a control group avoids a number of potential confounding factors and permits a clearer understanding of the profile of deficits in the MCI groups.

The recruitment strategy for MCI participants in SUPErB aimed to infuse the patient sample with those likely to have LB disease. Nevertheless, a number of participants were anticipated to receive an MCI-AD diagnosis after baseline assessment. The MCI-AD participants were diagnosed following exclusion of LB-symptoms or biomarkers, as well as positive identification of a NIA-AA defined MCI profile that is consistent with AD. As such, MCI-AD participants were not recruited specifically as MCI due to AD per se: they are likely to progress to AD, but also may have some LB features.

Substantial neocortical LB burden in the context of established clinical and pathological AD has been argued to characterise a Lewy body variant of AD (McKeith et al., 2005). At post-mortem examination, many DLB cases will show concurrent AD pathology (Ballard et al., 2006). It is unclear how mixed pathologies may impact the phenotype, in terms of cognition and clinical features. Amyloid deposition in DLB, for example, has been correlated with fewer core clinical features (Tiraboschi et al., 2014) and greater cerebral atrophy and cognitive impairment (Nedelska et al., 2015; Nelson et al., 2009). However, recent work by Donaghy, Firbank, et al. (2018) failed to find differences in neuropsychological or neuropsychiatric profile, fluctuations or parkinsonism between amyloid-positive and amyloid-negative DLB cases using PET imaging. The phenomenon of multiple pathologies in many people with dementia makes attempts to delineate a clear, etiologically-orientated neuropsychological profile challenging. In particular, the role of tau and the possible synergistic interactions of concurrent AD and DLB pathology require elucidation in future studies.

In terms of the implications for the present study, the reality of mixed pathologies suggests that any significant differences that emerge between MCI groups are particularly notable: given that the MCI-AD group is slightly “Lewy” (in that they were initially approached for reports of features of LB disease), any impairments relative to MCI-LB should be of an even greater magnitude in “purer” MCI-AD. Comparison with the MCI-AD group therefore offers insight into how these pathologies differ in the MCI stage.

3.2 Methods

Recruitment and inclusion/ exclusion criteria

MCI patients were recruited in two primary ways. Firstly, volunteers from a previous study in MCI-LB by the same group were contacted in anticipation of their annual follow-up and invited to move into the SUPErB study if desired. This study, LewyPro, was a pilot study with equivalent entry criteria although with a less-detailed set of assessments for early DLB. Secondly, patients were recruited through consultants in regional National Health Service (NHS) trust old age psychiatry, neurology and memory services and through case-note searching by staff from the North-East Local Research Network of the Dementias & Neurodegenerative Diseases Research Network (NE-DeNDRoN). These patients with MCI and at least one symptom suggestive of DLB are approached through their consultant via a letter

with information about the study and an agreement form for the Newcastle research team to contact them.

Control participants were recruited from a voluntary database of individuals interested in participating in research, which is maintained and searched by staff from NE-DeNDRoN. Eligible carers of the MCI group were also informed of the study if they expressed interest in participating in research.

Inclusion screening criteria

Prior to assessments, participants must be at least sixty years of age, medically/ pharmacologically stable, willing and able to give informed written consent to participate in the study, and not have a record MMSE score of less than 20. Participants were excluded in cases of clinical evidence of dementia, including a Clinical Dementia Rating over 0.5, history or evidence from neurological examination of clinical stroke or major cerebrovascular disease on brain imaging, a Parkinson's disease diagnosis according to the Movement Disorder Society (Postuma et al., 2015) over a year before cognitive decline, diagnosis of a movement disorder or other serious neurological condition, or severe mental illness (current major depression, bipolar disorder, schizophrenia). Women within a year of menopause were excluded. In order to permit MIBG imaging, participants with class II or worse heart disease according to the New York Heart Association classification or a history of myocardial infarction within the past 12 months were excluded. In order to permit SPECT and CT, participants must have been able to lie flat with sufficient comfort for thirty minutes and tolerate the enclosed MRI scanner (i.e. no claustrophobia). Pharmacologically, participants must not have been taking prescription of tricyclic antidepressants, tramadol or labetalol. Additional inclusion/ exclusion criteria is outlined below by group (patients and controls).

MCI inclusion and exclusion criteria

Following assessment, all MCI patient participants must firstly meet diagnosis for MCI regardless of aetiology following criteria by NIA-AA workgroups (Albert et al., 2011). Other patient inclusion criteria are an MMSE score over 20, and independence in activities of daily living (see Table 3). The latter inclusion criteria is especially crucial as an important delineating characteristic between diagnoses of MCI and dementia. It was asked that a spouse, close relative or established carer

accompany the subject to study visits and to act as an informant (minimum contact twice weekly). However, if no suitable person was available, participants could

Table 3 Summary of criteria for Mild Cognitive Impairment diagnoses for MCI with Lewy body disease (MCI-LB; Probable or Possible) and MCI due to Alzheimer's disease in the SUPErB study.

MCI criteria for all patients		
○ NIA-AA workgroup criteria for MCI (Albert et al., 2011) ○ MMSE > 20 ○ Intact activities of daily living ○ No dementia ○ No Parkinson's disease diagnosed more than a year before cognitive decline ○ Medical and pharmacological stability		
MCI subtype criteria:		
MCI-LB Probable	**MCI-LB Possible**	**MCI-AD**
Either: ○ Two positive symptoms of DLB (visual hallucinations, cognitive fluctuations, REM Behaviour Sleep Disorder, parkinsonism), or ○ One symptom and one positive biomarker of Lewy body disease (abnormal FP-CIT or MIBG)	○ One positive symptom or one biomarker indicative of Lewy body disease.	○ NIA-AA MCI decline characteristic of Alzheimer's disease ○ No symptoms or biomarkers indicative of Lewy body disease

complete the study without the carer assessments being completed. Patients must not have dementia.

Control exclusion and inclusion criteria

Healthy control subjects were free of memory complaints or concerns by others, not on anti-dementia or anti-Parkinson's disease drugs and, following assessment, had MMSE scores equal or above 26. They had no evidence of any movement disorder at screening or assessment and normal MRI scans.

MCI diagnosis

Patients were diagnosed by a consensus panel of expert Old Age Psychiatrists (Professor Alan Thomas, Dr Paul Donaghy, and Dr John-Paul Taylor). Firstly, NIA-AA MCI diagnosis (Albert et al., 2011) was confirmed. Secondly, the two primary clinicians (Professor Thomas and Dr Donaghy) reviewed each participant's clinical data individually to determine the presence of the four core clinical features of DLB (cognitive fluctuations, visual hallucinations, RBD, spontaneous cardinal features of parkinsonism), according to 2017 consensus criteria (McKeith et al.,

2017). These decisions were made blind to imaging results. In cases where the primary two clinicians did not agree, the third clinician (Dr Taylor) made the final decision. Procedures for imaging assessments are described separately below.

These six diagnostic features (fluctuations, visual hallucinations, RBD, parkinsonism, and abnormal FP-CIT SPECT or MIBG) were used to classify participants as MCI-LB Probable (NIA-AA MCI plus one or more clinical features or one clinical feature and one positive biomarker), MCI-LB Possible (NIA-AA MCI plus one or clinical features or one positive biomarker), MCI-AD (NIA-AA MCI without any DLB features, with decline characteristic of AD, and absence of symptoms of other aetiologies), and controls.

Design and procedure

SUPErB is a large, multiple day study that includes neuropsychological evaluations, carer questionnaires, numerous imaging and biomarker studies, and clinical evaluations. Participants completed a thorough baseline neuropsychological and clinical evaluation, as well as blood sampling, imaging (MRI, DaTSCAN, MIBG, EEG), and autonomic readings across five or more study days. All potential subjects who agree to enter the study were first seen in their own home or, if they preferred, at a dedicated NHS research unit, in the presence of their carer or family member. The researcher (author) explained the aims, structure, demands and risk of the study. Following any questions that may arise, capacity to give consent was reaffirmed by the author before the participant provided their written consent. Throughout testing days, participants were asked if they would like any breaks between tasks to avoid fatigue, and participants were reminded that they can cease testing and/ or withdraw from the study at any time without restriction.

Neuropsychological pen and paper tasks were typically administered at the participant's home on the first visit. Computerised tests were given in a quiet clinical room at the final visit. Participants were given verbal instructions by the researcher and understanding of the task demands were confirmed before each test was administered. Where the participant was unable to understand how to complete the task, the task was omitted. Administration of these pen-and-paper and computerised tasks took place over the course of two separate study days, and supplementary testing to complete outstanding tasks was sometimes necessary due to time constraints and participant fatigue. In total, completion of the tests took between 3 and 4.5 hours.

No financial incentives or remuneration were provided in exchange for participation in this study, but taxi transportation to and from the study sites and meals on testing days were provided as appropriate. Informed written consent was collected by the author at the first visit, typically at the participants' homes. Ethical approval was obtained for the patient cohort by the NHS Research Ethics Committee including an amendment to recruit the control group. Since study subjects do not have dementia they had capacity to give consent. This was formally checked during the consent process following Good Clinical Practice and Mental Capacity training completed by the author. To preserve anonymity and confidentiality, any data leaving the site identified participants by a unique study identification code only, approved by the Research Ethics committee. The study complies with the 1998 Data Protection Act. All study records and Investigator Site Files were kept in a locked filing cabinet with restricted access.

SUPErB is a five-year longitudinal study. After this baseline year, participants are invited to return to the campus (or home visits when requested) for yearly follow-ups consisting of the neuropsychological evaluation, carer questionnaires and repeat biomarker testing for some participants (pending funding and appropriateness). This continues for four follow-up visits or until a participant converts to a dementia diagnosis. The primary aim of SUPErB is to prospectively evaluate the diagnostic utility of MIBG in predicting conversion to dementia over the course of five years, while this PhD focusses on the cross-sectional baseline data in order to clarify the neuropsychological profile of this novel patient group.

I (the author) selected the neuropsychological battery with the support of my supervisors. Programming of the computerised tasks was adapted for the study by myself with guidance from Dr Michael Firbank, Dr Rachel Moss and Dr Andreas Finkelmeyer. I personally took consent and medical history for all participants and administered, scored, and analysed all of the neuropsychological tests, except in a few, rare occasions in which illness or double-booking necessitated administration of the tasks by another trained researcher. The groups were created based on clinical and imaging assessments completed and interpreted by other members of the SUPErB team. These are described further below.

Materials

Demographics and other background variables

Participant sex, date of birth, age, years of education, highest qualification attained were collected. Questionnaires and clinical assessments are described below.

National Adult Reading Test (NART; Nelson, 1982)

Premorbid intelligence was estimated using the National Adult Reading Test (NART) (Nelson, 1982), which consists of 50 words of irregular pronunciation presented on paper and read aloud by participants. Pronunciation is checked for correctness by the researcher using phonetic spellings. Premorbid IQ is then estimated by the following formula: Predicted Full-Scale IQ = 128 - 0.83 x NART error score (S.E. est. = 7.6).

Geriatric Depression Scale – Short Form (GDS-15; Sheikh & Yesavage, 1986)

Depressive symptomology was evaluated by the Geriatric Depression Scale – Short Form (GDS-15; Sheikh & Yesavage, 1986), a self-report measure specific for use in older populations with good reported reliability (0.81; Almeida & Almeida, 1999; current study Cronbach's α = .934) and validity (de Craen, Heeren, & Gussekloo, 2003). Questions pertain specifically to mood over the past week.

MDS-Unified Parkinson's Disease Rating Scale (Goetz et al., 2008)

The UPDRS' motor subsection was used to assess motor impairment in patients. Total score is calculated by summing scores for the five measures (rigidity, tremor at rest, bradykinesia, action tremor, facial expression).

Lawton Instrumental Activities of Daily Living Scale (IADL; Lawton & Brody, 1969)

IADL assesses an older person's hypothetical ability to complete tasks related to daily functions, whether or not they are regularly performed by the person and separate from physical disability. The eight tasks queried are: using a telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Scores range from 0 (highest functional impairment) to 8 (full functional capacity).

Neuropsychiatric Inventory with Caregiver Distress Scale (NPI-D; Cummings et al., 1994)

Informants (carers; if available) complete the NPI-D with the researcher in order to assess behavioural symptoms typical of dementia syndrome. The inventory consists of twelve domains assessed for presence, severity and frequency over the past month: hallucinations, delusions, agitation/ aggression, depression/ dysphoria, anxiety, elation/ euphoria, apathy/ indifference, disinhibition, irritability/ lability, aberrant motor behaviour, sleep, and appetite/ eating disorders. Higher scores indicate greater neuropsychiatric impairment. Because the NPI-D does not include measures of fluctuations, which are particularly relevant to DLB, two fluctuation scales were administered separately.

Clinical Assessment of Fluctuations Scale (CAF; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000)

Informants complete the CAF together with a trained clinician. The scale consists of two portions relating to the (1) frequency and (2) duration of fluctuating cognition/ consciousness over the month prior to assessment. Scoring of each subscale is between zero and four and an overall total is computed by multiplying the two subscales. Scores can range from 0 (no fluctuations) to 16 (severe fluctuations). Limitations to the scale have been suggested based on its dependency on clinician ability and the qualitative nature of several questions (Lee, Taylor, & Thomas, 2012). Due to the fluctuations characterising the condition, DLB patients are expected to score higher than AD patients on this scale (O'Brien et al., 2014).

Dementia Cognitive Fluctuations Scale (DCFS; Lee et al., 2014)

The DCFS is completed by an informant to quantify fluctuations using four scales: variation in function, daytime sleepiness, daytime lethargy and overall level of consciousness. These subscales have been shown to be successful in differentiating DLB from AD (Lee et al., 2014).

North East Visual Hallucinations Interview (NEVHI; Mosimann et al., 2008)

The NEVHI is an informant-based semi-structured interview to screen for hallucinations. The emotions, cognitions and behaviours associated with the hallucinations, if present, are also assessed (Mosimann et al., 2008).

Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982)

The CDR is completed by a clinician to determine the patient's overall level of functional impairment due to dementia across six domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. A total score is computed using an algorithm in which 0.5 is consistent with MCI or dementia (Morris, 1993). A score of zero indicates absence of dementia. Scores of 1-3 is in line with a dementia diagnosis. The CDR, like CAF, is dependent on clinician skill as other sources of impairment, such as physical disability, must be ruled out.

Hoehn and Yahr Scale (Hoehn & Yahr, 1998)

The Hoehn and Motor Scale is a widely used measure original developed in PD to assess motor severity. It relates to both unilateral/ bilateral involvement and compromised balance/ gait. Parkinsonian motor impairment can be ranked in severity from unilateral (stage 1), bilateral without balance difficulties (stage 2), bilateral with postural instability (stage 3), loss of physical independence (stage 4), and wheelchair or bed-bound without assistance (stage 5) (Goetz et al., 2004).

Global cognitive assessment

Global cognitive function is assessed using Addenbrooke's Cognitive Examination-Revised (ACE-R; Mioshi , Dawson, Mitchell, Arnold, & Hodges, 2006) and the MMSE, which is extracted from the ACE-R. MMSE is the one of the most frequently used generally cognitive assessment tools and is well validated in various patient groups including MCI (Aarsland, 2016).

MIBG imaging

MIBG cardiac imaging was carried out within the medical physics department of the Royal Victoria Infirmary NHS hospital in Newcastle upon Tyne. Subjects are firstly administered medication to block thyroid uptake of any free iodine following standard clinical protocol. After the absorption period of the thyroid block, subjects receive a single intravenous bolus of 111 MBq (3mCi) of ^{123}I-MIBG followed by a saline flush. Planar images in anterior view are then obtained at 20 minutes post-injection (early image) and 240 post-injection (delayed image). SPECT chest imaging uses a dual-headed gamma camera and low energy, high resolution collimator. Images were analysed using established methods of regions of interest (ROI; polygonal) manually drawn over the entire heart, including the left ventricular cavity. A rectangular ROI is also set on the upper mediastinum. Heart to mediastinum (H/M)

ratios are computed for both early and delayed images. MIBG uptake is quantified as the fraction of mean count per pixel in the heart ROI over mean count per pixel in the upper mediastinum. Throughout the MIBG procedure and prior to discharge, subjects are observed for any signs of adverse reactions, excessive inflammation at the injection site or surrounding tissue.

From the MIBG scans, heart-to-mediastinum ratio (HMR) values were measured by two researchers and averaged. Any cases of more than 10% disagreement in values were reviewed by the researchers towards consensus ratings. The optimum threshold for normality was computed by adapting previous values obtained in a multicentre study (2.10; Yoshita et al., 2006) to the cameras used in the present study using a phantom calibration method and the control group for normalization. Two control participants were excluded from this calculation due to abnormal scans. The threshold was determined to be <1.86 as abnormal.

DaTscan

^{123}I-FP-CIT SPECT is likewise administered from the outpatient medical physics department following standard clinical procedure. Intravenously, thyroid-blocking medication is administered followed by the 185 MBq of ^{123}I-FP-CIT. Approximately 4 hours after injection, multiple views of the head over around a 360-degree orbit are acquired using a dual-headed gamma camera. Imaging itself lasts about 30 minutes. Subsequently, image reconstruction produces transverse sections with an axial resolution under 10mm full width at half maximum. Each FP-CIT SPECT image was evaluated using the Benamer scale and a panel of five experienced clinicians (Dr Paul Donaghy, Professor Alan Thomas, Ms Gemma Roberts, Dr George Petrides, and Dr James Lloyd) to avoid the potential bias of a single rater (Benamer range 0-3; Benamer et al., 2000; Colloby et al., 2008). Panel members met in person to discuss uncertain cases, defined as a 3:2 split (or 3:1:1; 2:2:1, or 2:1:1:1). Where there was full consensus or 4 panellists in agreement this was taken as the final rating. Final Benamer rating for each participant was normal (0) or abnormal (0-1) for the purpose of diagnosis.

3.3 Cohort profile

Patient groups

Seventy-five MCI participants were recruited over the course of 23 months. Thirty-two control participants were recruited so that groups remained comparable for age and gender. After consent and baseline study assessments, fourteen participants (including one control) were withdrawn from the study prior to completion

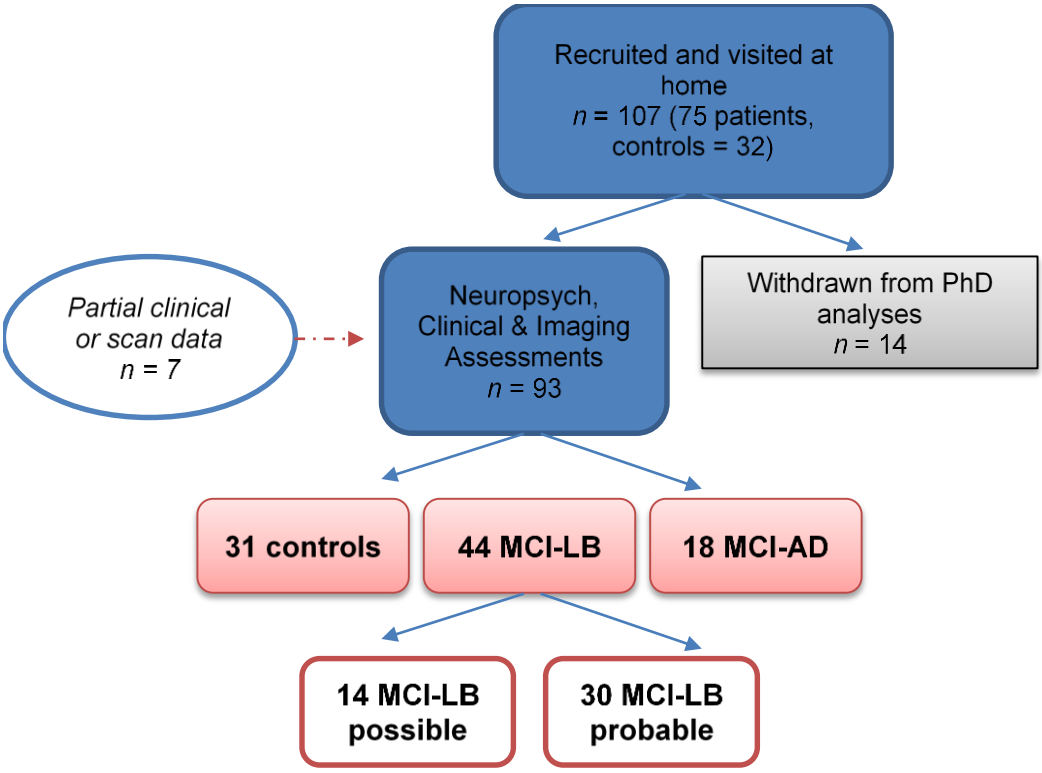

Figure 2 Flow chart showing the recruitment, withdrawal and ultimate allocation of SUPErB study volunteers to the four groups.

for reasons of medical delay (*n* = 3), voluntary removal (n = 5), dementia/ advanced impairment (*n* = 5), and insufficient impairment (*n* = 1). See Figure 2 and Appendix C for complete information on removed participants. This resulted in a final groups of 31 controls, 44 MCI-LB patients and 18 MCI-AD patients. The MCI-LB group was further diagnosed as 14 MCI-LB Possible and 30 MCI-LB Probable individuals.

Demographics

Demographic data by participant group is presented in Table 4 on page 42. Overall, patients ranged in age from 60 to 89 and subgroups remained matched by age. The MCI-LB groups, however, have a predominance of males and lower scores of premorbid IQ estimates relative to controls and MCI-AD. The mean premorbid IQ estimates for controls and MCI-AD groups are quite high overall. MCI groups did not differ on CDR or IADL, indicating any impact on independent function was very limited and in line with MCI. There was no difference in NPI-D scores. Global cognitive status (MMSE and ACE-R scores) did not differ between patient subtypes.

As expected, control global cognitive scores were in the normal range and significantly higher than each MCI subtype. MCI-LB Probable patients scored significantly higher (M = 5.27, SD = 3.91) than controls (M = 1.32, SD = 1.82) on GDS self-reports of depression, but MCI-AD and MCI-LB groups were not statistically different.

Biomarker Results

Eighteen of 28 MCI-LB Probable and 4 of 14 MCI-LB Possible participants who received MIBG imaging had abnormal scans. Seventeen of the 30 MCI-LB Probable group had abnormal panel-rated DaTSCAN. In total, thirteen of the 30 MCI-LB Probable participants had both abnormal MIBG and DaTSCAN. No MCI-AD participants had abnormal DaTSCAN or MIBG scans. Nine of the 14 MCI-LB Possible participants had a biomarker indicative of LB disease.

Core symptoms and related scales

In MCI-LB Probable, RBD and cognitive fluctuations were the most common consensus symptoms (66.67% of group for both). No participants were positive for neuroleptic sensitivity, which was originally included when planning the study in diagnostic criteria but removed when 2017 criteria were published. MCI-LB Probable participants had the following numbers of core symptoms: n = 1 with four symptoms, n = 6 with three symptoms, n = 12 with two symptoms, and n = 11 with one symptom and at least one abnormal biomarker. Five of the 14 MCI-LB Possible group were diagnosed based on cognitive fluctuations as a core symptom, rather than a positive biomarker. The participants were interviewed to determine that fluctuations were consistent with LB disease rather than AD. The difference between controls and MCI-LB Probable in mean CAF and UPDRS scores did not reach significance, but MCI-LB Probable have significantly higher scores on DCFS (p = .006) and NEVHI (p = .004) than controls.

Table 4 Demographics (means, and standard deviations in brackets) of the dementia groups (LBD and AD) and age-matched controls. Note: the 'MCI Post Hoc' column shows the results of analyses comparing the MCI-AD and MCI-LB groups only.

	Controls (n = 31)	MCI-LB Probable (n = 30)	MCI-LB Possible (n = 14)	MCI-AD (n = 18)	All group comparison	MCI-LB Probable vs MCI-AD
Age (years)	73.84 (7.29)	74.73 (7.00)	75.93 (7.34)	76.89 (8.50)	$F(3,89) = 0.72$, $p = .542$	$t(46)=0.95$, $p = .346$
Age range	61-89	60-87	61-87	62-89		
Gender (female, male)	8, 23	7, 23	4, 10	10, 8	$X^2(2) = 6.18$, $p = .045$	$X^2(1) = 5.11$, **$p = .024$**
NART IQ	114.57 (8.27)	106.60 (10.10)	104.71 (10.98)	112.61 (9.00)	$F(3,88) = 5.53$, $p = .002$ Control > MCI-LB Possible, $p = .010$, & MCI-LB Probable, $p = .008$	$t(46)=2.08$, **$p = .043$**
Hoehn and Yahr Stage[1]	All stage 0	18 stage 0, 5 stage 1, 4 stage 2, 1 stage 3, 2 missing	13 stage 0, 1 stage 1	All stage 0		
CDR[2]		0.45 (0.15)	0.50 (0.00)	0.53 (0.12)		$t(45)=1.84$, $p = .072$
UPDRS[3]	5.42 (4.42)	24.37 (15.15)	17.36 (10.13)	16.94 (10.76)	$F(3,89) = 15.75$, $p < .001$ Control < MCI-LB Probable, $p < .001$, MCI-LB Possible, $p = .005$, & MCI-AD, $p = .003$	$t(46)=-1.82$, $p = .076$
IADL[4]		12.32 (3.71)	12.86 (4.66)	12.20 (4.23)		$t(38)=-0.09$, $p = .926$
Fluctuations (%)		66.67%	7.14%	16.7%*		
Visual Hallucinations (%)		16.67%	0%	0%		
Parkinsonism (%)		40%	14.29%	0.0%		
RBD[5] (%)		66.67%	14.29%	0.0%		
Neuroleptic sensitivity (%)		0.0%	0.0%	0.0%		
Abnormal FP-CIT SPECT[6] (%; panel rating)	6.5%	56.67%	35.71%	0.0%		
Abnormal MIBG[7] (%)	6.5%	64.29%	28.57%	0.0%		
Mean total core features	0.00 (0.00)	1.90 (0.84)	0.36 (0.50)	0.17 (0.38)		
Positive biomarkers only (%; MCI-LB only)		0%	64.29%			
ACE-R[8]	92.74 (4.41)	83.20 (8.81)	79.43 (9.78)	83.00 (8.28)	$F(3,89) = 13.61$, **$p < .001$**	$t(46)=-0.08$, $p = .938$

					Controls > MCI-LB Probable, MCI-LB Possible, & MCI-AD, all *p*s < .001	
MMSE[9]	28.42 (1.18)	26.33 (2.62)	26.36 (2.41)	26.78 (1.93)	$F(3,89) = 6.36$, **$p = .001$,** Controls > MCI-LB Probable, $p = .001$, MCI-LB Possible, $p = .013$, & MCI-AD, $p = .042$	$t(46)=0.63$, $p = .535$
GDS[10]	1.32 (1.82)	5.27 (3.91)	3.67 (2.69)	3.56 (3.11)	$F(3,89) = 8.88$, **$p < .001$** Controls < MCI-LB Probable, $p < .001$	$t(46)=-1.58$, $p = .121$
NPI-D[11]		16.04 (12.35)	12.64 (13.83)	14.67 (11.21)	$F(2,51) = 0.34$, $p = .717$	$t(38)=-0.35$, $p = .727$
NEVHI[12]	0.10 (0.54)	3.23 (4.55)	1.54 (2.70)	0.47 (1.33)	$F(3,87) = 6.73$, **$p < .001$** MCI-LB Probable > Controls, $p < .001$	**$t(36.9)=-3.10$, $p = .004$**
CAF[13]		4.26 (4.18)	1.64 (2.27)	2.47 (3.27)		$t(40)=-1.43$, $p = .159$
DCFS[14]		9.07 (3.45)	8.00 (3.49)	6.13 (2.53)		**$t(40)=-2.89$, $p = .006$**

**Participants with only cognitive fluctuations are evaluated for fluctuations consistent with AD in order to obtain a MCI-AD diagnosis.*

1 Hoehn and Yahr Stage = Stages 0 (asymptomatic), 1 (unilateral movement only), 2 (bilateral involvement without impairment of balance), 3 (mild to moderate involvement, some postural instability), 4 (severe disability), 5 (wheelchair or bedridden unless aided).

2 CDR = the Clinical Dementia Rating

3 MDS-UPDRS = Unified Parkinson's Disease Rating Scale (motor subsection) (Postuma et al., 2015)

Geriatric Depression Scale

4 IADL = Instrumental Activities of Daily Living (New Score)

5 RBD = Rapid Eye Movement Sleep Behaviour Disorder

6 FP-CIT SPECT = ^{123}I-N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane (FP-CIT) single-photon emission computed tomography (SPECT)

7 MIBG = metaiodobenzylguanidine

8 ACE-R = Addenbrooke's Cognitive Examination-Revised

9 MMSE = Mini Mental State Examination (Folstein et al., 1975)

10 GDS = Geriatric Depression Scale

11 NPI-D = Neuropsychiatric Inventory (Cummings et al., 1994)

12 NEVHI = North-East Visual Hallucinations Interview

13 CAF = Clinical Assessment of Fluctuations

14 DCFS = the Dementia Cognitive Fluctuation Scale (Lee et al., 2014)

3.4 Discussion

In the present study, 62 patients were recruited based on suspected LB disease and were clinically diagnosed by Old Age Psychiatrists to have MCI following NIA-AA criteria. The MCI-AD and control groups did not show any symptoms or biomarkers suggestive of LB disease, except for two control participants with abnormal MIBG. Those control volunteers had normal clinical presentation, intact cognition and no other evidence of LB disease. All other controls also displayed intact global cognitive scores, in line with normal ageing. Of the 44 MCI-LB diagnosis, 30 were found to have two or more core clinical symptoms of DLB or one core symptoms and on positive biomarker. About one third of the MCI-LB Probable group only displayed one of the four clinical features of DLB used in diagnosis. Thus, these participants would have been only given a Possible MCI-LB diagnosis without the use of biomarkers to aid diagnosis. Clinical diagnosis of even advanced DLB is often challenging: even with the expertise of specialised clinicians, the core symptoms are problematic to assess. Both visual hallucinations and parkinsonism are observed in other neurologic and psychiatric conditions, and may be subtle in early manifestations (Walker & Walker, 2009). Fluctuations, for example, can occur over the course of minutes, hours, or much longer periods that may not be reliably detected during clinical assessment or through informant report (McKeith, 2007). My findings therefore emphasize the importance of the addition of biomarkers to the most recent consensus guidelines (McKeith et al., 2017).

Demographically, the results are generally in line with expectations for the subgroups. Subgroups did not differ significantly in age or measures of self-reported depression. All MCI subtypes show worse motor impairment as measured by UPDRS than controls. UPDRS has previously been demonstrated to measure motor impairment severity independent of cognitive function (Ballard et al., 1997). As such, future chapters will consider how psychomotor function contributes to performance on cognitive tasks between groups. Motor function using UPDRS will be considered alongside scores on tasks that are particularly motor-dependent. UPDRS scores did not differ significantly between MCI-AD and MCI-LB, but the raw difference is quite high. This lack of significance is likely attributable to low powering due to the small number of MCI-AD participants and the non-specific contribution to UPDRS rating scores associated with ageing and age-related diseases.

High estimates of premorbid IQ were demonstrated in both controls and MCI-AD, relative to the MCI-LB groups, however. This is unsurprising as often healthy

control groups consist of individuals engaged with research and familiar with university settings, thus making it likely that they are more highly educated. The NART was originally standardized based on data from individuals 20 to 70 years of age (Nelson & Willison, 1991). Although reading ability is thought to be largely stable (Nelson & Willison, 1991), it is possible the older age of the patient groups partly explains the low scores. We also found a predominance of men in the clinically diagnosed MCI-LB groups. Previous meta-analyses (Vann Jones & O'Brien, 2014) and epidemiological studies (Savica et al., 2013; Yue et al., 2016) have not reported DLB to be more prevalent among men. However, Kane et al. (2018), in a clinical study analysis using a large sample size (*n* = 4,504 dementia diagnoses) and two service locations, did find a significant association between male gender and DLB prevalence. This has also been demonstrated in neuropathological work (Klatka, Louis, & Schiffer, 1996).

In conclusion, the SUPErB study has created four groups based on clinical diagnoses with the aid of biomarkers. The control group's global cognitive, clinical and biomarker profiles are in line with expectations of normal healthy ageing. In the subsequent chapters, their data will be useful in comparing MCI patients' performance on neuropsychological tasks. The MCI subtypes show equivalence on demographic factors such as age and activities of living that might confound neuropsychological interpretation. However, differences in estimates of intelligence and gender distribution between groups warrant further consideration.

Chapter Four: Neuropsychological profile of MCI-LB in the SUPErB study

4.1 Introduction

Review of the literature suggests that despite similar global cognitive capacity, MCI-AD and MCI-LB display different neuropsychological profiles. It is unclear, however, whether the groups can be reliably discriminated or if the most salient impairments of the advanced dementia stage are manifest at this MCI stage. For example, only eleven of the extracted outcome variables in MCI-LB showed significant difference from MCI-AD after bias-correction. Donaghy, Taylor, et al. (2018) conducted a post-hoc discriminant analysis of the four variables that were significantly different between MCI-LB and MCI-AD (ACE-R fluency and visuospatial, digit vigilance time and angle task result). The low sensitivity (64%) and specificity of (68%) led the authors to conclude that "the heterogeneity of cognitive impairment observed in MCI-LB and MCI-AD was reflected in the poor discriminant ability... Thus, though a pattern of prominent executive and visuospatial dysfunction is supportive of a diagnosis of MCI-LB it is not sufficient to warrant a diagnosis of MCI-LB in isolation" (p. 5). The importance of clinical assessment, over neuropsychological evaluation, in MCI-LB diagnosis is therefore stressed. However, neuropsychological measurement remains a critical tool in neurodegeneration research and clinical practice (Smith & Bondi, 2013). The inclusion of HCs and more nuanced cognitive modelling may advance the predictive ability of neuropsychological testing.

4.2 Methods

Materials

The study aims to firstly clarify the broad neuropsychological profile of the emergent diagnostic category of MCI-LB, as well as MCI-AD, using a battery of standard tasks. More experimental tasks are also utilized and are mostly addressed in chapters 5 and 6. The present chapter presents the battery of individual tasks that will be compared between groups. In chapter 4, these tasks will be used to create data-driven composite scores using principal components analysis (PCA) for use in MRI analyses and hierarchical linear modelling in order to consider the mediating role of domain-general resources like processing speed and executive function. The tasks are described below, organized by the domain they are intended to target (Table 5): visuospatial, executive function, verbal memory, psychomotor speed and working

Table 5 Tasks administered in SUPErB, organized a priori by domain.

Domain	Tasks
Global Cognitive Measure	Addenbrooke's Cognitive Examination-Revised (ACE-R) Mini-Mental State Examination (MMSE)
Visuospatial	Corsi blocks Visual Patterns Task Modified Taylor Complex Figure (MTCF) Pareidolia Test
Verbal Learning and Memory	Rey Auditory Verbal Learning (Rey, 1964): Graded Naming Test
Executive Function	Trail Making Task B Digit Span backwards Stroop C-W Verbal Fluency (FAS)
Processing Speed	DSST Symbol Copy Error Check Trail Making Task A Simple reaction time Choice reaction time
Working Memory Capacity	Digit Span forward

memory capacity. In addition to the global cognitive measures (ACE-R and MMSE, discussed in Chapter Two), fifteen other neuropsychological tasks were administered (eight pen and paper, three computerized). Two additional computerised, experimental tasks (Continual Performance Test and Metacognition Test) were administered and are discussed in later chapters.

Visuospatial function

Corsi Blocks

This touchscreen, computerised version of the classic Corsi blocks task (Corsi, 1972) quantifies the capacity of spatial sequential working memory. Participants must mimic the order in which some of blue squares presented on the screen are illuminated. The task ends after three consecutive trial failures.

Visual Patterns Task (VPT; Della Sala , Gray, Baddeley & Wilson, 1997)

This computerised adaptation of the task developed by Della Sala et al. (1997) presents participants with a square matrix pattern in which some of the cells are filled in black for 2000ms. This stimuli matrix is then removed (3000ms interstimulus interval [ISI]) and participants must reproduce the pattern in a blank grid of the same size by clicking on the squares that were black using a standard external mouse.

There is no time limit to respond and responses can be changed until the participant clicks the “enter” key and moves onto the next stimulus.

Stimuli begin as a 2x2 matrix with 2 black squares (targets), increasing to 3x2 (3 targets), 3x3 (4 targets), 4x3 (5 and 6 targets), 4x4 (7 and 8 targets), 5x4 (9 and 10 targets), 5x5 (11 and 12 targets), and 6x5 (13, 14 and 15 targets). There are three stimuli in the 2- and 3-target levels. Beginning at 4 targets, 6 stimuli are presented, 3 that are “high verbal coding” and 3 that are “low verbal coding” conditions. Brown, Forbes, and McConnell (2006) explicitly acknowledged the possibility of verbal coding within the VPT and separated the stimuli into subsets of High and Low verbalization patterns. A subset of these two sets of stimuli are used within this task. In the few cases in which participants did not feel comfortable using the external computer mouse to complete this task, they were instructed to touch the squares on the screen to indicate their selections. The author then used the mouse to match their touch responses and verbally confirmed that it was as they desired before moving on. Necessity of this approach was recorded and analysed for potential confounding effects. The VPT intends to capture short-term static visual memory, without the spatio-sequential demands of tests like Corsi blocks.

Modified Taylor Complex Figure (MTCF)

The MTCF was completed by only 82 participants as it was added to the testing battery after testing had begun. Time taken to complete the copy and recall conditions were recorded for 49 and 43 participants respectively. A second rater (Calum Hamilton) marked 19 participants’ drawings, blind to diagnostic group, to confirm reliability of the rating scales. Intra-class correlation coefficients were acceptable for both copy (0.96) and recall (0.95) conditions. The MTCF was used in the present study as it has previously been shown to be comparable to the more-commonly used ROCF in terms of resistance to verbal encoding and accuracy in assessing visuospatial memory (Hubley & Tremblay, 2002); moreover, the MTCF may be easier to copy for older adults (Hubley, 2010). This was deemed appropriate to avoid fatigue or floor effects in a population of mildly cognitively impaired older adults.

Pareidolia Task

This is a 40-item neuropsychological test which evokes and measures visual illusions similar to visual hallucinations observed in patients with dementia with Lewy

bodies and Parkinson's disease (Yokoi et al., 2014). Participants are asked to report whether a face is visible within the images, after completing three practice trials. Within the set of forty images, eight contain faces. Participants are scored on the number of correct answers, misses and false alarms (pareidolias). Example stimuli with and without a face are shown in Figure 3.

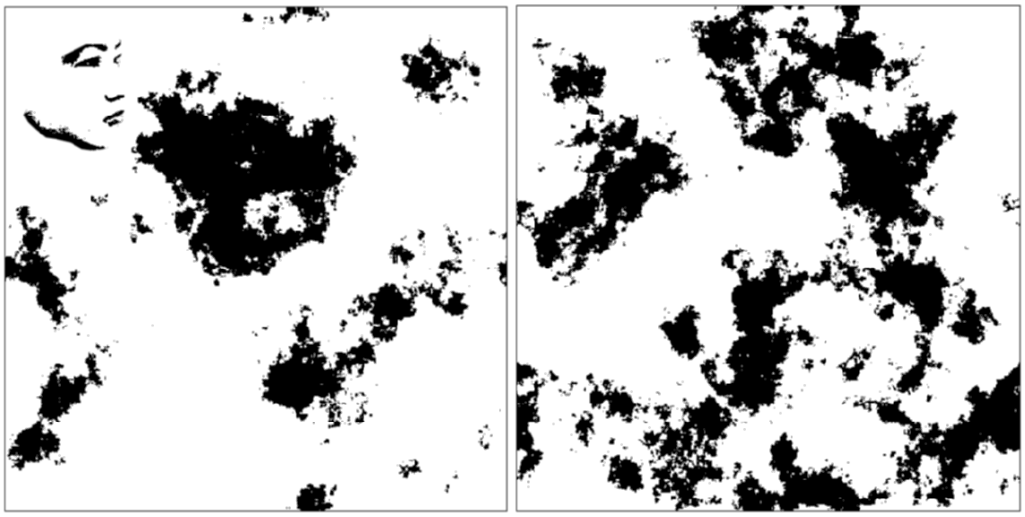

Figure 3 Pareidolia test example stimuli with a face present (L) and absent (R).

Verbal Learning and Memory

Graded Naming Test

A measure of semantic memory in which participants must name 30 black and white drawings. Participants may take their time to answer and proceed and return to previous items. In cases of certain incorrect responses, the experimenter offered verbal responses or pointed when appropriate to reorient the participant.

RAVLT (Rey, 1964)

A test of verbal learning with two lists of 15 words presented verbally across 7 trials. Memory of list A is evaluated with both immediate (5 consecutive trials), short-term delayed recall, and longer-term (approximately 20 minutes) delayed recall. List B is presented immediately recalled once. Following the longer delay condition, recognition of the two lists and distractor words follow. Because the most delayed recall condition is dependent on how well List A was first learned, the percentage recalled of the maximum score from the first five conditions is calculated. Retroactive interference is calculated by subtracting the fifth trial of list A (T5) from the short delay (T6) score, quantifying how subsequent learning impairs recall of previously-learned

target material (Postman & Underwood, 1973). Proactive interference is calculated by subtracting the first A trial (T1) from the first/ only B trial (B) and thus represents the detriment due to prior learning in recalling "subsequently presented target material (Postman & Underwood, 1973)." Interference scores thus involve an executive component that will be discussed further. Due to the number of potential

Table 6 RAVLT outcome measures and descriptions.

RAVLT Outcome Measure	Description
Max T1:T5	The sum of scores from first five free recall trials (Trials 1 to 5)/ "learning - episodic memory"
"Learning"	The score of Trial 5 minus the score of Trial 1
Short Delay	Number of words freely recalled from list A after presentation of list B.
Long Delay	Number of words freely recalled 25 minutes after Short Delay recall trial.
Percent Remembered at Long Delay (from max T1:T5)	The percentage of a participant's maximum words recalled in trials 1 to 5 that are remembered at the Long Delay free recall trial. ([Long Delay/ Max T1:T5]*100)
Retroactive Interference (T6-T5)	The difference between the number of List A words freely recalled at Short Delay and trial 5.
Proactive Interference (B-T1)*	The difference between the number of List B words freely recalled minus the number of List A words recalled at trial 1.
Recognition False B*	The number of List B words falsely identified as being from List A in the delayed recognition trial.

outcome variables of the RAVLT, the ones that will be analysed in the present study are presented in Table 6.

Executive Function

Trail Making Task B (Trails B)

Trails B is a pen and paper task that assesses both attention and task switching. In Trails B, there are both numbers and consecutive letters presented within circles arranged on a page, unlike Trails A which includes only numbers. Participants must draw a line between the circles in ascending order, alternating between number and letter. The researcher interrupts in cases of mistakes and directs the participant to continue from the last correct circle. Time to completion is scored and interference scores are also calculated. Interference is frequently reported using Ratio (Trails B/ Trails A) or Difference (Trails B-Trails A) (Arbuthnott & Frank, 2000; Giovagnoli et al., 1996). The Ratio interference score has been argued to be a more accurate assessment of executive function impairment. For example, a ratio score greater than 3 was associated set-switching impairment, but Difference was not (Arbuthnott and

Frank, 2000). Typically, Trails B administration is meant to be curtailed if the participant takes longer than five minutes to complete. The present study allowed participants to take as long as was needed, and use of a ratio or difference interference score allows quantification of executive function impairment even in very slow completers.

Digit Span backwards

Digit span is a measure of working memory that requires participants to recall strings of verbally-presented digits both forwards and backwards. In the backwards condition, the lowest level is two numbers up to 8 numbers. The maximum scores are 14 for each condition (forwards and backwards) and a cumulative maximum of 28. The test ends when the participant does not correctly answer at least one of the two stimuli for a level. In cognitive models, the backwards condition places greater demands on the central executive or executive function than digit span forwards, which is a more pure measure of phonological loop capacity.

Verbal Fluency (FAS)

Participants are asked to generate as many unique words as possible beginning with F, A and S within sixty seconds. They are instructed to avoid proper nouns. Running totals were taken every fifteen seconds and a total score computed.

Stroop Test

This test consisted of two conditions: colour (C) and colour-word (CW). Both use a one-page piece of paper with columns of block-letter words: BLUE, GREEN, RED and BROWN. The font is coloured so that each word has an incongruous colour font (RED in green ink, for example). In C, participants must go down the column reading allowed the printed words as quickly as possible. In CW, the written word must be ignored and the colour of the ink said aloud. CW thus requires the participant to inhibit the reading of the word and attend to the colour ink. Following the method of Golden (1978), participants are given 45 seconds to complete each version as quickly as possible. The number of correct words or colours is recorded. Interference scores are also calculated, in various ways. In the present study, two methods were used. Firstly, the classical method subtracts the CW from the C score (C-CW; Hammes, 1978). Secondly, a ratio interference effect is calculated to correct for colour-naming speed (C-CW/C).

Processing speed

Digit Symbol Substitution Test (DSST)

DSST is a pen and paper task in which participants reference a number-symbol key to write the correct symbol below a list of 96 randomly ordered numbers presented in a grid as quickly as possible within 90 seconds. The number of correct symbols drawn is recorded. A Coding time variable is be derived as the time per item in completing the DSST-original (90 seconds) minus the time per item in Symbol Copy (90 seconds), reversed so that a higher score indicates a faster mental coding speed. Early work by Salthouse (1992) demonstrated that controlling for performance on a simple speed test removed 95% of the age-related variance in DSST. However, the DSST clearly necessitates other resources including graphomotor and perceptual speed, as well as potential executive function and memory components (Joy, Kaplan, & Fein, 2004; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2006).

Symbol Copy

An adaptation of DSST, Symbol Copy, was first included on the Weschler Intelligence Scales (WAIS)-RI (Kaplan, Fein, Morris, & Delis, 1991). Participants must simply copy each symbol in the grid into an empty box directly below it as fast as possible in 90 seconds. The test intends to isolate DSST's graphomotor component (Joy, Fein, Kaplan, & Freedman, 2000). A small meta-analysis by Joy and Fein (2001) reported that Symbol Copy, like DSST, has a strong negative relationship with age that becomes significantly stronger beginning at age 50.

Error Check

Another DSST variant, Error Check was first developed by Joy et al. (2000) to capture the coding processes involved in DSST without graphomotor demands. Error Check involves scanning a completed DSST for errors in relation to the key above and marking any with a pencil slash as quickly as possible in 90 seconds.

Trail Making Task A

Participants must draw lines between 25 numbered circles in ascending order as quickly as possible without making a mistake. Time to completion is scored.

Simple and Choice reaction time (SRT and CRT, respectively)

These two computerised tests measure speed of reaction to a stimuli. In SRT, the participant must depress an external, handheld button as quickly as possible upon presentation of a white X on a black screen. In CRT, the white stimulus presented is an arrow pointing either to the left of the right. The participant holds one external button in each hand and must depress the correct button (left if arrow points left, for example) as quickly as possible. The inter-stimulus interval in both tasks varies and the stimulus disappears upon button press. Each task lasts about 150 seconds total. Mean reaction time is calculated as the primary outcome measure. In CRT, only the reaction times of the correct button presses are included. Participants receive training on use of the response module. If physical limitations or discomfort made use of the external buttons impossible, the test was discontinued to avoid participant distress and the influence of motor disability on test performance. These two tasks are addressed in more detail in chapter five.

Working memory capacity

Digit Span forward

In the forward condition of Digit Span, two sets of between three and nine digits are read aloud to participants. Each level (3 digits, 4 digits, so on) scores 0, 1 or 2 points depending on how many of the two sets were correctly recalled by the participant. As with Digit Span backwards, the test ends when the participant does not correctly recall at least one of each span level.

Treatment of data

Data was analysed using the Statistical Package for the Social Sciences, V. 21 (SPSS , IBM Corp, 2013). Variables (in this and subsequent chapters) were assessed for outliers and normality. Data exceeding Z=+/- 3.0 were considered for potential exclusion. Outliers can have substantial (Osborne & Overbay, 2004), deleterious effects on statistical analyses by increasing error variance and reducing statistical power. Multivariate analyses (performed in Chapters 6-9) also require that assumptions of sphericity and normality be met, and outliers can problematize such assumptions if they are not distributed randomly (Osborne, 2012). Transformations and removal of outliers remains debated in statistical literature, but conscientious data cleaning is generally assumed to improve generalizability of results (Osborne,

2012). In the case of mean differences between groups (*t*-tests and analysis of variance [ANOVAS]), Osborne (2012) demonstrates tendency for increased accuracy with removal of extreme scores and little evidence that Type I error risk increases. As only 1% of subjects should be 3 or more SDs from the mean, this initial screen prior to visual inspection is a useful means of identifying potential outliers (Osborne & Overbay, 2004).

Normality was assessed firstly visually through the use of histograms and secondly using measures of skewness and kurtosis in questionable instances, following suggestions from Osborne (2012). In cases of relative normality to the distribution (through visual inspection), 6 data observations above or below 3.0 SDs were removed. As suggested by Tabachnick and Fidell (2007) and Howell (2007), moderate skewness was adjusted using square root transformations and substantial skewness with Logarithmic base 10 transformation. In both cases, negative skews required use of a constant, square root of (K-X) for example. Transformations were performed on 12 variables, as shown in Appendix D, to achieve acceptable skew and kurtosis values. Other variables were reversed as appropriate so that increasing scores always indicate better performance. Neuropsychological outcome measures are limited to variables representative of the constructs and suitable to the target population in order to facilitate meaningful interpretation and remove redundancy.

Given that MCI-LB is an emergent diagnostic category, neuropsychological data was firstly measured by individual outcome measure, presented below by domain. Univariate independent-samples *t*-tests were run between MCI-LB Probable and MCI-AD, the primary comparison of interest, to determine differences in neuropsychological function. One-way ANOVAs were then run between all four participant groups (controls, MCI-AD, MCI-LB Probable and MCI-LB Possible) to evaluate cognitive profile of MCI groups relative to controls. The MCI groups did not differ by age, but did differ by gender and NART IQ. However, analysis of covariance (ANCOVA) was not utilized in order to retain statistical power. Moreover, use of ANCOVA should be limited to situations in which the intrinsic properties of the population do not include the potential covariate (Miller & Chapman, 2001). That is, group allocation is not purely random and may be associated with greater likelihood of male gender and low education level in the case of MCI-LB. Forest plots were constructed to visually demonstrate the cognitive profile of MCI-AD and MCI-LB Probable relative to controls. The direction of effect sizes was reversed as appropriate to reflect deficits as negative effect size, for example number of errors.

Data was entered into an Excel effect size calculator that is freely distributed online by the Centre for Evaluation and Monitoring (CEM; Coe, R, retrieved from http://www.cem.org/effect-size-calculator). The calculator produces a bias-corrected ES and 95% confidence interval to estimate the difference between the two means in terms of the pooled estimate of SD. It is bias-corrected based on a factor provided by Hedges and Olkin (1985). Effect sizes and confidence intervals were plotted by domain (verbal learning and memory, visuospatial learning and memory, working memory, and executive function) and organized highest to lowest effect size for MCI-LB Probable versus controls. Separate graphs were constructed for closer comparison of performance by domain.

Percentiles

The present study aimed to quantify the magnitude of difference between MCI groups and controls while recognizing that inter-individual variation in performance can be great. Thus, performance is presented in terms of effect sizes and significance testing as well as percentile standing based on the control data. Data from the control group was used to generate percentile ranking and percentage of each MCI group scoring at or below the 5th and 16th percentiles, which capture scores 1.5 and 1.0 *SD*s below control means, respectively. These two cut-offs are often used in psychometric criteria for MCI, and performance below the 5th percentile of controls has been considered by both clinicians and researchers as a clinically significant level of cognitive impairment, indicating unusually low scores (Gauthier et al., 2006; Litvan et al., 2012; Porter et al., 2006). Following recommendations of Crawford, Garthwaite, and Slick (2009), the percentage of scores that fall below the score of interest includes half of those obtaining the precise cut-off score.

Stepwise discrimination analysis

Following means significance testing of each individual task outcome measure, any variables showing significant differences between MCI-AD and MCI-LB probable will be entered into a stepwise discrimination analysis to determine the maximal differentiation between groups. Firstly, these tasks would be used to predict group membership including controls and, secondly, only with the MCI participants. The first analysis allows us to understand how the groups cluster within the overall neuropsychological space of the battery. The second is based on a more clinical/

applied perspective to consider whether and how MCI-LB Probable can be separated from MCI-AD based on neuropsychological scores.

Discriminant analysis is similar to regression analysis by creating a model that predicts group membership (control, MCI-LB [probable or probable and possible], MCI-AD) based on linear combinations of the predictors. A stepwise approach retains the variables that maximally separate the groups and discards variables which do not provide the best discrimination between groups in a step-by-step process. At each step, the variable that would best discriminant the groups is added and each is re-evaluated with each subsequent addition. In SPSS, the model starts without any predictors and then iteratively adds the predictor with the largest F to Enter value above a minimum threshold (3.84; value for removal 2.71 or lower). The final model provides two or more functions. The first function is the most powerful "differentiating dimension" and "maximizes the difference between the values of the dependent variable. The second function maximizes the difference between the values of the dependent variable while controlling the first function. A weighted discriminant score is then calculated from the two or more functions for each participant that determines which group they should be assigned based on the model. Centroids are computed that are the mean discriminant score for each group. The model is evaluated on the null hypothesis that the centroids of the groups are equal, and this can be graphically represented. Prior to running the discriminant analysis, variables are re-checked for outliers and Shapiro-Wilk test is used to test assumption of normality.

4.3 Results

4.3.1 Neuropsychological results by theoretical domain

All four groups were compared on task-level performance. The results of each task outcome measure are summarised below by cognitive domain. Descriptive statistics and between-group comparisons can be found in Appendix E.

Verbal Learning and Memory

As expected in the verbal domain, at least one MCI group performed more poorly than controls on every outcome variable except for RAVLT Proactive interference and the Graded Naming Test. MCI-AD performed significantly worse than MCI-LB Probable on short-term free recall on the RAVLT, with a medium effect size (*g* = 0.60). At the long delay recall (25 minutes), the two MCI subgroups did not

differ significantly. However, if quantified as the percentage recalled from their maximum during the learning period, MCI-AD participants recalled significantly fewer of at the long delay (*M*=38.23%, *SD*=35.67%) than MCI-LB (*M*=65.02%, *SD*=37.61%), to a large effect size (*g* = 0.73). The percentage recalled by MCI-LB Probable did not differ significantly from controls (*M*=71.59%, *SD*=19.52%). Retroactive interference (A6-A5) scores also differed significantly between MCI-AD (*M*=-3.72, *SD*=1.90*)* and MCI-LB Probable (*M*=-2.13, *SD*=2.60), *t*(46)=-2.25, *p* = .029, *g* = 0.70, and MCI-AD's poorer performance versus controls was on trend, *p* =.056. Retroactive interference indicates recall at first presentation of a second list is impaired following the task of recalling the first list. MCI-LB Probable or Possible and MCI-AD performed significantly worse than controls on 6 of the 10 tasks. Statistically, homogeneity of variances was not confirmed for ACE Language or RAVLT Percent Remember at Long Delay, suggesting the significant results on these tasks must be interpreted cautiously.

Visuospatial Learning and Memory

In the visuospatial domain, MCI-LB Probable (*M*=8.08, *SD*=3.59) scored significantly worse on VPT High than MCI-AD (*M*=10.80, *SD*=2.93), *p*=.019, and controls (*M*=13.38, *SD*=3.26), *p*<.001. However, the effect size of this difference is small *(g* = 0.28). In the Low condition of the VPT, the difference between MCI-LB Probable and MCI-AD was on trend (*p*=.065). MCI-LB possible versus controls did reach significance (*p* = .043), with MCI-LB Possible scoring significantly lower on the VPT Low semantic condition (*M*=4.83, *SD*=2.69) than MCI-AD (*M*=8.13, *SD*=2.64). The MCI-LB Probable group also performed worse on the Pareidolia task outcome measures with a large effect size (*g* = 0.79); however, these variables are severely skewed in their distribution with notable ceiling/ floor effects (depending on the variable). Attempts at transformation were unsuccessful. As such, results of the comparisons are problematic to interpret. This test's format is likely more suitable to categorical cut-offs based on performance. The six other measures of visuospatial ability did not reveal differences between MCI-LB and MCI-AD. MCI-LB Probable or Possible performed significantly worse than controls on all of the ten measures. In contrast, MCI-AD was only significantly worse than controls on three variables (MTCF Recall, MTCF Percent Recall and VPT High). As in the verbal domain, several variables did not meet homogeneity of variance assumption (ACE Visuospatial, VPT Ratio, Pareidolia, MTCF Copy).

Executive function and working memory

In the executive domain, two tasks showed significant differences between MCI-AD and MCI-LB. Firstly, MCI-LB Probable produced significant fewer words in FAS (*M*=30.10, *SD*=15.47) than both MCI-AD (*M*=39.89, *SD*=12.22, *p*=.027) and controls (*M*=43.77, *SD*=9.84, *p*<.001). The significant difference between MCI-LB Probable and MCI-AD was large (*g* = 0.70). Secondly, MCI-LB has significantly lower Stroop interference scores using the classical formula (C-CW; Hammes, 1971) with the largest effect size of all of the neuropsychological comparisons (*g* = 1.20). However, when Ratio approach is used, which corrects for speed of reading, the effect disappears. The other seven outcome measures did not show a significant difference between MCI-LB Probable and MCI-AD. In comparison to controls, MCI-LB Probable scored significantly lower on all variables except for Stroop Classical Interference and Digit Span Forwards (*p*s>.05), the latter of which is a working memory capacity task. MCI-AD scores were significantly lower than controls on three of the ten variables (Stroop CW, Stroop Ratio Interference, and Trails B). Homogeneity was not met via Levene's statistic (<.05) by FAS, Trails B and Trails Difference.

Processing Speed

MCI-LB Probable performed significantly worse than MCI-AD on three of the seven processing speed measures, all related to the DSST and all with large effect sizes: DSST (*p*=.011, *g* = 0.83), Error Check (*p*=.002, *g* =1.09), and DSST Coding Time (*p*=.013, *g* = 0.83). Relative to controls, MCI-LB performance was significantly slower on all tasks, while MCI-AD was only impaired on three (DSST, Symbol Copy and DSST Coding Time). Performance on Stroop was also poorer in MCI-LB Probable than MCI-AD in the C (word) condition, *p*=.015, with a large effect size (0.94). Homogeneity of variance was not met by Trails A or SRT, neither of which showed significant differences between MCI-AD and MCI-LB Probable.

MCI-LB Possible comparisons

In several instances the difference in mean performance between MCI-LB Possible and controls was significant while it was not for MCI-LB probable and controls. For example, MCI-LB Possible scored significantly lower than controls on ACE Language, *p* = .002 (controls versus MCI-LB Probable on trend, *p* = .080),

RAVLT Percent Recalled at Long delay, p = .024 (controls versus MCI-LB Probable, p .847, significant difference with MCI-AD t-test), and MTCF % Retained, p = .005 (controls versus s, p = .118; MCI-AD also lower scores than controls, p = .004).

4.3.2 Forest plots of effect sizes: MCI-LB Probable and MCI-AD

The primary comparison of interest in the present chapter is between MCI-AD and MCI-LB Probable, a diagnostic category with at least two clinical symptoms or biomarkers indicative of Lewy body disease, and thus more likely to be associated with LB disease than MCI-LB Possible, which requires only one symptom or biomarker for diagnosis. Forest plots of the effect sizes of comparisons of MCI-LB Probable and MCI-AD with controls are presented in figures 4-7 on the following pages. In the verbal domain, MCI-AD's prominent memory impairments relative to controls are clearly shown by the consistently large effect sizes. MCI-LB Probable versus controls is less consistently significant in the verbal domain, and significant differences are rarely more severe than one SD below controls. In contrast, the processing speed domain shows a predominance of deficits in MCI-LB, with very large effect sizes. DSST reveals the largest impairment in MCI-LB relative to controls in any of the domains (g = -1.99). While processing speed and verbal learning and memory show clear divergence between groups, the visuospatial and executive function domain profiles are less clear. In visuospatial, there is clear divergence on pariedolias, with a large effect size in MCI-LB Probable and a nonsignificant comparison with MCI-AD relative to controls; however, this interpretation is limited by the severe ceiling effects of the variable. MCI-AD appears often similarly impaired to MCI-LB Probable, for example in MTCF, Trails and Digit Span Backwards.

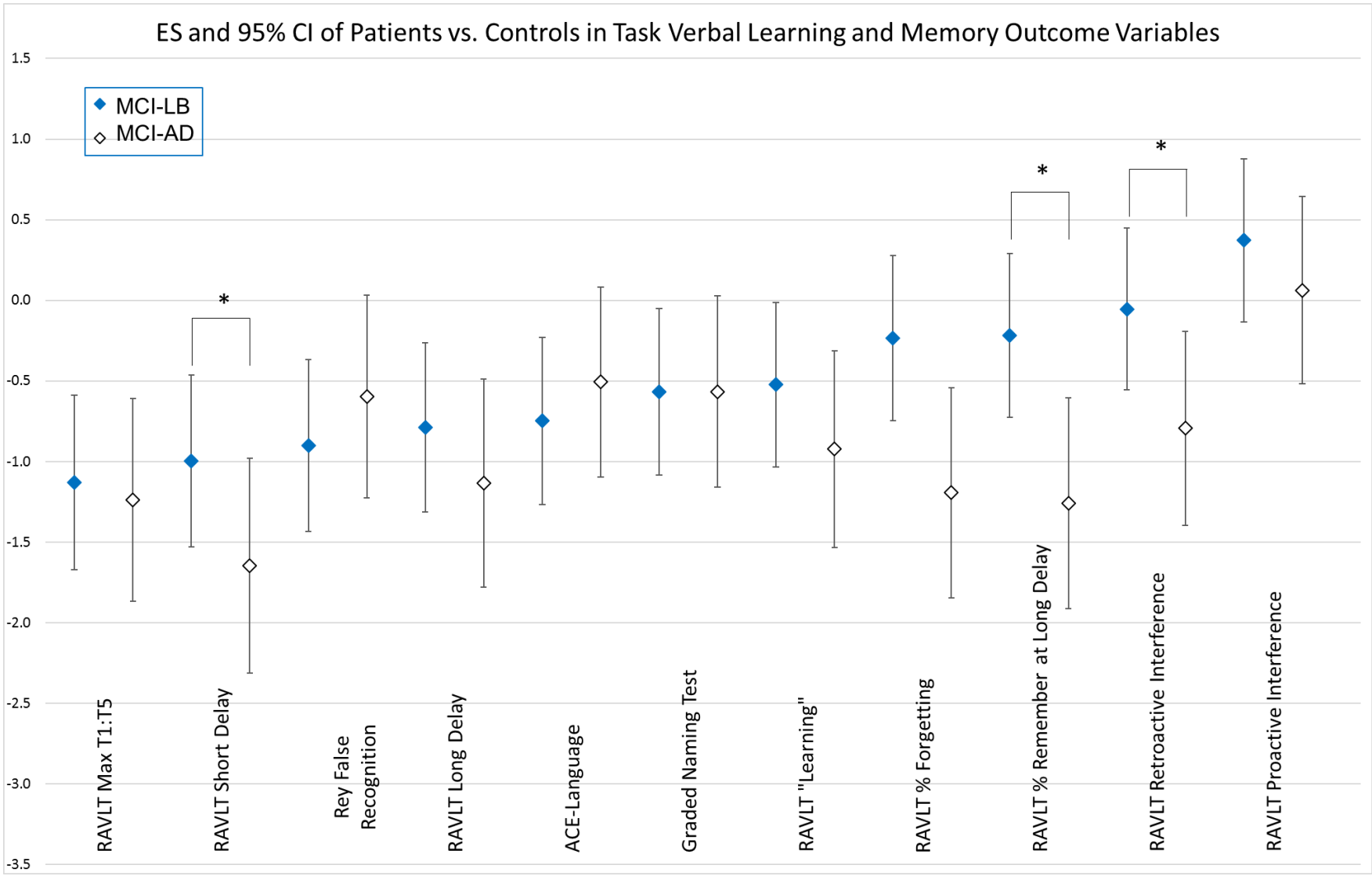

Figure 4 Bias-corrected effect sizes and confidence intervals of the difference in scores by MCI subtypes (MCI with Lewy bodies and MCI with Alzheimer's disease) versus controls on tasks targeting the verbal domain. Asterisks (*) indicate significance at the p < .05 level.

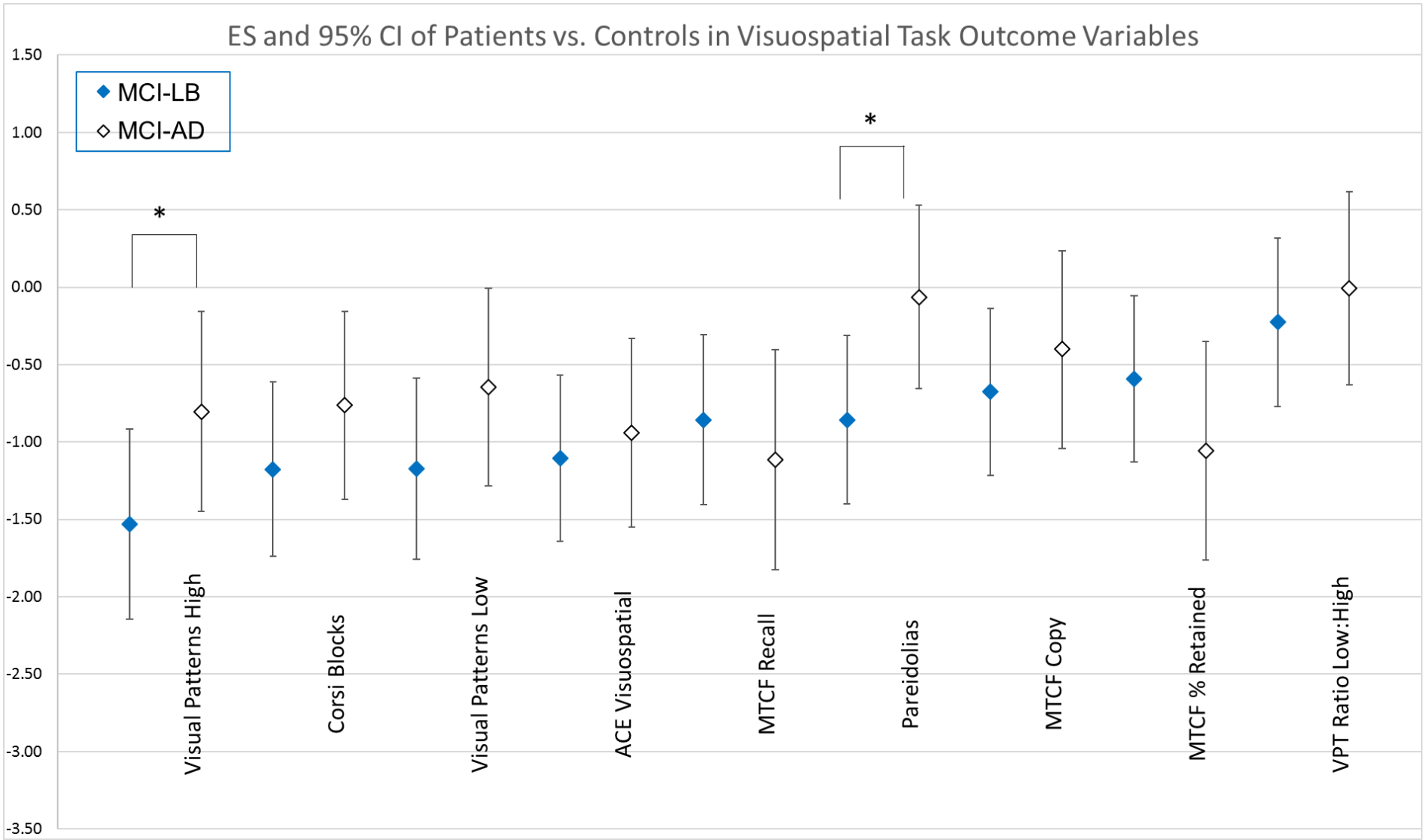

Figure 5 Bias-corrected effect sizes and confidence intervals of the difference in scores by MCI subtypes (MCI with Lewy bodies and MCI with Alzheimer's disease) versus controls on tasks targeting the visuospatial domain. Asterisks (*) indicate significance at the p < .05 level.

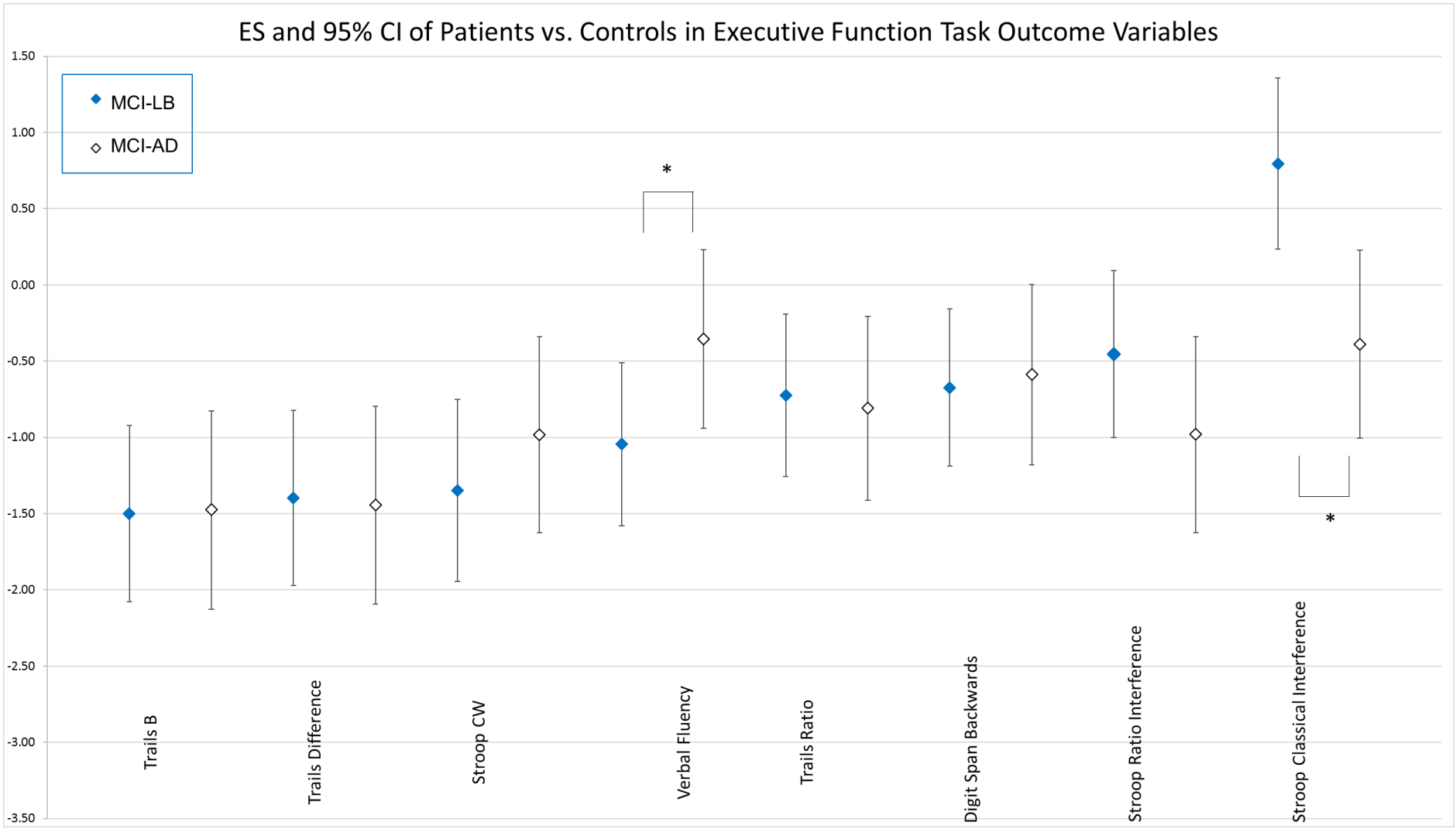

Figure 6 Bias-corrected effect sizes and confidence intervals of the difference in scores by MCI subtypes (MCI with Lewy bodies and MCI with Alzheimer's disease) versus controls on tasks targeting the executive function. Asterisks (*) indicate significance at the p < .05 level.

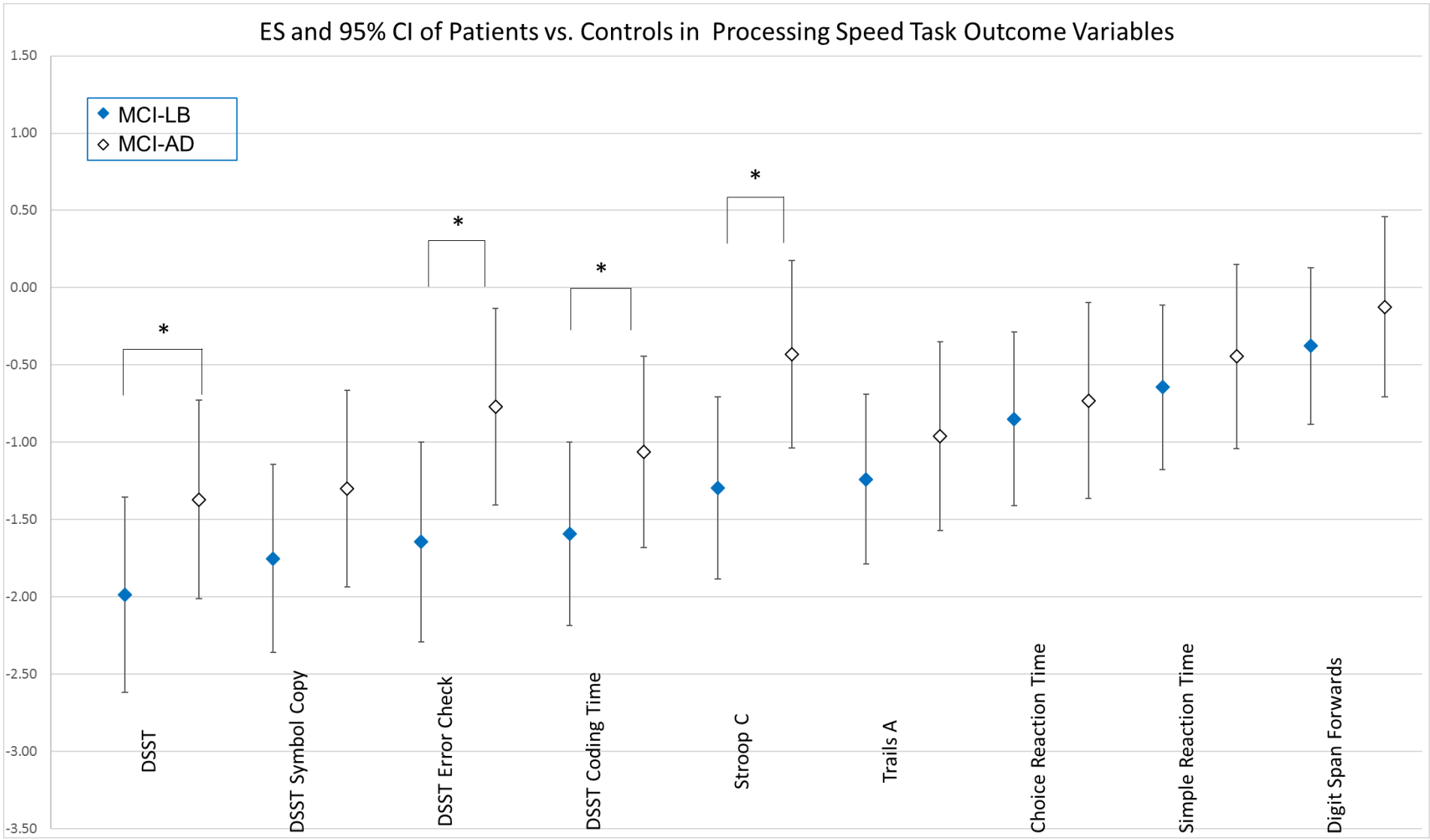

Figure 7 Bias-corrected effect sizes and confidence intervals of the difference in scores by MCI subtypes (MCI with Lewy bodies and MCI with Alzheimer's disease) versus controls on tasks quantifying processing speed. Asterisks (*) indicate significance at the p < .05 level.

