Neurocognitive patterns and progression of mild cognitive impairment with Lewy bodies or Alzheimer's disease

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Abstract

Mild cognitive impairment is a heterogeneous condition; while typically viewed as the transition stage between healthy cognitive function and dementia, the cognitive and clinical patterns of this condition vary, as do its prognosis. The two most common neurodegenerative dementias, dementia with Lewy bodies and Alzheimer's disease, differ in their clinical features, patterns of cognitive impairment, and prognosis. It is not known whether the respective mild cognitive impairment stages preceding onset of dementia also differ in these characteristics. Two cohorts of people with recent mild cognitive impairment diagnosis were assessed, undergoing annual review of cognition, diagnosis and presence of clinical features of Lewy body disease by an expert panel of old age psychiatrists, and repeated imaging, to reach a consensus diagnosis of either mild cognitive impairment due to Alzheimer's disease, or with Lewy bodies, in line with current consensus criteria for these. Making use of annually repeated cognitive assessment and clinical diagnostic information, the longitudinal progression of these two conditions was characterised with flexible statistical methods, using the first cohort for model development, and the second for validation: different trajectories of decline in specific cognitive domains were observed in the diagnostic groups, reflecting typical patterns of impairment in their respective dementia syndromes. Mild cognitive impairment with Lewy bodies was also observed to have a worse prognosis, in keeping with its dementia stage, with a greater risk of progressive cognitive decline, and faster onset of dementia. Individuals with neuropsychiatric symptoms (cognitive fluctuations and visual hallucinations) were also at more risk of decline than those with slower-developing features (REM sleep behaviour disorder or parkinsonism) or those with Alzheimer's disease. Mild cognitive impairment with Lewy bodies may therefore feature early cognitive, clinical, and prognostic differences from Alzheimer's disease, reflecting its eventual dementia syndrome.

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Contributions to work

Contributions by the candidate

Over the course of this work I contributed to the running of the ^{123}I-MIGB Scintigraphy Utility as a biomarker for Prodromal DEmentia with Lewy Bodies (SUPErB) study. This included travel throughout North-East England, assisting in recruitment of healthy older adults and healthcare service users onto this study, undertaking informed consent procedures to induct participants onto this study, and administering standardised neuropsychological assessments at baseline and at follow-up visits providing data analysed in this thesis.

I contributed to the collection of resting state electroencephalography (EEG) recordings from participants (not included in this work). I was also one of a number of study team members who provided support to the patients and public involved in this study, by escorting them to appointments for clinical scans. These contributions in total amounted to over three-hundred appointments with research participants over a period spanning from December 2017 to December 2019.

Collating pre-existing data from the pilot 'LewyPro' study, and data which arose over the course of the SUPErB study to date, I undertook necessary data cleaning and organised information from multiple databases into a usable format. I also performed primary analysis of cross-sectional and longitudinal characteristics of the healthy and cognitively impaired groups as presented within this work. Data collection for the SUPErB study was temporarily arrested throughout Spring-Summer of 2020 due to the COVID-19 viral pandemic; this limited the availability of longitudinal data for this cohort to less than anticipated in the initial project plan.

Contributions by supervisors and other researchers

Assessment of the LewyPro study cohort was undertaken by Dr Paul Donaghy, Nicola Barnett, and Kirsty Olsen. Initial consent and baseline cognitive assessment of SUPErB study recruits was undertaken by Dr Joanna Ciafone. Initial follow-up assessments were undertaken by Nicola Barnett and Denise Golden. Baseline and follow-up clinical assessments in the SUPErB study were undertaken by the clinical team consisting Dr Rory Durcan, Dr Sarah Lawley, and Sally Barker. Later follow-up neuropsychological assessment after October 2019 was continued by

Sammy Waite. Clinical diagnoses for both cohorts were undertaken by the expert old age psychiatry panel, consisting of Prof Alan Thomas, Dr Paul Donaghy, and Prof John-Paul Taylor. Initial recordings of EEG data prior to January 2018 were undertaken by Dr Ruth Cromarty and Dr Andy Hanson. Recruitment of participants from local services was facilitated by Dr Barbara Wilson and Bryony Storey. The administration of both studies was supported by Helen Kain.

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Abbreviations

ACE-R - Addenbrooke's Cognitive Examination - Revised

AD - Alzheimer's disease

ADAS-Cog - Alzheimer's Disease Assessment Scale – Cognitive Subscale

AIC – Akaike Information Criterion

ANOVA - Analysis of variance

B – Unstandardised beta coefficient

BIC – Bayesian Information Criterion

CAF - Clinician Assessment of Fluctuation

CAMCOG - Cambridge Cognitive Examination

CANTAB - Cambridge Neuropsychological Test Automated Battery

CDR – Clinical Dementia Rating

CI - Confidence interval

CIRS-G – Cumulative Illness Rating Scale for Geriatrics

CRT - Choice reaction task

CSF - Cerebrospinal fluid

DCFS – Dementia Cognitive Fluctuations Scale

DLB - Dementia with Lewy bodies

DSST – Digit-symbol substitution test

DVT – Digit vigilance task

EEG - Electroencephalography

ESS – Epworth Sleepiness Scale

FDG - Fluorodeoxyglucose

FP-CIT - ^{123}I-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane

GDS – Geriatric Depression Scale

GNT – Graded Naming Test

IADL – Instrumental Activities of Daily Living

IMD – Indices of multiple deprivation

LAT - Line angle task

LB - Lewy body

LCMM – Latent class mixed model(ling)

LMM – Linear mixed model(ling)

MCI - Mild cognitive impairment

MCI-AD - Mild cognitive impairment due to Alzheimer's disease

MCI-LB - Mild cognitive impairment with Lewy bodies

MDS - Movement Disorder Society

MIBG - ^{123}I-meta-iodobenzylguanidine

ML Maximum likelihood

MMSE – Mini-mental state examination

MoCA – Montreal Cognitive Assessment

MRI – Magnetic resonance imaging

MSM – Multi state model(ling)

MSQ – Mayo Sleep Questionnaire

MTCF – Modified Taylor Complex Figure

MTL - Medial temporal lobe

NART – National Adult Reading Test

NBM - Nucleus basalis of Meynert

NEVHI – North East Visual Hallucinations Inventory

NIA-AA – National Institute on Aging at National Institutes of Health and the Alzheimer's Association

NMDA - N-Methyl-d-aspartic acid

NPI – Neuropsychiatric Inventory

OR – Odds ratio

PCA - Posterior cortical atrophy

PD - Parkinson's disease

PDD – Parkinson's disease-dementia

PD-MCI – Parkinson's disease – mild cognitive impairment

PET - Positron-emission tomography

PPA - Primary progressive aphasia

PSG – Polysomnography

RAVLT – Rey Auditory Verbal Learning Test

RBD - REM sleep behaviour disorder

REM - Rapid eye movement

ROCF – Rey-Osterreith Complex Figure

RSWA - REM sleep without atonia

SD – Standard deviation

SE – Standard error

SEM – Structural equation model(ling)

SPECT – Single-photon emission computed tomography

SRT – Simple reaction task

TDP-43 - Transactive response DNA-binding protein 43

TMT – Trail Making Test

UPDRS – Unified Parkinson's Disease Rating Scale

WAIS – Wechsler Adult Intelligence Scale

Chapter 1. Conceptual Background

1.1 Dementia

Dementia is a common age-related disorder (Ferri *et al.*, 2006) characterised by the onset of a cognitive impairment that is sufficiently severe so as to interfere with capability to function independently (McKhann *et al.*, 2011) and consequently an increased reliance on family and caregivers to undertake daily activities such as cooking, cleaning, and self-care. The impairments characterising this clinical syndrome must represent a decline from the individual's previous level of function and be more severe than the relatively more subtle changes experienced in the normal process of ageing. While regional rates vary, dementia is a global issue with prevalence rates of approximately five to seven percent in people over the age of 60 (Prince *et al.*, 2013); while incidence rates are falling at estimated rates of 7-19% per decade in Europe and the United States (Wolters *et al.*, 2020), overall prevalence is rising, and is expected to continue to do so as the global population continues to age (Livingston *et al.*, 2020).

As a leading cause of disability and dependency in old age, dementia is responsible for a high level of societal burden, impaired quality of life, and financial cost to healthcare services. Worldwide costs have been recently estimated at over one trillion US dollars per year, and are projected to continue to rise (Wimo *et al.*, 2017).

1.1.1 Causes of dementia

Dementia is a heterogeneous clinical syndrome and may result from any one of many underlying pathophysiological processes, or a combination of these; neurodegenerative diseases, cerebrovascular disease, or genetic mutations being common examples. Less commonly, malnutrition or viral infection may also lead to dementia. Reflecting these varying underlying causes, individual cases of dementia may have highly variable clinical presentations. As many as 40% of cases of dementia have been estimated to be preventable through earlier interventions (Livingston *et al.*, 2017; Livingston *et al.*, 2020) to address twelve key risk factors; low education, hearing loss, traumatic brain injury, hypertension, alcohol misuse, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution. However, the

majority of dementia cases (neurodegenerative causes in particular) are currently not preventable and may require appropriately targeted disease-modifying therapies to treat or prevent.

Dementia due to Alzheimer's disease

The commonest cause (Barker *et al.*, 2002) of dementia is Alzheimer's disease (AD), estimated to account for between 60 and 80% of cases (Brenowitz *et al.*, 2017a; Kapasi *et al.*, 2017). AD is a neurodegenerative disease characterised by the accumulation of abnormal protein inclusions in the brain (Hyman *et al.*, 2012); primarily, hyperphosphorylated tau proteins form neurofibrillary tangles within neurons, and beta-amyloid proteins aggregate to form extracellular 'plaques' (Nelson *et al.*, 2011). These protein aggregates are associated with varying patterns of cortical atrophy and consequent dysfunction (Murray *et al.*, 2011). White matter damage in the form of demyelination and axonal degeneration secondary to cortical pathology (McAleese *et al.*, 2017b), and transactive response DNA-binding protein 43 (TDP-43) pathology also commonly co-occur (McAleese *et al.*, 2017a) and may contribute to clinical outcomes (James *et al.*, 2016).

The medial temporal lobes (MTL), which are important for memory and learning processes (Eichenbaum *et al.*, 2007; Bird, 2017), are particularly affected by typical AD-related atrophy (Jack *et al.*, 1998). Consequently, a dementia due to AD is often characterised cognitively by amnestic memory impairment, the severity of which is associated with the extent of MTL atrophy (Scheltens *et al.*, 1992). However, this atrophy is typically not isolated to the MTL alone (Rabinovici *et al.*, 2008), and so cognitive impairments may also extend to other functions such as attention (Malhotra, 2019), working memory (Baddeley *et al.*, 1991), or visuospatial functions (Wilson *et al.*, 2011).

This is further complicated by the considerable heterogeneity possible in patterns of AD-related pathology and atrophy, with hippocampal-sparing patterns of neuropathology (Murray *et al.*, 2011) and atrophy (Ferreira *et al.*, 2017) being atypical, but far from uncommon. Atypical subtypes such as this, or other rare patterns of neurodegeneration, may also give rise to a distinct clinico-cognitive syndrome, which may feature an earlier onset and different profile of cognitive impairment such as the particular speech and language dysfunction of a logopenic primary

progressive aphasia (PPA; Gorno-Tempini *et al.*, 2011) or visuospatial dysfunction characteristic of posterior cortical atrophy (PCA; Crutch *et al.*, 2012).

The diagnosis of AD may be supported by a number of biomarkers (Jack *et al.*, 2018). As AD is defined by the presence of abnormal amyloid and tau protein formations, AD-specific biomarkers typically aim to identify markers of abnormal accumulation of these proteins in vivo; currently these include elevated levels of phosphorylated tau or decreased amyloid-β_{42} (Blennow and Zetterberg, 2018) in cerebrospinal fluid (CSF), and the binding of particular positron-emission tomography (PET) ligands to cortical amyloid (Ossenkoppele *et al.*, 2015; Rice and Bisdas, 2017) or tau (Saint-Aubert *et al.*, 2017) accumulations. More general markers of neurodegeneration include cortical atrophy observed by MRI as introduced above, reduced cerebral glucose metabolism identified with fluorodeoxyglucose (FDG) PET, and increased total tau in CSF; however, these could reflect neurological damage attributable to other disease processes, which may also contribute to cognitive impairment, not just AD (Jack *et al.*, 2018).

Treatment and management

There are currently no disease-modifying therapies approved for any neurodegenerative dementia; recent trials looking to treat Alzheimer's disease have largely focussed on preventing accumulation of the hallmark neuropathological features of this disease (e.g. with anti-amyloid therapies), without any clear benefits shown to date (Reiss *et al.*, 2020). Treatment and management of dementia is therefore currently focussed on addressing the pathophysiological processes mediating relationships between the underlying disease and clinical symptoms, and on improving the psychological and social management of symptoms (e.g. in caregiving settings), as well as more effective prevention through modifiable health factors.

Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) are effective at attenuating the cognitive symptoms of Alzheimer's disease, though with only a modest effect (Birks, 2006), and considered as the frontline therapy for management of AD dementia, in addition to the less-favoured NMDA-receptor antagonist memantine (Schneider *et al.*, 2014). These treatments work to address the cholinergic deficiency which often results from degeneration of the nucleus basalis

of Meynert (NBM) and its cholinergic projections to the cerebral cortex in Alzheimer's disease (Hampel *et al.*, 2018) and related disorders. However, these treatments do not prevent worsening of symptoms, only reduce them for a time.
Efforts to more effectively treat or prevent dementia are complicated by the high degree of heterogeneity within this clinical syndrome. The effective management, treatment, or eventual prevention of a neurodegenerative dementia relies upon a clear understanding of the disease underlying it in each case.

While the commonest cause, AD is not the only cause of dementia. Cerebrovascular factors including stroke, infarcts, ischaemia and haemorrhages (O'Brien and Thomas, 2015) are common, with vascular pathology featuring in isolation in approximately 10% of dementia cases (Jellinger and Attems, 2011), but also often co-occurring alongside other pathologies (Attems and Jellinger, 2014; Brenowitz *et al.*, 2017a). These, and other neurodegenerative diseases can lead to cognitive impairment and dementia with varying additional symptoms, and may require different management and prevention strategies, particularly when considering putative disease-modifying therapies with specific pathological targets. One of these neurodegenerative conditions which has risen to prominence relatively more recently in the dementia literature is Lewy body disease; the resulting syndrome of dementia with Lewy bodies, and its cognitive prodrome, are the primary interest of this work.

1.2 Dementia with Lewy bodies

The pathology of Lewy body (LB) disease has long been associated with Parkinson's disease (PD), the clinical entity characterised by progressive motor impairment in later life (Hughes *et al.*, 1992). The hallmark pathological findings of PD are the formation of Lewy bodies and Lewy neurites in the substantia nigra in particular, as well as other areas of the basal forebrain and brain stem (Forno, 1996).

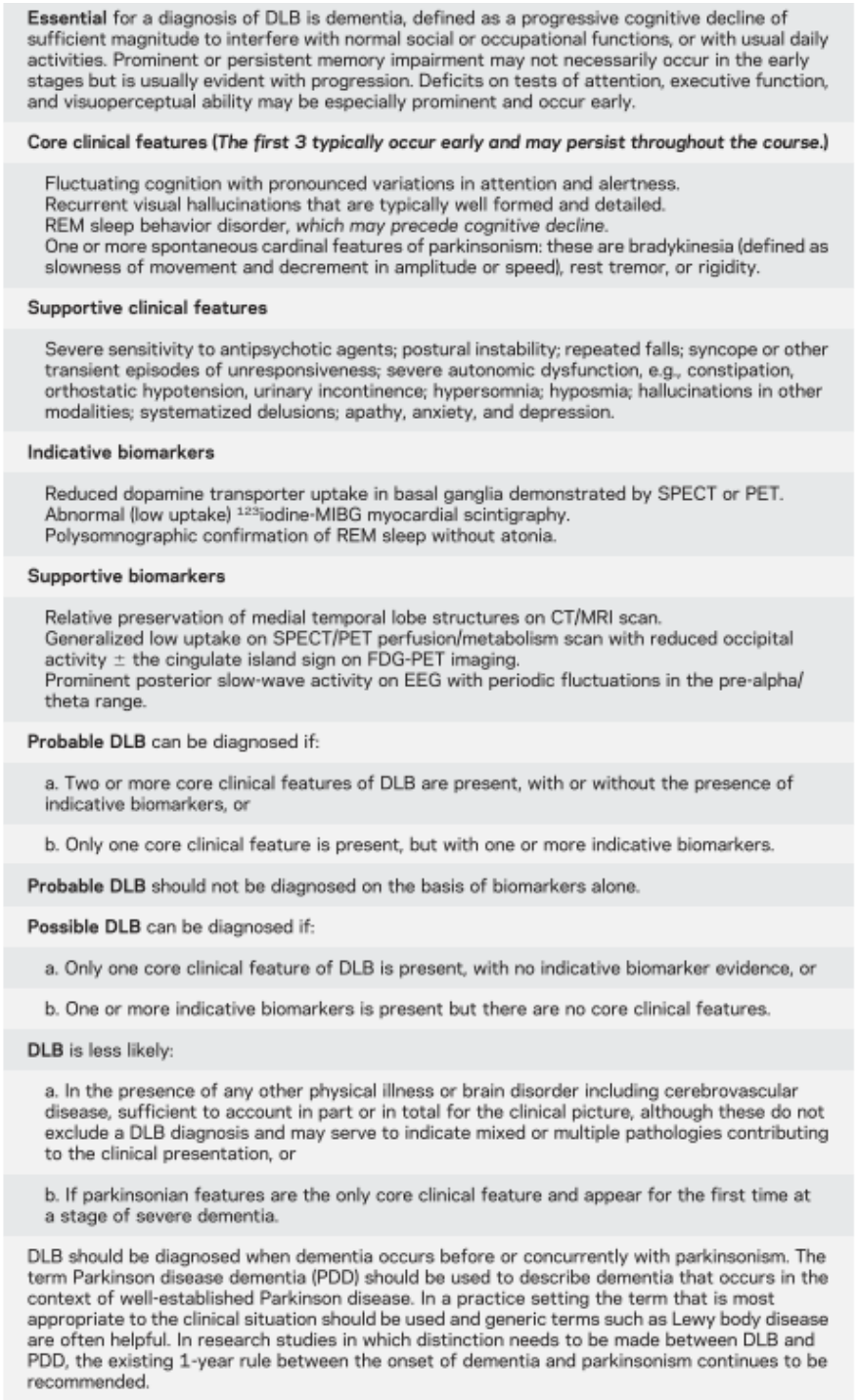
There has since been a growing recognition that more widespread sub-cortical and cortical Lewy body pathology is also a common cause of dementia, and is currently understood to be the

second most common cause of neurodegenerative dementia (Heidebrink, 2002; Jellinger and Attems, 2011; Vann Jones and O'Brien, 2014), after AD. Lewy body pathology is present in relative isolation in at least 8.5% of cases of dementia, and in up to 17.4% of cases in combination with other pathological findings (Jellinger and Attems, 2011). The associated clinico-cognitive syndrome has been described under various names historically, including 'Lewy body variant Alzheimer's disease' (Hansen *et al.*, 1990; Galasko *et al.*, 1994) and 'senile dementia of Lewy body type' (McKeith *et al.*, 1994), reflecting a previous lack of consensus in its conceptualisation, but since the formulation of consensus diagnostic criteria (McKeith *et al.*, 1996) this has been consistently identified as dementia with Lewy bodies (DLB) in the revised criteria (McKeith *et al.*, 2005; McKeith *et al.*, 2017).

Previous descriptions of DLB as a variant of AD (Olichney *et al.*, 1998) reflect the ostensible similarities between these syndromes in their clinical presentation, and common overlap in underlying neuropathological presentation, which remain as obstacles in distinguishing these in clinical research and practice. While both AD and DLB may feature insidious onset of single- or multi-domain cognitive decline, and consequently loss of independent function, DLB is a distinct form of dementia with its own particular challenges in diagnosis, treatment, and care reflecting the different underlying patterns of neuronal dysfunction (Taylor *et al.*, 2020). Despite this, relative to the prevalence expected from neuropathological studies (Jellinger and Attems, 2011; Brenowitz *et al.*, 2017a) DLB is apparently still under-diagnosed in clinical practice (Kane *et al.*, 2018) suggesting that more work is required to disentangle this syndrome from competing clinical diagnoses.

Current consensus criteria (McKeith *et al.*, 2017) for DLB require that ante-mortem diagnosis be made on the basis of the presence of specific core clinical features and indicative biomarkers, in addition to an all-cause dementia diagnosis as introduced in **Section 1.1** (McKhann *et al.*, 2011). These clinical features and biomarkers may specifically distinguish DLB from competing diagnoses such as AD, a vascular cognitive impairment, or a frontotemporal dementia. The current criteria include four equally weighted core clinical features, and three indicative

biomarkers, which in combination may distinguish DLB in clinical settings (**see Figure 1.1** reproduced from McKeith *et al.*, 2017).



Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior 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 clinical features

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.

Indicative biomarkers

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 biomarkers

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.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

b. One or more indicative biomarkers is present but there are no core clinical features.

DLB is less likely:

a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or

b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

Figure 1.1. Current consensus criteria for clinical diagnosis of DLB, adapted from McKeith *et al.* (2017), *Neurology*, 89, p. 3.

1.2.1 Core clinical features

Visual hallucinations

Hallucinations, erroneous sensory perceptions in the absence of any real stimulus, are a feature of a wide range of medical conditions, though they may also be a normal experience in certain situations e.g. hypnagogic hallucinations. Hallucinations may be simple or complex, may present in any of the sensory domains (e.g. as tactile, auditory, or visual hallucinations), and may sometimes develop when normal sensory input is disrupted or removed entirely; for example hallucinatory pain experienced in an amputated limb (Collins *et al.*, 2018), or auditory hallucinations after hearing loss (Waters *et al.*, 2018).

Visual hallucinations are a common feature in psychiatric, neurological, and ophthalmological disease (O'Brien *et al.*, 2020), occurring in 11-17% of AD cases, 5-14% of people with vascular cognitive impairments, and in 15-60% of people with primary visual impairment depending on the severity of sight loss (ffytche, 2009). Visual hallucinations may present as simple visual experiences without form (e.g. colours or simple shapes), misidentifications, or distortions of real stimuli, but may also present as more complex hallucinations with a clear form (e.g. as humans, objects or animals, in the absence of any real stimuli to misidentify or distort). Complex, well-formed visual hallucinations are a hallmark feature of DLB and are present in as many as 80% of developed cases (McKeith *et al.*, 2017) and may appear, though less commonly, at the very early stages (31.6% of cases; Lin *et al.*, 2018). Autopsy-confirmed cases of DLB are considerably more likely to have presented with visual hallucinations during life than AD cases (Luis *et al.*, 1999) and the development of visual hallucinations in an AD syndrome is highly indicative of the additional presence of LB pathology, and therefore a mixed AD-DLB dementia (Thomas *et al.*, 2018).

Because of the common and variable nature of visual hallucinations in other conditions, the nature of hallucinatory experiences must be carefully assessed by an experienced clinician. Simple visual hallucinations are a common feature in eye disease-related sight loss (ffytche, 2009), for which ageing is a considerable risk factor; age-related macular degeneration, the most common cause of visual impairment, has an estimated global prevalence of 11.2-15.1% (early)

and 2.2-3.9% (late) in those aged over 70 years. Amongst other psychiatric disorders, complex visual hallucinations often also occur in delirium, which is similarly associated with ageing and dementia (Inouye *et al.*, 2014), and in schizophrenia (Waters *et al.*, 2014). Consequently, consideration of the diagnostic relevance of visual hallucinations to suspected DLB must consider the complexity of the visual experience alongside any competing explanation for the hallucinations (Manford and Andermann, 1998; Terao and Collinson, 2000) on a case-by-case basis. In DLB, complex visual hallucinations may often take on forms of humans, animals, or objects, and may be sufficiently credible to compel the hallucinator to attempt to act on their presence (e.g. by attempting to interact with the person, or to tidy away the clutter caused by perceived objects) which may lead to a realisation that they are not real (Yumoto and Suwa, 2019). Descriptions of phenomena such as these, along with an absence for any alternative explanation for the visual experiences, may be highly supportive of a diagnosis of DLB.

While the exact aetiology responsible for visual hallucinations in DLB is uncertain, DLB is associated with focal functional disturbance in the cortical (Minoshima *et al.*, 2001; Fujishiro *et al.*, 2013) and sub-cortical (Delli Pizzi *et al.*, 2014) visual systems, without extensive structural atrophy. This particular pattern of pathological changes has been theorised (Erskine *et al.*, 2019) to be responsible for the form of visual hallucinations typical of DLB; functionally degraded visual input is misinterpreted downstream by preserved cortical structures, manifesting in well-formed hallucinations. The perception of visual hallucinations in general may be supported by an increased reliance, in some individuals, on top-down prior expectations rather than bottom-up sensory input due to attentional dysfunction (Collerton *et al.*, 2005; Zarkali *et al.*, 2019), a failure in source monitoring leading to internally-originating visual imagery to be misattributed to external stimuli (Allen *et al.*, 2008; Aynsworth *et al.*, 2017), or hyperexcitability in the structurally-preserved visual cortex (Burke, 2002). These different hypothesised causes may likely account for the varying presentations of visual hallucinations in disorders with widely differing pathophysiology.

In AD, PD and DLB, visual hallucinations have been consistently associated with particular patterns of pathophysiology, including cholinergic denervation (Court *et al.*, 2001), though

patterns may vary between diseases (Hepp *et al.*, 2013). Consequently cholinergic treatment may reduce the severity of visual hallucinations in DLB (Satoh *et al.*, 2010).

Cognitive fluctuations

Cognitive fluctuations, intra-individual variations in level of alertness, attention and arousal, and cognitive functioning, are commonly reported in most common types of dementia (Lee *et al.*, 2012), though they are considerably more likely to be observed in DLB. Fluctuating cognition and attention is present in as many as 90% of DLB cases (O'Dowd *et al.*, 2019), compared with 10% of AD cases (though these may be qualitatively different as noted below), and may be observed prior to onset of dementia in DLB (Donaghy *et al.*, 2017).

Apparent fluctuations may be reported in AD and vascular cognitive impairments, but are recognised as being qualitatively different in presentation (Bradshaw *et al.*, 2004). DLB-type fluctuations are described as periods of blank unresponsiveness while the patient is seemingly awake, lasting from seconds to minutes or even considerably longer, followed by a return to apparently normal alertness and lucidity; fluctuations are therefore worse in severity in DLB (Walker *et al.*, 2000a). This pattern of fluctuation has been theorised to reflect dysfunction of widespread networks responsible for regulating attention, arousal, and sleep (Matar *et al.*, 2019b; O'Dowd *et al.*, 2019) and may be traced back to a central cholinergic deficiency (Ballard *et al.*, 2002; O'Brien *et al.*, 2005; Schumacher *et al.*, 2020b). In comparison, fluctuations as described in AD have been reported by caregivers as periods of severe forgetfulness and repeated questioning often in response to environmental stressors, while retaining active alertness (Bradshaw *et al.*, 2004). Appearing to be episodes of particularly severe AD-typical amnestic memory impairments, fluctuations as described in this way would not be considered as symptomatic of DLB, and likely reflect a different pathophysiological process relating to the primary memory dysfunction, possibly interacting with other causes of periodic worsening of dementia symptoms such as ‘sundowning’, which may be reported in up to 82% of people with dementia (Boronat *et al.*, 2019).

REM sleep behaviour disorder

In healthy individuals, the rapid eye movement (REM) stage of sleep normally features a loss of muscle tone, paralysing the body and preventing movement during dreaming. REM sleep behaviour disorder (RBD) is a sleep disorder characterised by an aberrant lack of typical atonia in this sleep stage; this leads to the enactment of motor actions from vivid dreams, such as the thrashing of limbs, vocalisations, and grasping behaviours, which may lead to physical harm to self or others, as well as distress to bed-sharers (Boeve, 2010). RBD has been recognised as a common early presentation of synucleinopathic neurodegenerative diseases (Boeve *et al.*, 2001), and while it may remain as an isolated RBD syndrome for some time, this may develop into one of the multi-faceted synucleinopathies (i.e. PD or DLB).

A history of RBD is highly indicative of DLB (Ferman *et al.*, 2011), being present in 76% cases of autopsy-confirmed DLB, in comparison to only 4% of non-DLB, and is therefore considered to be a core feature of the syndrome. While a history of RBD is also a risk factor for development of other Lewy body diseases such as PD (Hickey *et al.*, 2007), people with either PD or DLB are considerably more likely to have experienced RBD than those with AD (Boeve *et al.*, 2001). A clear history of RBD is therefore highly predictive of underlying LB disease, even prior to onset of motor or cognitive symptoms; RBD may present in cases of eventual DLB or PD years and occasionally decades before the onset of cognitive or motor symptoms (Claassen *et al.*, 2010) and so may be one of the earliest observable symptoms of an underlying neurodegenerative process in some cases. Postuma *et al.* (2019) identified that, in isolated RBD without cognitive impairment or parkinsonism, 73.5% had developed PD or DLB after twelve years of follow-up, with an annual conversion rate of 6.3%. In this sample, a parkinsonism-first onset (i.e. PD) was slightly more common than a dementia-first onset (DLB), with PD occurring first in 56% of cases, versus DLB in 44%.

Definitive presence of REM sleep without atonia (RSWA) is confirmed with polysomnography (PSG) by the observed preservation of muscle tone during REM sleep. This allows for differential diagnosis of RBD from a potential non-REM stage parasomnia, which may mimic RBD based on informant or patient description alone (Boeve, 2010). RBD may also be quickly

screened with a questionnaire administered to an informant (Boeve *et al.*, 2011b), which is more feasible in studies of dementia where PSG confirmation of RSWA would be impracticable, though at a cost of specificity (74%), as non-REM stage parasomnias (e.g. obstructive sleep apnoea) may mimic RBD in this manner. While sensitivity was high in this sample (98%), all patients had a bed partner available as an informant as required by the questionnaire, which may not translate as well into community settings; this is a particular limitation given that among over 65s, the population of primary interest for dementia research and in clinical practice, living alone is both common, and increasing. In the developed world between 20-40% of individuals aged over 65 are estimated to live alone, largely reflecting increased separation, divorce, and widowhood in older age (Reher and Requena, 2018); while rates of living alone are lower in the developing world, those who live with extended family may not have a bed partner as an informant. In these cases, this questionnaire would not be appropriate to complete, and so the presence of RBD may be missed.

Parkinsonism

PD is clinically characterised by a distinct pattern of motor impairment (Postuma *et al.*, 2015) including resting tremor, rigidity, and bradykinesia. This broad group of symptoms is described as parkinsonism, which may be observed in conditions other than in PD itself; diagnosis of PD requires not only the presence of clinically-diagnosed parkinsonism, but also supportive information that these symptoms are due to PD and not any other condition. Conditions in which parkinsonism may arise include multiple system atrophy, progressive supranuclear palsy, normal pressure hydrocephalus, as a result of one or more strokes, or cerebellar abnormalities.

Due to the shared aetiology underlying both PD and DLB, parkinsonism is often also observed in DLB, occurring in up to 85% of cases at an advanced stage (Fujishiro *et al.*, 2008); current criteria dictate that symptoms of parkinsonism in DLB are in either insufficient number or severity to qualify an independent diagnosis of PD, or that their onset coincides with- or follows the emergence of cognitive impairment (preceding cognitive symptoms by fewer than 12 months; McKeith *et al.*, 2017). The presence of only one feature of parkinsonism is sufficient for this to be considered as a core feature of suspected DLB. As in PD, the presence of parkinsonian

signs in DLB is indicative of a dopaminergic deficiency (Miller and O'Callaghan, 2015), with neuronal loss in the substantia nigra leading to dysfunction of the nigrostriatal pathway and a consequent failure to initiate and sustain voluntary movements. In individuals an absence of parkinsonism, as seen in at least 15% of DLB cases (Fujishiro *et al.*, 2008), may therefore suggest a relative absence of dopaminergic dysfunction.

In DLB, the severity of parkinsonism and any changes over time may be quantified with part three of the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz *et al.*, 2008). With these scales any impairments are 'rated as seen'. Non-parkinsonian causes of motor impairment, e.g. arthritis, may therefore contribute to high scores in these. Clinical judgement of parkinsonism for diagnostic purposes must therefore be primarily guided by a holistic consideration of all information available and follow the Movement Disorder Society (MDS) criteria for these, rather than being based on scores on this rating scale alone.

1.2.2 Supportive clinical features

In addition to the core clinical features of DLB, a number of supportive features may also be observed; these are insufficiently sensitive and/or specific for use in diagnosis, but may support a diagnosis in the presence of one or more core clinical features (McKeith *et al.*, 2017). These features include: autonomic dysfunction (Horimoto *et al.*, 2003; Thaisetthawatkul *et al.*, 2004), neuroleptic sensitivity (McKeith *et al.*, 1992), olfactory dysfunction (Williams *et al.*, 2009), unexplained falls (Ballard *et al.*, 1999c) or postural instability, non-visual hallucinations or delusions (Ballard *et al.*, 1999a), mood disorders including apathy, anxiety, or depression (Rockwell *et al.*, 2000), excessive daytime sleepiness, unresponsiveness or syncope (Boddy *et al.*, 2007). While these features may not contribute directly to a diagnosis, they may assist clinicians in identifying potential candidates for detailed exploration of DLB and are important to recognise as likely impactors on quality of life for people with dementia and their caregivers.

Neuroleptic sensitivity

Long recognised as a suggestive clinical feature of DLB (McKeith *et al.*, 1996; McKeith *et al.*, 2005), Lewy body diseases are associated with a severe and life-threatening sensitivity to

neuroleptic treatment (McKeith *et al.*, 1992; McKeith *et al.*, 1995). Up to 50% of people with DLB exposed to these medications may demonstrate this neuroleptic sensitivity resulting in severe sedation or even death, in addition to common 'normal' side effects such as extrapyramidal symptoms. This may complicate efforts to treat neuropsychiatric symptoms of LB disease (Baskys, 2004). With an increase in clinical awareness of this risk, and risks associated with antipsychotics in other dementias (Ballard and Howard, 2006), neuroleptics are now much less likely to be prescribed to people with dementia. As a result, this symptom is less likely to occur and consequently the value of neuroleptic sensitivity as a feature for the diagnosis of DLB has diminished. Sensitivity to antipsychotic medication is therefore considered to be a supportive feature only in DLB diagnosis (McKeith *et al.*, 2017), but remains an important symptom to consider in clinical settings due to the potential for harm if overlooked (Taylor *et al.*, 2020).

1.2.3 Indicative biomarkers

The presence of indicative biomarkers of LB disease may aid in differential diagnosis of DLB from AD or other causes of dementia. A diagnosis of probable DLB may not be made on the basis of multiple biomarker presence alone without core clinical features: in this case a diagnosis of possible DLB would be made.