4.3.3 Percentiles

Tables 7 and 8 show neuropsychological outcome measures expressed as the percentage of the patient group (MCI-LB Probable and MCI-AD) performing at or below the 5th and 16th percentile cut-off scores, calculated using the control data as reference.

For the tests reported, almost all produced at least one outcome measure on which about 25–60% of the MCI-AD patient sample performed at or below 1 S.D. of controls (16th percentile). Particularly high proportion of MCI-AD were impaired at the 16th percentile level on RAVLT Short Delay (77.8%) and MTCF Percent Retained (75.0%). In contrast, only 38.5% of MCI-LB Probable was impaired at this level relative to controls. At the 5th percentile level, percentages of MCI-AD impaired were lower (5-33%), but particularly high proportions are observed in RAVLT Max T1:T5 (61.1%) and RAVLT Short Delay (66.7%), RAVLT Long Delay (50.0%), and RAVLT Percent Remembered at Long Delay (50.0%).

In the MCI-LB Probable group, particularly high proportions perform at or below the 16th percentile on processing speed measures (85.7% on Trails B, 81.5% on Trails Difference, 92.6% DSST, and 81.5% on Symbol Copy and Coding Time). In the visuospatial domain, 75.0% of MCI-LB Probable were at the 16th percentile on VPT High, but other tasks in this domain were considerably more modest (58.3% or lower). Smaller proportions of MCI-LB Probable were at the 5th percentile in the verbal domain (3.3-40.0%) and tasks such as Graded Naming Test (3.5%), Digit Span Forwards (3.3%) and Backwards (0.0%), MTCF Percent Retained (3.9%).

Substantial differences emerge in certain tasks by percentile. At the 5th percentile of controls, 50.0% of MCI-AD are impaired on RAVLT Long Delay versus only 20.7% of MCI-LB Probable. False recognition of List B also differs greatly, with only 3.5% of MCI-LB Probable impaired and 20.0% of MCI-AD impaired. In visuospatial tasks, much higher percentages of MCI-LB Probable versus MCI-AD occur at the 5th percentile on ACE Visuospatial (35.0% versus 13.9%), MTCF Copy (30.8% versus 14.3%), VPT High (66.7% versus 20.0%), VPT Low (43.8% versus 10.0%), VPT Ratio (29.2% versus 6.7%), and Pareidolias (34.6% versus 0.0%). Verbal fluency (FAS), which differs significantly between groups, have 46.7% of MCI-LB performing at or below the 5th percentile of controls in contrast to only 11.8% in MCI-AD. However, on MTCF Recall, almost half of MCI-AD are at the 5th percentile or lower than controls, and only 15.4% of MCI-LB Probable performing this poorly.

Table 7 5th percentile standing of MCI-Probable and MCI-AD patients (% of group).

	MCI-LB Probable	MCI-AD
ACE-R Total	53.3	55.6
MMSE	46.7	33.3
ACE-Language	26.7	16.7
RAVLT		
Max T1:T5	33.3	61.1
"Learning"	16.7	27.8
Short Delay	40.0	66.7
Long Delay	20.7	50.0
Percent Remembered at Long Delay (from max T1:T5)	20.9	50.0
Percent Forgetting	21.4	43.8
Retroactive Interference (A6-A5)	3.3	5.6
Proactive Interference (B-A1)	3.3	5.6
Recognition False B	3.5	20.0
Graded Naming Test	3.5	11.1
ACE-Visuospatial	35.0	13.9
Corsi blocks	39.3	22.2
MTCF		
Copy	30.8	14.3
Recall	15.4	41.7
% Retained	3.9	41.7
Visual Patterns		
High	66.7	20.0
Low	43.8	10.0
Ratio	29.2	6.7
Pareidola: pareidolias	34.6	0.0
Verbal Fluency (FAS)	46.7	22.2
Stroop		
C	40.0	11.8
CW	37.5	12.5
Ratio Interference	6.3	18.8
Trail Making Test		
A	36.7	22.2
B	42.9	33.3
Difference	37.0	33.3
Ratio	22.2	16.7
Digit Span		
Forwards	3.3	0.0
Backwards	0.0	11.1
DSST		
Original	37.0	16.7
Symbol Copy	48.2	33.3
Error Check	45.0	6.7
Coding Time	37.0	5.6
Reaction Time		
Simple	10.7	11.1
Choice	25.0	5.9

Table 8 16th percentile standing of MCI-Probable and MCI-AD patients (% of group).

	MCI-LB Probable	MCI-AD
ACE-R Total	61.7	58.3
MMSE	56.7	55.6
ACE-Language	50.0	33.3
RAVLT		
Max T1:T5	50.0	61.1
"Learning"	45.0	61.1
Short Delay	58.3	77.8
Long Delay	43.1	62.5
Percent Remembered at Long Delay (from max T1:T5)	27.6	53.1
Percent Forgetting	28.6	53.1
Retroactive Interference (A6-A5)	20.0	47.2
Proactive Interference (B-A1)	36.7	11.1
Recognition False B	51.7	46.7
Graded Naming Test	31.0	38.9
ACE-Visuospatial	65.0	58.3
Corsi blocks	48.2	36.1
MTCF		
Copy	42.3	28.6
Recall	42.3	66.7
% Retained	38.5	75.0
Visual Patterns		
High	75.0	46.7
Low	58.3	33.3
Ratio	33.3	20
Pareidola: pareidolias	53.9	29.4
Verbal Fluency (FAS)	53.3	27.8
Stroop		
C	56.0	23.5
CW	70.8	56.3
Ratio Interference	33.3	50.0
Trail Making Test		
A	56.7	33.3
B	85.7	66.7
Difference	81.5	66.7
Ratio	22.2	27.8
Digit Span		
Forwards	20.0	16.7
Backwards	40.0	38.9
DSST		
Original	92.6	72.2
Symbol Copy	81.5	66.7
Error Check	65.0	20.0
Coding Time	81.5	50.0
Reaction Time		
Simple	46.4	27.8
Choice	35.7	29.4

Twenty percent or more of MCI-LB Probable versus MCI-AD participant numbers are at the 5th percentile on various executive (Stroop CW) and processing speed (Stroop C, DSST, Error Check, Coding Time) measures. CRT similarly shows 25.0% of MCI-LB Probable at the 5th percentile level and only 5.9% of MCI-AD. When looking at the higher percentiles rankings, only 7.4% of MCI-LB Probable participants score above the 16th percentile of controls. In contrast 27.8% of MCI-AD score above that cut-off.

4.3.4 Discriminant analyses

Table 9 Tasks showing significant differences ($p < .05$) between MCI-LB Probable and MCI-AD groups, with redundant/ interrelated measures removed.

Domain	Outcome Variables
Verbal Learning and Memory	RAVLT Short Delay RAVLT Percent Maximum Recall at Long Delay RAVLT Retroactive Interference
Visuospatial Learning and Memory	VPT High Pareidolia
Executive Function	FAS Stroop C Stroop Classical Interference
Processing Speed	DSST Error Check Coding Time

Two post-hoc stepwise discriminant analyses were next run using the individual neuropsychological outcome variables that showed a significant difference between MCI-AD and MCI-LB Probable (Table 9) to determine which measures best discriminate between the groups. However, Coding Time, while significantly different between MCI-AD and MCI-LB probable, was not entered due to the high bivariate correlation with DSST ($r = .922$, $p < .001$), from which it is partially derived. Pareidolia was likewise omitted due to the substantial floor effect. Error Check was omitted due to substantial missing data. Missing data points were replaced using an expectation-maximization approach following Little's Missing Completely at Random Test (MCAR) test (see Chapter 4 for full details). Absence of multicollinearity was confirmed and assumptions of normality were checked using the Shapiro-Wilk statistic. RAVLT Max Recall at Long Delay, RAVLT Retroactive Interference and VPT Ratio failed this assumption; however, inspection of the Q-Q plots and histograms determined *near normality* was present and enabled continuation of the discriminant analysis.

Table 10 Test of Equality of group means from stepwise discriminant analysis predicting group membership (controls, MCI-LB Probable, MCI-AD).

	Wilks' Lambda	*F*	*df1*	*df2*	*p*-value
DSST	0.51	36.89	2	76	<.001
VPT High	0.65	20.21	2	76	<.001
RAVLT Short Delay	0.70	16.24	2	76	<.001
RAVLT % Recalled at Long Delay	0.85	6.74	2	76	.002
RAVLT Retroactive Interference	0.91	3.57	2	76	.033
FAS	0.81	9.09	2	76	<.001
Stroop C	0.74	13.60	2	76	<.001
Stroop Classical Interference	0.87	5.75	2	76	.005

Table 11 Wilks' Lambda of stepwise discriminant function analysis to predict group membership (controls, MCI-LB Probable or MCI-AD.

Test of Functions	Wilks' Lambda	Chi-square	*df*	*p*-value
1 through 2	0.42	66.15	4	<.001
2	0.85	12.75	1	<.001

MCI-LB Probable, MCI-AD and Control Discrimination

Firstly, the stepwise discriminant analysis was run with all control subjects, predicting group membership as control, MCI-AD or MCI-LB Probable. The highest F value of the eight predictor variables was DSST, $F(2,76) = 36.89$, $p < .001$, followed by VPT High, $F(2,76) = 20.21$, $p < .001$. The analysis resulted in two steps showing the best predictors for group membership were DSST and RAVLT Short Delay (Table 10). The other six variables were not entered into the model. The two models were both significant (ps < .001) and Wilks Lambdas of 0.42 and 0.85, respectively. Box's M was not significant ($p = .545$), indicating that the data do not differ significantly from multivariate normal and the analysis can proceed. The eigenvalue for the first function (loaded only by DSST) was substantially higher than the second, suggesting it may be sufficient in differentiating 84.8% group variance. However, as seen in Table 11, both functions are significant, suggesting that function 2 may contribute more discriminant value above and beyond function 1. Only DSST and RAVLT Short Delay were retained in the model. Function 1 (-3.81 + .09[DSST] +.09[RAVLT Short Delay] is highly correlated with DSST (0.967). Function 2 (0.31[RAVLT Short Delay] - 0.06[DSST]) relates to verbal memory, with RAVLT Short delay loading at 0.84.

Graphical representation of participants by the two discrimination functions clearly shows separation between the control group and the MCI groups (Figure 8). However, there substantial overlap of the MCI subtypes around the two group centroids. The Prior Probabilities table (Table 12), indicates the probability of random allocation to a group. The likelihood was 22.8% for MCI-AD, 38.0% for MCI-LB

Table 12 Probability of group membership by chance.

Prior Probabilities for Groups

Joanna_Diag_2	Prior	Cases Used in Analysis	
		Unweighted	Weighted
MCI-AD	.228	18	18.000
MCI-LB Probable	.380	30	30.000
Control	.392	31	31.000
Total	1.000	79	79.000

Table 13 Classification result showing the correct classification percentages.

Classification Results[a]

		Clinical Diagnosis	Predicted Group Membership			
			MCI-AD	MCI-LB Probable	Control	Total
Original	Count	MCI-AD	10	6	2	18
		MCI-LB Probable	3	23	4	30
		Control	0	4	27	31
	%	MCI-AD	55.6	33.3	11.1	100.0
		MCI-LB Probable	10.0	76.7	13.3	100.0
		Control	.0	12.9	87.1	100.0

a. 75.9% of original grouped cases correctly classified.

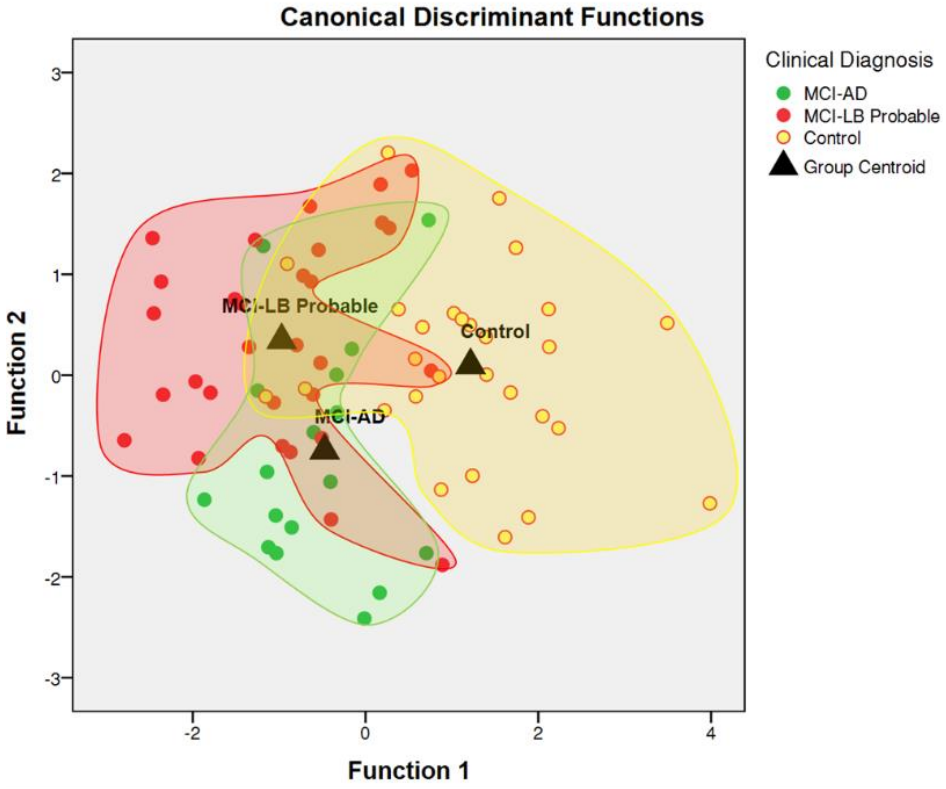

Figure 8 Participants (controls, MCI-LB Probable MCI-AD) plotted according to weighted composite scores on the two functions to predict group.

Probable, and 39.2% for controls for each group. In contrast, using the predictive function of the four variables, 75.9% of original grouped cases are correctly classified. This model is most successful in classifying Controls (87.1%), with 76.7% of MCI-LB cases also correctly classified. MCI-AD was only correctly classified at 55.6% (see Table 13). The lower *n* in the MCI-AD group likely contributed to this low classification rate; however, as demonstrated graphically, MCI-AD participants range substantially especially along the y-axis of function 2 (RAVLT Short Delay). Literature suggests that a useful model should provide at least 25% improvement than random calculation. This occurred for all three of the groups. As such, this model appears substantially improved from random.

Three and four group stepwise discriminant analysis without aberrant controls

The above stepwise discriminant analyses were re-run with the removal of four controls with positive biomarkers associated with Lewy body disease: SUP124MM and SUP133SF (abnormal panel-rated DaTSCAN), SUP160VB and SUP161ED (abnormal MIBG). This resulted in $n = 75$ and was pursued to rule-out the potential effects of underlying LB pathology on the cognitive results. As with the original approach, Box's M test was not significant and four steps were produced. The final models likewise retained DSST and RAVLT Short Delay in line with the findings with all controls. The classification results were 5.5%, 3.3% and 1.8% higher for MCI-AD, MCI-LB Probable and controls, respectively. Given the identical pattern of variable loadings, the results using all of the control subjects were carried forward into the analyses in later chapters.

Sensitivity and Specificity between MCI-AD and MCI-LB Probable only

Separately, the sensitivity and specificity of all eight variables for MCI-LB Probable were computed using receiver operating characteristic (ROC) analyses (Table 14). All of the ROC were significant at $p < .05$. Area under the ROC curve (where an area of 1 represents a "perfect" test in terms of sensitivity and specificity) were low for all outcome variables although DSST had the highest area (.729). Coordinates of the ROC curve were evaluated to determine cut-offs that maximized sensitivity while maintaining specificity at 50% or above when possible. Sensitivity of the pareidolia test was particularly poor. While sensitivity was highest for Stroop C (a psychomotor speed measure), specificities of all tests were low (50.0-66.7%).

Table 14 Prior probabilities, sensitivity and specificities (with cross-validation/ "leave-one-out" method) of the eight variables with significant difference in mean performance between MCI-AD and MCI-LB Probable.

Domain	Outcome Variables	Sensitivity	Specificity	Cut-Off Score	Area under the curve	*p*-value
Verbal Learning and Memory	RAVLT Short Delay	70.0%	55.6%	3.5 (above)	.684	.034
	RAVLT Percent Maximum Recall at Long Delay	70.0%	66.7%	55.1 (above)	.704	.019
	RAVLT Retroactive Interference	70.0%	61.1%	-3.5 (above)	.693	.027
Visuospatial Learning and Memory	VPT High	70.0%	50.0%	9.3 (below)	.698	.023
	Pareidolia (pareidolias)	61.5%	64.7%	39.5 (below)	.683	.044
Executive Function	FAS	73.3%	66.7%	38 (below)	.693	.027
	Stroop C	83.3%	55.6%	81.5 (below)	.722	.011
	Stroop Classical Interference	73.3%	50.0%	-52.5 (below)	.715	.013
Processing Speed	DSST	73.3%	50.0%	31.5 (below)	.729	.009
	Coding Time	73.3%	50.0%	-0.4 (below)s	.594	.282

Therefore, a stepwise discriminant analysis was run with only the MCI-AD and MCI-LB Probable data to determine a maximally-discriminant and specific formula for group determination. Again, the eight outcome variables with significant differences between the two groups were entered as predictors of binary group membership (MCI-AD, n = 18, or MCI-LB Probable, n = 30), except for Pareidolia, Coding Time and Error Check. All variables were significant in tests of quality of group means and Box's M test was not significant (p = .700). The model resulted in entry of the same variables in two steps: DSST, $F(1,46) = 7.98$, p = .007 and RAVLT Short Delay, $F(1,46) = 8.42$, p = .001. The analysis results in the discrimination formula: -1.83+ 0.11(DSST) - 0.22(RAVLT Short Delay). The function is most highly correlated with DSST (0.68) followed by RAVLT Short Delay (-0.49). The model correctly classified 72.9% of all cases. The classification results showed the model to have 86.7% sensitivity but only 50% specificity for correctly classifying clinically-defined MCI-LB Probable.

4.4 Discussion

The present chapter aimed to profile neuropsychological test performance in clinically-diagnosed MCI-LB (both Probable and Possible) and MCI-AD relative to healthy age-matched controls, primarily through the use of univariate analyses of the outcome measures from the test battery. While poorer performance relative to controls was anticipated, the use of forest plots, percentiles and discriminant analyses help to clarify the profiles of impairments in the two MCI diagnostic groups. From this cross-sectional work, clear differences between the MCI subtypes emerge that suggest that both conditions are associated with patterns of domain-level deficits in MCI as in their advanced dementia stages.

MCI-AD show worse impairments in verbal learning and memory

Both MCI-LB Probable and MCI-AD showed impairments relative to controls in the verbal domain. Both were impaired on RAVLT's maximum recalled during learning trials, short delay, long delay, and percent recalled at long delay. Scores on the learning trials of word list tasks like the RAVLT have been previously shown to be very sensitive to earliest impairments in AD (Fox, Olin, Erblich, Ippen, & Schneider, 1998). Fox et al. (1998) suggest this sensitivity relates to AD-specific pathology in the medial temporal lobe. MCI-AD also showed worse retroactive interference scores relative to controls and larger overall effect sizes in their impairments relative to controls. Performance by MCI-LB Probable, if significantly worse, was rarely more than one SD below control means. Overall, MCI-AD emerges with consistent impairments in the verbal learning and memory domain relative to controls, with medium and large effect sizes. In comparison to MCI-LB Probable, MCI-AD performs significantly poorer on three tests of verbal memory. Firstly, to a moderate effect size, MCI-AD patients remember significantly fewer words overall after short delay. The retention period is rather brief (the time it takes to administer the single List B immediate recall trial), but still relates to incidental long term memory rather than short term memory, as working memory is engaged and refreshed in completing the List B trial. Therefore, this significant finding points to impaired long term verbal memory in the MCI stage of AD.

However, through the use of percentiles (section 4.3.3), my results show that a substantial proportion of MCI-LB Probable individuals (40%) perform at or below the 5th percentile of control levels on the RAVLT verbal short term memory recall task.

This is in line with the findings on the same measure in Donaghy, Taylor, et al. (2018), and substantiates the conclusions by Ferman (2013), Kemp et al. (2017) and Yoon et al. (2015) that many DLB cases will show amnestic profiles in the MCI stage. However, only 20% of MCI-LB Probable perform at such a low level relative to controls on the long delay verbal memory test. By raw count of words recalled, the MCI groups did not differ significantly. That is, MCI-AD had significantly worse verbal memory in the long delay condition than MCI-LB Probable, but only when quantified as the proportion of an individual's maximum words recalled during the "learning" (first five immediate recall) trials. MCI-LB Probable group was also impaired on ACE's Language measure and recognition of List B at long delay, while MCI-AD was not. This points to impaired storage or recall ability in MCI-LB, rather than to encoding deficits per se. Under this interpretation, the results could suggest that the prominent retrieval deficit hypothesis of PD (Bronnick et al., 2011) may likewise apply to MCI-LB. This theory identifies memory impairments in PD as localized to retrieval deficits rather than impaired learning and encoding. It also now recognises a mediating role of executive dysfunction and poor semantic strategy use in verbal learning and memory (Bronnick et al., 2011). My review (Chapter 2) did suggest learning and encoding failures were reported frequently in MCI-LB, as in PD. Moreover, my results demonstrate executive function and semantic naming (Graded Naming Test) impairments in MCI-LB. As such, these could be considered as a potential mediators of verbal memory impairment in MCI-LB in future work, following the protocol of Bronnick et al. (2011). Bronnick et al. (2011) utilised the California Verbal Learning Test-2, a list-learning test highly similar to RAVLT, in PD to compute measures of recall, encoding, retention and recognition, as well as semantic clustering learning strategy use and executive function.

Methodologically, the finding also suggests the importance of using of adjusted scores in memory recall tasks when attempting to target long term episodic memory, particularly in clinical conditions where amnesia or hippocampal damage is suspected. Such measures of proportion recalled at long delay have previously been related to AD-status (Estévez-González, Kulisevsky, Boltes, Otermín, & García-Sánchez, 2003; Gomar, Conejero-Goldberg, Davies, Goldberg, & Initiative, 2014; Moradi et al., 2015). Indeed, an amnestic profile is the most salient cognitive feature of AD and early delayed recall impairment using the RAVLT may suggest development of this aetiology of dementia (Estévez-González et al., 2003; Tierney et al., 1996). Neurobiologically, this is consistent with higher pathological burden in the

hippocampus or other temporal structures (Helmstaedter & Elger, 1996; Ricci, Graef, Blundo, & Miller, 2012).

The short delay trial is an uncued, free recall condition, occurring after immediate free recall of the second list (List B), a distractor task. Through the use of a distractor task, the RAVLT, like various other memory tasks, is also able to quantify two measures of interference. Proactive Interference captures how prior learning can impair memory of subsequently-presented material (Postman & Underwood, 1973). In contrast to Proactive Interference, Retroactive Interference relates to how delayed recall will be negatively impacted by learning new material afterwards. Retroactive Interference is therefore typically assessed immediately following the intervening "distractor" task. Interference in general has been suggested as related to executive function and memory consolidation. Participants are not informed that they will be asked about the first list of words again. In order to perform well on the second list, they much refocus their attention on the new list of words, through the use of executive processes such as updating. If participants are unable to complete these executive tasks, this would be reflected in a poorer Proactive Interference score with fewer list B words remember in the single free recall condition. Empirical support for executive function's primary role in interference effects stems largely from work in patients with frontal lobe damage showing increased proactive (Gershberg & Shimamura, 1995; Smith & Jonides, 1999; Van der Linden, Bruyer, Roland, & Schils, 1993) and retroactive interference (Blusewicz, Kramer, & Delmonico, 1996; Luria, 1980), which also correlates with measures of executive function.

Instead, in the present study, MCI-LB and MCI-AD did not differ significantly in Proactive Interference scores, only Short Delay recall. This suggests that the subsequent poorer recall of List A words is likely unrelated to poor executive function. While there was no evidence of exaggerated proactive interference, MCI-AD had significantly lower scores of Retroactive Interference. Retroactive interference has previously been argued to be more strongly dependent on executive skills than Proactive Interference, by specifically requiring shifting to previously-learned stimuli (Torres, Flashman, O'Leary, & Andreasen, 2001). Indeed, MCI-AD perform worse than controls on Stroop CW and Ratio Interference, as well as Trails B and Trails Ratio Interference. These outcome measures relate to inhibition and set-shifting, respectively. Thus, it cannot be ruled out that the significantly poorer Retroactive Interference are not partly due to executive dysfunction. As an alternative, interference has also been posited as indicative of memory consolidation and storage

failure, due to poor medial temporal lobe integrity (Torres et al., 2001). Retroactive Interference scores are dependent on the Short Delay performance (T6-T5), which was significantly lower than both controls and MCI-LB Probable. Thus the poor long term verbal memory in MCI-AD may be responsible for the derived retroactive interference scores. The subsequent chapter aims to elucidate these outstanding questions through linear regression to consider how executive function may predict verbal abilities such as these outcome measures.

Executive Function

In executive function, results are mixed. The magnitudes of effect size of the differences relative to controls are similar between the MCI subtypes on a number of tasks (Trails B, Stroop CW, and Digit Span Backwards). However, MCI-LB do show executive dysfunction versus controls on six measures: phonemic verbal fluency (FAS), Stroop CW, Trails B, Trails Difference and Ratio and Digit Span Backwards. Executive impairment is not specific to MCI-LB, however, as MCI-AD is impaired relative to controls on four outcome measures (Stroop CW, Stroop Ratio Interference, Trails B and Trails Ratio). As a differentiating variables between subtypes, MCI-LB does perform worse than MCI-AD on verbal fluency, with a medium-large (0.7) effect size. This effect size is in line with those reported in executive function in the two studies in MCI-LB identified in the structured review (Cagnin, Bussè, Gardini, et al., 2015; Yoon et al., 2015). Contrary to expectation, both MCI-LB Probable and MCI-Possible show significantly less Stroop Interference effects when calculating using the “Classical” method (Golden, 1978). The effect disappears using the Ratio calculation, however, which “corrects” for word reading speed. In conjunction with inspection of the descriptive statistics of these variables, this suggest that this is an artefact of MCI-LB having a much slower reading speed.

Both MCI-AD and MCI-LB show impairment on the contrast of the simple and alternating conditions of Trails, which captures executive weighting. Simple difference scores (Trails Difference) and ratio indices (Trails Ratio) are the most common methods of this comparison (Salthouse, 2011), but larger sample sizes could allow for a more precise index using residuals derived after computing a “predicted” B score based on the A score (Salthouse, 2011). Salthouse (2011) found that both ratio and residual contrasts scores better “eliminated the influence of speed” than simple differences. In cases of smaller sample sizes, as in the present study, they argue that Trails Ratio has greater utility in capturing executive function

when residuals cannot be computed. It is thus more telling of executive dysfunction that both MCI-LB and MCI-AD are impaired on Trails Ratio, rather than an intact Trails Difference score as signalling spared function in MCI-AD.

Breitve et al. (2018) notes that only 11.9% (n = 8) of their DLB group were able to complete Trails B, versus 27.7% (n = 33) of the AD group. In the present study, 3 participants (2 MCI-LB Probable, 1 MCI-LB Possible) could not complete Trails B due to inadequate task comprehension. In addition, 6 other MCI-LB participants (4 MCI-LB Probable, 2 MCI-LB Possible) completed Trails B in over 300 seconds, which is the typical cut-off time in administering the task. Participants taking over this time may be scored as 300 second completers or removed from the study (Salthouse et al., 2000). Therefore, in the present study 100% of MCI-AD participants could complete Trails B, while 93.2% of MCI-LB Probable or Possible complete Trails B at all. If excluding participants taking over 300 seconds, the MCI-LB Trails B completion rate drops to 79.5%. This is markedly higher than in Breitve et al. (2018), and it will be clarifying to quantify at follow-ups in the SUPErB study how these numbers will change with disease progression to dementia. It is possible that decline on Trails B could closely mirror to the decline from MCI to dementia in LB disease.

As proposed by Miyake et al. (2000), executive functions may be delineated as relating to set-shifting, updating and inhibition. Set-shifting refers to switching between different task components or response rules, and this is commonly measured using Trails B or Trails Difference. In the sample, MCI-AD and MCI-LB therefore show comparable evidence of impaired set-shifting. Inhibition, in contrast, relates to the ability to suppress automatic (prepotent) responses in order to achieve the task demands. For example, in Stroop Colour-Word, the automaticity and ease of reading the printed word aloud must be inhibited in order to instead verbalize the colour of the font. Using Stroop Interference and Colour-Word Scores, the data suggest that both MCI-AD and MCI-LB struggle with inhibition. As discussed, the Stroop Classical Interference at first glance suggested superior inhibitory control by MCI-LB, but this was due to overall slowed speed of reading. While Classical Interference was problematic in this specific population, interference scores are generally preferable to the raw Colour-Word scores as they minimize the effects of differential colour processing speed, lexical access of colour words, and psychomotor speed in colour-word articulation (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). The Stroop Ratio Interference score was only impaired relative to controls in MCI-AD, thus suggesting that MCI-AD is associated with executive dysfunction, in

addition to its more typical amnestic profile. This has previously been demonstrated in both “amnestic MCI” (Kramer et al., 2006) and MCI-AD (Zhou & Jia, 2009, using Petersen et al. (2005) criteria).

The last component stressed by Miyake et al. (2000), updating, requires the monitoring and coding of new information for task relevancy and the revising or removal of now irrelevant information from working memory, in order to instead retain the incoming information. It is thus a dynamic management of working memory content, rather than passive storage (Miyake et al., 2000). Updating is traditionally captured using N-back tests, which were not included in the present study. However, the Continuous Performance Test-AX was included in the battery and has been used previously to consider the interplay of updating and task-switching (Kessler, Baruchin, & Bouhsira-Sabag, 2017). Analysis of the task may be able to more precisely delineate poor inhibition versus other failures of executive function and attention failures, such as updating and attentional lapses. This will be analysed and discussed in Chapter 6. However, Digit Span Backwards both taxes working memory and requires active updating and working memory manipulation. On this task, MCI-LB Probable and Possible performed had significantly worse recall than controls, suggesting poor updating. This did not occur in MCI-AD.

Working memory maintenance is also sometimes considered alongside Miyake et al.’s (2000) model as an executive function requiring active maintenance of information across a short delay. In contrast to updating, however, this does not involve active manipulation. This is often operationalized by Digit Span Forward, indicative of the capacity the phonological loop (Bull, Espy, & Wiebe, 2008). The results suggest “normal” capacity or integrity of this component in both MCI subtypes.

Executive dysfunction has been posited as especially prominent in LBD (Ballard et al., 2002), although the results of the present chapter are mixed. The comparisons in Stroop CW and Digit Span Backwards were not significant in contrast to Cagnin et al. (2015) and Yoon et al. (2015). MCI-LB are impaired in verbal fluency, however, relative to both MCI-AD and controls. Cagnin, Bussè, Gardini, et al. (2015) and Jicha et al. (2010) likewise found verbal fluency impairments in that group. However, Snyder, Miyake, and Hankin (2015), cautions that FAS is a less specific tool, and more precise measurements within the task should be utilized to disentangle executive subcomponents. For example, FAS can be scored based on switching (transitions between subcategories), clustering, or weighted scores encompassing these multiple elements of performance.

Taken together, a divergent patterns of impairment is not as immediately clear in executive function domain as verbal learning and memory or processing speed. However, by breaking down executive scores by components following Miyake et al. (2000) and Snyder et al. (2015), we can see that MCI-LB shows dysfunction in updating relative to controls, while MCI-AD does not. There remains substantial overlap in profile in this domain, however, as both subtypes are impaired in set-shifting and inhibition. Working memory maintenance/ capacity appears to be intact in both aetiologies at this stage in disease. MCI-AD, while hypothesized to be characterised by a verbal amnestic cognitive profile, also shows clear executive dysfunction.

Processing Speed and Attention

While MCI-AD showed pronounced deficits relative to both controls and MCI-LB Probable in the verbal domain, MCI-LB Probable show a consistent profile of slowed processing speed. MCI-LB Probable performed worse than controls on CRT, DSST, Symbol Copy, Error Check, Coding Time, and Trails A. Relative to MCI-AD, their performance was also significantly worse in DSST, Coding Time, Error Check and Stroop C (word reading). MCI-LB Probable performance on Trails A was no worse than MCI-AD; this stands in contrast to Cagnin, Bussè, Gardini, et al. (2015). Brønnick, Breitve, Rongve, and Aarsland (2016) also showed significantly worse performance on Trails A at baseline in mild probable DLB versus mild AD. In the longitudinal continuation of that same cohort, Breitve et al. (2018) demonstrated that Trails A performance declined more rapidly at follow up in mild probable DLB than mild AD, after adjusting for age, sex and education. Breitve et al. (2018) correctly suggest that Trails A is “relatively cognitively undemanding and motor tempo determines the performance to a degree”.

Processing speed is believed to be a distinct concept yet interrelated with working memory and executive function (Luszcz & Bryan, 1999). It is conceptualized as the domain-general speed of execution of basic cognitive functions (Nebes et al., 2000). It therefore limits the completion of higher-order activities, such as memory formation (Salthouse, 1992), that depend on basic operations to occur before the information held in working memory decays (Craik & Salthouse, 2011). The domain-general decline of processing speed has long been suggested as the likeliest factor in cognitive decline in ageing (Nebes et al., 2000; Salthouse, 1996b).

In neuropsychological research, there is a generally-accepted division in processing speed tasks that target psychomotor speed versus cognitive speed (Kail & Salthouse, 1994; Salthouse & Coon, 1993). Psychomotor speed, sometimes called sensorimotor speed or sensory-motor processes, are more motor-dependent and based on the time to complete a repetitive, motor-based task. Cognitive speed, in contrast, is generally measured using substitution or comparison tasks, like the DSST. Following the distinction in processing speed tasks outline above, Trails A can be taken as a psychomotor task. The other psychomotor processing speed tasks, like SRT and CRT, likewise did not show a significant difference between groups. Conversely, the largest effect size between an MCI subtype and controls was in DSST, a cognitive speed task, with MCI-LB Probable performing on average two SDs below the controls. MCI-AD was also impaired relative to controls on DSST and Coding Time (the only two processing speed tasks with a significantly worse score versus controls). The latter variable is derived from DSST and Symbol Copy to remove the role of graphomotor control in completion of the DSST. In this way, Coding Time specifically attempts to further isolate the cognitive processing speed from than the psychomotor processing speed. Taken together, this suggests cognitive speed and not the psychomotor component of processing speed tasks may be the impaired component in MCI-LB.

The DSST used extensively in clinical and research settings as a sensitive measure of processing speed (Salthouse, 1992; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2006). There is no doubt that processing speed is involved in the task: early work by Salthouse (1992) demonstrated that controlling for performance on a simple speed test removed 95% of the age-related variance in DSST. However, the DSST clearly necessitates other resources including graphomotor and perceptual speed, as well as potential executive function and memory components (Joy, Kaplan, & Fein, 2004; Van der Elst et al., 2006). Variations of DSST have been developed to delineate the processes involved. Symbol Copy (Kaplan, Fein, Morris, & Delis, 1991), performance on which MCI subtypes did not differ significantly, intends to isolate DSST's graphomotor component (Joy et al., 2000). Coding Time, calculated as the time per item in DSST minus the time per item in Symbol Copy, is conceptualized as a purer measure of processing speed similar to Error Check (Nebes et al., 2000); however, both variables includes visual scanning time in addition to mental operation time (Joy et al., 2003). Another test variant, Error Check, was first developed by Joy et al. (2000) to capture the coding processes involved in DSST without graphomotor

demands. In the present study, MCI-LB Probable were found to be significantly slow in completing Error Check. That Error Check and not Symbol Copy was differentially impaired in MCI-LB versus MCI-AD suggest that it is indeed cognitive speed, and not motor speed, that is the differentially impaired resource in MCI-LB.

The multifactorial nature of DSST and the evidence of its association with neurological dysfunction make it a useful exploratory tool in the study of ageing and MCI. Executive functions can also be investigated using the DSST, to consider the possibility that it is executive weighting and not speed of processing per se that is associated with higher-order impairments in MCI. My review of early PD showed that patients perform poorly on tasks with executive weighting, regardless of which domain they appear to target (working memory, processing speed, visuospatial and verbal learning), and despite general intact performance on simpler tasks in those domains (Trails A, RAVLT). In the wider literature, declines in executive function have been proposed more recently as intrinsic to cognitive healthy ageing and AD (Buckner, 2004), while executive dysfunction is considered a hallmark of DLB (Collerton et al., 2003; Foltynie et al., 2004; Muslimović et al., 2005) Therefore, it is important to consider the interplay of processing speed and executive function in the neuropsychological function of MCI-LB. The hypothesis that cognitive, not psychomotor speed nor executive deficits, is the critical factor in impairment in MCI-LB can be further investigated through more subtle analyses of the DSST and its variants, and will be pursued in Chapter 5.

Visuospatial

In the visuospatial domain, MCI-LB Probable performs significantly worse than controls on all but one measure while MCI-AD showed less consistently significant differences, with smaller effect sizes in only three of the nine outcome measures. MCI-LB Probable, relative to controls, demonstrated poor general visuospatial estimates (ACE Visuospatial), visuospatial working memory (Corsi Blocks), visuoconstruction (MTCF Copy, VPT High and Low), visuospatial memory (MTCF recall and as quantified as percent copy score and recall), and visuoperception (Pareidolias). MCI-LB Probable performed significantly worse than MCI-AD on only pareidolias and VPT High. Therefore, this is a more modest profile of impairment than reported by Cagnin et al. (2015), who showed significantly worse scores on visuospatial and visuoconstructive tests as well, although with small to medium effect sizes.

Relative to controls, MCI-LB, and not MCI-AD, showed impaired visuoconstructive ability. Poor visuoconstructive skills have previously been shown to predict quicker cognitive decline and more severe visual hallucinations in DLB (Hamilton et al., 2008). In conjunction with the results showing complex figure impairments in the MCI stage in LB, such tasks may serve an important role in charting trajectories of decline. Both MCI groups show poorer visuospatial memory than controls, even when controlling for copy scores. The effect size in MCI-AD in MTCF recall are larger than MCI-AD performance (percent copy score at recall), but the scores do not differ significantly between subtypes. The author was unable to identify any published studies that used the MTCF in DLB or MCI-LB, and very few studies in MCI generally. Paula, Costa, Andrade, Ávila, and Malloy-Diniz (2016) used a simplified version if the MTCF test and similarly found multidomain amnestic MCI participants were impaired relative to single domain amnestic MCI in figure copying, but no difference between MCI groups in recall. The ROCF is used more regularly in neuropsychological studies, and copy impairments relative to AD have been previously demonstrated by Cagnin, Bussè, Jelcic, et al. (2015) in MCI-LB and Ferman, Smith, Boeve, Graff-Radford, Lucas, Knopman, Petersen, Ivnik, Wszolek, and Uitti (2006) in established DLB.

Methodologically, use of the MTCF may have been confounded. Due to the large battery of cognitive tests and rigorous schedule of the SUPErB study in general, the retention interval before incidental recall was typically filled with other cognitive tests or questionnaires. In the validating study, an unchallenging, self-report “quality of life” questionnaire was used (Hubley & Tremblay (2002). Moreover, we did not include an immediate incidental recall condition in order to keep participants unaware of the recall that as to occur at the long delay condition. This procedure was chosen as the primary construct of interest was long term visuospatial memory, but immediate incidental recall helps to consolidate long term memory. This would conceivably make long delay recall easier, although this might not apply to MCI-AD due to the characteristic hippocampal atrophy. Thus, long delay recall after an immediate recall trial may actually magnify differences between MCI-LB and MCI-AD. By omitting immediate recall, the results should be a more conservative estimate of effect size of long term visuospatial memory deficits in MCI-AD. The deficits were larger, by effect size, than MCI-AD, but not to statistical significance.

The largest effect size in MCI-LB Probable relative to controls (bias-corrected d = -1.18) occurred in Corsi Blocks, on which MCI-AD was not impaired. This task

tests spatial-sequential visuospatial working memory in the forward direction only. It is used frequently as a core test of sequential spatial working memory with limited demand on executive functions and motor ability. This finding runs somewhat contrary to results from my structured review of findings in early and MCI-PD, in which visuospatial working memory was less frequently reported as impaired versus visuospatial memory or visuoconstruction. In more complex tasks like figure copying and the VPT, it is difficult to firmly attribute deficits to core components of visuospatial working memory as executive functions such as sustained attention, planning and organization and verbal coding are more likely to be automatically involved in their execution (Shin et al., 2006). Corsi Blocks is less easily reducible to other cognitive processes. The findings of the present study therefore provide evidence for impairments in more complex visuoconstructive and visuospatial working memory and long-term memory tasks, as well as core visuospatial working memory components.

However, evidence from multi-resource models indicate that both spatial and visual working memory tasks like MTCF, VPT and Corsi are supported by executive function (Thompson et al., 2006). Moreover, research indicates that the visuospatial domain is especially dependent on executive processes in spatial information storage and processing (Fisk & Sharp, 2003; Miyake, 2001; Vandierendonck, Kemps, Fastame, & Szmalec, 2004). This is in contrast to verbal working memory, which has been shown to be more automatic and amenable to distinction between executive and slave processes (Fisk & Sharp, 2003). The verbal domain of working memory should be considered when interpreting visuospatial results as well, nevertheless. In addition to failures in executive functions and the episodic buffer, a lack of verbalization of visuospatial information may result in poor performance. There is considerable debate regarding translation of visuospatial information into verbal storage; however, Baddeley (2000) reminds that, “because of the efficiency of the phonological store in serial recall, adult subjects typically opt to name and subvocally rehearse visually presented items, thereby transferring the information from a visual to an auditory code” (p. 419). Research demonstrating that articulatory-suppression tasks interfere with performance in purported visuospatial tasks, such as Reverse Corsi Block, especially at higher-loads, supports this idea (Baddeley, 2000b; Vandierendonck et al., 2004). As discussed with processing speed, multivariate statistical techniques can be utilized to disentangle the contribution of these components in normal ageing (healthy control group) and pathology (MCI-AD and

MCI-LB. Chapter four will consider the potential role of a hierarchy of deficits and semantic scaffolding in execution of the visuospatial tasks.

Given the findings by Brønnick et al. (2016), we would have expected visuoperception to be similar in MCI-LB and MCI-AD, despite the poorer visuoconstructive abilities of MCI-LB. However, MCI-LB Probable reported significantly more pareidolic illusions than both MCI-AD and controls. A third of MCI-LB Probable participants performed at or below the 5th percentile of controls, while no MCI-AD participants did. However, as mentioned previously, this variable was extremely skewed. It shows a strong floor effect with 55% of participants receiving a score of zero. Transformations were attempted but unsuccessful in correcting for this, so it was deemed inappropriate for use in the multivariate analyses of forthcoming chapters. However, with further validation, the Pareidolia task could provide useful as a classifying variable using a predetermined cut-off, as demonstrated by existing work, predominantly out of Japan. Variants of the task have previously been shown to be powerful in discriminating between DLB and AD using ROC-determined optimal cut-off scores (81% sensitivity, 92% specificity; Mamiya et al., 2016). Yokoi et al. (2014) found a sensitivity of 0.71 and specificity of .80 when using a 2.5% cut-off for illusory responses in the same face pareidolia task used herein. This test was also found to correlate significantly with the total, severity and frequency scores of the NPI hallucination scale and an additional domain created for the study to quantify fluctuation. Pareidolia is an experimental task and its full analysis is outside of the scope of the present PhD, but future work could consider whether it could be harnessed for use in the context of MCI-LB, despite its problematic psychometric properties.

Percentiles

The use of percentile rankings, in addition to univariate analyses and forest plots by domain, allowed consideration of the individual differences in performance across measures. If only comparing scores between groups, interindividual variability can increase statistical variation In MCI-LB Probable, for example, three quarters of the group perform at least one SD below controls on VPT High, but other visuospatial tasks show more modest proportions of the group so impaired. In MCI-AD, about 25–60% of participants scored at or below least one SD of control means. Particularly high proportion of MCI-AD were impaired at the 16th percentile level on RAVLT Short Delay (77.8%) and MTCF Percent Retained (75.0%). In the MCI-LB Probable group,

particularly high proportions perform at or below the 16th percentile on processing speed measures (Trails B, Trails Difference, DSST, Symbol Copy, and Coding Time).

Moreover, certain tasks, while not differing significantly between subtypes, are associated with substantially different proportions of participants performing at or below cut off values. For example, MCI-LB Probable and Possible did not differ significantly in CRT mean response time with MCI-AD. However, at the 16th percentile of controls, only 7.4% of MCI-LB Probable participants score above this level, in contrast to 27.8% of MCI-AD participants. MCI subtypes were previously typically diagnosed to reflect MCI neuropsychological heterogeneity. Firstly, MCI was classified as amnestic and non-amnestic, depending on the degree of memory dysfunction (Donaghy & McKeith, 2014). The amnestic subtype has a high rate of progression to AD or vascular dementia, while non-amnestic MCI patients with deficits in other domains are more likely to convert to DLB, vascular or frontotemporal dementias (Ferman et al., 2011). The amnestic and nonamnestic MCI subtypes can be further differentiated based on whether other domains are impacted, i.e. single or multiple domain (Petersen et al., 2001). In the present study, clinical diagnoses were instead used, per emergent criteria from the DLB Consortium (McKeith et al., 2017) and in order to avoid circularity when focusing on neuropsychological performance. However, it would be illuminating to consider how the patients would be subdivided following the older neuropsychological criteria. Similarly, clinical or demographic traits may be shared by the participants scoring in the lower percentile cut-offs (Gallagher, Gray, Watson, Young, & Ferrier, 2014). These could relate to MCI disease-state specifically or perhaps reveal important characteristics impacting performance, such as motivation.

Percentiles were utilised in addition to between-group comparisons to permit a more in-depth exploration of the data that highlighted interindividual variation in the patient groups. It is also important to acknowledge that HCs are also likely to vary in performing at “impaired” levels at various tasks, and that overestimation of “normal” score levels can overestimate impairments in patients. Despite clinical assessment and global neuropsychological scores indicating normal cognitive status, some control participants will perform at “abnormal” levels according to normative data. Brooks et al. (2008), for example, found that healthy older adults frequently had at least one impaired memory score below the 5th percentile. However, this does not necessarily indicate impairment of a neural basis, but rather demonstrates the risk of “false positive” MCI (Binder, Iverson, & Brooks, 2009; Brooks et al., 2008). Future

work could take control variability into consideration by comparing performance of the study's sample of healthy controls with the extent of impairment that can be reasonably expected in a healthy control group, using methods such as Monte Carlo simulation as suggested by Crawford, Garthwaite, and Gault (2007). These issues also illustrate that there is a risk of overestimating deficits in patients, whether in the clinic or in research, when using single tests to represent a domain (Brooks et al., 2008). Chapter 5 will instead attempt to create data-driven composite scores, which also benefits from capturing the breadth of the domains more fully.

Discriminant analyses

Despite the discussion of the clear differences in performance between MCI subtypes in multiple domains, it is important to recognize that there is limited discriminant power of the neuropsychological tasks in isolation from clinical data. This was evidenced by the results of the stepwise and individually-run discriminant analyses. The DSST emerged as the most potent predictor of group allocation in both the three-way (including controls) and MCI subtype-only stepwise discriminant analyses, in line with my argument that processing speed is a critical determinant of cognition in MCI-LB. The eigenvalue for the first function was loaded only by DSST and was substantially higher than the second in both cases, suggesting it may be sufficient in differentiating the groups. However, the resulting classification results of both models remained low (75.9% and 72.9%, respectively). This is in line with findings from the LewyPro study that preceded the present work in SUPErB (Donaghy, Taylor, et al., 2018). Donaghy, Taylor, et al. (2018) entered the tasks that differed between subtypes (ACE-R fluency, ACE-R visuospatial, digit vigilance [mean reaction time], and angle discrimination [visuoperceptive]). These tasks that differ between MCI groups are congruent with the present study, although the testing battery was not identical. The results are similar in retaining visuospatial and processing/ attentional measures. However, Donaghy, Taylor, et al. (2018) concludes that,

> *"the heterogeneity of cognitive impairment observed in MCI-LB and MCI-AD was reflected in the poor discriminant ability of four cognitive tests. Thus, though a pattern of prominent executive and visuospatial dysfunction is supportive of a diagnosis of MCI-LB, it is not sufficient to warrant a diagnosis of MCI-LB in isolation. This illustrates the supportive role of neuropsychological assessment in the diagnosis of MCI-LB in combination with a thorough clinical assessment for other features associated with Lewy body disease" (p. 5).*

Limitations

The analyses of the present chapter have several limitations that should be noted. Firstly, and applicable to subsequent chapters, the MCI-AD group is limited in size (18 participants). Statistical power in MCI subtype comparisons may therefore be limited. While differentiating between cognitive performance in MCI-AD and MCI-LB is an aim of this thesis, comparisons between MCI-LB and controls will be discussed in detail. Similarly, this chapter used univariate approaches to compare mean performance between groups. Despite the large number of univariate analyses performed, corrections for multiple comparisons was not pursued. This was due to the exploratory nature of these patient groups, but this increases the chance of type 1 errors. Therefore, multivariate approaches will be primarily utilized hereafter. Prior to this, PCA will be run to attempt to reduce redundancy in the large dataset.

Another important limitation concerns diagnostics. The cross-sectional nature of this study and the use of emergent criteria means that some diagnoses will likely be changed at follow up. The specificity and sensitivity of MCI-LB diagnostic criteria remains unclear. Moreover, four control subjects demonstrated possible Lewy pathology via biomarker testing. While these imaging results are questionable, their clinical examinations had pointed to “healthy” cognitive statuses. Nevertheless, the discriminant analyses were re-run having excluded these participants, and no substantial differences emerged. If these participants do have latent LB disease, it would be only in the early stages and likely present only in the heart or brainstem, as captured by the FP-CIT and MIBG images, rather than in the higher cortical areas.

The longitudinal design of the SUPErB study should provide clarification on these issues, however. Such studies are much-needed in DLB to understand which neuropsychological declines may signal higher likelihood or speed of progression to dementia. Yoon et al. (2015) reported such findings. Their MCI-LB group developed DLB with an average follow-up period of 4.9 years. In comparison with a stable MCI group (non-converters), converters performed worse at baseline in the domains of visuospatial ability and memory (ROCF recognition and copy), executive function (Stroop Colour, Verbal Fluency), working memory/ attention (Digit Span Forwards and Backwards), and verbal learning and memory (Seoul Verbal Learning Test delayed recall). The same or similar tasks were used in the present study, and it will be elucidating to track how they relate to participants’ status at follow-up over the coming years.

Conclusions and next steps

As discussed in chapter two, advances in neuroimaging and other methods of identifying biomarkers in vivo are greatly accelerating diagnostics in the MCI stage; nevertheless, neuropsychological measurement remains a critical tool in neurodegeneration research and clinical practice (Smith & Bondi, 2013). My results show that the cognitive impairment typical of established Lewy body disease and AD is evident in the MCI phase in patients diagnosed clinically. In line with the limited retrospective work in MCI-LB, this group shows impaired attention, visuospatial and executive function (Cagnin, Bussè, Gardini, et al., 2015; Jicha et al., 2010; Yoon et al., 2015). MCI-AD is associated with verbal learning and memory deficits, although there is likewise evidence of executive dysfunction and slowed cognitive speed. The use of traditional significance testing alongside effect sizes, percentile standings and discriminant analysis permitted a more in-depth analysis of neuropsychological data in the current chapter.

Overall, the findings of poorer visuospatial and executive ability in MCI-LB than MCI-AD is in line with previous work (Alescio-Lautier et al., 2007; Cagnin, Bussè, Gardini, et al., 2015; Donaghy, Taylor, et al., 2018). However, processing speed emerged as the most potent differentiator of MCI-LB Probable from both controls and MCI-AD, suggesting that processing speed may offer additional value in understanding and recognizing cognitive impairment in the MCI stages of disease. The following chapters will attempt to disentangle the contribution the domain-general resources of processing speed and executive function to higher-order cognitive activities such as visuospatial function, long term visual memory, and verbal learning and memory.

Analyses were run in the present study with MCI-LB Possible as well for completeness. However, the interpretation focussed on the MCI-LB Probable diagnostic category as it is more robustly representative of LB disease by definition. MCI-LB Probable are very unlikely to be the “worried well,” that is, misdiagnosed control subjects, because they have confirmed clinical symptoms. MCI-LB Possible and MCI-AD, on the other hand, have less demonstrable clinical symptoms of either aetiology. The interpretation of MCI-LB Possible relative to MCI-LB Probable remains to be clarified, and this will be best achieved during longitudinal follow up, when the potential progression of biomarkers and symptoms in these patients will become clear. It will be intriguing to consider whether MCI-LB Possible should be considered as a milder form of MCI-LB Probable or, alternatively, if it captures a more highly

heterogeneous group than MCI-LB Probable, consisting of a mixture of individuals likely to convert to DLB, those that remain “stable” MCI cases, or even those who revert to normal cognition (“false positive” MCI). MCI-AD, on the other hand, had the highest proportion of misclassification in my stepwise discriminant analysis. There is an a priori expectation that some MCI-AD participants will be revealed at follow-up to be stable MCI, demonstrate “normal” cognitive status or show LB pathology. For these reasons, MCI-LB Probable will continue to be the primary group of interest in the present study as they are the most representative of the underlying pathology of interest. Instances in which MCI-LB Probable and MCI-AD do differ significantly (despite the potential presence of LB pathology in a large proportion of MCI-AD) may indicate especially salient neuropsychological effects of LB disease.

Chapter Five: The component structure of cognitive performance in MCI and healthy older controls

5.1 Introduction

Overview

In Chapter Four, univariate analyses of outcome variables from the battery provided understanding of the neuropsychological profiles of the patient subgroups broadly. In particular, the emergent classification of MCI-LB Probable was clarified through visualization using forest plots and discriminant analyses relative to age-matched healthy controls and MCI-AD. Processing speed emerged as particularly impaired in MCI-LB: their worse performance on DSST relative to controls had the largest effect size of all the tasks (g = -1.99), and the second largest effect size relative to MCI-AD (g = -1.20). Particularly high percentages of MCI-LB Probable performed at or below the 16th percentile of control performance in multiple processing speed indices. MCI-LB was also observed to have impairments in executive and visuospatial abilities.

Data reduction techniques

The use of a comprehensive neuropsychological battery of established, standard measures, as well as a few more experimental tasks (VPT, Pareidolia Test), resulted in a large number of outcome variables in the present study. Use of a comprehensive battery of neuropsychological tests, while useful to capture the breadth of the domains, poses several methodological challenges. Firstly, a large number of variables can make more advanced modelling unwieldy and requires substantial correction for multiple comparisons, reducing power. The univariate analyses of Chapter Three, for example, were not corrected for the high number of ANOVAs and independent samples t-tests performed. Multivariate techniques, such as hierarchical linear modelling, will also benefit from the use of targeted neuropsychological variables in order to retain power. Secondly, a large number of tests can be unwieldy to report in entirety in journal articles and may result in selection biases in presenting only significant results. Thirdly, the use of large batteries can often lead to contradictory findings within domains. However, by omitting tasks the breadth of a domain construct may be lost. Executive function, for example, involves multiple components including set-shifting, updating, and monitoring (Miyake et al., 2000). These may therefore not be reliably and validly captured by any single executive function outcome measure. The use of composite

domain scores may help to overcome these methodological challenges. Composites have been suggested to help bypass task idiosyncrasy, avoid multiple comparisons, and increase the power of detection of cognitive change (Crane et al., 2012; Gibbons et al., 2012). This approach is advantageous in terms of reducing large datasets into manageable variables for multivariate analyses and facilitating comparisons between studies.

A common technique of composite scores is to use of a priori determined domains. Composites are derived from variables grouped by theory-driven assumptions of the task outcome variables and the domain itself. Composites are typically operationalized as average z-scores of a number of variables to retain the facets of the domain. Alternatively, a data-driven approach can be a more sophisticated method of reducing redundancy, in a bottom-up manner. The data may reveal to be organized analogous to the *a priori* domain assumptions and one can be more confident in the appropriateness of these groupings. Moreover, in a data-driven approach the process of determining the composites itself can be illuminating: performed iteratively and both using the sample as a whole and separately by subgroup, the procedure offers insight on underlying factor structure of neuropsychological performance.

The present chapter therefore analysed the neuropsychological data using principal components analysis (PCA). PCA is a multivariate data reduction technique to extract the crucial data and reduce redundancy from a dataset by using a smaller number of linear combinations that captures the more numerous correlations among a set of variables (Abdi & Williams, 2010). Mathematically, PCA minimizes the sum of the squared perpendicular distances to the axis of the principal component (Truxillo, 2003). This is achieved by transformation of data to a coordinate system that places the largest linear combination of data variance on the first dimension, the second largest on the second dimension, and so on. (Rodríguez, de Paz, Rocha, & Riverola, 2008). Principal components produced by the PCA are composites of original variables, weighted to contain both common and unique variance. These methods of combination retain maximal variance from the original variables, but each composite ultimately includes weighting from all entered items. Instead, the variables identified as loading together will be used to manually create unweighted composites (average z-scores). The PCA will be employed using an iterative method in which variables are selectively removed and added to determine how tests of interest may change loadings on the components. When performed by whole sample and separately by

subgroup, PCA can therefore demonstrate whether the processes that are particularly consequential in neuropsychological performance differ by group.

Rotation methods in PCA

In factor analysis, one of the primary decisions is the type of rotation used, as this will impact how the extracted components are interpreted. Rotation in factor analyses like PCA optimizes the factor structure so that the importance of the extracted factors is equalized (Field, 2009). There are two primary approaches to rotation used in PCA, with ongoing debate as two which is most useful, orthogonal or oblique (Field, 2009; Stevens, 2002). While each of the two approaches has multiple methods of implementation, the two primarily used are Varimax (orthogonal) and direct Oblimin (oblique).

Varimax rotation (Kaiser, 1958) is the most popular rotation method in PCA (Abdi & Williams, 2010). The method iteratively searches for a model in which the linear combination of retained variables maximizes the variance of the squared loadings (Abdi & Williams, 2010). It prioritizes the creation of factors that are as independent as possible from others. The variables that are retained will load very highly onto only one component. Each component will be loaded by generally a fewer number of these highly-loaded variables, and the remaining variables will load by zero or to a very small amount. Component matrices in PCAs run with Varimax rotation are hence more readily interpretable: each variable will only be associated with one component, and each component includes a smaller number of variables. This allows for useful, theoretical distinction between the components; however, this is at the expense of minimizing the representation of potential, complex interrelationships between the cognitive processes.

In contrast to Varimax rotation, Oblimin rotation results in a model that permits correlation between the extracted factors. The procedure results in two matrices: pattern and structure. The pattern matrix shows the loadings of each variable on a component after removal of the influence of other variables. In contrast, the structure matrix provides the unadjusted factor loading coefficients of each variable. Therefore, if the factors are independent, i.e. orthogonal, the pattern and structure matrices will match. Divergence between the matrices is also useful in illustrating where variables/ factors load across the data rather than stand independently. Indeed, the expectation in neuropsychology is substantial interdependence between cognitive processes (Field, 2009).

These differing techniques provide an opportunity for a process by which both the orthogonal and oblique rotation methods are used and compared towards development of a final, stable model in which the two methods converge. This method has been recommended by several authors (Pedhazur & Pedhazur Schmelkin, 1991; Stevens, 2002) as serving to create "interpretable composite scores for use in subsequent regression analyses" while also better understanding the "factor structure underlying the tests and processes employed" through the iterative process. Using Oblimin rotation, variables with multiple loadings across the factors will be iteratively removed, with the strengths of the factor re-assessed at each step. Attention will be paid to whether certain processes or variables emerge as important in the data structure, perhaps by loading across multiple factors. Through process, factors of increasing independence will be produced until the pattern and structure matrices of the Oblimin matrix will converge. At this point, by definition, the model will be orthogonal, and thus identical to the Varimax rotation solution in terms of which variables load onto which factors.

This approach thus offers two important opportunities for data analyses. Firstly, the robust dataset will be reduced to interpretable composite scores informed by the data and for use in subsequent regression analyses. Secondly, by comparing the two rotation methods, the interrelatedness of the tests and processes targeted by the variables will be better understood. However, given that this is a data-driven approach, with the above-mentioned advantages in understanding this novel patient group, use of the resulting factors involves subjective interpretation by the researcher. The components are interpreted in an attempt to accurately capture the breadth of clustered variables, but such readings are subjective and likely incomplete.

5.2 Methods

Materials and participants

The neuropsychological tasks, outcome measures, and administration procedures are described in Chapter 4.2. All outcome variables were assessed for appropriateness for use in the PCA (described below). PCAs were attempted both as the entire group (*n = 93;* controls, MCI-AD and MCI-LB Probable and Possible) and separately by subgroup (controls [*n* = 31], MCI-AD [*n* = 18] and MCI-LB Probable [*n* = 30]). See Chapter Two for full description of participants.

Data cleaning and assessment

Following recommendations of Field (2009) and Stevens (2002), the data were firstly cleaned for use in the PCA. Of tests with multiple possible outcome measures, only the most representative of specific cognitive processes were extracted. The RAVLT in particular produces a large number of outcome variables. Because of the anticipated relevancy of this test to MCI-AD in particular, the nine most common outcome measures were retained at this early stage. The remaining variables were then assessed along a number of criteria for inclusion in analysis. Variables with large ceiling effects or a high proportion of missing data were removed. All those variables retained had a maximum of n = 13 (14%) missing data points, which were replaced using an expectation-maximization approach. Little's Missing Completely at Random Test (MCAR) test was run to test whether data were missing completely at random; however, Little's MCAR test was significant, Chi-Square (501) = 577.78, p = .010. MCAR was repeated without variables that were derived from others, specifically Trails Difference, Trails Ratio, Stroop Ratio, VPT Ratio, RALVT Percent Forgetting and Coding Time. In this case, the MCAR test was not significant, Chi-Square (350) = 374.09, p = .180. SPSS's expectation-maximization approach was used to replace the missing values from 20 variables. The derived values (Trails Difference, Trails Ratio, Stroop Ratio, VPT Ratio, Coding Time) were then re-computed.

PCA procedure

Standard exclusion of low-loadings (r < .03) may be too lenient a criterion for PCA data cleaning. Instead, correlation matrices of retained variables were inspected before entry into the PCA for any extreme values or extremely high, weak or nonsignificant correlations. Such variables were evaluated and removal considered in favour of others with a greater number of moderate, significant correlations. Matrices were sorted into order of correlation strengths can be found in Appendix H.

PCAs were performed using both orthogonal and oblique rotations with Kaiser normalisation as an exploratory approach, as outlined in more detail below. For each PCA, the factorability of the variables was addressed using the Kaiser-Mayer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. KMO statistics range from 0 to 1, with values close to 1 indicating data are most appropriate for factor analysis. If KMO is close to zero, this indicates a large sum of partial

correlations versus the sum of correlations, leading to indistinct, unstable factors. Kaiser (1974)) recommends cut-off of values greater than 0.5 as “acceptable” (0.5-0.7 as “mediocre”, 0.7-0.8 “good”, 0.8-0.9 “great”) (Hutcheson & Sofroniou, 1999). A significant Bartlett’s test of sphericity indicates that there is a suitable relationship between the entered variables (Stevens, 2002). In contrast to orthogonal rotations like Varimax, oblique rotations (Oblimin) result in two rotated component matrices: pattern and structure. Typically, the pattern matrix is preferred for interpreting factors because the coefficients indicate the unique load of a given factor onto variables. The coefficients are thus similar to standardized partial regression coefficients in quantifying the relative increase in score (in SDs) if a participant’s latent factor score increased one SD, if other factors are held constant (Thompson, 2004). However, pattern matrices are more unstable and susceptible to small sample sizes (Gorsuch, 1983). Structure matrixes, on the other hand, provides coefficients indicating the zero-order correlation between a factor and a variable; that is, they are without reference to relationship with other factors (Thompson, 2004). If two factors are highly correlated, the difference in the pattern loading and structure loading of a variable will be greater. The loading coefficient will not necessarily rise equally upon both factors, as the loading can represent different aspects of the variable’s variance (Thompson, 2004). As such, Oblimin rotation provides valuable information on the relative independence of each variable or shared component across the resulting factors. Through the iterative process of re-assessing the strength of these factors as those variables that are multiple-loading are removed, a set of independent factors will be produced. As described above, when the pattern and structure matrices are equivalent this indicates equivalency with orthogonal rotation. Orthogonal rotation produces uncorrelated factors, i.e. factors that are as unique as possible; hence, variables can be interpreted based on their loadings by only one factor without concern for others that may also effect that item.

5.3 Results

5.3.1 PCA #1: Whole group

PCA #1 - Correlation matrix

Low numbers of significant correlations were observed with RAVLT Proactive interference (all $r < .3$), RAVLT Percent Max Recalled at Long Delay, RAVLT Percent Forgetting, RAVLT Retroactive Interference, and VPT Ratio. These variables were removed, which also removed some of the very high loadings observed. The average correlation strength of Digit Forward was 0.21 and it was also removed. In order to

eliminate prevalence of very high loadings (over .8), the following variables were removed: Trails Ratio, Trails B, MTCF Percent Retained, VPT Low, RAVLT Long Delay, and DSST Coding Time. In these cases of high correlations between pairs of variables, the variable with a higher number of significant correlations within the target range (.3< *r* < .8) was retained. This resulted in 21 remaining variables for initial entry in the PCA. Recommended guidelines for dataset with n < 300 recommend 5-10 cases per included variables (Kass & Tinsley, 1979). Use of 21 variables with *n* = 79 equates to only 3.8 cases per variable, outside of the recommendation. However, given the novel nature of the dataset and the iterative procedure utilized within the PCA, the decision was made to enter this higher number of variables. Appendix E contains additional output from the iterative process of PCA#1 described below.

Table 15 PCA 1: Communalities (whole group; initial model)

	Extraction
ACE Language	0.42
RAVLT Max T1:T5	0.86
RAVLT "Learning"	0.69
RAVLT Short Delay	0.77
RAVLT Recognition B	0.78
ACE Visuospatial	0.64
Corsi	0.69
MTCF Recall	0.70
VPT High	0.77
FAS	0.63
Stroop C	0.84
Stroop CW	0.81
Stroop Ratio Int.	0.83
Trails Difference	0.73
Digit Backwards	0.69
DSST	0.90
Symbol Copy	0.82
Error Check	0.83
Trails A	0.78
SRT	0.64
CRT	0.70

PCA #1 - Varimax Rotation

The PCA was first run using Varimax rotation. The factorability of the variables was confirmed in the initial, unrotated model using KMO = .840. Bartlett's test of sphericity was significant (X^2 = 1344.59, *df* = 210, p < .001). Inspection of the Anti-image Matrices output showed the diagonals of the correlation were all greater than 0.5, with the lowest value being .528 (Stroop Ratio Interference). Communalities ranged from .419 to .895 (*M* = 0.738; see Table 15). In PCA, initial communalities are

Table 16 PCA 1: Varimax rotatated component matrix (whole group; initial model)

	Component				
	1	2	3	4	5
ACE Language	.211	.439	.156	.339	-.208
RAVLT Max T1:T5	.351	.804	.040	.059	.296
RAVLT "Learning"	.183	.803	-.050	.016	.095
RAVLT Short Delay	.156	.764	.209	.118	.323
RAVLT Recognition B	.068	.287	.085	-.058	.827
ACE Visuospatial	.265	.284	.669	.208	.044
Corsi	.212	.161	.384	.270	.629
MTCF Recall	.075	.484	.636	.218	.071
VPT High	.394	.491	.514	.327	.030
FAS	.752	.032	.003	.219	-.135
Stroop C	.760	.217	.312	-.332	-.098
Stroop CW	.744	.256	.174	.344	.198
Stroop Ratio Int.	-.233	-.034	.097	-.817	-.319
Trails Difference	.668	.267	.328	.257	.205
Digit Backwards	.261	.194	.198	.720	-.158
DSST	.818	.274	.281	.196	.182
Symbol Copy	.798	.172	.293	.128	.214
Error Check	.796	.243	.286	.174	.149
Trails A	.706	.273	.360	.262	.088
SRT	.377	-.153	.666	-.154	.051
CRT	.308	-.063	.731	-.052	.253

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization; converged in 8 iterations.

1.00, based on the assumption that all data variance is common. After extraction, the communalities indicate the common variance in the data structure. For example, Table 15 indicates that only 42% of the variance associated with ACE Language was shared variance, versus 90% associated with the DSST. From a factor-perspective, it can be said that 90% of DSST's variance was explained by the retained factors.

Five factors were extracted in the initial model. The first component explained 25.93% of the variance, with the subsequent three explaining 15.34%, 14.19%. 10.07% and 8.30% (cumulative variance = 73.83%). Acceptable threshold of loadings are debated, but using a criteria based on sample size is generally advised (Hair, Anderson, Tatham, & Black, 1998). Stevens (2002) suggests loadings are practically significant depending the sample size and recommends a formula based on the more stringent alpha level of .01 to avoid errors due to the multiple comparisons involved. Thus, for a two-tailed test with $\alpha = .01$ with 93 participants, absolute values of loadings between $n = 100$, >2(.256) = .512 and $n = 80$, >2(.286) = .572 would be significant.

The clustering of the variables on the five components (see Table 16) suggested that component 2 relates to verbal learning and memory (RAVLT: Max A1:A5, Learning, and Short Delay). Component 1 was loaded by processing speed

and executive function measures, such as FAS, Trails A and difference, Stroop, the DSST and its variants. Component 3 included both visuospatial (MTCF Recall, ACE-Visuospatial) and processing speed (SRT and CRT) variables. Components 4 and 5 were only loaded by two tasks each. In this initial model, no variables load above the threshold on more than one component, but two variables do not load above the threshold on any component: ACE Language and VPT High.

Table 17 PCA 1: Oblimin Rotation Pattern Matrix (whole group)

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.288	-.715	.038	-.243	.089
RAVLT "Learning"	.125	-.774	.074	-.009	.139
RAVLT Short Delay	.031	-.599	-.003	-.318	.302
RAVLT Recognition B	-.025	-.219	.008	-.880	-.161
ACE Visuospatial	.091	.010	-.017	.000	.777
Corsi	.072	.057	-.226	-.664	.219
MTCF Recall	-.140	-.191	-.026	-.032	.859
VPT High	.253	-.215	-.126	.029	.651
FAS	.863	.036	-.127	.167	-.171
Stroop C	.817	-.102	.487	.116	.081
Stroop CW	.738	-.115	-.242	-.111	.052
Stroop Ratio Int.	-.183	-.027	.845	.218	.034
Trails Difference	.634	-.057	-.119	-.184	.179
Digit Backwards	.196	-.007	-.596	.217	.408
DSST	.822	-.094	-.061	-.139	.081
Symbol Copy	.818	.006	-.008	-.209	.016
Error Check	.795	-.073	-.040	-.090	.109
Trails A	.662	-.077	-.110	-.002	.294
SRT	.346	.426	.295	-.191	.359
CRT	.218	.382	.190	-.400	.438

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization; converged in 19 iterations.

PCA #1: Oblique Oblimin Rotation – Initial Model for whole group

Direct Oblimin matrices were next computed for comparison with the Varimax (orthogonal) rotation, as discussed above, after removal of ACE-Language. In terms of variable distribution, the Oblimin oblique rotation appeared quite similar to the orthogonal Varimax solution. In the pattern matrix (Table 17, loadings below threshold shaded out), the first component loaded eight variables tapping executive function (FAS), more basic processing speed measures (Trails A, Symbol Copy, Error Check Stroop C), and processing speed with executive weighting (Stroop CW, Trails Difference). This therefore included executive function and processing speed outcome variables. Component 2 more matched the orthogonal solution as verbal

Table 18 PCA 1: Oblimin Rotation Structure Matrix (whole group)

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.494	-.804	-.120	-.469	.431
RAVLT "Learning"	.296	-.803	-.070	-.218	.322
RAVLT Short Delay	.355	-.704	-.125	-.531	.523
RAVLT Recognition B	.156	-.335	-.024	-.853	.166
ACE Visuospatial	.492	-.126	-.082	-.294	.824
Corsi	.385	-.131	-.252	-.754	.494
MTCF Recall	.341	-.315	-.097	-.326	.830
VPT High	.627	-.366	-.237	-.303	.813
FAS	.742	-.049	-.222	.000	.218
Stroop C	.777	-.134	.360	-.140	.442
Stroop CW	.842	-.281	-.362	-.349	.505
Stroop Ratio Int.	-.331	.159	.866	.264	-.191
Trails Difference	.799	-.221	-.227	-.428	.587
Digit Backwards	.428	-.153	-.648	.013	.475
DSST	.922	-.253	-.192	-.404	.571
Symbol Copy	.882	-.145	-.120	-.433	.509
Error Check	.890	-.221	-.165	-.354	.563
Trails A	.839	-.232	-.230	-.296	.655
SRT	.484	.335	.287	-.334	.517
CRT	.472	.246	.183	-.546	.617

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

learning and short term memory: RAVLT short delay, "Learning" and Max T1:T5. Component 5 was a visuospatial component somewhat similar to component 3 in the Varimax solution (ACE Visuospatial, MTCF Recall, VPT High). Only two variables loaded onto Components 3 and 4 (Component 3: Stroop Ratio Interference and Digit Backwards, Component 4: RAVLT recognition and Corsi). The Structure matrix (Table 18) also revealed that more than one variable loaded significantly (and above the more conservative threshold) across two measures: Trails A, DSST and VPT High. The reaction time measures (SRT and CRT) were not loaded above the threshold by a factor, as opposed to the varimax solution in which they were also loaded by component 3. These variables were thus iteratively removed one at a time from the Oblimin model. After removal of both CRT and SRT, KMO remained acceptable (0.845) and the components were loaded by the same variables in the Pattern matrix as prior to removal. However, in the Structure Matrix (Table 18) multiple variables loaded across more than one component. In particular, VPT High (visuospatial), Trails A (processing speed), and Trails Difference (executive function/ inhibition) loaded onto both components 1 and 5 beyond the threshold. Hence, with

an exploratory aim, three branches of PCA were pursued in which one of these three multi-loading variables were removed first.

Upon removal of VPT High, the KMO remained acceptable, test of sphericity remained significant (<.001), and all diagonals of anti-image matrix were above 0.500. Four components were extracted with cumulative percent explained of 74.34%. Component 1 remained loaded onto executive function and processing speed measures and Component 2 onto verbal learning and short term memory. Component 3 positively loaded onto Stroop Ratio Interference and negatively onto Digit Backwards. Component 4 remained associated with visuospatial ability, but was no longer loaded by ACE Visuospatial above the threshold and it also loaded onto RAVLT Recognition. The highest loading by Component 1 was 48.57%. No variables loaded across multiple components. Therefore, removing VPT High also resulted in a model in which the double loadings of Trails A and Trails Difference no longer occurred. In the subsequent steps, the following variables were removed (as justified by): ACE Visuospatial (not loaded by a component above the threshold in the pattern matrix), MTCF Recall (not loaded by a component above the threshold in the pattern matrix), Stroop Ratio Interference (correlation matrix diagonal < 0.500), and Digit Backwards (no longer loaded by a component in either matrix). Finally, this resulted in a model in which the pattern and structure matrices matched in terms of factor loadings. The model had an acceptable KMO (0.875) and three components that cumulatively explained 76.99% of the total variance. Components 1 and 2 remained similar in their loading interpretations. Component 1, explaining 54.84%, is interpreted as executive function and processing speed loadings (FAS, Trails A, Symbol Copy, Error Check Stroop C, Stroop CW, and Trails Difference). Component 2 (RAVLT Max, “Learning”, Short Delay) is a verbal learning and short term memory factor. Component 3, however, is less easily interpreted as it is loaded by RAVLT Recognition (verbal memory) and Corsi Blocks (visuospatial working memory).

In contrast to the matching matrices achieved in Branch 1, Branches 2 and 3 of PCA #1 (first removing Trails Difference and Trails A, respectively), failed to converge. Branch 2 proceeded until a second branching was necessary as both VPT High and RAVLT Recognition no longer loaded in the pattern matrix. First removing VPT High led to a model in which the Pattern and Structure Matrixes matched with three components. However, if RAVLT Recognition is removed, the model resulted in multiple loadings of processing measures across two components and failure to converge with iterative removal. Similarly, removal of Trails A first (Branch 3) resulted

in the need to remove Stroop Ratio Interference due to an unacceptable correlation matrix diagonal value. Following this, a multitude of variables (VPT High, DSST, Trails Difference, Digit Span Backwards and Corsi) are loaded by two components. Attempts to iterative remove these multiply-loading variables failed to result in a stable model.

Table 19 PCA 1: Optimised Model Rotated Component Matrix

	Component		
	1	2	3
RAVLT Max T1:T5	.328	.852	.243
RAVLT "Learning"	.152	.860	.006
RAVLT Short Delay	.203	.797	.338
RAVLT Recognition B	.011	.284	.838
Corsi	.334	.084	.810
FAS	.753	-.047	-.026
Stroop C	.776	.163	-.067
Stroop CW	.796	.326	.163
Trails Difference	.765	.211	.351
DSST	.866	.278	.249
Symbol Copy	.828	.214	.231
Error Check	.863	.211	.228
Trails A	.820	.267	.165

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization, converge in 4 iterations/

PCA #1 - Optimised Model Whole group

Within the first branch of PCA #1 (whole group), the matched loading of individual variables onto components indicates orthogonal factors. This was confirmed by performing an orthogonal Varimax rotation with the retained thirteen variables. The final model consists of three components (Table 19), which cumulatively explained 76.99% of total variance. Component 1 (42.48% variance explained) loads onto FAS, Stroop C and CW, Trails A and Difference, DSST, Symbol Copy, and Error Check. Thus, it clearly relates to speed of processing speed (DSST highest loading of .866), but executive weighting is also clear. It was thus interpreted as *executive function and processing speed*. Component 2 (20.05% variance explained) relates *to verbal learning and short term memory* (RAVLT Max T1:T5, "Learning", and Short Delay). These first two are similar to the results of the initial model. Lastly, Component 3 explained only 14.47% of variance and is less easily interpretable. It was loaded nearly equally strongly by Corsi and RAVLT Recognition. The KMO measure of sampling adequacy was excellent at .875. Barlett's test of sphericity was significant (X^2 = 832.96, *df* = 78, $p < .001$). Inspection

of the Anti-image Matrices output showed the diagonals of the correlation were all much greater than 0.5, with the lowest value 0.725 (RAVLT “Learning”). Communalities ranged from 0.570 (FAS) to 0.892 (*M* = 0.770).

5.3.2 PCA #2: Control Participants

PCA #2 - Correlation matrix

The PCA was then re-run for patients and control subjects separately from the point of correlation matrix inspection to investigate differences in the resultant models. The same procedure described for the whole group (see section 5.3.1) was pursued, although given the smaller number of controls (*n* = 31), a stricter approach of elimination at this point was taken. Entry of 15 variables with *n* = 31 equated to a very low 2.1 cases per variable, but the decision was made (as with the whole sample) to enter a higher number of variables for review during the PCA process. An acceptable threshold of loading for the control subsample was set as the absolute value .722, based on the lowest sample size provided by Stevens (2002) (*n* = 50). Because the control sample is only 31, interpretation must be made cautiously. In the correlation matrix, there were no significant low correlations ($r < .3$), but as in the whole group, very high correlations ($r > .8$) were observed between multiple pairs of outcome variables. The mean loadings of significant variables for controls (0.356) was higher than in the whole group (0.510), but there seemed to be fewer significant correlations between variables. Initial removal resulted in 15 variables entered into the PCA. See Appendix F for the correlation matrices and additional SPSS output for the PCA#2 summarized below.

PCA #2: Varimax Rotation (controls) initial model

The initial Varimax rotation showed sampling adequacy (KMO = .620) and a significant Bartlett’s Test of Sphericity ($X^2(105) = 361.96$, $p < .001$), but multiple variables had low anti-image correlation values. These variables were excluded iteratively. In the resulting model, KMO was very high (.813) and Bartlett’s Test again significant (X^2 (55) = 168.66, $p < .001$). Diagonals of the anti-image correlation matrix were high (all .713 or greater). The mean of the PCA communalities was 0.717, ranging from .580 (Digit Backwards) to .845 (FAS). Three factors were extracted in the initial model. The first component explained 47.35% of the variance, with the subsequent two explaining 15.01%, and 9.29%, for a cumulative variance explained of 71.65%.

However, when unacceptable thresholds (below .722) were removed, Digit Backwards, Trails A and Trails B did not load significantly onto a component. Component 1 consists of RAVLT Max T1:T5, Stroop CW and Symbol Copy. Its interpretation is difficult as it combines Verbal Learning, executive and psychomotor variables. Component 2 is clearly a *visuospatial component* with MTCF Recall, VPT High and VPT Low. The only variable loaded onto component 3 above the threshold was FAS (*executive function*). Thus, this initial model suggests an important role for executive function as it is prominent across two components.

PCA #2: Oblique Oblimin Rotation – Initial Model

Direct Oblimin matrices were next computed for comparison with the Varimax (orthogonal) rotation, as was pursued with the total sample. Again, three factors were extracted, and weak correlations between the extracted factors was observed. In this first Oblimin model, the pattern and structure matrices matched except for Trails A, which does not load above the predetermined threshold in the Pattern Matrix. As with the group overall, the Oblimin oblique and orthogonal Varimax rotation models were very similar. However, Varimax and Oblimin differed in the loadings of Trails A and B and Digit Backwards. Oblimin Component 1 matched Varimax in terms of RAVLT Max T1:T5, Stroop CW and Symbol Copy, plus the addition of DSST and Trails A. Thus, Component 1 might be interpreted as a *processing speed* component with strong executive and verbal learning loadings. Components 2 and 3 matched the Varimax initial model and are thus *visuospatial* and *executive components*, respectively.

Iterative removal of variables to obtain an optimized model led to a final model (KMO = .748) with seven retained variables. The matched loadings of the Pattern and Structure matrix using Oblimin rotation was reconfirmed with orthogonal Varimax rotation. The communalities for the PCA ranged from 0.560 (MTCF Recall) to .818 (Stroop CW), with a mean of .726. The final model includes only two components, explaining 50.44% and 22.13% variance respectively. Component 1 is interpreted as a factor of p*rocessing speed* with some executive weighting (DSST, Symbol Copy, Trails A and Stroop CW). Component 2 can be easily assumed to relate to v*isuospatial Memory*: MTCF Recall, VPT High and Low. This final two component solution retained the overall pattern of the initial Oblimin model that produced components representing *processing speed* and *visuospatial function*. However, through reaching this optimised model, no verbal variables were retained.

5.3.3 PCA #3: MCI-LB Patients

PCA #3 – Correlation Matrix

MCI-LB Probable had higher mean significant Pearson correlation values than controls and the group overall (0.529). The significant loadings were all above 0.300. Variables were removed due to problematic correlations as was done in the earlier models. This resulted in 17 variables for entry into the PCA. See Appendix I for the correlation matrix and supplementary output for PCA#3 summarized below.

PCA #3: Varimax Rotation (MCI-LB Probable) initial model

PCA was then run in MCI-LB Probable using Varimax rotation. Acceptable threshold of loading for the MCI-LB subsample (*n* = 44) was determined as .722 (Stevens, 2002). A number of the anti-image correlation matrix diagonals were below .500 at first entry and removed. After this, the KMO was acceptable (.787) and four factors were extracted, explaining a cumulative 79.32% of variance. However, after removal of loadings below .722 (borderline values in yellow), no component loaded Trails B and Trails A above the threshold. Component 1 (26.07% variance explained) consisted of *executive function and processing speed* variables (FAS, DSST, Symbol Copy and Stroop CW [marginal loading threshold]). Component 2 consisted of *visuospatial* variables (ACE Visuospatial, Corsi and MTCF Recall). Component 3 can be read as a *verbal learning and memory* factor (RAVLT Max T1:T1, Short Delay and Long Delay). Component 4 was similar to component 1 in capturing *processing speed* (Stroop C), with an emphasis on a cognitive/ working memory component (CRT).

PCA #3: Oblique Oblimin Rotation – Initial Model (MCI-LB Probable)

The seventeen variables were re-entered into a PCA with Oblimin (oblique) rotation. Again, four factors were extracted, and weak correlations between the extracted factors was observed. Unlike in the Varimax model, the Oblimin rotation yielded fewer variables loading across components. In the pattern matrix, the first component was loaded only by FAS above the threshold, showing the importance of executive function. The three lower components were similar to the Varimax solution. Component 2 represents *verbal learning and memory*, loaded by RAVLT Max Learning T1:T5, Short and Long Delay free recall. Component 3 can be clearly interpreted as *visuospatial* (ACE Visuospatial, Corsi and MTCF recall). Component 4 again represents a second *processing speed* measure (Stroop C, CRT). In the

structure matrix of this oblique rotation model, the DSST loaded on component 1, but loaded nearly to the pre-set threshold on component 4 as well. Similarly, Trails A loaded near threshold level on three components, suggesting strong correlations of the components with processing speed.

An optimised model was sought using iterative removal of variables with poor or absent loading or high collinearity. In the subsequent steps, processing speed measures (Trails A, Trails B and Stroop CW) were removed based on near-acceptable threshold loading in the Pattern Matrix across two components: component 1 (*executive and processing speed*) and 2 (*visuospatial*). Trails A, Trails B and Stroop CW were firstly removed one at a time. This resulted in a model with which the DSST loaded near but below the conservative threshold on two components that loaded other processing speed and executive function measures. At this stage, VPT High also emerged in the structure matrix as loading quite strongly onto *visuospatial* component 3, but was also moderately correlated (0.580) with the component loading onto *verbal learning and memory* variables (RAVLT Max T1:T5, Short and Long Delay). It was not loaded above a threshold in the pattern matrix (-0.624). At this stage, either DSST or VPT High could be removed. In both scenarios, processing speed measures (Symbol Copy, Stroop C, DSST) loaded strongly or moderately across two components.

Variables were removed in instances of falling below where the anti-image correlation diagonals fell below the threshold. If DSST was removed, the pattern and structure matrices eventually matched; however, two variables did not load above the pre-set threshold in the pattern matrix in this case (ACE Visuospatial, 0.675; MTCF Recall, 0.697). Component 1 (43.28% variance explained) can be interpreted again as v*isuospatial* (ACE Visuospatial, Corsi, MTCF Recall), component 2 (21.01% total variance explained) as v*erbal learning and memory* (RAVLT Max A1:A5, Short and Long Delay), and component 3 as a *processing speed* factor (Stroop C and CRT). The cumulative variance explained by the model was 77.77%. However, when VPT High was removed first instead of DSST, the extracted factors were less easily interpretable. Component 1 loaded onto both visuospatial *and processing speed* variables (ACE Visuospatial, MTCF Recall Stroop C and CRT). Component 2 remained a v*erbal learning and memory* component (RAVLT Max A1:A5, short and long delay). Component 3 was similarly difficult to interpret, with only two variables*:* FAS and Symbol Copy, relating to *executive and psychomotor speed.*

These divergent results suggested instability in the factor structure in the MCI-LB Probable data subset. To further investigate this, the Oblimin model was re-run with either DSST or VPT High omitted at first entry (*n* = 16 variables). A number of steps to remove variables with insufficient loading eventually failed to converge after 100 iterations. Therefore, without inclusion of these two variables at first entry, the models ultimately collapsed upon themselves.

5.3.4 PCA #4: MCI-AD Patients

Inspection of the MCI-AD correlation matrix revealed fewer, but broadly stronger significant correlations than in controls or MCI-LB (see Appendix J). The process of inspection of intercorrelations before entry into PCA was attempted as with the whole group and MCI-LB Probable samples; however, using the same criteria resulted in only three suitable variables for entry into the PCA. Instead, the decision was made to enter fourteen variables, given that the significant intercorrelations were of moderate size and the PCA was exploratory. However, upon entry of these fourteen variables, the PCA produced a model with an inadequate KMO score (.366). This is likely due to the small sample size (*n* = 18). For this reason, a PCA within the MCI-AD patient group was abandoned.

5.3.5 Composite calculation

When using the entire sample in the PCA (whole group), three stable components emerged, but the third component only consists of two variables, RAVLT Recognition and Corsi Blocks, which are difficult to interpret as representing a singular cognitive construct. Moreover, the exploratory PCA process utilised above revealed instability in the factor structure of MCI-LB Probable and that the MCI-AD was unsuitable for PCA, largely due to the small sample size (*n* = 18). As such, the decision was made to utilize the two control-informed composites of processing speed (DSST, Symbol Copy, Trails A and Stroop CW) and visuospatial memory (MTCF Recall, VPT High and Low) and the individual tests that emerged as important across the data when conducting the PCA. Specifically, the DSST and VPT High loaded across multiple components at multiple steps. Therefore, composites and the singular variables of interest were converted to control-centred *z*-scores for use in multivariate analyses in subsequent chapters.

5.4 Discussion

The present chapter aimed to reduce redundancy in the large dataset by determining appropriate composite scores using an exploratory PCA approach. The comprehensive neuropsychological battery resulted in a very large number of outcome measures, particularly in verbal learning and memory, all of which could be argued to validly capture aspects of a domain. Often domain-level composites are computed based on *a priori* theoretical assumptions about a domain; however, PCA can be used to provide confidence that tasks have been grouped to domains correctly. Moreover, the series of PCAs conducted also served to further clarify the profile of test performance and neuropsychological processes, both in the sample overall and individually for MCI-LB Probable patients and controls. The exploratory use of both Varimax (orthogonal) and Oblimin (oblique) rotation methods in the PCA allows consideration of which variables may be particularly important across domains within the data. Firstly, orthogonal rotation was used to produce factors that are maximally independent from each other. From this variable loading pattern, composite scores can be derived. Orthogonal rotation suffers, however, from ignoring the likely interrelatedness of neuropsychological processes. Therefore oblique rotation was used secondly. In an iterative process, variables were considered individually based on appropriate loadings (sufficient in magnitude [above the predetermined threshold] and unique to a single component). If the underlying structure of the data permits, this process leads to a stable model in which the oblique pattern and structure matrices are equivalent, which is then reconfirmed via a final orthogonal rotation. By using such a method in both the whole-group dataset and the group subsets separately (control, MCI-LB Probable, and MCI-AD), comparisons can be made regarding the underlying neurocognitive structure of performance. Unfortunately, MCI-AD consisted of too few participants to complete a PCA with enough power. However, inspection of the correlation matrix suggests that MCI-AD scores are less frequently correlated than in MCI-LB or controls, although those correlations that were significant tended to be quite strong. Additionally, the low number of significant associations between variables is likely in part due to the small sample size.

In MCI-LB Probable, the PCA process suggested that this data in isolation does not result in stable, discernible factors. Two divergent models with three extracted components were produced through iterative removal of variables in MCI-

LB Probable. In the first branch, components were interpreted as visuospatial, verbal learning and memory, and processing speed. In the second, the three components were visuospatial and processing speed combined, verbal learning and memory, and executive and psychomotor speed. In the second branch, it is difficult to interpret the first and third component as clean factors that relate to current theoretical understanding of cognitive domains. The first, for example, loads onto two visuospatial variables: one that measures visuospatial working memory (ACE Visuospatial) and one that taps visuospatial long-term memory (MTCF Recall). This shows domain-specific tasks in visuospatial ability loading alongside domain-general speed of processing measures. The factor may therefore be related to the processing speed component embedded within these visuospatial tasks, suggesting it is an important element of those tasks' completion. However, it is important to note that both of these visuospatial variables were loaded slightly below the pre-set threshold for acceptability following the formula by Stevens (2002). This could be further evidence of instability in the underlying data structure and/ or that only part of the visuospatial measures' variance is loaded by that factor, i.e. that that is related to processing speed.

The third component of the first branch in MCI-LB Probable also had loadings from both a processing speed measure (Stroop C), which has no motor component, and a motor-dependent measure of processing speed (CRT). CRT is the mean correct reaction time in a computerised left-right decision task. Both CRT and Stroop C measure processing speed and require sustained attention; however, the CRT requires attention be divided amongst two stimuli. It also has greater executive weighting by requiring decision making and response inhibition of the incorrect button (Magill & Anderson, 2007). Component 3 in the second model similarly combines executive (FAS) and psychomotor (Symbol Copy) measures. Thus, while these two components have substantial overlap and are not easily interpreted as representative of a unitary domain, they stress the importance of executive function and processing (including psychomotor) speed to the neurocognitive data of MCI-LB Probable. Taken together, it is possible that orthogonal rotation is unsuited to the cohort of MCI-LB Probable patients due to a less independent neurocognitive structure. Work in chapter 5 will attempt to fractionate the processes and resources that have emerged as salient across components in these analyses, namely processing speed and executive function.

In contrast to MCI-LB Probable and MCI-AD, the whole-group and control-only analyses did lead converge on acceptable models. With the whole-sample data, however, one of the three extracted components is difficult to interpret. Component 3 loads onto RAVLT Recognition, a cued long-term verbal recognition memory task, and Corsi, a visuospatial working memory task, targeting the inner scribe specifically (Logie & Pearson, 1997). It is unclear what shared factor could be loading onto these two outcome variables. Moreover, it is often recommended that factors load onto more than two variables to be assumed as suitably stable (Raubenheimer, 2004). Control data revealed a two-factor structure with only processing speed (including some executive weighting) and visuospatial memory components. In this way, the overall pattern of the initial Oblimin output that produced components representing processing speed and visuospatial function is retained, suggesting it is a more parsimonious representation of the trends in the control data overall. However, in this optimised model no verbal variables were retained. In contrast, in both the whole-group and MCI-LB subsets, the second-ranked components related to verbal learning and memory. MCI-LB Probable (both resultant models) produced a component loading onto RAVLT Max T1:T5, Short and Long Delay free recall. The data as a whole was modelled with a component with RAVLT Max T1:T5, Short Delay free recall, and the “Learning” score. Therefore, while composites of visuospatial and processing speed are supported by this control-informed PCA, verbal memory and learning will have to be investigated in the multivariate analyses separately using individual outcome measures.

It was hoped that PCA results could be compared between controls and disease-specific (MCI-LB Probable) datasets, especially given the equivocal results of the PCA of the data as a whole. However, this was not possible due to the failure of the MCI-LB Probable PCA to suitably converge and the unclear factors that emerged from the entire group. The decision was made to utilize the control-informed composites of processing speed (DSST, Symbol Copy, Trails A and Stroop CW) and visuospatial memory (MTCF Recall, VPT High and Low). This approach has several advantages. Firstly, the control group was specifically recruited for the study in order to provide more reliable and valid normative data, particularly for tracking longitudinal changes in the future. Controls were recruited to match on age and gender (to entire MCI sample). By using a local control group as the normative data, there is also an increased likelihood of equivalence between groups in unquantified socioeconomic and geographical variable. Secondly, this design helps to avoid idiosyncrasies in test

administration that might occur. The control volunteers underwent the same battery of neuropsychological tests, largely in the same order, and in the same testing contexts as patient volunteers. Thus, the control data and PCA results have utility in determining optimum composites. We can be further confident of the relevancy to the dataset as a whole as two components extracted from the control data are very similar to two of the three whole-group components. Lastly, the control visuospatial composite offers a cleaner, more distinct and theoretically-supported factor of visuospatial memory. The MCI-LB Probable visuospatial component, in contrast, clustered Corsi together with MTCF Recall. The latter variable is theoretically designed to target visuospatial long-term memory, while Corsi is taken as a "core" test of the inner scribe of the visuospatial component of multicomponent models of working memory (Logie & Pearson, 1997).

The individual tests that emerged as pertinent when conducting the PCA will also be utilized in the multivariate and MRI analyses in the subsequent chapters. Of particular interest instances are variables that consistently load significantly across two or more components. This may signal the contribution of the processes embedded in such measures to different components. Specifically in MCI-LB Probable, the DSST and VPT High loaded across multiple components at multiple steps. If these variables are removed, other processing or executive-weighted processing tasks begin to load across multiple components as well. VPT High and DSST were also excluded from the first step of the PCA, both together and separately, to determine the impact on the data structure. This led to a sequence of suboptimal models that did not match structure and pattern matrices, failure to converge within 25 iterations, and, ultimately, collapse into single-variable factors when 100 iterations were permitted. Taken together, this process of PCA in MCI-LB Probable revealed that order of entry of VPT High and DSST dictated whether the dataset produced a stable factor component structure. It is possible that features of VPT High and DSST are critically related to other processes and task performance. Therefore, their inclusion and loading across factors allowed production of models that retained other, related variables. By removing them, the structure of the data collapsed. While speculative, this suggests that VPT High and DSST may be especially important measures in understanding cognition in MCI-LB Probable.

The importance of processing speed was further emphasised within MCI-LB Probable when comparing results with controls. At initial Varimax rotation, the MCI-LB Probable data produced a model with two components relating to processing

speed with some executive weighting. At the first Oblimin rotation, the DSST is loaded by component 1 and (near-threshold) component 4. Similarly, Trails A loaded near to the conservative threshold level on three of the four components. This suggests strong correlations of the extracted components with processing speed in the pattern of MCI-LB Probable neuropsychological performance. In contrast, at first entry, control data did not produce a clear processing speed component, although component 1 did include a psychomotor (Symbol Copy) variable.

Very few studies report a PCA or factor analytic approach to psychological data in MCI or DLB. In MCI-AD, Chapman et al. (2011) reduced a dataset at baseline to PCA components for use in discriminant analyses to predict conversion to AD at follow up. The composites they produced, however, were weighted, both in terms of variable loadings across factors and differential weighting of components based on discriminant coefficients. Thus while quite statistically successful in predicting conversion (86% sensitivity, 83% specificity), the model was not used to consider domain-level performance separately. Within established AD, Fabrigoule et al. (1998) used PCA to argue for the importance of a “general factor” relating to cognitive control, i.e. executive function, in their sample. Interestingly, they also concluded that this factor was best characterised by the DSST and the Isaacs Set Test, a semantic verbal fluency test (Fabrigoule et al., 1998). DSST and Isaac Set Test scores had loadings on component 1 more than twice as large as on any other component, indicating their centrality to that underlying factor (Fabrigoule et al., 1998; Horn & Cattell, 1967). While the MCI-AD cohort was too small for analysis using PCA, the subsequent chapters will attempt to further consider the importance of speed of processing to disease-associated cognitive deficits in MCI, which has emerged as potentially critical in this chapter.

Conclusions and limitations

PCA analyses served as a data reduction technique to preserve the richness within the dataset in preparation for multivariate analyses. Control-informed composites help to reconfirm theoretical assumptions about grouping of processing speed and visuospatial measures. While the PCA was a useful approach given the dual aims of this chapter, it has certain limitations as well as important distinctions in interpretation from exploratory factor analysis (EFA), a different statistical method.

From my PCA results, I have computed composite scores as averaged control-adjusted *z*-scores of the individual variables loading most strongly onto

individual factors. However, PCA statistically allows for both common and unique variance, determining the linear combination of entered variables that will retain the maximum amount of information from the original data (Stevens, 2002). It is commonly misconstrued that PCA serves to provide definitive information on the underlying latent factors in the dataset. Such factors, argued to be demonstrated in EFA, are the unobservable variables that exert influence across variables and mediate any covariance (Brown, 2014; Santos et al., 2015; Thurston, 1947). However, factor analysis, not PCA, is the appropriate method for determining common factors (Stevens, 2002).

However, PCA has been demonstrated to provide very similar results to EFA (Fabrigar, Wegener, MacCallum, & Strahan, 1999), particularly when communalities are high, as in the present sample (Field, 2013). It is a popular approach that may be advantageous over EFA due to its computational simplicity and avoidance over-inflation of variance estimation that can occur in EFA (Guadagnoli & Velicer, 1988; Velicer & Jackson, 1990). In addition to PCA functioning to capture as much variance in the test battery as possible, the decision to use PCA instead of EFA is particularly appropriate in this novel diagnostic group. Results also indicate the magnitude of the association between an individual variable and each linear component, which can offer understanding of the neuropsychological profile of each group. In this way, PCA explored the loading of standard neuropsychological tests and processes onto shared components to better understand how cognitive structure may differ in MCI-LB. PCA, unlike EFA, also served to help compute composite scores corresponding to extracted principal components, one of the primary aims of the present chapter (Fabrigar et al., 1999).

Chapter Six: Hierarchical structure of neuropsychological performance in MCI-LB and MCI-AD

6.1 Introduction

A primary aim of this PhD was to consider how the hierarchical organisation of cognition may inform the conceptualisation of neuropsychological impairments in these conditions . Many studies in clinical populations suffer from use of complex tasks without a clear theoretical framework. To interpret results of complex tasks as indicative of a deficit in one cognitive component may ignore the participation and coordination of multiple cognitive resources. This can conflate deficits across constructs and explain some of the contradictory findings in the literature to date (Smith & Bondi, 2013). If they are not independent of each other, observed deficits should be conceptualised in a fundamentally different way (Gallagher et al., 2014). As such, models of cognition will first be introduced briefly below.

Models of Working Memory

In cognitive psychology, working memory refers to systems that are involved in performing complex cognitive tasks through the storage and manipulation of temporarily-held information (Baddeley, 2000b). In multicomponential models, working memory is fractionated into domain-specific components, with separate functions and capacities, that work to meet a task's demands (Logie, 2011). One of the most prominent multicomponential models was proposed by Baddeley and Hitch (1974) and has been supported by empirical evidence from psychological, neuropsychological, developmental and neuroimaging studies. In this model, the phonological and visuospatial divisions are "slave systems" to the central executive, which is an attentional control system. Within the phonological (verbal) loop, a subvocal articulatory system is proposed that allows rehearsal of information held in the passive, temporary verbal store. Logie (1995) expounded upon this model to further subdivide visuospatial working memory into similar components (Figure 10). In this model, the visual cache supports visuospatial working memory by holding temporary visual representations of recently-presented stimuli, with limits to the amount of complexity that can be retained (Luck & Vogel, 1997). The inner scribe alternatively retains spatial-sequential information, such as a short sequence of movements (Logie, 1995).

However, it is critical to remember that these components, regardless of reference to which specific model, will work in concert in the process of completing a

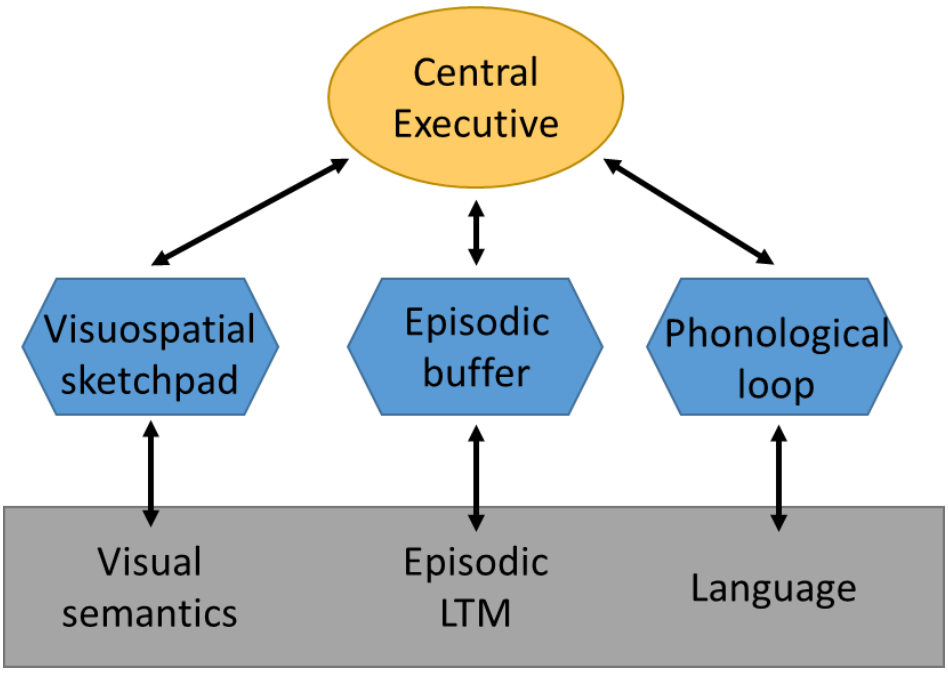

Figure 9 Working Memory Model adapted from Baddeley (2000)

task. Processing across modalities will support, or scaffold, memory performance (Brown & Wesley, 2013). For example, the visual cache has also been demonstrated to store verbally-described visual stimuli or haptic stimuli. Moreover, both episodic and semantic long term memory can be activated by visual mental imagery (Logie, 1995; Logie, 2003).

In the model proposed by Logie (1995), specifically, perceptual information first enters episodic memory. Many tasks purporting to target the subsystems require maintenance and frequent recall of information across trials, and thus benefit from this semantic, long-term memory scaffolding. Baddeley's (2000) model (Figure 9) includes the episodic buffer, which synthesizes long-term memory with information from the slave subsystems, and the Central Executive, which maintains attentional control of working memory (Baddeley, 1996b; Monaco, Costa, Caltagirone, & Carlesimo, 2013). Vandierendonck et al. (2004) found that central executive resources are employed when visuospatial sequences are longer than three or four items in order to assist with the maintenance of visuospatial representation. Thus, increasing span length, or task "memory load" will increase the engagement of the executive. Therefore, poor immediate recall of visuospatial information, for example, could be due to central executive dysfunction by not sufficiently utilizing the episodic buffer or long term memory scaffolding in retaining and applying task information.

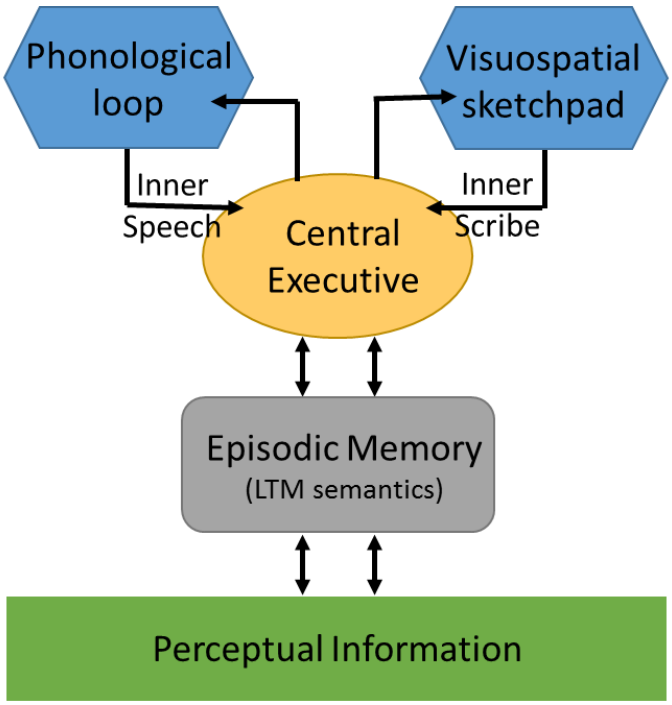

Figure 10 Working Memory Model adapted from Logie (1995, 2011)

Task errors may not relate to a deficit in "spatial working memory" per se, but rather indicate dysfunction or diminished capacity of the coordinating executive functions, episodic buffer, or, even, long term memory. Research indicates that the visuospatial domain (both storage and processing) is especially dependent on executive processes (Fisk & Sharp, 2003; Miyake, 2001; Thompson et al., 2006; Vandierendonck et al., 2004). This is in contrast to verbal working memory, which has been shown to be more automatic and amenable to distinction between executive and slave processes (Fisk & Sharp, 2003).

Visuospatial function in working memory

In addition to scaffolding by long-term memory and support of the central executive, visuospatial performance can depend on success of verbal coding. The engagement of the phonological loop and sub vocal rehearsal of verbal labels of visuospatial material can be important factors in many ostensibly "visuospatial" tasks (Logie & Pearson, 1997).

Early experimental work by Carmichael, Hogan, and Walter (1932) established that through the provision of different verbal labels, the recall of abstract line drawings could be manipulated. For example, if a rather amorphous drawing was accompanied by the words "eye glasses," participants would produce figures resembling glasses at free recall. The VPT (Della Sala et al., 1997) used in the

present study is a specific example of a matrix visuospatial task, frequently used in basic and applied psychological research studies to measure spatial working memory. These tasks, described in more detail in Chapter 3, involve black and white matrices in which the black squares must be retained and recalled over a short retention interval and recalled onto a blank white matrix. These matrices were designed to specifically tap the visual cache, and thus be difficult to verbally code (Della Sala et al., 1997; Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999). However, from the large set of initial stimuli, Brown et al. (2006) created and validated two subsets that were either especially easy to verbally recode ("VPT High") or least amenable to semantic labels ("VPT Low"). The High stimuli may resemble letters, numbers, symbols and shapes, or be more easily quickly verbally quantified. Such verbalisation, in a multi-componential model, allows an easing of pressure off the visuospatial sketchpad and an increase in its capacity. Brown et al. (2006) showed that visual working memory capacity was reliably higher in the "High" version of the VPT. Therefore, spatial working memory is not the only component affecting performance. This also emphasizes that the two discrete subsystems of working memory are able to cooperate when the demands of task require it. Vandierendonck et al. (2004), for example, begrudgingly acknowledges that flooding of visuospatial storage system may induce executive function and, as a last resort, verbalization of spatial information during task completion.

Based on similar evidence of executive function involvement within the visuospatial domain, Thompson et al. (2006) goes so far as to suggest tweaking of the multi-resource cognitive models to reflect the closer relationship between visuospatial and executive function than between the verbal system and executive function (indicating a lack of symmetry in the overall model). The demonstrated dependence of the visuospatial domain on executive function means that performance is dependent on both processes, and can thus be impacted by deficits in either.

In Chapter 3, MCI-AD showed less visuospatial impairment relative to controls than MCI-LB Probable. Significantly poorer scores were isolated to visuospatial memory (MTCF Recall and percent retained) and visuospatial working memory, but in the latter case only in the high verbalization subset (VPT High). This firstly suggests impaired passive storage impairments in the visuospatial domain, rather than poor visuoperceptive and visuoconstructive skills, due to MTCF Copy scores on par with controls. Poor performance on the VPT High but not VPT Low subsets could

be related to poor verbal coding or semantic scaffolding (automatic activation of long term memory or semantic) or executive functions, as discussed using above. MCI-LB, on the other hand, was impaired in all but visuospatial outcome measures, as well as many executive tasks, processing speed measures, and some verbal tasks. Statistical methods to model the contribution of such resources to task completion can help disentangle this issue, pinpoint where in the models the dysfunction lies, and how this may differ between MCI subtypes.

Processing Speed

Broad cognitive impairments that are observed across domains and tasks have also been posited as the secondary results of core, domain-general, primary impairments in cognitive resources. This is an ongoing debate in both the study of normal cognitive ageing and applied clinical work. Both executive function and processing speed have been posited as the potential candidates to explain both age- and disease-associated broader declines.

The term processing speed has been used to refer to a variety of measures that aim to quantify the speed of perceptual and cognitive processes. Processing speed is believed to be a distinct concept yet interrelated with working memory and executive function (Luszcz & Bryan, 1999). Processing speed is conceptualized as the domain-general speed of execution of basic cognitive functions (Nebes et al., 2000). It therefore limits the completion of higher-order activities, such as memory formation (Salthouse, 1992), that depend on basic operations to occur before the information held in working memory decays (Craik & Salthouse, 2011).

Salthouse (1996) suggests a theory in which slowed speed of processing explains age-related changes in cognitive performance in different domains. This argument hinges on the idea that slowed speed of processing that occurs in age will constrain an individual's performance on a task. In line with this, slowed processing speed has been strongly linked to cognitive aging, with cross-sectional studies suggesting it to explain up to 79% of age-related variance in many cognitive functions. In earlier cross-sectional work, Salthouse (1992) used DSST and concluded that the decline in processing speed with age was gradual and occurred across the score distribution. This is in contrast to the common pattern of decline in neuropsychological tasks in which a subset of individuals decline sharply while most remain at levels similar to younger cohorts. Instead, a decline across the score

distribution suggests a closer association between age and the construct (Albert & Moss, 1988; Lachman, 1986).

As such, the domain-general decline of processing speed has become considered the likeliest factor in cognitive decline in ageing (Nebes et al., 2000; Salthouse, 1996). Two mechanisms have been supported with empirical support. Firstly, cognitive processing may be too slow to "support behavioural performance in the specified time, leading to slowed and less accurate responding." Alternatively, slowed processing speed may prevent the simultaneous processing of task-related information before it degrades in working memory, which would result in increased errors.

This work has also been extended clinically, with studies investigating the hierarchical nature of cognition in neuropathological disorders. Within DLB, a small study by Kao et al. (2009) compared neuropsychological function in the synucleinopathies (PD, DLB and multiple system atrophy) and found that DLB displayed significant slower processing speed than the other two groups. Functionally, generalized slowing in everyday tasks, like activities of daily living, may be an early marker of change in MCI (Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008). Ballard, O'Brien, et al. (2001) also found processing speed, as measured by reaction time, to be the only attentional measure in deficit in DLB versus controls. Their AD participants, on the other hand, were not impaired relative to controls, leading them to suggest that DLB may be characterised by slowed central processing speed. However, it is unclear whether normal age-associated slowing accounts for much the slowing observed in pathologies. De Jager and Budge (2005), for example, report declines in processing speed over the course of a two-year population study in both controls and MCI. Processing speed measures did become predictive for MCI at follow-up, leaving open the possibility for MCI-specific slowing independent of decreases anticipated with healthy aging (De Jager & Budge, 2005).

Processing speed emerged as the impact domain in MCI-LB in Chapter 3, including the largest effect size relative to controls using the DSST, Due to its consistent and strong relationship with age, processing speed is sometimes 'factored out' to allow focus on specific, higher-level abilities such as executive function (Cepeda, Blackwell, & Munakata, 2013; Foster, Black, Buck, & Bronskill, 1997). This strategy typically involves the application of ANCOVA or hierarchical regression analysis. The premise here is that if a particular impairment (e.g., executive functioning) is mediated by another (e.g., processing speed) after establishing that

between-subjects differences exist, then entry of ‘group’ would not explain significant additional variance in the model.

Executive function

Executive functions are domain general higher-order processes involving the planning and regulation of goal-directed behaviours (Alvarez & Emory, 2006; Denckla, 1996). Executive functions have considerable overlap with the coordination aspect of working memory, but can be considered a broad, superordinate cognitive resource (Luszcz & Bryan, 1999). Executive function is related to processing speed, as the latter influences the efficiency and speed of the execution of its duties (Hasher & Zacks, 1979; Nebes et al., 2000).

In healthy ageing, mild executive function decline is common (Keys & White, 2000). In fact, Santos et al. (2015) argues that “evidence on age-associated memory and executive cognitive changes are so well-established that they might be considered the baseline against which other variables are analysed” (p. 2). In addition to processing speed, executive function has been proposed more recently as explaining cognitive dysfunction in pathologies such as late-life major depressive disorder (Baudic et al., 2004; Reppermund et al., 2014). Deficits in executive function have the potential to impair cognition at various stages, for example at both encoding and retrieval points in the case of memory function, thereby compounding their impact (Luszcz & Bryan, 1999). Interpretation of results can be complicated by studies that subsume processing speed as an executive function (Lockwood, Alexopoulos, & van Gorp, 2002). Conflation of these distinct yet interacting constructs will mask the mediating role of one resource, if it does in fact fully explain the decline.

As discussed in previous chapters, executive dysfunction is considered a hallmark of advanced DLB (McKeith et al., 2017) and to be related to frontal-subcortical degradation. However, the extent to which these advanced deficits are evident in MCI-LB is unclear. Kao et al. (2009) comparative study in synucleinopathies found mixed results in executive function tasks: DLB were no further impaired in those tending to involve language (digit span backwards, letter verbal fluency), but had more errors on other tasks than multiple system atrophy and PD groups. The structured review in MCI-LB concluded that early PD patients perform poorly on tasks with executive weighting, regardless of which domain they appear to target (working memory, processing speed, visuospatial and verbal

learning), and despite general intact performance on simpler tasks in those domains. The findings (Chapter 3) in executive performance were mixed, with only verbal fluency scores significantly poorer in MCI-LB Probable than MCI-AD. However, greater executive demands within a task may explain why MCI-LB Probable performed worse on certain visuospatial or verbal tasks and not others. Executive function may also explain variance in processing speed measures: a variety of tasks were used in the presence study and most likely necessitate varying amount of executive control. Even very simple tasks will require some maintenance of task goals and inhibition of background information, which may be more evident in aging populations (Cepeda et al., 2013).

Aims

The present chapter aimed to utilize a cognitive psychology framework to investigate whether some abilities, such as visuospatial or verbal function, are scaffolded by others, namely processing speed or executive function. Hierarchical linear regression will be used on the control-informed composite scores derived in Chapter 4 as well as individual outcome variables that emerged as pertinent from the univariate analyses of Chapter 3.

6.2 Methods

Materials and Participants

Composite processing speed and visuospatial scores were computed as average *z*-scores based on the mean and SD of controls. The variables included were determined by control-informed PCA results (see section 5.3.5). Single outcome measures were brought forward from Chapter 3 as *z*-scores adjusted to control-means to capture the other processes of interest (VPT High, VPT Low, Corsi, FAS, RAVLT Short Delay, Long Delay and Max T1:T5). Age and NART IQ were entered in the first step of every hierarchical linear regression (HLR) to account for pre-morbid intelligence and age-associated variance. See Chapter 3 for full description of tasks and Chapter 2 for participant details.

Data cleaning and assessment

The data presented in this study is post-initial data cleaning (for example, with outliers removed) as described in Chapter 3. To check for linearity and select which

HLRs models to execute, Pearson's (*r*) correlation coefficients were examined before regressions were conducted, and all analyses were two-tailed. Scatterplots of variables were inspected to confirm linearity between independent and dependent variables. HLR assumptions for independence of data, variable/predictor type (continuous) and no multicollinearity (variance inflation factor < 10; Myers, 1990) were met. Values of the residuals were confirmed to be independent using the Durbin-Watson statistic, which should be close to a value of 2: MCI-LB Probable (1.97), MCI-AD (2.22) and control (2.25) Durbin-Watson statistics were appropriate. Cook's Distance values were well under 1, suggesting individual cases are not unduly influencing the regression. The assumptions of homoscedasticity and normal distribution of residuals were met using regression plots and P-P plots, respectively. However, the residual plot was quite undulating in MCI-AD, suggesting the assumption of normality of residuals may be violated in this group. This is likely due to the small size of this group. As such, results in MCI-AD should be interpreted cautiously.

Between-group comparisons

Composite scores and control-weighted *z*-scores of individual outcomes measures were compared for differences between group subtype (MCI-LB Probable, MCI-AD, controls) using one-way ANOVA. Bivariate Pearson correlation coefficients were calculated between visuospatial outcome measures (visuospatial composite, VPT High and Low) and predictors (domain-general resources [processing speed composite, FAS], Corsi, and RAVLT Short Delay). RAVLT Short Delay was chosen in these analyses as it emerged in the univariate and discriminant analyses of Chapter 3 as the most critical and predictive verbal memory measure. Correlations were also calculated between domain general resources (executive function and processing speed) and measures of verbal learning and memory (RAVLT Max Recall T1:T5, Short and Long Delay).

To understand the relationship between neuropsychological processes such as executive functioning, processing speed, and verbal memory in controls versus MCI subtypes, a series of hierarchical multiple regressions (using the Enter method) were performed. The dependent variables consisted of the visuospatial composites, VPT High and VPT Low. The relationship between executive function and processing speed was also investigated by alternating order of entry. Following a similar statistical procedure as (Nebes et al., 2000) the proportion of diagnosis-related

variance was examined by entering “group” (control, MCI-AD or MCI-LB Probable) as the predictor variable after age and NART IQ. Secondly, separate regressions are run, entering variables of interest (namely processing speed) in the second step and Group in the third. This procedure controls for the variance due to those constructs before regressing MCI status (Nebes et al., 2000). The degree to which accounting for the first predictor decreases the variability explained by “group” therefore quantifies how much that processing resource mediates the MCI-related deficit (Nebes et al., 2000).

Table 20 Means (standard deviations) by subtype and p-value of the one-way ANOVA between MCI subtypes, MCI-LB Probable versus controls, and MCI-AD versus controls.

	MCI-LB	MCI-AD	Subtype comparison *p*-value	MCI-LB vs. Controls	MCI-AD vs. Controls
Processing Speed	-1.76 (1.07)	-1.17 (0.77)	.094	**<.001**	**<.001**
Visuospatial	-1.48 (1.22)	-0.98 (0.94)	.224	**<.001**	.005
VPT High	-1.84 (1.30)	-1.04 (1.04)	**.052**	**<.001**	.008
VPT Low	-1.69 (1.68)	-0.90 (1.07)	.119	**<.001**	.059
Corsi	-1.32 (1.20)	-0.87 (1.21)	.373	**<.001**	**.029**
FAS	-1.39 (1.57)	-0.40 (1.24)	**.032**	**<.001**	.562
RAVLT Max T1:T5	-1.24 (1.16)	-1.44 (1.37)	.815	**<.001**	**<.001**
RAVLT Short Delay	-1.12 (1.21)	-1.88 (1.31)	.077	**.001**	**<.001**
RAVLT Long Delay	-0.83 (1.04)	-1.31 (1.33)	.309	**.012**	**<.001**

6.3 Results

6.3.1 Group differences

Levene's test showed that the variances for the processing speed composite, $F(2,76) = 3.30$, $p = 0.042$, VPT Low, $F(2,76) = 3.69$, $p = 0.030$, and FAS, $F(2,76) = 4.02$, $p = 0.042$, were not equal. The between-subjects effect for group was significant as expected for each one-way ANOVA (DSST, VPT High, VPT Low, Corsi, FAS, RAVLT Short Delay, Long Delay and Max T1:T5), all *p*s < .001. One-way ANOVAs reconfirmed findings from Chapter 3 that MCI-LB Probable has significantly lower scores in VPT High (on trend) and FAS versus MCI-AD (see Table 20). In

comparison with controls, MCI-LB Probable performed significantly worse on all measures). MCI-AD was significantly impaired relative to controls on Processing Speed, Corsi, RAVLT Max T1:T5 , RAVLT Short Delay and RAVLT Long Delay.

Table 21 Pearson correlations between cognitive measures predictors and dependent visuospatial variables prior to hierarchical linear regression in MCI-LB Probable (n = 30), MCI-AD (n = 18) and controls (HC; n = 31).

	Visuospatial Composite			VPT High			VPT Low		
	MCI-LB	MCI-AD	HC	MCI-LB	MCI-AD	HC	MCI-LB	MCI-AD	HC
Processing Speed	**.659****	0.415	0.355	**.678****	0.441	0.302	**.674****	0.424	0.348
Corsi	**.452***	0.372	0.156	**.429***	0.384	0.017	**.388***	0.320	0.056
FAS	0.135	0.298	0.157	0.274	0.404	0.089	0.128	0.383	0.069
RAVLT Short Delay	**.501****	**.572***	0.296	**.523****	**0.575***	0.177	**.439***	0.432	0.289

*Significance at *p* = .01 level; ** Significance at *p* = .05 level.

By group, there was a significant correlation between Corsi and the visuospatial measures in MCI-LB Probable, where the variance explained was 20.4% of the visuospatial composite, 18.4% of VPT High, and 15.1% of VPT Low (Table 21). The other significant correlations are investigated further using multiple linear regression below. Moreover, FAS and the processing speed composite were significantly positively correlated with each other in all groups: MCI-LB Probable $r(28)=0.478$, $p = .008$, MCI-AD, $r(16)= 0.633$, $p = .003$, and controls, $r(29)=0.475$, $p = .007$. FAS was not significantly correlated with any of the visuospatial outcome measures. Processing speed was strongly positively correlated with all three visuospatial scores in MCI-LB (all *p*s < .001), but not in MCI-AD or healthy controls. Short delay free recall of the RAVLT was significantly associated with the visuospatial composites scores and with VPT High in both MCI subtypes. In MCI-LB Probable, there was a moderate positive correlation between RAVLT Short Delay and VPT Low, $r(28)=0.439$, $p = .015$, as well.

6.3.2 Predicting visuospatial composite

Table 22 Predicting visuospatial composites scores with group and processing speed composite in all groups (MCI-AD, MCI-LB Probable and controls).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age NART	0.22	0.20	0.22	10.72	**< .001**	**-0.38** **0.35**	**< .001** **.001**
Age NART Group	0.22 0.27	0.20 0.24	0.22 **0.05**	10.72 4.68	**< .001** **.034**	**-0.34** **0.33** **0.22**	**.001** **.002** **.034**
Age NART Proces. Speed	0.22 0.49	0.20 0.46	0.22 **0.26**	10.72 37.69	**< .001** **< .001**	-0.10 0.03 **0.64**	.287 .741 **< .001**
Age NART Proces. Speed Group	0.22 0.49 0.49	0.20 0.46 0.46	0.22 **0.26** 0.89	10.72 37.69 0.41	**< .001** **< .001** .524	-0.13 0.04 **0.62** 0.06	.287 .695 **.000** .524
Age & NART Exec. Func.	0.22 0.27	0.20 0,24	0.22 **0.05**	10.72 4.75	**< .001** **0.032**	**-0.35** **0.24** **0.24**	**.001** **.040** **.032**
Age NART Exec. Func, Group	0.22 0.27 0.31	0.20 0,24 0.27	0.22 **0.05** **0.04**	10.72 4.75 4.36	**< .001** **0.032** **.040**	**-0.32** **0.23** **0.23** **0.21**	**.002** **.046** **.039** **.040**
Age NART Exec. Func, Proces. Speed	0.22 0.27 0.49	0.20 0,24 0.46	0.22 **0.05** **0.22**	10.72 4.75 31.51	**< .001** **0.032** **<.001**	-0.09 0.05 -0.09 **0.70**	.364 .634 .409 **.000**
Age NART Proces. Speed Exec. Func,	0.22 0.49 0.49	0.20 0.46 0.46	0.22 **0.26** 0.01	10.72 37.69 0.69	**< .001** **<.001** .409	-0.09 0.05 **0.670** -0.09	.364 .634 **.000** .409

After entering age and NART IQ, group was entered in the second step and explains 5.0% of visuospatial composite scores, (see Table 22). If processing speed composite is entered at step 2, it accounts for 26.0% of visuospatial scores and is the only significant variable in the standardized regression model. Finally, processing speed was entered at step 2 before group at step 3. In this model, the effect of group disappears. Processing speed therefore explains the small but significant diagnosis-associated variance in visuospatial scores. Executive function accounts for a much smaller proportion of variance in visuospatial composite scores (5.0%, p = .032). If entered before Group, Group's explained variance drops to 4.0%, indicating 25.0% of the small amount of group-related variance in visuospatial scores is accounted for by executive function. Through manipulating order of entry, it is shown that executive

Table 23 Predicting VPT High with group and processing speed composite and executive function (FAS) in all groups (MCI-AD, MCI-LB Probable and controls).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age & NART	0.21	0.19	**0.21**	10.21	**<.001**	**-0.35** **0.37**	**.001** **.001**
Age & NART Group	0.21 0.25	0.19 0.22	**0.21** 0.04	10.21 3.61	**<.001** 0.61		
Age & NART Proces. Speed	0.21 0.49	0.19 0.47	**0.21** **0.28**	10.21 39.95	**<.001** **<.001**	-0.07 0.04 **0.66**	.485 .676 **.000**
Age & NART Exec. Func.	0.21 0.30	0.19 -.27	**0.21** **0.06**	10.21 9.01	**<.001** **.004**	**-0.31** 0.21 **0.33**	**.002** .058 **.004**
Age NART Proces. Speed Exec. Func,	0.21 0.49 0.49	0.19 0.47 0.46	**0.21** **0.28** 0.00	10.21 39.95 0.02	**<.001** **<.001** .885		
Age NART Exec. Func. Proces. Speed	0.21 0.30 0.49	0.19 -.27 0.46	**0.21** **0.06** **0.19**	10.21 9.01 27.23	**<.001** **.004** **<.001**	-0.07 0.04 0.02 **0.65**	.479 .703 .885 **.000**

function does not add unique variance above and beyond processing speed (*p* = .409).

To further fractionate visuospatial function, performance was analysed on the two subsets of VPT: VPT High and Low. Run as a single group, both processing speed and executive function (FAS) significantly predicted variance in VPT High, 28.0% and 6.0% respectively (Table 23). Order of entry of FAS and processing speed were iteratively alternated, revealing that FAS does not predict additional variance in VPT High beyond processing speed (*p* = .885). On the other hand, if processing speed is entered after FAS-associated variance is controlled for (step 2), it adds an additional 19.0% of variance to the model.

However, the model of group predicting VPT High after entering age and NART IQ was not significant (*p* = .61). Because of this, order of entry to predict group-associated variance was not pursued. Instead, the HLRs were re-run separately by group to determine if processing speed and executive function are interrelated in predicting VPT High (Table 24).

Table 24 Predicting VPT High from processing speed (composite) and FAS (executive function), separately by group.

	R^2	Adjusted R^2	ΔR^2	F Change	Sig. F Change
MCI-LB Probable					
Age, NART	0.24	0.187	**0.24**	4.33	**0.023**
Proces. Speed	0.50	0.439	**0.25**	13.14	**0.001**
MCI-AD					
Age, NART	0.14	0.02	0.14	1.17	0.338
Proces. Speed	0.27	0.12	0.14	2.64	0.127
Control					
Age, NART	0.10	0.03	0.10	1.46	0.251
Proces. Speed	0.11	0.01	0.02	0.50	0.487
MCI-LB Probable					
Age, NART	0.24	0.19	**0.24**	4.33	**.023**
Exec. Func.	0.25	0.16	0.01	0.27	.606
MCI-AD					
Age, NART	0.14	0.02	0.14	1.17	.338
Exec. Func.	0.30	0.16	0.17	3.41	.086
Control					
Age, NART	0.10	0.03	0.10	1.46	.251
Exec. Func.	0.10	0.00	0.01	0.13	.721

Processing speed does not predict VPT High performance in controls or MCI-AD. The only significant two-step model produced was in MCI-LB Probable, whereby processing speed explains additional 25.4% of variance explained in MCI-LB Probable VPT High scores after accounting for age and NART IQ associated variance.

RAVLT Short Delay was next utilised as an indicator of verbal ability in determining how that ability may impact VPT performance (Table 25). RAVLT Short Delay predicts VPT High scores in both MCI-AD (25.0%) and MCI-LB Probable (15.0%). Control VPT High scores were not successfully predicted by their RAVLT Short Delay scores. When order of entry is considered, processing speed contributes 7% less variance to VPT Low scores in MCI-LB Probable if RAVLT Short Delay is entered first, indicating shared variance between the two predictors. RAVLT Short Delay also predicts unique variance (8.0%) after processing speed is controlled, again emphasizing unique contribution of the memory measure to the model. Regardless of order of entry, however, processing speed adds additional unique variance in predicting VPT High scores in MCI-LB, beyond the overlap in variance with RAVLT Short Delay. In MCI-AD, the significance of RAVLT Short Delay predicting VPT High is lost (p = 0.60) when processing speed is entered first; however, this is likely due to loss of power as processing speed is not a significant predictor at second step in MCI-AD.

Table 25 Investigating order of entry in predicting VPT High from processing speed (composite) and RAVLT Short Delay, separately by group.

	R^2	Adjusted R^2	ΔR^2	F Change	Sig. F Change
MCI-LB Probable					
Age, NART	0.09	0.58	**0.09**	2.79	**0.106**
RAVLT S. Delay	0.40	0.33	**0.15**	6.55	**0.017**
MCI-AD					
Age, NART	0.14	0.02	0.14	1.17	0.338
RAVLT S. Delay	0.38	0.25	**0.25**	5.65	**.032**
Control					
Age, NART	0.10	0.03	0.10	1.46	0.251
RAVLT S. Delay	0.10	-0.01	0.00	0.05	0.824
MCI-LB Probable					
Age, NART	0.24	0.187	**0.24**	4.33	**0.023**
RAVLT S. Delay	0.40	0.33	**0.15**	6.55	**0.017**
Proces. Speed	0.58	0.51	**0.18**	10.70	**0.003**
MCI-AD					
Age, NART	0.14	0.02	0.14	1.17	0.338
RAVLT S. Delay	0.38	0.25	**0.25**	5.65	**0.032**
Proces. Speed	0.45	0.28	0.07	1.61	0.227
MCI-LB Probable					
Age, NART	0.24	0.187	**0.24**	4.33	**0.023**
Proces. Speed	0.50	0.44	**0.25**	13.14	**0.001**
RAVLT S. Delay	0.58	0.51	**0.08**	4.70	**0.040**
MCI-AD					
Age, NART	0.14	0.02	0.14	1.17	0.338
Proces. Speed	0.27	0.12	0.14	2.64	0.127
RAVLT S. Delay	0.45	0.28	0.18	4.26	0.60

Table 26 Predicting VPT Low with group and processing speed composite and executive function (FAS) in all groups (MCI-AD, MCI-LB Probable and controls).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age & NART	019	0,17	**0.19**	8.90	**<.001**	**-0.34** **0.33**	**.002** **.002**
Age & NART Group	0.19 0.21	0.17 0.18	0.19 0.02	8.90 1.73	**<.001** .193	**-0.32** **0.32** 0.14	**.003** **.003** .193
Age & NART Proces. Speed	0.19 0.46	0.17 0.44	0.19 **0.27**	8.90 37.01	**<.001** **<.001**	-0.06 0.01 **0.65**	.520 .896 **.000**
Age & NART Exec. Func.	0.19 0.23	0.17 0.20	0.19 **0.04**	8.90 4.08	**<.001** **.047**	**-0.32** 0.23 **0.23**	**.003** .054 **.047**
Age NART Proces. Speed Exec. Func,	0.19 0.46 0.47	0.17 0.44 0.44	0.19 **0.27** 0.01	8.90 37.01 1.04	**<.001** **<.001** .312	-0.47 0.32 **5.68** -1.02	.643 .753 **<.000** .312
Age NART Exec. Func. Proces. Speed	0.19 0.23 0.47	0.17 0.20 0.44	0.19 **0.04** **0.24**	8.90 4.08 32.27	**<.001** **.047** **<.001**	-0.05 0.03 -0.12 **0.72**	.643 .753 .312 **.000**

As executive function (FAS) and the processing speed composite were also both significantly correlated with VPT Low scores, the HLRs were re-run in predicting VPT Low (Table 26). In MCI-LB Probable, both processing speed and executive function (FAS) significantly predicted variance in VPT Low, 27.0% and 4.0% respectively. Analogous with the results in VPT High, FAS did not predict further variance in VPT Low after processing speed (p = .312), but processing speed adds an additional 24.0% (p < .001). As in VPT High, the model of group predicting VPT Low after entering age and NART IQ was not significant (p = .193), and the analyses we re-run separately by group.

In MCI-LB Probable we firstly see age and NART IQ explaining 21.0% of the variance (Table 27). Processing speed, in step two, explains an additional 27.0% of variance, p = .001. RAVLT Short Delay is on trend to explain 10.0% of the variance in VPT Low in MCI-LB. Regardless of order of entry, processing speed predicts significant amount of variance in VPT Low in MCI-LB: if RAVLT Short Delay is entered at stage 2, it adds an additional 21.0% unique variance.

Table 27 Predicting VPT Low from processing speed (composite) and RAVLT Short Delay).

	R^2	Adjusted R^2	ΔR^2	F Change	Sig. F Change
MCI-LB Probable					
Age, NART	0.21	0.15	**0.21**	3.59	**0.042**
Proces. Speed	0.48	0.42	**0.27**	13.24	**0.001**
MCI-AD					
Age, NART	0.04	-0.09	0.04	0.33	0.727
Proces. Speed	0.21	0.04	0.16	2.88	0.112
Control					
Age, NART	0.13	0.07	0.13	2.10	0.143
Proces. Speed	0.16	0.07	0.03	0.92	0.347
MCI-LB Probable					
Age, NART	0.21	0.15	**0.21**	3.59	**0.042**
RAVLT S. Delay	0.31	0.23	0.10	3.70	0.066
MCI-AD					
Age, NART	0.04	-0.09	0.04	0.33	0.727
RAVLT S. Delay	0.20	0.02	0.15	2.69	0.123
Control					
Age, NART	0.13	0.07	0.13	2.10	0.143
RAVLT S. Delay	0.16	0.06	0.03	0.79	0.383
MCI-LB Probable					
Age, NART	0.21	0.15	**0.21**	3.59	**0.042**
RAVLT S. Delay	0.31	0.23	0.10	3.70	0.066
Proces. Speed	0.52	0.44	**0.21**	10.78	**0.003**
MCI-LB Probable					
Age, NART	0.21	0.15	**0.21**	3.59	**0.042**
Proces. Speed	0.48	0.42	**0.27**	13.24	**0.001**
RAVLT S. Delay	0.52	0.44	0.04	2.05	0.165

6.3.4 Predicting verbal learning and memory scores

The relationship between processing speed and scores on verbal learning and memory were explored between MCI-LB Probable and controls as both groups had significant correlations between these variables. There was an overall (whole group) significant association between processing speed, executive function and RAVLT Max T1:T5, but this association was not evident within the MCI-AD in isolation (see Table 28). These participants were therefore omitted in order to focus on the effects in MCI-LB.

Table 28 Pearson correlations between cognitive measures predictors and dependent verbal learning and memory variables prior to hierarchical linear regression in MCI-LB Probable (n = 30), MCI-AD (n = 18) and controls (n = 31).

	RAVLT Max T1:T5			RAVLT Short Delay			RAVLT Long Delay		
	MCI-LB	MCI-AD	HC	MCI-LB	MCI-AD	HC	MCI-LB	MCI-AD	HC
Processing Speed	**.430***	.396	**.504***	.341	.269	**.402***	.207	.278	.351
FAS	.219	.112	.080	-.034	.035	.088	-0.12	-.002	-.026

*Significance at p = .01 level.

Table 29 Predicting RAVLT maximum number of words recalled during learning trials with processing speed (composite) in MCI-LB Probable and controls.

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age NART	0.29	0.27	0.29	11.72	**< .001**	**-0.44** **0.37**	**< .001** **.002**
Age NART Group	0.29 0.42	0.27 0.39	0.29 **0.13**	11.72 12.55	**<.001** **.001**	**-0.40** 0.20 **0.40**	**<.001** .077 **.001**
Age NART Proces. Speed	0.29 0.44	0.27 0.41	0.29 **0.15**	11.72 15.24	**< .001** **< .001**	**-0.23** 0.10 **0.50**	**.046** .419 **< .001**
Age NART Proces. Speed Group	0.29 0.40 0.47	0.27 0.39 0.43	0.29 **0.40** 0.02	11.72 39.58 2.23	**< .001** **< .001** 0.141	**-0.28** 0.10 **0.35** 0.21	**.021** .433 **.039** .141
Age NART Exec. Func.	0.29 0.33	0.27 0.29	0.29 0.03	11.72 2.84	**< .001** .097		

Firstly, HLRs were run to predict maximum recall during RAVLT learning trials (T1:T5; see Table 29). Age and NART were entered together in the first step, explaining 29.0% of variance. When entered in the second step, Group (MCI LB Probable or controls) explains 13.0% additional variance in RAVLT Max T1:T5. Processing speed, entered alternatively in the second step, explains a slightly higher 15.0% of score variance. However, by entering processing speed at step 2, Group no longer predicted a significant proportion of variance, $p = .141$. This indicates that processing speed explains all of the MCI-LB Probable-associated variance in RAVLT T1:T5 maximum free recall. FAS, in contrast, did not predict RAVLT Max T1:T5 scores in the analysis ($p = .097$).

Secondly, HLRs were re-run to predict scores on RAVLT Short Delay (Table 30). As executive function did not correlate significantly with Short Delay scores in the group overall, it was not included. Similar to RAVLT T1:T5, age and NART together explained 24.0% of RAVLT Short Delay score variance. If entered second, Group and processing speed both explain 9.0% of remaining variance. When processing speed is entered prior to Group, the effect of group disappears. As with RAVLT Max Recall T1:T5, the MCI-LB Probable-associated variance in RAVLT Short Delay recall is fully explained by processing speed.

Table 30 Predicting RAVLT Short Delay free recall during learning trials with processing speed (composite) in MCI-LB Probable and controls.

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age NART	0.24	0.21	**0.24**	9.03	**< .001**	**-0.31** **0.42**	**.010** **<.001**
Age NART Group	0.24 0.33	0.21 0.30	0.24 **0.09**	9.03 7.53	**< .001** **.008**	**-0.28** **0.28** **0.33**	**.015** **.023** **.008**
Age NART Proces. Speed	0.24 0.33	0.21 0.30	0.24 **0.09**	9.03 7.89	**< .001** **.007**	-0.14 0.21 **0.40**	.251 .123 **<.007**
Age NART Proces. Speed Group	0.24 0.33 0.357	0.21 0.30 0.31	0.24 **0.09** 0.02	9.03 7.89 1.61	**< .001** **.007** .210	-0.19 0.20 0.25 0.205	.152 .127 .171 .210

6.3.5 Comparison of processing speed and executive function by group

Table 31 Predicting processing speed composite by group in all participants, with and without entry of FAS (executive function).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age NART	0.36	0.34	0.36	21.10	**< .001**	**-0.43** **0.49**	**< .001** **< .001**
Age NART Group	0.29 0.43	0.27 0.40	**0.29** **0.07**	11.72 8.48	**<.001** **.005**	**-0.39** **0.47** **0.26**	**<.001** **<.001** **.005**
Age NART Exec. Func.	0.36 0.55	0.34 0.53	**0.36** **0.19**	21.10 30.00	**< .001** **< .001**	-0.38 0.27 0.48	**< .001** **.003** **< .001**
Age NART Exec. Func. Group	0.36 0.55 0.60	0.34 0.53 0.58	**0.36** **0.19** **0.05**	21.10 30.00 9.81	**< .001** **< .001** **.002**	**-0.34** **0.26** **0.47** **0.24**	**<.001** **.003** **<.001** **.002**

The interrelatedness of executive function and processing speed was next considered. In the group overall, FAS and processing speed composite were strongly positively correlated, *r*(75) = .613. After accounting for the variance associated with age and NART IQ, group predicts 7.0% of variance in processing speed composite scores (Table 31). Executive function as measured by FAS on the other hand, predicts 19.0% of processing speed score variance. If group is entered after FAS, it still explains 5.0% of score variance. Thus, FAS accounts for 40.0% of the group-associated variance in processing speed composite scores. Alternatively, FAS is not

significantly predicted by group allocation when entered after NART IQ and age, adj. R^2 = .21, $F(3,74) = 0.24$, p = .623.

6.4 Discussion

The present chapter aimed to investigate the hierarchical organisation of deficits in cognitive performance observed in Chapter 3. The results of Chapter 3 showed that processing speed was the most impaired domain in MCI-LB relative to both controls and MCI-AD. As both speed of processing and executive function are suggested as explanatory factors in disease- and age-associated impairments in cognitive ability, hierarchical linear regressions were utilized to determine whether they predict score variance in domain-specific abilities such as verbal or visuospatial learning and memory. Chapter 4 similarly emphasized the role of processing speed across the structure of neuropsychological performance in MCI-LB. PCA analyses of control data resulted in a processing speed factor, again suggesting that this may be a predictive component in healthy ageing as well. However, the results of the present chapter's multivariate analyses indicate that processing speed is predictive of MCI-LB-associated declines in visuospatial and verbal ability.

Firstly, correlational analyses indicated strong relationship between faster processing speed and higher scores on visuospatial tasks ([MTCF recall, VPT High and Low). In contrast, processing speed did not correlate with visuospatial ability in controls or MCI-AD. Processing speed was also significantly related to verbal learning ability in MCI-LB Probable, and not the other two groups. Secondly, a series of HLRs run to predict both visuospatial memory and verbal learning indicates that processing speed fully accounts for the small but significant diagnosis-associated variance in visuospatial composite scores. Run separately by group, processing speed predicts 25.7% of visuospatial composite scores in MCI-LB Probable. Similar results were found with the VPT task. Neither MCI-AD nor controls demonstrated an association between their visuospatial scores and speed of processing. In addition to visuospatial scores, processing speed was associated with verbal learning ability in MCI-LB Probable, but not MCI-AD. HLRs were run between MCI-LB and controls because both groups had significant correlations between processing speed and verbal learning/ memory measures. These analyses indicate that the group-associated variance in verbal learning (13.0%) and in verbal memory (short delay; 9.0%) is completely explained by processing speed differences. As such, processing speed was predictive of MCI-LB Probable scores across visuospatial working

memory, long-term memory, visuosconstruction (MTCF) and even verbal learning (RAVLT). While speculative, it is possible that this can be attributed to cognitive de-differentiation in the subtype (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Lindenberger & von Oertzen, 2006; see Chapter 10). In contrast, the results provide no evidence for a predictive role of executive function in domain-specific abilities. FAS did predict a small amount (4-6%) of diagnosis-related variance in visuospatial scores. However, through the use of sequential entry in the multiple regression, we have demonstrated that this relationship is fully explained by processing speed. As such, the sample provides evidence for a processing speed mediated decline in LB disease in the MCI stage.

Executive function in MCI

The limited evidence of executive function's predictive ability of visuospatial tasks is out of line with existing literature that suggests the visuospatial domain is particularly dependent on such skills (Thompson et al., 2006). VPT scores, however, seems to be unrelated to executive abilities, suggesting this cognitive resource is less critical to its performance than processing speed and verbal memory. In healthy controls, there was no significant relationship between executive function and the VPT, while patients show a strong association between their speed of processing and higher scores on the VPT. However, it is possible that the measure of executive function (FAS) may be limited in its ability to capture executive function fully. As introduced in chapter 3, executive functions have previously been empirically delineated to relate to a number of processes including set-shifting, updating and inhibition (Miyake et al., 2000). Phonemic verbal fluency tasks like FAS are commonly used as measures of executive function (Snyder et al., 2015). However, despite its seeming simplicity, FAS engages other non-executive processes like semantic knowledge (Rende, Ramsberger, & Miyake, 2002). Conversely, using FAS alone to capture executive ability may draw conclusions about only a narrow aspect of executive function. Executive function has been argued since Teuber (1972) to have the quality of both "unity" and "diversity." Subcomponents of executive functions can be separated from each other, but relate to a common underlying factor (Teuber, 1972). A plethora of models differ in conceptualization of the interrelatedness of executive function, from two-factor levels with supervisory top-down functions managing lower-level processes (Shallice, 2002) to the central executive that integrates functions in a less hierarchical manner (Baddeley, 1996a). Regardless,

behavioural measurement of executive functions may require more extensive testing in order to capture the breadth of the construct (Snyder et al., 2015). Future work in MCI should consider utilizing more tasks that can be analysed in conjunction in order to both localize where dysfunction may operate in executive tasks and to offer clarify on the multitude of models of executive function proposed. Furthermore, as a simultaneous-presentation task, the VPT inherently requires fewer executive resources than serial-sequential visuospatial tasks, which requires retention of both item and order information (Rudkin, Pearson, & Logie, 2007). Other visuospatial tasks in this population might reveal executive dysfunction differently. Therefore, while the present study does not provide evidence of executive-mediated declines in verbal or visuospatial function in MCI, we cannot fully rule out the importance of executive functions without further testing.

Visuospatial Function in MCI-LB

The analyses in the present chapter re-emphasize the poor visuospatial function in MCI-LB Probable demonstrated in Chapter 3. Such deficits are expected in synucleinopathies (Kao et al., 2009) and in DLB in particular (McKeith et al., 2017), and were thus anticipated in MCI-LB specifically. VPT offered the opportunity to consider how the structure and interrelatedness of components in working memory may function differently in MCI subtypes, which differ in terms of location of neural damage (Brown et al., 2006). Findings suggest that verbal memory ability is important to MCI-LB performance on these tasks. The high verbal-coding subset was developed and validated by Brown et al. (2006) as being prone to verbal labels; thus, the association between verbal learning ability and VPT High scores are not unexpected. However, this only occurred in MCI-LB Probable. While not significant, 10% of variance in the low-verbal coding subset would be predicted by verbal memory ability in MCI-LB Probable as well. Again, this did not reach statistical significance and could be investigated using a larger cohort. However, if confirmed, it could indicate that MCI-LB is recruiting verbal coding as an intact neuropsychological process, in order to compensate for the significant deficits in the visuospatial store. Such compensatory scaffolding has been demonstrated to occur in normal ageing (Park & Reuter-Lorenz, 2009); however, as the relationship between verbal memory and VPT does not exist in controls in this data, this may be a mechanism specific to LB pathology.

One of the potential mechanisms that may explain the higher recall in VPT High and its relationship to verbal memory is concreteness. This is a concept that is usually studied in the context of verbal memory, but has applicability to the visuospatial domain as well. The concreteness effect is based on improved memory for “concrete” words (e.g. bed) versus abstract words (e.g. freedom) (Schwanenflugel, Harnishfeger, & Stowe, 1988). Retention and recall of concrete words benefit from processing across modalities, i.e. visual elaboration to support the verbal coding (Paivio, 1991). However, others have argued that increased “concreteness” impedes high-fidelity recollection of visuospatial information, particularly if it is abstract in nature (Brandimonte, Hitch, & Bishop, 1992; Schooler & Engstler-Schooler, 1990).