Abnormal uptake of dopamine transporter to the basal ganglia

Using N-ω-fluoropropyl- 2β-carbomethoxy- 3β-(4-iodophenyl) nortropane (FP-CIT) single-photon emission computed tomography (SPECT) or PET imaging, presynaptic dopamine transporters in the basal ganglia may be visualised and interpreted by an experienced analyst to assess dopaminergic deficiencies. Visual ratings of images may be dichotomised as showing either normal or abnormal uptake, an ordinal visual rating scale may be used (Benamer *et al.*, 2000), or semi-quantitative automated analyses may be performed (Colloby *et al.*, 2004) for increased granularity; the latter option appears to offer slightly more accuracy than visual ratings (McCleery *et al.*, 2015), and in modern clinical practice and research settings, both methods are often used alongside one another.

DLB and PD patients are likely to display abnormalities of dopamine transporter FP-CIT binding in the corpus striatum in comparison with healthy controls, while AD patients as a group do not (Hu *et al.*, 2000; O'Brien *et al.*, 2004), except in advanced cases where tauopathy may affect the brainstem and substantia nigra. Abnormal dopaminergic imaging is present in 77.7% of clinically probable DLB cases *versus* 6.9% of clinically probable AD (McKeith *et al.*, 2007a). Patterns of abnormality vary, and these may present as unilateral or bilateral reductions or absences of uptake in the putamen alone or may also extend symmetrically or asymmetrically to the caudate, reflecting progressive degeneration of pre-synaptic dopaminergic neurons. Use of FP-CIT imaging has high diagnostic accuracy in DLB, with good sensitivity and specificity (McKeith *et al.*, 2007b; Papathanasiou *et al.*, 2012), and its utility in diagnosis has been supported by autopsy validation (Thomas *et al.*, 2017).

Comparison of repeated FP-CIT scans after 1-year of follow up has indicated that uptake abnormalities in DLB may progressively worsen over time (Colloby *et al.*, 2005). Some DLB cases may present with initially normal transporter uptake on FP-CIT, with abnormalities emerging further into the disease course (van der Zande *et al.*, 2016), while others may present with abnormal uptake at the prodromal stages prior to onset of dementia (Thomas *et al.*, 2019). However, not all cases of DLB have any notable dopaminergic dysfunction even by death; 10% of cases of DLB have normal projections from the substantia nigra to the striatum at autopsy (Thomas *et al.*, 2017). Abnormal dopamine transporter uptake may therefore be characterised as a progressive degenerative process with different staging between individuals, and even absence of degeneration in some cases, which may partially account for the observed variability in patterns of abnormality found in cross-sectional studies. The presence of a normal FP-CIT uptake on initial imaging does not necessarily preclude the eventual emergence of abnormal dopaminergic imaging further into the disease course, but in some cases may suggest a relative sparing of the dopaminergic system, which may be associated with an absence of parkinsonism.

Abnormal myocardial uptake of 123I-MIBG

Reduced uptake of ^{123}I-meta-iodobenzylguanidine (MIBG; a noradrenaline analogue that binds to presynaptic noradrenaline receptors) to the heart, relative to the mediastinum, may be observed by means of myocardial scintigraphy in DLB (Watanabe *et al.*, 2001). Low cardiac uptake of MIBG may reflect early cardiac denervation (Orimo *et al.*, 2005) related to the pathological effects of alpha-synuclein present in the sympathetic nervous system (Beach *et al.*, 2010). This biomarker may be useful to discriminate DLB from AD (Yoshita *et al.*, 2006), particularly in the early stages of dementia (Yoshita *et al.*, 2015); both sensitivity and specificity for separating DLB from AD appear better in mild dementia (77.4% and 93.8%, respectively) than in moderate or severe dementia (59.6% and 83.3%). As pathologically-identified cardiac denervation has been found to separate a mixed AD-DLB pathology from pure AD (Serrano *et al.*, 2020), cardiac MIBG may also show promise in identifying a mixed AD-DLB clinical syndrome ante mortem.

MIBG scintigraphy therefore may have diagnostic utility as an alternative to, or when used in conjunction with (Shimizu *et al.*, 2016), dopaminergic imaging to aid in the differential diagnosis of DLB or a mixed syndrome from AD. Aside from AD, MIBG imaging may also help discriminate DLB and PD from other syndromes with overlapping clinical presentations such as progressive supranuclear palsy, multiple system atrophy, and frontotemporal dementias (Kashihara *et al.*, 2006; Estorch *et al.*, 2008), which FP-CIT imaging may be unable to distinguish between (Morgan *et al.*, 2012). However, several factors may complicate the application of MIBG to everyday clinical practice including availability of radioligands, experience in undertaking imaging, and rates of cardiovascular comorbidity or of prescription of contraindicative medications. Therefore within clinical settings in the United Kingdom, cardiac MIBG does not currently appear to be favourable to the more widely used FP-CIT SPECT in detecting cases of DLB (Kane *et al.*, 2019), though this could change if clinical experience in utilising this develops further.

While a valuable comparison in clinical diagnostic settings, comparing the information garnered from MIBG and FP-CIT imaging may be a false dichotomy in research settings; these two

imaging methods assess differing pathophysiological processes (cardiac sympathetic denervation in the former, nigrostriatal dopaminergic denervation in the latter) which likely differ between individuals, given the considerable variation in patterns of LB neuropathology and pathophysiology: some individuals may have abnormalities in one system or the other, some in both, and some in neither. These differing biomarkers may reflect different clinical phenotypes, albeit with some natural degree of overlap.

Polysomnography (PSG)-confirmed REM sleep without atonia

The presence of PSG-confirmed REM sleep without atonia is highly indicative of DLB; in patients with reported RBD as a clinical symptom this biomarker is particularly specific for LB diseases (Boeve *et al.*, 2013). Confirmation of REM sleep without atonia may assist in the differential diagnosis of RBD from non-REM sleep parasomnias which may mimic RBD based on patient or informant report but may not be indicative of the presence of Lewy body disease. However, this procedure is laborious, expensive, and may not be practical or ethical to undertake in people with moderate-to-severe dementia.

1.2.4 Supportive biomarkers

A wider range of biomarkers are associated with a respective differential diagnosis of either AD or DLB. These markers lack the sensitivity or specificity required to assist in diagnosis but may provide a further depth of understanding of underlying disease processes, or heterogeneity of dementia features, particularly in research settings.

While AD is typified by extensive atrophy of the MTL, and in particular the hippocampi, such atrophy is typically less severe in DLB (Burton *et al.*, 2008). MTL volume is not completely preserved in DLB however, and when compared to healthy controls a significant degree of atrophy may still be observed (Barber *et al.*, 1999). Hippocampal atrophy in DLB may reflect the additional contributions of co-occurring AD pathology (Nedelska *et al.*, 2015; van der Zande *et al.*, 2018b). A relative preservation of the hippocampi specifically, and MTL in general (e.g. on structural MRI) may therefore be supportive of a diagnosis of DLB, but is most likely not

sufficiently specific to DLB (as atypical hippocampal-sparing patterns may occur in AD), nor sensitive to it (as hippocampal atrophy may co-occur in DLB) to be considered as an indicative biomarker.

While the occipital lobes are largely spared from structural atrophy in both DLB and typical AD (Middelkoop *et al.*, 2001), functional disruption of the visual pathways is typical of DLB. In comparison with AD, DLB features occipital hypoperfusion (Lobotesis *et al.*, 2001) and hypometabolism (Ishii *et al.*, 1999). This may help partially explain some of the cognitive and clinical symptoms experienced in DLB, as discussed later. The cingulate island sign is a particularly specific pattern of posterior hypometabolism which may be found in DLB, with reduced occipital metabolism but a relative sparing of the posterior cingulate cortex. This pattern of hypometabolism is not typically found in AD (Imabayashi *et al.*, 2016), but may become less useful as LB disease develops and the sign becomes less clear, which may reflect an increase in AD co-pathology in more advanced DLB (Iizuka *et al.*, 2017). Generalised reductions in metabolism or perfusion, reduced occipital activity specifically, or the cingulate island sign in particular may therefore also be supportive of a DLB diagnosis.

Resting state electroencephalography (EEG) has suggested that DLB is associated with dominant frequency slowing over the posterior derivation in comparison with AD (Bonanni *et al.*, 2008). More specifically, this pattern of slowing appears to be associated with cognitive fluctuations in DLB (Stylianou *et al.*, 2018). Focal posterior slow-wave activity may therefore be a suggestive biomarker for DLB. EEG may also offer further context in research settings as to the network dysfunctions underlying particular clinical symptoms, e.g. as a marker for the cholinergic deficiency which may contribute to cognitive fluctuations or visual hallucinations (van der Zande *et al.*, 2018a; Schumacher *et al.*, 2020b).

1.2.5 Neuropathology

While possible or probable diagnoses may be made of suspected AD and DLB in life, the cause of the dementia may only be confirmed with certainty upon death and autopsy. DLB is characterised by a pathology distinct from the amyloid- and tauopathy which defines AD

(Hyman *et al.*, 2012). DLB is a synucleinopathy, characterised by the presence and progressive aggregation of Lewy bodies and Lewy neurites in neurons of the cortex or brainstem; both Lewy bodies and neurites contain aggregates of alpha-synuclein protein (Spillantini *et al.*, 1998). In addition to its presence in the central nervous system, alpha-synuclein may also present within the peripheral nervous system in LB disease (Beach *et al.*, 2010), which may result in autonomic dysfunctions and MIBG imaging abnormalities. This underlying pathology is shared by DLB, PD in which it was first described, and Parkinson's disease-dementia (PDD); these distinct clinical syndromes are currently conceptualised as different outcomes sharing the underlying pathology of Lewy body disease (McKeith *et al.*, 2017).

The staging and spread of Lewy body pathology in the brain, and presence of AD co-pathology, is variable, with significant differences between individuals (Brunnström *et al.*, 2012) which may contribute to the heterogeneous presentation of symptoms within DLB (Morenas-Rodríguez *et al.*, 2018; Coughlin *et al.*, 2020), and the variable timings of parkinsonism and dementia that contribute to diagnosis of DLB, PD, or PDD.

It is rare for a clinical diagnosis of DLB to manifest from a 'pure' Lewy body disease; Lewy bodies can often be accompanied by AD pathology, with significant levels of amyloid deposition in some cases (Gomperts *et al.*, 2008). Neurofibrillary tangles may also be present in DLB, but are less typical or prolific than in clearly defined AD (Fujishiro *et al.*, 2008). Recent neuropathological data has suggested that mixed pathologies may be underestimated in ante-mortem clinical diagnoses (Selvackadunco *et al.*, 2019) with additional features of DLB often being missed in clinical AD. The positive identification of concurrent DLB and AD during life is of particular importance given the poorer clinical prospects associated with a mixed AD-LB aetiology underlying dementia (Brenowitz *et al.*, 2017a).

Caution must be exercised in interpreting the apparent abundance of mixed pathologies in post-mortem studies however, as these may not entirely reflect the neurodegenerative processes driving early clinical change; increasing age is associated with the presence of AD pathology at autopsy, ranging from 15% at age 70, 65% at age 85, to 75% at age 95 (Farfel *et al.*, 2019). This

is the case even in unimpaired groups, with up to 40% of apparently cognitively healthy subjects having AD-associated pathological findings by the ages of 80-85 (Selvackadunco *et al.*, 2019). Cases of DLB may therefore develop more AD-type pathology towards the later stages of dementia and prior to death but may be inaccurate to describe as a clinically mixed syndrome at the early stages. Post-mortem samples are a snapshot of the end-stage of a long period of degeneration, and in some cases an eventual mixed neuropathological profile may not be an accurate reflection of the biological processes responsible for their preceding clinical syndrome, especially when clinical and cognitive data are derived from the mild or prodromal stages.

While additional pathological processes may not always reach a sufficient threshold in the early or intermediate stages of decline to have a clear clinical contribution, in some cases the presence of sufficiently evident mixed pathologies may manifest in a mixed clinical profile (Thomas *et al.*, 2018); this might complicate prospective diagnosis, and may also contribute to variance in cognitive decline. In cases of mixed AD-DLB with a high neuropathological Braak staging however, the presence of clinical features of DLB within the mixed dementia syndrome may be obscured, contributing to misdiagnosis (Merdes *et al.*, 2003). Furthermore, cases of mixed AD-DLB with missed diagnosis of DLB features feature a poorer prognosis with faster cognitive decline than either pure-, or clinically-diagnosed mixed pathologies (Malek-Ahmadi *et al.*, 2019).

AD and LB pathologies therefore have significant degrees of overlap and are not mutually exclusive. This may account in part for the difficulties in distinguishing these diseases prior to autopsy, and the lack of symptomatic homogeneity within each disease.

1.2.6 Prognosis, treatment, and management

As a result of the distinct pathophysiology and clinical presentation, DLB has a different prognosis to AD, as well as particular treatment and management needs.

Prognosis

A diagnosis of DLB is associated with much greater burden to caregivers and lower ability to live well (Wu *et al.*, 2018a). Increased carer stress in DLB is associated with symptoms of psychosis, mood disturbance, daytime sleepiness, and the experience of cognitive fluctuations (Lee *et al.*, 2013). Delays in diagnosis and lack of guidance or support may also play a role in caregiver distress in DLB (Killen *et al.*, 2016). As a result, those with a diagnosis of DLB have a greater reliance on residential care (Mueller *et al.*, 2017), and an increased risk of hospitalisation, with greater lengths of stay, which is similarly associated with the presence of psychotic symptoms (Mueller *et al.*, 2018).

Consequently, a recent meta-analysis has demonstrated that DLB has a shorter average survival time after diagnosis (4.11 years) than AD (5.66 years), independent of age, gender, and level of cognitive functioning (Mueller *et al.*, 2019). DLB also results in increased economic healthcare costs, with those costs increasing with each core clinical feature observed, and being particularly high in those experiencing fluctuating attention and cognition (Espinosa *et al.*, 2020).

Treatment and management

The multi-faceted nature of underlying pathophysiology and resultant symptoms in DLB may complicate treatment and require a holistic management strategy, as reviewed by Taylor *et al.* (2020), particularly as therapeutics which typically target one type of symptom may have an adverse effect on entirely different symptoms; for example, treatment of hallucinations and delusions with typical anti-psychotics may lead to a severe sensitivity reaction (as noted previously) while treatment of motor symptoms with dopaminergic medications may worsen psychotic symptoms (Goldman *et al.*, 2008).

In general, cholinesterase inhibitors are well tolerated in DLB and have shown utility in treating both cognitive symptoms and neuropsychiatric symptoms (Taylor *et al.*, 2020); donepezil and rivastigmine being the best supported examples of these, and therefore common in clinical use. The efficacy of such treatments supports the key role of cholinergic deficiencies in the clinical presentation of DLB. Levodopa, the front-line pharmacological treatment for PD, may have

utility in reducing parkinsonism in DLB, however as noted above, dopamine therapy may worsen psychotic symptoms in up to one in three patients, requiring careful balance of risk. Deep brain stimulation, while effective at alleviating motor symptoms of PD, is contraindicated for DLB as this may worsen cognitive impairments when they are already present (Mehanna *et al.*, 2017). RBD may be managed with a range of treatments, including clonazepam, melatonin, or memantine, as well as non-pharmacological interventions to change sleep hygiene and environment.

1.2.7 Section summary

DLB is a common neurodegenerative syndrome recognised as possessing distinctive clinical and pathological features, and consequently has particular management needs in healthcare settings. Prospective diagnosis may be complicated by common clinical and pathological overlap with AD, but a number of clinical features and biomarkers have been described which may appropriately distinguish these syndromes ante-mortem. A diagnosis of DLB has implications for both the prognosis of a dementia syndrome, as well as for the treatment and management of this.

1.3 Prodromal dementia

The symptoms of neurodegenerative diseases typically emerge gradually as the underlying pathophysiology develops from the asymptomatic pre-clinical stage, to the prodromal stage when mild symptoms begin to emerge, before reaching the fully manifest clinical stage (Jack *et al.*, 2010). In AD, this prodromal stage will typically present as worsening cognitive functioning developing from mild cognitive impairment (discussed in detail in the following section) towards eventual dementia (Verlinden *et al.*, 2016; Han *et al.*, 2017).

LB disease has a heterogeneous presentation with a wide range of potential clinical features. Accordingly, the prodromal stages of DLB may also have different characteristics in different individuals (McKeith *et al.*, 2016), including not only cognitive-onset, but also delirium-, or psychiatric-onset presentations prior to dementia (McKeith *et al.*, 2020). RBD (Claassen *et al.*, 2010), psychiatric symptoms (Jicha *et al.*, 2010), or parkinsonism (Aarsland *et al.*, 2010), may be

present for some time before onset of cognitive symptoms, and these may similarly be conceptualised as different early symptoms of an underlying synucleinopathy which may be prodromal manifestations of eventual DLB, PD, or multiple system atrophy (another less-common synucleinopathy, which does not fall under the spectrum of LB disease).

While wider definitions vary in the literature, within this work the 'prodromal stage of DLB' is considered as an umbrella term, including the early symptomatic stages of the many different recognised diagnostic routes into DLB including, for example, psychiatric-onset cases or isolated RBD which may not yet display (overt) cognitive symptoms. Clinically-diagnosed mild cognitive impairment is therefore considered as the *cognitive* prodrome of DLB, being only one of these many possible prodromal DLB conditions, and the best characterised and most common.

1.3.1 Mild cognitive impairment with Lewy bodies

Currently conceptualised as a transitional stage between normal cognitive ageing and dementia, individuals experiencing a greater-than-normal decline in cognitive functioning but with preserved independent daily functioning may be diagnosed with mild cognitive impairment (MCI; Albert *et al.*, 2011). As increasing attention is being paid to the prodromal stages of dementia syndromes such as DLB and AD in an effort to improve diagnostics and develop treatments, MCI has therefore developed into a central concept in current research representing the cognitive prodrome to dementia. Recent prevalence estimates for MCI in those aged 60 or older range from 5.13% to 29.9%, increasing with age (Overton *et al.*, 2019). While some MCI patients will return to normal functioning, and others will remain stable within the MCI category, due to the progressive nature of neurodegenerative disease there is a high likelihood of eventual conversion to dementia after a diagnosis of MCI (Gauthier *et al.*, 2006), with typical estimates ranging from 5-20% per year, though this may vary greatly by the definition of MCI used and the assessment setting, to as high as 39% per year, as reviewed by Belleville *et al.* (2017); when drawing from community settings, conversion from MCI to dementia is relatively low, while in neurodegenerative-oriented settings, these may be higher, reflecting different conceptualisations of MCI.