In Brown and Wesley (2013), a series of experiments aimed to determine the source of the benefit of the higher verbalization VPT stimuli. They argued that there were three theoretically-derived possibilities. Firstly, subvocal rehearsal of verbal codes in working memory’s phonological loop may retain visual patterns over the short retention period (Baddeley, 2007; Logie, 2011). Secondly, long-term memory and semantics that are automatically activated by visual stimuli would scaffold performance (Logie, 2011). Thirdly, the episodic buffer’s multimodal integration of semantic information, visual stimuli and executive resources facilitate VPT High performance (Baddeley, 2000a). Through the use of a dual-task articulatory suppression paradigm, Brown and Wesley (2013) conclude that is does not derive from the phonological loop. Moreover, while central executive functions were implicated in the increased capacity of the visual cache, the authors argue that automatic semantic activation is the most likely source of the high-verbalization benefit (Brown & Wesley, 2013; Mate, Allen, & Baqués, 2012). In the low VPT, older cognitively-intact adults who reported “mostly” or “always” using verbal strategies to help complete the visuospatial task had higher scores than those who “rarely” or “never” used a dual strategy (Brown & Wesley, 2013). However, this predictive effect of self-reported strategy lose was not present in the High VPT version. This suggest “a second source of increased task performance, specifically related to higher verbalisation, which may be the automatic use of semantic knowledge” (Brown & Wesley, 2013, p. 333). In my results, both MCI-LB and MCI-AD VPT High scores were predicted by their verbal memory ability. If VPT High performance is dependent on automatic semantic elaboration, rather than articulatory rehearsal per se, one might expect to see this effect more clearly in MCI-AD, due to its characteristic

amnestic profile and hippocampal pathology. However, the difference between groups on mean VPT High score was only on trend. Brown and Wesley (2013) also suggest an active aspect of long-term activation in remembering abstract visuospatial stimuli, which would increase the executive demands of the task; however, the data do not support this hypothesis in the context of MCI, as there was no relationship between executive ability and VPT performance when considered by subtype.

Chapter 10 considers the potential clinical relevancy of this evidence of verbal coding in more detail. Overall, visuospatial working memory remains less understood than the verbal domain (Vandierendonck & Szmalec, 2011). Accordingly, it may be necessary to take “steps-back” from such complex tasks and to investigate the usefulness of the models and validity of the tasks. Tasks that validly and reliably manipulate one component of cognition are extremely valuable (Luciana, Conklin, Hooper, & Yarger, 2005). However, some would argue that the ability to isolate and study individual cognitive components is unlikely or lacks ecological validity (Thompson et al., 2006).

Limitations and future work

As in previous chapters, analyses of the MCI-AD data subset are limited by the small sample size. Failure to see significant correlations between neuropsychological variables as well as demographics (such as age and premorbid IQ) could be consequent to a lack of power. Specifically, when predicting VPT High with verbal memory ability, the relationship drops to on trend when processing speed is entered first. However, in univariate analysis processing speed is not associated with VPT High. Therefore, it is important that conclusions regarding findings in the MCI-AD group are interpreted cautiously. The study had aimed overall to compare performance in the two MCI subtypes, but lower numbers of MCI-AD participants than expected challenge execution of this aim. Analyses in the subsequent chapters will continue to consider MCI-AD in an exploratory manner, but by necessity the focus will be on MCI-LB Probable relative to controls.

Methodologically, the VPT’s association with measures of information processing speed may have been influenced by the short presentation time during the task. The VPT is typically administered with a presentation time of 3000ms (Della Sala et al., 1997), which is shorter than the 2000ms presentation procedure used in the present study. Tasks in which stimuli have shorter presentation times may show greater interrelatedness in the constructs of processing speed and the particular

subcomponent of working memory that is targeted, such as the visual cache. This will remain an ongoing methodological challenge in the study of processing speed and working memory. Another limitation and challenge for future research is the potential construct overlap and validity issues in measuring processing speed alongside other neuropsychological components, particularly executive function. In the present data, executive function and processing speed were strongly positive correlated. Executive function explained 40% of the group-related variance in processing speed. Thus while executive function (FAS) did not show a strong relationship with measures of broader cognitive function, it is clearly interrelated with processing speed itself. Conceptually, executive functions work over a longer time frame than working memory (Duke & Kaszniak, 2000). In this way, they may be especially influenced by differential speeds of processing. Indeed, in normal ageing psychomotor speed largely explained age-related decline in executive function (Keys & White, 2000). However, whether psychomotor speed or a more 'cognitive' component is the critical factor in MCI remains unclear.

In the present chapter, a processing speed composite was used based on the results of the PCA, in an attempt to capture the breadth of the construct and avoid various methodological challenges (see chapter 4). However, two possibilities will be investigated in the coming chapters. Firstly, can one task validly capture "processing speed"? The HLR was re-run using only the DSST (one of the variables included in the processing speed composite) and similarly predicted visuospatial function. If the DSST can be used in place of a larger battery to capture processing speed, this may have clinical utility in identifying MCI-LB. However, the DSST certainly involves other cognitive components. Of the Weschler Intelligence Scales (Wechsler, 1944), it is the most sensitive to neurological dysfunction of the subtests (Lezak, 1995; Van der Elst et al., 2006). However, this sensitivity is nonspecific as impairment in either processing or graphomotor speed could induce similar deficits (Joy, Fein, & Kaplan, 2003). Therefore, Chapter 7 will attempt to fractionate the DSST into its cognitive and graphomotor components. Secondly, the relationship between processing speed, attention and reaction time will be considered. The computerised reaction time tests did not reveal a difference between MCI subtypes, and MCI-LB performed in line with controls on SRT. Traditional processing speed measures may fail to capture intermittent long response latencies, which might be a hallmark of MCI-LB given the phenotype of generalized slowing. Alternatives to a Gaussian conceptualisation of reaction times will be investigated in Chapter 8.

Chapter Seven: Analysing components of processing speed using the Digit Symbol Substitution Test (DSST)

7.1 Introduction

Chapters four, five and six suggest that processing speed as measured by DSST may be a core deficit in MCI-LB: it not only resulted in the largest observed effect size (Chapter 4), but can statistically account for deficits in other domains (visuospatial and verbal memory; Chapter 6). DSST is often implied to be a "pure" measure of processing speed; however, it is in fact a complex task that likely engages a multitude of cognitive processes in its completion (Cepeda et al., 2013). The current chapter aims to differentiate the DSST as a measure of processing speed, to understand how the contributing processes are impaired in MCI-LB Probable.

As mentioned previously, the DSST (Wechsler, 1944) is a processing speed measure used frequently and in a variety of populations. Its ubiquity seems highly justified. It's sensitive to neurological dysfunction (Lezak, 1995; Van der Elst et al., 2006) and is highly (negatively) correlated with age, with typical (*r*) coefficients between -.46 and -.77 (Joy et al., 2000). It has been used to study factors relating to intelligence (see DeLuca & Kalmar, 2013 for a review) as well as to attempt to delineate the factors of cognitive decline in ageing. A meta-analysis by Hoyer, Stawski, Wasylyshyn, and Verhaeghen (2004) reaffirmed that older adults complete DSST significantly slower than younger adults, to a very large effect size (*d* = -2.07 based on 141 studies). The DSST and other substitution tasks are also commonly used in clinical populations; for example, substitution tasks are included as suggested criteria for the MDS's neuropsychological definition of PD-MCI (Litvan et al., 2012).

The complexity of the task has been acknowledged by the development of variations by WAIS and independent laboratories in order to help delineate the processes involved. An adaptation of DSST, Symbol Copy, was first included on WAIS-R (Kaplan et al., 1991) to isolate DSST's graphomotor component (Joy et al., 2000). Participants must simply copy each symbol in the grid into an empty box directly below it as fast as possible. A small meta-analysis by Joy and Fein (2001) reported that Symbol Copy, like DSST, has a strong negative relationship with age that becomes significantly stronger beginning at age 50. Moreover, Symbol Copy and DSST have been reported to share 36% to 50% of their variance: a substantial

proportion but nevertheless indicative of other predictive processes within DSST (Joy & Fein, 2001; Joy, Fein, & Kaplan, 2003).

Another test variant, Error Check, was first developed by Joy et al. (2000) to capture the coding processes involved in DSST without graphomotor demands. Error Check involves scanning a completed DSST for errors in relation to the key above and marking any with a pencil slash. Visual scanning speed has been reported to explain 23% of the variance in DSST, a smaller contribution than Symbol Copy (Joy et al., 2003). A third variable that is often investigated in such studies is Coding Time. Based on the principles of mental chronometry (Jensen, 2006), the difference when subtracting the time per item to complete Symbol Copy from that of DSST represents the mental processing time. Coding Time also increases with age, with significantly more time spent on coding than on copying in later decades (Joy et al., 2000). This variable is conceptualized as a purer measure of processing speed resources than Error Check (Nebes et al., 2000); however, both variables include visual scanning time in addition to mental operation time (Joy et al., 2003). The multifactorial nature of the DSST and its variants, as well as the evidence of its association with neurological dysfunction, make it a useful exploratory tool in the study of subtypes of MCI. In particular, the DSST tests will be analysed together to consider the contribution of cognitive processing speed and graphomotor speed to the psychomotor task. To the author's knowledge, such a method of deconstructing the DSST has not been pursued in AD, DLB or MCI previously.

There is also a methodological need to question whether motor impairments associated with LB disease may confound interpretation of performance on these processing speed tasks. As stated above, previous chapters have pointed to a salient difference between MCI subtypes in processing speed. Moreover, HLRs run in Chapter 5 indicate a potential mediating role of processing speed (as measured by both DSST alone and a composite including DSST) to higher-order cognitive abilities, including visuospatial working memory and long-term memory, visuoconstructive ability, and verbal learning. Using Symbol Copy, fine motor impairment did not differ between groups; however, the impairments on the DSST could nevertheless be explained by the motor symptoms that are typical in MCI-LB. As such, the UPDRS will be used in conjunction with the DSST sub-analyses to determine the role of gross motor dysfunction in completion of these commonly used processing speed measures.

The present chapter will utilize a hierarchical linear regression approach to examine how processing resources, constructed through the DSST test variants, and motor impairment (UPDRS) explain MCI-LB-related variance in DSST. It is predicted that graphomotor speed will emerge as the primary predictor of DSST, as in previous research, but that processing speed (Error Check and Coding Time) will explain additional MCI-related variance. Whether the impact of processing and graphomotor speed differs between groups will be determined.

7.2 Methods

Participants

Participant recruitment, demographic and broad cognitive scores for the group (control [*n* = 31], MCI-AD [*n* = 18] and MCI-LB Probable [*n* = 30]) can be found in previous chapters.

Materials

The DSST, Symbol Copy and Error Check were administered as part of the large battery of neuropsychological tasks (see Chapter 4 and Appendix K for copies of the tasks). Coding Time was calculated as the DSST time per item minus the Symbol Copy time per item. Neuropsychological data was first analysed for outliers and normality. Missing data points were replaced using MCAR and Coding Time was computed from the DSST and Symbol Copy. Scores were converted to standardized *z*-scores adjusted to control means. As described in more detail in Chapter 2, the Unified Parkinson's Disease Rating Scale (UPDRS) was scored by an experienced clinician during baseline assessment.

Background variables

As discussed above, performance on the DSST is well-established to have inverse relationship with increasing age. By firstly regressing age-associated variance in DSST, the analyses will better reveal differences due to cognitive status. Subgroups differed significantly in terms of estimates of premorbid IQ (NART), with significantly lower mean scores in the MCI-LB Probable group. As such, all HLRs were run with NART IQ and age entered in the first step.

Treatment of data

Variables were assessed for normality. One outlier in Coding Time (*z*-score = -5.34) from the MCI-LB Probable group was removed. Coding Time was substantially positively skewed and was therefore log transformed. Inspection of histograms and skew and kurtosis statistics confirmed the transformation was successful.

7.3 Results

Table 32 Mean (standard deviation) of adjusted z-scores of DSST and variants, with independent samples t-test results of comparison between MCI subtypes.

	MCI-LB Probable*	MCI-AD*			
n	30	18	*t*-stat	*p* value	Effect size (*g*)
DSST	-1.94 (0.87)	-1.25 (0.69)	2.82	**.007**	0.85
Symbol Copy	-2.00 (1.20)	-1.34 (1.05)	1.92	.062	0.57
Error Check	-1.87 (1.14)	-0.73 (0.71)	4.29	**<.001**	1.14
Coding Time**	-6.99 (2.31)	-5.51 (0.99)	3.04	**.004**	0.77
UPDRS	24.37 (15.15)	16.94 (10.76)	1.98	.076	0.53

** MCI subtype scores significantly lower than controls (n = 31) at p < .01*
*** MCI-LB Probable Coding Time n = 29*

As was shown in the univariate analyses of Chapter Four and replicated above (Table 32), MCI-LB Probable has significantly worse performance than MCI-AD on the DSST, Error Check and Coding Time indices. The differences in Symbol Copy (graphomotor speed) and UPDRS were not significant. Both MCI groups had significantly lower scores than controls on all measures (all *p*s < .01), including UPDRS (control *M* = 5.42, *SD* = 4.42). In the total sample, a strong positive relationship was observed between DSST and the variants Error Check, *r*(79) = .899, *p* < .001, and Symbol Copy, r(79) = .830, *p* < .001. Symbol Copy and Error Check were positively correlated with each other, r(79) = .739, *p* < .001, as were Error Check and Coding Time, *r*(74) = .832, *p* < .001.

HLRs were run to investigate how the variants predict DSST performance in the group overall (Appendix L). Firstly, NART IQ and age were entered in the first step of every HLR, predicting 28.1% of variance (*p* < .001). Secondly, the amount of diagnosis-related variance on DSST was examined by entering “group” (control, MCI-

Table 33 Predicting DSST and Group status after UPDRS scores.

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. B Coefficients	Std. B Sig
Age &						**-0.36**	**<.001**
NART IQ	.281	.262	**.281**	14.64	**<.001**	**0.45**	**<.001**
Age &						**-0.30**	**.001**
NART IQ	.281	.262	**.281**	14.64	**<.001**	**0.39**	**< .001**
Group	.421	.398	**.141**	17.97	**< .001**	**-0.38**	**< .001**
Age &						**-0.20**	**.027**
NART IQ	.281	.262	**.281**	14.64	**<.001**	**0.29**	**.002**
UPDRS	.446	.424	**.166**	22.14	**<.001**	**-0.35**	**.001**
Group	.508	.481	**.062**	9.17	**.003**	**-0.27**	**.003**
Age &						-0.09	.186
NART IQ	.281	.262	**.281**	14.64	**<.001**	0.09	.231
UPDRS	.446	.424	**.166**	22.14	**<.001**	-0.05	.529
Symbol Copy	.702	.686	**.256**	62.57	**<.001**	**0.67**	**< .001**
Group	.716	.696	.014	3.48	.066	-0.13	.066
Age &						-0.09	.186
NART IQ	.281	.262	**.281**	14.64	**<.001**	0.09	.231
Symbol Copy	.698	.686	**.418**	102.41	**<.001**	**0.67**	**.000**
UPDRS	.702	.686	.004	0.88	.351	-0.05	.529
Group	.716	.696	.014	4.48	.066	-0.13	.066
Age &						-0.02	.730
NART IQ	.281	.262	**.281**	14.64	**<.001**	0.03	.555
UPDRS	.446	.424	**.166**	22.14	**<.001**	-0.08	.134
Error Check	.837	.828	**.390**	174.54	**<.001**	**0.79**	**< .001**
Group	.864	.855	**.028**	14.60	**<.001**	**-0.18**	**< .001**
Age &						-0.09	.105
NART IQ	.281	.262	**.281**	14.64	**<.001**	**0.18**	**.003**
UPDRS	.441	.418	**.148**	19.40	**<.001**	**-0.13**	**.045**
Coding Time	.770	.757	**.329**	103.15	**<.001**	**0.64**	**< .001**
Group	.812	.799	**.042**	15.86	**<.001**	**-0.23**	**< .001**

LB or MCI-AD) as the second-step predictor. Group explained 14.1% of the variance in DSST ($p < .001$). Next, separate regression analyses were performed with the DSST variants entered in the second steps and Group in the third (see Table 33). This procedure accounts for the variance due to those constructs before regressing cognitive status (Nebes et al., 2000). The degree to which controlling for the first predictor decreases the variability explained by group therefore quantifies the processing resource's mediation of the cognitive status-related deficit (Nebes et al., 2000). Accounting for Error Check, Symbol Copy or Coding Time results in Group continuing to contribute a significant but small 1.6% ($p = .049$), 3.7% ($p < .001$) or 6.2% ($p < .001$) of remaining DSST variance. Therefore, Symbol Copy explains the highest proportion of cognitive status-related variance on the DSST ([(14.1-1.6)/14.1]*100 = 88.7%). However, none of the variants or the Coding Time index alone fully explain group relationship with DSST. As both Error Check and Coding Time are intended to capture the cognitive aspects of the DSST with minimal graphomotor involvement, their order of entry with Symbol Copy was next considered. Regardless of order of entry, the scores explain additional variance in

DSST. Moreover, group still explains 1.6% or 1.8% of DSST variance after both Symbol Copy and Error Check or Coding Time are included (*p*s = .002), indicating some diagnosis-associated variance in scores remains unexplained by the variants. The proportion of variance explained is similar to the contribution by group after entering only Symbol Copy, suggesting that adding Error Check/ Coding Time to the model add little predictive value in group-related DSST score variance.

Despite entering UPDRS at step 2, Symbol Copy still explains an additional 25.6% of DSST score variance. UPDRS does not add significant variance if entered after Symbol Copy. Moreover, regardless of whether UPDRS or Symbol Copy is entered before the other, the only significant standardized β coefficient in the resultant four-step model is Symbol Copy. Together this indicates that Symbol Copy and DSST are related to each other beyond the motor impairment quantified by UPDRS. UPDRS does decrease the ΔR^2 upon entry of Error Check (from .543 to .390) or Coding Time (from .446 to .329), perhaps indicating that motor ability persists in these variants designed to minimize its role. However, ΔR^2 associated with Group in the final step does not decrease substantially (after Error Check: from .037 to .028; after Coding Time: from .062 to .042), suggesting this finding is not particularly relevant to group allocation. To further analyse the relationship of the variants with DSST, HLRs were run separately by group (Table 34).

Table 34 Predicting DSST with Error Check and Symbol Copy separately by group.

Model	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Δ	Std. B Coefficients	Std. B Sig
Control							
Step 1							
Age & NART IQ	.349	.301	**.349**	7.24	**.003**	**-0.41** **0.50**	**.015** **.004**
Step 2							
Age &						0.00	.974
NART IQ	.349	.301	**.349**	7.24	**.003**	0.11	.338
Symbol Copy	.464	.402	**.115**	5.58	**.026**	0.25	.077
Error Check	.789	.755	**.325**	38.39	**<.001**	**0.68**	**< .001**
Age &						0.00	.974
NART IQ	.349	.301	**.349**	7.24	**.003**	0.11	.338
Error Check	.760	.732	**.411**	44.47	**<.001**	**0.68**	**<.001**
Symbol Copy	.789	.755	.029	3.41	.077	0.25	.077
Age &						-0.13	.081
NART IQ	.349	.301	**.349**	7.24	**.003**	0.08	.245
Symbol Copy	.464	.402	**.115**	5.58	**.026**	**0.36**	**< .001**
Coding Time	.929	.918	**.465**	163.94	**<.001**	**0.73**	**< .001**
Age &						-0.13	.081
NART IQ	.349	.301	**.349**	7.24	**.003**	0.08	.245
Coding Time	.864	.848	**.515**	98.42	**<.001**	**0.73**	**<.001**
Symbol Copy	.929	.918	**.065**	22.96	**<.001**	**0.36**	**<.001**
Age &						**-0.28**	**.003**
NART IQ	.349	.301	**.349**	7.24	**.003**	**0.21**	**.012**
Coding Time	.864	.848	**.515**	98.42	**<.001**	0.60	**<.001**
Error Check	.877	.858	.013	2.68	.114	0.22	.114
Age &						**-.276**	**.003**
NART IQ	.349	.301	**.349**	7.24	**.003**	**.212**	**.012**
Error Check	.760	.732	**.411**	44.47	**<.001**	.219	.114
Coding Time	.877	.858	**.117**	23.88	**<.001**	**.601**	**.000**
MCI-LB Probable							
Step 1							
Age & NART IQ	.225	.168	**.225**	3.93	**.032**	**-0.44** 0.25	**.017** .159
Step 2							
Age &						-0.03	.731
NART IQ	.225	.168	**.225**	3.93	**.032**	-0.01	.874
Symbol Copy	.671	.634	**.446**	35.31	**< .001**	**0.28**	**.024**
Error Check	.854	.830	**.182**	31.07	**< .001**	**0.70**	**< .001**
Age &						-0.03	.731
NART IQ	.225	.168	**.225**	3.93	**.032**	-0.01	.874
Error Check	.819	.799	**.594**	85.57	**<.001**	**0.70**	**<.001**
Symbol Copy	.854	.830	**.034**	5.81	**.024**	**0.28**	**.024**
Age &						-0.07	.413
NART IQ	.240	.182	**.240**	4.12	**.028**	0.08	.318
Symbol Copy	.668	.628	**.427**	32.18	**<.001**	**0.39**	**.001**
Coding Time	.863	.840	**.195**	34.22	**<.001**	**0.60**	**<.001**
Age &						-0.07	.413
NART IQ	.225	.168	**.225**	3.93	**.032**	0.08	.318
Coding Time	.773	.745	**.532**	58.46	**<.001**	**0.60**	**<.001**
Symbol Copy	.863	.840	**.091**	15.88	**.001**	**0.39**	**.001**
Age &						0.05	.579
NART IQ	.240	.182	**.240**	4.12	**.028**	0.09	.278
Coding Time	.773	.745	**.532**	58.46	**<.001**	**0.43**	**.004**
Error Check	.858	.834	**.085**	14.41	**.001**	**0.54**	**.001**
Age &						0.05	.579
NART IQ	.240	.182	**.240**	4.12	**.028**	0.09	.278
Error Check	.799	.775	**.559**	69.48	**<.001**	**0.54**	**.001**
Coding Time	.858	.834	**.059**	9.94	**.004**	**0.43**	**.004**

MCI-AD							
Step 1							
Age & NART IQ	.130	.014	.130	1.12	.353	-0.34 -0.06	.199 .809
Step 2							
Age & NART IQ Symbol Copy Error Check	.130 .595 .829	.014 .508 .776	.130 **.465** **.234**	1.12 16.08 17.79	.353 **.001** **.001**	0.00 **-0.31** **0.46** **0.59**	.990 **.029** **.004** **.001**
Age & NART IQ Error Check Symbol Copy	.130 .666 .829	.014 .594 .776	.130 **.536** **.163**	1.12 22.47 12.40	.353 **<.001** **.004**	0.00 **-0.31** **0.59** **0.46**	.990 **.029** **.001** **.004**
Age & NART IQ Symbol Copy Coding Time	.130 .595 .973	.014 .508 .964	.130 **.465** **.378**	1.12 16.08 180.19	.353 **.001** **<.001**	-0.04 -0.09 **0.58** **0.65**	.472 .078 **<.001** **<.001**
Age & NART IQ Coding Time Symbol Copy	.130 .668 .973	.014 .597 .964	.130 **.538** **.305**	1.12 22.70 145.34	.353 **<.001** **<.001**	-0.04 -0.09 **0.65** **0.58**	.472 .078 **<.001** **<.001**
Age & NART IQ Coding Time Error Check	.130 .668 .760	.014 .597 .686	.130 **.538** **.092**	1.12 22.70 4.99	.353 **<.001** **.044**	-0.06 -0.17 **0.45** **0.47**	.711 .303 **.042** **.044**
Age & NART IQ Error Check Coding Time	.130 .666 .760	.014 .594 .686	.130 **.536** **.094**	1.12 22.47 5.10	.353 **<.001** **.042**	-.058 -.172 **.469** **.448**	.711 .303 **.044** **.042**

Symbol Copy entered after NART IQ and age explains 11.5% of the variance in controls. However, when Error Check (visual scanning) is first accounted for, Symbol Copy no longer explains significant variance in controls. In MCI-LB Probable, however, Symbol Copy explains a much greater proportion of DSST score variance at step 2 (44.6%). Moreover, if entered after Error Check, Symbol Copy still explains a small but significant additional residual variance (3.4%). Within the MCI-AD sample, Symbol Copy entered first explains a similar amount of variance as in MCI-LB Probable (46.5%). After entering Error Check or Coding Time first, Symbol Copy still explains 16.3% and 30.5% unique variance respectively.

Across the three groups, Coding Time explains similar amounts of DSST score variance: 51.5% in controls, 53.2% in MCI-LB Probable, and 53.8% in MCI-AD (all *p*s < .001). It explains the highest amount of variance at Step 2 in controls of the three variants (Coding Time, Error Check or Symbol Copy). Order of entry using Error Check and Coding Time was considered, as both are intended to isolate cognitive processing speed with limited graphomotor demands. In controls, Error Check does not add significant variance if entered after Coding Time ($p = .114$). If Error Check is added first, Coding Time contributes an additional 11.7% of DSST score variance ($p < .001$). In contrast, in both MCI-LB Probable and MCI-AD both

processing speed measures (Error Check and Coding Time) contribute unique variance regardless of order of entry (all *p*s < .05). In the MCI-LB Probable group, specifically, entering Coding Time before Error Check decreases the latter's variance explained by 84.8% ([(.559-.08)/.559]*100). In the opposite scenario, Error Check accounts for 88.9% of Coding Time's prediction of DSST scores, indicating shared variance between the tasks.

Table 35 Predicting DSST scores using participant age, NART IQ and UPDRS scores in the first step, followed by DSST variants if applicable.

Model	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. B Coefficients	Std. B Sig
Control							
Step 1							
Age, NART IQ & UPDRS	.349	.274	**.349**	4.65	**.010**	**-0.41** **0.50** -0.01	**.051** **.005** .957
MCI-LB Probable							
Step 1							
Age, NART IQ & UPDRS	.232	.144	.232	2.62	.072	-0.40 0.23 -0.09	.043 .210 .630
MCI-AD							
Step 1							
Age, NART IQ & UPDRS	.465	.351	**.465**	4.06	**.029**	-0.21 -0.06 **-0.59**	.330 .766 **.010**
Step 2							
Age, NART IQ & UPDRS Symbol Copy Error Check	.465 .624 .829	.351 .508 .758	**.465** **.159** **.206**	4.06 5.48 14.46	**.029** **.036** **.003**	0.00 **-0.30** -0.03 **0.45** **0.58**	.996 **.043** .870 **.020** **.003**
Age, NART IQ & UPDRS Error Check Symbol Copy	.465 .727 .829	.351 .643 .758	**.465** **.262** **.102**	4.06 12.45 7.21	**.029** **.004** **.020**	0.00 **-0.30** -0.03 **0.58** **0.45**	.996 **.043** .870 **.003** **.020**
Age, NART IQ & UPDRS Symbol Copy Coding Time	.465 .624 .977	.351 .508 .967	**.465** **.159** **.353**	4.06 5.48 184.41	**.029** **.036** **<.001**	-.035 -.085 -.091 **.523** **.637**	.474 .091 .161 **<.001** **<.001**
Age, NART IQ & UPDRS Coding Time Symbol Copy	.465 .834 .977	.351 .782 .967	**.465** **.368** **.143**	4.06 28.76 74.91	**.029** **<.001** **<.001**	-0.04 -0.09 -0.09 0.64 0.52	.474 .091 .161 **<.001** **<.001**

In order to ensure that gross motor impairment was not responsible for group differences in Symbol Copy, DSST, Error Check or Coding Time performance, HLRs predicting DSST were run separately by group entering UPDRS in the first step (Table 35). UPDRS was not retained in the first, one-step model in controls (β = -

0.01, p = .957) or MCI-LB Probable (β = -0.09, p = .630), indicating that it is not predictive of DSST scores. Subsequent models with UPDRS were thus not run in those subgroups.

7.4 Discussion

Main findings and implications for MCI-LB

The present chapter aimed to utilize hierarchical linear regression to examine how cognitive and psychomotor resources, assessed through the DSST test variants, explain group differences in overall DSST performance. In the group overall, DSST and Symbol Copy were found to share 41.8% of their variance, in line with previous work (Joy & Fein, 2001; Joy et al., 2003). This reconfirms the role of graphomotor speed in predicting DSST performance. Contrary to expectations, Error Check was the strongest predictor of DSST performance in the group overall (after first accounting for age and premorbid IQ) and explained considerably more variance in DSST(54.3%) than previously reported (Joy et al., 2003). Alternatively, Joy et al. (2003) found graphomotor speed to be the best predictor of DSST in a study with healthy undergraduates, with Error Check explaining only 23% (Joy et al., 2003). As argued by Laux and Lane (1985), different underlying resources may indeed be important to DSST performance in different populations.

In MCI, graphomotor speed explains almost half of the variance in DSST scores. Conversely, it predicts only 11.5% of DSST score variance in controls. This figure is much lower than expected in healthy older controls, especially as substantial motor slowing in ageing is anticipated even in SRT tasks (Sobin & Sackheim, 1997). If valid, this suggests that processing speed task differences between healthy older adults and MCI patients may be particularly driven by differences in graphomotor speed. However, it is possible that the closer association of graphomotor speed and DSST in patients is due to their broader motor impairments or parkinsonism severity, present in many MCI-LB patients. In order to address this potential confound, whole-group analyses were re-run with the inclusion of UPDRS scores. This revealed that graphomotor speed explains an additional quarter of DSST score variance even after controlling for UPDRS scores. In contrast, clinical motor ratings (UPDRS) did not add additional unique variance above and beyond Symbol Copy. Regardless of order of entry, graphomotor speed, and not UPDRS, is retained as a significant predictor of the DSST, indicating that it is capturing fine motor speed independent of

parkinsonism. Moreover, group-associated variance did not drop substantially when UPDRS was included in the model. Taken together, these findings suggest that gross motor function, while related to both graphomotor speed and processing speed, does not confound interpretation of performance on these tasks, including Symbol Copy. Therefore, use of the DSST and its variants appears to be reliable even in MCI conditions typified by clinical motor impairments.

While fine motor speed is important to DSST completion, the results also provide support that the DSST is a measure of information (cognitive) processing speed beyond its graphomotor component. Within MCI-LB Probable, for example, Error Check predicted the largest proportion of variance in DSST of the three measures. Graphomotor speed only added a small amount of unique variance when cognitive speed (Coding Time) or visual scanning (Error Check) were controlled. This indicates that while graphomotor speed remains an important process in DSST performance, the DSST can be assumed to successfully capture cognitive speed, as intended. Thus the importance of the DSST and processing speed more broadly to the neurocognitive structure of MCI-LB, discussed in the earlier chapters of this thesis, is further supported. Chapter four, for example, showed that the DSST produces the largest deficit in performance in MCI-LB Probable relative to controls. Moreover, it was found to be the statistically strongest predictor of group allocation in the discriminant analyses, whether discriminating only between MCI subtypes or across all participants (including controls). Taken together, this suggests that the DSST may have utility in differentiating MCI subtypes from each other, and from controls, despite the presence of motor symptoms in MCI-LB. However, this requires confirmation in larger samples.

It should be noted that UPDRS scores accounted for much of the variance associated with graphomotor speed in the MCI-AD group. This did not occur in MCI-LB or controls. However, the standardized beta coefficient of UPDRS in the final model was not significant in MCI-AD. It is thus unwise to make strong inferences about this finding. Future work specific to MCI-AD could consider whether motor and graphomotor impairments in completion of the DSST threaten its validity as a processing speed measure.

Other distinct processes have been suggested as involved in completion of the DSST that were not taken into consideration in the present chapter. For example, incidental memory (non-instructed and non-intentional learning that facilitates completion during the task) has been investigated in DSST in the past using paired-

associates tests (Burik, 1950; Erber, Botwinick, & Storandt, 1981; Murstein & Leipold, 1961). Following completion of the DSST and without prior warning, participants are asked to reproduce the symbols for each digit without use of the key. Such research has generally concluded that incidental learning only very minimally aids performance and, if it occurs, is secondary to processing or graphomotor speed in determining DSST scores (Joy et al., 2003; Joy et al., 2004; Kreiner & Ryan, 2001; Stephens, 2006). However, incidental memory may play an increasingly determinant role in task completion after age 50 (Joy et al., 2004), possibly due to cognitive de-differentiation. As such, it may be relevant to these samples. It seems unlikely, that incidental memory could be involved in Symbol Copy completion due to the narrow demands of the task. Error Check performance would be more likely scaffolded by executive or visuospatial abilities (Sweet et al., 2005). While executive function has not emerged in previous chapters as particularly impaired in MCI-LB, its role in processing speed tasks should still be considered. Such tasks likely involve varying amount of executive control, and even the simplest tasks will require some maintenance of a task goal and the filtering of background information. Moreover, the only processing speed outcome variable in which MCI-LB Probable did not perform significantly worse than controls is SRT. This suggests that basic psychomotor speed is not impaired per se, but that higher task demands or executive weighting are needed to reveal impairments in MCI-LB. The structured review (Chapter 2) suggests a similar dynamic in PD. Early PD patients perform poorly on tasks with executive weighting, regardless of which domain they appear to target (working memory, processing speed, visuospatial and verbal learning), and despite general intact performance on simpler tasks in those domains (Trails A, RAVLT). Chapter 8 will therefore consider how performance on more challenging speed of processing tasks reveal differences in MCI-LB. In particular, the Continuous Performance Test will be used as it requires sustained attention (higher task demands). Errors on the test can also be inspected to consider how they may reflect executive dysfunction, such as impaired inhibition or updating.

In addition to the issue of executive weighting and sustained attention, which will be addressed in Chapter 8, performance on DSST tests may also depend on oculomotor control. Such control would fall under the umbrella term of perceptual speed, rather than cognitive or graphomotor speed. For example, within Error Check saccadic eye movements are required to move from scanning the completed DSST to scanning the key above it. Saccadic eye movement may be less obviously

involved in Symbol Copy, but the ability to maintain visual attention on the lines of symbols would certainly be necessary for a quick completion. Therefore, Coding Time, being derived from the DSST and Symbol Copy, should remove some of the variance associated with visuoperceptive control. Oculomotor control is also relevant in the context of ageing, as saccadic latency has been shown to increase after 30 years of age (Hikosaka, Takikawa, & Kawagoe, 2000). To the author's knowledge, no study has examined eye movement in DSST in DLB or MCI, nor during Symbol Copy or Error Check in any population. However, Stephens (2006), using DSST, found no evidence of different eye movements in older versus younger healthy participants; however, this study must be interpreted cautiously as only 18 individuals were tested. Moreover, time spent searching the key was not considered, which was specifically noted as a potential separate resource by Salthouse (1978) and is clearly a major component of Error Check. If oculomotor dysfunction is found to be important in the performance of such tasks, this would lend credence to an opposing theory of cognitive dysfunction in aging, the Common Cause Hypothesis, first proposed by Baltes and Lindenberger (1997). This perspective argues that sensory abilities are intrinsically linked to brain integrity and are in fact the critical factor in cognitive decline (Baltes & Lindenberger, 1997). Baltes and Lindenberger (1997) presented evidence that measurements of sensory function provided a better model of the declines observed ageing than processing speed. However, it is possible that sensorimotor resources and processing speed are similarly strong contributors to cognition in older adults (Salthouse, 1994). Analyses to consider the role of these resources are beyond the scope of the present chapter and hence cannot be ruled out as explanatory.

Conclusion

In conclusion, while the DSST and related coding tests aim to quantify speed of processing, they are complex tasks that required a number of cognitive resources (Lezak, Howieson, Loring, & Fischer, 2004). The present chapter aimed to fractionate DSST performance following a processing resource account by considering the role of visual scanning and graphomotor speed to its performance. Secondly, processing speed measures were evaluated with reference to broader motor symptoms to consider the former's validity in MCI-LB. These results provide greater confidence in utilization of the DSST as a valid measure of cognitive processing speed in healthy controls and MCI-LB Probable specifically.

Chapter Eight: Intraindividual variability in attention

8.1 Introduction

Analyses in the previous chapters have emphasized the importance of speed of processing to the neuropsychology of MCI-LB. Separate analyses of the DSST using graphomotor variants also suggest that slowed processing speed is due to cognitive slowing and not simply slowed motor responses. In general as well as within the present project, processing speed is typically indexed by tasks involving attentional cognitive resources, such as the DSST, Stroop and Trails. Attentional difficulties are common in advanced DLB (as well as PD and PDD) and have been shown to be more pronounced than in AD (Baddeley et al., 2001; Ballard et al., 2002). Ballard, O'Brien, et al. (2001), for example, argues that slowed central processing speed is specific to DLB and not demonstrable in AD patients with MMSE scores of more than 10. The present study has demonstrated that attentional deficits are evident in the MCI-LB phase as well. However, the computerised SRT and CRT tests were not different between MCI subtypes, and MCI-LB did not differ significantly from controls on SRT. Moreover, a review concluded preclinical AD to be characterized by subtle attentional dysfunction, with slowed speed of processing also reported in 43% of the included studies (Twamley, Ropacki, & Bondi, 2006). Hence, it is unclear whether processing speed and poor attention can serve to distinguish between MCI subtypes or if it is common to MCI aetiologies.

Reaction time testing can be problematic due to the tendency to focus on mean (average) performance over a given temporal period, i.e. measures of central tendency. Such an emphasis in line with the current dominating perspective of general stability in developmental research (Hultsch, Strauss, Hunter, & MacDonald, 2008; Jackson, Balota, Duchek, & Head, 2012). It is a framework that presumes a similar trajectory of change for all individuals over time, and thus conceptualizes average, age-related effects (Hultsch et al., 2008). In contrast, within-person variability, or inconsistency, has received much less attention in the fields of developmental and cognitive psychology. Inconsistency concerns fluctuations in reaction time that occur on a trial-by-trial basis, rather than a generalized slowing that would be reflected in mean performance (Jackson, Balota, Duchek, & Head, 2012). Such intraindividual variability (IIV) has typically been viewed as ‘noise’ in standard reaction time paradigms. However, it has since been proposed as a “coherent, interpretable steady-state ‘hum’ that describes the base condition of the individual”

(Nesselroade, 1991, p. 94) and should not be dismissed as invariance/error. Indeed, analyses have shown that IIV is strongly internally consistent, correlates reliably with independent measures of cognitive fluctuations, and offers additional information on an individual's attentional profile beyond mean speed of response (Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). As such, an alternative to Gaussian (normal) distribution modelling may be required to capture long latencies. It may be advantageous to include intermittent long responses, as they may be a hallmark of MCI-LB due to its clinical feature of cognitive fluctuations. Background on IIV in aging and pathology as well as ex-Gaussian modelling approaches are discussed in the following sections.

Sustained attention

Tasks that quantify reaction times are typically measures of attention. Some of the most prominent and distinguishing neuropsychological impairments of DLB have been demonstrated by tasks requiring attention (Calderon et al., 2001; Ferman, Smith, Boeve, Graff-Radford, Lucas, Knopman, Petersen, Ivnik, Wszolek, Uitti, et al., 2006; Walker, Allen, Shergill, & Katona, 1997). The concept of attention includes abilities, states of consciousness and processes that focus cognition, although a singular definition is elusive and often differs by context (Zomeren & Brouwer, 1994). It has been suggested to include multiple sub-processes such as selective, focused and sustained attention (Tröster, 2008). The latter is believed to be particularly impaired in DLB. Sustained attention concerns attention occurring over a length of time, thus requiring vigilance, continual effort, as well as elements of selective and focused attention (Cohen, Sparling-Cohen, & O'Donnell, 1993; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Sustained attention is less passive than anticipation and is typified by tasks that require intense, active processing.

Scientific investigation of sustained attention has its roots in 1950s military research on signal detection, using tasks in which a signal must be detected during long periods of inactivity (Jerison, 1970). Signal detection, however, is just one example of a task that necessitate intact sustained attention. Indeed, most neuropsychological tests, while perhaps targeting other cognitive components, will be influenced by deficits in sustained attention due to the conceptual dependence of attention on time (Ibarretxe-Bilbao et al., 2009). Time is a predictor of attention and measuring attention depends on whether or how it changes over time. Selective attention, for example, could be targeted separately from sustained attention at a

given moment; however, because information is processed sequentially over a period of time, in both most real-life situations and laboratory cognitive tasks sustained attention is engaged.

Attentional dysfunction in DLB and AD

Brief consideration of the differences in attentional dysfunction between DLB and AD is warranted, particularly as clinicopathological studies suggest that DLB is often misdiagnosed as AD during a patient's lifetime (Hansen, Salmon, 1990; McKeith, Fairbairn, 1994). In general, attentional impairment is statistically greater in DLB than in AD and may serve as a reliable differentiating factor (Ballard, O'Brien, et al., 2001; Calderon et al., 2001; Collerton et al., 2003); but, such findings have not always been replicated (Galasko, Katzman, Salmon, & Hansen, 1996; Gnanalingham et al., 1997; Salmon et al., 1996). Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al. (2000) found fluctuations to be both more prevalent and more severe in DLB (81%) in contrast to both AD (8% AD) and vascular dementia (18%), thus representing the largest difference in symptom frequency between the causes of dementia. In a study using a matched control group, AD had intact performance in sustained attention (Calderon et al., 2001). Conversely, DLB performed below AD participants in attentional tasks requiring sustained, selective or divided attention, in addition to most visuospatial tasks (Calderon et al., 2001). The findings confirm relevancy of attentional dysfunction in clinical practice, where assessing severity may help differentiate between DLB and AD (Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). However, attention deficits will be more pronounced and less qualitatively distinguishable as both conditions advance, obscuring difference between the groups (Ballard et al., 1995). Dementia patients are often unable to tolerate sustained attention tasks and, in the case of DLB, motor symptoms often worsen with disease progression, complicating standardized, computerised testing. As such, the MCI stage may offer an important window for researching attentional dysfunction.

IIV and Normal Ageing

There is a well-established increase in inconsistency in neurocognitive speed with age believed to reflect decreasing functional status of the central nervous system (de Frias, Dixon, Fisher, & Camicioli, 2007; Hultsch & MacDonald, 2004a; Hultsch et al., 2008; Li & Lindenberger, 1999) and cognitive ability (Bunce,

MacDonald, & Hultsch, 2004; Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994; West, Murphy, Armilio, Craik, & Stuss, 2002). IIV has a U-shaped developmental trajectory across the lifespan, being highest in childhood and older age, particularly after the mid-70s (Hultsch et al., 2008). These age-related trends are independent of motor decline, practice, fatigue and age-related difference in mean performance level (Williams, Hultsch 2005; Bruce, Macdonald, Hultsch 2004).

Cognitively, IIV may underlie decreased age-related performance in a number of domains. For example, Hultsch, MacDonald, and Dixon (2002) found that inconsistency in reaction time tests predicted poorer perceptual speed, working memory and episodic memory performance. The relationship between variables was also stronger as age increased (Hultsch et al., 2002). In a six-year longitudinal study by MacDonald, Hultsch, and Dixon (2003), variability explained 96% of the variance in performance in subsequent testing periods. Declines in all cognitive measures were significantly predicted by inconsistency in SRT and CRT tasks taken at the first testing session (MacDonald, Hultsch, et al., 2003). IIV seems to be a critical predictor of cognitive ageing (Hultsch & MacDonald, 2004b) and is also associated with poorer prognoses in aging. In a five-year longitudinal study of healthy older adults, inconsistency in reaction time was a significantly greater risk factor for pathological status, like MCI, than slower mean reaction time (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010).

Sustained attention tasks are especially relevant to study of age-associated cognitive decline as they require intense, endogenous focus (Braver, Satpute, Rush, Racine, & Barch, 2005). Indeed, situations requiring a high degree of cognitive control are some of the most effective in revealing age-related cognitive changes (Braver et al., 2005). This may be especially true when response inhibition (May, Zacks, Hasher, & Multhaup, 1999; Spieler, Balota, & Faust, 1996) or active maintenance of working memory (Craik, Morris, & Gick, 1990; Daigneault & Braun, 1993) are required, as is the case with the Continuous Performance Test-AX (CPT-AX) described in detail below. In addition to healthy ageing, increased IIV has been demonstrated in various neurological conditions such as traumatic brain injury (Stuss, Pogue, Buckle, & Bondar, 1994), PD (Burton, Strauss, Hultsch, Moll, & Hunter, 2006) and dementia (Gordon & Carson, 1990).

IIV in MCI and AD

Increased IIV in reaction time may precede the development of cognitive decline (Bielak et al., 2010; Cherbuin, Sachdev, & Anstey, 2010; Lövdén, Li, Shing, & Lindenberger, 2007; MacDonald, Hultsch, et al., 2003). IIV, for example, is higher in both MCI and AD versus healthy ageing (de Frias et al., 2007; Gorus, De Raedt, Lambert, Lemper, & Mets, 2008). Dementia research has primarily focussed on AD, with consistent reports of elevated IIV (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Murtha, Cismaru, Waechter, & Chertkow, 2002). Duchek et al. (2009), for example, found that increased variability was associated with both age and early stage AD diagnosis when using coefficient of variation (CoV) to quantify IIV. Furthermore, CoV in Stroop task performance discriminated apolipoprotein E4 carriers from non-carriers in healthy older controls. Hultsch et al. (2000) investigated the contribution of neurological and somatic health status to variability and found IIV to be related to overall cognitive performance and predictive of AD independent of performance level. Their findings suggest IIV to be a stable cognitive trait relating to central nervous system integrity, rather than to potentially transient somatic health status. Other studies have similarly controlled for potential confounding variables, such as severity of dementia and parkinsonism, motor status and reaction time latency, to demonstrate that increased IIV in DLB nevertheless remains (Ballard, O'Brien, et al., 2001; Ballard et al., 2002; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000).

IIV has also been shown in MCI to be predictive of conversion to dementia (reviewed in Jackson et al., 2012; Phillips, Rogers, Haworth, Bayer, & Tales, 2013). Indeed, IIV may represent an early indicator of an underlying pathological and progressive decline in brain integrity before decreases in mean level performance become evident. For example, IIV in a target detection task was found to be predictive of which amnestic MCI patients converted to dementia by 2.5 years follow-up (Tales et al., 2012). Non-converters displayed equivalent variability at baseline as healthy controls (Tales et al., 2012). As a possible confound to this finding, MMSE scores were lower at baseline in converters versus non-converters (Tales et al., 2012). However, as MMSE did not correlate with or predict IIV within each of the groups, the authors concluded it was unlikely that the poorer general cognitive status of the converter group accounts for the difference in IIV observed (Tales et al., 2012). Gorus et al. (2008) found variability and response latency were greater in cognitively impaired persons, with speed of processing decreasing with degree of impairment

(moderate AD versus mild AD versus amnestic MCI). The study also utilized a paradigm of increasingly complex reaction times tasks to delineate motor and cognitive components of performance. Gorus et al. (2008) found that longer reaction time latencies were associated with both the cognitive and motor aspects of the task, while IIV mainly related to the cognitive component of reaction times. As such, IIV is a more purely cognitive task index and is less dependent on motor speed variability. The IIV measure was also the best predictor of amnestic MCI status, over mean processing speed, highlighting the additional value of variability above and beyond response latency (Gorus et al., 2008).

Other work in MCI contradicts this picture of IIV. Christensen et al. (2005), also using HLRs, found greater IIV in MCI, but IIV did not predict diagnostic status beyond mean levels of reaction time performance. This study had a narrow patient age range (60-64 years) and used basic reaction time tasks (SRT/ CRT), which may have failed to capture the phenomenon. Conversely, both Dixon et al. (2007) and Strauss, Bielak, Bunce, Hunter, and Hultsch (2007) found variability to be superior to response latency in differentiating patient groups. These studies shared some participants and used a wider age range (64-90+) and a stricter definition of MCI than Christensen et al. (2005), which may explain the differing results. Moreover, the tasks of Dixon et al. (2007) and Strauss et al. (2007) included those of higher complexity such as the n-back choice reaction time task. MCI may therefore be associated with greater IIV relative to healthy controls but only on tasks requiring additional executive functions, such as manipulating held information, cognitive set switching, or inhibition (Strauss et al., 2007). This is line with similar concerns in identifying age-related deficits discussed above.

IIV and DLB

Of the existing IIV research in DLB, studies typically include both DLB and AD or other dementia patient groups. Overall, results of such studies suggest that variability is greater in DLB than in AD (Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000; Walker, Ayre, Perry, et al., 2000), including on tasks specifically targeting vigilance or sustained attention (Ballard et al., 1995). Bradshaw, Saling, Anderson, Hopwood, and Brodtmann (2006) for example, found greater IIV in DLB in all aspects of attention measured, including simple reaction times, focused selective attention, divided attention and supervisory attentional control, even when matched on dementia stage and severity. Walker, Ayre, Cummings, Wesnes, McKeith,

O'Brien, et al. (2000) used a 90 second CRT and demonstrated second-to-second fluctuations in cognition and EEG. In line with Ballard et al. (2002) and Bradshaw et al. (2006), Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al. (2000) found that greater IIV in DLB persisted despite controlling for dementia and parkinsonism severity or mean response time latency. Interestingly, the forced-choice, two-response paradigm used in that study is less cognitively demanding than the more challenging n-back task. As discussed above, more challenging tasks have been shown to be necessary to reliably reveal increased IIV in the case of AD patients (Strauss et al., 2007). This further supports the hypothesis that IIV will be more pronounced in DLB than in AD.

CPT-AX and other paradigms for measuring attention and IIV

Historically, neuropsychological assessment of inconsistency of attention has relied on behavioural observation and pen-and-paper or oral tasks, such as digit span. These can be useful measures of attention *span*, but they do not target aspects such as selective or sustained attention (Cohen et al., 1993) nor require substantial cognitive effort (Zomeren & Brouwer, 1994). Simple attentional tasks do not always reveal deficits in dementia (Gnanalingham et al., 1997; Salmon et al., 1996; Walker et al., 1997), although this has been successfully reported in a few studies (Hansen et al., 1990). Moreover, the aforementioned dependency of attention on time is difficult to manipulate using most pen-and-paper tasks (Cohen et al., 1993). For these reasons, their appropriateness in differentiating between dementia syndromes is questionable (Bradshaw et al., 2006). Instead, more complex, standardised attentional tasks that target specific subcomponents (sustained, selective, divided, etc.) are needed to elicit and reliably capture differential performance in dementia subtypes (Tröster, 2008).

The advent of technologies such as the tachistoscope and, subsequently, computers, allowed increased standardization, reliability and nuance in studying attention through reaction time (Cohen et al., 1993). The CPT was one of the earliest computerised neuropsychological paradigms to be widely adapted and has been used to illustrate deficits in a variety of conditions including schizophrenia (Nuechterlein, 1983) and Attention Deficit Disorder (Epstein et al., 2003). Presently, a number of versions of CPTs are available for commercial and research use and have collectively come to be the most regularly used to assess sustained attention. While varying in particularities, a CPT presents stimuli (typically numbers or letters)

sequentially and requires participants to attend to and respond to a target stimulus while ignoring non-target distractor stimuli over an extended testing period. Performance on CPTs correlates well with other information processing-based measures and speeded tests of attention and executive function (such as Stroop and Trails) and benefits from good test-retest reliability in healthy older adults (Braver et al., 2005).

CPT-AX is a conditional variant of CPT in which responses to the target ("X") should only be made when it occurs immediately after an "A". Some versions require a different response (typically a second button is pressed) to any non-target stimuli (Braver et al., 2005). Regardless of the response requirement, AX paradigms importantly have executive demands, primarily context maintenance, inhibition and set shifting, in addition to requiring sustained attention. This increases the difficulty relative to simpler reaction time tasks. CPT-AX also has the value of multiple outcomes measures, including correct responses, errors of omission and commission, and reaction time, as well as secondary/ derived signal detection measures. Signal detection analyses are useful in investigating error type between groups, but does not address IIV nor directly quantify performance variability over time.

CPT-AX is also useful in measuring IIV due to its complexity. Age-related increases in IIV are greater when using more complex tasks. West et al. (2002), for example, found IIV to be greater in older versus younger participants in higher executive control conditions of the sustained attention task, but comparable in the low executive control conditions. Bradshaw et al. (2006) used a task modelled on the Visual Focussed Attention Test (Eriksen & Eriksen, 1974) to manipulate task complexity and investigate how executive function demands impact sustained attention. As expected, DLB were significantly more variable in task conditions with added executive control and spatial processing demands (Bradshaw et al., 2006). The executive weighting of CPT-AX should may be particularly useful for discriminating MCI-LB given that executive impairment is an earlier and more pronounced feature of DLB than of AD (Calderon et al., 2001; Collerton et al., 2003; Mori et al., 2000; Mosimann et al., 2004). However, while early executive impairment was demonstrated in LewyPro (the precursor the SUPErB) (Donaghy, O'Brien, Colloby, et al., 2015), it was less clear in my univariate analyses (see section 4.4).

The ex-Gaussian model and modelling of CPT-AX in MCI

Previously discussed studies in DLB to date have generally used rather crude measures of IIV, typically either the individual SD, CoV (individual SD divided by the individual's mean) or interquartile range. However, reaction time distributions are typically positively skewed, leading to overestimation of population medians if using only sample medians to define the curve (Miller, 1988). Such descriptive statistics often fail to sufficiently characterize the shape of a distribution of response time data by viewing longer latencies as noise and obscuring critical features of the curve. For example, two distributions of reaction times could be viewed as equivalent based on their means, but nevertheless have highly different modal portions of the distribution (*mu*) or tail length (*tau*) (Heathcote, Popiel, & Mewhort, 1991). Tail features may be especially important to DLB, as discussed below.

Recent work has applied alternative mathematical techniques to better model empirical reaction time measures and therefore understand IIV, in particular using an exponentially-modified Gaussian (or ex-Gaussian) distribution. The ex-Gaussian distribution modifies the Gaussian curve (normal distribution) by combining it with an exponential distribution (Ratcliff, 1979; see figure 1). The symmetrical Gaussian/ normal curve is extremely common to a variety of human processes, such as perceptual and motor tasks (Lacouture & Cousineau, 2008), but will omit the positive skew that typifies reaction time data in the tail of the distribution. The exponential distribution, in contrast, is characteristic of decision processes (Luce, 1986; chapter 6). The resulting summation of these two models provides a probabilistic function that is more representative of reaction time data, such as of the CPT-AX. In particular, the right-sided skew of reaction times are included, preserving the variability data rather than only focusing on central tendency. The ex-Gaussian curve has three parameters of interest: *mu* (mean), *sigma* (SD) and *tau* (the exponentially distributed tail of the distribution). Because the sum of *mu* and *tau* is equal to the arithmetic mean of the reaction time distribution, ex-Gaussian and Gaussian distributions can be directly compared.

Lacouture and Cousineau (2008) explain that ex-Gaussian's growing popularity is due to its theoretical justification, provision of easily interpreted parameters and facilitation of hypothesis testing on underlying cognitive processes of reaction time tasks. *Sigma* has generally become conceptualized as indicative of response preparation or execution problems, primarily from work in ADHD (Fassbender et al., 2009; Schall & Hanes, 1998; Vaurio, Simmonds, & Mostofsky,

2009). *Tau*, alternatively captures the strength of the slow-tail of the ex-Gaussian distribution and is believed to reflect trials in which "lapses in attention," i.e. cognitive microfluctuations, have occurred (Lee et al., 2015; Leth-Steensen, Elbaz, & Douglas, 2000; Tamm et al., 2012). *Tau* may therefore be particularly relevant to DLB and neurological integrity. Distributional parameters are likely differentially impacted in normal ageing and pathologies including DLB. Tse (2010), for example, demonstrated that age was associated with both a greater positive skew (larger *tau* values) and changes in *mu* on attentional control reaction time tasks, but only *tau* was impacted by early AD status. Balota (2010), in a twelve-year longitudinal study, found that *tau* (as well as Stroop error rates) significantly discriminated between converts to AD and nonconverters, beyond most other psychometric measures. Balota (2010) concludes that *tau* may be an early marker of likelihood to develop AD.

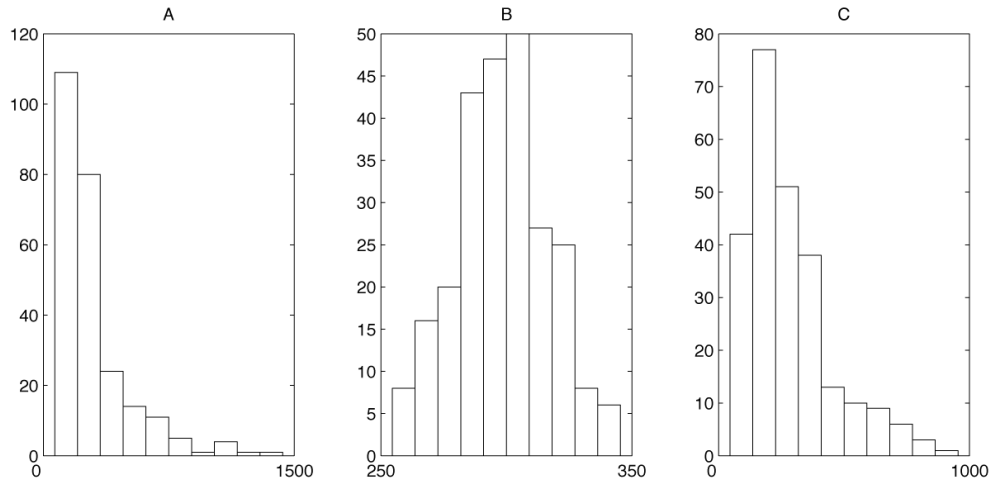

Figure 11 Three distributions of response times with same sample mean. Panel (A) exponential function distribution. Panel (B) normal distribution. Panel (C) ex-Gaussian function distribution. Image taken from Lacouture and Cousineau (2008).

Hypotheses and Aims

Reaction times, signal detection indices, IIV, and types of errors made within CPT-AX, a sustained attention task will be analysed to allow greater understanding of MCI-LB Probable cognitive performance in situations requiring sustained attention, context maintenance and response inhibition relative to healthy controls and MCI-AD. It is hypothesized that increased IIV in reaction time performance will be observed in both MCI groups. Ex-Gaussian modelling techniques will be used to delineate and investigate the components of IIV within the SRT and CRT paradigms in addition to

CPT-AX. Evidence that increased IIV in MCI is associated with greater likelihood of conversion to AD in MCI subjects makes it difficult to confidently predict how MCI-AD and MCI-DLB will differ in their IIV subcomponents (reviewed in Phillips et al., 2013). However, the prominent executive dysfunction associated with advanced DLB makes it likely that IIV will be elevated in MCI-LB Probable in CPT-AX performance. Lastly, IIV will be investigated as underpinning function in higher cognitive activities (visuospatial function and global cognitive scores) and compared to the DSST. The final comparison is in order to consider whether IIV offers utility above and beyond processing speed as measured by the DSST, which emerged as the strongest predictor of group allocation and the task showing the largest effect size between MCI-LB Probable and controls (see Chapter 4). Processing speed, as measured by DSST, was also a significant predictor of visuospatial scores, global cognitive function, and verbal learning (Chapter 6).

8.2 Methods

Participants

See Chapter two for participant recruitment, initial screening, diagnostic group allocation process, and full study testing procedures. The computerised reaction time tests were completed by different numbers of participants due to technical issues and testing time restrictions. Demographic details (by group) are presented in the results sections below.

Procedure

The computerised reaction time tests were completed as part of the larger battery of SUPErB. Participants were generally tested in a dedicated study room at the Clinical Ageing Research Unit, Institute for Ageing and Health, Newcastle University on the fifth and final visit of the SUPErB study (see Chapter 2). Testing was completed at participants' homes as needed due to time constraints. Regardless of location, the testing took place in a darkened room at a desk using a 12.5 inch screen laptop. The reaction time tests were administered as part of the larger computerised battery (see section 4.2).

Materials

Computer and external buttons

All participants were trained on how to hold the external buttons in their hands. Thumbs or pointer fingers could be used to depress the button. The author ensured the participant could comfortably and accurately use the buttons in cases of any motor issues such as arthritis or tremor. One participant (MCI-LB Probable) was unable to show adequate comprehensive of the task demands and their data were omitted from the following analyses.

Simple (SRT) and choice (CRT) reaction time

SRT and CRT are 40-trials tasks measuring reaction time to a visual stimulus. Participants must respond “as quickly as possible” using external buttons to an intermittently appearing stimulus, either a white “X” (SRT) or white arrow (CRT) that appears in the centre of a black screen. In CRT, participants must press the left or right button if the arrow is pointing to the left or right, respectively. Stimuli displays for up to 3000ms without a keypress, with a minimum display time of 500ms. Interstimulus interval (ISI) is randomly determined, with a minimum wait of 1500ms. Responses are recorded as the first key press response time in SRT, unless there is “no response” or “anticipated” response (less than 100ms. For CRT, reaction times are either “correct,” “multiple key press” (both pressed simultaneously), or “incorrect” (wrong key pressed). Both SRT and CRT have 40 stimuli, corresponding to 40 reaction time measures per participant, unless in cases of nonresponse. Distribution of the results were assessed using *z*-scores as discussed further in the results section.

CPT-AX

A modified version of the CPT-AX was administered. As introduced above, the CPT-AX is a test of sustained attention measured using reaction times and hit/ error rates. In the centre of a grey screen, white, 40 point letters appear consecutively (presentation time = 85ms, ISI = 900ms) Participants are required to respond with a keypress “as quickly as possible” to “X” when it has come immediately following an “A” (“AX” trial). Participants are instructed to not respond to any other letters. There was no specific training period, but paper examples of the stimuli were used and comprehension of the instructions was assessed by the researcher prior to administering the task. Of the 240 pairs of letters, AX trials requiring a response

Table 36 Description of the different response types in the CPT-AX task.

Presentation Pair and Response Type	Description	Frequency of occurrence
AX Hit	Correct target with keypress occurring on the "X"	70%
AY False Alarm	Non-target that comes after an "A": "A, B, C, F, G, J, N, O, Q, S, U, V, W, Y, Z". High frequency of AX targets in task primes participants to respond after A's as a response would be correct in the majority of cases. Avoidance of AY errors requires inhibition of response.	5%
BX False Alarm	X that occurs after a non-A; Avoidance of BX errors requires intact context maintenance, i.e. participants must keep an up-to-date representation of the previous stimulus in order to correctly withhold a response	10%
BY False Alarm	Non-X after non-A; indicative of general sustained attention dysfunction.	10%
Other A False Alarm	"A" always, before something other than X, i.e. the A in "AY" false alarms; indicative of general sustained attention dysfunction.	5%

appear frequently (70% of pairs). "AY" and "BX" false alarm pairs each make up of 10.0% of the total stimuli pair presentations. Target presentation was pseudo-randomized. The primary outcome measures are % hits (high = better attention performance), % miss (AX errors; high = inadequate focus on stimuli, slow processing speed, or inability to respond rapidly), and false alarms errors of commission of four types (AY errors, BX errors, BY errors, and other A errors; response to non-targets or failure to inhibit responding), and the reaction time ex-Gaussian parameters of mu, *sigma* and tau. Hit rates were calculated as the proportion of correct responses to the "AX" trials. In cases of hit rates of 1 or false alarm rates of 0, small constant adjustments were used to allow for signal detection calculations: correct hit rate = 1 – 1/(2n) where n = 140 (maximum possible number of hits); false alarm rates = 0 + 1/(2n) where n = 60, max possible number of false alarms. This correction was adapted from Macmillan and Kaplan (1985). Error rate descriptions are presented in Table 36.

Three signal detection measures were computed from the primary measures: response criterion, discrimination index (*d'* calculated based on total number of errors of commission and of omission*)* and context *d'* following the methods in Robinson et al. (2013). Response criterion represents target detection at the expense of greater false alarms and is calculated as -0.5*(*z(*proportion hits)+*z*(proportion false alarms). Higher response criterion values relate to a stricter response criterion in which a response requires higher confidence the correct target (AX) is present. Increasing response criterion values relate to increasing misses, but fewer false alarms. *d'* is

calculated as *z*(proportion hits)-*z*(proportion total false alarms), i.e. the total number of hit minus the total number of errors of omission. Context *d'* is calculated as *z*(proportion hits) – *z*(proportion BX false alarms). Both *d'* and context *d'* provide measures of accuracy based on the standardized scores. However, context *d'* bases accuracy only on trials with intact context processing.

Treatment of data

Data were analysed using the SPSS version 24, Microsoft Excel 2016 and MATLAB R2017a. Raw data was trimmed based on established absolute cut-offs for reaction times with any responses below 100 ms removed (Luce, 1986). Keypresses were considered valid if occurring within the ISI but after the 100 ms cut-off. Errors in the CRT (incorrect keypress, nonresponse, or anticipated) and the CPT-AX were coded appropriately. Only RTs from correct responses ("hits" in the case of CPT-AX) were entered into the ex-Gaussian analyses. This resulted in total numbers of reaction times for ex-Gaussian modelling of 2,890 from the SRT, 2,643 from the CRT, and 10,441 from the CPT-AX. The ex-Gaussian probability density function was fit to the correct response times of the three tasks separately using the DISTRIB toolbox (Lacouture & Cousineau, 2008) in MATLAB. Three parameters of the ex-Gaussian distribution are estimated per individual using this function; *mu*, *sigma*, and *tau*. For between-group and mixed-ANOVA comparisons, all data were checked for assumptions including normal distribution using the Shapiro-Wilk test and inspection of histograms. Age, UPDRS and NART IQ were firstly entered as covariates but removed if they were not significant in the model. Reaction time data was also analysed through the creation of eight equal Vincentile bins that rank order means from the fastest 12.5% to the slowest response latencies of each task separately. This allows visualization of the data without prior assumptions regarding shape (Balota, Yap, Cortese, & Watson, 2008).

8.3 Results

8.4.1 CPT-AX errors and signal detection measures

Overall, seventy-two participants completed the CPT. However, one participant was removed due to hardware malfunction. Three participants had accuracy scores of less than 50.0% and were removed. This left a total sample size of 69 (see Table 37). Hit Rate was transformed exponentially. AY and A error rates

Table 37 CPT-AX Hit, Error/ False Alarm Percentages and signal detection indices presented by Group.

Measure	Control		MCI-LB Probable		MCI-AD	
	n = 29		*n* = 24		*n* = 16	
	M	*SD*	*M*	*SD*	*M*	*SD*
Hit Rate	96.59%	4.04%	82.61%	12.87%	90.89%	7.39%
Miss Rate	3.41%	4.04%	17.39%	12.87%	9.12%	7.39%
AY False Alarm	18.82%	16.76%	26.22%	21.33%	25.00%	21.73%
BX False Alarm	8.91%	8.68%	15.80%	11.66%	12.24%	11.02%
BY Error Rate	0.14%	0.77%	2.08%	2.75%	0.78%	1.68%
Other A Error Rate	3.48%	4.11%	13.95%	10.80%	9.86%	8.48%
d'	0.94	1.08	-1.10	1.46	-0.05	1.19
d'-context	0.88	0.99	-1.08	1.81	0.03	1.61
Response criterion	-0.11	0.42	0.18	0.88	-0.07	0.56

were moderately positive skewed and transformed using square root. However, there was large positive skew in BY Rate (2.04) that could not be successfully corrected with transformation.

Age, NART IQ and UPDRS were evaluated as potential covariates (ANCOVA), however, none were significant and were not used in subsequent analyses. One-way ANOVAs show that groups differed significantly in Hit Rate, misses (%), BY-errors and “other-A” errors (all *p*s < .01). There was a statistically significant difference between group in Hit Rate, $F(2,66) = 16.68$, $p < .001$). Tukey post-hoc testing showed MCI-LB Probable had a lower hit rate than both controls ($p < .001$, $d = 1.47$) and MCI-AD ($p = .013$, $d = 0.79$), with large effect sizes. The difference between MCI-AD and controls was not statistically significant ($p = .100$).

Both MCI-LB Probable ($p < .001$, $d = 1.28$) and MCI-AD ($p = .034$, $d = 0.96$) committed more “other A” errors than controls, but the MCI subtypes did not differ ($p = .261$). MCI-LB Probable also made more BY ($p = .001$, $d = 0.96$) errors than controls, but not MCI-AD ($p = .523$). The ANOVA for BX was on trend, $F(2,66) = 2.92$, $p = .061$, with post-hoc Tukey comparisons showing significantly higher rates of BX errors in MCI-LB Probable than controls ($p = .048$, $d = 0.67$). Groups did not differ on AY False Alarm rates ($p = .355$).

One Hit Rate and one False Alarm Rate required correction as described in the Methods. Overall, groups did not differ in their response criterion (“C”), $F(2,66) = 1.50$, $p = .230$, but the one-way ANOVA was significant for *d’* ($F(2,66)=17.63$, $p < .001$) and *d’*-context ($F(2,66) = 11.83$, $p < .001$). MCI-LB Probable showed poorer target discriminability relative to controls ($p < .001$) and MCI-AD ($p = .035$), as measured by *d’*. Using *d’*-context, MCI-LB Probable again performed worse than controls ($p < .001$), with the comparison with MCI-AD on trend ($p = .055$). *d’* was re-assessed by ANCOVA, evaluating age, NART IQ and UPDRS scores as covariates.

However, none of the covariates were significant and the other signal detection measures were no re-run using ANCOVA.

8.4.2 Ex-Gaussian analyses of SRT, CRT and CPT-AX

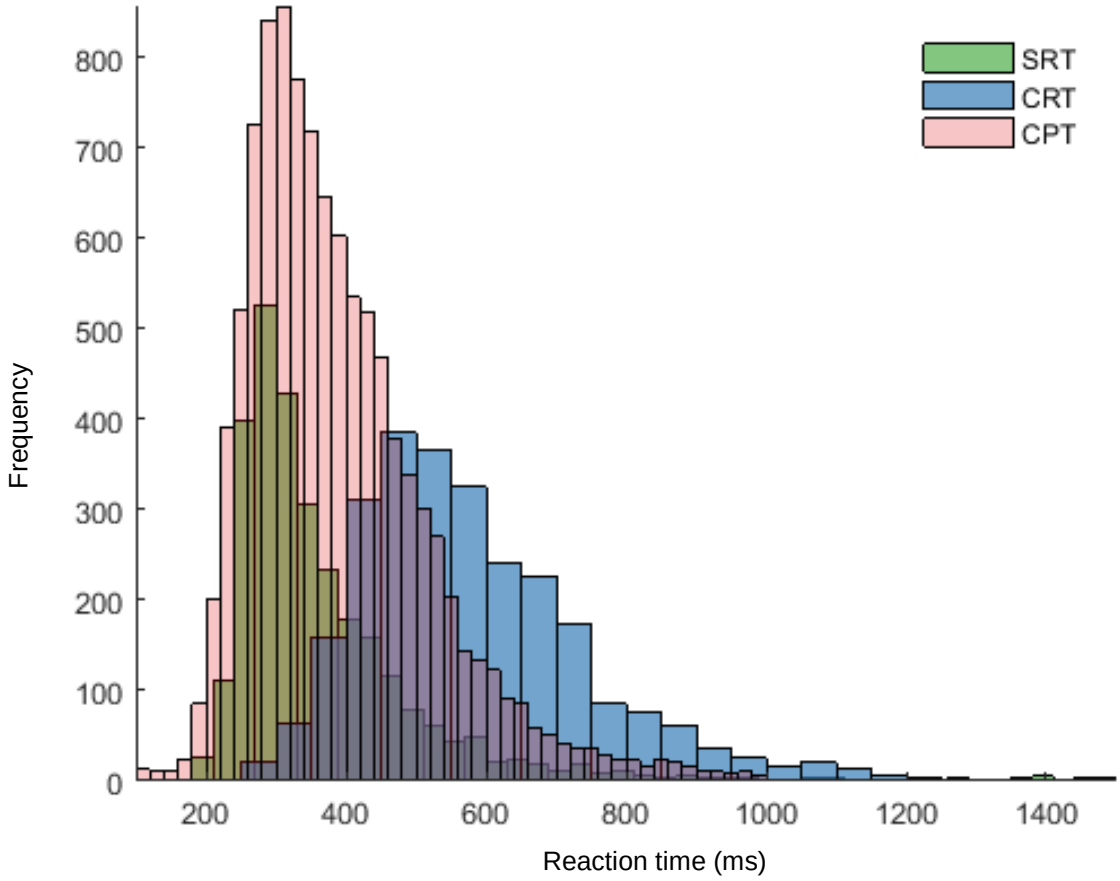

Figure 12 Histograms of response time (ms) distributions of the three reaction time tests (Simple Reaction Time [SRT], Choice Reaction Time [CRT] and Continuous Performance Test-AX [CPT-AX]) for all participants.

Histograms of response reaction times indicated non-normal distributions of the data, with positive skews in line with an ex-Gaussian distribution (Figure 12). SRT was completed by 74 participants. Responses were considered “anticipated” if they occurred before or less than 100msec after stimulus presentation. After cleaning data of anticipated and non-responses, all remaining reaction times were above 100 msec. After removal of the incorrect responses and outliers, the total sample had a mean reaction time of *M* = 372 msec, *SD* = 156.7 (see Table 38). The ex-Gaussian distribution failed to fit three cases. CRT was completed by 70 participants. 95% of keypresses were correct in the group overall (96% in controls, 94% in MCI-LB

Table 38 Ex-Gaussian indices of reaction time performances on three tasks (Simple Reaction Time [SRT], Choice Reaction Time [CRT], and Continuous Performance Test AX [CPT-AX]) by participant subgroup.

	Controls			MCI-LB			MCI-AD		
	Mu	Sigma	Tau	Mu	Sigma	Tau	Mu	Sigma	Tau
n	*27*			*26*			*18*		
SRT	275.32 (42.34)	20.02 (15.31)	50.12 (24.88)	316.01 (89.59)	34.16 (30.45)	73.12 (32.64)	287.86 (79.14)	23.99 (26.03)	99.45 (70.94)
n	*16*			*23*			*14*		
CRT	462.51 (82.39)	48.58 (17.01)	60.82 (21.30)	543.64 (141.31)	82.18 (47.12)	95.59 (38.20)	490.33 (73.52)	72.23 (31.81)	97.81 (44.98)
n	*28*			*26*			*17*		
CPT-AX	298.06 (62.05)	39.27 (22.92)	75.31 (39.39)	292.38 (94.19)	46.95 (33.12)	114.46 (57.38)	286.84 (42.88)	48.54 (32.18)	110.37 (29.97)

Probable and 95% in MCI-AD). Overall, 64% of participants made at least one "wrong" keypress. Groups did not differ significantly in total errors of all types committed, p = .228. All but correct keypresses were removed and all remaining reaction times were above 100 msec. From the remaining 2,634 reaction times, the total sample had a mean reaction time of M = 585.83 msec, SD = 177.77. The ex-Gaussian model failed to fit 17 cases. Data were re-run using a less conservative trimming method (±3.0 SDs) but it was equally as unsuccessful. Therefore, the original output was retained. In the CPT-AX, 254 reaction times of less than .100 seconds were removed. The short interstimulus interval of this task makes data trimming unnecessary. The mean reaction time for correct hits was 379.56 msec, SD = 141.58. The ex-Gaussian model failed to fit CPT-AX data from two participants. See Appendix M for more details on data cleaning, such as removal of anticipated and non-responses, for the three tasks.

One-way ANCOVAs were run on the ex-Gaussian measures entering age as a covariate. UPDRS was initially included as well but it was not significant and removed from all subsequent analyses (all ps > .05). The between-subjects effects of the models were not significant in SRT *mu* (p = .141), SRT *sigma* (p = .121); CRT *mu* (p = .096), CPT-AX *mu* (p = .141), or CPT-AX *sigma* (p = .458). One-way ANCOVA showed groups differ significantly in CRT *sigma* ($F(2,49) = 4.06$, p = .023 *partial* η^2 = .142. Age was not significant in the model (p = .711). Post-hoc tests show MCI-LB Probable CRT *sigma* values are significantly greater than in controls (p = .020, d = 0.95).

For the CRT, *tau* differed significantly by group, $F(2,49) = 4.02$, p = .024, *partial* η^2 = .141. Post-hoc analyses show MCI-LB Probable have significantly larger *tau* values than controls (p = .031, d = 1.12). MCI-AD was not significantly different

relative to controls (p = .089) and MCI-LB (p = 1.00); however, the marginal means and SDs of *tau* are very similar for both MCI subtypes. The CRT comparisons are likely very underpowered due to the poor fit in the ex-Gaussian model. However, groups also differ significantly in CPT-AX *tau* using one-way ANCOVA with age as a covariate, $F(2,68) = 5.42$, p = .007, *partial* η^2 =.137. Age was on trend for significance in the model (p = .051). Post-hoc pairwise comparison shows that *tau* measures are greater in MCI-LB Probable (p = .007, d = 0.80) than in controls. MCI-AD did not differ significantly from controls (p = .090) or MCI-LB Probable (p = 1.00). One-way ANCOVA for difference in SRT *tau* was significant, $F(2,67) = 6.36$, p = .003, *partial* η^2 = .160. Age was not significant in the model (p = .651). MCI-AD had significantly higher SRT *tau* values than controls (p = .002, d = 0.93).

8.4.3 Vincentile plots and mean reaction times

Vincentile plots were created to illustrate reaction time data by rank order of means. Vincentiles were analysed with a 3 (Group) × 3 (Task) × 8 (Vincentile Bin) mixed-factor ANOVA. There was a significant main effect of group $F(2,64) = 5.04$, p = .009, indicating differences in reaction times regardless of task or bins. There was also a significant main effect of task, $F(1.71, 128) = 150.46$, p < .001, with mean reaction times in CRT significantly slower than in both SRT and CPT-AX (both *ps* < .001). There was also a significant interaction between task and group, $F(3.41,109.15) = 7.76$, p = .013. Figure 13 and Figure 14 show both MCI-LB Probable and MCI-AD with longer response latencies than controls on SRT and CRT, but no difference between MCI subtypes. There was a significant main effect of bin, $F(1.31,83.67) = 562.99$, p < .001, and a significant interaction between group allocation and bin, $F(2.62,83.67) = 11.91$, p < .001, indicating that reaction times differ in controls and MCI depending on Vincentile bin. The task x Vincentile bin interaction was also significant, $F(3.07,196.34) = 15.86$, p < .001, indicating that the reaction times of bins were longer for one of the tasks than the other. However, the three-way interaction between group, task and Vincentile bin was not significant, $F(6.14,196.34) = 1.18$, p = .317. Therefore, the data does not indicate that the task x Vincentile bin interaction effect is different for the three different groups.

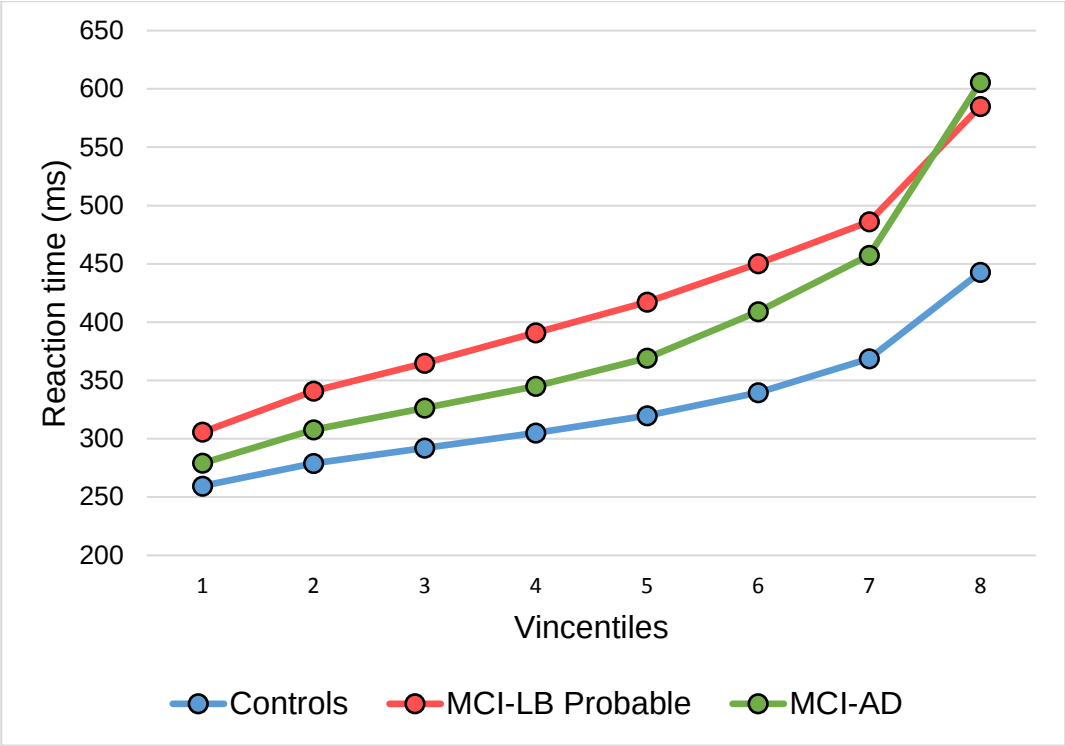

Figure 13 Simple Reaction Time task mean reaction times by Vincentile bin, separated by group (control, MCI-LB Probable and MCI-AD).

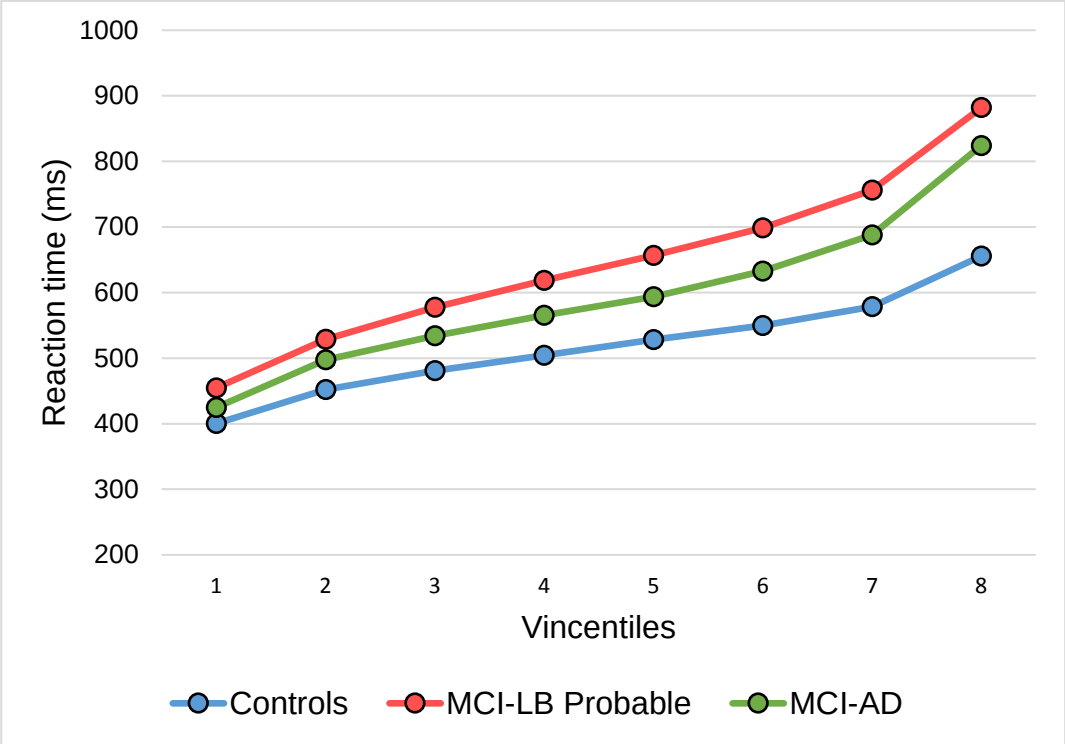

Figure 14 Choice Reaction Time task mean reaction times by Vincentile bin, separated by group (control, MCI-LB Probable and MCI-AD).

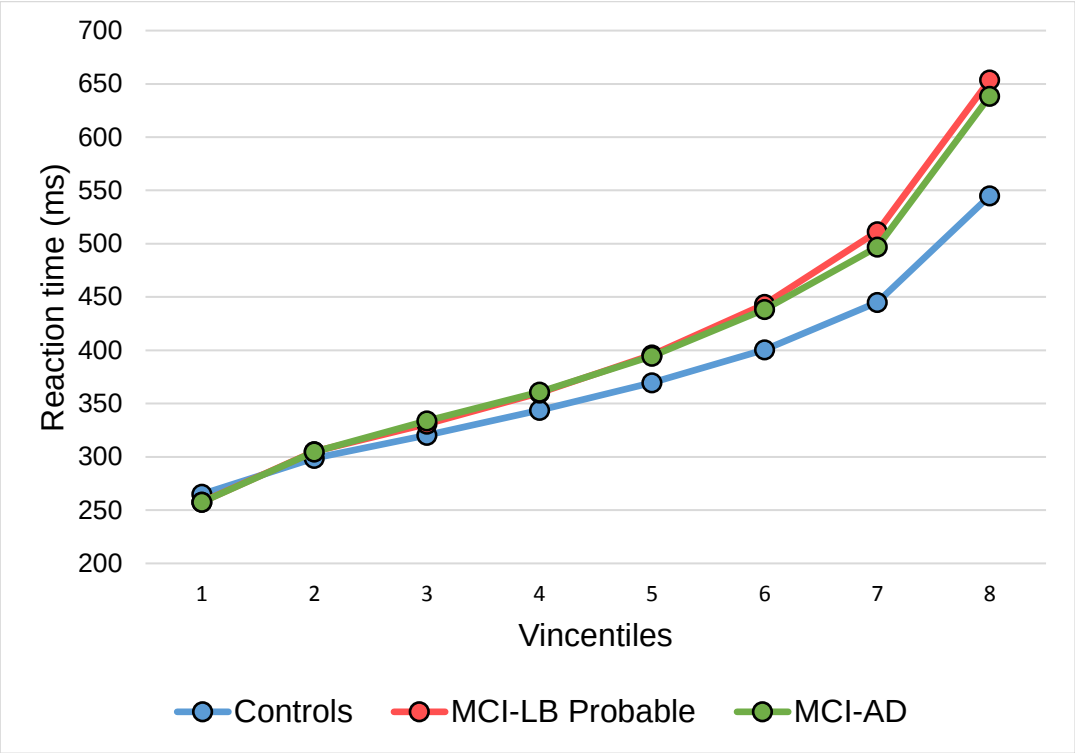

Figure 15 Continuous Performance Test-AX task mean reaction times by Vincentile bin, separated by group (control, MCI-LB Probable and MCI-AD).

Post-hoc one way ANOVAs indicated that MCI-LB Probable had significantly longer response latencies than controls in Vincentiles bins 4-8 in SRT, 2-8 in CRT, and 7-8 in CPT-AX (see Figure 15; all *p*s < .05). MCI-AD had significantly longer reaction times than controls in the last bin of each task.

8.4.4 Relationship with visuospatial and global cognitive function

It was next considered whether IIV (*tau)* is an equivalent, or possibly superior, predictor of group variance in higher-order cognitive ability above speed of processing. When considering only MCI-LB Probable and control subjects, 19.0% of Visuospatial Composite scores are explained by group (p < .001). DSST scores fully account for this group-associated variance when entered at the second step after age and NART IQ ($\Delta R^2 = 0.21$, $p < .001$). HLRs were run to predict visuospatial composite and ACE-R (global cognitive measure) scores using SRT and CPT-AX *tau* (see Table 39). SRT, but not CPT-AX ($p = .214$), *tau* explained significant a significant amount of variance visuospatial composite scores (5%), thus accounting for 42% of group-associated variance in the visuospatial composite. Manipulation of order of entry in the multiple regressions showed that SRT *tau*-associated variance in

Table 39 Predicting MCI-LB Probable and control visuospatial composites scores with group, DSST and tau (Simple Reaction Time and Continuous Performance Test-AX).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age						**-0.36**	**.002**
NART	0.28	0.26	0.28	11.12	**< .001**	**0.43**	**<.001**
Age						**-0.32**	**.002**
NART	0.28	0.26	0.28	11.12	**< .001**	**0.23**	**.036**
Group	0.47	0.44	**0.19**	20.14	**<.001**	**0.48**	**<.001**
Age						-0.17	.110
NART	0.28	0.26	0.28	11.12	**< .001**	0.13	.248
DSST	0.49	0.46	**0.21**	22.72	**< .001**	**0.57**	**< .001**
Age						-0.21	.047
NART	0.28	0.26	0.28	11.12	**< .001**	0.13	.252
DSST	0.49	0.46	**0.21**	22.72	**< .001**	0.37	.023
Group	0.52	0.48	0.03	3.48	.068	0.26	.068
Age &						**-0.35**	**.008**
NART	0.31	0.28	0.31	11.03	**< .001**	**0.32**	**.008**
SRT tau	0.36	0.32	**0.05**	4.01	**.051**	**-0.26**	**.051**
Age						**-0.34**	**.006**
NART	0.31	0.28	0.31	11.03	**< .001**	0.20	.096
SRT tau	0.36	0.32	**0.05**	4.01	**.051**	-0.14	.270
Group	0.47	0.43	**0.11**	9.76	**.003**	**0.38**	**.003**
Age &						-0.30	.040
NART	0.34	0,31	0.34	12.65	**<.001**	0.41	.002
CPT tau	0.36	0.32	0.02	1.58	.214	-0.18	.214
Age						**-0.23**	.067
NART	0.31	0.28	0.31	11.03	**< .001**	0.14	.264
SRT tau	0.36	0.32	**0.05**	4.01	**.051**	-0.12	.901
DSST	0.49	0.44	**0.12**	11.33	**.002**	**0.51**	**.002**
Age						-0.23	.067
NART	0.28	0.26	0.31	11.03	**< .001**	0.14	.264
DSST	0.49	0.46	**0.18**	16.53	**<.001**	0.51	.002
SRT tau	0.49	0.44	0.00	0.02	.901	-0.02	.901

visuospatial composite scores is completely accounted for by DSST if it is entered in the second step.

Table 40 Predicting MCI-LB Probable and control global cognitive (Addenbrooke's Cognitive Examination [ACE-R] scores with group, DSST and tau (Simple Reaction Time and Continuous Performance Test-AX).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. Beta Coefficients	Std. Beta Sig
Age						**-0.25**	**.020**
NART	0.39	0.37	**0.39**	18.37	**< .001**	**0.60**	**<.001**
Age						**-0.21**	**.028**
NART	0.39	0.37	**0.39**	18.37	**< .001**	**0.44**	**<.001**
Group	0.52	0.49	**0.13**	14.64	**< .001**	**0.39**	**<.001**
Age						-0.06	.528
NART	0.39	0.37	**0.39**	18.37	**< .001**	**0.31**	**.003**
DSST	0.59	0.57	**0.20**	27.30	**< .001**	**0.55**	**< .001**
Age						-0.08	.425
NART	0.39	0.37	**0.39**	18.37	**< .001**	0.31	.004
DSST	0.59	0.57	**0.20**	27.30	**< .001**	0.47	.002
Group	0.60	0.57	0.01	0.72	.400	0.11	.400
Age &						-0.19	.125
NART	0.34	0.32	0.34	12.87	**< .001**	**0.49**	**< .001**
SRT tau	0.40	0.37	**0.06**	4.62	**.037**	**-0.27**	**.037**
Age						**-0.18**	**.130**
NART	0.34	0.32	0.34	12.87	**< .001**	**0.39**	**.002**
SRT tau	0.40	0.37	**0.06**	4.62	**.037**	-0.17	.168
Group	0.47	0.42	**0.07**	5.98	**.018**	**0.30**	**.018**
Age &						-0.15	.252
NART	0.41	0.39	0.41	17.56	**< .001**	0.56	<.001
CPT-AX tau	0.43	0,40	0.02	1.64	.206	-0.18	.206
Age						-0.06	.602
NART	0.34	0.32	0.34	12.87	**< .001**	**0.29**	**.014**
SRT tau	0.40	0.37	**0.06**	4.62	**.037**	-0.02	.896
DSST	0.54	0.50	**0.14**	13.66	**.001**	**0.54**	**.001**
Age						-0.06	.602
NART	0.34	0.32	**0.34**	12.87	**< .001**	0.29	.014
DSST	0.54	0.51	**0.19**	19.89	**<.001**	0.54	.001
SRT tau	0.54	0.50	0.00	0.02	.896	-0.02	.896

Multiple regressions were lastly run to consider the prediction of global cognitive scores from core processes (see Table 40). In the MCI-LB Probable and control sample, group accounted for 13.0% of ACE-R score variance after entry of age and NART IQ in step one ($p < .001$). The relationship between CPT-AX and ACE-R was not significant ($p = .206$). Both DSST (20.0%) and SRT *tau* (6.0%) predicted ACE-R scores (both *p*s < .001). Entering Group at step three after DSST showed that DSST fully explained group-associated variance in ACE-R, while SRT *tau* entered at step two only decreased the group-associated variance by 46.15%. Order of entry confirmed that DSST predicts additional unique variance above and

beyond entry of age, NART IQ, and SRT *tau*. SRT *tau,* conversely does not add any additional variance if entered after DSST (p = .896).

8.4 Discussion

The present chapter employed reaction time tests (SRT, CRT and CPT-AX) to consider how sustained attention and reaction time components vary with increasing executive demands. Tasks with executive function weighting have been previously shown to best reveal differences in IIV in the context of both ageing and neuropathology. It was anticipated that the increased executive function demands of CPT-AX in particular would be effective at demonstrating increased IIV in the MCI stage of LB disease. Its use may be particularly advantageous for use in the MCI stage, in which parkinsonism may be less pronounced and confounding to the response modality.

Firstly, analysis of the reaction time data using Vincentile plots indicated that MCI-LB Probable participants were significantly slower than controls across much of the RT distribution in the SRT and CRT tasks. This suggests that MCI-LB diagnosis is associated with longer response latencies, particularly in the slower Vincentiles. In the case of CRT, these slower trials should signal increased burden on attentional and decision-making resources (Jackson & Balota, 2013). However, mean response latency did not differ significantly between the MCI-LB Probable and either the control or MCI-AD groups in most of the distribution of CPT-AX results This emphasizes the need to consider modelling reaction time data from such tests in ways other than the typical Gaussian distribution. While not substantially slower than controls, MCI-LB Probable were significantly impaired in response accuracy in the CPT-AX. Overall, they demonstrated reduced hit rate, increased error rate and poorer target discrimination, relative to both MCI-AD and control groups (with large effect sizes). This suggests sustained attention may serve as a discriminating deficit, specific to MCI-LB. However, increased misses could be due to various causes, including slowed cognitive processing speed, slowed psychomotor speed, or lapses in attention. Ex-Gaussian modelling was therefore used to decompose the subcomponents of reaction time that are linked to specific cognitive processes.

Ex-Gaussian results

On the SRT, groups did not differ in the mean (*mu*) or SD (*sigma*) of the Gaussian component of the ex-Gaussian model. There was likewise no difference in

groups in terms of CRT *mu* or CPT *mu* or sigma. CRT *sigma* was greater in MCI-LB Probable versus controls, reflecting a greater variation in the Gaussian portion of the distribution. However, the results from the CRT overall must be interpreted cautiously as there were a high number of participants whose data could not be fitted by the ex-Gaussian model. Overall, these results indicate no difference between the groups in terms of *mu* and *sigma*. As suggested by Luce (1986), *mu* and *sigma* represent the transduction components, i.e. the sensory processing and motor response (Luce, 1986).

Tau, on the other hand, quantifies the mean of the exponential portion of the ex-Gaussian curve. It is increasingly understood to represent the decision component of reaction times and is suggested to relate more specifically to attentional control (Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007; Tse, Balota, Yap, Duchek, & McCabe, 2010). Increasing *tau* values indicates a greater right skew in the distribution due to increased variability in response latencies. Thus, *tau* is indicative of greater fluctuations in cognitive decision-making time (Lacouture & Cousineau, 2008; Luce, 1986). Despite entering age as a covariate, which has a strong established relationship with IIV, MCI subtypes differed from controls in *tau*. Moreover, the subtypes emerged with different profiles of increased variability. In the more executive weighted-tasks (CRT and CPT-AX), MCI-LB Probable has greater IIV. In contrast, MCI-AD is associated with increased IIV in SRT. As stated above, it is difficult to interpret CRT results because of the frequent failure of data fitting the ex-Gaussian model. This was generally due to a high number of errors by a number of participants. However, if we consider only the SRT and CPT-AX, results suggest that more cognitively demanding tasks reveal increased IIV in MCI-LB Probable. This is in line with previous chapters' findings of executive dysfunction in MCI-LB, suggesting that the common deficits in established DLB (Calderon et al., 2001; Collerton et al., 2003; Mori et al., 2000; Mosimann et al., 2004) are observable in this pre-dementia stage. The CPT-AX task specifically requires sustained attention through both its length of completion (approximately eight minutes) and required vigilance (Cohen et al., 1993). These results are in line with previous work suggesting that poor sustained attention is a hallmark of DLB. In contrast, MCI-AD has pronounced IIV in the simpler SRT task, and therefore may be associated with a more basic psychomotor slowing. The format of the CPT-AX is faster paced than SRT, with a regular and short interstimulus interval. While both measure sustained attention, the SRT only requires focus on a single stimulus and requires only one

appropriate type of response, which can be preplanned. Therefore, it is a more pure measure of processing speed (Gentier et al., 2013). CRT and CPT-AX, in contrast, involve executive control and decision-making processes (Gentier et al., 2013; Magill & Anderson, 2007).

Clinical motor impairment was included in initial analyses as a potential confound. However, it was not a significant covariate in any of the models. This is in line with previous work in DLB that stresses that increased IIV in DLB is independent of motor and parkinsonism symptoms (Ballard, O'Brien, et al., 2001; Ballard et al., 2002; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). For example, Gorus et al. (2008) reports that variability (*tau*) is primarily related to the cognitive subprocess of reaction time. Longer latencies (*mu* and *sigma*) instead reflect both motor and cognitive task demands (Gorus et al., 2008). Chapter 9 will also consider how UPDRS scores may covary with these measures using HLRs.

CPT errors and detection indices

The role of executive dysfunction in sustained attention was explored through the examination of error types in the CPT-AX. The version used was optimized for high response competition through the use of a high target frequency. Intact inhibition is required to avoid AY errors. Neither MCI group differed from controls in committing AY False Alarms, suggesting that both groups have intact inhibition relative to controls. This does not fit with the findings in Stroop CW and Stroop Difference, which captures inhibitory control, and in which both MCI-AD and MCI-LB performed more poorly than controls (Chapter 3). However, controls also made substantial AY errors in the CPT-AX: 18.8% versus 25.0% and 26.2% frequency in MCI-AD and MCI-LB Probable, respectively. This perhaps indicates that the task itself is quite difficult for older populations. In the CPT-AX, the high target frequency creates a bias, even in cognitive heathy participants, to respond with a keypress after seeing an "A" as it is the appropriate response the majority of the time. The speed and high frequency of response targets may mask true differences in inhibition between the groups.

Similarly, while MCI-AD did commit more "other-A" errors than controls, they did not differ from controls in terms of signal detection or any other errors types. Intact sustained attention in MCI-AD is in line with previous work in the construct (Calderon et al., 2001). However, previous work specifically in CPT-AX by Braver et al. (2005) showed AD participants made more BX errors than age-matched healthy

controls. This did not occur in the present sample. This may be due to the small sample size. MCI-LB Probable, on the other hand, did have higher rates of BX errors than controls. BX errors are most likely related to updating and context processing abilities (Robinson et al., 2013). To avoid BX errors, participants must update and monitor a representation of the previous stimulus in their working memory so that an incorrect response will be inhibited (Robinson et al., 2013). Such "context processing" is an important factor in general executive functioning and cognitive control, particularly in response-competition scenarios such as the CPT-AX (Rush, Barch, & Braver, 2006). Whether based on task instructions or on prior processing of stimuli, these internal context representations must be continually maintained and updated based on changing exogenous cues (Braver & Barch, 2002; Braver & Cohen, 2000). The present results may therefore indicate that MCI-LB Probable is associated with impaired updating or context processing. However, there was no difference between MCI subtypes, interpreting these deficits as specific to MCI-LB remains speculative.

If, with replication, higher rates of BX errors in MCI-LB are confirmed, this would introduce the possibility of an *Inhibitory Deficit* (ID) account of cognitive decline (Hasher & Zacks, 1988). In this model, inhibition is proposed as the explanatory mechanism across declines in various cognitive abilities with age (Hasher & Zacks, 1988). In pathologies such as AD, reports of inhibitory failure have been mixed, with evidence that some inhibitory mechanisms remain intact as well as arguments for a generalized breakdown in inhibition above and beyond age-associated impairments (Amieva et al., 2002; Balota & Ferraro, 1996; see Collette, Van der Linden, & Salmon, 1999 for a review). Little work has focused on inhibition specifically in DLB, but the ID account of cognitive decline offers a possible alternative to the similarly parsimonious processing speed account of Salthouse (1996). As mentioned in Chapter 3, my battery of neuropsychological tasks did not include a pen-and-paper updating task (such as an N-back test), so we are unable to determine if BX errors successfully correlate with more established measures of inhibition. This emphasizes the need to include updating tasks in future studies.

Consideration of the pattern of error rates allows some inferences to be made about differentiated executive functions in MCI-LB. However, the combined false alarm rate was also significantly higher in MCI-LB than controls. Moreover, the MCI-LB Probable group committed significantly more BY-errors than controls. BY-errors are made in the absence of any response competition (Robinson et al., 2013). The

erroneous keypress is neither preceded by an “A” that would cue the participant nor based on presentation of an “X” that warrants a keypress in correct contexts. Instead, BY errors may suggest that there may be a generalized impairment in the population (MacDonald, Pogue-Geile, Johnson, & Carter, 2003; Robinson et al., 2013). Indeed, the MCI-LB Probable group demonstrated poorer signal detection accuracies overall. Taken together, this suggests there may be a non-specific attentional impairment in MCI-LB Probable, related specifically to the cognitive, decision making component as evidenced by the increased *tau* parameter. MCI-AD, in contrast to MCI-LB, appears to be associated with intact sustained attention in terms of signal detection and errors generally, in line with previous work in the construct (Calderon et al., 2001).

There are several limitations to the present analyses. Firstly, MCI subtypes did not differ significantly with each other in most measures including CPT-AX errors and *tau*. It is possible that the CPT-AX task is too difficult for not only MCI patients but also healthy older adults to complete, as suggested by their substantial commission of AY False Alarms. The task is quite long by necessity: ex-Gaussian modelling requires at least 40 and ideally a greater number of correct reaction times. Longer interstimulus intervals would further lengthen the test, but could help ameliorate the potential issues caused by high task difficulty. Other technical adjustments to the analysis pipeline could be advantageous. For example, no practice trials were included in the CPT-AX. Therefore, the first seconds of the task might be considered “learning” periods and could be excluded. While a very conservative approach was taken in trimming outliers in the reaction time data prior to ex-Gaussian analysis, scripts are also available to determine a data-driven, optimal SD cutoff.

Further work could consider programming and subsequent analysis of CPT-AX tasks in blocks, such as pursued in Robinson et al. (2013). The high rate of target stimuli in this version of the CPT-AX means that over time it would be increasingly difficult for participants to inhibit a response following an “A” cue in AY error scenarios. Increased AY errors over the time course of the task was demonstrated to occur in Bipolar Disorder, consistent with an expectancy cue (Robinson et al., 2013). However, in MCI-LB, it is unclear whether such a pattern would emerge or whether potential fluctuations over the testing period with lead to a “phasic loss of context maintenance over the course of the task” (Robinson et al., 2013, p. 461). In this latter scenario, AY errors would not increase with time.

Conclusions and future work

In conclusion, MCI-LB shows increased IIV using *tau*, but only in tasks with greater complexity and executive loading, particularly context maintenance. MCI-AD, on the other hand, has higher IIV in simpler psychomotor response tasks (SRT). In contrast, groups did not differ in the Gaussian components of the model (*mu* and *sigma*), emphasizing the benefits of using ex-Gaussian modeling and *tau* rather than mean latencies in reaction time analyses. As with IIV in healthy ageing, increased variability in MCI is associated with a number of negative outcomes for patients including impaired activities of daily living, lower performance on other cognitive tests and "proximity to death" (see Hultsch et al., 2008 for a review). As such, IIV may be a relevant and consequential predictive marker of MCI-LB. The presence of multiple types of high error rates relative to controls suggests that there may be a generalized impairment, either in executive functions or sustained attention per se, that may facilitate or explain this increased variability. However, overall, the analyses did not provide evidence that IIV is a more useful construct than speed of processing in the neuropsychology of MCI-LB. While increased IIV was predictive of the poorer global cognitive assessment and visuospatial ability of MCI-LB Probable relative to controls, the DSST captured greater variance. Indeed, speed of completion of the DSST was a stronger predictor of visuospatial ability and ACE-R total score than an MCI-LB Probable diagnosis itself. Accordingly, IIV does not appear to add unique explanatory power above and beyond DSST in predicting these broader cognitive abilities. Chapters 4 and 5 aimed to consider the hierarchical organisation of cognition.

Chapter Nine: Exploratory analysis of the relationship between cognitive performance, white matter integrity and clinical measures

9.1 Introduction

This thesis has focused on determining the neuropsychological profile of clinically-defined MCI-LB, in comparison to both healthy age-matched controls and MCI-AD patients, and with consideration of the hierarchical structure of such deficits. The larger SUPErB study is extremely comprehensive, and includes a range of other assessments including bloodwork, olfactory testing, carer questionnaires, and MRI. The final empirical chapter will briefly explore how the salient neuropsychological findings of the primary PhD analyses relate to selected elements of the wider cohort data. Firstly, and as explained in more detail below, the potential relationship between processing speed and white matter integrity will be explored, given that the former emerged as a substantially impaired resource in MCI-LB that explains significant variance in higher-order task performance in that group only. Secondly, because MCI-LB Probable showed increased IIV, *tau* will be analysed in association with clinical measures of cognitive fluctuations, one of the most prominent symptoms of DLB.

White matter integrity in MCI-LB

Fast transmission in the central nervous systems is facilitated by the myelin of white matter pathways; as such, the myelin integrity of white matter tracts is posited as the primary determinant of speed of processing (Manoach et al., 2007). Work in normal ageing, neurodegenerative dementias such as DLB, and other neurological conditions have utilized various imaging techniques, such as magnetic resonance imaging (MRI), to explore the neural correlates of processing speed and, to a lesser extent, IIV, in vivo. DTI is a relatively recently-developed MRI technique that enables visualization and quantification of the integrity of white matter microstructure using principles of water diffusion (Assaf & Pasternak, 2008). As diffusion along white matter tracts is faster than perpendicularly, the normalized SD of the diffusivities, known as fractional anisotropy (FA), provides a measure of white matter microstructure integrity in vivo (Assaf & Pasternak, 2008). Decreased FA indicates less directionally-oriented diffusion along tracts and less intact white matter integrity. Mean diffusivity (MD), the other primary DTI measure, represents the perpendicular

diffusivity along tracts. Decreased integrity of structural barriers (i.e. the myelin) would be reflected by lower MD values. Existing studies in DLB report decreases in FA (Firbank et al., 2007; Kantarci et al., 2010), with some reporting particularly widespread abnormalities (Bozzali et al., 2005; Lee et al., 2010; Watson et al., 2012).

DTI has been used in a plethora of studies to link white matter integrity to speed of processing (for example: Madden et al., 2004; Shimony et al., 2009; Turken et al., 2008), including specifically in MCI (Christensen et al., 2005). DTI may be especially useful in MCI as it can quantify changes in white matter at the subvoxel level prior to the gross structural changes that are targeted in conventional MRI (Bozzali et al., 2005). DTI measures have been reported as an earlier imaging biomarker than grey matter atrophy in predicting progression from intact cognition to amnestic AD (Zhuang et al., 2013). DTI should thus be particularly relevant to DLB given that early stages of disease are not typified by neuronal *loss* but by neuronal *dysfunction*, in contrast to AD (Bamberger & Landreth, 2002; Katsuse, Iseki, Marui, & Kosaka, 2003; Molina et al., 2002).

As mentioned, the relationship between white matter integrity and elevated IIV has also been demonstrated (Britton, Meyer, & Benecke, 1991; Tamnes, Fjell, Westlye, Østby, & Walhovd, 2012). Tamnes et al. (2012), for example, found lower IIV to be associated with increased white matter integrity (both FA and MD), independent of sex, age and median response time in a sample of children and adolescents. The rapid, moment-to-moment nature of IIV in processing speed, unlike other behavioural measures, is suited to capture endogenous sources of variability. Exogenous changes such as affective states and somatic complaints would show fluctuations over longer timespans, for example with test-re-testing over a period of days or weeks. The fluctuations encapsulated by IIV measures are alternatively more likely to relate to neural network and neurotransmitter efficiency (Phillips et al., 2013).

However, research into white matter connectivity, processing speed and IIV in DLB is sparse, particularly in early stages of the condition (see Mak et al., 2014 for a review). The CPT, in particular, may be a useful tool to link gross cognitive fluctuations to IIV and white matter integrity as it is suggested as a sensitive and valid measure of brain and physiological function. For example, CPT performance deficits are present in a number of neuropathological conditions, including conditions impacting subcortical and white brain matter, including Multiple Sclerosis (MS; Wilken et al., 2003), human immunodeficiency virus (HIV; Karlsen, Reinvang, & Frøland, 1992), and cerebrovascular disease (Jerskey et al., 2009). To the author's

knowledge, only one study to date has used a CPT task and MRI analyses in DLB. Although Sanchez-Castaneda et al. (2010) investigated grey matter atrophy they found decreased anterior cingulate and prefrontal volume correlated with worse performance on the CPT in DLB. The atrophy was also significantly correlated to visual hallucination severity as measured by NPI (Sanchez-Castaneda et al., 2010). However, no studies have utilised CPT-AX and an ex-Gaussian approach in linking cognition to white matter integrity in DLB.

Cognitive fluctuations

Cognitive fluctuations are one of the core symptoms of DLB and involve spontaneous and pronounced variations in attention, alertness and arousal (McKeith et al., 2017). Episodes may resemble delirium, with fluctuations as profound "such that at times she was able to hold a conversation, albeit with some expressive dysphasia, whilst on other occasions she was mute and unable to stand without assistance" (Byrne, Lennox, Lowe, & Godwin-Austen, 1989, p. 713). Mini-Mental State Examination scores may change by more than 50% day-to-day in DLB (Byrne et al., 1989). While a common symptom in other causes of dementia such as AD (20%; Escandon, Al-Hammadi, & Galvin, 2010; Kolbeinsson & Jonsson, 1993) and vascular dementia (35-50%; Hachinski et al., 1975; Román et al., 1993), cognitive fluctuations are especially prevalent in DLB, reported in nine out of ten patients (Byrne et al., 1989; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000), as well as in PDD. Lee et al. (2012) suggest that cognitive fluctuations are aetiologically related to the presence of LB pathology in the LBDs.

Cognitive fluctuation severity has been operationalized using various methods. A systematic review on the identification of cognitive fluctuations in dementia by Lee et al. (2012) concluded that there is a dearth of empirical evidence on how fluctuations are clinically assessed. Their search found that only two published studies reported on scale utility in clinical settings (Ferman et al., 2004; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). Standard methods of quantifying fluctuations, primarily caregiver or clinician observation, can be problematic. Informant questioning, for example, is used regularly but is most reliable in discriminating DLB from AD when "fluctuations" concern daytime sleepiness, lethargy, staring into space or disorganized speech, rather than cognition per se (McKeith et al., 2017). Clinician assessment is typically only sensitive to extreme manifestations in DLB and are vulnerable to poor inter-rater reliability, with reports as

low as 58% (Mega et al., 1996). Reaction time testing has been promoted as an alternative to informant-based assessment scales that provides greater objectivity; however, such tests are not routinely utilised in clinical practice. Given the limitations of assessment, the severity and prevalence of cognitive fluctuations in DLB may be grossly underestimated (Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000). Fluctuations have also been independently associated with additional negative downstream effects in DLB, such as impaired activities of daily living (Ballard, Walker, O'Brien, Rowan, & McKeith, 2001). As such, a valid and reliable means of quantifying fluctuating attention, which is suited to the clinical setting, is needed.

"Microfluctuations" are proposed as rapidly-occurring, transient changes in performance at a second-to-second level, but which are linked to the broader cognitive, behavioural and functional changes of fluctuations in DLB (Bradshaw et al., 2006; Walker, Ayre, Cummings, Wesnes, McKeith, O'Brien, et al., 2000; Walker, Ayre, Perry, et al., 2000). Bradshaw et al. (2006) suggests that while not clearly evident at a clinical level, these microfluctuations are demonstrable and correlate with the more protracted fluctuating pattern. Bradshaw et al. (2006) summarize the proposal that, "this fluctuating attentional profile may represent a quantifiable measure of the gross fluctuations in cognition and global performance that have long been regarded as a cardinal clinical feature of DLB but paradoxically have been problematic to identify in a reliable manner" (p. 1130). Could elevated IIV, a measure of intermittent long response latencies, serve to capture these "microfluctuations" in attention? Microfluctuations have been targeted primarily by looking at fluctuations in attention using computerised reaction time-based tests. As discussed in Chapter 8, while there has been some success, few studies have utilised advance modelling techniques or targeted MCI-LB specifically. *Tau*, as derived from attentional tasks such as CPT-AX and SRT, could be argued conceptually analogous to "microfluctuations," and might therefore capture fluctuating cognition over a shorter time interval (Nesselroade, 1991). As such, we suggest that reaction time tasks might have additional utility as proxies for the gross clinical fluctuations within a relatively concise, laboratory task setting.

Hypotheses and aims

Because the larger SUPErB study collected DTI images and clinical measures of cognitive fluctuations, the decision was made to explore the relationship of the

neuropsychological findings with these variables in an exploratory chapter. Whether white matter integrity relates to processing speed (DSST) or IIV (*tau*) will be investigated. Secondly, it is posited that IIV (*tau*) may be correlated with clinical measures of cognitive fluctuations, which would suggest *tau* as representative of microfluctuations in cognition.

9.2 Methods

Participants and materials

The MRI sequence was administered to 80 participants, but 13 MCI-LB Possible participants were excluded from analysis in the present chapter. Three participants' MRI data were removed due to excessive head movement during the scan that could not be corrected. This resulted in analysis of 28 healthy control participants (mean age = 72.96, *SD* = 7.04, range 61-89), 14 MCI-AD (mean age = 75.14, *SD* = 8.44, range 62-89) and 25 MCI-LB (mean age = 73.92, *SD* = 7.04, range 60-87) patients. The groups did not differ significantly in age ($F(2,64)=23.11$, $p = .657$). Bivariate Pearson correlations were run between variables of interest. Multiple regressions were carried out using a stepwise procedure to predict visuospatial composite scores, with age and NART IQ entered in the first step of the model.

MRI acquisition and procedure

All MRI data were acquired at the Newcastle Magnetic Resonance Centre by experienced radiographers and with direction from Dr Michael Firbank who set the acquisition protocol (see Appendix N). DTI data pre-processing steps and analyses were completed by the author. MRI used a 3-Tesla Phillips Achieva clinical system with an 8-channel head coil. Scan data were transferred to a Linux-based workstation and analysed using the Functional MRI of the Brain software library (FSL, v 5.0). Distortion effects were corrected for following an adaptation of the technique of Shen et al. (2004) and affline registration in FMRIB's Linear Image Registration Tool matched pairs of diffusion weighted images together. The eddy-corrected DT images were visually inspected for indications of severe motion. A brain mask corrected for high signal dropout using Statistical Parametric Mapping (SPM).

FA and MD can be reliably analysed voxelwise to determine between-group differences (Smith et al., 2007; Wen, Steffens, Chen, & Zainal, 2014). Following

image pre-processing, voxel-wise analysis of the data was performed by FSL's Tract Based Spatial Statistics (TBSS; Smith et al., 2006). FA images were created by fitting a tensor model to the raw diffusion data and then brain-extracted using BET (Smith, 2002). All subjects' FA data were aligned to the pre-defined FSL FMRIB58 FA map using a resolution of 1 mm in the standard Montreal Neurological Institute 152 adult brain template space. Data was visually inspected for issues with the nonlinear transformation (Smith et al., 2006). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton.

The resulting data was used in two ways. Firstly, a global FA (gFA) and global MD (gMD) value was calculated per participant for analysis with neuropsychological domains. gFA and gMD reflect the average FA and MD, respectively, across the entire white matter skeleton. Secondly, pre-processed data was fed into voxelwise cross-subject statistics using Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014), a permutation method for non-parametric *t*-tests. Randomise utilised 500 permutations and the threshold-free cluster enhancement (TFCE) test statistic, resulting in TFCE corrected statistical maps. Three contrasts were run with randomise: (1) between-group differences in FA, MCI-LB Probable versus controls, (2) voxelwise correlations with demeaned age, and (3) voxelwise correlations with DSST scores. The JHU White-Matter Tractography Atlas was utilised with FSLeyes to determine the white matter tracts showing any significant correlations.

9.3 Results

Group differences in global DTI measures and fluctuation scales

Means and SD for global white matter integrity measures and fluctuation scales were computed by group (see Table 41). One-way ANOVA indicated that groups did not differ significantly in gFA ($F(2,64) = 0.68$, $p = .511$) or gMD ($F(2,64) = 0.95$, $p = .393$). Independent-samples T tests showed MCI-LB Probable had significantly higher DCFS scores than MCI-AD ($t(40) = -2.89$, $p = .006$, $d = 0.97$). The difference in CAF was nonsignificant ($p = .159$).

Table 41 Means (standard deviations) of global fractional anisotropy (gFA) and mean diffusivity (gMD), and two measures of clinical fluctuations (DCFS, CAF).

	gFA*	gMD*	DCFS	CAF
Controls *n* = 28	0.46 (0.02)	7.72 (0.28)	-	-
MCI-LB Probable *n* = 25 (27 with DCFS, CAF)	0.46 (0.03)	7.85 (0.38)	9.07 (3.45)	4.26 (4.18)
MCI-AD *n* = 14 (15 with DCFS, CAF)	0.46 (0.2)	7.79 (0.39)	6.13 (2.53)	2.47 (3.27)

*Pre-transformed values. gMD values in 10^{-4}

Using TBSS, no between-group differences were found in FA after correcting for age (see Appendix O for complete brain images). Figure 16 shows the axial, sagittal and coronal views of the brain standard superimposed with the FA skeleton (in yellow; aligned at voxel 72x139x103) and TFCE corrected *t*-statistical map with significant voxels associated with age in red, indicating the lowest p-values. The contrast with demeaned age showed significant negative correlations with FA in regions in the right hemisphere, including (proceeding ventrally) areas around the anterior corpus callosum and the anterior corona radiata, Anterior thalamic radiation, Forceps minor and the inferior fronto-occipital fasciculus.

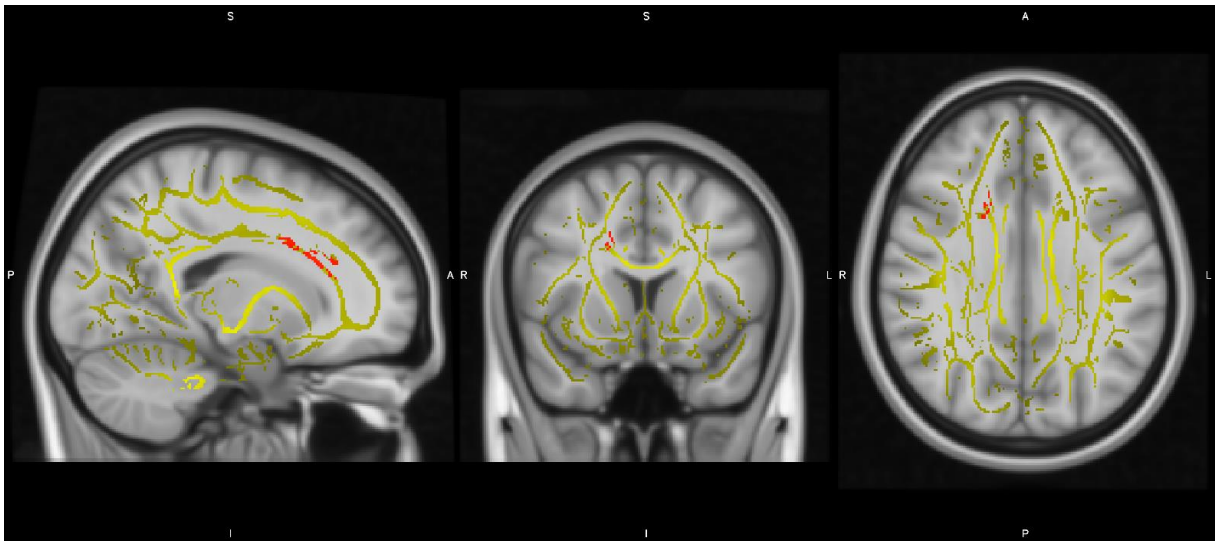

Figure 16 TFCE corrected statistical map of significant voxelwise correlations with age in red over the mean FA skeleton in yellow (all participants).

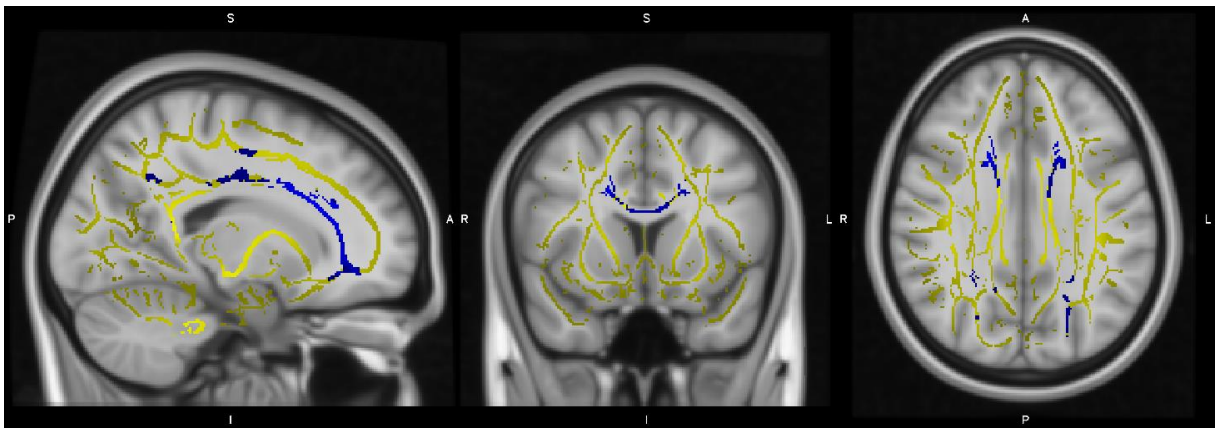

Figure 17 TFCE corrected statistical map of significant voxelwise correlations with DSST (all participants; significant voxels in blue).

Inspection of the statistical maps indicates that substantially more white matter regions are significantly associated with DSST after TFCE correction than are associated with age Figure 17. In particular, voxels in the corpus callosum (genu and body), the right cingulum (connecting to the hippocampus), the left superior corona radiata, the right posterior thalamic radiation (including optic radiation) and unclassified areas of the left posterior occipital lobe (see Appendix M). This emphasizes the close association between DSST and white matter integrity, with a stronger relationship in the present sample than even with age.

Relationship between DTI measures and demographics, clinical measures and cognitive processes

gFA and gMD correlated significantly with age in both controls (gFA, $r(27) = -0.42$, $p = .027$; gMD, $r(27) = 0.58$, $p = .001$) and MCI-AD (gFA, $r(13) = -0.60$, $p = .024$; gMD, $r(13) = 0.68$, $p = .008$). There was no significant relationship in MCI-LB Probable. The relationship between NART IQ and the DTI indices was not significant in any group. There was no significant correlations between the DTI indices, DSST or IIV and the clinical fluctuation scales (DCFS and CAF; see Appendix P) in MCI-LB Probable. Excluding MCI-LB Probable patients without clinical symptoms of fluctuations yielded the same results.

The relationship between DTI indices and the primary neuropsychological processes of interest (SRT and CPT-AX tau, DSST, visuospatial composite) were also considered in the group overall (Table 42). Both gFA and gMD weakly significantly correlated with DSST and the visuospatial composite, with higher white matter integrity values associated with higher neuropsychological scores. The

Table 42 Whole group Pearson correlations between DTI indices and neuropsychological processes.

	gFA	gMD	SRT *tau*	CPT-AX *tau*	DSST
gMD *n* = 67	**-0.90****				
SRT *tau* *n* = 62	-0.22	0.20			
CPT-AX *tau* *n* = 63	-0.10	0.16	**0.51****		
DSST *n* = 67	**0.34****	**-0.31***	**-0.55****	**-0.48****	
Visuospatial composite *n* = 67	**0.26***	**-0.31***	**-0.38****	**-0.36****	**0.65****

*Correlation significant at the *p* = .05 level, **p = .01 level.

correlation with *tau* was not significant in the group overall; however, within controls, there were moderately strong, significant negative relationships between gFA and SRT *tau* ($r(25) = -0.42$, $p = .033$) and gFA and CPT-AX *tau* ($r(27) = -0.49$, $p = .008$). Similarly, gMD was moderately positively associated with CPT-AX *tau* values, ($r(27) = 0.46$, $p = .014$), indicating greater IIV is associated with lower measures of global white matter integrity. Greater IIV as measured by SRT and CPT-AX *tau*s was also weakly-to-moderately associated with slower DSST times and lower visuospatial composite scores. The relationship between cognitive fluctuation ratings, IIV and DTI indices was also considered only in those MCI-LB Probable with cognitive fluctuations identified in their clinical examination. However, no correlation between these variables was significant.

9.4 Discussion

This exploratory chapter aimed to consider how two of the most important processes in the neuropsychology of MCI-LB Probable emerging from previous chapters (speed of processing and intra-individual variability) relate to DTI and clinical fluctuation severity, measures collected as part of the larger SUPErB study.

Differences in white matter integrity between groups

The results showed no differences in white matter integrity between groups; that is, healthy controls and patients with clinically defined MCI-LB Probable or MCI-AD had similar global and voxelwise measure of FA and MD across the entire white matter skeleton, after controlling for age

Between-group differences were expected given the existing literature demonstrating decreased white matter integrity in advanced DLB and different areas of damage in DLB versus AD. In particular, a predominance of posterior FA changes and relatively intact frontal white matter has been previously shown in DLB. Watson et al. (2012), for example, investigated the relationship between white matter integrity and general neuropsychological functioning using DTI in DLB, AD and healthy controls. They found DLB patients had decreased FA particularly in parieto-occipital white matter tracts as well as the left thalamus and pons, while frontal lobes white matter was relatively intact. Posterior white matter damage been demonstrated elsewhere in this population (Colloby et al., 2002; Firbank, Colloby, Burn, McKeith, & O'Brien, 2003; Ishii et al., 1999; Pasquier et al., 2002), and data from Watson et al. (2012) emphasize this predominance by the proportion of voxels showing significantly lower FA that healthy controls: 21% in posterior regions versus only 3.2% in frontal regions. FA was also decreased in AD patients, but in a much more general pattern (Watson et al., 2012). Both Watson et al. (2012) and Bozzali et al. (2005) suggest that the demonstrated occipital white matter damage may be a pathophysiological explanation for the prominent visuospatial and visual hallucinatory symptoms of DLB, with the former going so far as to suggest it as a potential tool for differential diagnosis. The corpus callosum, strongly associated with speed of processing, has also been shown to have lower ratings of white matter integrity in DLB (Bozzali et al., 2005).

The lack of significant difference in the integrity of the white matter skeleton between groups precluded localization of where tract damage may relate specifically to DSST completion. However, the DSST was significantly associated with white matter integrity in a voxelwise analysis, including in the corpus callosum, the right cingulum, the left superior corona radiata, the right posterior thalamic radiation (including optic radiation) and the posterior occipital lobe. A number of these areas (the corpus callosum, thalamic radiation and occipital lobes) were cited by Watson et al. (2012) and Bozzali et al. (2005) as impacted in DLB. It is possible that between-group differences in the MCI stage are subtle and escape capture by the rather basic DTI methods employed in the present study. However, given that DSST emerged as critical to MCI-LB neuropsychology, it is noteworthy that in MCI-LB it is closely associated with white matter areas affected in advanced DLB. Indeed, inspection of the statistical maps indicate a more substantial association of white matter with the DSST than with age. This is particularly striking given the long-standing and

extensive evidence of increasing age's close relationship with white matter. White matter volume decreases with age, reaching peak volume in the mid-30s before losing 3% to 20% of volume (Lebel et al., 2012; Park & Reuter-Lorenz, 2009). Clearly, the DSST is a powerful neuropsychological tool with strong associations with white matter. It may perhaps hint at white matter tracts that will show increasing damage with disease progression.

Replication of these analyses would also be useful to rule out Type II error. Less conservative TFCE corrections in the voxelwise analysis, or simply a larger cohort, could be used to confirm equivalence in white matter structure between the patient groups. Future work should also continue to consider how neuropsychological deficits relate to white or grey matter structural damage; however, such efforts may be undermined by the likely involvement of multiple regions, mechanisms or association cortices in DLB-related neurodegeneration (Bozzali et al., 2005). In addition to structural analyses, DTI data could use tractography methods to segment and analyse specific white matter tracts. Tractography algorithms automatically delineate tracts by assuming that the principal direction of axonal diffusion in a voxel is parallel to the main diffusion direction, the largest eigenvalue associated with that voxel. Such a method will allow consideration of connectivity issues in more depth and perhaps reveal significant correlations with processing speed measures.

Variability, cognitive fluctuations and white matter integrity

As hypothesized, less variable healthy controls have better measures of white matter integrity (global FA and MD). However, there was little evidence that *tau* serves as a proxy measure of microfluctuations in MCI-LB. As expected, fluctuation rating scale (DCFS) scores were higher in MCI-LB Probable than MCI-AD; however, we did not see the anticipated associations between attentional impairment (increased variability) and clinical cognitive fluctuations. This is in contrast to reports that attention is the most impacted cognitive domain in patients with fluctuations (Ballard, Walker, et al., 2001; Ballard et al., 2002; Walker et al., 1999).

While IIV has strong conceptual links to fluctuating cognition, these results do not suggest it is related to clinically-assessed fluctuation severity. How to best assess cognitive fluctuations in DLB will remain an important challenge for clinical research studies going forward (Lee et al., 2012). One of the cited difficulties for clinicians in this regard is the variability of tests and the similarity between DLB and AD in later stages (Mega et al., 1996). For example, the CAF, used in the present study,

consists of open-ended questions and its accurate completion is highly dependent on the skills of the administering clinician. MCI-LB is an advantageous stage in disease progression to conduct research on fluctuations as participants are more able to tolerate sustained attention tasks and are generally less burdened by motor symptoms. Therefore, effort to develop a neuropsychological measure of fluctuations in the MCI phase remains justified.

Future research could also consider variability and MCI-LB symptomology in terms of visual hallucinations. There have been similar efforts to link occipital white matter damage to hallucinations in DLB as with cognitive fluctuations. Fluctuations in sustained attentional are likewise associated with a high prevalence of visual hallucinations (Calderon et al., 2001; Lee et al., 2012). In DLB, visual hallucinations are typically complex, fully-formed, and varying in terms of patients' emotional reaction and degree of insight into them (McKeith et al., 2017). Varanese et al. (2010) reports visual hallucinations are more common in individuals with dementia who also have cognitive fluctuations. A model proposed by Collerton, Perry, and McKeith (2005) argues that recurrent complex visual hallucinations are due to a combination of dysfunction in attentional binding and visuoperception. When attention to visual stimuli is reduced, proto-objects, units of bound visual information accessed as a coherent object, are experienced in the visual field and result in the phenomenology of a visual hallucination (Collerton et al., 2005; Rensink, 2000; Rensink, O'Regan, & Clark, 1997). A study in DLB by O'Brien, Firbank, Mosimann, Burn, and McKeith (2005) in DLB provides further evidence for attentional dysfunction's contribution to visual hallucinations by demonstrating that patients with a decreased frequency of hallucinations at follow up showed increased perfusion in the posterior cingulate and precuneus. These neuronal regions are associated with attentional activation, suggesting improved attention was responsible for mitigation of hallucination symptoms (O'Brien et al., 2005). Given such evidence and the finding of an association between IIV and visuospatial ability, it suggested that IIV be considered in relation to visual hallucinations in MCI-LB in future work. However, as with cognitive fluctuations, few unproblematic clinical measures of visual hallucination severity are in use.

Limitations

The present chapter utilised data collected for the larger SUPErB study rather than my PhD per se. It is thus limited in scope and was not intended to be a

comprehensive evaluation of neither white matter integrity nor cognitive fluctuation symptoms.

In addition, the other ex-Gaussian components of the reaction time tests were not considered. *Tau* was anticipated as the best index for the likely association between IIV and white matter. This assumption was made given past work showing increased *tau* in MCI-AD versus controls and a strong negative relationship between IIV and white matter volume (Jackson et al., 2012). In that study, smaller *tau* composite scores were associated with greater volumes of cerebral white matter and more regions of interest than *sigma* (Jackson et al., 2012). *Tau* has also been demonstrated as the ex-Gaussian subcomponent most closely related to working memory and executive functions measures, which in turn are hypothesized as strongly dependent on underlying white matter integrity (Balota et al., 2010; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Schmiedek et al., 2007; Tse et al., 2010). However, Jackson et al. (2012) did find that smaller *mu* composite scores were also associated with larger volumes of cerebral white matter and the inferior parietal lobule. Therefore, future work could also consider whether *sigma* or *mu* in relationship to white matter integrity.

Chapter Ten: General discussion

This concluding chapter will provide a summary of the results of the proceeding empirical results (section 9.1), a discussion of their implications (section 9.2), comments on the strengths and limitations of the work more broadly (section 9.3) and recommendations for future research (section 10.4).

10.1 Summary of results

The objective of this PhD was to establish the neuropsychological profile of MCI with Lewy bodies following the most recently published clinical criteria for this emergent diagnostic category (McKeith et al., 2017). Recruitment and baseline testing of MCI patients and healthy age- and sex-matched controls led to the creation of four clinically-defined participant groups: controls, MCI-LB Probable, MCI-LB Possible and MCI-AD. In comparing MCI-LB (Possible and Probable), equivalence was found in demographic factors and global cognitive measures, although groups differed in premorbid IQ and sex distribution.

Results of univariate analysis of neuropsychological scores indicated that MCI-LB and MCI-AD display cognitive impairments in line with the advanced stages of DLB and AD, respectively. The MCI-LB groups in particular were characterised by poor abilities in attention, visuospatial and executive function tasks. MCI-AD, conversely, demonstrated an amnestic profile of verbal learning and memory deficits. However, MCI-AD also scored poorly in executive function measures and had slowed speed of processing relative to controls. In addition to univariate group comparisons, percentile standings and discriminant analysis were used to quantify impairments in MCI-LB and MCI-AD. Overall, MCI-LB Probable was best discriminated and typified by slow processing speed. Processing speed, and not executive function, was associated with higher-order cognitive activities such as visuospatial function, long term visual memory, and verbal learning and memory.

PCA analyses served as a data reduction technique to preserve the richness within the dataset in preparation for multivariate analyses. Attempts to use PCA within the MCI-LB subset failed due to multiple loadings of the DSST and other processing speed/ attentional tasks. Control-informed composites helped to reconfirm theoretical assumptions about grouping of processing speed and visuospatial measures.

Multivariate analyses demonstrated that processing speed accounted for the group-associated variance in visuospatial and verbal ability. In MCI-LB Probable, processing speed was associated with visuospatial working and long term memory, visuoconstruction, and verbal learning and memory. In contrast, processing speed did not correlate with visuospatial or verbal learning ability in controls or MCI-AD. The processes involved in the processing speed task DSST were then investigated using hierarchical linear regressions. Results showed that cognitive processing speed time was the most important contributor to DSST and that MCI-LB associated variance in the DSST is independent of motor impairment (UPDRS).

Chapter 8 considered the role of variability in speeded reaction time tests. Elevated IIV occurred in MCI-LB in tasks with executive function weighting (CRT) or requiring sustained attention (CPT-AX). MCI-LB also had higher error rates relative to controls suggesting generalized impairment, either in executive functions or sustained attention per se, that may facilitate or explain this increased variability. Alternatively, the simple motor reaction time task (SRT) elicited higher IIV in MCI-AD. In Chapter 4, no differences between MCI patients and controls was found in SRT nor CRT mean reaction time. This emphasizes the benefits of using ex-Gaussian modeling and considering *tau*, rather than simply mean response latencies, in reaction time task analyses. *Tau* was also associated with group-related variance in visuospatial ability and global cognitive scores, but it explained less variance than DSST in those domains. Chapter 9, an exploratory chapter, considered the relationship between clinical symptoms, white matter integrity as measured by DTI, and IIV and DSST, the neuropsychological variables that emerged as most important in the previous chapters. Contrary to expectations, groups did not differ in white matter integrity. Moreover, *tau* did not relate to measures of white matter integrity nor to clinical measures of cognitive fluctuation severity.

10.2 Interpretation and implications of results

This study is a crucial step towards better understanding of cognitive dysfunction in the emergent diagnostic classification of MCI-LB. Based on my results, it can be expected that clinically-defined MCI-LB patients will present with cognitive impairments in the same domains as advanced DLB. That is, MCI-LB was impaired relative to both controls and MCI-AD in visuospatial ability, executive function, attention and processing speed. Verbal learning and memory dysfunction was also

observed relative to controls in MCI-LB, although deficits were significantly smaller than those in the MCI-AD group.

Similarly, MCI-AD and MCI-LB were similar in showing executive dysfunction (set-shifting and inhibition) but intact working memory capacity and maintenance relative to controls (Miyake et al., 2000). While MCI-LB did also show evidence of impaired updating, which was not observed in MCI-AD, these results suggest executive dysfunction may be a less useful differentiating factor in the MCI stage. This is surprising, given its acceptance as a hallmark of DLB and associated neuropathologies. A profile of non-amnestic decline with executive and attentional dysfunction has been repeatedly linked to the nigrostriatal dopamine depletion observed in LB diseases (Foltynie et al., 2004; Goldman et al., 2014a; Muslimovic, Post, Speelman, & Schmand, 2005). Auning et al. (2011), using ^{123}I-FP-CIT SPECT, reports 79% of DLB cases show striatal dopamine transporter loss, while reduced caudate nucleus uptake is associated with executive impairment in both DLB and PD (Aarsland, 2016). Experimentally, studies have also succeeded in inducing executive dysfunction through the manipulation of dopaminergic (levodopa) medication in PD patients (Cools, Barker, Sahakian, & Robbins, 2001; Kehagia et al., 2012). However, it is important to note that it has been suggested that PD as a dysexecutive syndrome is an oversimplification. There may alternatively be two subgroups of PD-MCI: (1) an executive dysfunction/ frontostriatal subtype that shows less association with the development of PDD, and (2) a posterior-cortical type more likely to progress to PDD and characterized by poor visuospatial and semantic skills (Williams-Gray et al., 2009; Williams-Gray et al., 2013; Wu et al., 2012). In a review, Goldman et al. (2014a) argues that this distinction would have important clinical and therapeutic implications. Clarification, perhaps through longitudinal studies, could be made as to whether similar subtypes can be demonstrated in MCI-LB, which may explain my equivocal findings.

One of the most salient findings in the present project was the importance of processing speed to the neuropsychological performance of MCI-LB. Processing speed accounted for substantial variance in scores on higher-order tasks in the group, including visuospatial working and long term memory, visuospatial construction (drawing), verbal learning, and global cognition. The differences between groups in visuospatial and verbal learning scores were also fully statistically explained by processing speed. One of the most commonly used measures of processing speed is the DSST, although there are many other tasks employed in

various studies. This project provides evidence of the task's utility as a valid measure of processing speed in MCI-LB. This is particularly notable given that MCI-LB is a synucleinopathy with substantial overlap with PD. Clinical diagnosis of these conditions includes motor impairments, which might obviously call into question interpretation of any impairments on motor-dependent cognitive tasks. It would be easy to dismiss a trend of slowed psychomotor or cognitive speed as dependent on motor function. Performance on the DSST is indeed related motor speed; however, my analyses show that it also succeeds in capturing cognitive processing speed independent of both fine motor speed and gross motor symptoms. As such, the DSST quantifies cognitive speed as intended in this population.

In MCI-AD, findings of impaired long-term episodic verbal memory offer further evidence that a typical AD profile can be expected in the early MCI phases of disease as well. It is also of note that the MCI-AD group was identified from an initial MCI patient cohort recruited on the basis of suspected Lewy body disease. In this way, demonstrable significant differences in cognitive scores between groups are even more impressive than if the MCI-AD group had been sourced from individuals presenting to their physicians as a more typical, "pure" AD participant.

10.3 Thesis overall strengths and limitations

Major strengths of this thesis include the comprehensive neuropsychological assessment administered and the robust, clinical classification of the cohort. Participants underwent clinical examination, bloodwork, and multiple neuroimaging modalities, including two of the three indicative biomarkers in the new consensus criteria (FP-CIT and MIBG; McKeith et al., 2017). MCI diagnoses were determined by consensus of expert Old Age Psychiatrists, blind to previous diagnoses and following separate MIBG analysis and panel-rated FP-CIT (see Chapter 3). Many of the healthy control volunteers were family members of MCI volunteers, ensuring some overlap between the groups in education and socioeconomic background. The groups nevertheless differed significantly in premorbid IQ estimates overall. Age and premorbid IQ were thus included in regression analyses in Chapters 6-7 and the ANCOVAs in Chapter 8, due to their strong association with many of the neuropsychological task employed. As such, SUPErB benefits from a rigorous diagnostic protocol and clear, reliable clinical diagnosis of MCI participants, with statistical consideration of their demographics.

Secondly, the thesis has presented the neuropsychological profile of these clinically defined MCI groups, in particular the novel MCI-LB Probable category. Not only were cognitive deficits relative to controls considered in each task, but domain-level scores and percentiles were utilised. The data-reduction technique served to combine the extensive range of tasks into composites that were determined to best capture the variability in the data. Using these composites in the multivariate analyses facilitated interpretation of the results, better captured the breadth of each domain, and minimised the risk of Type I error.

Thirdly, a cognitive psychological approach was employed to demonstrate a hierarchical structure in the neuropsychology of MCI-LB Probable. This technique allowed us to reach the conclusion that higher-order deficits in global cognitive ability, visuospatial and verbal abilities were fully statistically explained by processing-speed. As discussed above, this has implications to the larger field of psychology by positing a processing speed-mediated model of decline, rather than an executive function mediated decline.

Fourthly, speed of processing was investigated in greater detail by analysing the subcomponents of completion of the DSST, which indicated that the DSST successfully captures cognitive speed of processing in addition to simpler motor speed in this population. This is an important finding due to the frequent motor slowing observed in LB disease. An ex-Gaussian modelling technique was employed to consider variability in reaction time in addition to mean response latency. Lastly, the thesis briefly addressed the potential relationship between (1) the neuropsychological processes that emerged as most important in MCI-LB and (2) white matter integrity, a potential neurobiological source of such deficits, both globally and through voxelwise analysis.

However, there are several limitations to the thesis that should be acknowledged, in addition to the specific critiques addressed in each empirical chapter. The MCI-LB Probable group had a predominance of men, as expected by previous studies (Nelson et al., 2010), and the potential of neuropsychological differences related to sex was not considered. Females, for example, generally perform better on verbal memory tasks, as well as some visuospatial memory tasks (Herlitz, Airaksinen, & Nordström, 1999). In terms of ageing, older women tend to outperform older men in verbal memory, although gender differences in speeded or non-verbal working memory were not observed (Aartsen, Martin, & Zimprich, 2004).

More specifically, females over 60 years of age complete the DSST more quickly than their male counterparts.

Similarly, medication was not taken into consideration. Cholinesterase inhibitors, in particular, are regularly prescribed to improve cognition in DLB (McKeith et al., 2017). Their action can substantially improve attention and executive function performance in MCI (Carter, Caine, Burns, Herholz, & Lambon Ralph, 2012; Herholz, 2008). Their use in the cohort was not investigated, although volunteers must have been pharmacologically stable for one month prior to commencing participation. Future studies (and analyses of this dataset) could benefit from including sex and educational level in their analyses and accounting for anticholinesterase use. Alternatively, MCI participants and controls could be matched on educational level during recruitment, and the sample could be limited to drug-naïve MCI volunteers. It is unlikely, however, that such a study design would be achievable.

Another potential limitation is the exclusion of MCI-LB Possible from analyses in Chapters 5-9. As discussed previously, this decision was made in order to isolate the most "Lewy" MCI patients within the cohort. Doing so allows us to most assuredly draw inferences about the neuropsychology of the emergent MCI-LB diagnostic category, the main purpose of this thesis. However, loss of the MCI-LB Possible participants does decrease the statistical power of analyses. Future analyses of this dataset could consider inclusion of those MCI-LB Possible, particularly those patients with a positive FP-CIT scan.

10.4 Future directions

As described in Chapter 3, the larger SUPErB study will follow volunteers for up to five years after baseline assessments. This will offer a wealth of longitudinal data and, critically, indicate the characteristics of participants that go on to convert dementia within that time frame. Such information may reposition the findings in the present cross-sectional work. For example, Breitve et al. (2018) found worse visuoconstructional ability in DLB than AD at baseline, but no association between visuospatial function and the rate of cognitive decline or dementia severity. Longitudinal follow-ups will determine whether the deficits identified in MCI-LB in the present study, particularly processing speed, is informative in terms of conversion to dementia or functional or cognitive decline. Moreover, MCI studies are at risk of the inclusion of "contamination" by healthy individuals (Petersen et al., 1999, p. 307). For example, a substantial proportion of individuals receiving an MCI diagnosis are "false

positives" who will revert to normal cognition or have long-standing, non-progressive poor performance (see Brooks et al., 2008 for a review). De Jager and Budge (2005) and Koepsell and Monsell (2012), for example, found 13% and 16% of participants with baseline cognitive impairment showed normal cognitive status at four- and one-year follow up, respectively. Higher figures (38% and 31%, respectively) have been reported in other incidence studies (Manly et al., 2008; Roberts et al., 2014). Indeed, the temporal instability of the concept of MCI is one of the major concerns in its use, which is most relevant to clinical settings but could also remain a challenge in research. Various sources of MCI's diagnostic instability have been identified, including fluctuations in mood and somatic comorbidities and practice effects. Cognitive profiles in MCI can range broadly and with disease progression, and may reflect mixed pathologies that may have differential trajectories of decline and potential remission of cognitive deficits (Goldman, Williams-Gray, Barker, Duda, & Galvin, 2014b; Mosimann et al., 2004). Indeed, the high prevalence of multiple pathologies in dementia makes attempts to delineate a clear, etiologically-orientated neuropsychological profile challenging. However, Roberts et al. (2014) and Koepsell and Monsell (2012) both found that those with MCI that revert to normal cognition still had a higher risk of later converting to dementia. This suggests that MCI has "prognostic value" regardless of its temporal instability. Other concerns and controversies surrounding the concept of MCI include whether classification should be clinical or algorithmic, such as using neuropsychological data as discussed in Chapter 2, the applicability to different populations, and the reliability of putative biomarkers (Gauthier & Touchon, 2005; Petersen et al., 2014). Longitudinal data will be critical in determining whether MCI remains a useful concept and diagnostic category despite these limitations.

Statistically, several alternative methods may improve future work using the tasks employed herein. Firstly, staircase methods may offer a means to determine optimal interstimulus interval in an MCI sample on computerized tasks such as the SRT, CRT and CPT-AX. Staircasing is a rather simple adaptive method used in psychophysics that estimates the perceptual threshold for 50% correct detection of a stimulus using an "up-down" procedure (Cornsweet, 1962; Leek, 2001). Stimulus presentation is adjusted based on the accuracy of the previous response or responses until the threshold is reached. Secondly, in interpreting the results of a large battery of neuropsychological tasks, a more advanced perspective can be taken to understand what constitutes abnormally low performance. Within a healthy

population, a certain proportion will be expected to exhibit at least one abnormally low test score. The extent of patient impairment, based on the control group, could thus be overestimated. Crawford et al. (2007), for example, recommend a Monte Carlo method that can be applied to any test batteries to help account for variance in control and patient populations. This method also facilitates for comparison between studies without relying on normative data (Crawford et al., 2007).

Thirdly, better measures of processing speed may be developed from a task perspective or alternative statistical analyses. Task-based improvements could include staircasing, as described above, or further manipulation of executive weighting in the CPT-AX. For example, the present study used a target frequency of 70%. This was in order to increase the cognitive demands of the task, specifically executive function: a high proportion of targets creates a strong response tendency, increases response competition during the non-target stimuli, and increases the error rate (Conners, Epstein, Angold, & Klaric, 2003; MacDonald, Pogue-Geile, et al., 2003; Silverstein, Weinstein, & Turnbull, 2004). This allowed me to consider how error types would differ between groups. However, low target frequencies have been argued to be purer measures of sustained attention, by clearly requiring sustained "vigilance" to respond to the occurrence of an infrequent event (Carter, Russell, & Helton, 2013). Indeed, lower frequencies may place less demand on the motor control of participants (Carter et al., 2013). While my DSST analyses suggest that motor and cognitive processing speed components can be measured separately in MCI-LB, it might be nevertheless advantageous to minimize motor determinants of performance in future reaction time tests.

Furthermore, while these results suggest a processing speed, rather than executive, mediated model of decline in MCI-LB, executive function is a broad class of cognitive processes that may not have been fully captured by the present study's battery (see Chapter 6). Future work should aim to capture the multifaceted nature of the construct of executive function, and this may be possible while simultaneously measuring processing speed. An alternative to the cognitive psychological framework taken in the present PhD, which presumes overlap or hierarchy in cognitive processes (Baddeley, 1996b; Logie, 1995), could be taken in this regard. For example, the Attention Network Test (ANT; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) is based on the spotlight-theory of attention (Posner, Snyder, & Davidson, 1980) and conceptualises attention as consisting of interrelated systems of executive control, orienting, and alerting (Posner & Petersen, 1990). Cromarty et al.

(2018) used the ANT test to demonstrate slowed mean reaction time in a combined DLB and PDD group, relative to controls and AD. In terms of attention, however, the LBD and AD groups did not differ in executive control or orienting efficiency (Cromarty et al., 2018), suggesting that the ANT may not be useful in identifying differences in attention between dementia subtypes. The ANT has also been shown to have questionable psychometric properties, including poor reliability and substantial interrelatedness of the purportedly independent networks (MacLeod et al., 2010). As such, there remains an unmet need to develop or adopt a task that can simultaneously deconstruct attention and quantify processing speed.