Two principal methods of diagnosing and classifying MCI sub-types exist; individuals with MCI may be assessed with a neuropsychological assessment battery, and assigned a sub-type dependent on the domains of observed impairment (amnestic or non-amnestic, single- or multi-domain; Winblad *et al.*, 2004) in which they score below a given threshold. For example, individuals may be defined as amnestic MCI when scoring greater than 1.5 standard deviations below education and age-adjusted mean scores on a specific episodic memory test (Craft *et al.*, 2012) or non-amnestic if the primary cognitive dysfunction exists in a non-memory domain. While this method helps classify objective domains of cognitive impairment, these thresholds are arbitrary and may be insensitive to meaningful decline in individuals with a high functioning at baseline. Furthermore, this method makes it difficult to explore disease-specific neuropsychological outcomes, as the outcome measures are not independent of the diagnostic criteria.

An alternative method is to classify MCI according to disease-specific clinical features; as the clinical symptoms, and many biomarkers, of DLB and AD-type dementia may manifest in individuals long before loss of capacity for independent living, it may be possible to identify individuals likely to be in the prodromal stages of DLB or AD, and consequently assign a specific diagnosis of MCI with Lewy bodies (MCI-LB; Belden *et al.*, 2015; Donaghy *et al.*, 2017) or AD (MCI-AD; Jicha *et al.*, 2010) should they otherwise meet disease-specific clinical criteria despite not yet meeting the threshold of functional impairment required for a dementia diagnosis. This method may be preferable when research is interested in the differences in neuropsychological patterns associated with different diseases, as the diagnostics remain independent of the outcome measures.

As a developing field of study, with a significant degree of heterogeneity between and within subtypes (amnestic or non-amnestic, single or multi-domain), MCI is still being firmly conceptualised; particularly in the case of MCI-LB. The use of clinically-guided differential MCI diagnoses may be gaining traction, with the recent publication of consensus criteria for diagnosis of prodromal DLB, including MCI-LB, in research settings (McKeith *et al.*, 2020). In the long term these criteria will require validation demonstrating that MCI-LB reliably converts to DLB,

and MCI-AD to AD-type dementia, as well as eventual autopsy validation of clinical diagnoses, to ensure that that these translate adequately to use in clinical practice.

Non-degenerative MCI

Understanding the MCI syndrome is complicated by the emergence of non-degenerative cases. While rates vary depending on diagnostic method and sampling setting, it is not uncommon for MCI cases to remain apparently stable for long periods of time, with past research into MCI in AD samples identifying stability in as few as one in three cases (Pagani *et al.*, 2010) or even in a majority (55%) of cases (Huang *et al.*, 2000). As noted previously, this heterogeneity likely reflects intangible differences in recruitment and clinical assessment (e.g. when considering moderate depression as an exclusion for MCI diagnosis) leading to differing rates of inclusion of non-degenerative cases.

After further information comes to light (e.g. after follow-up assessment without any clear decline), what was previously considered to be a neurodegenerative MCI may be alternatively characterised as a non-degenerative vascular cognitive impairment (O'Brien and Thomas, 2015), a stable MCI with objective dysfunction but no clear decline (Villemagne *et al.*, 2008), a subjective cognitive impairment with self-reported dysfunction but no objective evidence of dysfunction (SCI; Prichep *et al.*, 2006; Slot *et al.*, 2018) or fall under the umbrella of the newly-emerging concept of a functional cognitive disorder (Pennington *et al.*, 2015; McWhirter *et al.*, 2019). The latter concept describes cognitive dysfunctions which arise and become reinforced in a cyclical manner through psychological factors primarily (e.g. a patient with health anxiety who erroneously comes to believe that they have a cognitive impairment may become sensitive to normal everyday cognitive mistakes, leading to a loss of cognitive automaticity and therefore objective dysfunction, reinforcing the root anxiety); this represents an attempt at formalising some of the common psychological causes of cognitive dysfunction in the absence of neurodegenerative disease. Cognitive symptoms are known to arise secondary to a mood disorder, being common during and after major depression (Hammar and Årdal, 2009; Baune *et al.*, 2010), as an outcome of sleep disturbance (Lal *et al.*, 2012), health anxiety (Hodgson *et al.*, 1999; Boone, 2009), or a myriad of other possible causes (Stone *et al.*, 2015). Non-degenerative

cases of MCI such as these may partly account for the low transition rates from MCI to dementia in some settings, where neurodegenerative-specific cases of MCI are included alongside degenerative cases (Mitchell and Shiri-Feshki, 2009), reflecting differences in conceptualisation of MCI between research centres.

Early identification of non-declining-, and by extension, declining-MCI cases has important applications in clinical and research settings. Neurodegenerative and non-degenerative MCI cases are likely to have different therapeutic and management needs within memory and psychiatric services; effective treatments may target particular symptoms underlying a non-degenerative cognitive disorder, such as metacognitive processes (Bhome *et al.,* 2019) or depression (McIntyre *et al.,* 2013). Given the different underlying aetiology of their MCI, non-degenerative cases may also be inappropriate to include in clinical trials targeting neurodegenerative processes. Additionally, the misdiagnosis of a neurodegenerative disorder in a subjective or functional syndrome may cause undue distress, reinforce apparent impairments, and contribute to a loss of quality of life (e.g. due to stigma associated with the diagnosis).

Even excluding non-degenerative cases, there remains uncertainty as to how quickly a degenerative MCI may develop into dementia, the extent to which particular neurodegenerative factors might influence this transition, and how specific patterns of cognitive impairment might be related to decline.

Section summary

Mild cognitive impairment is a heterogeneous neurocognitive disorder with numerous potential causes; where this cause is a neurodegenerative disease such as AD or LB disease, MCI may represent the cognitive prodrome of an eventual dementia syndrome. Differential characterisation of the MCI stages of AD and DLB is a focus of current research, given the potential benefits of earlier intervention. Research and treatment of neurodegenerative MCI is complicated by the presence of non-degenerative cases mimicking neurodegenerative types.

1.4 Patterns of cognitive impairment in Lewy body and Alzheimer's diseases

A greater understanding has developed of the particular patterns of neurocognitive impairment that develop in DLB in comparison with AD. While these may lack the predictive power required to contribute to differential diagnosis in isolation, they provide further clues as to the underlying development of dementia in different diseases and are commonly included in disease-specific criteria. Clinicians may benefit from an improved understanding of the expected trajectory of cognitive decline, and which domains may be more or less affected in patients.

1.4.1 Global cognition

Global cognitive functions are taken to represent the sum of all domain-general and –specific functions, and therefore are conceptually a general measure of cognitive ability. A wide range of neuropsychological tests are available to assess global cognitive functioning in clinical and research settings, with suitability being largely dictated by the length of time available for testing, the level of detail or sensitivity desired by the practitioner, or the particular focus of a given study. The mini-mental state exam (MMSE; Folstein *et al.*, 1975) is widely used in clinical settings and offers a quick view of global cognitive functioning. While offering reasonably good sensitivity for dementia, the MMSE lacks sensitivity in the early stages of dementia and MCI (Arevalo-Rodriguez *et al.*, 2015) or in the cases where deficits present in non-memory domains of cognition (Votruba *et al.*, 2016), such as visuospatial functions, to which only one of 30 possible marks is allocated. Despite such limitations, the previous ubiquity of the MMSE in research and clinical practice means it is familiar to a global audience, and may help contextualise the levels of cognitive impairment in any given sample in a more accessible way than less-familiar alternatives. The MMSE may also be useful in settings where time is particularly limited. A similar test, the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) also sees widespread use as an alternative brief screening test to the MMSE, but with better sensitivity to mild dementia (Smith *et al.*, 2007) and more equal assessment of non-memory domains (e.g. executive dysfunction), though this again is limited by a narrow scoring range.

Various more detailed alternatives to the MMSE or MoCA also exist, with varying utility in research and clinical settings; the Addenbrooke's Cognitive Examination (ACE) and its revised versions (ACE-R and ACE-III; Mioshi *et al.*, 2006) offer a reasonable balance of sensitivity and time-cost, and so are commonly administered in memory services in the United Kingdom. The ACE and ACE-R both allow for derivation of an MMSE score, and all three variants provide a total global cognitive functioning score, and relatively more balanced assessment of different cognitive domains in which the MMSE is insensitive, such as visuospatial skills and verbal fluency (Bak and Mioshi, 2007). Meta-analysis has indicated that the ACE-R has superior sensitivity to both the ACE and MMSE in detecting impairment within a dementia population (Larner and Mitchell, 2014). However, all versions of the ACE are more time-intensive than the MMSE, and so may not be agreeable in all settings. A myriad of additional assessments see varying degrees of use in clinics and research; the Dementia Rating Scale (Mattis, 1988), Cambridge Cognitive Examination (CAMCOG; Huppert *et al.*, 1995), and Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog; Wesnes, 2008) also see extensive use in assessing global function in clinical or research settings. As in the ACE, these assessments provide domain-specific sub-scores to contextualise any observed impairments, with greatly expanded scoring ranges for more granularity of assessment.

Automated computerised batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB; Sahakian and Owen, 1992) or detailed neuropsychological testing procedures such as the Wechsler Adult Intelligence Scale (WAIS) provide more in-depth information and may be capable of detecting even mild impairments, but are financially- and time-costly, limiting their utility in routine clinical assessments.

Likely reflecting the predominance of AD in clinical settings, many common global cognitive screening tests disproportionately measure episodic memory functions, and so these may provide unequal descriptions of level of function in atypical non-amnestic neurodegenerative syndromes. For example, a total ACE-R score of 75 in an amnestic syndrome may not be comparable to a total ACE-R score of 75 in a non-amnestic dysexecutive syndrome. There is little in the way of an evidence-based consensus as to how each domain should be relatively weighted in its

contribution towards a global cognitive measure; indeed, the very notion of a general cognitive or intelligence measure is controversial in itself.

As discussed below, premorbid intelligence may be estimated in dementia through the administration of a 'hold test' (a test in which performance does not deteriorate in a given condition); these may allow for estimation and adjustment of an individual's level of function prior to onset of disease to account for the relative deterioration and cognitive reserve. In AD and DLB, and in normal ageing, these often take the form of vocabulary tests, and so are discussed in depth in the language section which follows. Later life intelligence and cognitive reserve may bolstered by a number of protective factors, including educational attainment (Chapko *et al.*, 2018) and socioeconomic status over the life-course (Staff *et al.*, 2018). A person with a neurodegenerative disease but with high educational attainment and from a low-deprivation background may still perform relatively well on global tests, obscuring any true cognitive impairment. Conversely, an individual from a highly deprived background with low educational attainment may score relatively poorly on global cognitive assessments, but this might not represent a decline from their normal level. Therefore there may be value in accounting for the influence of these variables when considering an individual's level of functioning in clinical settings (in a holistic manner, or with adjusted cut-off scores), or accounting for these in analyses in research settings (as confounding variables).

1.4.2 Domain-specific cognitive dysfunctions in dementia

Providing further context as to the specific impairments underlying global decline, notable differences have been found between AD and DLB groups in the specific domains of cognition which are found to be impaired (Walker *et al.*, 1997). These domains may be best assessed by dedicated neuropsychological testing, but some clinical-oriented cognitive assessments such as the ACE-R, CAMCOG, or ADAS-Cog may also provide domain-specific sub-scores with varying degrees of granularity with less time cost.

Episodic memory and learning

A wide range of tests are available to assess episodic memory performance and long-term learning capacity; the Wechsler Memory Scale (Wechsler, 1945) and its revised versions (Wechsler, 1997) may be sensitive to early memory changes, but has a high time and financial cost. However, subscales of this test are commonly administered in dementia research, such as the logical memory subtest, which has identified better memory performance in DLB than in AD (Ferman *et al.*, 2006; Oda *et al.*, 2009).

Verbal learning tests, either cued or un-cued, are also commonly used either as stand-alone tests of episodic memory, or as a subtest within tests of global function; common examples in dementia research being the California (Delis *et al.*, 1988), Hopkins (Benedict *et al.*, 1998), or Rey (RAVLT; Vakil and Blachstein, 1997) verbal learning tests, or the free and cued selective reminding test. These are broadly comparable in their approach, requiring the progressive learning of lists of words which must be recalled or recognised over several trials. Tests such as these have shown utility in assessing amnestic memory dysfunction in DLB, PD and AD (Ferman *et al.*, 2006; Filoteo *et al.*, 2009), and in the MCI stage of AD (Estevez-Gonzalez *et al.*, 2003).

While AD is characterised by progressive impairment of episodic memory, dysfunctions in this domain are typically less severe in DLB; a finding observed with verbal learning tests (Ferman *et al.*, 2006), the Wechsler logical memory sub-test (Oda *et al.*, 2009), and CAMCOG memory sub-scores (Ballard *et al.*, 1999b). More in-depth exploration of this phenomenon indicates that while both groups may be equally impaired in ability to freely recall learned information, DLB is associated with a non-amnestic pattern, being capable of cued recognition of learned information despite failure of overt recall (Hamilton *et al.*, 2004). This suggests that the greater memory impairment found in AD may in part be due to failures to efficiently encode and store information to memory, with this function being comparatively preserved in DLB.

These distinct patterns of memory impairment may reflect the different pathological patterns found in AD and DLB; different regions of the MTL are known to support different aspects of

the episodic memory system, with the hippocampus in particular being crucial for recollection of learned information (Eichenbaum *et al.*, 2007). Regardless of whether a dementia appears clinically as AD or DLB, greater MTL atrophy specifically is associated with a greater level of episodic memory impairment (Barber *et al.*, 1999). Clinically-diagnosed DLB typically features less MTL and hippocampal atrophy than AD (Barber *et al.*, 2000), and within clinical cases of DLB, the presence in cerebrospinal fluid of AD-positive biomarkers has been associated with greater levels of MTL atrophy (van der Zande *et al.*, 2018b) than in apparently pure DLB.

Episodic memory impairment in dementia may therefore be an outcome of hippocampal atrophy related to AD pathology, and possibly therefore a mixed dementia when observed in an otherwise clinically evident case of DLB. However, while relying to a clear extent on hippocampal preservation to function adequately, long-term memory functions do not occur in isolation from either cognitive or neuroanatomical perspectives; localised damage to other brain regions, such as the frontal lobes (Jetter *et al.*, 1986), has been demonstrated to impact on memory function. Effortful encoding and retrieval of memory relies upon adequate attention being paid to the information at hand and may be further aided through the use of mnemonic strategies. Furthermore, adequate encoding and retrieval of the visual, verbal and semantic features of memories must also be presumed to rely upon relative preservation of their respective cognitive functions, such as verbal and visuospatial perception and working memory functions, and associated neural substrates of these. Impairments of memory must therefore be dissociated from impairments of other domain-specific functions (e.g. considering the limits imposed by verbal attention and working memory capacity when assessing recalled information, as in Ferman *et al.* (2013)) to fully understand the root cause behind observed dysfunctions; while episodic memory dysfunctions are certainly correlated with hippocampal atrophy, they could also arise in some cases from pathophysiology affecting other domains, or domain-general cognitive networks. This warrants further exploration with carefully selected neuropsychological tests, and controlling for other domains of impairment; a primary impairment in information processing, attention, or working memory may manifest in failed recall later but would not be accurately described as an amnestic memory impairment.

Despite the focus afforded to episodic memory impairments, dysfunction of other memory systems is common in many dementia syndromes, including semantic memory (discussed in this text within the context of language functions) and working memory (Baddeley *et al.*, 1991). Reduced working memory capacity may contribute to impaired function in other domains, such as episodic memory failure, producing an early bottleneck in performance. Working memory is currently theorised to be domain-specific (Cocchini *et al.*, 2002), and reliant upon the recruitment of preserved lower-level sensory networks (Gayet *et al.*, 2018) and so auditory and visuospatial working memory will be specifically addressed in relation to their respective domains below.

Visuospatial skills

The broad category of visuospatial functions encompasses a variety of cognitive processes, ranging from simple perception of visual features such as colour and shape, to higher-order cognitive functions such as spatial mental re-orientation and visual construction. Disruption of lower-level functions may reflect specific dysfunction of the visual system and visual cortex, whereas higher-level tasks may be vulnerable not only to dysfunction of visual perception and imagery, but also secondary dysfunction arising from other cognitive domains due to the greater task complexity.

After discounting non-cognitive causes of impaired visual acuity, such as eye disease or inadequate use of corrective lenses, simple visual perception may be assessed with tests of sensitivity to differences in colour (Farnsworth, 1943), orientation (Benton *et al.*, 1978), form (De Renzi *et al.*, 1969) or motion (Vaina, 1989). These represent the simple, specific features of visual stimuli which form the building blocks of more complex visual functions, such as perception of a scene or object, or imagery.

Visual working memory functions appear to be highly related to visual perception (Kang *et al.*, 2011) and may represent the link between lower-level perceptual functions and higher-level complex processing in the visual domain, operating as an emergent function of the same cortical regions and cognitive networks responsible for more passive processing of visual sensory

information (Harrison and Tong, 2009), allowing for the maintenance of a number of visual features in a single mental image for a brief period. Visuospatial dysfunctions could therefore manifest in reduced visuospatial working memory capacity in MCI and dementia with fewer contributions from domain-general cognitive resources than higher-order functions (e.g. visual construction tasks), while incorporating more visual features in a single assessment than simple perceptual tasks, though this remains under-explored in DLB currently. Though not commonly used in this setting, Corsi block-tapping or similar short-term visual retention tasks (Della Sala *et al.*, 1999) may therefore be appropriate to assess visuospatial dysfunctions in MCI. Given the increased complexity of working memory tasks, other domain-general cognitive resources may represent an additional barrier to completion however, with processing speed limitations or executive dysfunctions being potential causes of failure despite maintenance of primary visual functions.