Other advanced techniques for modelling IIV may also be useful in MCI. The ex-Gaussian approach utilized in Chapter 8 was successful in demonstrating that intra-individual variability was elevated in MCI subtypes differently, depending on the executive weighting of the reaction time test. However, the ex-Gaussian model, while commonly used, has been criticized for linking subcomponents of reaction time to specific cognitive processes. For example, the present study assumed *tau* as indicative of periodic attentional lapses or "microfluctuations" (Kieffaber et al., 2006; Matzke & Wagenmakers, 2009). Some argue that this link is tenuous and not sufficiently supported by theory (Osmon, Kazakov, Santos, & Kassel, 2018). Alternatively, a number of other models have been argued to have more theoretical support for interpreting parameters as representative of specific cognitive processes (see Osmon et al., 2018 for a review). For example, Drift Diffusion Modelling (Ratcliff, 1978; Ratcliff & McKoon, 2008) is predicated on a model of reaction time in which the cognitive components (sensory-perceptual encoding, response execution duration, etc.) vary randomly from trial to trial. Of course, models may differ in their usefulness depending on both the tasks and populations, and some authors suggest that the same data should be examined using multiple models to determine the optimal approach (Osmon et al., 2018).

Further work is also needed to determine the clinical relevance of these findings. For example, evidence from Chapter 6 that cognitive de-differentiation occurs in MCI-LB may suggest a rehabilitative pathway. Analyses using the VPT showed that MCI-LB's verbal ability is related to their visuospatial memory performance, even when remembering stimuli that are validated as least-susceptible to verbal coding. It is possible that MCI-LB may be recruiting intact neuropsychological processes, like verbal recoding, in order to compensate for, or "scaffold", the significant deficits in the visuospatial store. Compensatory scaffolding

is expected across development including in normal ageing, during which complementary neural pathways are recruited in order to complete cognitive tasks that rely on declining neural circuits (see Park & Reuter-Lorenz, 2009 for a review). A number of correlational studies have established that cognitive engagement across the lifespan, such as educational attainment and cognitive effort, is associated with better intellectual function in later life (Schooler, Mulatu, & Oates, 1999, for example). Moreover, declines associated with AD are less severe or delayed in individuals with high cognitive stimulation (Bennett et al., 2003; Stern et al., 1994).

More direct measures of semantic ability or a dual-task framework could be used in future studies to confirm whether cognitive scaffolding truly occurs differently in MCI-LB during completion of the VPT. Articulatory suppression tasks, for example, can be used to interfere with verbal rehearsal, and thus confirm whether such phonological engagement modulates visuospatial memory (Baddeley, 2000b; Vandierendonck et al., 2004). For example, during the VPT retention interval, participants could be required to repeat the word “the,” which impedes the operation of the phonological loop, in one condition of the task. Such a paradigm is challenging for patients but may be possible in MCI, when cognitive decline is not too advanced. Evidence of cognitive scaffolding using the VPT could have consequential implications for cognitive rehabilitation, for example through training in verbal recoding strategy use. In a randomized controlled trial, Kinsella et al. (2009) found significant improvements in prospective memory scores and increased knowledge and implementation of memory strategies after five weeks of training in amnestic MCI. Using semantic strategy training, Miotto et al. (2013) similarly demonstrated improvements in word list recall in patients with acquired prefrontal cortex lesions. Unfortunately, if speed of processing is confirmed to be the critical factor in predicting visuospatial memory success, efforts to increase this core resource have previously failed in MCI (Barnes et al., 2009).

The evidence of differential performance by aetiology in MCI in the present thesis is also relevant to clinical trials for dementia. Indeed, neuropsychology remains crucially important in the development of any breakthrough pharmaceutical treatment. With the highest fail rate in the industry and a 30% greater cost per successful development than in other specialties, there is decreasing investment in research and development in neurodegeneration and a number of major pharmaceutical companies recently either downsized (Pfizer, Sanofi and Janssen) or closed (GSK, AstraZeneca and Novartis) their departments. A major barrier to

successful drug development in dementia is failure to detect subtle changes in cognition during the trials. These incredibly expensive and lengthy trials require early evidence of success (often improvements in cognitive performance) to justify their continuation, yet may use bulky global cognitive measures or clinical measures such as CDR to track changes over time. Burdick et al. (2014), for example, found the MMSE was only 45% successful in identifying PD patients with dementia. Investment in developing valid and reliable neuropsychological measures that can detect small effect sizes across shorter time spans will be essential. As such, it is suggested that processing speed tasks and advanced modelling techniques are further developed to ensure that any positive changes to cognition are recognised before a trial is forced to cease.

Any intervention will need to be administered early in disease course, and thus reliable identification of suitable patients for (firstly) clinical trials and (subsequently) treatment implementation is needed. Differences in the profiles of MCI-LB and MCI-AD that emerged in the present study suggest promising directions in early diagnosis and the identification of differential cognitive processes between the causes of dementia. The significant differences found between MCI-LB and MCI-AD are especially noteworthy given the recruitment process of SUPErB (as discussed in section 4.4). Future work, including ongoing analyses within the longitudinal SUPErB study, will help to elucidate how processing speed functions as a core mechanism of cognitive performance in MCI-LB.

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Appendices

Appendix A. Extracted data from structured review (PD-MCI and MCI-LB)

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
PD-MCI Summary: Stroop Interference		Executive function	PD-MCI Summary: Stroop Interference Condition			127				-0.73	-0.95	-0.51
Hessen (2016)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference condition	80.30	17.90	13	57.20	15.60	25	-1.38	-2.12	-0.64
Poletti (2012)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference condition	25.50	17.20	18	17.00	7.80	100	-0.87	-1.38	-0.35
Wang (2015)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference condition	19.64	9.24	96	15.34	4.97	163	-0.62	-0.88	-0.37
		Executive function	Early PD Summary: Stroop Interference Condition			379					-0.51	-0.22
Broeders (2013)	early PD v HCs	Executive function	Stroop Color-Word Test: interference condition	121	55	59	95	24	40	-0.57	-0.98	-0.16
	early PD v HCs	Executive function	Stroop Color-Word test: interference condition	28.40	11.30	133	31.20	8.60	133		-0.51	-0.03
Aarsland (2009)	early PD v HCs	Executive function	Stroop Color-Word test: interference condition	26.10	11.50	187	30.10	9.60	166	-0.37	-0.58	-0.16
		Executive function										
Bocanegra (2015)	PD-MCI v HCs	Executive function	INECO Frontal Screening	18.00	4.54	17	22.71	1.65	17	-1.35	-2.09	-0.60
Poletti (2012)	PD-MCI v HCs	Executive function	Frontal Assessment Battery	12.80	2.50	18	16.70	1.80	100	-2.02	-2.58	-1.46
Poletti (2012)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference errors	-1.70	3.40	18	-0.40	1.20	100	-0.76	-1.27	-0.24
Anderson (2013)	PD-MCI v HCs	Executive function	Frontal Assessment Battery	15.2	2.57	19	17.4	1.1	21	-1.11	-1.78	-0.44
Anderson (2013)	PD-MCI v HCs	Executive function	Hayling Sentence Completion	4.00	2.12	19	6.10	1.00	21	-1.26	-1.94	-0.58
Anderson (2013)	HCs	Executive function	Modified 6-Elements	3.1	0.97	19	3.4	0.9	21	-0.31	-0.94	0.31
Anderson (2013)	HCs	Executive function	Rule Shift	2.3	1.06	19	3.4	0.6	21	-1.27	-1.95	-0.59
Song (2008)	PD-MCI v HCs	Executive function	Go-no-go test	17.10	4.39	20	19.48	1.30	33	-0.82	-1.39	-0.24
Galtier (2016)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference index	-2.35	6.83	26	-4.67	7.97	20	0.31	-0.28	0.90
Dalrymple (2011)	PD-MCI v HCs	Executive function	Action (verb) fluency	-0.81	0.9	36	0.66	1	50	-1.52	-2.00	-1.03
Dalrymple (2011)	PD-MCI v HCs	Executive function	Semantic fluency: Category swtich	-0.63	1.00	36	0.86	1.20	50	-1.32	-1.79	-0.85

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Dalrymple (2011)	PD-MCI v HCs	Executive function	Stroop Color-Word Test: interference index	-0.94	1.30	36	0.52	0.50	50	-1.57	-2.06	-1.08
Peraza (2017)	PD-MCI v HCs	Executive function	Tower of London	14.11	2.50	36	17.27	1.22	29	-1.54	-2.09	-0.98
Yu (2012)	PD-MCI v HCs	Executive function	Matrix Reasoning: WAIS-III	9.65	2.52	44	11.86	2.46	84	-0.89	-1.27	-0.50
Wang (2015)	PD-MCI v HCs	Executive function	Frontal Assessment Battery	14.34	1.52	96	16.16	1.48	163	-1.21	-1.49	-0.94
Dujardin (2007)	early PD v HCs	Executive function	Stroop Color-Word Test: interference index	26.14	16.74	14	18.40	5.90	15	0.61	-0.14	1.35
Dujardin (2007)	early PD v HCs	Executive function	Trail Making test: Oral version	20.27	9.52	####	15.47	4.66	15.00	0.63	-0.12	1.38
Dujardin (1999)	early PD v HCs	Executive function	Stroop Color-Word Test: interference errors	-5.13	5.60	17	-2.06	1.84	17	-0.72	-1.41	-0.03
Dujardin (1999)	early PD v HCs	Executive function	Stroop Color-Word Test: interference index	-76.93	40.83	17	-49.02	19.11	17	-0.85	-1.56	-0.15
Miah (2012)	early PD v HCs	Executive function	IED (CANTAB): categories achieved	8.13	1.82	23	8.32	1.25	20	-0.12	-0.72	0.48
Miah (2012)	early PD v HCs	Executive function	IED (CANTAB): total errors adjusted	39.87	42.35	23	32.68	31.78	20	0.19	-0.41	0.79
Miah (2012)	early PD v HCs	Executive function	SWM (CANTAB) - strategy score	35.48	3.98	23	32.47	6.00	20	0.59	-0.02	1.20
Miah (2012)	early PD v HCs	Executive function	Stockings of Cambridge: initital thinking time	-14.99	8.53	23	-10.37	4.52	20	-0.65	-1.27	-0.04
Miah (2012)	early PD v HCs	Executive function	Stockings of Cambridge: problems solved in minimum moves	7.57	2.02	23	8.11	1.20	20	-0.31	-0.92	0.29
Miah (2012)	early PD v HCs	Executive function	Vienna perseveration task: R2	-23.66	8.07	23	-19.36	4.8	20	-0.62	-1.24	-0.01
Miah (2012)	early PD v HCs	Executive function	Vienna perseveration task: R1	-1.09	1.12	23	-1.15	0.79	20	0.06	-0.54	0.66
Ibarretxe-Bilbao (2009)	early PD v HCs	Executive function	Ekman Facial Recognition	42.5	10.5	24	51	4.5	24	-1.04	-1.64	-0.43
Ibarretxe-Bilbao (2009)	early PD v HCs	Executive function	Iowa Gambling Task	5.16	30.7	24	36.5	22.7	24	-1.14	-1.75	-0.53
Broeders (2013)	early PD v HCs	Executive function	Tower of London	6.10	1.80	59	7.60	1.90	40	-0.81	-1.23	-0.39

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Elgh (2009)	early PD v HCs	Executive function	Mental control (WMS)	6.16	1.94	88	6.47	1.83	30	-0.16	-0.58	0.25
Hessen (2016)	PD-MCI v HCs	Executive function	Trails B	-207.60	93.10	13	-82.30	35.80	25	-2.00	-2.81	-1.20
Poletti (2012)	PD-MCI v HCs	Executive function	Trails B	-147.40	45.40	18	-81.30	34.00	100	-1.83	-2.38	-1.28
Dalrymple (2011)	PD-MCI v HCs	Executive function	Trails B	-1.07	1.10	36	0.69	0.50	50	-2.16	-2.70	-1.63
Costa (2015)	PD-MCI v HCs	Executive function	Trails B	-227.8	105.3	48	-102.1	36.6	20	-1.37	-1.94	-0.80
Biundo (2014)	PD-MCI v HCs	Executive function	Trails B	-259.18	172.10	49	-78.67	94.49	18	-1.15	-1.72	-0.57
Broeders (2013)	early PD v HCs	Executive function	Trails B	-107	46	59	-75	21	40	-0.84	-1.25	-0.42
Elgh (2009)	early PD v HCs	Executive function	Trails B	-160.43	79.95	88	-98.83	41.83	30	-0.85	-1.27	-0.42
Poletti (2012)	PD-MCI v HCs	Executive function	Card Sorting: Categories Achieved (Wisconsin Modified)	3.10	0.90	18	4.80	1.20	100	-1.45	-1.99	-0.92
Poletti (2012)	PD-MCI v HCs	Executive function	Card Sorting: perseverative errors (Modified)	-4.90	2.50	18	-3.10	3.00	100	-0.61	-1.12	-0.10
Galtier (2016)	PD-MCI v HCs	Executive function	Card Sorting: categories Achieved (Wisconsin)	1.12	1.03	26	3.88	1.97	20	-1.80	-2.49	-1.11
Levin (1989)	early PD v HCs	Executive function	Card Sorting: categories Achieved (Wisconsin)	4.30	1.40	41	4.80	1.30	41	-0.37	-0.80	0.07
Levin (1989)	early PD v HCs	Executive function	Card Sorting: perseverative errors (Wisconsin)	-6.70	4.90	41	-4.20	4.10	41	-0.55	-0.99	-0.11
Yu (2012)	PD-MCI v HCs	Executive function	Card Sorting: Categories Achieved (Modified)	4.2	1.95	44	5.96	1.22	84	-1.16	-1.55	-0.77
Yu (2012)	PD-MCI v HCs	Executive function	Card Sorting: perseverative errors (Modified)	-4.66	5.22	44	-2.33	2.75	84	-0.61	-0.99	-0.24
Costa (2015)	PD-MCI v HCs	Executive function	Card Sorting: Categories Achieved (Modified)	3.90	1.90	48	5.70	0.70	20	-1.08	-1.63	-0.53
Costa (2015)	PD-MCI v HCs	Executive function	Card Sorting: perseverative errors (Modified)	-5.20	5.20	48	-2.00	2.30	20	-0.69	-1.23	-0.16
Broeders (2013)	early PD v HCs	Executive function	Card Sorting: Categories Achieved (Modified Wisconsin)	4.20	1.60	59	5.10	1.30	40	-0.60	-1.01	-0.19
Broeders (2013)	early PD v HCs	Executive function	Card Sorting: perseverative errors (Modified Wisconsin)	-4.90	3.80	59	-3.50	5.40	40	-0.31	-0.71	0.10

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Cooper (1991)	early PD v HCs	Executive function	Card Sorting: categories Achieved (Wisconsin)	3.55	0.35	60	4.19	0.39	37	-1.74	-2.21	-1.26
Cooper (1991)	early PD v HCs	Executive function	Card Sorting: perseverative errors (%) (Wisconsin)	-26.20	1.69	60	-22.10	1.64	37	-2.43	-2.97	-1.90
Elgh (2009)	early PD v HCs	Executive function	Card Sorting: categories Achieved (Wisconsin)	2.06	1.37	88	2.53	1.36	30	-0.34	-0.76	0.08
Elgh (2009)	early PD v HCs	Executive function	Card Sorting: perseverative errors (Wisconsin)	-12.42	6.16	88	-11.00	4.78	30	-0.24	-0.66	0.17
Poletti (2012)	PD-MCI v HCs	Executive function	Semantic fluency: category unspec	13.40	1.40	18	13.30	2.20	100	0.05	0.26	-0.45
Song (2008)	PD-MCI v HCs	Executive function	Semantic fluency: animals	13.75	3.55	20	18.24	5.04	33	-0.97	0.30	-1.56
Galtier (2016)	PD-MCI v HCs	Executive function	Semantic fluency: animals	15.04	3.36	26	16.94	5.53	20	-0.42	0.30	-1.01
Dalrymple (2011)	PD-MCI v HCs	Executive function	Semantic fluency: category unspec	-0.08	1	36	1.31	0.9	50	-1.46	0.24	-1.94
Levin (1989)	early PD v HCs	Executive function	Semantic fluency: foods	15.10	5.20	41	17.20	3.50	41	-0.47	0.22	-0.91
Yu (2012)	PD-MCI v HCs	Executive function	Semantic fluency: fruit, fish, vegetable	35.52	8.33	44	39.25	8.16	84	-0.45	0.19	-0.82
Benito-Leon (2011)	early PD v HCs	Executive function	Semantic fluency: animals	10.90	5.20	46	12.90	4.00	138	-0.46	0.17	-0.80
Biundo (2014)	PD-MCI v HCs	Executive function	Semantic fluency: category unspec	37.96	7.95	49	44.67	9.38	18	-0.79	0.28	-1.35
Broeders (2013)	early PD v HCs	Executive function	Semantic fluency: animals	19.90	5.50	59	22.70	4.60	40	-0.54	0.21	-0.95
Cooper (1991)	early PD v HCs	Executive function	Semantic fluency: animals	18.60	0.60	60	19.60	0.60	37	-1.65	0.24	-2.12
Elgh (2009)	early PD v HCs	Executive function	Semantic fluency: animal, colour, fruit	38.95	9.30	88	46.03	10.98	30	-0.72	0.22	-1.15
Sanyal (2014)	PD-MCI v HCs	Executive function	Semantic fluency: animals	11.37	0.88	90	16.70	2.42	280	-2.47	0.15	-2.77
Wang (2015)	PD-MCI v HCs	Executive function	Semantic fluency: category unspec	13.23	2.36	96	15.26	3.23	163	-0.69	0.13	-0.95

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Aarsland (2009)	early PD v HCs	Executive function	Semantic fluency: animals	17.50	5.50	195	19.20	5.40	170	-0.31	0.11	-0.52
Poletti (2012)	PD-MCI v HCs	Executive function	Phonemic fluency	25.50	8.60	18	34.30	10.10	100	-0.88	-1.40	-0.37
Song (2008)	PD-MCI v HCs	Executive function	Phonemic fluency (COWAT)	22.20	10.27	20	31.45	11.46	33	-0.83	-1.40	-0.25
Galtier (2016)	PD-MCI v HCs	Executive function	Phonemic fluency	18.27	6.86	26	26.06	9.60	20	-0.94	-1.55	-0.32
Dalrymple (2011)	PD-MCI v HCs	Executive function	Phonemic fluency (D-KEFS)	0.07	1.3	36	0.8	1.2	50	-0.58	-1.02	-0.14
Levin (1989)	early PD v HCs	Executive function	Phonemic fluency (FAS, Benton, 1983)	38.10	13.60	41	38.40	12.20	41	-0.02	-0.46	0.41
Costa (2015)	PD-MCI v HCs	Executive function	Phonemic fluency: "phonological" unspec	25.6	9.9	48	35.7	5.4	20	-1.13	-1.68	-0.57
Biundo (2014)	PD-MCI v HCs	Executive function	Phonemic fluency: "phonological" unspec	34.55	9.62	49	36.56	9.22	18	-0.21	-0.75	0.33
Broeders (2013)	early PD v HCs	Executive function	Phonemic fluency (COWAT)	30.80	10.30	59	35.90	9.70	40	-0.50	-0.91	-0.10
Elgh (2009)	early PD v HCs	Executive function	Phonemic fluency (FAS)	39.65	14.43	88	43.00	12.23	30	-0.24	-0.65	0.18
Wang (2015)	PD-MCI v HCs	Executive function	Phonemic fluency: "phonological" unspec	7.14	2.28	96	10.25	3.36	163	-1.03	-1.30	-0.76
Yu (2012)	PD-MCI v HCs	Visuospatial	Visual Reproduction (nonverbal, WMS-III): recognition	40.14	44	4.03	43.30	84	2.95	-0.94	-1.32	-0.55
Song (2008)	PD-MCI v HCs	Visuospatial	Rey Figure - Recognition	19.70	20	2.03	20.61	33	1.06	-0.60	-1.17	-0.03
Galtier (2016)	PD-MCI v HCs	Visuospatial	8/30 Spatial Recall Test -- Learning (7/24 SRT adaptation Barbizet & Cany, 1968)	22.08	26	6.59	30.00	20	7.73	-1.10	-1.72	-0.47
Galtier (2016)	PD-MCI v HCs	Visuospatial	8/30 Spatial Recall Test - Long term (7/24 SRT adaptation Barbizet & Cany, 1968)	4.20	26	1.89	5.64	20	2.00	-0.73	-1.33	-0.13
Elgh (2009)	early PD v HCs	Visuospatial	Brief Visuospatial memory test - free recall delayed (20m)	7.05	88	2.64	9.10	30	2.29	-0.80	-1.22	-0.37
Elgh (2009)	early PD v HCs	Visuospatial	Brief Visuospatial memory test - recognition	5.37	88	0.93	5.73	30	0.45	-0.43	-0.85	-0.01
Broeders (2013)	early PD v HCs	Visuospatial	Faces delayed (WMS, 20m)	36	59	3.6	38.3	40	3.4	-0.65	-1.06	-0.24
Broeders (2013)	early PD v HCs	Visuospatial	Faces immediate (WMS)	31.8	59	4.4	35.4	40	3.7	-0.86	-1.28	-0.45
Galtier (2016)	PD-MCI v HCs	Visuospatial	Block design (WAIS-III)	8.00	26	5.14	15.29	20	4.06	-1.52	-2.18	-0.86

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	Fragmented letters	0.15	36	0.90	0.60	50	0.70	-0.56	-1.00	-0.13
Levin (1989)	early PD v HCs	Visuospatial	Benton's Facial Recognition Task	44.00	41	4.60	46.30	41	3.90	-0.53	-0.97	-0.09
Levin (1989)	early PD v HCs	Visuospatial	Ghent Task	32.00	41	2.90	33.40	41	2.50	-0.51	-0.95	-0.07
Levin (1989)	early PD v HCs	Visuospatial	Hooper Visual Organization	14.10	41	3.10	15.00	41	2.20	-0.33	-0.77	0.10
Levin (1989)	early PD v HCs	Visuospatial	Nonverbal embedded figures	8.40	41	1.70	9.30	41	1.10	-0.62	-1.07	-0.18
Yu (2012)	PD-MCI v HCs	Visuospatial	Block design (WAIS-III)	9.30	44	2.31	11.48	84	2.29	-0.94	-1.33	-0.56
Biundo (2014)	PD-MCI v HCs	Visuospatial	Fragmented letters (VOSP)	17.51	49	2.87	19.06	18	1.70	-0.58	-1.13	-0.03
Aarsland (2009)	early PD v HCs	Visuospatial	Cube (VSOP)	9.30	195	1.30	9.70	171	0.80	-0.36	-0.57	-0.16
Aarsland (2009)	early PD v HCs	Visuospatial	Silhouettes (VOSP)	18.50	195	4.20	19.50	171	3.90	-0.25	-0.45	-0.04
Galtier (2016)	PD-MCI v HCs	Visuospatial	8/30 Spatial Recall Test: Learning	22.08	26	6.59	30.00	20	7.73	-1.10	-1.72	-0.47
Galtier (2016)	PD-MCI v HCs	Visuospatial	8/30 Spatial Recall Test: Long term	4.20	26	1.89	5.64	20	2.00	-0.73	-1.33	-0.13
Galtier (2016)	PD-MCI v HCs	Visuospatial	Block design (WAIS-III)	8.00	26	5.14	15.29	20	4.06	-1.52	-2.18	-0.86
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	Fragmented letters	0.15	36	0.90	0.60	50	0.70	-0.56	-1.00	-0.13
Yu (2012)	PD-MCI v HCs	Visuospatial	Block design (WAIS-III)	9.30	44	2.31	11.48	84	2.29	-0.94	-1.33	-0.56
Yu (2012)	PD-MCI v HCs	Visuospatial	Visual Reproduction: recognition	40.14	44	4.03	43.30	84	2.95	-0.94	-1.32	-0.55
Biundo (2014)	PD-MCI v HCs	Visuospatial	Fragmented letters (VOSP)	17.51	49	2.87	19.06	18	1.70	-0.58	-1.13	-0.03
Levin (1989)	early PD v HCs	Visuospatial	Benton's Facial Recognition Task	44.00	41	4.60	46.30	41	3.90	-0.53	-0.97	-0.09
Levin (1989)	early PD v HCs	Visuospatial	Ghent Task	32.00	41	2.90	33.40	41	2.50	-0.51	-0.95	-0.07
Levin (1989)	early PD v HCs	Visuospatial	Hooper Visual Organization	14.10	41	3.10	15.00	41	2.20	-0.33	-0.77	0.10
Levin (1989)	early PD v HCs	Visuospatial	Nonverbal embedded figures	8.40	41	1.70	9.30	41	1.10	-0.62	-1.07	-0.18
Broeders (2013)	early PD v HCs	Visuospatial	Faces delayed (WMS, 20 min)	36	59	3.6	38.3	40	3.4	-0.65	-1.06	-0.24

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Broeders (2013)	early PD v HCs	Visuospatial	Faces immediate (WMS)	31.8	59	4.4	35.4	40	3.7	-0.86	-1.28	-0.45
Aarsland (2009)	early PD v HCs	Visuospatial	Cube (VSOP)	9.30	195	1.30	9.70	171	0.80	-0.36	-0.57	-0.16
Aarsland (2009)	early PD v HCs	Visuospatial	Silhouettes (VOSP)	18.50	195	4.20	19.50	171	3.90	-0.25	-0.45	-0.04
Poletti (2012)	PD-MCI v HCs	Visuospatial	Benton Judgement of Line Orientation test	17.50	5.20	18	24.80	2.80	100	-2.22	-2.80	-1.64
Galtier (2016)	PD-MCI v HCs	Visuospatial	Benton Judgement of Line Orientation test	9.20	3.44	26	13.41	1.33	20	-1.51	-2.17	-0.85
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	Benton Judgement of Line Orientation test	0.03	0.90	36	0.68	0.60	50	-0.87	-1.32	-0.42
Levin (1989)	early PD v HCs	Visuospatial	Benton Judgement of Line Orientation test	10.00	3.60	41	10.10	2.80	41	-0.03	-0.46	0.40
Broeders (2013)	early PD v HCs	Visuospatial	Benton Judgement of Line Orientation test	24.40	4.10	59	26.60	3.50	40	-0.56	-0.97	-0.15
Elgh (2009)	early PD v HCs	Visuospatial	Benton Judgement of Line Orientation test	23.41	4.52	88	25.40	3.49	30	-0.46	-0.88	-0.04
Wang (2015)	PD-MCI v HCs	Visuospatial	Benton Judgement of Line Orientation test	14.44	1.52	96	21.22	2.58	163	-3.01	-3.37	-2.65
Elgh (2009)	early PD v HCs	Visuospatial	BVMT: recognition	5.37	0.93	88	5.73	0.45	30	-0.43	-0.85	-0.01
Song (2008)	PD-MCI v HCs	Visuospatial	Rey Figure - Recognition	19.70	20	2.03	20.61	33	1.06	-0.60	-1.17	-0.03
Elgh (2009)	early PD v HCs	Visuospatial	BVMT: delayed recall (20 min)	7.05	2.64	88	9.10	2.29	30	-0.80	-1.22	-0.37
Cooper (1991)	early PD v HCs	Visuospatial	ROCF (60 min)	11.30	1.41	60	12.90	1.11	37	-1.22	-1.66	-0.77
Sanyal (2014)	PD-MCI v HCs	Visuospatial	Constructional Praxis (unspecified)	-3.53	1.28	90	-2.16	1.09	280	-1.20	-1.45	-0.95
Biundo (2014)	PD-MCI v HCs	Visuospatial	ROCF (10 min)	13.65	5.99	49	18.88	5.75	18	-0.87	-1.43	-0.31
Costa (2015)	PD-MCI v HCs	Visuospatial	ROCF (20 min)	9.20	5.90	48	16.40	6.10	20	-1.19	-1.75	-0.64
Song (2008)	PD-MCI v HCs	Visuospatial	ROCF (20 min)	14.00	7.99	20	17.08	5.61	33	-0.46	-1.02	0.10
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	ROCF (30 min)	-0.85	1.20	36	0.84	1.40	50	-1.27	-1.74	-0.80
Poletti (2012)	PD-MCI v HCs	Visuospatial	ROCF (unspecified)	9.00	6.10	18	17.10	4.10	100	-1.81	-2.36	-1.26
Yu (2012)	PD-MCI v HCs	Visuospatial	Visual Reproduction (unspecified)	47.02	21.75	44	55.60	20.39	84	-0.41	-0.78	-0.04

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
PD-MCI Summary: delayed recall of drawings		Visuospatial	PD-MCI Summary: delayed recall of drawings			305				-1.03	-1.19	-0.87
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	ROCF: short delay recall (3 min)	-0.76	1.40	36	1.08	1.20	50	-1.42	-1.89	-0.94
		Visuospatial										
Costa (2015)	PD-MCI v HCs	Visuospatial	ROCF	10.00	6.30	48	17.00	7.10	20	-1.06	-1.61	-0.51
Song (2008)	PD-MCI v HCs	Visuospatial	ROCF	15.28	7.61	20	17.27	4.91	33	-0.32	-0.88	0.24
Poletti (2012)	PD-MCI v HCs	Visuospatial	ROCF	8.90	5.00	18	17.60	5.00	100	-1.73	-2.28	-1.18
Yu (2012)	PD-MCI v HCs	Visuospatial	Visual Reproduction	64.14	18.31	44	76.56	13.71	84	-0.80	-1.18	-0.42
PD-MCI Summary: immediate recall of drawings		Visuospatial	PD-MCI Summary: immediate recall of drawings			130				-0.94	-1.19	-0.70
Cooper (1991)	early PD v HCs	Visuospatial	Visual reproduction	10.20	0.34	60	11.60	0.27	37	-4.40	-5.15	-3.66
Broeders (2013)	early PD v HCs	Visuospatial	Clock Drawing Test	12.70	1.30	59	13.10	1.20	40	-0.31	-0.72	0.09
Wang (2015)	PD-MCI v HCs	Visuospatial	Clock Drawing Test	8.18	1.12	96	8.98	1.11	163	-0.72	-0.98	-0.46
Sanyal (2014)	PD-MCI v HCs	Visuospatial	Constructional Praxis	-2.65	0.56	90	-0.82	0.54	280	-3.35	-3.69	-3.01
Biundo (2014)	PD-MCI v HCs	Visuospatial	Clock drawing test (free drawing)	12.80	2.30	49	14.67	0.59	18	-0.92	-1.49	-0.36
Costa (2015)	PD-MCI v HCs	Visuospatial	Drawings Copy	8.60	1.50	48	10.40	1.30	20	-1.23	-1.79	-0.67
PD-MCI Summary: Other Copy Tasks	PD-MCI summary	Visuospatial	PD-MCI Summary: Other Copy Tasks			283				-1.56	-1.74	-1.38
		Visuospatial										
Cooper (1991)	early PD v HCs	Visuospatial	ROCF Copy	25.10	1.11	60	28.70	0.85	37	-3.50	-4.14	-2.86
Biundo (2014)	PD-MCI v HCs	Visuospatial	ROCF Copy	31.17	4.69	49	33.99	4.57	18	-0.60	-1.15	-0.05
Costa (2015)	PD-MCI v HCs	Visuospatial	ROCF Copy	27.20	5.50	48	32.40	2.60	20	-1.06	-1.61	-0.51

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Dalrymple (2011)	PD-MCI v HCs	Visuospatial	ROCF Copy	-0.85	1.30	36	0.24	0.80	50	-1.04	-1.50	-0.58
Song (2008)	PD-MCI v HCs	Visuospatial	ROCF Copy	32.20	3.74	20	33.23	1.91	33	-0.37	-0.93	0.19
Poletti (2012)	PD-MCI v HCs	Visuospatial	ROCF Copy	21.70	7.30	18	34.00	2.90	100	-3.16	-3.80	-2.51
PD-MCI Summary: ROCF Copy	PD-MCI summary	Visuospatial	PD-MCI Summary: ROCF Copy			171				-1.54	-1.98	-1.10
Dujardin (2007)	early PD v HCs	Processing speed/Attention	Digit Symbol Coding (oral)	44.07	14	6.34	55.00	15	8.31	-1.43	-2.25	-0.61
Dujardin (1999)	early PD v HCs	Processing speed/Attention	Stroop: color naming	-87.73	17	####	-81.56	17	22.64	-0.24	-0.92	0.43
Dalrymple (2011)	PD-MCI v HCs	Processing speed/Attention	Stroop: color naming	-0.49	36	0.80	0.14	50	0.80	-0.78	-1.22	-0.34
Dalrymple (2011)	PD-MCI v HCs	Processing speed/Attention	Stroop: word reading	-0.37	36	0.80	0.28	50	0.80	-0.80	-1.25	-0.36
Peraza (2017)	PD-MCI v HCs	Processing speed/Attention	Power of Attention	######	37	####	########	30	101.18	-1.25	-1.78	-0.72
Yu (2012)	PD-MCI v HCs	Processing speed/Attention	Digit Symbol Substitution Test	9.70	44	2.19	11.85	84	2.28	-0.95	-1.33	-0.57
Yu (2012)	PD-MCI v HCs	Processing speed/Attention	Processing speed index	98.79	44	####	110.47	84	10.89	-1.04	-1.42	-0.65
Yu (2012)	PD-MCI v HCs	Processing speed/Attention	Symbol searching	9.86	44	2.53	11.98	84	2.11	-0.93	-1.31	-0.55
Broeders (2013)	early PD v HCs	Processing speed/Attention	Digit Symbol Substitution Test	40.80	59	####	53.50	40	10.00	-1.17	-1.60	-0.73
Broeders (2013)	early PD v HCs	Processing speed/Attention	Stroop: color naming	-63.00	59	####	-56.10	40	10.00	-0.53	-0.94	-0.12
Broeders (2013)	early PD v HCs	Processing speed/Attention	Stroop: word reading	-47.80	59	9.90	-42.70	40	7.60	-0.56	-0.97	-0.15
Elgh (2009)	early PD v HCs	Processing speed/Attention	Electronic tapping test (left)	40.82	88	####	56.14	30	6.09	-1.12	-1.56	-0.69
Elgh (2009)	HCs	speed/Attention	Electronic tapping test (right)	46.51	88	####	61.17	30	6.11	-1.07	-1.51	-0.63

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Aarsland (2009)	early PD v HCs	Processing speed/Attention	Stroop: sum of color & word naming	129.00	193	####	141.00	171	24.40	-0.42	-0.63	-0.21
Dujardin (1999)	early PD v HCs	Processing speed/Attention	Brown-Peterson Consants Recall	44.88	0.33	17	44.65	1.00	17	0.30	-0.38	0.98
Ibarretxe-Bilbao (2009)	early PD v HCs	Processing speed/Attention	CPT II: d'	0.82	0.3	24	0.84	0.4	24	-0.06	-0.62	0.51
Ibarretxe-Bilbao (2009)	early PD v HCs	Processing speed/Attention	CPT II: Hit RT	-456.97	58.4	24	-420.88	61.5	24	-0.59	-1.17	-0.01
Peraza (2017)	PD-MCI v HCs	Processing speed/Attention	"Power of Attention"	1400.65	172.04	37	1217.46	101.18	30	-1.25	-1.78	-0.72
Yu (2012)	PD-MCI v HCs	Processing speed/Attention	Working Memory index	102.56	13.7	44	111.13	12.88	84	-0.65	-1.02	-0.27
Dujardin (2007)	early PD v HCs	Processing speed/Attention	Digit Ordering Test	90.89	12.66	14	87.32	9.83	15	0.31	-0.43	1.04
Dujardin (1999)	early PD v HCs	Processing speed/Attention	Brown-Peterson Consants Recall	44.88	0.33	17	44.65	1.00	17	0.30	-0.37	0.98
Dalrymple (2011)	PD-MCI v HCs	Processing speed/Attention	Digit Ordering Test	-1.63	0.80	36	-0.59	0.90	50	-1.20	-1.66	-0.73
Levin (1989)	early PD v HCs	Processing speed/Attention	Auditory Trails	22.80	5.70	41	24.90	2.80	41	-0.46	-0.90	-0.02
Biundo (2014)	PD-MCI v HCs	Processing speed/Attention	Digit Ordering Test	4.14	1.71	49	6.83	2.43	18	-1.38	-1.97	-0.79
Biundo (2014)	PD-MCI v HCs	Working Memory	Corsi Test	4.95	0.97	49	5.22	1.69	18	-0.22	-0.76	0.32
Costa (2015)	PD-MCI v HCs	Working Memory	Corsi Backward	4.10	1.00	48	4.60	0.70	20	-0.54	-1.06	-0.01
Costa (2015)	PD-MCI v HCs	Working Memory	Corsi Test	4.70	0.90	48	4.90	0.80	20	-0.23	-0.75	0.30
Elgh (2009)	early PD v HCs	Working Memory	BVMT (Brief Visuospatial memory test) - free recall immediate	17.45	6.61	88	21.87	6.28	30	-0.67	-1.10	-0.25
Levin (1989)	early PD v HCs	Working Memory	Benton Visual Retention (MMQ version; 1974)	9.50	3.00	41	10.70	2.60	41	-0.42	-0.86	0.01

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Levin (1989)	early PD v HCs	Working Memory	Corsi Test	4.90	1.20	41	5.30	0.80	41	-0.39	-0.83	0.05
Miah (2012)	early PD v HCs	Working Memory	Pattern recognition memory: percentage correct	90.94	6.49	23	89.91	7.26	20	0.15	-0.45	0.75
Miah (2012)	early PD v HCs	Working Memory	Spaital working memory (CANTAB) - total between errors	-32.96	16.55	23	-25.74	20.69	20	-0.38	-0.99	0.22
Miah (2012)	early PD v HCs	Working Memory	Spatial short term memory (CANTAB) - span length	5.22	1.00	23	5.63	1.07	20	-0.39	-0.99	0.22
PD-MCI summary		Working Memory	Corsi Test			115				-0.56	-0.86	-0.25
Peraza (2017)	PD-MCI v HCs	Working Memory	Pattern recognition memory (CANTAB)	83.90	17.27	37	98.00	2.50	30	-1.08	-1.59	-0.56
Peraza (2017)	PD-MCI v HCs	Working Memory	Spatial Recognition Memory (correct answers, CANTAB)	18.02	2.80	36	21.89	1.61	29	-1.63	-2.19	-1.07
Poletti (2012)	PD-MCI v HCs	Working Memory	Corsi Test	4.20	0.40	18	4.90	0.60	100	-1.21	-1.73	-0.68
Biundo (2014)	PD-MCI v HCs	Working Memory	Digit Forward	5.21	1.00	49	5.39	1.12	18	-0.17	-0.71	0.37
Broeders (2013)	early PD v HCs	Working Memory	Digit Forward	12.1	2.9	59	12.2	3.5	40	-0.03	-0.43	0.37
Costa (2015)	PD-MCI v HCs	Working Memory	Digit Forward	5.50	1.10	48	5.90	0.80	20	-0.39	-0.91	0.14
Dujardin (2007)	early PD v HCs	Working Memory	Digit Forward	5.36	0.84	14	6.00	0.84	15	-0.74	-1.49	0.01
Elgh (2009)	early PD v HCs	Working Memory	Digit Forward	8.62	1.86	88	8.93	1.87	30	-0.17	-0.58	0.25
Song (2008)	PD-MCI v HCs	Working Memory	Digit Forward	5.80	1.47	20	7.85	0.83	33	-1.82	-2.47	-1.16
Wang (2015)	PD-MCI v HCs	Working Memory	Digit Forward	6.81	1.02	96	7.89	1.07	163	-1.02	-1.29	-0.76
Yu (2012)	PD-MCI v HCs	Working Memory	Digit forward	7.65	1.33	44	7.78	1.46	84	-0.09	-0.46	0.27
Poletti (2012)	PD-MCI v HCs	Processing speed/Attention	Trails A	-101.30	18	####	-45.10	100	20.10	-2.06	-2.63	-1.49
Dalrymple (2011)	PD-MCI v HCs	Processing speed/Attention	Trails A (Giovagnoli, 1996)	-0.93	36	0.90	0.35	50	0.70	-1.61	-2.10	-1.11
Yu (2012)	PD-MCI v HCs	Processing speed/Attention	Trails A (color)	-70.71	44	####	-47.88	84	15.68	-0.94	-1.32	-0.56

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Benito-Leon (2011)	early PD v HCs	Processing speed/Attention	Trails A (errors)	1.50	46	4.10	2.30	138	4.90	-0.17	-0.50	0.17
Costa, Zabberoni (2015)	PD-MCI v HCs	Processing speed/Attention	Trails A (Giovagnoli, 1996)	-66.50	48	####	-37.20	20	13.90	-1.18	-1.74	-0.63
Biundo (2014)	PD-MCI v HCs	Processing speed/Attention	Trails A	-51.20	49	####	-27.94	18	13.82	-0.46	-1.00	0.09
Broeders (2013)	early PD v HCs	Processing speed/Attention	Trails A	-46.10	59	####	-35.60	40	10.60	-0.53	-0.94	-0.12
Elgh (2009)	early PD v HCs	Processing speed/Attention	Trails A	-58.97	88	####	-35.60	30	12.37	-0.96	-1.39	-0.53
Dujardin (2007)	early PD v HCs	Executive function/ Working Memory	Digit Backwards	3.78	0.97	14	3.73	1.33	15	0.04	-0.69	0.77
Song (2008)	PD-MCI v HCs	Executive function/ Working Memory	Digit Backwards	3.70	1.08	20	3.69	1.61	33	0.01	-0.55	0.56
Ibarretxe-Bilbao (2009)	early PD v HCs	Executive function/ Working Memory	Digit Backwards	5.38	1.90	24	7.21	1.70	24	-1.00	-1.60	-0.40
Galtier (2016)	PD-MCI v HCs	Executive function/ Working Memory	Digit Backwards	4	1.47	26	4.41	1.37	20	-0.28	-0.87	0.30
Yu (2012)	PD-MCI v HCs	Executive function/ Working Memory	Digit Backwards	4.70	1.58	44	5.49	1.61	84	-0.49	-0.86	-0.12
Costa (2015)	PD-MCI v HCs	Executive function/ Working Memory	Digit Backwards	3.80	1.50	48	4.20	0.70	20	-0.30	-0.82	0.22
Broeders (2013)	early PD v HCs	Executive function/ Working Memory	Digit Backwards	8.2	2.5	59	9.9	2.9	40	-0.63	-1.04	-0.22
Elgh (2009)	early PD v HCs	Executive function/ Working	Digit Backwards	5.09	2.00	88	5.90	2.31	30	-0.39	-0.80	0.03
Wang (2015)	PD-MCI v HCs	Executive function/ Working Memory	Digit Backwards	3.51	0.83	96	4.17	0.89	163	-0.76	-1.02	-0.50
Wang (2015)	PD-MCI v HCs	Verbal	Similiarities	15.72	96	2.43	16.81	163	2.87	-0.40	-0.65	-0.15

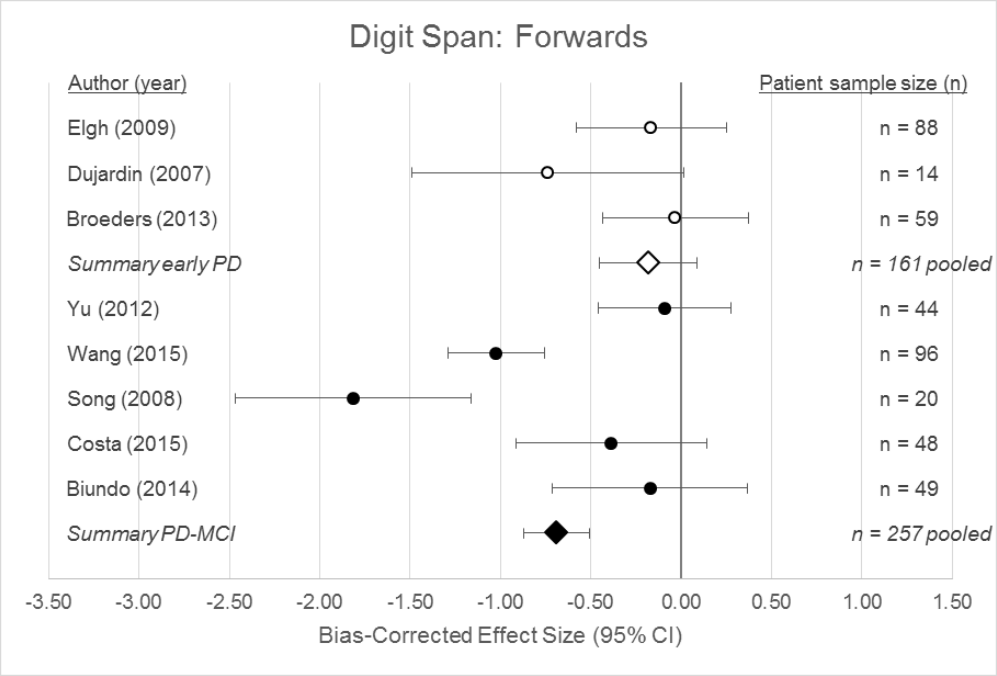
Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Elgh (2009)	early PD v HCs	Verbal	Verbal Paired Associative Learning: easy (WMS)	16.4	88	1.85	16.73	30	1.36	-0.19	-0.60	0.23
Elgh (2009)	early PD v HCs	Verbal	Verbal Paried Associative Learning: hard (WMS)	5.99	88	3.33	7.1	30	2.87	-0.34	-0.76	0.07
Broeders (2013)	early PD v HCs	Verbal	Similiarities (WAIS-III)	21.30	59	5.90	25.70	40	3.50	-0.86	-1.28	-0.44
Broeders (2013)	early PD v HCs	Verbal	Visual Association Test	11.60	59	0.90	11.90	40	0.60	-0.38	-0.78	0.03
Biundo (2014)	PD-MCI v HCs	Verbal	Prose memory tests	13.13	49	4.69	16.14	18	4.04	-0.66	-1.21	-0.10
Biundo (2014)	PD-MCI v HCs	Verbal	Word Paired-Associated task (Novelli et al, 1996)	9.14	49	3.07	12.11	18	3.46	-0.93	-1.49	-0.36
Biundo (2014)	PD-MCI v HCs	Verbal	Similiarities (WAIS-IV)	8.02	49	3.27	11.00	18	1.94	-0.99	-1.55	-0.42
Costa, Zabberoni (2015)	PD-MCI v HCs	Verbal	Prose Recall: Delayed	4.80	48	1.60	5.70	20	1.10	-0.60	-1.14	-0.07
Costa, Zabberoni (2015)	PD-MCI v HCs	Verbal	Prose Recall: Immediate	5.10	48	1.50	5.90	20	1.20	-0.56	-1.09	-0.03
Benito-Leon (2011)	early PD v HCs	Verbal	Line drawings common objects: delayed free recall (5m)	3.20	46	1.70	3.80	138	1.70	-0.35	-0.69	-0.02
Benito-Leon (2011)	early PD v HCs	Verbal	Line drawings common objects: immediate free recall	3.80	46	1.30	4.10	138	1.30	-0.23	-0.56	0.10
Yu (2012)	PD-MCI v HCs	Verbal	Logical memory: recognition (WMS)	22.48	44	4.34	25.73	84	6.57	-0.55	-0.92	-0.18
Yu (2012)	PD-MCI v HCs	Verbal	Similarities: WAIS-III	10.55	44	2.71	11.79	84	2.34	-0.50	-0.87	-0.13
Levin (1989)	early PD v HCs	Verbal	Logical memory: cued (WMS)	11.40	41	3.90	13.90	41	3.00	-0.71	-1.16	-0.27
Bocanegra (2015)	PD-MCI v HCs	Verbal	Kissing and Dancing Test (Bak & Hodges, 2003)	46.70	17	3.40	50.59	17	1.28	-1.48	-2.24	-0.72
	PD-MCI v HCs	Verbal	Summary PD-MCI			195				-0.96	-1.15	-0.76
Hessen (2016)	PD-MCI v HCs	Mem	RAVLT 5 trial sum	36.20	9.30	13	45.30	8.60	aa	-1.01	-1.72	-0.30
Poletti (2012)	PD-MCI v HCs	Mem (verbal episodic)	RAVLT	28.00	5.60	18	41.90	7.10	100	-2.00	-2.56	-1.44
Song (2008)	PD-MCI v HCs	Mem	HVLT	18.85	4.42	20	22.84	3.39	33	-1.03	-1.62	-0.44
Costa, Zabberoni (2	PD-MCI v HCs	Episodic Mem	RAVLT	29.80	9.10	48	46.00	9.00	20	-1.77	-2.37	-1.17
Wang (2015)	PD-MCI v HCs	Mem	HVLT 3 trial sum	17.50	2.89	96	19.45	3.65	163	-0.57	-0.83	-0.32

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Summary early PD	early PD v HCs		*Summary early PD*			336				-0.55	-0.72	-0.38
Broeders (2013)	early PD v HCs	Mem	RAVLT 5 trial sum	41.4	9.6	59	50.7	7.7	40	-1.04	-1.47	-0.61
Elgh (2009)	early PD v HCs	Episodic memory (verbal)	FCRST sum	24.58	7.40	88	30.00	6.10	30	-0.76	-1.18	-0.33
Aarsland (2009)	early PD v HCs	Verbal memory	CVLT total	36.00	12.30	189	40.50	11.00	170	-0.38	-0.59	-0.17
Dalrymple (2011)	PD-MCI v HCs	Learning/ Mem	CVLT II-short form (30s)	**-0.79**	**1.00**	**36**	**0.92**	**1.20**	50	**-1.51**	-2.00	-1.03
Summary PD-MCI c	PD-MCI v HCs		*Summary PD-MCI*			**257**				**-1.25**	-1.43	-1.08
Hessen (2016)	PD-MCI v HCs	Mem	*RAVLT (20 min)*	**6.30**	**2.50**	**13**	**9.00**	**2.10**	25	**-1.18**	-1.90	-0.46
Poletti (2012)	PD-MCI v HCs	Mem (verbal episodic)	*RAVLT (20 min)*	**5.20**	**1.50**	**18**	**9.00**	**2.30**	100	**-1.72**	-2.26	-1.17
Song (2008)	PD-MCI v HCs	Mem	*HVLT (25 min)*	**5.95**	**2.28**	**20**	**7.88**	**1.58**	33	**-1.02**	-1.60	-0.43
Galtier (2016)	PD-MCI v HCs	Learning/ Mem	CVLT (20 min)	**9.48**	**3.57**	**26**	**12.06**	**4.07**	20	**-0.67**	-1.27	-0.07
Dalrymple (2011)	PD-MCI v HCs	Learning/ Mem	CVLT II-short form (10 min)	**-0.50**	**0.90**	**36**	**0.72**	**0.80**	50	**-1.43**	-1.91	-0.95
Costa, Zabberoni (2	PD-MCI v HCs	Episodic Mem	*RAVLT (20 min)*	**5.80**	**2.40**	**48**	**9.70**	**2.30**	20	**-1.63**	-2.21	-1.04
Wang (2015)	PD-MCI v HCs	Mem	*HVLT (20 min)*	**4.31**	**1.62**	**96**	**6.13**	**1.47**	163	**-1.19**	-1.46	-0.92
Broeders (2013)	early PD v HCs	Mem	*RAVLT (20 min)*	**8.3**	**2.7**	**59**	**11**	**2.7**	40	**-0.99**	-1.42	-0.57
Elgh (2009)	early PD v HCs	Episodic memory (verbal)	FCRST (20 min)	15.18	1.32	88	15.17	1.08	30	**0.01**	-0.41	0.42
Galtier (2016)	PD-MCI v HCs	Learning/ Mem	CVLT: cued; "long term" delay	**10.20**	**3.27**	**29**	**13.06**	**3.13**	20	**-0.88**	-1.47	-0.28
Summary PD-MCI Recognition			*Summary PD-MCI*			*142*				**-0.07**	-0.29	0.14

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Song (2008)	PD-MCI v HCs	Mem	HVLT	21.25	1.77	20	21.36	1.51	33	**-0.07**	-0.62	0.49
Galtier (2016)	PD-MCI v HCs	Learning/ Mem	CVLT	14.08	1.78	26	14.50	1.52	20	**-0.25**	-0.83	0.34
Wang (2015)	PD-MCI v HCs	Mem	HVLT	8.72	1.25	96	8.79	1.73	163	**-0.04**	-0.30	0.21
Broeders (2013)	early PD v HCs	Mem	RAVLT	**28.2**	**1.7**	**59**	**29**	**1.8**	**40**	**-0.46**	-0.86	-0.05
Aarsland (2009)	early PD v HCs	Verbal memory	CVLT II: Free recall total sum (immediate + delayed)	**49.70**	**18.80**	**175**	**57.60**	**16.80**	**163**	**-0.44**	-0.66	-0.23
Song (2008)	PD-MCI v HCs	Naming tests	Boston Naming Test	49.45	5.20	20	52.12	6.33	33	-0.44	-1.00	0.12
Galtier (2016)	PD-MCI v HCs	Naming tests	Naming test (Druks & Masterson, 2000)	16.27	2.78	26	18.76	1.43	20	-1.07	-1.69	-0.44
Biundo (2014)	PD-MCI v HCs	Naming tests	Naming task (Novelli, 1986)	25.35	2.12	49	27.83	1.72	18	-1.22	-1.79	-0.64
Sanyal (2014)	PD-MCI v HCs	Naming tests	Boston Naming Test: abridged	10.36	0.92	90	12.92	1.98	280	-1.43	-1.69	-1.17
Summary PD-MCI	PD-MCI v HCs	Naming tests				220				-1.40	-1.59	-1.21
Levin (1989)	early PD v HCs	Naming tests	Boston Naming Test: short form	24.70	3.60	41	24.80	3.70	41	-0.03	-0.46	0.41
Broeders (2013)	early PD v HCs	Naming tests	Boston Naming Test	26.3	3	59	27.7	2	40	-0.53	-0.93	-0.12
Elgh (2009)	early PD v HCs	Naming tests	Boston Naming Test	50.44	7.53	88	51.63	6.65	30	-0.16	-0.58	0.25
Levin (1989)	early PD v HCs	Verbal	Logical memory: delayed	10.30	4.20	41	13.10	3.10	41	-0.75	-1.20	-0.30
Yu (2012)	PD-MCI v HCs	Verbal	Logical memory: delayed	16.32	9.99	44	24.04	9.16	84	-0.81	-1.19	-0.43
Benito-Leon (2011)	early PD v HCs	Verbal	Logical memory: delayed	2.60	2.20	46	3.30	2.30	138	-0.31	-0.64	0.03
Cooper (1991)	early PD v HCs	Verbal	Logical memory: delayed	2.9	0.3	60	4.3	0.45	37	-3.81	-4.49	-3.14

Author (year)	groups?	Domain	Outcome measure	Patient group M	Pt SD	Pt n	Control M	Control SD	Control N	Bias corrected (Hedges)	CI for Effect Size - lower	CI for Effect Size - upper
Elgh (2009)	early PD v HCs	Verbal	Logical memory: delayed	6.43	3.01	88	8.23	3.12	30	-0.59	-1.01	-0.17
Summary early PD	early PD v HCs	Verbal				235				-0.83	-1.04	-0.61
Levin (1989)	early PD v HCs	Verbal	Logical Memory: immediate	9.50	3.50	41	12.20	3.00	41	-0.82	-1.27	-0.37
Yu (2012)	PD-MCI v HCs	Verbal	Logical Memory: immediate	28.89	12.09	44	38.93	10.92	84	-0.88	-1.26	-0.50
Benito-Leon (2011)	early PD v HCs	Verbal	Logical Memory: immediate	3.80	1.60	46	4.00	1.80	138	-0.11	-0.45	0.22
Cooper (1991)	early PD v HCs	Verbal	Logical Memory: immediate	5.7	0.32	60	7.9	0.5	37	-5.49	-6.36	-4.61
Elgh (2009)	early PD v HCs	Verbal	Logical Memory: immediate	7.95	2.81	88	9.93	2.96	30	-0.69	-1.11	-0.27

Appendix B. Graphical comparison of equivalent tasks using data extracted in the structured review.



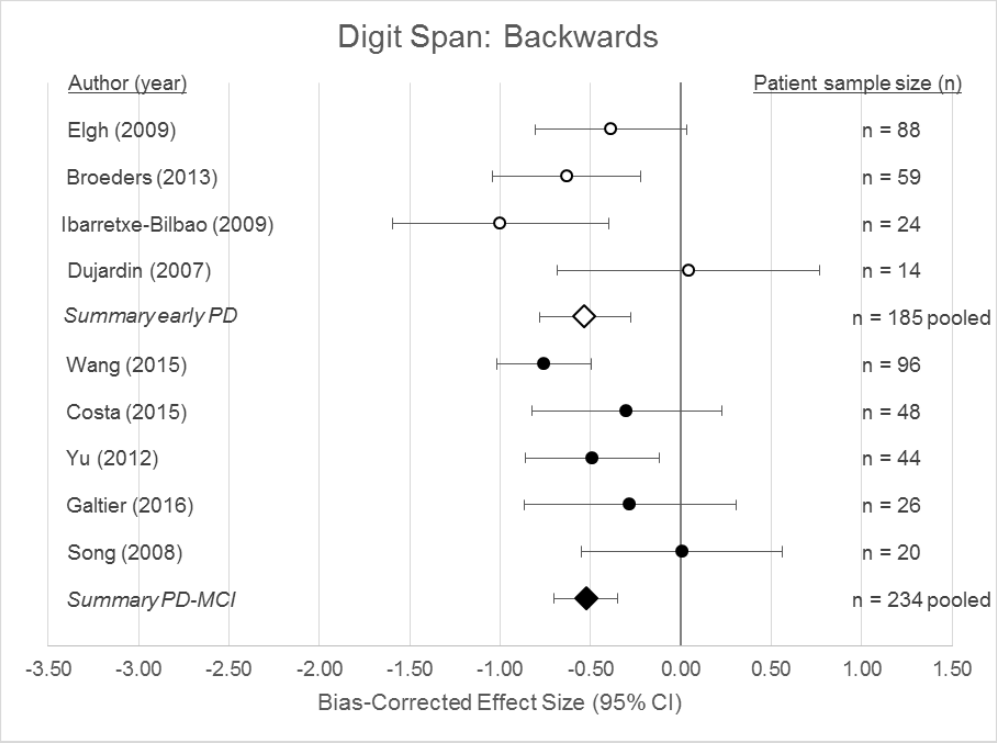
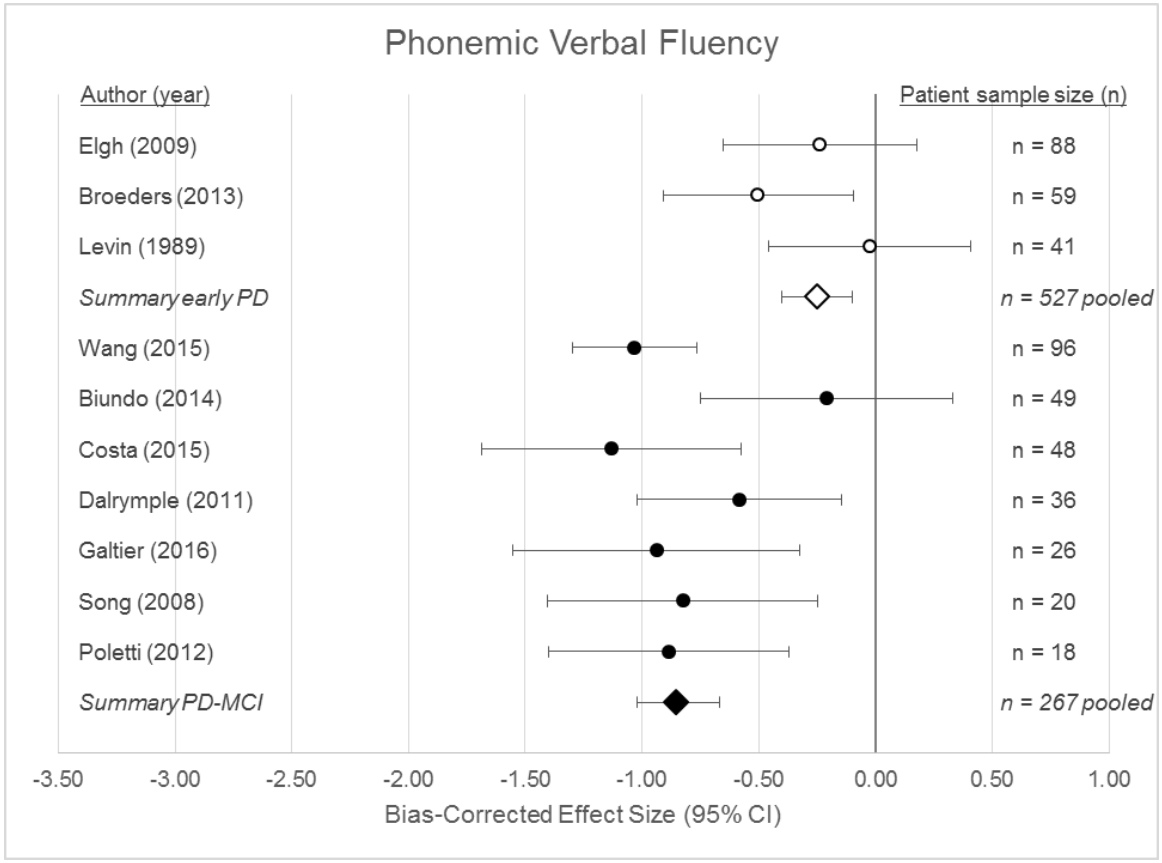


Fig.BA1 and B2. Bias-corrected effect sizes of Digit Span Forwards and Backwards in PD-MCI (black points) and early PD (white points) relative to controls, showing both individual studies (circles) and summary effect sizes by group (diamonds).



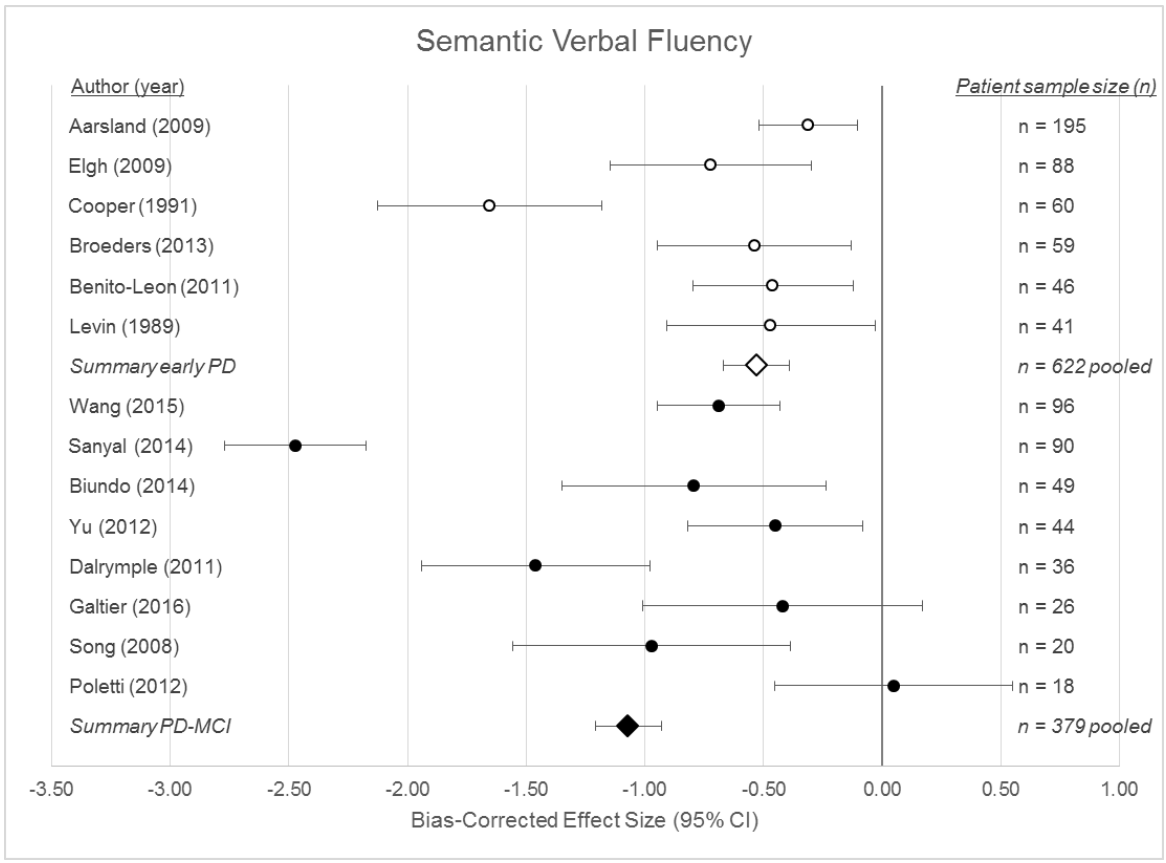


Fig.s B3 and B4. Bias-corrected effect sizes of semantic verbal fluency scores in (a) PD-MCI (black points) and (b) early PD (white points) relative to controls in individual studies (circles) and as a summary effect size by group (diamonds).

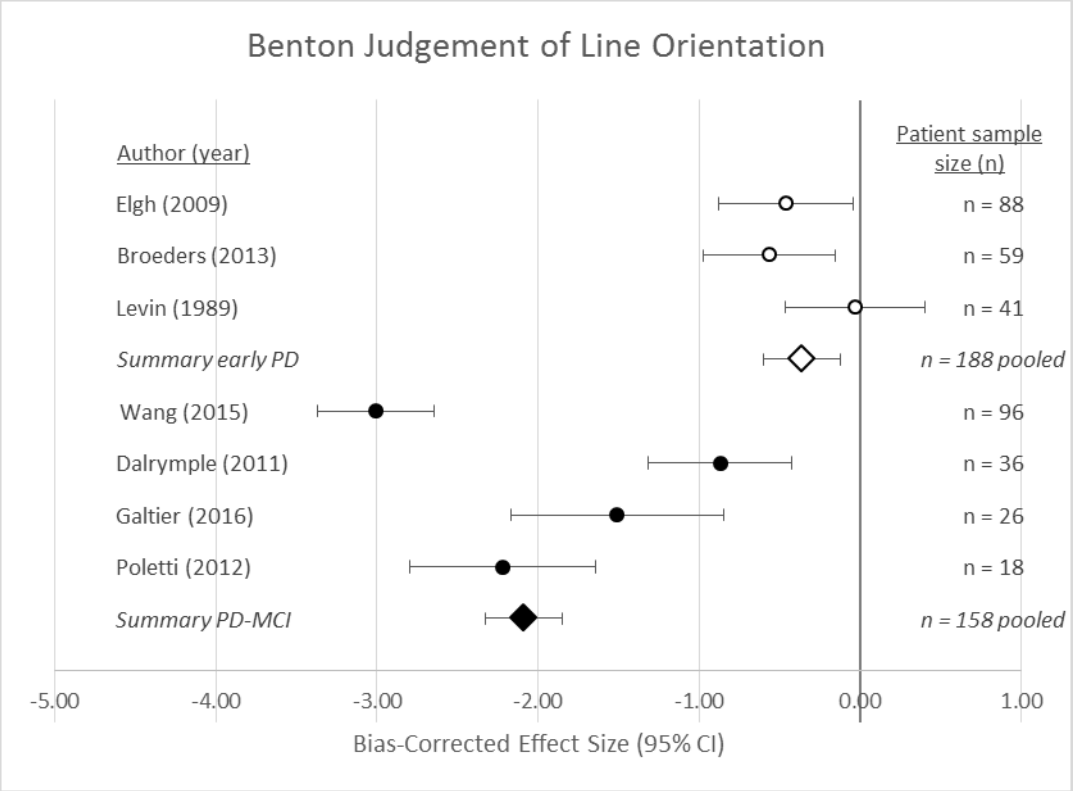


Fig. B5. Bias-corrected effect sizes of semantic verbal fluency scores in PD-MCI (black points) and early PD (white points) relative to controls in individual studies (circles) and as a summary effect size by group (diamonds).

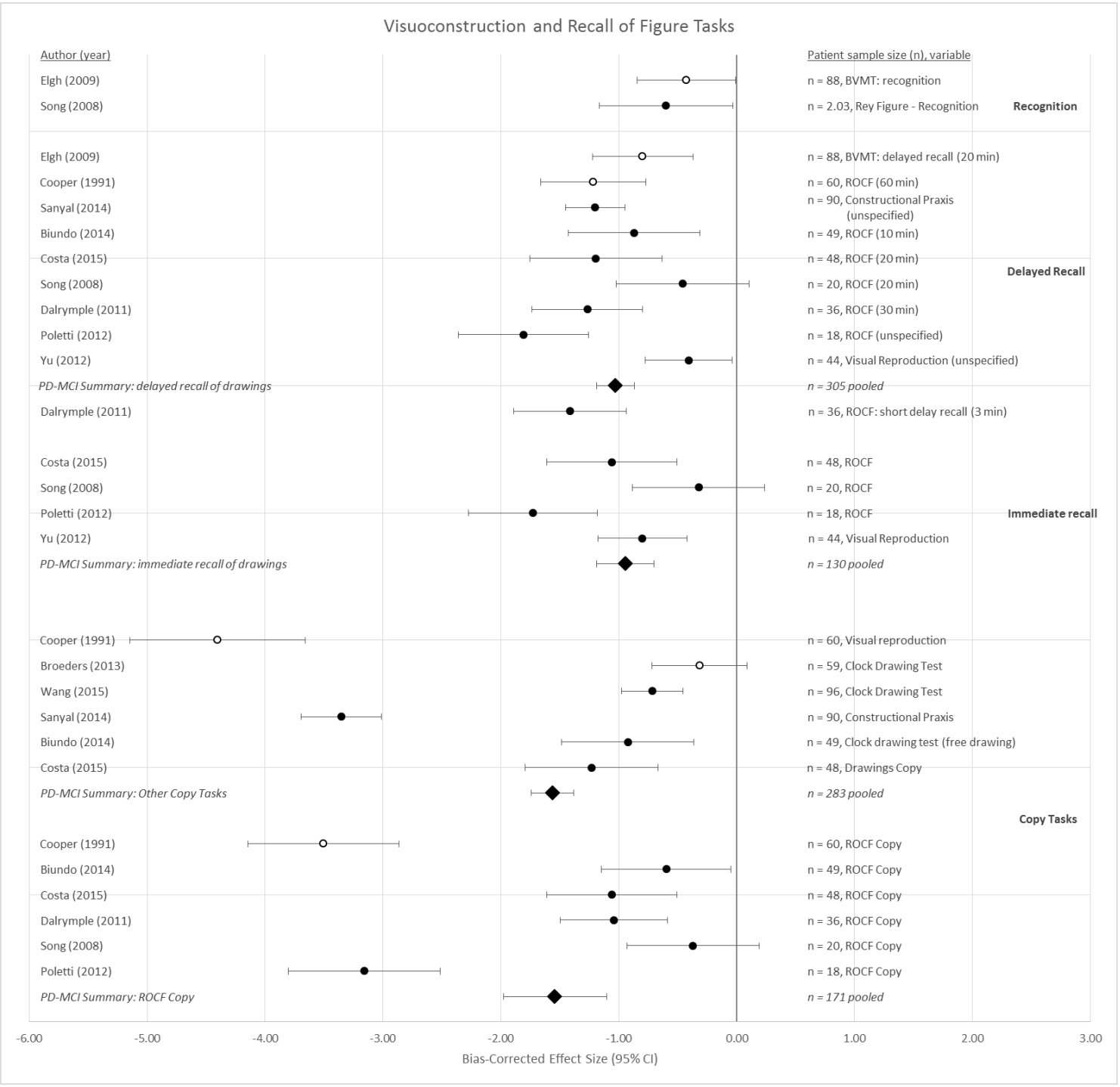


Fig. B6. Bias-corrected effect sizes of visuospatial copying and recall tasks in PD-MCI (black points) and early PD (white points) relative to controls in both individual studies (circles) and as a summary effect size by group (diamonds). (BVMT = Brief Visuospatial Memory Test; ROCF = Rey-Osterrieth Complex Figure).

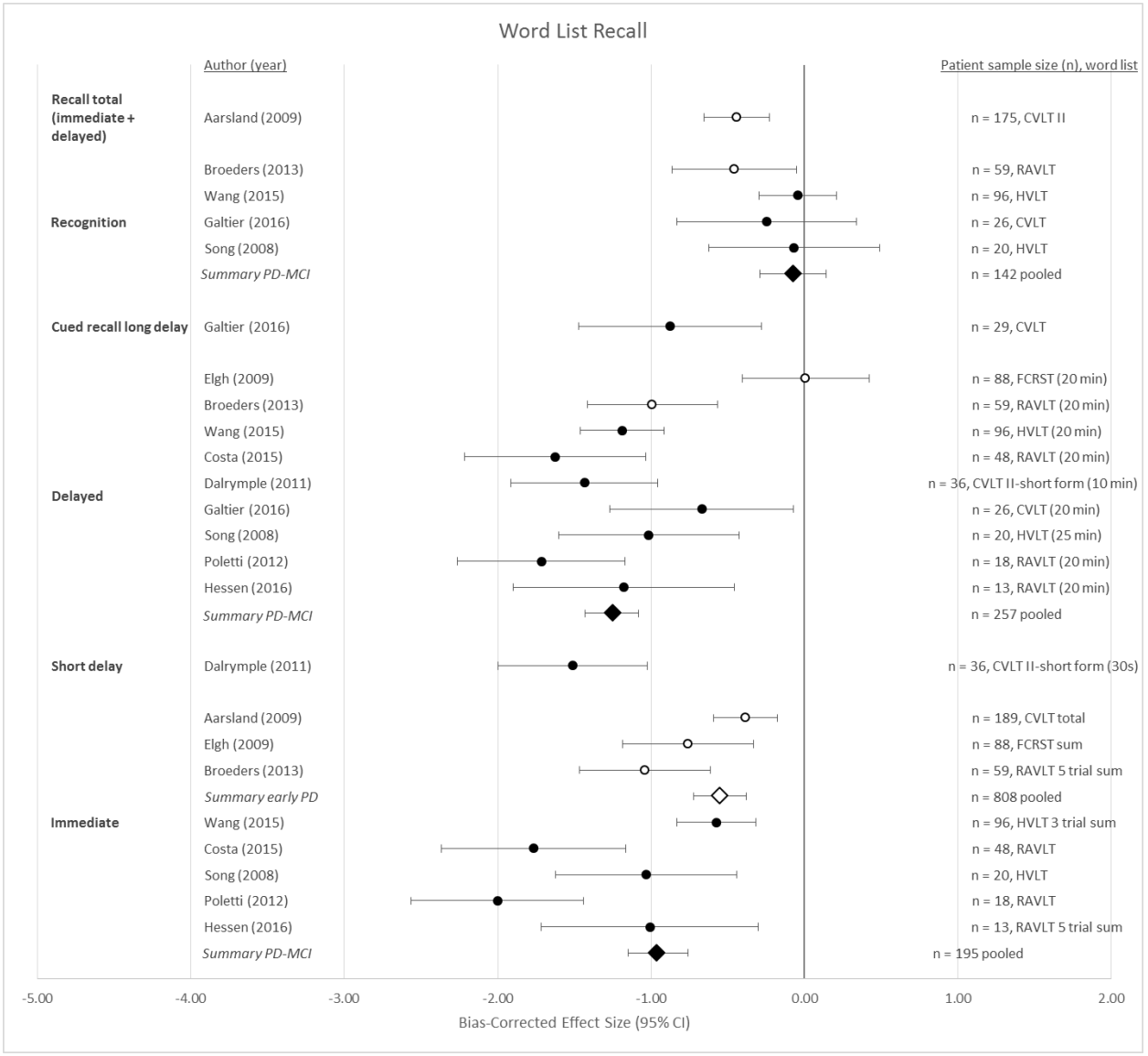


Fig. B7. Bias-corrected effect sizes of word list verbal learning and memory tasks in PD-MCI (black points) and early PD (white points) relative to controls in both individual studies (circles) and as a summary effect size by group (diamonds). (CVLT = California Verbal Learning Test; FCRST = Free and Cued Selective Reminding Test; HVLT = Hopkins Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test).