Progressively more complex tasks include free drawing, or guided copying of a visual figure, which are common components in both dedicated visuospatial tests, and tests of global cognition. Short examples being the overlapping pentagons copying (Folstein *et al.*, 1975) or clock drawing (Shulman *et al.*, 1986) tests; longer and more complex figure copy tests, such as the Rey-Osterreith (ROCF; Rey, 1941) or Taylor (Taylor, 1969) tasks have greater scoring resolution and a higher ceiling on performance, but there may be a floor effect for highly impaired individuals. While these tests may assess higher-level visuospatial functions which may more directly reflect cognitive dysfunctions with real-world implications, complex tasks may be vulnerable to either compensation from other cognitive domains preserving performance (e.g. use of strategies or heuristics) or conversely, may show apparent visuospatial dysfunction which is actually secondary to a different impairment (e.g. motor dysfunction limiting drawing ability despite preserved visuospatial skills).

The application of a range of such assessments has provided evidence that in comparison to typical AD-related dementia syndromes, DLB is known to result in a greater level of impairment of a range of visuospatial functions (Mosimann *et al.*, 2004). This includes lower-level impairment in perception of size, shape, orientation and colour (Mori *et al.*, 2000; Simard *et al.*,

2003; Matar *et al.*, 2019a), and higher-level dysfunction in guided copying (Ala *et al.*, 2001) and free drawing of complex figures (Gnanalingham *et al.*, 1997). PD also demonstrates similar patterns of visuospatial dysfunction (Weil *et al.*, 2016), although this is more severe in DLB (Mosimann *et al.*, 2004). Furthermore, these visuospatial dysfunctions worsen at a faster rate in DLB than in AD (Smirnov *et al.*, 2020).

Visuospatial dysfunctions may arise in DLB as a result of the functional disruptions observed in this condition, including reduced metabolic activity and perfusion in the occipital lobes (Ishii *et al.*, 1999; Lobotesis *et al.*, 2001). Whilst AD has typically less visuospatial impairment than DLB, the uncommon syndrome of posterior cortical atrophy (PCA), which may arise from a number of neurodegenerative aetiologies – most commonly AD, is also characterised by pronounced cortical-visual dysfunction (McMonagle *et al.*, 2006). Direct comparison with DLB has suggested that the respective visual dysfunctions are qualitatively different (Metzler-Baddeley *et al.*, 2010) with primarily higher-level visual functions being disrupted in DLB, but both low- and high-level functions being impaired in PCA, reflecting the extensive degeneration of occipital and parietal lobes in this syndrome (Crutch *et al.*, 2012). However, this comparison is somewhat limited as, unlike DLB, PCA cohorts are a specific sub-group defined by their occipital atrophy and consequent visuospatial deficits; as discussed in greater depth later (**see 1.4.4**) cognitive sub-groups may also exist within DLB, and the inclusion of cases of DLB without visuospatial impairments could dilute this comparison with PCA.

As discussed previously, visuospatial cognitive impairments and misperceptions have been theorised (Uchiyama *et al.*, 2012) to contribute in part to the visual hallucinations experienced in DLB; degraded visual input may be reconstructed downstream into well-formed hallucinations. Further exploration is warranted to ascertain whether individuals experiencing visual hallucinations show a greater level of visuospatial impairment, or if the presence of either one of visual hallucinations or visuospatial impairment might anticipate the eventual onset of the other.

While the sporadic nature of visual hallucinations can make them difficult to assess in clinical or research settings, DLB patients have been found to show a greater responsiveness to visual

illusions and misperceptions than those with AD, as assessed with a pareidolia task (Uchiyama *et al.*, 2012). Regardless of whether or not they report experiencing visual hallucinations, individuals with DLB are more likely than AD patients or controls to misperceive the forms of objects or people in ambiguous or visually-noisy stimuli.

It may be necessary to dissociate other contributions to the visuospatial dysfunctions observed in DLB; ophthalmic dysfunction may contribute to degraded input, motor dysfunction may affect the ability to reproduce figures accurately in constructional tasks, and slowed processing speed may impair overall task performance in tasks with a high cognitive load, or in timed tasks.

Attention and executive functions

A number of cognitive functions fall under the broad category of attention and executive functions, including the ability to appropriately direct and sustain attention, inhibit inappropriate responses or actions, form plans, make decisions, think abstractly, and to follow complex instructions. Normal performance in tests of attention and executive functioning is generally understood to rely upon frontal lobe integrity (Stuss and Benson, 1984), and frontal lobe lesions typically lead to impairment in these domains (Baldo *et al.*, 2001; Demakis, 2004). Consequently, a prominent attention and executive dysfunction is particularly characteristic of a frontotemporal dementia (Rascovsky *et al.*, 2002; Stopford *et al.*, 2012). However, while attention and executive functions are sensitive to frontal lobe integrity, evidence for their specificity to this anatomical region is more limited (Alvarez and Emory, 2006), and so impairments of attentional control and other executive functions are also common in AD and other dementias without prominent frontal degeneration (Perry *et al.*, 2000).

Differences have been identified between AD and DLB in performance in a range of attentional and executive tasks. Stroop tasks, requiring response inhibition and goal maintenance under time pressure, are relatively more impaired in DLB than AD (Calderon *et al.*, 2001), as is performance on part B (TMT-B) of the Trail Making Test (Ferman *et al.*, 2006) which requires repeated switching between two parallel tasks; these are suggestive of an impairment in cognitive flexibility, which could reflect pathological changes to a task-switching network

comprising the basal ganglia, anterior cingulate, prefrontal and posterior parietal cortices (Leber *et al.*, 2008).

Verbal fluency tasks are a common hybrid test of both executive and verbal functions, with impairments in letter fluency tests being particularly associated with frontal lobe dysfunction, for example as observed in motor neurone disease (Quinn *et al.*, 2012), and therefore theorised to reflect executive dysfunction to a greater extent than category fluency tasks which appear to rely more on verbal skills (Shao *et al.*, 2014). Both letter and category fluency tasks are commonly included in neuropsychological testing batteries to assess executive and verbal functions, with DLB typically featuring greater impairments of letter fluency than AD (Calderon *et al.*, 2001; Ferman *et al.*, 2006). Verbal fluency tests have a high ceiling on performance and so may be appropriate for assessing mild cognitive impairment as in dementia, but may be particularly sensitive to age, education, and gender effects (Bolla *et al.*, 1990).

Various measures of processing speed may fall under the umbrella of executive and attentional processes, encompassing a wide range of cortical processes from simple reaction time tests of pure psychomotor speed, to more complex tasks reflecting a combination of various attention and executive functions. Both AD and DLB have slowed reactions relative to healthy controls (Bradshaw *et al.*, 2006), with response times in DLB also being slower and more variable than in AD; a pattern which remains after controlling for levels of parkinsonism, suggesting that this is not just an outcome of slowed motor responses.

Attentional and executive dysfunctions are therefore seen as particularly characteristic of DLB, and have been theorised to underlie cognitive fluctuation symptoms (Walker *et al.*, 2000a). Meanwhile, executive dysfunction in DLB may reflect direct or indirect disruption of normal frontal lobe functions due to degeneration of cortical or subcortical regions (e.g. the striatum).

Speech, language, and semantic memory

A number of common cognitive functions may be considered as language-related skills, including speech production, reading, and semantic memory. Early declines in speech and

language are characteristic of particular patterns of neurodegeneration resulting in syndromes such as a PPA (Gorno-Tempini *et al.*, 2011), but semantic memory impairments may also be seen in typical AD (Hodges and Patterson, 1995). Semantic memory dysfunctions are typically assessed with object-naming tasks such as the Graded Naming Test (GNT; McKenna and Warrington, 1980) which is particularly sensitive to left temporal lesions. AD and DLB perform comparably in object naming tests (Noe *et al.*, 2004), and do not reliably differ in their semantic memory impairments.

In mild dementia, tests of reading are reasonably resilient to declining cognition (Schmand *et al.*, 1998), though in moderate or severe dementia these may also begin to decline. As reading tests are typically insensitive to mild cognitive dysfunction, they are often useful as hold-test estimators of premorbid functioning in clinical and research settings where premorbid cognitive measures are rarely available, as discussed previously. Common examples of tests which assess reading skills as a proxy of premorbid function include the Wechsler Test of Adult Reading (Wechsler, 2001) and the National Adult Reading Test (NART; Nelson and Willison, 1991), which both require pronunciation of atypically or ambiguously spelled words. These tests may therefore be used to adjust for individual differences in premorbid intelligence across both AD and DLB, using vocabulary as a proxy.

As noted previously DLB and AD groups do show differences in verbal fluency tasks, which rely upon language skills to an extent. However, if these groups do not display differences in semantic memory impairments, these differences may be presumed to reflect differing levels of executive dysfunction instead. Impairments of goal maintenance, failure to use effective search strategies, and lack of inhibition of previous responses may explain poorer verbal fluency performance despite otherwise preserved language skills.

Auditory digit-span tasks may assess verbal working memory (e.g. Grégoire and Van Der Linden, 1997), reliant upon integrity of the theorised ‘phonological loop’ which is responsible for short-term rehearsal and processing of speech, and hence may show impairment in aphasic syndromes (Wright and Fergadiotis, 2012). Both DLB and AD show impairment on digit span

tasks, but do not appear to differ in this (Calderon *et al.*, 2001). Forward digit span tasks may be a relatively pure measure of auditory working memory capacity, reflecting the number of items that can be held sequentially in the phonological loop, but due to their simplicity may be less sensitive to early dysfunction in dementia than the more complex, but less pure, backwards digit span, which shows sensitivity to dysfunction earlier (Lambon Ralph *et al.*, 2003).

1.4.3 Domain-specific dysfunction in mild cognitive impairment

In comparison to healthy controls (Kemp *et al.*, 2017), clinically-diagnosed "probable prodromal DLB" (NIA-AA criteria MCI with two or more core clinical features of DLB, analogous to "probable MCI-LB" as described in this work) has been shown to feature impairments in a wide range of cognitive functions: visuospatial functions, particularly visuoconstructive functions (as assessed by copy of the ROCF), and executive functions (Trail Making Test parts A and B, and the frontal assessment battery) being impaired relative to normative data (> 1.5 SDs worse than normal mean performance). Additionally, MCI-LB featured poorer recall and recognition memory, impaired social cognition, and dyspraxia (though not to the point of objective 'impairment' based on normative scores available).

Therefore, cognitive impairments associated with the presence of Lewy body disease features may already be multidimensional at the MCI stage. Episodic memory impairments were observed with a multi-domain amnestic cognitive profile in approximately half of cases, which may be attributed to primary attentional and executive dysfunctions limiting memory performance (Bryan *et al.*, 1999), or the effects of additional AD pathology. However, clinically-suspected mixed AD-DLB cases were excluded, and hippocampal atrophy ratings did not significantly differ between prodromal DLB and healthy comparators. Alongside clinical diagnosis of MCI, parkinsonian rigidity and fluctuating cognition were the most common clinical feature of DLB in this sample (76% of cases for both), followed by visual hallucinations (65%), bradykinesia (59%) and resting tremor (27%). RBD was either not assessed, or not reported. These cases likely represent a particular subset of probable MCI-LB cases, recruited from memory services with clinical MCI, but with clear mixed AD cases excluded and RBD not

apparently assessed, and so may naturally differ from other samples with a differing pathophysiology.

As reviewed by Ciafone *et al.* (2019), there has been limited data comparing the cognitive profiles of MCI-LB with MCI-AD, and existent examples have typically been underpowered with small sample sizes (e.g. Jicha *et al.*, 2010). However, recent data have suggested that AD and LB disease may manifest in different patterns of cognitive dysfunction in the MCI stages, reflecting their eventual dementia profiles; amnestic MCI is more likely to convert to AD-type dementia, while a non-amnestic is more likely to convert to DLB (Ferman *et al.*, 2013), consistent with the greater association between AD neuropathology and amnestic memory dysfunction. More directly related, when diagnosed according to clinical DLB features present in MCI, probable MCI-LB is associated with poorer attentional functions, verbal fluency, and visuospatial performance than is MCI-AD (Donaghy *et al.*, 2018); this cross-sectional study was directly built upon in this work.

However, recent retrospective study of MCI-LB cases has identified different baseline cognitive profiles between MCI-AD and MCI–LB, consistent with those found in their respective dementia syndromes; MCI-AD featuring poorer memory performance, and MCI-LB poorer non-memory domain performance (van de Beek *et al.*, 2020). Different domain-specific longitudinal trajectories were also identified, as discussed later in this chapter.

Cognitive dysfunctions in other LB and prodromal DLB syndromes

To supplement these findings, comparisons may be drawn from the related study of mild cognitive impairments which emerge within established PD (PD-MCI), given the shared underlying pathology of this syndrome with MCI-LB; however, it should be noted that diagnostic criteria for MCI in PD differ to NIA-AA criteria for this (Albert *et al.*, 2011), which may have consequences for direct comparison of these results. NIA-AA criteria for MCI are based on clinical reasoning, including scores derived from global or domain-specific cognitive tests, but are ultimately independent from any cut-off score for neuropsychological tests in particular cognitive domains. In comparison, PD-MCI is specifically defined by the presence of

scores below pre-determined thresholds on domain-specific tests, e.g. memory scores between 1-2 SDs below healthy norms (Litvan *et al.*, 2012; Goldman *et al.*, 2015) in addition to clinical PD. This may present issues of circularity in cases where groups are assessed on cognitive outcome measures which are not independent of, or possibly even identical to, the neuropsychological assessments which helped define those same groups. Accordingly, while PD-MCI may be readily contrasted with healthy controls, it may be less easy to compare the cognitive outcomes to those found in MCI-AD, due to the differently characterised MCI underlying these.

In contrast with healthy controls, PD-MCI has been associated with impairments in a broad range of cognitive domains as reviewed by Ciafone *et al.* (2019), showing executive and processing speed dysfunction including greater Stroop task interference, poorer word production in verbal fluency tests, and impairments in Trail Making Test parts A (TMT-A) and -B (TMT-B). Visuospatial performance is typically poorer in PD-MCI, including visual perception (line orientation perception), visuoconstruction and visual memory (copy and recall, respectively, of complex figure tasks) dysfunction. Verbal working, episodic and semantic memory may also show dysfunction, with poorer digit span performance, word list retention, and object naming, which is consistent with findings of memory impairment in MCI-LB and DLB (though these being less severe than in AD).

Comparisons may also be drawn from prodromal presentations of DLB characterised by early isolated RBD; as these are characterised at the early stage prior to apparent cognitive symptoms, they may provide important perspectives on the earliest cognitive changes which may precede eventual MCI-LB or DLB. In individuals recruited from a sleep centre with PSG-confirmed RBD, but no parkinsonism or dementia, executive (TMT-B), verbal fluency, and verbal learning (RAVLT) dysfunctions were typical of those who converted to dementia, and visuospatial performance (block design and complex figure copy) often declined in the lead-up to dementia, but at sub-clinical thresholds (Génier Marchand *et al.*, 2018). Therefore, while executive dysfunctions may be apparent at the early stages of prodromal DLB, visuospatial dysfunctions may progressively emerge over the course of MCI or even the early stages of dementia. While providing important context, the cognitive profiles of RBD-prodromal DLB may not directly

translate to the more generally-defined MCI-LB which may or may not include RBD as a feature; by definition, cases with initially isolated RBD represent a more specific sub-group of prodromal DLB which could have differing underlying neuropathological changes, and consequently differing cognitive patterns. It remains to be seen whether different patterns of LB symptomatology are associated with different patterns of cognitive impairments.

1.4.4 Heterogeneity in cognitive profile within disease groups

As identified in the respective sections above, it is known that neurodegenerative diseases such as AD may manifest in any one of a number of heterogeneous clinical syndromes including PCA and PPA, reflecting the varying patterns of underlying neuropathology (Galton *et al.*, 2000), and each characterised by distinct cognitive, clinical, and behavioural profiles unlike that of the 'typical' amnestic syndrome. While less explored in DLB it remains possible that, underlying the broad group differences observed from typical AD, patterns of domain-specific cognitive impairment may also differ between individuals with DLB.

Numerous case reports have described PPA (Caselli *et al.*, 2002; Teichmann *et al.*, 2013; Watanabe *et al.*, 2020) and PCA (Yoo *et al.*, 2020) syndromes developing into or alongside apparent DLB. As highlighted previously, Ferman *et al.* (2013) described the cognitive profiles of MCI as predictors of transition to clinical AD or DLB; in addition the expected association between single-domain amnestic MCI and eventual AD, eventual DLB was slightly more typically preceded by a single-domain non-amnestic profile than multi-domain (either amnestic or non-amnestic). While the exact breakdown is not clearly reported (those with single-domain impairments in attention are not differentiated from those with multi-domain attention and visuospatial), it appears that the MCI prodrome of DLB may present most often with *either* visuospatial *or* attentional impairments. These prodromal cognitive profiles may converge by the time that DLB becomes fully clinically manifest, though this again remains under-explored.

As also highlighted by Ferman *et al.* (2013), amnestic memory dysfunctions preceding DLB are predominantly only one aspect of a multi-domain profile of impairment, unlike in typical AD.

Section summary

When performing at comparable levels of global cognitive function, AD and DLB show different patterns of domain-specific dysfunction reflecting their varying neurodegenerative processes. AD has a typically amnestic profile in dementia, while DLB has relatively worse impairment in attention, executive, and visuospatial functions. In both syndromes, speech and language skills are generally comparable, and relatively spared. While the evidence base is not extensive, the MCI stages of DLB and AD appear to feature cognitive profiles similar to those found in the dementia syndromes. In both disease groups, early cognitive sub-types may exist, though further exploration is required in DLB to establish if these are found in clinically-defined MCI-LB, and whether these converge over time. The presence of amnestic memory impairment in DLB or MCI-LB may reflect a mixed AD-LB syndrome, though this is currently speculative.

1.5 Longitudinal decline

While comparisons of cross-sectional performance on neuropsychological tests can be useful to help conceptualise the typical cognitive differences between DLB and AD, neurodegenerative dementias are syndromes primarily characterised by progressive deterioration. The very nature of cross-sectional studies means they can provide only a snapshot of a declining process; with uncertainty over the start point, groups may not be observed at comparable times, and it may be unclear if any group differences are diverging, converging, or consistent over time. Therefore, further exploration must be undertaken into how global and domain-specific cognitive functions deteriorate over time in these diseases. A fuller understanding of the progressive deterioration of different cognitive domains from the prodromal to final stages of severe dementia or death may improve the clinical and research utility of neuropsychological testing, and provide information as to when these cognitive deficit differences emerge to better inform selection of screening and outcome measures.

1.5.1 Longitudinal progression of dementia

Global decline in dementia with Lewy bodies versus Alzheimer's disease

There have been efforts to explore the long-term decline of cognitive function in DLB; principally in regards to deterioration of global cognitive functioning in comparison with AD. DLB and AD are both associated with progressive decline in global cognitive function over time (Boyle *et al.*, 2017), and DLB appears to have a shorter time to death after onset of symptoms (Williams *et al.*, 2006), but results vary as to whether global cognitive function in DLB declines at a faster or comparable rate to AD.

Some research has reported no difference in rates of cognitive decline in AD and DLB (Ballard *et al.*, 2001a; Walker *et al.*, 2012) over one-year periods using the CAMCOG and MMSE, respectively; Breitve *et al.* (2018) also did not identify any difference in rate of cognitive decline over a four-year period using the MMSE and a battery of domain-specific tasks. However in the longest-running comparable study to date, Rongve *et al.* (2016) identified a faster decline in MMSE performance in DLB than AD over five years of follow-up. Meanwhile, in the largest comparable study exploring differences in global cognitive decline to date (Kramberger *et al.*, 2017), DLB was associated with a faster decline in MMSE scores than AD after controlling for baseline performance.

Difficulty arises in comparing rates of decline in tests of global cognitive functioning, however; with AD being the most common cause of dementia (Harvey *et al.*, 2003), many common clinical screening tests are sensitive by design towards an AD-type dementia profile characterised predominantly by memory impairment (Cullen *et al.*, 2007) and so may be less sensitive to patterns of decline in DLB. As noted earlier, in the MMSE only one out of thirty possible points available are concerned with visuospatial skills with no direct test of executive dysfunction, and in the MoCA both visuospatial and executive functions combine to provide five out of thirty points; this limits the sensitivity to decline in patients with primarily visuospatial or executive impairments (i.e. the cognitive profile associated with DLB). While this is a reflection of the specialised screening purposes of these assessments given the predominance of AD in clinical dementia settings, the use of more balanced composite scoring systems, or accounting

for declines in individual cognitive domains, may be preferable to explore how cognition declines over time in DLB as compared with AD in research settings.

Despite the lack of consensus from cognitive outcomes, there is reasonably strong evidence that DLB features a faster clinical decline to death (Mueller *et al.*, 2019) and hospitalisation (Mueller *et al.*, 2018) than AD, with a median survival time of 3.3 years (male) and 4.0 years (female) after diagnosis with DLB, versus 6.7 and 7.0 years respectively in AD (Price *et al.*, 2017), after controlling for age and comorbidity. DLB is also associated with greater reliance on caregiving, and poorer quality of life for patients and caregivers (Wu *et al.*, 2018a). Therefore, while cognitive measures may be insensitive to differences in decline, more clinically specific measures such as increased dependency, transition to full-time care, or death, may be more sensitive to differences in decline. The mechanisms for this poorer prognosis are unclear, but have been theorised to include the effects of cognitive decline, parkinsonism, autonomic dysfunction, falls, and psychosis (Mueller *et al.*, 2019), highlighted by aggravating factors such as a reduced cough reflex contributing to aspiration pneumonia (Ebihara *et al.*, 2020) as a single example.

Domain-specific cognitive decline

When accounting for specific domains of impairment, different rates of change have been found between AD and DLB (Stavitsky *et al.*, 2006), with AD showing a faster decline in recognition memory despite parity between the groups at baseline. With this difference in decline excepted, differences in cognitive profile between DLB and AD were observed to be clearest at the earliest stages, with the decline of non-memory domains eventually leading to a convergence of profiles of cognitive impairment between the groups at the advanced stages of dementia.

More recently, Smirnov *et al.* (2020) described domain-specific differences in progression between neuropathologically-confirmed AD, DLB, and PDD. Compared to AD, DLB had greater impairment and faster decline in visuospatial and executive functions. AD had greater memory impairments, but did not decline faster, and AD and DLB did not differ in language impairments or rate of decline. Compared to DLB, PDD had worse executive dysfunction and

faster decline in this, less memory dysfunction, and slower decline in language functions. This may suggest that not only does LB pathology manifest in different cognitive profiles and longitudinal patterns of decline from AD, but that the differing patterns of pathology in LB disease (e.g. those manifesting in PDD rather than DLB) may also lead to subtle differences in cognitive presentation, providing evidence for heterogeneity in cognitive progressions, as well as in clinical patterns in LB disease. In this study however, 71% of pathologically-confirmed DLB cases had received a living clinical diagnosis of AD, possibly due to the absence of FP-CIT imaging or RBD assessment, with recruitment predating more recent diagnostic criteria. While DLB is underdiagnosed in clinical settings, other studies have found lower rates of non-matching diagnoses (Selvackadunco *et al.*, 2019) and so this DLB sample may represent a more qualitatively AD-like sample than the broader DLB population, accounting for the only subtle differences in memory performance between AD and DLB.

Overall results are mixed however, with a study over a four-year period, but lacking neuropathological confirmation, finding limited evidence of any differences in rates of decline on specific neuropsychological tests (e.g. Breitve *et al.*, 2018). There is currently little consensus on the most appropriate neuropsychological tests for assessing dysfunction in different domains in DLB, and it is possible that some of this inconsistency between research findings may be resolved as further agreement is reached on the best assessment methods; both cross-sectionally, and longitudinally.

1.5.2 Longitudinal progression of mild cognitive impairment

Relative even to the volume of longitudinal research into cognitive impairment in DLB, there is a notable paucity of information on how the cognitive profiles differ between AD and DLB at the MCI stage (MCI-AD and MCI-LB, respectively), and especially in how these develop over time in prospectively-recruited and clinically-diagnosed groups.

Previous longitudinal research has indicated that baseline neuropsychological profiles in an MCI cohort can be predictive of eventual conversion to either AD or DLB (Williams *et al.*, 2006; Belden *et al.*, 2015); independent of the presence or absence of memory impairment in MCI,

predominantly visuospatial and executive dysfunctions are observed to be indicative of an MCI that will convert to DLB, consistent with the executive and visuospatial dysfunctions typical of DLB. These studies do not, however, follow up on cognitive measures beyond the baseline.

Retrospective longitudinal comparison of MCI-LB and MCI-AD

The closest comparable research available has explored longitudinal decline in a cohort retrospectively diagnosed as MCI-LB from the Amsterdam Dementia Cohort (van de Beek *et al.*, 2020); participants met criteria for probable MCI-LB (possible MCI-LB were excluded) based either on either eventual diagnosis of probable DLB according to clinical criteria, or a retrospective diagnosis of MCI concomitant with either two or more core clinical DLB features, or one core clinical feature with abnormal FP-CIT imaging. FP-CIT imaging abnormalities were highly over-represented in this group (abnormal in 98%), though not all were offered this, and parkinsonism was the most common clinical DLB feature, in 70% of cases; visual hallucinations and fluctuations (51%) and RBD (47%) were far less common, which may suggest that the recruitment methods for this sample were more biased towards a dopaminergic dysfunction-prominent MCI-LB group. The MCI-AD group were defined as MCI (NIA-AA criteria) with CSF markers positive for AD (reduced $A\beta_{42}$, and elevated total- and phosphorylated-tau).

In addition to the previously identified baseline differences (worse attention and executive function, and better memory function in probable MCI-LB), both groups appeared to deteriorate in parallel in executive and visuospatial functions, but MCI-LB featured a faster deterioration in attentional functions, assessed with a compound score of the TMT-A, forward digit span, and a Stroop task, and less rapid decline in memory (visual association test and recall of the Dutch verbal learning test). This study provides the first longitudinal data on the development of MCI into an eventual DLB syndrome, suggesting that there may be different longitudinal patterns in MCI-LB to MCI-AD, though with retrospective diagnoses this may not translate as readily into clinical settings where diagnoses are, by their very nature, prospective.

It therefore remains unclear as to how individual prospects for progression differ after prospective MCI diagnosis, given a diagnosis of either AD or a LB syndrome. This represents a

notable gap in the literature and affords an opportunity to explore how different patterns of neuropsychological impairment might present at the clinically-defined MCI stages of AD and DLB, how these prospectively progress over time within individuals and diagnostic groups, and how these may be linked with other clinical symptoms and biomarkers associated with either DLB or AD.

1.5.3 Heterogeneity of progression in Lewy bodies and Alzheimer's disease

As noted previously, within any particular neurodegenerative disease, there is wide variation in individual course of decline, with some individuals progressing rapidly from MCI to dementia, or from mild to severe dementia, while others may decline slowly, remain stable, or even regress (from apparent MCI to a normal level of functioning). There have been some efforts to understand mechanisms and predictors of a rapid course of decline, as this may have implications for clinical practice and research.

In AD, different patterns of brain atrophy have been associated with a varying prognosis, with a less aggressive course of decline in those with hippocampal-sparing or no measurable atrophy relative to the more typical pattern of hippocampal atrophy (Ferreira *et al.*, 2017), which may account for some of the clinical heterogeneity within this disease; such cases may be more likely to be classified as a stable MCI, subjective cognitive impairment, or a functional cognitive disorder during life.

While slower progressing cases have not been clearly explored in DLB, there have been numerous reports on individual cases progressing with particularly rapid deterioration (Gaig *et al.*, 2011), to the extent that they may mimic Creutzfeldt-Jakob disease in clinical presentation (Ukai *et al.*, 2010; Saint-Aubert *et al.*, 2016), a disease for which a precipitous decline in cognitive function is more typically characteristic (Tschampa *et al.*, 2001). This could suggest that heterogeneity in decline may also exist within DLB as in AD, which would not be accounted for in analyses which average across individuals. Such inter-individual variability is evident in visualisations of individual-level cognitive trajectories provided by Rongve *et al.* (2016), with

many deteriorating rapidly while others remain relatively stable in both AD and DLB, but unaccounted-for in their analysis which treats diagnostic groups as homogeneous.

In addition to relatively slow decline, previous studies have identified atypically rapid decline in 10-30% of AD cases (Dumont *et al.*, 2005; Cortes *et al.*, 2008; Aubert *et al.*, 2015; Nance *et al.*, 2019), though methods and definitions vary. Whether a rapid decline occurs at a comparable rate in AD and DLB, or is more common in one than the other, is as yet unclear -in part due to this lack of consistency in defining rapid decline in AD, but also due to a lack of exploration of distinct cognitive trajectories in DLB cohorts.

Cases of rapid decline may be due to the effects of multiple pathologies; neuropathological studies have identified co-morbid Lewy body pathology in approximately 16% of clinical AD diagnoses (Selvackadunco *et al.*, 2019), and this has been separately associated with a faster cognitive decline (Blanc *et al.*, 2017; Brenowitz *et al.*, 2017b; Malek-Ahmadi *et al.*, 2019) and progression of clinical severity (Brenowitz *et al.*, 2017a) than in AD or DLB alone. In pathologically-confirmed DLB, but not AD, early visuospatial dysfunctions have been associated with a subsequent rapid global decline (Hamilton *et al.*, 2012) and higher likelihood of experiencing visual hallucinations over the course of disease progression. This association remained after controlling for baseline function, suggesting that the aetiology underlying visuospatial symptoms may be related to a more severe progressive DLB profile.

In addition to disease-specific explanations, there are several other potential causes of apparent rapid decline. Cognitive reserve, reflecting educational attainment and numerous other lifelong factors, may protect against apparent cognitive decline at early stages of MCI (Ye *et al.*, 2013), however as this progresses and this reserve is ‘depleted’ at the more advanced stages, cognitive decline may be faster than anticipated based on their baseline function, leading those with higher reserve to ‘catch up’ with those with less reserve. Despite this, low education (and presumably therefore low cognitive reserve) is a risk factor for clinical progression of dementia (Xue *et al.*, 2017). Another possibility is that in regions with greater health inequality, delayed access to memory services may lead to an apparent rapid drop in function, when individuals are simply

entering services at a later stage. Of course, any or all of these factors may be at play, and may vary between individual cases, therefore being important to consider in analysis.

Section summary

DLB has a worse prognosis than AD and may also feature a faster cognitive decline. The cognitive progression of MCI, differentially diagnosed according to clinical symptoms, remains to be explored; MCI-LB may decline faster to than MCI-AD if the patterns from the respective dementia syndromes are already evident at this earlier stage. Rapid declining cases of MCI may reflect a mixed AD-LB syndrome or a more aggressive pattern of underlying pathology, while stable cases of MCI may reflect a non-degenerative cause, though both require further exploration.

1.6 Chapter summary

Lewy body disease is a common neurodegenerative cause of MCI and dementia; the clinical syndromes of MCI-LB and DLB may be respectively distinguished from MCI-AD or dementia due to AD by the presence of core clinical features and/or indicative biomarkers. DLB and AD are known to differ in their prognosis with DLB often having a poorer outlook, as well as differing in their cognitive profiles. There is emerging evidence that the domain-specific cognitive impairments seen in MCI-LB and MCI-AD may reflect their eventual dementia syndromes, but it is unclear how these progress over time, and whether these decline at comparable or different rates. This represents a clear gap in the research that needs addressing with a comprehensively assessed, prospective cohort of MCI patients, with differential diagnosis of either MCI-AD or MCI-LB.

In response to this research question, it was hypothesised that those with MCI-LB would develop with a pattern of domain-specific cognitive impairments reflecting those found in DLB, that MCI-LB would have a worse prognosis than MCI-AD with greater risk of cognitive decline and shorter time to onset of dementia, and that there would be heterogeneity within MCI-LB, with specific clinical characteristics being associated with differing rates of decline.

Chapter 2. Background to Statistical Methods

2.1 Longitudinal methods

There are a variety of statistical approaches which may be undertaken to model longitudinal progression, as intended in this work. Selection of an appropriate method must be guided by the desired conceptualisation of the data (e.g. reducing multiple observations to a single continuous trajectory, or accounting for factors influencing changes in discrete states over time) and constraints imposed by the data itself (number of observations, balance of observation timings, and clustering within samples). In this chapter, common approaches to these challenges from the DLB and related literature are reviewed, and alternative methods are discussed where appropriate.

2.1.1 Characterising longitudinal change in outcomes of neurodegenerative disease

Jack *et al.* (2010) conceptualised the cognitive and clinical decline in neurodegenerative diseases (typified by AD) as a hypothetical sigmoidal curve of biomarker progression associated with a varying rate of cognitive decline; with individuals appearing at the pre-clinical stages to be cognitively normal with immeasurably slow or stable progression despite insidious neurodegeneration, eventually leading to periods of more rapid cognitive decline leading to the early clinical presentations of MCI and dementia (though not necessarily a sigmoidal curve of cognitive decline). While this hypothetical conceptualisation is not typically reflected in research due to the limitations imposed on the data in shorter-scale studies, it provided a reasonable starting point to build from when considering the progression of continuous outcomes in this work (i.e. longitudinal change in cognitive function).

This work sought to characterise the changes in cognitive functions over time in individuals presenting at the early clinically-manifest stages of AD and LB disease, as their MCI progressed towards dementia. Building on previous research into the dementia stages of these diseases, it was hypothesised that MCI-LB would feature a faster decline and different pattern of domain-specific cognitive trajectories in comparison to MCI-AD, comparable to the differences observed

between DLB and AD. The availability of repeated cognitive and clinical measures in these prospective cohorts allowed for a variety of approaches to analysing cognitive trajectories.

2.1.2 Traditional approaches and growth curve modelling

There are several analytical approaches which may describe the progression of cognitive and clinical symptoms of neurodegenerative diseases. Traditional methods include repeated measures *t*-tests and ANOVA for change scores at discrete time-points, these being simple but somewhat inflexible to violations of their assumptions, such as imbalance in the times or number of observations between subjects. Such methods are therefore most appropriate when a balanced follow-up schedule is observed, e.g. when assessing cognitive decline between two observations: baseline and twelve-month follow-up (Walker *et al.*, 2012). They are also largely limited in their potential to describe an overall time trend across observations, being restricted to comparisons between discrete time-points and therefore failing to account for all available information in a parsimonious manner.

In comparison, growth curve models are a more flexible approach that allow for the description of continuous within-person change in longitudinal data. Growth curve analysis (also known by various other terms e.g. trajectory modelling) may be undertaken within mixed-effects or structural equation modelling (SEM) frameworks (Curran *et al.*, 2010), both approaches having respective strengths and limitations. Despite their differences as discussed below, both methods arguably have as much in common as their differences, and may typically provide comparable results when appropriately specified (Chou *et al.*, 1998).