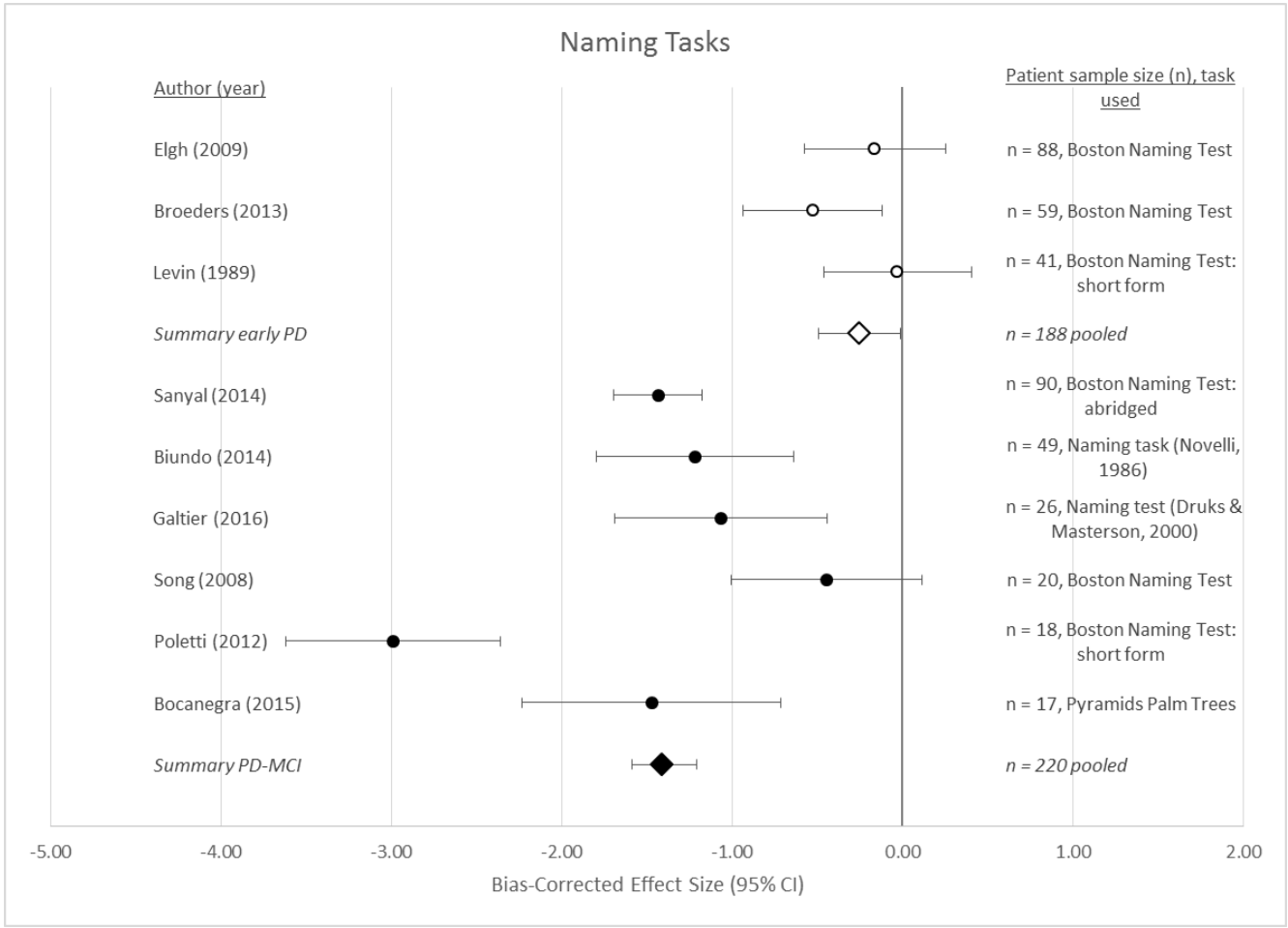


Fig. B8. Bias-corrected effect sizes of naming tests in PD-MCI (black points) and early PD (white points) relative to controls in both individual studies (circles) and as a summary effect size by group (diamonds).

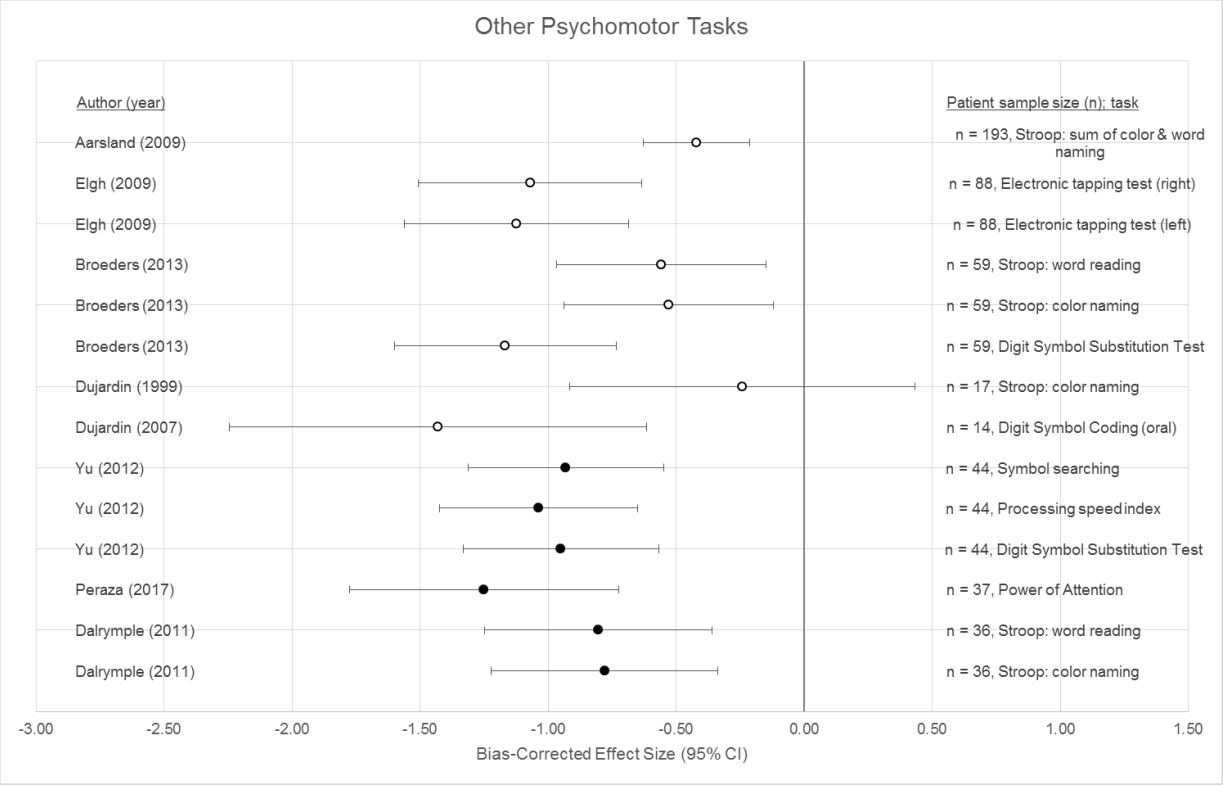
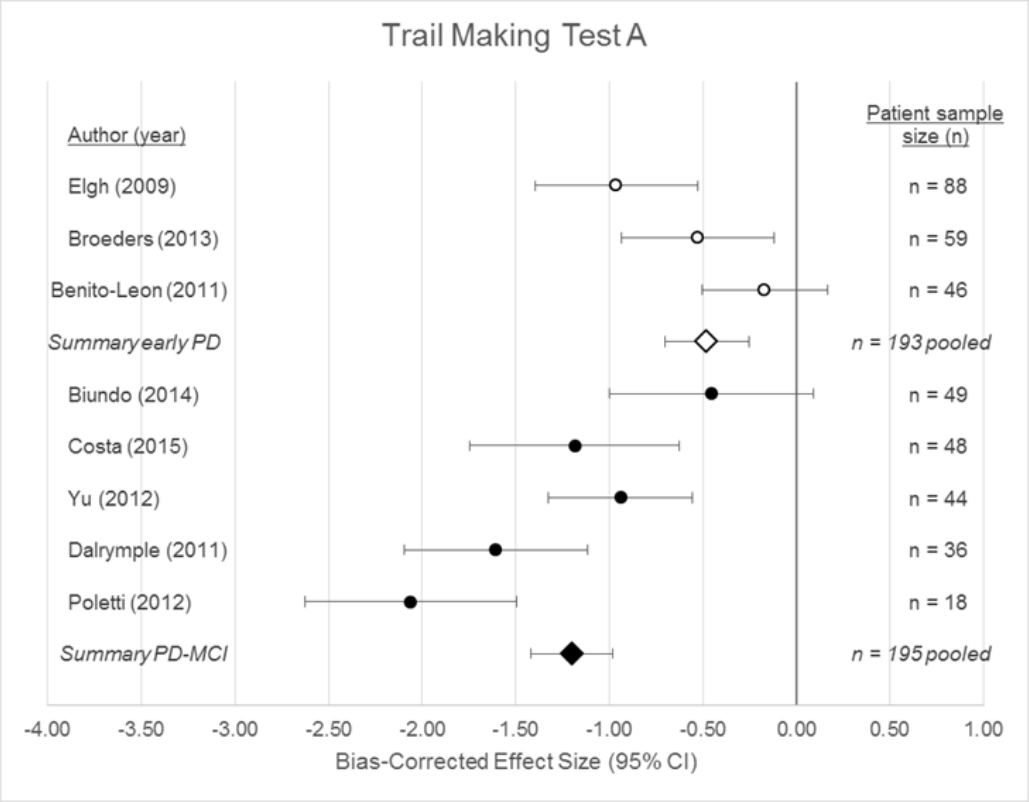


Figure B9. Bias-corrected effect sizes of tasks measuring psychomotor speed in PD-MCI (black) and early PD (white) relative to controls in individual studies.



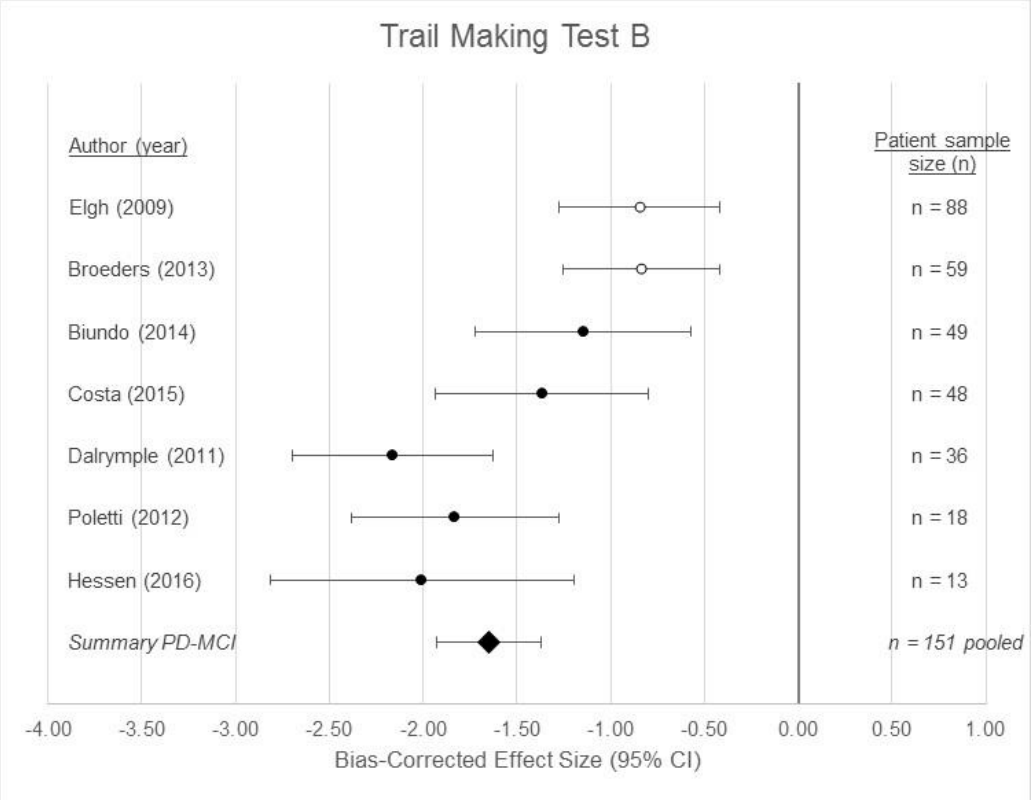


Figure B10 and B11. Bias-corrected effect sizes of Trail Making Tests A and B in PD-MCI (black points) and early PD (white points) relative to controls, showing both individual studies (circles) and summary effect sizes by group (diamonds).

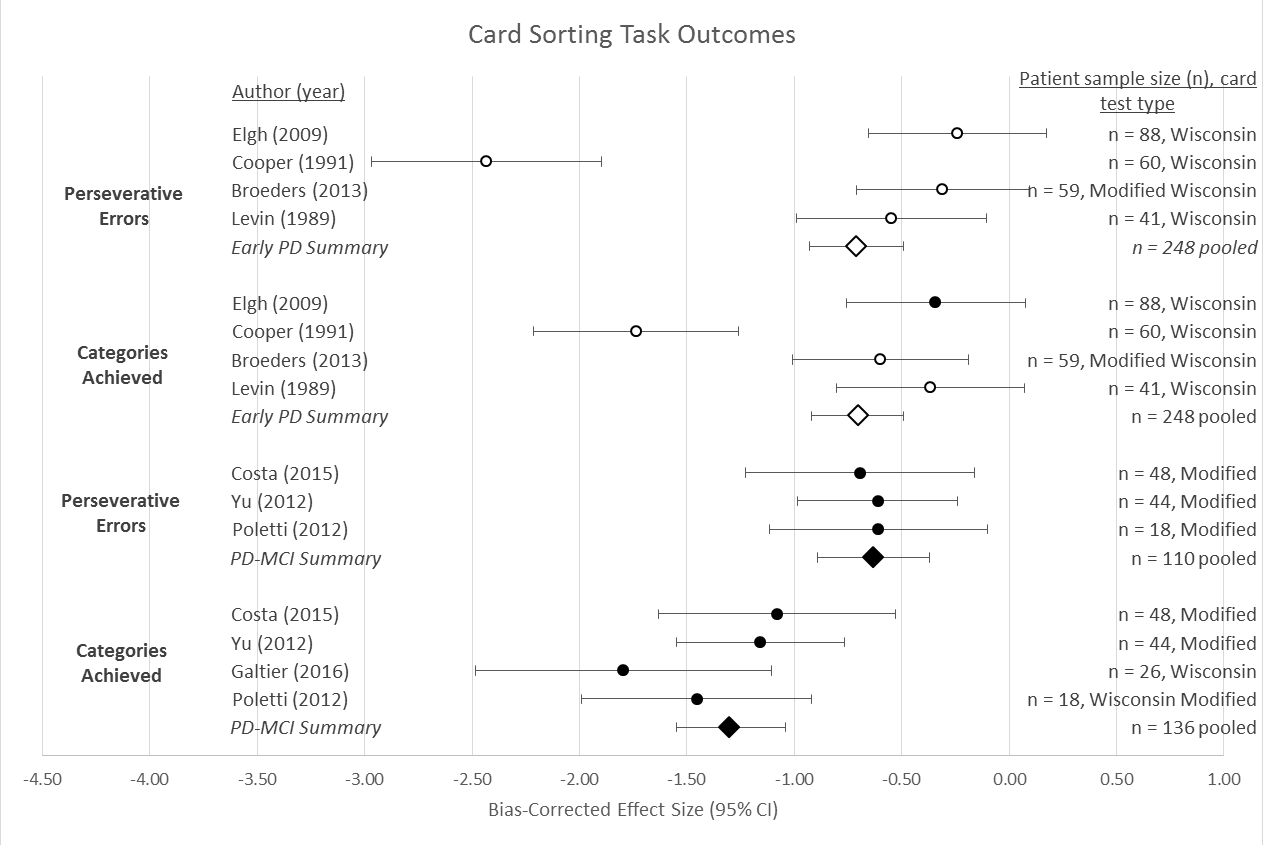


Figure B12. Bias-corrected effect sizes of card sorting tasks in PD-MCI (black points) and early PD (white points) relative to controls, showing both individual studies (circles) and summary effect sizes by group (diamonds).

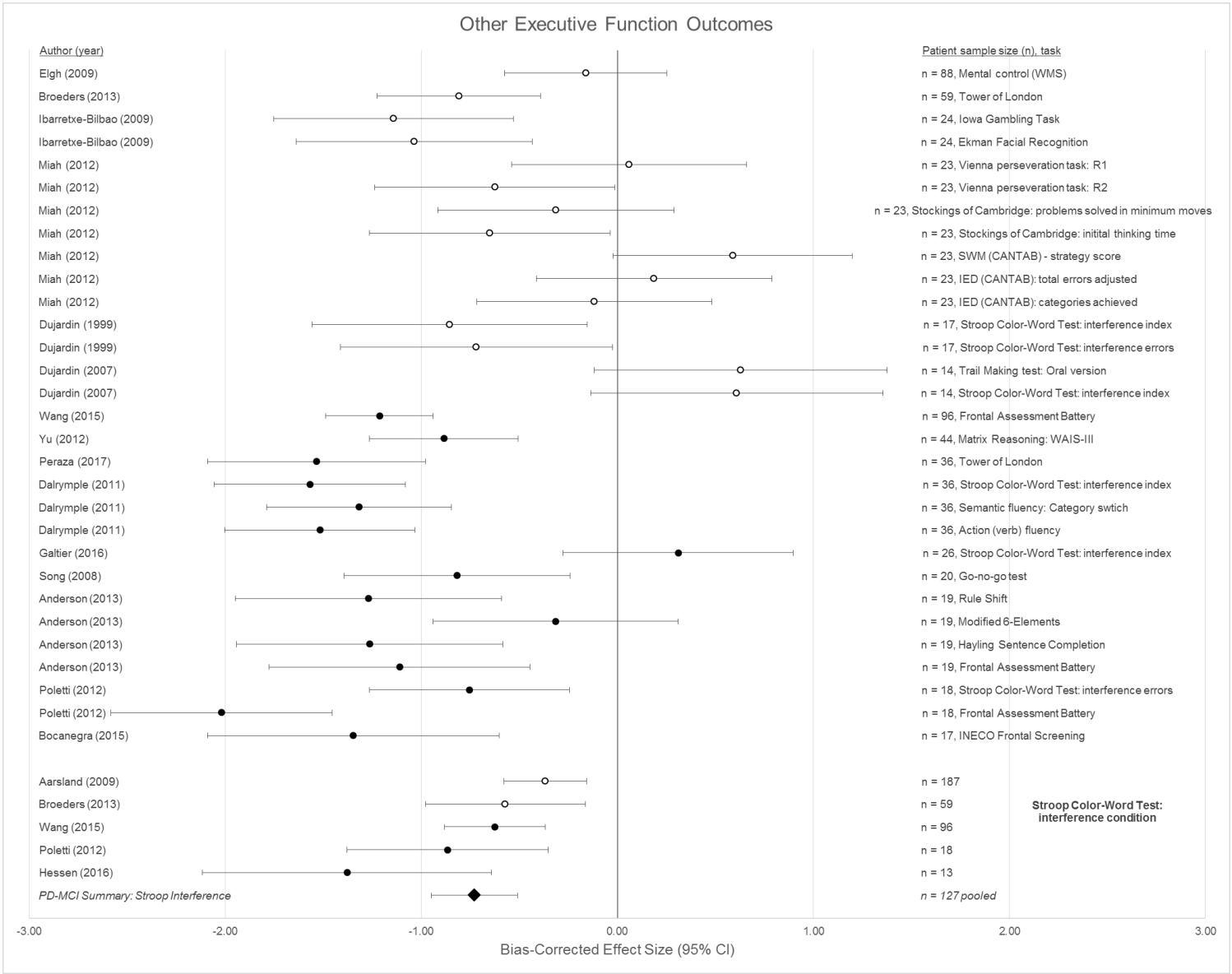


Figure B13. Bias-corrected effect sizes of additional executive function tasks in PD-MCI (black points) and early PD (white points) relative to controls, showing both individual studies (circles) and summary effect sizes by group (diamonds).

Appendix C. Reasons for removal from PhD Analyses of SUPErB Study data.

No Consent, n = 1

SUP001ES

Voluntary Removal, n = 1

SUP170BR

Too Impaired at V2, n = 5

SUP110GH, SUP135AL, SUP139RC, SUP142RJ, SUP173GO

Insufficient Impair., n = 1

SUP081MB

Medical delay, n = 2

SUP168JD, SUP171MM

Before imaging, n = 4

SUP146BN (voluntary/vision), SUP108CV (pain, partial neuropsychological assessment),

SUP125PS**:** no clinic, scans or computer (voluntarily withdrawn),

SUP101RH: no clinic, scans or computer (voluntarily withdrawn)

Participants with partial clinical/ scan data:

Partial Clinical or Scan Data

SUP010PH: no clinic or scans (voluntarily withdrawn)

SUP015PT: no MIBG or DaT (clinic in LewyPro)

SUP055PJ: no MRI/ MIBG

SUP107AB: no DaTSCAN

SUP144RD: no MRI (deceased)

SUP156HF: no scans (deceased)

SUP085MS: no MRI

Appendix D. Outliers removed and transformations performed, by neuropsychological task

Table A-1. Outliers removed by individual task.

Variable Name	Participant	Raw score	*z*-score
F (FAS)	SUP088PS	33	3.81
A (FAS)	SUP161ED	27	3.31
Trails A	SUP117PE	253.58	5.85
Trails B			
Stroop_CW_items	SUP055PJ	97	5.16
RAVLT_Percent_Forgetting	SUP089DK	-2.0	-5.58409
RAVLT_Percent_T5_recalled	SUP089DK	300	5.58409
DSST Error Check	SUP034RS	84.00	3.19281

Table A-2. Transformations performed by neuropsychological task.

Variable	**Skew +/-**	**Dir. Δ?**	**Orig. Skew**	**Orig. Kurt.**	**Trans used**	**New Skew**	**New Kurt.**
Stroop Classical Interference		**Y**			**Changed direction only**		
Stroop Ratio Interference					**Changed direction only**		
RAVLT Percent Forgetting		**Y**	.374	-.580	**Changed direction only**		
RAVLT "Miss" List B		**Y**			**Changed direction only**		
RAVLT Forgetting		**Y**			**Changed direction only**		
RAVLT Proactive interference (B-A1)		**Y**			**Changed direction only**		
Pareidolia	**+**	**Y**	2.63	7.42	-1*SQRT(X)	-1.15	.534
Trail Making Test A	**++**	**Y**	3.112	13.82	-1*Lg10(X)	-.824	.893
Trail Making Test B	**+**	**Y**	1.71	2.68	-1*SQRT(X)	-1.11	.704
Trails Making Test Difference (B-A)	**+**	**Y**	2.12	5.44	-1*SQRT(X)	-1.11	1.26
Trail Making Test Ration (B/A)	**+**	**Y**	1.71	3.10	-1*SQRT(X)	-1.22	1.49
Coding Time (DSST)	**++**	**Y**	2.68	9.65	-1*LG10(X)	-.474	.772
Simple Reaction Time	**++**	**Y**	3.50	13.83	-1*LG10(X)	-2.06	5.13
Choice Reaction Time	**+**	**Y**	2.56	11.10	-1*SQRT(X)	-.675	7.90
Corsi Blocks	**+**	**N**	.871	2.27	SQRT(X)	-.312	.881
VPT Ratio (high/ low)	**+**	**Y**	1.20	.720	-1*SQRT(X)	.889	.272

Appendix E. Charts of univariate analysis between-groups

Table A-3. Comparison of the four subgroups on measures of verbal learning and memory, with t-tests between MCI-AD and MCI-LB Probable and one-way ANOVAs between all four groups.

Task	Controls (*n* = 31)	MCI-LB Probable (*n = 30*)	MCI-LB Possible (*n* = 14)	MCI-AD (*n* = 18)	MCI-LB Probable vs. MCI-AD	All group one-way ANOVA
Graded Naming Test	23.58(4.18)	21.24(3.95)	20.86(4.85)	21.00(4.98)	*t*(45)=-0.18, *p* = .855	*F*(3,88) = 2.26, *p* = .087
ACE-Language	24.87(1.18)	23.73(1.78)	22.64(2.65)	24.06(2.10)	*t*(46)=0.57, *p* = .573	*F*(3,89) = 5.10, ***p* = .003** Control > MCI-LB Probable, *p* = .002 Control > MCI-LB Possible, *p* = .080
RAVLT Max T1:T5	11.39(2.23)	8.63(2.58)	8.14(2.77)	8.17(3.05)	*t*(46)=-0.57, *p* = .574	*F*(3,89) = 9.36, ***p* < .001** Control > MCI-LB Probable, *p* < .001, MCI-LB Possible,

						p = .001, & MCI-AD *p* < .001
RAVLT: "Learning"	5.58(2.13)	4.30(2.68)	3.79(1.97)	3.22(3.08)	*t*(46)=-1.28, *p* = .208	*F*(3,89) = 3.93, ***p* = .011** Control > MCI-AD *p* = .011
RAVLT Short Delay	8.94(2.78)	5.83(3.36)	4.36(3.18)	3.72(3.64)	***t*(46)=-2.04, *p* = .047, *g* = 0.60**	*F*(3,89) = 12.75, ***p* < .001** Control > MCI-LB Probable, *p* = .002, MCI-LB Possible, *p* < .001, & MCI-AD *p* < .001
RAVLT Long Delay	8.35(3.27)	5.66(3.46)	3.86(3.18)	4.00(4.62)	*t*(43)=-1.36, *p* = .180	*F*(3,86) = 7.86, ***p* < .001** Control > MCI-LB Probable, *p* = .023, MCI-LB Possible,

						p = .001, & MCI-AD *p* = .001
RAVLT Percent Remembered at Long Delay (from max T1:T5)	71.59(19.52)	65.02(37.61)	42.55(31.91)	38.23(35.67)	***t*(43)=-2.33, *p* = .025, *g* = 0.73**	*F*(3,86) = 5.73, ***p* = .001** Control > MCI-LB Possible, *p* = .024, MCI-AD, *p* = .004
RAVLT: Retroactive Interference (A6-A5)	-2.00(2.25)	-2.13(2.60)	-3.36(1.86)	-3.72(1.90)	***t*(46)=-2.25, *p* = .029, *g* = 0.70**	*F*(3,89) = 3.16, ***p* = .029** Control > MCI-AD, ***p* = .056**
RAVLT: Proactive Interference (B-A1)	-0.94(1.63)	-0.30(1.75)	-0.50(1.40)	-0.83(1.54)	*t*(46)=-1.07, *p* = .291	*F*(3,89) = 0.90, *p* = .444
Rey Recognition False B*	-0.98(0.84)	-1.73(0.80)	-1.83(1.00)	-1.57(1.20)	*t*(20.71)=0.47, *p* = .642	*F*(3,82) = 4.30, ***p* = .007** Control > MCI-LB Probable, *p* = .012, Control > MCI-LB

						Possible, *p* = .049

** Direction change transformation.*

Table A-4. Comparison of the four subgroups on measures of visuospatial learning and memory, with t-tests between MCI-AD and MCI-LB Probable and one-way ANOVAs between all four groups.

Task	Controls (*n* = 31)	MCI-LB Probable (*n* = *30*)	MCI-LB Possible (*n* = 14)	MCI-AD (*n* = 18)	MCI-LB Probable versus MCI-AD	All group one-way ANOVA
ACE-Visuospatial	15.52(0.85)	13.70(2.15)	14.00(1.84)	14.44(1.50)	*t*(46)=1.29, *p* = .204	*F*(3,89) = 6.81, ***p* < .001** Control > MCI-Probable, *p* < .001, & MCI-LB Possible, *p* = .025
Corsi blocks*	6.09(1.17)	4.57(1.37)	5.08(1.52)	5.12(1.37)	*t*(44)=1.33, *p* = .191	*F*(3,82) = 6.44, ***p* = .001** Control > MCI-Probable, *p* < .001
MTCF Copy	34.37(1.59)	33.32(3.92)	31.21(4.82)	30.75(7.54)	*t*(38)=1.19, *p* = .242	*F*(3,78) = 2.84, ***p* = .043**

						Control > MCI-Probable, *p* = .041
MTCF Recall	16.67(5.77)	11.90(5.14)	9.50(3.89)	9.92(6.42)	*t*(36)=-1.02, *p* = .313	*F*(3,76) = 7.85, ***p* < .001** Control > MCI-LB Probable, *p* = .009, MCI-LB Possible, *p* = .001, & MCI-AD *p* = .003
MTCF % Retained	48.52(16.96)	39.10(14.08)	30.23(11.32)	29.81(18.48)	*t*(36)=-1.71, *p* = .096	*F*(3,76) = 6.30, ***p* = .001** Control > MCI-LB Possible, *p* = .005, & MCI-AD *p* = .004
Visual Patterns (high)	13.38(3.26)	8.08(3.59)	8.50(3.06)	10.80(2.93)	***t*(37)=2.46, *p* = .019, *g* = 0.28**	*F*(3,76) = 13.33, ***p* < .001** Control > MCI-LB Probable, *p* < .001 &

						MCI-LB Possible, $p < .001$. Controls > MCI-AD $p = .072$ MCI-AD > MCI-LB Probable, $p = .065$
Visual Patterns (low)	10.04(3.02)	6.00(3.80)	4.83(2.69)	8.13(2.64)	$t(37)=1.90$, $p = .065$,	$F(3,76) = 10.90$, ***p* < .001** Control > MCI-LB Probable & MCI-LB Possible, $ps < .001$ MCI-AD > MCI-LB Possible, ***p* = .043**
VPT Ratio	0.76(0.17)	0.70(0.33)	0.54(0.27)	0.76(0.17)	$t(36.1)=0.72$, $p = .476$	$F(3,76) = 2.61$, ***p* = .057** Control > MCI-LB Possible, ***p* = .047**

Pareidola: pareidolias*	0.56(0.25)	0.96(0.41)	0.68(0.34)	0.66(0.22)	*t*(40.20)=2.69, ***p* = .010, *g* = 0.79**	*F*(3,82) = 4.68, ***p* = .005** Control < MCI-LB Probable, *p* = .020

*MTCF % Retained = (recall/copy)*100)*
**Transformed variable with means and standard deviations taken post-transformation.*

Table A-5. Comparison of the four subgroups on measures of executive function, with t-tests between MCI-AD and MCI-LB Probable and one-way ANOVAs between all four groups.

Task	Controls (*n* = 31)	MCI-LB Probable (*n* = *30*)	MCI-LB Possible (*n* = 14)	MCI-AD (*n* = 18)	MCI-LB Probable versus MCI-AD	All group one-way ANOVA
Verbal Fluency (FAS)	43.77(9.84)	30.10(15.47)	25.93(12.24)	39.89(12.22)	***t*(46)=2.29, *p* = .027, *g* = 0.70**	*F*(3,89) = 9.54, ***p* < .001** Control > MCI-LB Probable & MCI-LB Possible, *p*s < .001, MCI-AD > MCI-LB Probable, *p* = .054

						MCI-AD > MCI-LB Possible, *p* = .014
Stroop CW (items)	34.04(8.82)	22.58(7.79)	19.09(6.56)	25.13(9.12)	*t*(38)=0.95, *p* = .351	*F*(3,76) = 12.76, ***p* < .001** Control > MCI-LB Probable, *p* < .001, MCI-LB Possible, *p* < .001, & MCI-AD, *p* = .005
Stroop Classical Interference*	-51.95(12.77)	-41.42(13.38)	-43.82(15.27)	-56.94(12.38)	***t*(38)=3.70, *p* = .001, *g* = 1.20**	*F*(3,76) = 5.57, ***p* = .002** MCI-LB Probable > Control , *p* = .026 MCI-LB > MCI-AD Probable, *p* = .003 MCI-LB Possible > MCI-AD, *p* = .063

Stroop Ratio Interference*	-0.60(0.09)	-0.64(0.09)	-0.68(0.14)	-0.70(0.10)	*t*(38)=1.66, *p* = .106	*F*(3,76) = 3.60, ***p* = .018** Control > MCI-AD, *p* = .020
Trails B*	-8.02(1.46)	-12.23(3.73)	-12.16(3.71)	-10.77(2.36)	*t*(44)=1.48, *p* = .146	*F*(3,86) = 12.83, ***p* < .001** Control > MCI-LB Probable & MCI-LB Possible, *p*s < .001, MCI-AD, *p* = .008
Trails Difference*	-5.61(1.63)	-9.28(3.38)	-9.50(3.58)	-8.40(2.30)	*t*(43)=0.97, *p* = .339	*F*(3,85) = 11.50, ***p* < .001** Control > MCI-LB Probable & MCI-LB Possible, *p*s < .001, MCI-AD, *p* = .004

Trails Ratio*	-1.44(0.21)	-1.65(0.34)	-1.66(0.34)	-1.63(0.24)	*t*(43)=0.24, *p* = .812	*F*(3,85) = 3.50, ***p* = .019** Control > MCI-LB Probable, *p* = .034
Digit Span Forwards	8.81(2.54)	7.93(2.00)	7.29(2.02)	8.50(2.26)	*t*(46)=0.91, *p* = .370	*F*(3,89) = 1.77, *p* = .159
Digit Span Backwards	7.03(2.58)	5.50(1.85)	4.86(1.75)	5.56(2.28)	*t*(46)=0.09, *p* = .927	*F*(3,89) = 4.30, ***p* = .007** Control > MCI-LB Probable, *p* = .037, & MCI-LB Possible, *p* = .014

** Transformed variables with means and standard deviations taken post-transformation.*

Table A-6. Comparison of the four subgroups on measures of processing speed, with t-tests between MCI-AD and MCI-LB Probable and one-way ANOVAs between all four groups.

Task	Controls (*n* = 31)	MCI-LB Probable (*n* = *30*)	MCI-LB Possible (*n* = 14)	MCI-AD (*n* = 18)	MCI-LB Probable versus MCI-AD	All group one-way ANOVA
DSST	46.07(10.73)	25.53(9.55)	31.23(15.31)	32.61(7.42)	***t*(43)=2.65, *p* = .011, *g* = 0.83**	*F*(3,85) = 19.25, ***p* < .001** Control > MCI-LB Probable, MCI-LB Possible & MCI-AD, all *p*s < .001
DSST Symbol Copy	95.86(18.01)	60.28(22.16)	69.81(26.36)	71.66(18.88)	*t*(43)=1.79, *p* = .081	*F*(3,85) = 15.15, ***p* < .001** Control > MCI-LB Probable, *p* < .001, MCI-LB Possible, *p* = .002, & MCI-AD, *p* = .001

DSST Error Check	48.68(9.61)	31.34(11.49)	33.33(20.41)	41.73(9.04)	***t*(31.92)=3.30, *p* = .002, *g* = 1.09**	*F*(3,71) = 10.75, ***p* < .001** Control > MCI-LB Probable**, *p* < .001, &** MCI-LB Possible, *p* = .004 MCI-AD > MCI-LB Probable, *p* = .047
DSST Coding Time*	-0.01(0.16)	-0.33(0.23)	-0.24(0.26)	-0.17(0.13)	***t*(43)=2.58, *p* = .013, *g* = 0.83**	*F*(3,85) = 13.11, ***p* < .001** Control > MCI-LB Probable, *p* < .001, MCI-LB Possible, *p* = .004, & MCI-AD, *p* = .030 MCI-AD > MCI-LB

						Probable, *p* = .058
Trails A*	-1.49(0.14)	-1.74(0.25)	-1.71(-.24)	-1.63(0.16)	*t*(46)=1.64, *p* = .107	*F*(3,88) = 8.89, ***p* < .001** Control > MCI-LB Probable, *p* < .001, & MCI-LB Possible, *p* = .007
Stroop C (items)	85.98(14.87)	64.40(18.04)	62.91(15.91)	78.88(19.37)	***t*(40)=2.54, *p* = .015. *g* = 0.94**	*F*(3,78) = 9.68, ***p* < .001** Control > MCI-LB Probable, *p* < .001, MCI-LB Possible, *p* = .001 MCI-AD > MCI-LB Probable, *p* = .037
Simple Reaction Time*	-2.52(0.08)	-2.60(0.15)	-2.61(0.23)	-2.57(0.14)	*t*(44)=0.69, *p* = .495	*F*(3,85) = 19.25, *p* = .163

Choice Reaction Time*	-22.13(3.82)	-25.32(3.60)	-26.14(5.95)	-24.55(2.11)	*t*(43)=0.81, *p* = .425	*F*(3,80) = 4.22, ***p* = .008** Control > MCI-LB Probable, *p* = .021, & MCI-LB Possible, *p* = .016

**Transformed variables with mean and standard deviation taken post-transformation.*

Appendix F. Principle components analysis performed on entire sample (including controls, MCI-LB and MCI-AD)

PCA #1 – Whole group

Table A7 Pearson bivariate correlations of neuropsychological outcome measures (whole group)

	ACE Lang.	RAVLT Max T1:T6	RAVLT Learning	Rey Short Delay	Rey Long Delay	RAVLT % Max at Long Delay	RAVLT % "Forgetting"	RAVLT Retro. Int.	RAVLT Proact. Int.	RAVLT Recog. B	ACE Visuospatial
	-0.218	-0.187	-0.196	-0.053	0.050	-0.218	-0.187	-0.161	-0.218	-0.215	-0.205
	-0.206	-0.179	-0.161	0.130	0.056	-0.181	-0.155	-0.098	-0.215	-0.208	-0.186
	-0.106	-0.075	-0.113	0.132	0.071	-0.113	-0.141	-0.082	-0.184	-0.138	-0.141
	0.022	0.065	-0.030	0.177	0.163	-0.068	-0.117	-0.029	-0.179	-0.069	0.008
	0.076	0.140	-0.009	1	0.190	-0.068	-0.095	-0.024	-0.173	0.005	0.131
	0.090	0.174	0.031	0.275	0.191	-0.054	-0.094	-0.016	-0.156	0.014	0.149
	0.114	1	0.075	0.277	1	0.021	-0.081	-0.010	-0.143	0.046	0.201
	0.130	0.233	0.094	-0.284	0.234	0.045	-0.059	-0.005	-0.118	0.076	0.213
	0.141	0.275	0.108	-0.285	-0.252	0.056	-0.044	-0.002	-0.112	0.083	1
	0.164	-0.282	0.184	-0.291	0.258	0.063	-0.037	0.003	-0.112	0.084	0.242
	0.194	0.295	0.211	0.305	0.267	0.064	-0.025	0.008	-0.102	0.145	0.264
	1	0.3	1	-0.365	-0.267	0.066	-0.023	0.010	-0.089	0.201	0.28
	0.223	0.341	0.226	0.376	0.28	0.102	-0.009	0.012	-0.083	0.211	0.281
	0.226	-0.355	0.241	0.382	-0.284	0.107	-0.003	0.025	-0.075	0.213	0.3
	0.242	0.356	0.242	0.394	0.314	0.122	-0.002	0.027	-0.064	1	0.304
	0.264	0.376	0.254	0.401	-0.325	0.130	0.000	0.033	-0.052	0.235	-0.338
	0.266	0.382	0.262	0.416	0.332	0.131	0.004	0.048	-0.048	0.238	0.351
	0.267	0.413	0.269	0.421	0.35	0.149	0.019	0.065	-0.047	0.241	-0.367
	0.287	0.43	0.28	0.422	0.352	0.160	0.022	0.084	-0.047	0.25	0.379
	0.307	-0.432	0.281	0.432	0.37	0.162	0.027	0.090	-0.033	0.254	0.387
	0.312	0.441	0.285	0.439	0.386	0.181	0.037	0.113	-0.015	0.274	0.394
	0.32	0.481	0.287	-0.453	0.4	0.201	0.039	0.116	0.008	0.291	0.412
	0.322	0.489	-0.289	0.469	0.4	1	0.147	0.145	0.025	0.298	0.443
	0.324	0.491	0.31	0.47	0.411	0.227	0.185	0.149	0.102	0.306	0.483
	0.328	0.497	0.351	0.471	0.413	0.242	1	0.158	0.105	0.309	0.49
	0.341	0.515	0.358	0.486	0.446	0.392	0.247	1	0.120	-0.312	0.511
	0.346	0.537	0.363	0.487	0.469	0.413	-0.33	0.258	0.141	0.316	0.52
	0.369	0.538	0.38	0.517	0.503	0.425	-0.351	-0.279	1	-0.422	0.528
	0.376	0.578	0.385	0.518	0.587	0.454	-0.422	0.31	0.247	0.43	0.534
	0.385	0.593	0.437	0.542	-0.624	0.519	-0.453	0.328	0.269	0.469	0.591
	0.4	0.709	0.503	0.635	0.819	0.635	-0.464	0.392	-0.279	0.519	0.639
	0.4	0.821	0.542	0.838	0.821	0.819	-0.624	-0.464	-0.284	0.528	0.645
	-0.401	0.838	0.709	0.855	0.855	-0.902	-0.902	0.487	-0.284	0.587	0.645
M all corr	0.221	0.327	0.238	0.319	0.280	0.160	-0.088	0.082	-0.033	0.190	0.306
M sig corr only	0.319333333	0.461461538	0.345428571	0.446642857	0.423807692	0.3224	0.474125	0.359714286	0.26975	0.348833333	0.430333333

Table A-7 Pearson bivariate correlations of neuropsychological outcome measures (whole group)

	Corsi	MTCF Recall	MTCF % Retain	VPT High	VPT Low	VPT Ratio	FAS	Stroop C	Stroop CW	Stroop Ratio Int.	Trails B
	-0.095	-0.147	-0.180	-0.047	-0.118	-0.214	-0.219	-0.184	-0.199	-0.219	-0.203
	-0.048	-0.091	-0.055	-0.037	-0.081	-0.203	-0.181	-0.083	-0.102	-0.206	-0.112
	-0.009	-0.075	-0.047	0.048	0.107	-0.199	-0.161	-0.003	-0.059	-0.205	0.012
	0.025	0.171	0.026	0.149	0.113	-0.194	-0.082	-0.002	0.003	-0.196	0.037
	0.185	0.187	0.085	1	0.181	-0.186	-0.015	0.021	0.160	-0.147	0.064
	0.207	0.217	0.206	0.235	1	-0.184	0.014	0.084	0.211	-0.138	1
	0.211	1	1	0.243	0.264	-0.161	0.056	0.113	1	-0.113	0.258
	0.216	0.25	0.226	0.306	0.285	-0.160	0.085	0.120	0.266	-0.091	0.306
	1	-0.262	0.23	-0.312	0.291	-0.152	0.108	0.161	0.305	-0.055	0.306
	0.223	0.266	0.232	-0.342	0.331	-0.106	0.132	0.190	0.317	-0.022	0.352
	0.227	0.28	0.241	-0.352	0.336	-0.097	0.171	0.194	0.322	0.008	0.358
	0.236	0.328	0.241	0.385	-0.348	-0.094	0.171	0.216	0.38	0.019	0.366
	-0.268	-0.33	0.246	0.41	0.352	-0.091	0.185	1	0.39	0.120	-0.371
	0.28	0.343	0.257	0.411	-0.354	-0.088	0.219	0.226	0.4	0.134	0.4
	-0.327	0.347	0.26	0.423	0.366	-0.075	1	0.232	0.404	0.161	0.417
	0.37	0.358	0.264	0.431	0.373	-0.053	0.236	0.275	0.448	1	0.418
	0.382	0.398	0.266	0.437	-0.378	-0.030	0.245	0.347	0.468	-0.247	0.422
	0.382	0.404	0.284	0.442	0.4	-0.010	0.264	0.356	0.481	-0.252	0.466
	0.394	-0.413	0.297	0.476	0.446	-0.009	0.275	0.373	0.486	0.269	-0.487
	0.402	0.425	0.306	0.483	0.47	0.011	0.312	0.387	0.49	0.276	0.497
	0.423	0.438	0.306	0.518	0.489	0.025	0.336	0.409	0.538	-0.282	0.509
	0.424	0.441	0.31	-0.531	-0.493	0.050	0.365	0.412	0.545	-0.285	0.534
	0.443	0.441	-0.325	0.565	0.499	0.063	-0.401	0.423	-0.553	-0.312	0.557
	0.446	0.456	0.331	0.576	0.545	0.083	0.431	0.443	-0.56	-0.327	0.577
	0.448	0.46	0.351	0.578	0.55	0.090	-0.436	-0.452	0.565	-0.333	0.661
	0.459	0.466	-0.351	0.645	0.613	0.131	0.443	-0.469	-0.604	-0.355	0.673
	0.475	0.469	0.376	0.66	0.626	0.134	0.481	0.568	0.644	-0.357	0.704
	0.483	0.475	0.394	0.666	0.645	0.206	0.502	0.577	0.691	-0.364	0.713
	0.484	0.517	0.439	0.667	0.645	1	0.508	0.585	0.704	-0.371	0.768
	0.528	0.591	0.442	0.672	0.647	-0.253	0.509	0.634	0.75	-0.378	0.78
	-0.541	0.613	0.446	0.673	0.661	-0.291	0.556	0.644	0.762	-0.402	0.806
	0.557	0.666	0.454	0.716	0.726	-0.342	0.611	0.66	0.771	-0.484	-0.923
	0.558	0.909	0.909	0.871	0.871	-0.354	0.636	0.678	0.791	-0.604	0.999
M all corr	0.278	0.321	0.257	0.366	0.335	-0.053	0.223	0.277	0.340	-0.144	0.359
M sig corr only	0.312	0.359076923	0.337846154	0.391142857	0.365111111	0.31	0.326277778	0.3654	0.392346154	0.346941176	0.473407407

Table A-7 Pearson bivariate correlations of neuropsychological outcome measures (whole group)

	Trails Diff.	Trails Ratio	Digit Forward	Digit Backwards	DSST	Symbol Copy	Error Check	Coding Time (DSST)	Trails A	SRT	CRT
	-0.194	-0.068	-0.156	-0.151	-0.214	-0.156	-0.184	-0.218	-0.089	-0.160	-0.155
	-0.112	-0.044	-0.098	-0.088	-0.173	-0.152	-0.005	-0.208	-0.002	-0.117	-0.143
	0.010	-0.016	-0.069	-0.033	-0.024	-0.029	0.027	-0.180	0.033	-0.064	-0.097
	0.039	0.090	-0.054	0.000	-0.023	0.004	0.045	-0.156	0.066	-0.022	-0.091
	0.063	0.105	-0.052	0.005	0.122	0.107	1	-0.151	0.201	0.026	0.075
	1	1	0.011	0.056	1	1	-0.253	-0.113	1	0.031	0.158
	0.256	-0.248	0.071	0.084	0.254	0.232	0.26	-0.068	0.233	0.046	0.162
	0.306	-0.274	0.085	0.114	0.284	0.262	0.274	-0.025	0.246	0.085	0.164
	0.309	0.276	0.094	0.120	0.316	0.264	0.298	0.027	-0.291	0.102	0.171
	0.35	-0.289	0.107	0.184	0.346	0.298	0.31	0.063	0.307	0.114	0.207
	0.351	-0.312	0.113	0.191	-0.355	0.32	0.328	0.102	0.314	0.114	0.215
	0.359	-0.325	0.130	0.207	0.363	0.353	0.332	1	0.385	0.116	1
	-0.364	-0.325	0.131	0.215	0.413	-0.357	-0.333	-0.262	0.385	0.140	0.233
	0.4	-0.339	0.147	1	0.428	0.386	0.358	-0.267	-0.402	0.163	0.234
	0.411	-0.365	0.174	0.295	0.441	0.398	0.401	-0.268	0.413	0.177	0.238
	0.412	-0.367	0.207	0.297	0.471	0.424	0.402	0.269	0.421	0.185	0.257
	0.416	-0.367	0.217	0.304	0.477	0.432	-0.42	-0.291	0.423	0.187	0.277
	0.46	0.383	1	0.305	-0.48	0.483	0.433	-0.338	0.423	0.219	-0.339
	-0.481	-0.401	0.23	0.343	0.484	0.491	0.438	-0.348	0.456	1	0.358
	0.491	-0.401	0.232	0.353	0.489	0.509	0.459	-0.352	-0.48	-0.274	0.379
	0.502	-0.413	0.233	0.365	0.511	0.537	0.515	-0.355	0.481	0.306	-0.379
	0.52	-0.432	0.243	0.366	0.593	0.55	0.528	-0.379	0.508	0.317	0.39
	0.558	-0.469	0.245	-0.367	-0.622	-0.57	0.556	0.383	-0.526	0.352	0.402
	0.568	-0.493	-0.247	0.369	0.626	0.576	-0.617	-0.42	0.585	0.358	0.409
	0.647	-0.526	-0.248	0.402	0.636	0.611	0.645	-0.436	0.639	0.359	0.41
	0.66	-0.531	0.254	0.411	0.66	0.634	0.667	-0.447	0.716	0.366	0.412
	0.691	-0.541	0.256	0.413	0.672	0.702	0.678	-0.452	0.724	0.385	0.418
	0.702	-0.553	0.258	0.417	0.755	0.713	0.739	-0.48	0.726	0.387	0.423
	0.755	-0.57	0.28	0.445	0.768	0.724	0.762	-0.48	0.75	0.387	0.433
	0.766	-0.617	0.298	0.468	0.791	0.739	0.766	-0.481	0.781	0.428	0.477
	0.781	-0.622	0.305	0.476	0.799	0.771	0.78	-0.487	0.799	-0.447	0.491
	-0.937	-0.923	0.324	-0.484	0.83	0.83	0.814	-0.56	0.806	0.509	0.499
	0.999	-0.937	0.445	0.489	0.899	-0.888	0.899	-0.888	0.814	0.699	0.699
M all corr	0.354	-0.300	0.157	0.229	0.380	0.339	0.361	-0.220	0.359	0.196	0.254
M sig corr only	0.535259259	0.455518519	0.2732	0.387842105	0.438851852	0.386074074	0.393535714	-0.34947619	0.393925926	0.334285714	0.320047619

Appendix G. Correlation matrix for entire sample (including controls, MCI-LB and MCI-AD)

Table A-8 PCA 1 - Component Correlation Matrix (whole group; initial model)

Component	1	2	3	4	5
1	1.000	-.139	-.132	-.268	.515
2	-.139	1.000	.153	.165	-.156
3	-.132	.153	1.000	.015	-.070
4	-.268	.165	.015	1.000	-.349
5	.515	-.156	-.070	-.349	1.000

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

Tables A 8-9: Removal of SRT

Removed Simple Reaction time (not loading above threshold in either matrix):
KMO = .846

Pattern Matrix[a]

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.201	.829	-.008	-.137	-.010
RAVLT “Learning”	.027	.874	.026	.096	.027
RAVLT Short Delay	-.036	.723	-.050	-.215	.202
RAVLT Recognition B	-.029	.246	.031	-.855	-.130
ACE Visuospatial	.108	-.003	-.009	-.012	.777
Corsi	.091	-.075	-.187	-.683	.276
MTCF Recall	-.136	.168	.006	-.043	.865
VPT High	.230	.236	-.127	.045	.623
FAS	.840	-.071	-.120	.142	-.143
Stroop C	.837	.084	.506	.095	.115
Stroop CW	.703	.164	-.263	-.078	.023
Stroop Ratio Int.	-.122	-.041	.887	.165	.096
Trails Difference	.621	.067	-.115	-.184	.191
Digit Backwards	.153	.041	-.624	.245	.348
DSST	.802	.136	-.076	-.119	.070
Symbol Copy	.811	.065	-.039	-.181	-.003
Error Check	.784	.072	-.031	-.095	.126
Trails A	.645	.099	-.117	.007	.283
CRT	.294	-.239	.136	-.365	.400

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
Rotation converged in 12 iterations.

Structure Matrix

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.467	.918	-.200	-.374	.376
RAVLT “Learning”	.267	.863	-.129	-.124	.267
RAVLT Short Delay	.329	.832	-.208	-.442	.470
RAVLT Recognition B	.156	.396	-.034	-.866	.179
ACE Visuospatial	.489	.263	-.144	-.266	.833
Corsi	.390	.228	-.270	-.778	.529
MTCF Recall	.341	.395	-.121	-.311	.861
VPT High	.618	.498	-.304	-.253	.810
FAS	.745	.117	-.258	.014	.219
Stroop C	.789	.251	.302	-.112	.445
Stroop CW	.835	.439	-.448	-.289	.474
Stroop Ratio Int.	-.311	-.241	.915	.221	-.153
Trails Difference	.797	.367	-.296	-.396	.584
Digit Backwards	.413	.238	-.700	.065	.451
DSST	.917	.430	-.286	-.349	.546
Symbol Copy	.876	.349	-.232	-.372	.470
Error Check	.893	.365	-.234	-.320	.561
Trails A	.835	.389	-.312	-.246	.641
CRT	.469	.029	.037	-.483	.561

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Tables A 10-11: Removal of CRT

Removed CRT: KMO = .845

Pattern Matrix[a]

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.165	.860	-.022	-.044	-.110
RAVLT “Learning”	-.022	.900	.006	-.011	.106
RAVLT Short Delay	-.057	.756	-.060	.165	-.178
RAVLT Recognition B	.004	.200	.075	-.076	-.859
ACE Visuospatial	.134	-.067	.020	.804	-.042
Corsi	.136	-.141	-.137	.334	-.700
MTCF Recall	-.115	.122	.030	.875	-.057
VPT High	.230	.212	-.119	.618	.038
FAS	.831	-.108	-.112	-.117	.105
Stroop C	.847	.081	.501	.113	.102
Stroop CW	.692	.181	-.270	.007	-.059
Stroop Ratio Int.	-.099	-.062	.890	.111	.152
Trails Difference	.632	.030	-.095	.215	-.199
Digit Backwards	.127	.087	-.650	.294	.276
DSST	.802	.139	-.077	.065	-.106
Symbol Copy	.815	.079	-.042	-.011	-.157
Error Check	.790	.051	-.021	.139	-.101
Trails A	.646	.080	-.111	.286	.001

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

a. Rotation converged in 9 iterations.

Structure Matrix

	Component				
	1	2	3	4	5
RAVLT Max T1:T5	.470	.936	-.207	.395	-.374
RAVLT “Learning”	.269	.857	-.124	.296	-.143
RAVLT Short Delay	.330	.859	-.220	.483	-.430
RAVLT Recognition B	.163	.404	-.031	.198	-.890
ACE Visuospatial	.493	.296	-.159	.848	-.239
Corsi	.395	.257	-.282	.542	-.778
MTCF Recall	.344	.428	-.135	.876	-.284
VPT High	.619	.538	-.324	.821	-.223
FAS	.748	.128	-.263	.230	.015
Stroop C	.790	.310	.271	.424	-.040
Stroop CW	.835	.488	-.475	.470	-.255
Stroop Ratio Int.	-.310	-.244	.919	-.167	.249
Trails Difference	.801	.406	-.315	.592	-.374
Digit Backwards	.409	.273	-.723	.444	.093
DSST	.917	.488	-.318	.538	-.302
Symbol Copy	.874	.413	-.268	.451	-.317
Error Check	.895	.413	-.259	.560	-.283
Trails A	.836	.435	-.336	.643	-.211

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

BRANCH 1: remove VPT High first.

Tables A12-13: Following removal of Digit Backwards from Branch #1.

Pattern Matrix[a]

	Component		
	1	2	3
Rey_max_A1_A5	.171	.831	.087
RAVLT_Learning	.007	.911	-.146
Rey_T6	.036	.777	.212
Rey_recog_false_B_TRANSDIR_replaced	-.132	.164	.849
Corsi_TotalScore_TRANS_replaced	.254	-.106	.813
FASTotal_replaced	.821	-.180	-.110
stroop_C_items_replaced	.811	.052	-.189
stroop_CW_items_replaced	.778	.187	.029
Trails_difference_replaced	.745	.035	.251
DSST_orig_replaced	.853	.108	.120
DSST_copy_replaced	.825	.048	.115
DSST_error_replaced	.863	.039	.109
Trails_A_TRANS_replaced	.814	.119	.037

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
a. Rotation converged in 6 iterations.

Structure Matrix

	Component		
	1	2	3
Rey_max_A1_A5	.505	.925	.428
RAVLT_Learning	.303	.862	.175
Rey_T6	.386	.865	.495
Rey_recog_false_B_TRANSDIR_replaced	.175	.413	.869
Corsi_TotalScore_TRANS_replaced	.449	.273	.849
FASTotal_replaced	.722	.086	.064

stroop_C_items_replaced	.776	.287	.063
stroop_CW_items_replaced	.856	.486	.319
Trails_difference_replaced	.831	.400	.478
DSST_orig_replaced	.927	.466	.404
DSST_copy_replaced	.876	.394	.370
DSST_error_replaced	.909	.397	.371
Trails_A_TRANS_replaced	.869	.434	.314

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

BRANCH 2: remove Trails Difference first.

Tables A14-15: Following removal of Digit Backwards.

Pattern Matrix[a]

	Component		
	1	2	3
Rey_max_A1_A5	.240	.089	-.793
RAVLT_Learning	.076	-.084	-.915
Rey_recog_false_B_TRANSDIR_replaced	-.241	.669	-.305
ACE_VisSpat	.364	.609	.159
Corsi_TotalScore_TRANS_replaced	.055	.832	.040
MTCF_Recall_replaced	.152	.689	.014
FASTotal_replaced	.830	-.180	.079
stroop_C_items_replaced	.810	-.062	-.016
stroop_CW_items_replaced	.762	.100	-.178
DSST_orig_replaced	.815	.145	-.157
DSST_copy_replaced	.795	.129	-.087
DSST_error_replaced	.804	.173	-.074
Trails_A_TRANS_replaced	.756	.197	-.081

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
a. Rotation converged in 8 iterations.

Structure Matrix

	Component		
	1	2	3
Rey_max_A1_A5	.476	.472	-.887
RAVLT_Learning	.276	.281	-.903
Rey_recog_false_B_TRANSDIR_replaced	.097	.687	-.488
ACE_VisSpat	.561	.693	-.157
Corsi_TotalScore_TRANS_replaced	.369	.839	-.278
MTCF_Recall_replaced	.416	.743	-.277
FASTotal_replaced	.740	.114	-.066
stroop_C_items_replaced	.790	.259	-.200
stroop_CW_items_replaced	.847	.462	-.408
DSST_orig_replaced	.912	.520	-.417
DSST_copy_replaced	.867	.470	-.336
DSST_error_replaced	.890	.513	-.342
Trails_A_TRANS_replaced	.853	.521	-.346

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Tables A16-17: Final matching matrices of Branch 2.
KMO = .882, 3 components 74.61% cumulative, #1 explains 54.86%

Pattern Matrix[a]

	Component		
	1	2	3
Rey_max_A1_A5	.164	.899	-.033
RAVLT_Learning	-.008	.899	-.104
Rey_T6	-.057	.797	.213
ACE_VisSpat	.136	-.120	.820
Corsi_TotalScore_TRANS_replaced	.042	.001	.697
MTCF_Recall_replaced	-.120	.089	.875
VPT_High_correct_replaced	.262	.184	.594
FASTotal_replaced	.877	-.128	-.148
stroop_C_items_replaced	.789	-.002	-.018
stroop_CW_items_replaced	.723	.199	.089
DSST_orig_replaced	.815	.147	.112
DSST_copy_replaced	.812	.092	.071
DSST_error_replaced	.787	.049	.184
Trails_A_TRANS_replaced	.661	.063	.303

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
a. Rotation converged in 6 iterations.

Structure Matrix

	Component		
	1	2	3
Rey_max_A1_A5	.485	.946	.463
RAVLT_Learning	.276	.847	.305
Rey_T6	.348	.874	.551
ACE_VisSpat	.500	.308	.833
Corsi_TotalScore_TRANS_replaced	.390	.337	.719
MTCF_Recall_replaced	.350	.447	.856
VPT_High_correct_replaced	.627	.555	.809
FASTotal_replaced	.756	.133	.230
stroop_C_items_replaced	.779	.285	.374
stroop_CW_items_replaced	.842	.511	.541
DSST_orig_replaced	.926	.504	.586
DSST_copy_replaced	.882	.429	.518
DSST_error_replaced	.897	.428	.599
Trails_A_TRANS_replaced	.836	.450	.661

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

BRANCH 3: Trails A removed first.

Tables A18-19: Final matching matrices of Branch 3.

Pattern Matrix[a]

	Component			
	1	2	3	4
Rey_max_A1_A5	.186	.863	-.032	-.086
RAVLT_Learning	-.016	.895	-.056	.078
Rey_T6	-.036	.769	.192	-.153
Rey_recog_false_B_TRANSDIR_replaced	.032	.251	-.013	-.800
ACE_VisSpat	.141	-.080	.745	-.088
Corsi_TotalScore_TRANS_replaced	.171	-.091	.459	-.608
MTCF_Recall_replaced	-.103	.107	.838	-.085
VPT_High_correct_replaced	.235	.210	.638	.056
FASTotal_replaced	.837	-.121	-.049	.183
stroop_C_items_replaced	.850	-.003	-.130	-.029
stroop_CW_items_replaced	.730	.188	.093	.010
Trails_difference_replaced	.648	.038	.256	-.154
digitBack_replaced	.130	.134	.576	.467
DSST_orig_replaced	.819	.134	.104	-.052
DSST_copy_replaced	.841	.071	.012	-.116
DSST_error_replaced	.805	.040	.138	-.079

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.
a. Rotation converged in 16 iterations.

Structure Matrix

	Component			
	1	2	3	4
Rey_max_A1_A5	.500	.937	.419	-.270
RAVLT_Learning	.282	.852	.280	-.089
Rey_T6	.362	.863	.506	-.335
Rey_recog_false_B_TRANSDIR_replaced	.195	.416	.236	-.851
ACE_VisSpat	.494	.286	.799	-.210
Corsi_TotalScore_TRANS_replaced	.425	.276	.610	-.683
MTCF_Recall_replaced	.366	.420	.843	-.237
VPT_High_correct_replaced	.629	.540	.830	-.114
FASTotal_replaced	.750	.135	.293	.135
stroop_C_items_replaced	.787	.268	.301	-.088
stroop_CW_items_replaced	.846	.495	.533	-.113
Trails_difference_replaced	.806	.412	.623	-.266
digitBack_replaced	.424	.319	.616	.332
DSST_orig_replaced	.927	.491	.578	-.175
DSST_copy_replaced	.885	.411	.482	-.212
DSST_error_replaced	.897	.410	.572	-.187

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

TABLE A-20 Component Transformation Matrix of PCA#1 – Whole group optimised model

Component	1	2	3
1	.835	.439	.331
2	-.548	.707	.447
3	-.038	-.555	.831

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

Table 1 PCA 1: Optimised Model Total Variance explained by component (whole group)

	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	7.13	54.84	54.842	5.52	42.48	42.48
2	1.81	13.94	68.777	2.61	20.05	62.52
3	1.07	8.21	76.988	1.88	14.47	76.99
4	0.59	4.53	81.519			
5	0.55	4.22	85.738			
6	0.42	3.20	88.936			
7	0.37	2.82	91.752			
8	0.29	2.26	94.010			
9	0.25	1.93	95.938			
10	0.19	1.49	97.431			
11	0.17	1.32	98.752			
12	0.09	0.70	99.447			
13	0.07	0.55	100.000			

Extraction Method: Principal Component Analysis.

Appendix H Principle Components Analysis conducted on control subsample only.

PCA #2 – Controls

Table A-21 PCA 2 - Pearson bivariate correlations of neuropsychological outcome measures (controls)

	ACE Lang.	RAVLT Max T1:T6	RAVLT Learning	Rey Short Delay	Rey Long Delay	RAVLT % Max at Long Delay	RAVLT % "Forgetting"	RAVLT Retro. Int.	RAVLT Proact. Int.	RAVLT Recog. B	ACE Visuospatial
	-0.232	-0.327	-0.246	-0.337	-0.326	-0.299	-0.344	-0.344	-0.337	-0.293	-0.259
	-0.189	-0.322	-0.107	-0.188	-0.117	-0.225	-0.289	-0.272	-0.293	-0.188	-0.109
	-0.162	-0.227	-0.107	-0.065	-0.040	-0.189	-0.275	-0.098	-0.272	-0.188	-0.094
	-0.117	-0.223	-0.098	0.088	-0.026	-0.133	-0.161	-0.090	-0.239	-0.186	-0.087
	-0.068	0.066	-0.096	0.130	0.014	-0.076	-0.153	-0.058	-0.227	-0.185	-0.049
	-0.052	0.080	-0.076	0.177	0.019	-0.062	-0.147	-0.025	-0.213	-0.178	0.001
	-0.040	0.100	-0.065	0.187	0.133	-0.037	-0.141	-0.025	-0.211	-0.154	0.024
	-0.039	0.159	-0.038	0.193	0.146	-0.007	-0.116	-0.008	-0.204	-0.153	0.030
	-0.025	0.176	-0.019	0.211	0.156	0.018	-0.112	0.011	-0.183	-0.141	0.035
	-0.013	0.205	0.003	0.213	0.169	0.048	-0.094	0.013	-0.139	-0.141	0.043
	0.017	0.210	0.041	0.228	0.177	0.055	-0.061	0.022	-0.126	-0.140	0.070
	0.028	0.221	0.062	0.247	0.190	0.056	-0.060	0.029	-0.108	-0.137	0.091
	0.035	0.223	0.158	0.251	0.195	0.056	-0.040	0.035	-0.095	-0.111	0.118
	0.070	0.255	0.165	0.264	0.196	0.093	-0.032	0.039	-0.090	-0.096	0.121
	0.117	0.263	0.181	0.277	0.202	0.096	-0.031	0.040	-0.088	-0.064	0.121
	0.128	0.277	0.187	0.283	0.207	0.121	0.002	0.046	-0.077	-0.022	0.123
	0.130	0.277	0.190	0.288	0.231	0.133	0.025	0.066	-0.054	-0.017	0.136
	0.159	0.295	0.198	0.289	0.235	0.138	0.038	0.079	-0.049	0.035	0.158
	0.208	0.306	0.218	0.306	0.239	0.158	0.044	0.096	-0.037	0.128	0.199
	0.220	0.344	0.231	0.323	0.246	0.185	0.147	0.118	-0.024	0.136	0.220
	0.225	1	0.234	0.327	0.251	0.186	0.165	0.126	0.060	0.167	0.231
	0.238	0.433	0.246	0.334	0.285	0.241	0.190	0.169	0.082	0.184	0.234
	0.242	0.438	0.261	0.351	0.354	0.264	0.208	0.177	0.095	0.189	0.234
	0.244	-0.446	0.283	1	1	0.332	0.351	0.189	0.096	0.205	0.251
	0.252	0.449	0.313		0.398	1	1	0.235	0.158	0.242	0.252
	0.269	0.454	0.316	0.396		-0.422	0.356	0.277	0.197	0.323	0.255
	0.308	0.465	0.334	-0.408	-0.442	-0.477	-0.446	0.310	0.199	0.335	0.261
	0.317	0.468	1		-0.451	0.481	0.515	0.313	0.317	1	0.277
	0.327	0.481	0.359	0.482	0.47	0.49	-0.55	0.332	1	0.41	0.313
	0.332	0.506		-0.631	0.825	0.552		1	-0.442	-0.44	1
	0.343	0.529	-0.38	0.67	0.835	0.67	-0.631	0.431	-0.477	0.47	0.395
	1	0.783	0.506	0.783	-0.849	0.88	-0.849	0.508	0.508	0.552	0.401
	0.364	0.825	0.508	0.835	0.88	-0.985	-0.985	0.515	0.515	-0.553	0.443
Mean all corr	0.140	0.265	0.155	0.252	0.188	0.101	-0.092	0.129	-0.023	0.030	0.165
Mean sig corr only	0.364	0.523083333	0.423	0.559	0.616777778	0.619625	0.610625	0.484666667	0.4855	0.485	0.413

	Corsi	MTCF Recall	MTCF % Retain	VPT High	VPT Low	VPT Ratio	FAS	Stroop C	Stroop CW	Stroop Ratio Int.	Trails B
	-0.274	-0.212	-0.175	-0.201	-0.279	-0.288	-0.211	-0.225	-0.266	-0.350	-0.237
	-0.204	-0.161	-0.141	-0.188	-0.275	-0.213	-0.203	-0.138	-0.178	-0.339	-0.188
	-0.168	-0.108	-0.139	-0.154	-0.231	-0.179	-0.153	-0.105	-0.147	-0.322	-0.126
	-0.153	-0.094	-0.082	-0.133	-0.195	-0.154	-0.107	-0.049	-0.088	-0.304	-0.077
	-0.138	-0.017	-0.039	-0.090	-0.095	-0.105	-0.097	-0.036	-0.025	-0.279	-0.060
	-0.052	-0.013	-0.022	0.017	-0.038	-0.101	-0.062	0.014	0.017	-0.274	0.029
	-0.037	0.020	0.021	0.019	-0.036	-0.068	-0.046	0.020	0.053	-0.241	0.056
	-0.019	0.063	0.064	0.035	0.056	-0.065	-0.033	0.022	0.118	-0.237	0.064
	0.017	0.151	0.110	0.085	0.069	-0.037	-0.026	0.043	0.154	-0.216	0.156
	0.039	0.155	0.133	0.089	0.077	-0.003	-0.003	0.064	0.155	-0.212	0.172
	0.056	0.156	0.146	0.095	0.117	0.021	0.030	0.085	0.179	-0.201	0.176
	0.062	0.158	0.154	0.147	0.184	0.024	0.038	0.096	0.184	-0.187	0.207
	0.070	0.181	0.173	0.177	0.184	0.049	0.069	0.125	0.185	-0.179	0.228
	0.093	0.194	0.185	0.189	0.199	0.053	0.070	0.190	0.219	-0.175	0.252
	0.095	0.204	0.198	0.191	0.223	0.063	0.080	0.193	0.246	-0.145	0.252
	0.133	0.210	0.209	0.217	0.234	0.064	0.088	0.219	0.246	-0.141	0.283
	0.145	0.227	0.221	0.219	0.239	0.075	0.089	0.222	0.305	-0.109	0.316
	0.176	0.231	0.225	0.220	0.241	0.090	0.096	0.224	1	-0.065	1
	0.176	0.237	0.236	0.228	0.272	0.100	0.183	0.231	0.356	-0.046	0.386
	0.178	0.264	0.247	0.240	0.277	0.111	0.209	0.308	0.398	-0.008	0.438
	0.179	0.284	0.307	0.248	0.289	0.159	0.231	0.311	0.426	0.042	0.474
	0.186	0.306	0.313	0.255	0.290	0.185	0.332	0.344	-0.475	0.199	0.502
	0.195	0.311	0.314	0.263	0.340	0.251	0.333	0.354	0.482	0.224	0.509
	0.198	1	0.347	1	0.347	0.288	0.338	1	0.501	0.269	0.509
	0.211	0.392	1	-0.358	0.349	0.304	1	-0.358	0.529	1	0.512
	0.233	0.418	0.359	0.359	1	0.310	0.356	-0.44	0.542	0.356	0.529
	0.251		0.401	0.365	0.367	0.354	0.361	0.456	0.553	-0.408	0.573
	0.307	0.482	0.432	0.432	0.386	1	0.366	0.467	0.573	-0.422	0.581
	0.311	-0.489	-0.494	0.465	0.411	-0.38	-0.406	0.483	0.616	-0.451	0.615
	0.335	0.502		0.474	0.418	0.41	0.467	0.501	0.641		0.628
	1	0.51	0.509	0.482		0.49	0.506		0.68	0.506	0.691
		0.515	0.516	0.582	0.633	-0.55	0.512	0.529	-0.721	-0.598	-0.839
		0.985	0.985	0.649	0.649	0.633	0.563	0.53	0.77	-0.721	0.997
Mean all corr	0.137	0.227	0.219	0.201	0.216	0.088	0.151	0.188	0.249	-0.136	0.291
Mean sig corr only	0.4675	0.526222222	0.5255	0.462888889	0.469285714	0.4926	0.442125	0.475444444	0.550866667	0.48975	0.585533333

	Trails Diff.	Trails Ratio	Digit Forward	Digit Backwards	DSST	Symbol Copy	Error Check	Coding Time (DSST)	Trails A	SRT	CRT
	-0.216	-0.327	-0.239	-0.241	-0.350	-0.289	-0.304	-0.326	-0.339	-0.232	-0.203
	-0.186	-0.266	-0.226	-0.141	-0.140	-0.229	-0.252	-0.299	-0.176	-0.112	-0.196
	-0.116	-0.259	-0.145	-0.065	-0.058	-0.183	-0.185	-0.288	-0.137	-0.097	-0.187
	-0.090	-0.252	-0.140	-0.037	-0.054	-0.117	-0.040	-0.231	-0.109	-0.064	-0.126
	-0.061	-0.246	-0.111	-0.029	-0.032	-0.107	-0.037	-0.223	-0.031	0.005	-0.116
	0.013	-0.229	-0.101	-0.024	0.011	-0.090	0.011	-0.196	0.048	0.041	-0.087
	0.049	-0.226	-0.058	0.040	0.056	0.035	0.096	-0.188	0.070	0.046	-0.019
	0.055	-0.195	0.001	0.044	0.091	0.121	0.123	-0.176	0.082	0.060	0.028
	0.139	-0.168	0.002	0.095	0.111	0.133	0.159	-0.154	0.093	0.090	0.093
	0.164	-0.162	0.003	0.177	0.158	0.173	0.177	-0.140	0.169	0.110	0.118
	0.178	-0.117	0.018	0.217	0.167	0.194	0.187	-0.126	0.169	0.138	0.125
	0.202	-0.109	0.070	0.220	0.185	0.217	0.225	-0.116	0.175	0.139	0.158
	0.213	-0.087	0.077	0.276	0.198	0.250	0.228	-0.094	0.185	0.145	0.164
	0.242	-0.065	0.133	0.283	0.204	0.264	0.232	-0.090	0.218	0.150	0.167
	0.261	-0.007	0.150	0.311	0.225	0.270	0.233	-0.087	0.226	0.151	0.172
	0.277	-0.001	0.183	0.338	0.248	0.288	0.237	-0.082	0.227	0.156	0.175
	0.313	0.005	0.187	0.343	0.251	0.327	0.238	-0.058	0.236	0.219	0.191
	1	0.025	0.189	0.348	0.271	0.340	0.285	-0.049	0.244	0.234	0.196
	0.367	0.042	0.222	0.349	0.272	0.354	0.287	-0.033	0.260	0.234	0.217
	0.433	0.075	0.226	1	0.278	1	0.290	-0.029	0.277	0.240	0.232
	0.465	0.079	0.255	0.359	0.306	0.361	0.333	-0.019	0.306	0.246	0.242
	0.482	0.158	0.270	0.368	1	0.368	0.351	-0.001	1	0.260	0.246
	0.506	0.167	0.271	0.392	-0.386	0.401	1	0.011	0.365	0.276	0.250
	0.51	1	0.277	0.396	0.465	0.449	0.403	0.126	0.366	0.278	0.277
	0.515	-0.358	0.283	0.403	0.53	0.482		0.197	0.405	0.287	0.283
	0.516	-0.358	0.304	0.405	0.563	0.485	0.454	0.261	0.411	0.288	0.284
	0.542	-0.386	0.305	0.426	0.582	0.509	0.483	0.327	0.456	0.295	0.304
	0.563	-0.406	0.306	0.468	0.64		0.485	0.351	0.562	0.353	0.304
	0.573	-0.468	0.314	-0.468	0.659	0.562	0.573	1	0.563	1	0.313
	0.574	-0.489	0.348	0.574	0.68	-0.598	0.615	-0.475	0.628	-0.456	0.353
	0.659	-0.494	1	0.581	0.691	0.64	0.616		0.641	-0.491	1
	-0.88	-0.839	0.406	0.582	0.715	0.77	0.765	0.506	0.715	0.544	0.421
	0.997	-0.88	0.448	0.582	0.828	-0.804	0.828	-0.804	0.765	0.553	0.487
Mean all corr	0.281	-0.177	0.158	0.260	0.284	0.216	0.288	-0.061	0.275	0.154	0.178
Mean sig corr only	0.572133333	0.519777778	0.427	0.461846154	0.612636364	0.536384615	0.5628	0.569	0.534272727	0.511	0.454

Table A-22 PCA 2 Varimax initial model total variance explained by component (controls)

	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	5.21	47.35	47.35	3.42	31.06	31.06
2	1.65	15.01	62.36	2.66	24.16	55.22
3	1.02	9.29	71.65	1.81	16.43	71.65
4	0.81	7.39	79.03			
5	0.61	5.57	84.60			
6	0.45	4.10	88.70			
7	0.40	3.60	92.31			
8	0.30	2.70	95.00			
9	0.24	2.15	97.15			
10	0.17	1.51	98.66			
11	0.15	1.34	100.00			

Extraction Method: Principal Component Analysis.