2.1.3 Structural equation modelling of longitudinal trajectories

The SEM approach to growth curve modelling provides a flexible framework for characterising longitudinal changes in a given latent process (in this instance, cognitive function) as observed by multiple measurements (e.g. repeated instances of one or more cognitive tests), while effectively accounting for measurement error in these. Models may be readily extended to incorporate complex structures of latent and manifest variables as in any SEM analysis, which is

a particular strength of this method given sufficient observations to support the conceptual structure.

However, SEM approaches are typically reliant upon the times of observations being roughly comparable between participants such as in longitudinal studies with follow-up conducted in waves, with data therefore suitable for a 'wide-format' layout (with one row per participant, and multiple observations separated across separate variables) as required by most common statistical packages for SEM, such as *lavaan* for *R* (Rosseel, 2012), *Mplus*, or *Amos*, amongst others. Consequently, SEM approaches to latent growth curve modelling of cognitive change in MCI and dementia may be more suitable for studies with complex outcome variable structures, sufficient observations to support the necessary model structure, but with reasonable uniformity of follow-up timings (with some degree of flexibility allowed) between participants, such as the baseline, 6-, 12-, 24-, 36-month follow-up schedule of the Alzheimer's Disease Neuroimaging Initiative (e.g. Johnson *et al.*, 2012). There are therefore few examples of latent growth curve models such as these in the DLB literature, though there are relatively more examples in the broader field of cognitive ageing (e.g. Muniz-Terrera *et al.*, 2009; Zaninotto *et al.*, 2018), or in the larger field of literature in AD.

2.1.4 Mixed-effects modelling

While a mixed-effects modelling approach does not offer quite the same strengths in complexity as SEM in accounting for measurement error and wider variable structures and relationships, the modelling methods are more resilient to variance in observation times between individuals as they typically require data in a 'long-format' with time treated as a continuous variable, and are also reasonably robust when dealing with missing data (Pinheiro and Bates, 2006). Due primarily to the unbalanced nature of observations in the LewyPro and SUPErB studies, a mixed-effects framework was adopted for growth curve analysis of continuous outcome measures in this work, as described further in **Section 2.3**.

Section summary

Growth curve modelling is a flexible approach to longitudinal analysis of repeated measures data. The two common frameworks for undertaking this, structural equation- and mixed-effects

modelling, each have their respective strengths, but can be largely comparable in many cases. A mixed-effects framework was considered as suitable for this work due to its flexibility with highly variable observation times.

2.2 Growth curve shapes

Both SEM and mixed-effects approaches may be used to describe a variety of growth curve shapes; the most common being relatively simple linear and curvilinear trajectories (e.g. quadratic slopes), though with sufficient observations and an appropriate relationship between the outcome measure and time, more complex non-linear trajectories such as that posited by Jack *et al.* (2010) could be appropriately described (Capuano *et al.*, 2018).

Comparable research into cognitive decline in dementia varies in approach; simple linear models are common in prospective clinical cohorts (Rongve *et al.*, 2016; McDade *et al.*, 2018; Malek-Ahmadi *et al.*, 2019), which typically have more detailed assessment, but consequently smaller sample numbers and fewer observations; naturally at least three observations must be available per subject for any trajectory other than a linear one to be described. Aside from their statistical simplicity, linear models may also be relatively simple to conceptualise for a broad audience but will fail to accurately describe any real non-linear trajectory.

With sufficient observations, larger longitudinal studies often identify quadratic or similar accelerating trajectories of cognitive decline in normal ageing (Muniz Terrera *et al.*, 2008), and in the lead up to, and after, dementia diagnosis (Wilkosz *et al.*, 2010; Verlinden *et al.*, 2016; Baker *et al.*, 2017; Rajan *et al.*, 2017; Wang *et al.*, 2019). These trajectories may be expected due to the non-linear nature of biological processes presumed to underlie normal and pathological cognitive decline, as exemplified by the curvilinear decline in hippocampal volume associated with normal ageing (Yang *et al.*, 2013). Decline in MCI towards dementia may also be characterised by a comparable cognitive trajectory, though this has not yet been assessed in MCI-LB, and trajectories of decline may differ between aetiologies.

Appropriate model development is to investigate both a linear and curvilinear trajectory to identify patterns of cognitive change. Model selection is undertaken using an appropriate measure of relative model fit (e.g. Akaike or Bayesian Information Criteria) to assess the value of including non-linear terms in addition to the simpler linear term. For the purpose of this work, curvilinear trajectories of cognitive progression were therefore considered in all analyses of continuous cognitive outcomes, and assessed for suitability by visual inspection and when any improvement in model fit was observed in comparison to the simple linear model. However due to the limited sample size and number of observations, a linear trajectory was anticipated to be the best-fitting in most cases, as in the most comparable previous literature (Rongve *et al.*, 2016; van de Beek *et al.*, 2020); this is an acknowledged limitation of the current data being unable to reflect the assumed complexity of the underlying neurocognitive declines.

2.3 (Linear) mixed-effects modelling

Mixed-effects models are an extension of general(ised) linear models which allow analysts to account for non-independence of data, such as when multiple observations are taken from one individual as in a typical longitudinal study. Consequently, mixed-effects models may be used to estimate growth curve models, as identified in **Section 2.1.2**. Their utility is not restricted to longitudinal analyses however, as they may be reasonably applied to other types of studies with simple or complex random effects structures to account for.

2.3.1 Strengths of mixed-effects models

The key strengths of mixed models are their reasonable robustness when observations are taken at unbalanced time-points (Pinheiro and Bates, 2006; Locascio and Atri, 2011), or when there is data missing, as is the case in the LewyPro (**Chapter 3**) and SUPErB (**Chapter 7**) studies due to censoring, death, drop-out, and adaptive scheduling.

Both general and generalised linear mixed models (LMM) have been used in a number of longitudinal studies to compare rates of cognitive decline in DLB and AD (Smits *et al.*, 2015; Rongve *et al.*, 2016; Kramberger *et al.*, 2017; Breitve *et al.*, 2018; Malek-Ahmadi *et al.*, 2019; Yu *et al.*, 2019; Giil and Aarsland, 2020), and retrospectively in prodromal DLB (van de Beek *et*

al., 2020). Simple LMMs may therefore be the most typical approach taken within this field when characterising the longitudinal progression of continuous cognitive and non-cognitive outcomes of neurodegenerative diseases, being relatively flexible and familiar to the desired audience. For this reason, LMM was the first approach taken in characterising the longitudinal decline in global and domain-specific cognitive function in **Chapters 4, 8 and 9**.

2.3.2 Practical considerations for mixed-effects models

Within *R* software, a number of packages provide functions for mixed-effects modelling, with *lme4* (Bates et al., 2015) currently being the most popular and well-supported. While *lme4* does not provide *p*-values in the model output, due to statistical concerns with their approximation and uses, the extension package *lmerTest* (Kuznetsova *et al.*, 2017) may provide these, by default using Satterthwaite approximation, and so these are often used in conjunction. While there are valid concerns over the current use and interpretation of *p*-values in research publishing (Wasserstein and Lazar, 2016), it remains an expectation that these are reported transparently alongside other information, and so this method was considered as suitable for analysis of the LewyPro and SUPErB longitudinal data.

The key research question, whether different neurodegenerative diseases are associated with different trajectories of cognitive decline, has typically been answered within comparable LMM and similar methods by testing the inclusion of a time x diagnostic group interaction in other studies (Stavitsky *et al.*, 2006; Smits *et al.*, 2015; Rongve *et al.*, 2016; van de Beek *et al.*, 2020), and so this method was also adopted in these analyses.

2.3.3 Limitations

While their simplicity and consequent flexibility may be a strength of these methods, LMMs can also be limited by their simplicity. As observed in data visualisations provided by Rongve *et al.* (2016), Baker *et al.* (2017), and McDade *et al.* (2018), global cognitive trajectories can be highly variable between individuals within a given neurodegenerative syndrome. Typical statistical approaches which average across these differences may provide adequate estimates of the predicted level and progression of cognitive function in a group, and any broad differences from

other groups, but may fail to appropriately describe the cognitive trends experienced by any individual within this group, or any subgroups which may have different patterns and trajectories from the overall group.

In real-world research settings this heterogeneity, if identified and accounted for, could have meaningful contributions in research and clinical practice; for instance, aiding in the identification of people with declining rather than stable MCI, and consequently in identifying those who may benefit more from potential future treatments. We therefore want to consider that the whole population does not have one homogenous pattern of change, and that the scenarios given above (some people decline, others improve) are considered in analyses.

Section summary

LMM is a common method of analysing longitudinal data in retrospective and prospective observational studies into the progression of outcomes in neurodegenerative diseases such as AD and DLB. While reasonably flexible, simple LMMs are limited by their inability to describe latent trends in the data which may have more clinical and research utility than the average group trajectory.

2.4 Latent class mixed modelling

Latent class mixed modelling (LCMM) allows mixed-effects models to be extended to identify latent classes (prior-unknown subgroups) with distinct trajectories, clustering by statistical similarity of growth curve. Within a longitudinal model, this could take the form of subgroups differentiated by starting point, rate of progression, shape of slope, or a combination of these. Latent class approaches to longitudinal data are less common than traditional LMM in the immediate MCI and DLB literature, and so may be less familiar to the intended audience, but have shown promise in identifying heterogeneity of cognitive trajectories in AD (Wilkosz *et al.*, 2010; Leoutsakos *et al.*, 2015), all-cause dementia (Baker *et al.*, 2017), and retrospectively in pre-clinical dementia (Verlinden *et al.*, 2016), prior to differential diagnosis.

2.4.1 Strengths of latent class mixed models

The key strength of LCMM over more typical LMM methods is its utility in accounting for heterogeneity within samples, such as by identifying non-responders in a clinical trial, or non-decliners and super-decliners in a purported neurodegenerative sample. In this regard it addresses the main limitation of LMM identified above (see **Section 2.3.3**). Due to the heterogeneous nature of decline in MCI and dementia, LCMM methods may be valuable in appropriately characterising the varying experiences of people receiving a prospective MCI diagnosis, and may be able to characterise non-decline in an objective, data-driven manner, in the absence of any normative data for age-related longitudinal decline.

2.4.2 Undertaking latent class mixed modelling

Packages such as *lcmm* (Proust-Lima et al., 2017) and *flexmix* for *R* software allow for data-driven identification of latent classes in longitudinal data, accounting for any effect on model fit in a data-driven manner, rather than the (relatively more) arbitrary cut-offs which have been used to identify distinct groups in similar cohorts such as quantile splits or rule-of-thumb .

Identified latent classes may be used in a simple descriptive manner as by Wilkosz *et al.* (2010) but may also be treated as outcomes of a predictive model such as a logistic regression or in support-vector machine learning (Leoutsakos *et al.*, 2015; Baker *et al.*, 2017). The suitability of these predictive models must be considered on an individual basis, as with insufficient observations, or the inclusion of too many parameters, the validity of any predictive estimates may be questionable.

Building upon the experience of applying LMM to describe cognitive decline over the course of MCI in **Chapters 4, 8 and 9**, LCMM methods were subsequently used to identify groups with distinct cognitive trajectories within the heterogeneous MCI cohorts in **Chapters 5, 8 and 9**, with the intention of identifying relatively fast and slow sub-groups, and early predictors of these trajectories. As an unsupervised method, it remained possible that other unexpected latent trajectories may have been identified, rather than those conceptually anticipated, and so this analysis was exploratory in nature.

2.5 Multi-state modelling

Where longitudinal outcome data are discrete, such as when exploring transitions from MCI to dementia, these previously-noted methods would not be appropriate. Typical approaches taken in exploring prognosis within neurodegenerative diseases utilise survival curve models to assess change in discrete states over time; for example, the differing survival times of DLB and AD demonstrated by Price *et al.* (2017). These models can similarly be applied to the analysis of 'survival' from MCI to dementia to establish risks of clinical transition between these syndromes (e.g. Aerts *et al.*, 2017). Survival models such as these may be conceptualised as simple two-state examples of the more flexible wider family of multi-state models (MSM).

2.5.1 Strengths of multi-state models

In the event that more discrete states may be observed between the first and last state (as in the cohorts available in this work), MSM may provide more flexibility than a typical survival model; for example, accounting for competing risks in a single model, or including transitionary stages of disease severity with different survival rates, e.g. mild, moderate, or severe heart disease (Cannon *et al.*, 2017). These methods are not new, but are less typically utilised in the research fields of dementia and cognitive impairment. For the cohorts included in this work, a strength of MSM methods was the ability to account for the dynamic nature of the MCI syndrome, with core clinical LB symptoms emerging over time which were not present initially, which may have been associated with increased risk of transition to dementia.

2.5.2 Practical considerations in multi-state models

The *msm* package (Jackson, 2011) for *R* software allows for the construction of multi-state and competing risk models. Time varying or invariant covariates may then be included into the models to explore their associations with rates of transition between states.

As repeated observations were available for each participant in addition to their survival time, data on symptom emergence could be utilised in addition to their initial clinical profile; MSM was therefore considered to be a promising approach for exploring the risks of transition from MCI to dementia or death, and any association between these and Lewy body symptomatology,

or other demographic variables. In contrast to other methods of incorporating time-varying covariates into survival analysis, this method does not require the manual specification of separate start and end times for each observation period. This analysis, and its results, are presented in **Chapters 6, 8 and 9** for the development, validation, and combined cohorts, respectively.

2.5.3 Limitations

One major limitation of this method is its applicability to smaller sample sizes, as in the cohorts available for this work. The flexibility of MSM (i.e. the number of states that may be conceptualised, and the dynamic transitions possible between these) may only be adequately realised given a sufficiently large number of observations overall, and a sufficient number of transitions observed between these states; with a lack of precedent, this analysis was anticipated to be exploratory in nature.

2.6 Chapter summary

To address the overall research question – whether the different neurodegenerative diseases, Lewy body disease or Alzheimer's disease, are associated with different patterns and progressions of mild cognitive impairment – three main analytical approaches were considered as appropriate. Each of these explored the fundamental research question from a different angle; these are summarised in **Table 2.1**.

Mixed-effects models explored the differences between diagnostic groups in their average rates of decline in global and domain-specific cognitive function. Latent class mixed models identified sub-groups of decline and non-decline within the overall MCI cohort, and explored the associations between Lewy body disease symptoms and subsequent trajectories of decline. Finally, multi-state models assessed the annual risks of clinical conversion from MCI to dementia with death as a competing risk, comparing the rates of conversion between cases of MCI with and without specific DLB symptoms.

These analyses were explored with a development cohort, and models were assessed with an independent validation cohort. Finally, the two cohorts were combined to provide the best possible evidence.

Table 2.1. Summary of methods.

	Summary
Mixed-effects modelling	
Chapters	4, 8 & 9
Outcome measures	Average global and domain-specific cognitive trajectories
Diagnostic measure	Differential diagnosis
Strengths	Simplicity and familiarity
Limitations	Little account for heterogeneity within groups
Latent class mixed modelling	
Chapters	5, 8 & 9
Outcome measure	Latent global cognitive trajectories
Diagnostic measures	Differential diagnosis and specific diagnostic characteristics
Strengths	Ability to identify heterogeneous sub-groups
Limitations	Limited sample size for predicting smaller latent classes
Multi-state modelling	
Chapters	6, 8 & 9
Outcome measure	Transitions between clinical states (MCI/dementia/death)
Diagnostic measures	DLB diagnostic characteristics accumulation and specific individual characteristics
Strengths	Definitive and clinically relevant outcome measure
Limitations	Low number of observed transitions for this method

Chapter 3. LewyPro Study Background

Building on previous research into the clinical and imaging profiles of DLB, the LewyPro study aimed to characterise MCI as a prodrome of DLB; a relatively novel approach at the time (McKeith *et al.*, 2016) prior to recent codification of MCI-LB research diagnostic criteria (McKeith *et al.*, 2020). This study undertook annual follow-ups with an MCI cohort to track rates of decline and eventual conversion to dementia in groups differentially diagnosed as either MCI-LB or MCI-AD based on contemporary clinical criteria for DLB.

Using data from this study, the aim of this work was to explore how MCI-LB and MCI-AD progressed clinically and cognitively towards the comparatively well-researched concepts of DLB and AD-type dementia, assessing if the differing underlying pathologies had different patterns and trajectories of cognitive decline, how Lewy body symptomatology developed over time, and whether different aetiologies were associated with different speeds of transition to dementia.

It was hoped that this study would provide further clarity as to the profiles and timelines of cognitive impairment in different neurodegenerative diseases, and might assist researchers and clinicians in considering appropriate tests and outcome measures for MCI-LB.

3.1 Participants

3.1.1 Screening

Beginning in February 2013, and ending in February 2016, patients were screened from local healthcare trusts in North-East England; those considered were aged 60 years or older, had a health service clinical diagnosis of MCI, and the reported possible presence of any symptom non-specifically associated with DLB, but also found in AD (e.g. unspecified sleep disturbance or a history of falls), or any core clinical symptoms of DLB (McKeith *et al.*, 2017).

3.1.2 Consent and assessment

Of those screened, 90 were eligible for inclusion initially and provided written, informed consent to undergo baseline assessment within the research study to further assess suitability. Ethical approval for this study was given by the National Research Ethics Service Committee North East – Newcastle and North Tyneside 2 (Research Ethics Committee No. 12/NE/0290).

For inclusion, all participants had to be medically stable, with no change in prescribed medication within the last month prior to baseline assessment. Exclusion criteria were the presence of dementia or lack of objective cognitive impairment at baseline, possible frontotemporal or vascular aetiology based on clinical features or previous imaging findings, or an established history of PD for more than one-year preceding onset of cognitive impairment.

After baseline assessment, four participants were excluded due to the presence of dementia, three were excluded due to the presence of only subjective cognitive impairment or an atypical static MCI, six withdrew prior to completing baseline assessment, and one was excluded after diagnosis of a frontotemporal dementia at follow-up. Seventy-six participants were therefore eligible and included.