Table A-23. PCA #2 (controls) – Initial Varimax rotation Component Transformation Matrix

Component	1	2	3
1	.736	.532	.419
2	-.449	.846	-.286
3	-.506	.022	.862

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

Table A-24 PCA 2 - Varimax initial model communalities (controls)

	Initial	Extraction
RAVLT Max T1:T5	1.000	.648
MTCF Recall	1.000	.620
VPT High	1.000	.796
VPT Low	1.000	.651
FAS	1.000	.845
Stroop CW	1.000	.821
Trails B	1.000	.766
Digit Backwards	1.000	.580
DSST	1.000	.824
Symbol Copy	1.000	.706

Trails A	1.000	.624

Extraction Method: Principal Component Analysis.

Table A-25 PCA 2 - Varimax rotated component matrix (controls; initial model)

	Component		
	1	2	3
RAVLT Max T1:T5	.745	.237	-.192
MTCF Recall	-.024	.732	.290
VPT High	.161	.878	-.013
VPT Low	.210	.776	-.065
FAS	.177	.043	.901
Stroop CW	.872	.053	.239
Trails B	.500	.490	.526
Digit Backwards	.432	.573	.257
DSST	.719	.167	.529
Symbol Copy	.803	.114	.220
Trails A	.633	.283	.378

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization, converged in 4 iterations.

Table A-26 PCA 2 – Initial Oblimin Rotation Component Correlation Matrix (controls)

Component	1	2	3
1	1.000	.368	.250
2	.368	1.000	.161
3	.250	.161	1.000

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

Table A-27 PCA 2 – Initial Oblimin Rotation Pattern Matrix (controls)

	Component		
	1	2	3
RAVLT Max T1:T5	.770	.113	-.362
MTCF Recall	-.178	.776	.227
VPT High	.008	.901	-.130
VPT Low	.083	.785	-.182
FAS	.142	-.005	.874

Stroop CW	.923	-.114	.068
Trails B	.425	.415	.388
Digit Backwards	.348	.521	.120
DSST	.722	.031	.380
Symbol Copy	.837	-.036	.056
Trails A	.615	.172	.233

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization, converged in 11 iterations.

Table A-28 PCA 2 – Initial Oblimin Rotation Structure Matrix (controls)

	Component		
	1	2	3
RAVLT Max T1:T5	.721	.338	-.151
MTCF Recall	.164	.747	.307
VPT High	.307	.883	.017
VPT Low	.326	.786	-.035
FAS	.359	.188	.909
Stroop CW	.898	.236	.281
Trails B	.674	.633	.561
Digit Backwards	.569	.668	.291
DSST	.828	.357	.565
Symbol Copy	.838	.281	.259
Trails A	.736	.436	.414

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Table A-29 PCA 2 - Oblimin final model pattern matrix (controls).

	Component	
	1	2
MTCF Recall	-.048	.763
VPT High	.003	.872
VPT Low	.074	.819
Stroop CW	.935	-.110
DSST	.873	.001
Symbol Copy	.865	-.005
Trails A	.771	.176

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization, converging in 4 iterations.

Given that neither Trails B nor Digit Backwards loaded above the threshold in either model (although Trails B in particular loaded moderately on the three components), each was iteratively removed. If Digit Backwards is first removed, Trails B remains loading similarly moderately but below the conservative threshold. Therefore, Trails B was removed first, followed by Digit Backwards. In the resulting model, two components were retained. Neither components loaded onto FAS nor RAVLT Max T1:T5 above the threshold. Removal of these variables results in the same model regardless of which is removed first.

Table A-30. PCA #2: Control (Oblimin) final model structure matrix.

	Component	
	1	2
MTCF Recall	.203	.747
VPT High	.291	.873
VPT Low	.344	.844
Stroop CW	.899	.199
DSST	.873	.289
Symbol Copy	.863	.281
Trails A	.829	.430

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Table A-31. PCA #2: Control (Oblimin) final model component correlation matrix.

Component	1	2
1	1.000	.330
2	.330	1.000

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

Table A-32 PCA 2 - Final Varimax model rotated component matrix (controls)

	Component	
	1	2
MTCF Recall	.079	.744
VPT High	.147	.860
VPT Low	.209	.821
Stroop CW	.903	.050
DSST	.861	.149
Symbol Copy	.851	.141
Trails A	.789	.303

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization, converged in 3 iterations.

Table A-33 PCA 2 - Final optimised model communalities (controls)

	Initial	Extraction
MTCF Recall	1.000	.560
VPT High	1.000	.762
VPT Low	1.000	.717
Stroop CW	1.000	.818
DSST	1.000	.763
Symbol Copy	1.000	.745
Trails A	1.000	.715

Extraction Method: Principal Component Analysis.

Table A-34 PCA 2 – final model's total variance explained (controls).

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadingsa
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	3.531	50.441	50.441	3.531	50.441	50.441	3.247
2	1.549	22.129	72.569	1.549	22.129	72.569	2.419
3	.630	8.993	81.563				
4	.481	6.871	88.433				
5	.374	5.337	93.770				
6	.268	3.828	97.598				
7	.168	2.402	100.000				

Extraction Method: Principal Component Analysis.
a. When components are correlated, sums of squared loadings cannot be added to obtain a total variance.

Appendix I. Principle Components Analysis conducted on MCI-LB subsample only.

MCI-LB Probable had higher mean significant Pearson correlation values than controls and the group overall (0.529). The significant loadings were all above 0.300. Variables were moved for having very few significant correlations: ACE Language (2), RAVLT Percent Forgetting (3), RAVLT Proactive Interference (2), RAVLT B Recognition (2), Digit Forward (2), Digit Backwards (2), MTCF Percent Retained (4), VPT Ratio (4). After removal of these variable, RAVLT Retroactive only had three significant correlations and was remove. Of the remaining variables, very high correlations (r > .8) were observed between thirteen pairs of outcome measures (see Appendices). In order to remove these high correlations while minimizing removal of variables, RAVLT Learning, VPT Low, Trails Ratio, Trails Difference, Error Check, DSST Coding Time, and SRT were removed. The remaining high correlations between Stroop C-TrailsA, Trails A-DSST, and Stroop C-DSST were retained due to the variables' high number of correlations with other variables that were within the target range. This resulted in 17 variables for entry into the PCA.

After removal of these variable, RAVLT Retroactive only had three significant correlations and was remove. Of the remaining variables, very high correlations (r > .8) were observed between thirteen pairs of outcome measures (see Appendices).

RAVLT Max and Learning
VPT High and VPT Low
Stroop CW and DSST Original
Stroop CW and Error Check
Stroop CW and Trails A
Trails A and DSST
Trails A and Error Check
Trails B and Trails Ratio
Trails B and Trails Difference
Trails Ratio and Trails Difference
DSST and Error Check
Symbol Copy and DSST Coding Time
Simple Reaction Time and **Choice Reaction Time**

Deletion of RAVLT Learning, VPT Low, Trails Ratio, Trails Difference, Error Check, DSST Coding Time, and SRT. The remaining high correlations, between Stroop C-TrailsA, Trails A-DSST, and Stroop C-DSST were retained due to the high number of correlations in the target range with other variables. This resulted in 17 variables for entry into the PCA. The

Table A-35 PCA 3 - Pearson bivariate correlations of neuropsychological outcome measures (MCI-LB Probable)

	ACE Lang.	RAVLT Max T1:T6	RAVLT Learning	Rey Short Delay	Rey Long Delay	RAVLT % Max at Long Delay	RAVLT % "Forgetting"	RAVLT Retro. Int.	RAVLT Proact. Int.	RAVLT Recog. B	ACE Visuospatial
	-0.348	-0.291	-0.277	-0.307	-0.293	-0.297	-0.333	-0.219	-0.297	-0.288	-0.298
	-0.257	-0.286	-0.274	-0.237	-0.239	-0.296	-0.316	-0.185	-0.293	-0.254	-0.218
	-0.254	-0.167	-0.142	-0.193	-0.117	-0.158	-0.307	-0.181	-0.197	-0.189	-0.204
	-0.238	-0.157	-0.116	-0.110	-0.105	-0.092	-0.288	-0.169	-0.179	-0.148	-0.118
	-0.077	-0.156	-0.017	-0.090	-0.012	-0.067	-0.206	-0.157	-0.156	-0.130	-0.092
	-0.008	-0.110	-0.015	-0.034	0.004	-0.066	-0.197	-0.157	-0.147	-0.117	-0.025
	0.099	-0.008	0.004	0.055	0.024	-0.044	-0.175	-0.106	-0.132	-0.041	-0.005
	0.113	0.032	0.006	0.066	0.055	-0.036	-0.174	-0.101	-0.117	-0.018	0.054
	0.134	0.044	0.084	0.113	0.077	-0.033	-0.157	-0.083	-0.108	-0.008	0.064
	0.138	0.054	0.093	0.130	0.119	-0.026	-0.128	-0.066	-0.099	-0.001	0.081
	0.143	0.081	0.094	0.144	0.145	-0.015	-0.118	-0.065	-0.097	0.047	0.113
	0.145	0.101	0.109	0.198	0.174	0.024	-0.046	-0.039	-0.057	0.071	0.147
	0.149	0.109	0.130	0.216	0.178	0.050	0.039	-0.038	-0.048	0.081	0.151
	0.175	0.147	0.167	0.221	0.187	0.051	0.041	-0.031	-0.046	0.090	0.163
	0.182	0.165	0.213	0.300	0.205	0.058	0.062	-0.029	-0.037	0.092	0.174
	0.183	0.169	0.231	0.302	0.241	0.062	0.065	-0.008	-0.036	0.093	0.231
	0.184	0.219	0.256	0.309	0.246	0.081	0.065	0.043	-0.025	0.114	0.256
	0.209	0.246	0.289	0.312	0.246	0.107	0.066	0.054	-0.022	0.116	0.312
	0.219	0.281	0.296	0.333	0.253	0.107	0.099	0.056	-0.011	0.130	0.342
	0.237	0.337	0.339	0.338	0.255	0.111	0.103	0.061	0.012	0.135	0.347
	0.239	0.338	0.345	0.340	0.257	0.116	0.110	0.079	0.014	0.140	1
	0.256	0.360	0.347	0.358	0.264	0.143	0.146	0.093	0.024	0.171	0.364
	0.262	0.360	1	1	0.278	0.163	0.149	0.114	0.054	0.184	0.374
	0.265	1	0.371	0.406	0.304	0.203	0.165	0.115	0.144	0.228	0.377
	0.268	0.366	0.378	0.41	1	0.204	0.197	0.154	0.167	0.237	0.437
	0.303	0.412	-0.381	0.439	0.364	0.264	0.241	0.187	0.184	0.257	0.451
	0.304	0.426	0.418	0.466	0.382	1	0.296	0.240	0.265	0.264	0.482
	0.315	0.495	0.435	0.467	0.417	0.39	0.302	1	0.266	0.330	0.51
	0.338	0.532	0.467	0.472	0.472	0.432	0.333	-0.381	0.285	0.337	0.534
	0.338	0.57	0.472	-0.485	-0.503	0.466	1	0.39	0.333	0.337	0.654
	1	0.655	0.472	0.523	0.655	0.484	-0.503	0.467	1	1	0.664
	0.368	0.736	0.501	0.736	0.763	0.763	-0.565	-0.512	-0.485	-0.376	0.669
	0.46	0.824	0.824	0.797	0.797	-0.881	-0.881	-0.565	-0.512	0.401	0.672
Mean all corr	0.177	0.239	0.216	0.242	0.215	0.099	-0.028	-0.001	-0.011	0.100	0.263
Mean sig corr only	0.414	0.557333333	0.4719	0.5201	0.544125	0.569333333	0.649666667	0.463	0.4985	0.3885	0.515666667

Table A-35 PCA 3 - Pearson bivariate correlations of neuropsychological outcome measures (MCI-LB Probable)

	Corsi	MTCF Recall	MTCF % Retain	VPT High	VPT Low	VPT Ratio	FAS	Stroop C	Stroop CW	Stroop Ratio Int.	Trails B
	-0.259	-0.316	-0.333	-0.269	-0.326	-0.341	-0.296	-0.349	-0.307	-0.356	-0.213
	-0.185	-0.146	-0.124	-0.258	-0.231	-0.335	-0.219	-0.162	-0.108	-0.338	-0.066
	0.039	-0.138	-0.097	-0.039	-0.132	-0.307	-0.217	-0.157	-0.106	-0.291	-0.065
	0.051	-0.103	-0.048	-0.022	-0.083	-0.213	-0.212	-0.120	0.024	-0.238	-0.057
	0.066	-0.099	-0.046	0.047	0.041	-0.204	-0.168	-0.029	0.066	-0.218	0.042
	0.070	-0.077	-0.031	0.058	0.043	-0.198	-0.148	-0.026	0.119	-0.212	0.050
	0.071	-0.063	-0.009	0.065	0.050	-0.197	-0.124	0.014	0.142	-0.209	0.146
	0.094	0.060	0.001	0.083	0.065	-0.185	-0.117	0.138	0.184	-0.193	0.221
	0.109	0.090	0.006	0.230	0.071	-0.169	-0.077	0.163	0.241	-0.175	0.237
	0.119	0.093	0.012	0.233	0.128	-0.168	-0.034	0.166	0.264	-0.128	0.246
	0.126	0.109	0.028	0.235	0.136	-0.162	0.064	0.204	0.300	-0.116	0.288
	0.143	0.147	0.041	0.262	0.149	-0.154	0.086	0.228	0.315	-0.105	0.307
	0.154	0.153	0.041	0.274	0.278	-0.146	0.119	0.255	0.340	-0.063	0.309
	0.163	0.211	0.042	0.310	0.289	-0.110	0.128	0.281	1	-0.001	0.330
	0.205	0.219	0.065	1	0.349	-0.110	0.149	0.294	0.371	0.061	0.331
	0.209	0.246	0.097	0.364	1	-0.083	0.152	0.300	0.378	0.074	0.339
	0.265	0.274	0.101	-0.376	0.388	-0.077	0.213	0.333	-0.387	0.107	0.345
	0.317	0.288	0.106	0.429	0.406	-0.046	0.219	1	0.426	0.165	1
	0.332	0.296	0.119	0.435	0.412	-0.017	0.241	0.371	0.43	0.166	0.366
	0.332	0.314	0.135	0.465	0.425	-0.011	0.265	0.425	0.437	0.208	0.374
	0.344	1	0.165	0.474	-0.433	0.041	0.268	-0.441	-0.478	0.233	-0.384
	1	0.41	0.175	0.485	0.439	0.052	0.274	0.451	0.484	0.263	-0.454
	0.377	0.417	0.198	-0.487	0.44	0.055	0.285	0.465	0.534	0.266	0.506
	0.386	0.418	0.233	0.506	-0.53	0.070	0.318	0.487	-0.597	0.271	0.542
	0.388	0.429	0.250	0.523	0.541	0.088	0.326	0.525	0.654	1	0.542
	0.401	0.432	0.256	0.57	0.561	0.111	0.331	0.542	0.664	-0.376	0.561
	-0.416	0.437	0.294	0.654	0.605	0.171	0.333	0.555	0.665	-0.376	0.647
	0.429	0.438	0.344	0.654	0.627	0.271	1	0.625	0.675	-0.384	0.719
	0.438	0.487	1	0.66	0.658	1	0.425	0.644	0.7	-0.397	0.732
	0.484	0.605	0.382	0.676	0.665	-0.379	0.43	0.65	0.719	-0.416	0.737
	-0.503	0.664	0.392	0.689	0.672	0.392	-0.455	0.675	0.806	-0.433	0.756
	0.542	0.689	0.484	0.709	0.7	-0.487	0.51	0.712	0.809	-0.475	-0.895
	0.544	0.76	0.76	0.905	0.905	-0.53	0.552	0.761	0.883	-0.597	0.999
Mean all corr	0.207	0.265	0.153	0.320	0.282	-0.072	0.140	0.302	0.323	-0.099	0.289
Mean sig corr only	0.446181818	0.5155	0.5045	0.558944444	0.553352941	0.447	0.4744	0.555266667	0.584052632	0.43175	0.614266667

Table A-35 PCA 3 - Pearson bivariate correlations of neuropsychological outcome measures (MCI-LB Probable)

	Trails Diff.	Trails Ratio	Digit Forward	Digit Backwards	DSST	Symbol Copy	Error Check	Coding Time (DSST)	Trails A	SRT	CRT
	-0.198	-0.349	-0.189	-0.197	-0.356	-0.209	-0.338	-0.348	-0.179	-0.197	-0.209
	-0.067	-0.326	-0.181	-0.170	-0.341	-0.185	-0.335	-0.298	-0.038	-0.170	-0.197
	-0.066	-0.286	-0.158	-0.169	-0.169	-0.157	-0.147	-0.277	-0.036	-0.150	-0.154
	-0.048	-0.274	-0.128	-0.154	-0.037	-0.092	-0.101	-0.259	0.000	-0.128	-0.129
	0.041	-0.269	-0.083	-0.142	-0.033	-0.009	-0.026	-0.258	0.041	-0.097	0.012
	0.052	-0.257	-0.079	-0.130	0.001	0.054	0.032	-0.231	0.062	-0.041	0.028
	0.149	-0.239	-0.072	-0.129	0.105	0.098	0.065	-0.206	0.134	0.014	0.054
	0.217	-0.237	-0.026	-0.120	0.110	0.111	0.097	-0.167	0.140	0.044	0.084
	0.239	-0.217	-0.005	-0.044	0.187	0.116	0.145	-0.103	0.178	0.071	0.086
	0.246	-0.209	0.000	-0.041	0.237	0.119	0.149	-0.097	0.230	0.077	0.092
	0.274	-0.174	0.004	0.024	0.253	0.197	0.263	-0.090	0.318	0.116	0.106
	0.293	-0.154	0.004	0.028	0.265	0.211	0.264	-0.072	0.333	0.130	0.143
	0.302	-0.150	0.014	0.032	0.314	0.221	0.309	-0.041	0.347	0.144	0.145
	0.326	-0.138	0.024	0.060	0.332	0.332	0.317	-0.018	0.360	0.144	0.183
	0.328	-0.092	0.028	0.079	0.358	0.337	0.337	-0.012	1	0.152	0.203
	0.337	-0.079	0.032	0.103	1	1	1	0.012	-0.379	0.153	0.208
	0.339	-0.048	0.050	0.111	0.446	0.368	0.406	0.052	0.386	0.154	0.216
	0.347	-0.036	0.052	0.113	-0.453	0.418	-0.417	0.074	-0.39	0.182	0.240
	0.360	0.041	0.055	0.126	-0.471	0.437	0.418	0.107	-0.397	0.230	0.296
	1	0.056	0.083	0.136	0.472	-0.438	0.425	0.115	0.414	0.233	0.309
	-0.376	0.062	0.088	0.149	0.495	0.44	0.467	0.322	0.42	0.263	0.310
	-0.446	0.263	0.098	0.151	0.501	0.474	0.482	1	0.429	0.293	0.328
	0.485	0.322	0.105	0.187	0.51	0.509	-0.482	-0.387	-0.447	0.300	0.339
	0.525	1	0.142	0.217	0.51	0.523	0.532	-0.417	0.644	0.307	0.342
	0.541	-0.376	0.147	0.221	0.627	0.552	0.658	-0.435	0.669	0.349	1
	0.544	-0.39	0.149	0.230	0.66	0.632	0.695	-0.439	0.676	1	0.371
	0.632	-0.438	0.154	0.235	0.711	0.647	0.709	-0.441	0.691	0.364	0.406
	0.7	-0.471	0.169	0.264	0.732	0.65	0.712	-0.446	0.7	0.42	0.414
	0.711	-0.478	0.250	0.265	0.761	0.664	0.718	-0.447	0.726	-0.435	-0.439
	0.718	-0.482	0.302	0.303	0.763	0.691	0.737	-0.453	0.756	0.446	0.472
	0.726	-0.503	1	1	0.845	0.695	0.809	-0.454	0.806	0.509	0.523
	-0.913	-0.895	0.46	-0.475	0.883	0.763	0.833	-0.455	0.833	0.555	0.625
	0.999	-0.913	0.587	0.587	0.904	-0.922	0.904	-0.922	0.845	0.914	0.914
Mean all corr	0.282	-0.204	0.093	0.086	0.337	0.280	0.322	-0.185	0.311	0.192	0.222
Mean sig corr only	0.639692308	0.549555556	0.5235	0.531	0.632	0.577823529	0.612	0.481454545	0.589333333	0.520428571	0.5205

PCA #3 - Removal steps

Table A-36 PCA 3 - Varimax initial model, total variance explained (MCI-LB Probable)

	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	7.13	47.52	47.52	3.91	26.07	26.07
2	2.16	14.43	61.94	3.01	20.06	46.13
3	1.48	9.87	71.82	2.83	18.87	64.99
4	1.13	7.50	79.32	2.15	14.33	79.32
5	0.78	5.22	84.54			
6	0.57	3.81	88.35			
7	0.43	2.87	91.22			
8	0.33	2.21	93.43			
9	0.25	1.68	95.11			
10	0.23	1.56	96.67			
11	0.15	0.99	97.66			
12	0.12	0.82	98.48			
13	0.10	0.64	99.12			
14	0.09	0.62	99.74			
15	0.04	0.26	100.00			

Extraction Method: Principal Component Analysis.

Table A-37PCA 3 - Varimax rotated component matrix (MCI-LB Probable; initial model)

	Component			
	1	2	3	4
RAVLT Max T1:T5	.374	.031	.856	-.064
RAVLT Short Delay	.052	.151	.909	.180
RAVLT Long Delay	-.051	.176	.881	.071
ACE Visuospatial	.148	.742	.086	.389
Corsi	.302	.763	-.025	-.213
MTCF Recall	-.092	.780	.309	.320
VPT High	.379	.626	.432	.182
FAS	.815	-.142	-.066	-.044
Stroop C	.473	.208	.179	.718
Stroop CW	.710	.463	.208	.256
Trails B	.694	.411	.176	.132
DSST	.787	.282	.251	.388
Symbol Copy	.759	.174	.075	.413
Trails A	.634	.502	.153	.362
CRT	.174	.117	.032	.851

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization, converging in 6 iterations.

Table A-38 PCA 3 - Oblimin Component Correlation Matrix (MCI-LB; initial model)

Component	1	2	3	4
1	1.000	.161	-.259	-.238
2	.161	1.000	-.307	-.262
3	-.259	-.307	1.000	.343
4	-.238	-.262	.343	1.000

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

Table A-39 PCA 3 - Oblimin rotation pattern matrix (MCI-LB Probable; initial model)

	Component			
	1	2	3	4
RAVLT Max T1:T5	.302	.906	.093	.168
RAVLT Short Delay	-.094	.931	.023	-.093
RAVLT Long Delay	-.184	.910	-.032	.022
ACE Visuospatial	-.091	-.023	-.705	-.346
Corsi	.163	-.092	-.874	.303
MTCF Recall	-.352	.218	-.725	-.255
VPT High	.170	.372	-.566	-.090
FAS	.868	-.060	.135	.057
Stroop C	.301	.099	-.041	-.729
Stroop CW	.551	.141	-.410	-.195
Trails B	.569	.124	-.385	-.068
DSST	.646	.194	-.179	-.346
Symbol Copy	.656	.016	-.086	-.400
Trails A	.454	.070	-.438	-.315
CRT	.014	-.056	.061	-.905

Extraction Method: Principal Component Analysis.

Rotation Method: Oblimin with Kaiser Normalization.

Converged in 20 iterations.

Table A-40 PCA 3 - Oblimin rotation structure matrix (MCI-LB Probable; initial model)

	Component			
	1	2	3	4
RAVLT Max T1:T5	.384	.883	-.206	-.109
RAVLT Short Delay	.072	.933	-.271	-.306
RAVLT Long Delay	-.034	.884	-.256	-.183
ACE Visuospatial	.170	.269	-.793	-.560
Corsi	.303	.124	-.784	-.011
MTCF Recall	-.069	.450	-.788	-.477
VPT High	.398	.597	-.755	-.422
FAS	.810	.024	-.052	-.087
Stroop C	.501	.350	-.399	-.840
Stroop CW	.726	.407	-.663	-.504
Trails B	.705	.352	-.594	-.368
DSST	.806	.443	-.524	-.612
Symbol Copy	.776	.253	-.398	-.590
Trails A	.653	.360	-.685	-.592
CRT	.204	.164	-.235	-.872

Upon removal of DSST, Symbol Copy, a measure of psychomotor speed, then emerged as loading strongly but below the .722 threshold on two components in both the matrices. Removing Symbol Copy, FAS (executive function) dropped below the acceptable threshold (0.500) in the anti-image correlation matrix diagonal. At this point, the two matrices match; however, two variables are not loaded above the pre-set threshold in the pattern matrix (ACE Visuospatial, 0.675; MTCF Recall, 0.697). Component 1 (43.28% variance explained) can be interpreted again as v*isuospatial* (ACE Visuospatial, Corsi, MTCF Recall), component 2 (21.01% total variance explained) as v*erbal learning and memory* (RAVLT Max A1:A5, Short and Long Delay), and component 3 as a p*rocessing speed* factor (Stroop C and CRT). The cumulative variance explained by the model is 77.77%. All anti-image correlation diagonals are above 0.500 and Bartlett's test of sphericity was significant, X2(28)=102.5, $p < .001$. However, the KMO remains acceptable but mediocre (0.664).

However, if VPT High is removed first instead of DSST, Corsi must then be removed (anti-image correlation matrix diagonal < 0.500). At this stage, we again see processing speed measures (Stroop C and DSST) loading strongly/ moderately onto two components. The model then again matches if we accept 0.716 for Choice

Reaction Time threshold. These extracted factors differ from the previous, with component 1 as loading both on v*isuospatial and processing speed* variables (ACE Visuospatial, MTCF Recall Stroop C and Choice Reaction Time). Component 2 remains a v*erbal learning and memory* component (RAVLT Max A1:A5, short and long delay). Component 3 is similarly difficult to interpret, with only two variables*:* FAS and Symbol Copy, relating to *executive and psychomotor speed.*

Appendix J. Correlation matrices MCI-AD subsample only (Principle Components Analysis not conduced due to small sample size).

Pink shading indicates moderate significant correlations at $p < .05$, but dark grey shading notes significant correlations that are very high ($r > .8$). ACE Visuospatial and Stroop C items did not correlation significantly with any variables and were removed. As in controls and MCI-LB, Trails B and Trails Difference correlated very highly ($r = .956$) and the latter was removed. High loadings were shown between RAVLT outcome variables, and as such RAVLT Max and Long Delay were removed. Other pairs of highly correlated variables were identified and the latter was removed: DSST Original and DSST Coding Time, MTCF Recall and MTCF Percent retained, and Stroop Ratio Interference and Stroop CW items. The following variables were also removed for low numbers of significant correlations: Simple Reaction Time, DSST Copy, Corsi Blocks and Choice Reaction Time.

Table A-41 Correlation matrix of MCI-AD subsample only.

	ACE Lang.	RAVLT Max T1:T6	RAVLT Learning	Rey Short Delay	Rey Long Delay	RAVLT % Max at Long Delay	RAVLT % "Forgetting"	RAVLT Retro. Int.	RAVLT Proact. Int.	RAVLT Recog. B	ACE Visuospatial
	-0.345	-0.315	-0.453	-0.329	-0.125	-0.194	-0.453	1	-0.432	-0.199	-0.311
	-0.284	-0.231	-0.367	-0.186	-0.116	-0.190	-0.379	0.461	-0.333	-0.186	-0.305
	-0.249	-0.231	-0.332	-0.186	-0.093	-0.068	-0.305	0.349	-0.302	-0.134	-0.077
	-0.180	-0.123	-0.322	-0.152	-0.091	-0.040	-0.265	0.347	-0.252	-0.132	-0.041
	-0.156	-0.098	-0.195	-0.092	-0.085	-0.030	-0.198	0.339	-0.155	-0.122	-0.038
	-0.138	-0.090	-0.192	-0.023	-0.056	-0.027	-0.156	0.311	-0.136	-0.119	0.001
	-0.056	-0.019	-0.107	-0.005	-0.036	-0.011	-0.156	0.304	-0.119	-0.112	0.009
	0.047	-0.011	-0.040	-0.002	-0.023	0.015	-0.154	0.209	-0.100	-0.054	0.057
	0.064	0.008	-0.017	0.018	-0.002	0.031	-0.151	0.177	-0.056	-0.038	0.130
	0.067	0.009	0.021	0.035	-0.001	0.057	-0.143	0.162	-0.054	-0.030	0.148
	0.103	0.052	0.116	0.049	0.093	0.063	-0.133	0.143	-0.024	-0.018	0.174
	0.116	0.073	0.130	0.082	0.095	0.073	-0.117	0.118	-0.019	-0.016	0.175
	0.124	0.112	0.138	0.139	0.118	0.080	-0.116	0.105	-0.005	-0.014	0.181
	0.146	0.153	0.149	0.196	0.130	0.080	-0.110	0.073	0.012	-0.013	0.184
	0.161	0.162	0.151	0.196	0.181	0.084	-0.087	0.068	0.048	0.021	0.196
	0.174	0.191	0.158	0.202	0.195	0.110	-0.065	0.051	0.073	0.033	0.213
	0.191	0.246	0.181	0.250	0.202	0.162	-0.023	0.032	0.082	0.047	0.215
	0.215	0.262	0.182	0.259	0.204	0.167	-0.005	0.023	0.124	0.051	0.230
	0.220	0.328	0.195	0.314	0.220	0.174	0.025	0.014	0.130	0.081	0.263
	0.245	0.387	0.232	0.402	0.282	0.192	0.045	0.002	0.143	0.087	0.273
	0.285	0.415	0.238	0.432	0.348	0.263	0.136	-0.011	0.148	0.238	0.304
	0.292	0.426	0.254	0.461	0.404	0.441	0.137	-0.014	0.211	0.254	0.305
	0.310	1	0.260	1	1	1	0.140	-0.048	0.223	0.262	0.312
	0.325	0.475	0.326	0.536	0.534	0.486	1	-0.070	0.253	0.282	0.362
	0.325	0.476	0.356	0.546	0.553	0.494	-0.478	-0.082	0.265	0.324	0.374
	0.349	0.49	0.399	0.551	0.558	0.549	-0.52	-0.099	0.321	0.468	0.387
	0.365	0.525	0.462	0.575	0.572	0.557	-0.558	-0.113	0.326	1	0.406
	0.379	-0.596	0.468	0.577	0.581	0.558	-0.559	-0.116	0.346	0.582	0.420
	0.402	0.634	1	-0.63	0.826	0.685	-0.596	-0.129	0.359	0.673	0.430
	1	0.685	0.536	0.673	0.836	0.746	-0.63	-0.141	0.385	0.716	0.462
	0.486	0.716	0.557	0.746	0.881	0.872	-0.769	-0.173	0.407	-0.769	1
	0.491	0.881	0.572	0.836	-0.894	0.916	-0.894	-0.267	1	0.826	0.469
	-0.499	0.882	0.634	0.882	0.916	-0.956	-0.956	-0.332	0.6	0.872	0.6
Mean all corr	0.151	0.239	0.172	0.253	0.249	0.222	-0.227	0.082	0.105	0.147	0.227
Mean sig corr only	0.492	0.636	0.57475	0.6552	0.7151	0.6819	-0.662222222	NA	0.6	0.739666667	0.5345

	Corsi	MTCF Recall	MTCF % Retain	VPT High	VPT Low	VPT Ratio	FAS	Stroop C	Stroop CW	Stroop Ratio Int.	Trails B
	-0.379	-0.289	-0.247	-0.393	-0.357	-0.299	-0.431	-0.437	-0.447	-0.412	-0.380
	-0.352	-0.141	-0.186	-0.290	-0.288	-0.284	-0.285	-0.421	-0.321	-0.380	-0.233
	-0.197	-0.089	-0.143	-0.166	-0.271	-0.213	-0.190	-0.290	-0.267	-0.372	-0.154
	-0.106	-0.021	-0.106	-0.008	-0.006	-0.198	-0.186	-0.280	-0.110	-0.370	-0.018
	-0.098	-0.001	-0.073	0.048	0.056	-0.137	-0.120	-0.271	-0.097	-0.345	0.014
	-0.054	0.008	-0.049	0.110	0.068	-0.070	-0.107	-0.249	-0.082	-0.299	0.018
	-0.040	0.049	0.037	0.135	0.122	0.006	-0.106	-0.213	0.023	-0.288	0.084
	-0.039	0.063	0.048	0.209	0.130	0.023	-0.073	-0.199	0.033	-0.285	0.148
	-0.020	0.124	0.119	0.211	0.161	0.049	-0.024	-0.197	0.048	-0.279	0.163
	0.016	0.205	0.149	0.241	0.210	0.050	-0.024	-0.195	0.055	-0.252	0.182
	0.055	0.208	0.159	0.254	0.238	0.058	-0.002	-0.194	0.063	-0.221	0.204
	0.064	0.217	0.180	0.278	0.314	0.081	0.008	-0.183	0.063	-0.192	0.227
	0.089	0.249	0.180	0.363	0.320	0.138	0.032	-0.136	0.093	-0.184	0.253
	0.103	0.260	0.195	0.365	0.321	0.156	0.035	-0.116	0.110	-0.166	0.259
	0.148	0.265	0.209	0.369	0.321	0.162	0.067	-0.111	0.130	-0.098	0.262
	0.165	0.282	0.232	0.378	0.356	0.167	0.112	-0.092	0.139	-0.054	0.271
	0.174	0.285	0.252	0.384	0.383	0.181	0.137	-0.077	0.153	-0.041	0.284
	0.184	0.301	0.253	0.399	0.406	0.182	0.186	-0.058	0.213	-0.011	0.328
	0.195	0.302	0.253	0.404	0.420	0.195	0.230	-0.046	0.223	-0.005	0.373
	0.210	0.307	0.273	0.437	0.432	0.210	0.264	-0.024	0.238	-0.001	0.375
	0.271	0.324	0.274	1	0.441	0.239	0.316	-0.011	0.245	0.008	0.397
	0.274	0.328	0.324	0.469	1	0.271	0.323	0.010	0.264	0.025	0.430
	0.279	0.339	0.325	0.494	-0.478	0.284	0.333	0.018	0.366	0.058	0.459
	0.301	0.374	0.347	-0.52	0.49	0.307	0.350	0.023	0.392	0.097	1
	0.311	1	1	0.525	0.509	0.323	0.355	0.037	0.398	0.119	0.486
	0.320	0.475	0.476	0.571	0.534	0.362	0.373	0.049	0.419	0.124	0.502
	0.384	0.546	0.551	0.574	0.539	0.363	0.383	0.051	0.447	0.177	0.559
	0.404	0.549	0.558	0.575	0.559	0.385	0.404	0.140	0.459	0.270	0.594
	0.426	0.553	0.558	0.581	0.573	0.393	1	0.176	1	1	0.594
	1	-0.559	-0.558	0.594	0.657	0.426	0.494	0.337	0.495	0.498	0.676
	0.486	0.637	0.571	0.637	0.69	0.438	0.602	0.398	0.506	-0.499	0.757
	0.577	0.657	0.573	0.732	0.739	1	0.605	1	-0.506	-0.506	-0.916
	0.582	0.981	0.981	0.863	0.863	0.739	0.696	0.498	0.613	-0.747	0.999
Mean all corr	0.174	0.266	0.234	0.328	0.317	0.181	0.174	-0.032	0.162	-0.110	0.279
Mean sig corr only	0.548333333	0.619625	0.60325	0.594583333	0.602818182	0.739	0.59925	0.498	0.53	0.5625	0.675888889

	Trails Diff.	Trails Ratio	Digit Forward	Digit Backwards	DSST	Symbol Copy	Error Check	Coding Time (DSST)	Trails A	SRT	CRT
	-0.370	-0.433	-0.183	-0.421	-0.441	-0.223	-0.372	-0.447	-0.433	-0.432	-0.333
	-0.223	-0.393	-0.132	-0.244	-0.343	-0.184	-0.248	-0.441	-0.412	-0.367	-0.329
	-0.151	-0.357	-0.098	-0.134	-0.302	-0.155	-0.173	-0.437	-0.314	-0.267	-0.322
	-0.016	-0.352	-0.091	-0.090	-0.279	-0.087	-0.143	-0.431	-0.156	-0.231	-0.315
	0.023	-0.343	-0.062	-0.065	-0.267	-0.040	-0.100	-0.314	-0.113	-0.231	-0.280
	0.023	-0.321	-0.049	-0.023	-0.265	-0.040	-0.017	-0.248	-0.058	-0.186	-0.230
	0.080	-0.311	-0.048	-0.023	0.010	0.002	-0.002	-0.233	-0.044	-0.186	-0.221
	0.130	-0.289	-0.038	-0.020	0.103	0.015	0.051	-0.231	-0.030	-0.176	-0.180
	0.158	-0.247	-0.027	-0.011	0.148	0.050	0.052	-0.223	0.089	-0.122	-0.133
	0.174	-0.244	-0.021	0.017	0.151	0.057	0.057	-0.176	0.110	-0.117	-0.129
	0.195	-0.231	0.006	0.031	0.170	0.087	0.095	-0.152	0.129	-0.111	-0.112
	0.230	-0.230	0.016	0.058	0.180	0.097	0.103	-0.143	0.209	-0.089	-0.106
	0.246	-0.223	0.018	0.111	0.184	0.111	0.146	-0.141	0.282	-0.056	-0.097
	0.250	-0.186	0.037	0.149	0.192	0.115	0.149	-0.141	0.292	-0.044	-0.093
	0.252	-0.137	0.045	0.159	0.202	0.122	0.176	-0.138	0.302	-0.039	-0.040
	0.271	-0.125	0.115	0.217	0.239	0.135	0.182	-0.085	0.314	-0.038	-0.001
	0.279	-0.123	0.170	0.316	0.247	0.146	0.208	-0.062	0.359	-0.036	0.037
	0.324	-0.120	0.210	0.325	0.249	0.180	0.278	-0.023	0.393	-0.030	0.095
	0.350	-0.099	0.254	0.336	0.262	0.196	0.305	0.001	0.415	-0.008	0.097
	0.362	-0.068	0.312	0.355	0.316	0.202	0.310	0.017	0.442	-0.006	0.129
	0.383	-0.046	0.333	0.369	0.348	0.205	0.314	0.021	0.460	0.058	0.165
	0.420	-0.013	0.346	0.383	0.387	0.231	0.345	0.048	0.462	0.058	0.184
	0.447	0.012	0.366	0.387	0.392	0.328	0.376	0.048	0.462	0.105	0.227
	1	0.021	0.376	0.397	0.420	0.337	0.442	0.056	1	0.146	0.230
	0.489	0.116	0.378	0.407	0.430	0.362	1	0.058	0.492	0.156	0.241
	0.491	0.136	0.379	0.412	0.437	0.375	0.477	0.080	0.506	0.163	0.316
	0.539	0.270	0.412	0.419	1	0.460	0.485	0.095	0.551	0.174	0.321
	0.574	1	1	0.438	0.489	1	0.494	0.097	0.561	0.175	0.336
	0.586	-0.475	-0.475	1	0.502	0.485	0.613	0.116	0.605	0.186	0.345
	0.68	-0.499	-0.499	0.477	0.561	0.495	-0.647	0.130	0.69	0.231	0.426
	0.726	-0.647	0.551	0.492	0.696	0.602	0.676	0.148	0.726	0.247	0.430
	-0.933	-0.916	0.586	0.509	0.729	0.729	0.68	1	0.732	1	1
	0.999	-0.933	0.594	-0.747	0.752	-0.936	0.752	-0.936	0.757	0.714	0.714
Mean all corr	0.272	-0.206	0.145	0.181	0.239	0.165	0.214	-0.093	0.296	0.019	0.072
Mean sig corr only	0.668555556	-0.694	0.541	0.55625	0.6215	0.6494	0.603	-0.936	0.624444444	0.714	0.714

Appendix K. Digit Symbol Substitution Test, Symbol Copy and Error Check

Participant I.D……. Date……

DIGIT SYMBOL (DSST) – Original

Instruction: Copy the appropriate symbol below each digit according to this key

SAMPLES																									
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4	
1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3	
6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	
9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6	

Participant I.D……. Date…….

Symbol Copy

Instruction: Copy the symbol from the top row to the bottom row

SAMPLES																							
⊥	—	⊐	∧	⊥	⊏	×	⊥	—	⊐	⊥	—	⊏	⊥	⊐	⊔	⊥	⊐	—	⊏	⊔	○	⊐	—	⊏
—	⊔	⊏	⊥	∧	○	⊐	⊔	∧	⊥	=	⊔	⊏	○	⊐	∧	⊥	×	—	=	⊔	×	⊏	∧	⊐
○	⊥	⊔	—	=	⊥	×	⊐	×	⊏	○	⊔	=	⊏	×	⊐	∧	⊥	○	—	⊔	⊏	○	⊐	∧
=	⊥	×	—	∧	=	⊏	○	×	⊔	=	∧	—	×	⊔	⊥	=	⊏	×	○	⊐	∧	=	×	○

2

Participant I.D……. Date…….

DIGIT SYMBOL (DSST) – Error Check

Instruction: In this sheet, somebody else already copied the symbols below each digit. However, this person made a few mistakes. Try to find and mark these mistakes – you do not need to correct them.

1	2	3	4	5	6	7	8	9
ㄴ	ㅡ	○	×	ㅋ	∧	ㅁ	=	ㅗ

SAMPLES																											
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4			
ㅡ	ㅗ	○	ㅁ	ㅡ	∧	=	ㅡ	ㄴ	○	ㅡ	∧	×	ㅡ	=	ㅋ	ㅡ	○	ㄴ	ㅗ	ㅡ	∧	○	ㄴ	×			
1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3			
ㄴ	○	×	ㅡ	ㅁ	∧	○	ㅋ	=	ㅡ	ㅁ	ㅋ	×	∧	○	ㅁ	ㅡ	×	ㄴ	ㅗ	ㅋ	=	×	ㅁ	∧			
6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7			
∧	ㅡ	ㅋ	ㄴ	∧	ㅡ	=	×	ㅁ	×	○	ㅋ	ㅗ	×	=	○	ㅗ	ㅡ	∧	ㄴ	ㅋ	×	∧	ㄴ	ㅁ			
9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6			
ㅗ	ㅡ	=	×	ㅁ	ㄴ	×	∧	=	ㅋ	ㅗ	ㅁ	∧	=	ㅋ	ㅡ	○	×	=	∧	○	ㅁ	ㅡ	=	∧			

3

Appendix L. Hierarchical multiple regressions to predict DSST scores from its variants in the whole group.

Table A-42 Hierarchical multiple regressions to predict DSST scores from its variants (Symbol Copy, Error Check), Coding Time Index, and demographics (age and premorbid IQ [NART]).

	R^2	Adjusted R^2	ΔR^2	*F* Change	Sig. *F* Change	Std. B Coefficients	Std. B Sig
Age & NART IQ	.281	.262	**.281**	14.64	**<.001**	**-0.36** **0.45**	**<.001** **<.001**
Age & NART IQ Group	.281 .421	.262 .398	**.281** **.141**	14.64 17.97	**<.001** **< .001**	**-0.30** **0.39** **-0.38**	**.001** **< .001** **< .001**
Age & NART IQ Symbol Copy	.281 .698	.262 .686	**.281** **.418**	14.64 102.41	**<.001** **<.001**	-0.10 0.09 **0.70**	.147 .214 **<.001**
Group	.714	.698	**.016**	4.02	**.049**	**-0.14**	**.049**
Age & NART IQ Error Check	.281 .823	.262 .816	**.281** **.543**	14.64 227.16	**<.001** **<.001**	-0.03 0.04 **0.82**	.530 .433 **<.001**
Group	.860	.852	**.037**	19.11	**<.001**	**-0.20**	**<.001**
Age & NART IQ Coding Time	.281 .739	.262 .728	**.281** **.446**	14.64 124.91	**<.001** **<.001**	**-0.12** **0.20** **0.67**	**.035** **.001** **<.001**
Group	.801	.790	**.062**	22.47	**<.001**	**-0.26**	**<.001**
Age & NART IQ Error Check Symbol Copy	.281 .823 .873	.262 .816 .866	**.281** **.543** **.049**	14.64 227.16 28.23	**<.001** **<.001** **<.001**	-0.01 -0.01 **0.65** **0.28**	.912 .857 **<.001** **<.001**
Group	.889	.881	**.016**	10.47	**.002**	**-0.14**	**.002**
Age & NART IQ Coding Time Symbol Copy	.281 .739 .858	.262 .728 .850	**.281** **.446** **.119**	14.64 124.91 60.42	**<.001** **<.001** **<.001**	-0.05 0.08 **0.51** **0.40**	.286 .126 **<.001** **<.001**
Group	.876	.868	**.018**	10.39	**.002**	**-0.15**	**.002**
Age & NART IQ Symbol Copy	.281 .698	.262 .686	**.281** **.418**	14.64 102.41	**<.001** **<.001**	-0.01 -0.01 **0.28**	.912 .857 **<.001**

Error	.873	.866	**.174**	99.80	**<.001**	**0.65**	**<.001**
Check							
Group	.889	.881	**.016**	10.47	**.002**	**-0.14**	**.002**
Age &						-0.05	.286
NART IQ	.281	.262	**.281**	14.64	**<.001**	0.08	.126
Symbol	.693	.681	**.401**	95.40	**<.001**	**0.40**	**< .001**
Copy							
Coding	.858	.850	**.165**	83.62	**<.001**	**0.51**	**< .001**
Time							
Group	.876	.868	**.018**	10.39	**.002**	**-0.15**	**.002**

Appendix M. Data cleaning for ex-Gaussian investigation of intraindividual variability in Simple Reaction Time, Choice Reaction Time and Continuous Performance Test-AX tests.

SRT: Across the total group, 39 anticipated responses and 10 non-responses were removed. These anticipated responses came from 19 participants (*n* = number of anticipated responses per person): 11 (*n* = 1), 3 (*n* = 2), 2 (*n* = 3), 1 (*n* = 4), 1 (*n* = 5) and 1 (*n* = 7). Non-responses came from 6 different participants, with 4 participants with one non-response each, 1 participant with 2 non-responses, and 1 participants with 4 non-responses. Whole-group *z*-scores were computed from the remaining reaction times. While the ex-Gaussian approach is utilized in order to retain long response latencies, 21 data points were removed for being over 4.0 SD above the mean.

CRT: There were seven "anticipated" responses that all occurred prior to stimulus presentation by four participants: three participants made one anticipatory keypress each and one participant made four anticipatory keypresses. Four non-responses made by four different participants. In addition, there were 38 multiple keypresses and 88 wrong keypresses, the latter made by 45 participants. Twenty data points were removed as they were greater than 4.0 SDs from the mean of the whole sample.

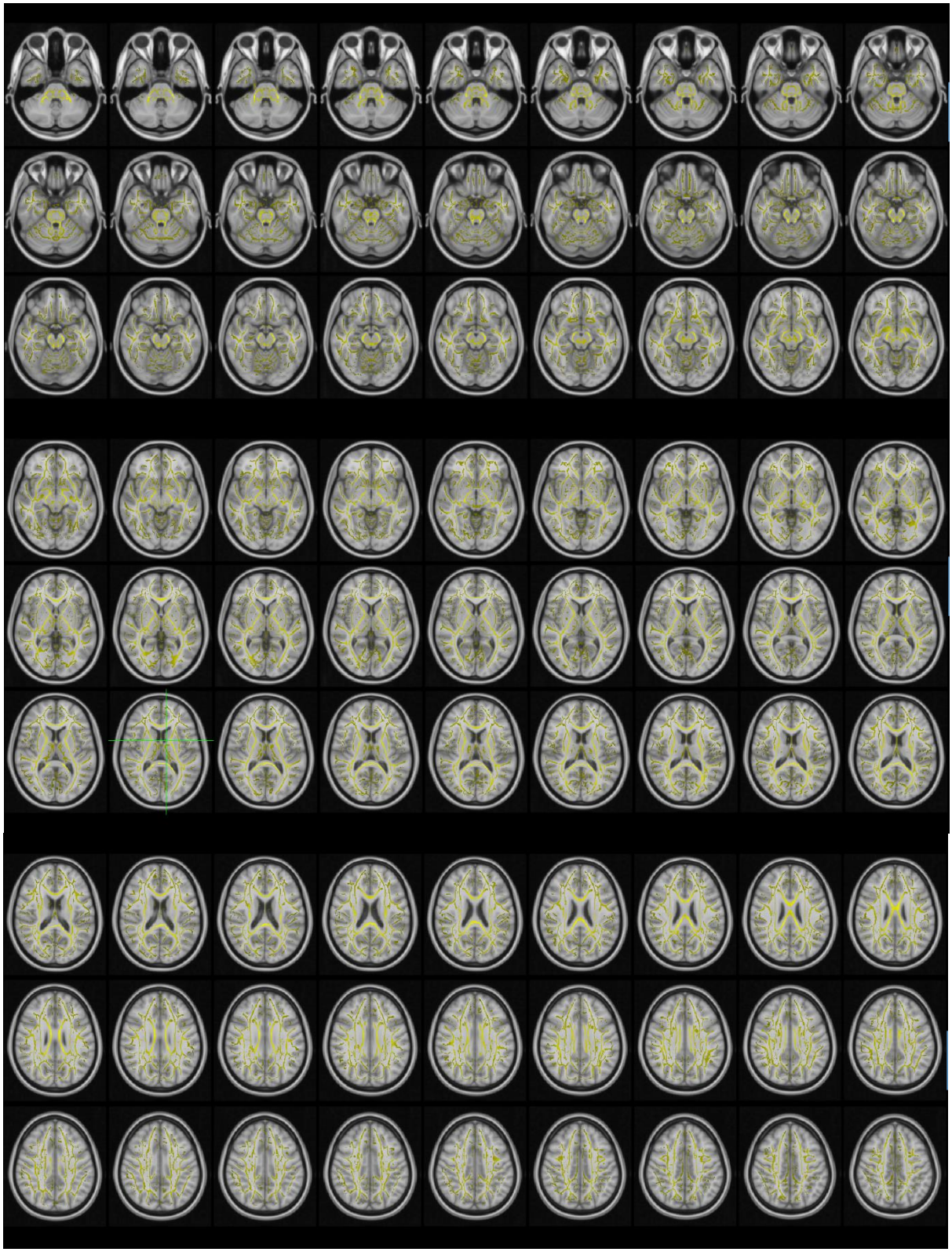
CPT-AX: One-hundred and thirty-nine data points were above 3.0 *z*-scores above the mean; however, no z-scores were over 4.36 and Inspection of a histogram suggests that this dataset is appropriate for ex-Gaussian analysis. It was therefore entered into the algorithm without removal of any outliers.

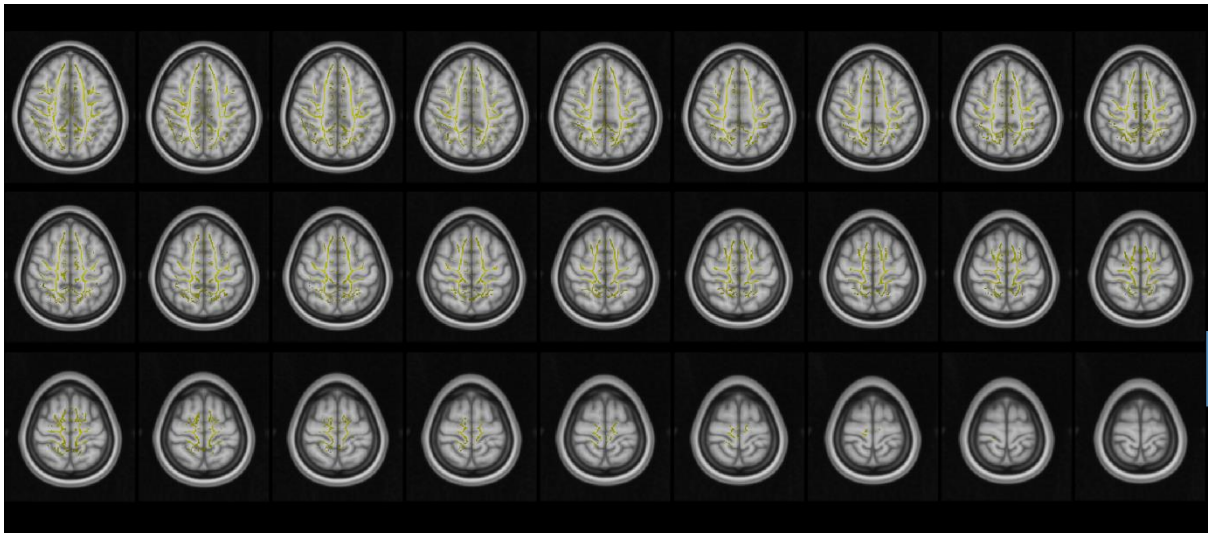
Appendix N. Magnetic resonance imaging (MRI) acquisition protocol (created by Dr Michael Firbank)

T1-weighted whole brain magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MPRAGE) images were acquired in the sagittal plane (TR=8.3ms, TE=4.6ms, flip angle=8°, inversion delay=1250ms, 216x208 matrix; slice thickness=1.0 mm) yielding 180 slices through the brain. A fluid attenuated inversion recovery (FLAIR) sequence (TR=11000ms, TE=125ms, IR=2800ms, Turbo SE factor = 27; refocus angle=120°, slice thickness=3mm) yielded 50 slices. Diffusion tensor acquisition parameters were: repetition time (TR) = 6103, echo time (TE) = 70 ms, SENSE factor = 2, field of view 270x270 mm, acquisition matrix = 124x120, 59 2.11 mm thick slices, echo-planar imaging factor (EPI-SE) = 63, foldover = AP b = 0 (6 averages), b = 1000 (64 directions), acquisition time = 7 minutes, 20 seconds.

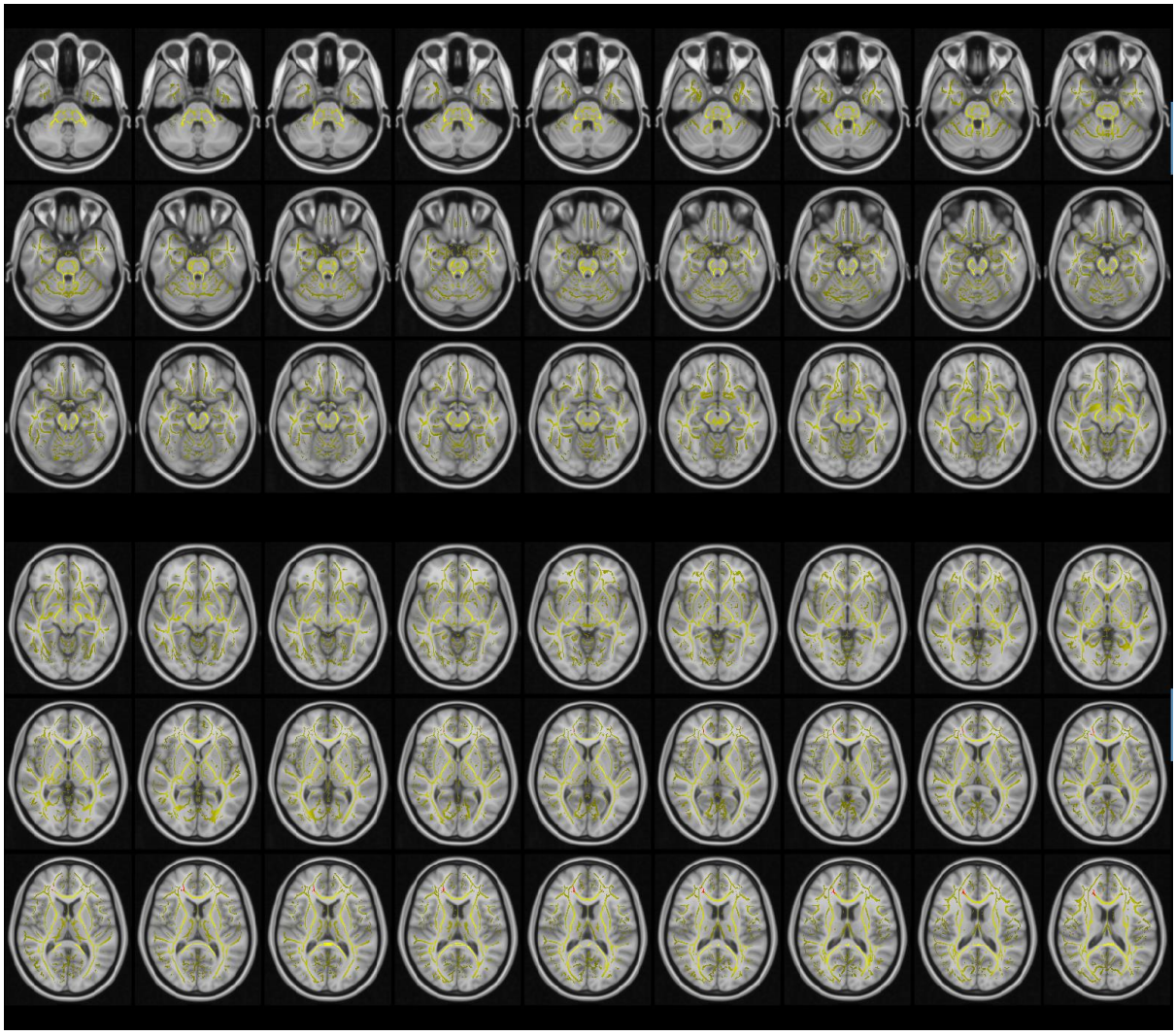
Appendix O. Additional FMRIB Software Library (FSL) brain images to complement Chapter 9's exploratory analyses.

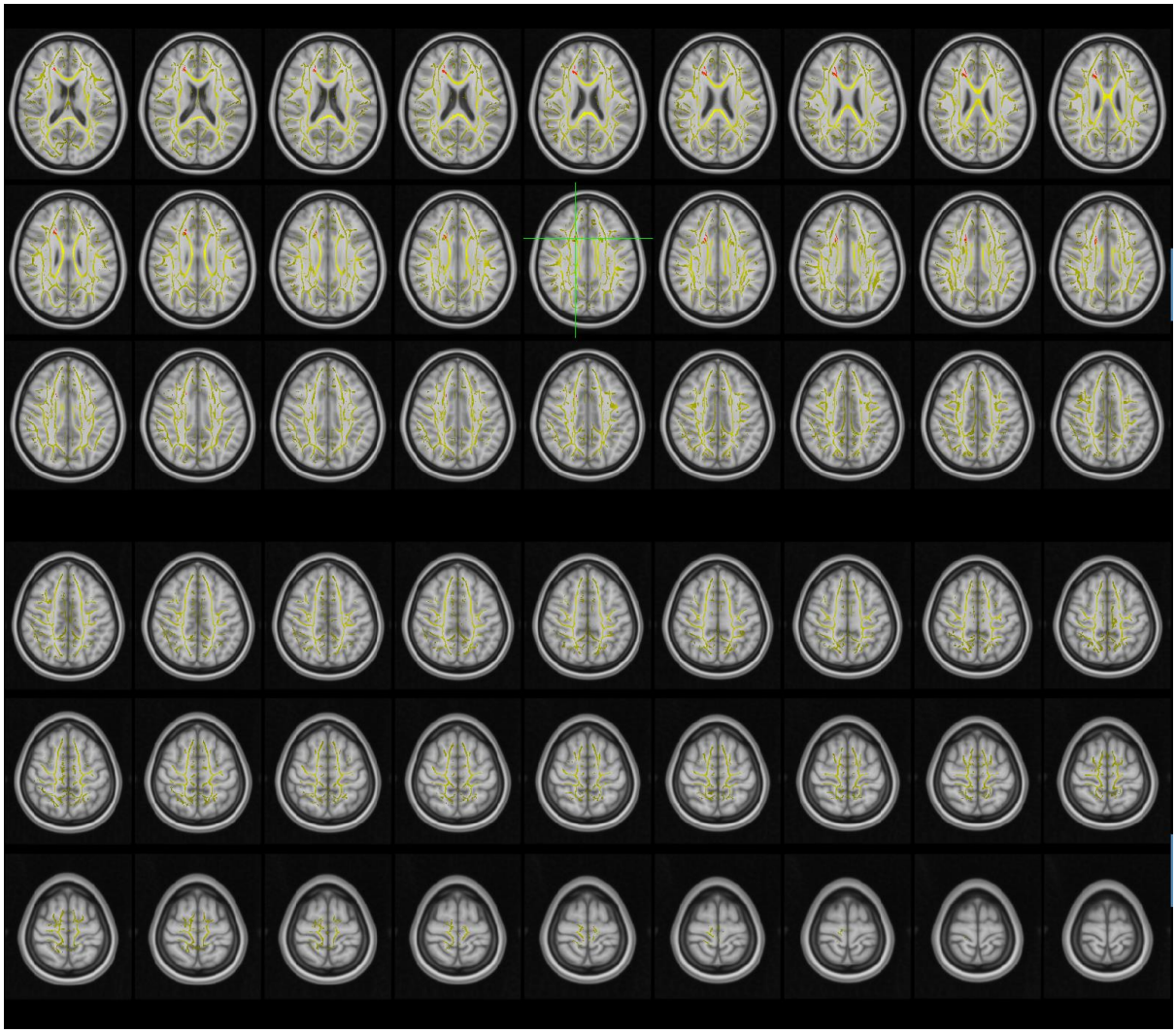
Group differences MCI-LB Probable versus Controls **after** controlling for age (lightbox view; no significant voxels)



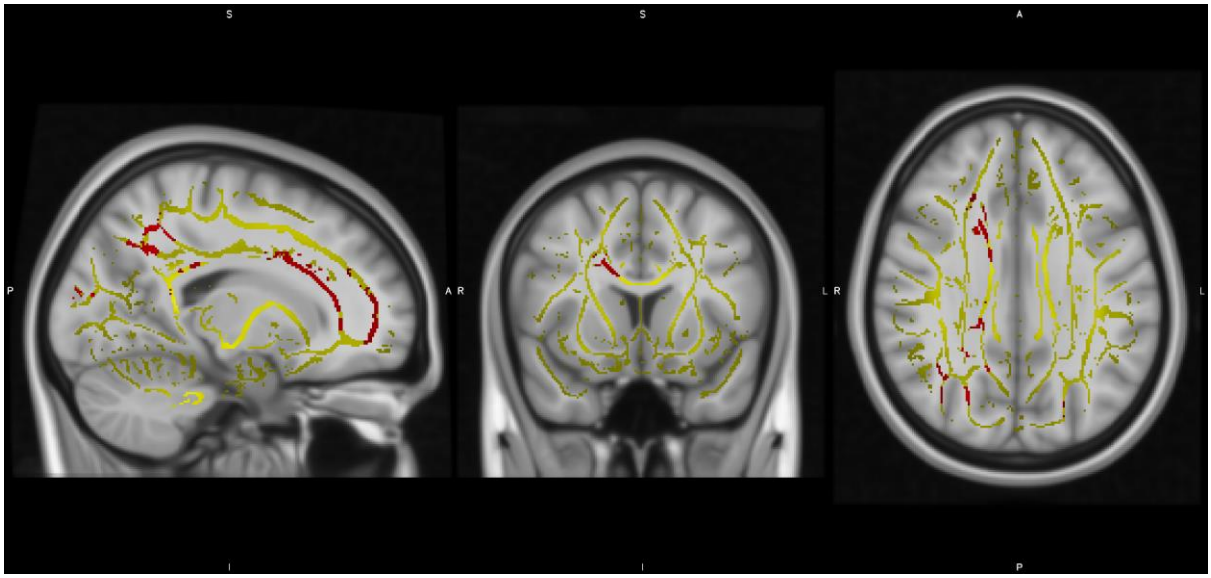


TFCE-corrected significant associations between voxelwise FA and age with all participants (in red; lightbox view):

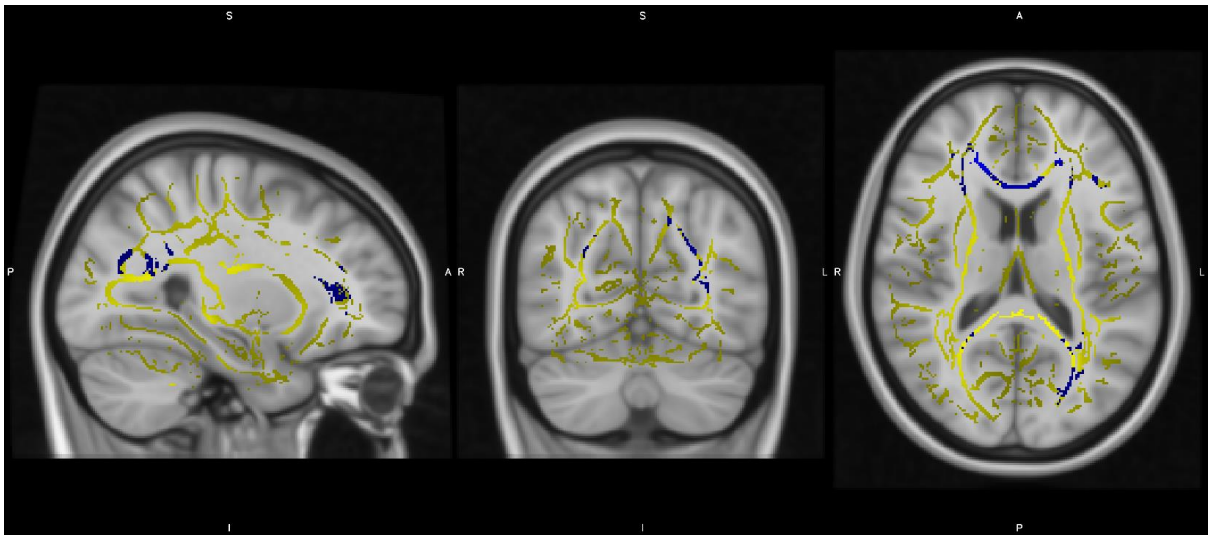




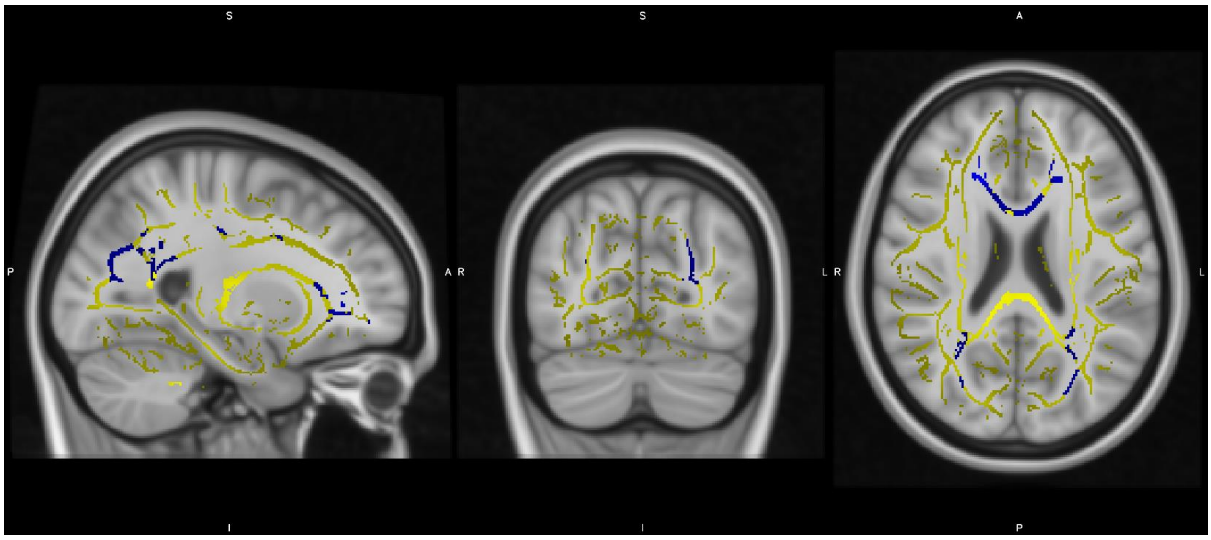
TFCE-corrected voxelwise differences in FA between MCI-LB Probable and controls without controlling for age associations (ortho view [72x139x103]; significant voxels in red).



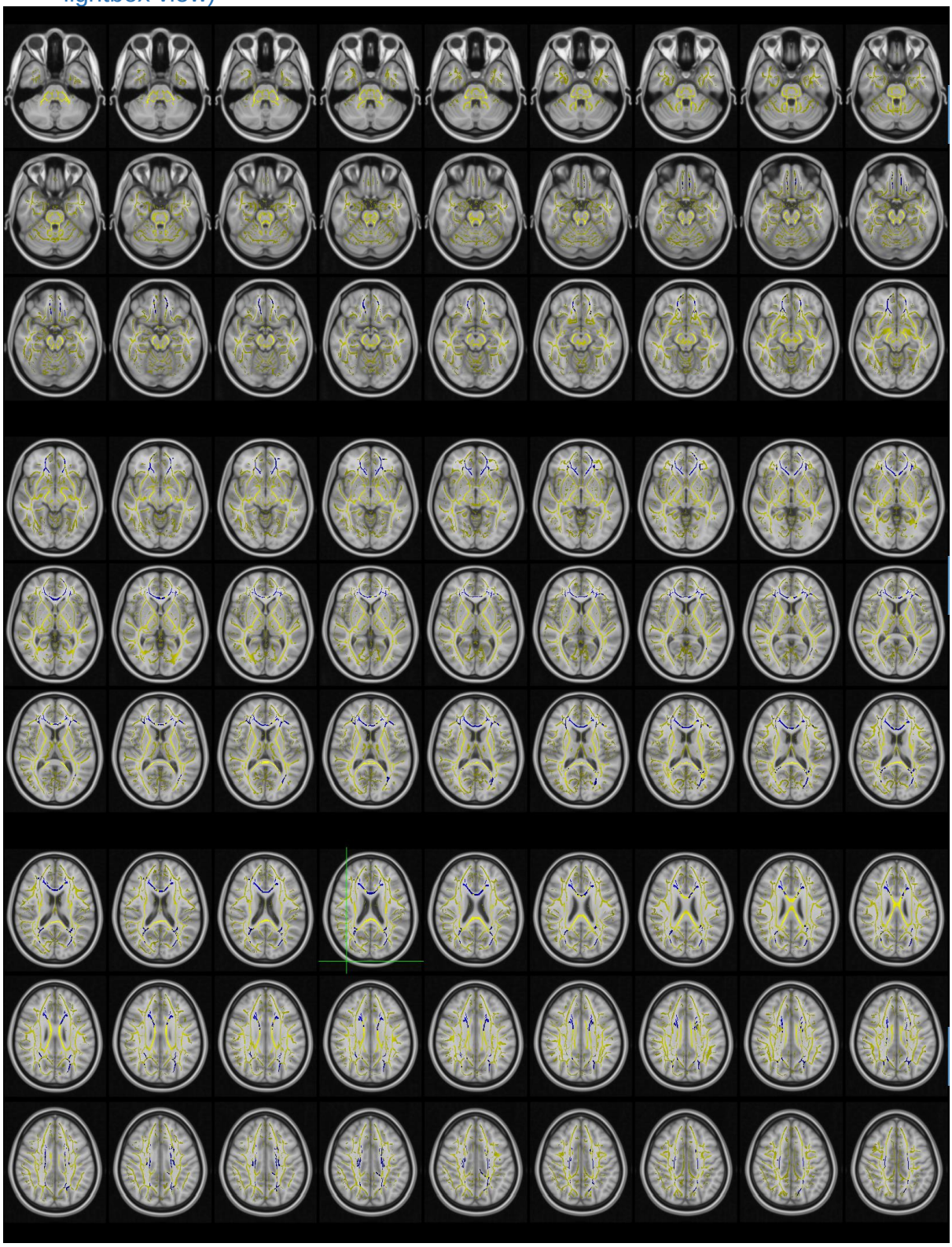
TFCE-corrected statistical map showing significant correlations between FA and DSST for MCI-LB Probable and controls only (significant voxels in blue; ortho view aligned at voxel 62x50x87)



TFCE-corrected statistical map showing significant correlations between FA and DSST for MCI-LB Probable and controls only (significant voxels in blue; ortho view aligned to show “unclassified area” of the posterior occipital lobe).



TFCE-corrected statistical map showing significant correlations between FA and DSST for MCI-LB Probable and controls only (significant voxels in blue; lightbox view)



Appendix P. Correlation matrix between global white matter measures (gFA and gMD) and clinical fluctuation scales (DCFS, CAF) in patients.

Table A-45. **Correlation matrix between global white matter measures (global Fractional Anisotropy and global Mean Diffusivity) and clinical fluctuation scales (Dementia Cognitive Fluctuation Scale [DCFS], Clinical Assessment of Fluctuation [CAF]) in MCI-LB Probable and MCI-AD.**

	MCI-LB Probable		**MCI-AD**	
	DCFS	CAF	DCFS	CAF
gFA	0.09 (*p* = .682)	-0.07 (*p* = .757)	0.07 (*p* = .822)	-0.06 (*p* = .850)
gMD	-0.07 (*p* = .757)	0.12 (*p* = .585n)	-0.18 (*p* = .564)	-0.01 (*p* = .978)