Participants were followed-up annually unless they withdrew, converted to dementia or other serious illness, or died. Once all available participants had completed at least a 2nd year follow-up, to ensure the availability of a sufficient number of observations for this work, the dataset was locked for initial analysis. The available data at each observation point, and any loss to follow-up or censoring are detailed in **Figure 3.1**.

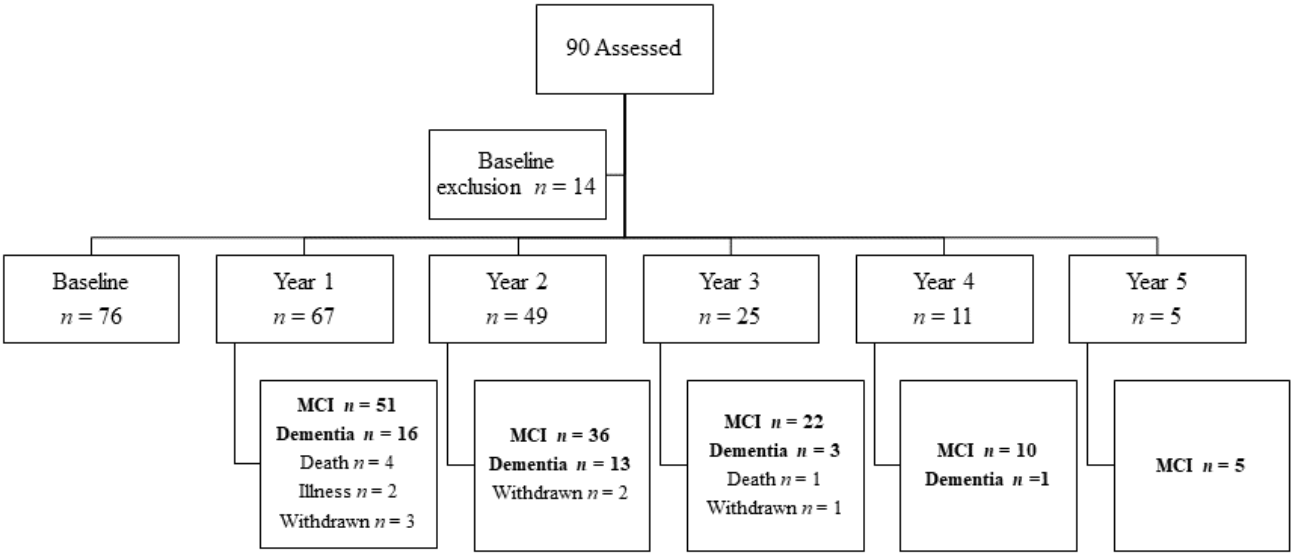


Figure 3.1. Data availability (bold) and loss at each observation year in the LewyPro study cohort.

Where possible, an informant was also sought from family or close friends for each participant, with permission, to provide further information on clinical features, functional independence, and neuropsychiatric symptoms. Eight participants (10%) did not have any informant available.

3.2 Diagnosis

A semi-structured interview was undertaken by a medical doctor with the participant and their informant, where available. Clinical notes from this interview were used to rate the presence of neurocognitive impairment, either MCI or dementia, independently by a three-person panel of experienced old age psychiatrists. MCI diagnoses were made in accordance with NIA-AA criteria (Albert *et al.*, 2011) given evidence and concern of relative cognitive decline without loss of independent functioning.

Differential diagnosis of MCI was undertaken in the same manner as the later formalised consensus criteria for diagnosis of MCI-LB in research settings (McKeith *et al.*, 2020): The presence or absence of four core clinical features of DLB (RBD, parkinsonism, complex visual hallucinations, and cognitive fluctuations) was rated in each case by the same panel producing a consensus for each feature's presence or absence. Results from dopaminergic imaging, as noted below, were also included as an additional diagnostic characteristic, to which the rating panel

were blind when assessing clinical features. Diagnostic criteria for DLB (McKeith *et al.*, 2005) were adapted for MCI, so that participants with MCI and none of four core DLB diagnostic features plus normal FP-CIT imaging were classified as MCI-AD. Those with MCI plus one of four core DLB features, or no core DLB features but abnormal FP-CIT imaging, were classified as possible MCI-LB. Participants with two or more core DLB features, or one core DLB feature and abnormal FP-CIT, were classified as probable MCI-LB.

Severity of neurocognitive impairment (MCI or dementia) and presence of core Lewy body symptoms was re-evaluated at each annual follow-up visit according to the same criteria. Those who had converted to dementia were diagnosed according to the relevant criteria for AD (McKhann *et al.*, 2011), DLB (McKeith *et al.*, 2005), vascular cognitive impairment (Román *et al.*, 1993), or a frontotemporal dementia (Rascovsky *et al.*, 2011), with the latter two being cause for exclusion as noted previously; cases with either vascular or frontotemporal aetiology at follow-up within MCI or upon development of dementia were retrospectively excluded.

3.2.1 Clinical features

Data on the presence and accumulation over time of specific clinical features was available for each participant, assisting in conceptualising specific patterns of disease and their development over time. Quantitative and semi-quantitative scales were available to measure severity of some symptoms, such as the UPDRS-III for assessing parkinsonism (Ballard *et al.*, 1997), the North East Visual Hallucinations Inventory (NEVHI) for visual hallucinations (Mosimann *et al.*, 2008), the Clinician Assessment of Fluctuation (CAF; Walker *et al.*, 2000b) and Dementia Cognitive Fluctuation Scale (DCFS; Lee *et al.*, 2014) for cognitive fluctuations, and the Mayo Sleep Questionnaire (MSQ; Boeve *et al.*, 2011a) for RBD.

Functional independence was assessed with the Instrumental Activities of Daily Living (IADL) scale (Lawton and Brody, 1969). In addition to standard (0-8) scoring range, this was also quantified with an extended scoring system treating each item as a scale rather than a binary score, so total scores may range from eight to 31 (Cromwell *et al.*, 2003), with total IADL scores reflecting greater functional impairment. The Epworth Sleepiness Scale (ESS; Johns, 1991)

assessed participants' levels of daytime sleepiness in various situations, providing a total daytime sleepiness score. The Geriatric Depression Scale (GDS; Yesavage *et al.*, 1983) was used to assess participants' present state of depressiveness at each visit. The Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) assessed overall neuropsychiatric symptomatology.

3.2.2 Biomarkers

Dopaminergic function was assessed with FP-CIT SPECT imaging (O'Brien *et al.*, 2004), offered to all included participants at baseline regardless of suspected diagnosis. Images were visually rated as either normal or abnormal by an experienced consensus panel blind to clinical information and diagnosis (Thomas *et al.*, 2019). Imaging results were incorporated into differential diagnoses to provide an additional diagnostic characteristic. Seventy-four of 76 participants consented to FP-CIT imaging, while two did not consent. In both who did not consent, there were sufficient clinical diagnostic features of DLB to receive a diagnosis of probable MCI-LB without dopaminergic imaging results: both featured cognitive fluctuations, complex visual hallucinations, and parkinsonism, while one of the two also had RBD, which the other did not.

3.3 Neuropsychological assessment

Several neuropsychological measures were available at baseline and follow-up to provide as complete of a neurocognitive profile as possible, with consideration for overall time cost.

3.3.1 Global cognition

Total score on the ACE-R (Mioshi *et al.*, 2006) was used to measure global cognitive functioning. MMSE scores were also derived from this test, allowing comparison of group levels of global cognitive impairment with a wider range of published research. The ACE (Ahmed *et al.*, 2008) and ACE-R (Yoshida *et al.*, 2012) have displayed good sensitivity to cognitive decline in MCI as well as dementia, and the latter is commonly used in memory services within the United Kingdom.

3.3.2 Attention and executive functions

To account for the diverse types of attention and executive functions, a range of tests was used to explore these thoroughly at every year of assessment.

Verbal fluency was assessed with the FAS letter-fluency test, which has shown greater sensitivity to frontal lesions than temporal in comparison with similar category-fluency tests (Baldo *et al.*, 2006). Additionally, ACE-R fluency sub-scores were available. In participants with comparable language skills, any differences in verbal fluency should be due to executive impairments.

Raw and cognitive processing speeds were measured with computerised simple (SRT) and binary-choice (CRT) reaction time tasks using handheld response buttons; the former measures how quickly a subject may react to the appearance of a (visual) stimulus, while the latter measures how quickly they may distinguish between the stimulus and a competing target. These tasks have been indicated to be relatively pure measures of processing speed (the speed at which the subject may parse information as it arises), with minimal demand on executive functions (Albinet *et al.*, 2012), and therefore favourable to alternatives such as trail making tests for this purpose.

Sustained and selective attention were also assessed with a computerised continuous performance digit-vigilance task, which had previously been successfully used to measure attentional impairment in DLB (Watson *et al.*, 2017).

Completion times for the Trail Making Test parts A (TMT-A) and B (TMT-B) respectively assessed visual attention and processing speed, and executive functioning. While less pure as measures of processing speed than reaction time tasks, these assessments are low in time and material costs, and have high utility in clinical settings.

3.3.3 Memory and learning

The RAVLT was administered at baseline to assess memory encoding, recall, and recognition processes (Schmidt, 1996); this test is sensitive to differences in amnestic memory dysfunction between DLB and AD (Ferman *et al.*, 2006), but also detects cognitive differences between MCI-AD and healthy controls (Estevez-Gonzalez *et al.*, 2003), and may help characterise amnestic versus non-amnestic MCI syndromes (Ferman *et al.*, 2013). Verbal learning tests such as this allow for the assessment of multiple memory processes at once, and even within a single model given enough observations (e.g. Gross *et al.*, 2013), but come with a higher time cost and participant burden than many other clinically-oriented assessments, and so these were not routinely used as a repeated measure after baseline. Memory sub-scores were available from the ACE-R at every year of assessment to provide measures of longitudinal progression of memory.

3.3.4 Visuospatial functions

A computerised line-orientation judgement task (LAT), run in MATLAB software, was used to assess visuo-perceptual skills in participants, having shown previous suitability in assessing visuo-perceptual dysfunction in DLB (Wood *et al.*, 2013a). Similar line-orientation tests have shown particular sensitivity to lesions of the posterior parietal cortex (Tranel *et al.*, 2009), and so might represent a relatively pure measure of spatial perception in particular, with little-to-no motor component.

The ACE-R visuospatial sub-score was also available from each year; this uses a diverse array of brief tasks including visuo-construction drawing tasks to assess a wide range of visual skills, albeit in less depth.

3.3.5 Speech, language, and intelligence

Language skills were expected to remain relatively stable in both control and MCI groups; the GNT (McKenna and Warrington, 1980) was used to assess language skills at baseline. Participants self-reported their number of years spent in formal education. The NART (Nelson and Willison, 1991) was completed by a subset of the sample at a later time, but not available for

all LewyPro participants. Language sub-scores of the ACE-R assessed any other changes at follow-up.

It was considered necessary to control for the confounding effects of premorbid functioning and health inequalities on intelligence and clinical progression in the absence of the NART. Participants reported their number of years spent in formal education to assess the former, and local deprivation was estimated from publicly available national deprivation statistics provided for each participant's local neighbourhood (Department for Communities and Local Government, 2011). While education was prospectively assessed at baseline, deprivation statistics were calculated retrospectively, and so not available in initial analyses.

3.4 Procedure

A longitudinal repeated-measures design was utilised. Measures were taken at baseline, and again at annual follow-ups, to track differences in within-subject progression between diagnostic groups in a mixed design.

3.4.1 Baseline testing

At baseline participants were consented, screened, and undertook all pen-and-paper neuropsychological assessments in a single visit. Medical review and imaging were undertaken at separate visits within the baseline year for a total of three visits; median time between first and final baseline visit was 21 days.

3.4.2 Follow-up testing

Pen-and-paper and computerised neuropsychological testing, as well as medical review, was undertaken within a single session at each annual follow-up. Tests which are insensitive to change or vulnerable to practice effects were not repeated and so available only at baseline. This general streamlining of data collection was also necessitated by the increasing number of participants requiring testing as the cohort developed over time, and to reduce participant burden. Assessments not administered at follow-up were the RAVLT, NART and GNT.

Data for participants who had converted to dementia after passing baseline screening was censored, and they did not undertake any further assessment. Where participants were lost to follow-up due to a clinically relevant reason, such as conversion to dementia or death, this was recorded where appropriate. After all available participants had completed two or more follow-up visits in the summer of 2018, the dataset was locked for analysis as presented here.

3.5 Analysis

Data from each year were extracted from wide-format databases in SPSS (one row per participant, repeat observations across separate databases for each timepoint), cleaned and combined into long-format data frames suitable for longitudinal analysis with *R* software (one row per observation with subject as a grouping variable and timepoint as a continuous variable). All data were routinely checked for anomalies or inconsistencies, and any suspected input errors were manually checked against the original paper records.

Chapter 4. LewyPro: Longitudinal Decline in MCI-AD and MCI-LB

Past research into the cognitive outcomes of Lewy body and Alzheimer's diseases had previously focussed on the dementia stages. While the cognitive prodromes of these diseases had been explored, this was predominantly in cross-sectional or retrospective studies, or without differential clinical diagnosis. This chapter is adapted from a manuscript accepted for publication (Hamilton *et al.*, 2020a).

DLB and AD present with different patterns of impairments in particular cognitive domains (Gurnani and Gavett, 2017), and have been observed to decline at different rates; various studies report a more aggressive course in DLB than AD in rate of cognitive decline (Rongve *et al.*, 2016), though this is mixed, with some studies finding no difference in speed of decline over shorter periods (Walker *et al.*, 2012).

Cross-sectional data have provided preliminary information on the cognitive profiles of MCI with Lewy bodies (MCI-LB) in comparison with MCI-AD and healthy controls (Ferman *et al.*, 2013; Kemp *et al.*, 2017; Donaghy *et al.*, 2018), suggesting that the DLB-like cognitive profile of greater visuospatial and executive impairment, and less amnestic memory dysfunction, may already be evident at the MCI stage. There is emerging evidence that the prodromal stages of DLB may differ in their cognitive trajectories from an idiopathic REM sleep behaviour disorder syndrome (Génier Marchand *et al.*, 2018), but the clinical MCI stages of AD and DLB have not been compared longitudinally in a prospective setting.

4.1 Aims and hypotheses

We aimed to utilise the longitudinal data now available to better characterise the cognitive profiles and trajectories in the LewyPro cohort. We hypothesised that MCI-LB and MCI-AD would display differing trajectories of cognitive decline, specifically: greater episodic memory decline with MCI-AD, and greater impairments in visuospatial, attention, and executive functions in MCI-LB. We also hypothesised that MCI-LB would show a more rapid global cognitive decline than MCI-AD, consistent with findings from comparable longitudinal studies of DLB and AD (Rongve *et al.*, 2016).

4.2 Methods

4.2.1 Participants and diagnosis

Seventy-six eligible participants were included from the LewyPro study, with recruitment and diagnosis as described in **Chapter 3**.

Participants were re-assessed every 12 months in a prospective longitudinal design. Presence of the four core clinical DLB features (RBD, cognitive fluctuations, complex visual hallucinations, and parkinsonism), and severity of neurocognitive impairment (MCI or dementia) were re-appraised at annual follow-ups by the clinical panel, with FP-CIT imaging results incorporated blind to clinical information. Participants were not followed-up after transition to dementia.

4.2.2 Materials

Cognitive measures

Outcome measures were the ACE-R, from which MMSE score was derived, as were domain-specific sub-scores for Attention and Orientation (0-18), Verbal Fluency (0-14), Memory (0-26), Visuospatial Function (0-16), and Language (0-26).

TMT-A and TMT-B, and FAS verbal fluency were also administered annually, with the latter two used to assess executive functions.

Computer-run tests included simple (SRT) and binary choice (CRT) reaction, and digit vigilance (DVT) tests of attention, and a line angle discrimination task (LAT) to assess visual perception (Wood *et al.*, 2013a).

Baseline-only tasks were the Rey Auditory Verbal Learning Test (RAVLT), Graded Naming Test (GNT), and computerised motion-detection task (Wood *et al.*, 2013a). These were not re-administered at follow-up due to time-constraints.

Clinical measures

In the semi-structured clinical interview, the UPDRS-III, ESS and GDS were administered to patients. The IADL scale, NEVHI, NPI, MSQ, CAF and DCFS were administered to informants. CDR and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) were completed based on clinical history.

4.2.3 Analysis

Baseline differences

As in the baseline study (Donaghy *et al.*, 2018), cross-sectional differences between groups were compared at baseline using one-way ANOVA and chi-square tests.

Longitudinal decline

LMM assessed cognitive change in the overall MCI cohort, and any effect of diagnosis. Analyses were undertaken in *R* software using the packages *lme4* (Bates *et al.*, 2015) and *lmerTest* (Kuznetsova *et al.*, 2017).

Time, as a continuous fixed effect, predicted cognitive outcome, while controlling for conceptually-relevant covariates (education, age, gender). Models included random intercept and slope at the subject level, allowing for correlation between these when indicated by improved model fit. Both Akaike- (AIC) and Bayesian Information Criterion (BIC) were considered as complementary measures of model fit, with decrease in either representing an improvement in model fit when including a parameter, but the latter being the more conservative benchmark. Diagnostic group was then incorporated as a fixed effect, interacting with time where appropriate, in all models; if this did not improve model fit, an alternate best-fit (by BIC) model is also reported.

Development models were fit by full maximum likelihood, and final reported models by restricted maximum likelihood methods. MCI-AD is treated as the reference group for comparison.

Significance level was defined as $p < .05$ and no adjustment was made for multiple testing given the exploratory nature of this analysis, with domain-specific primary hypotheses requiring independent tests.

4.3 Results

4.3.1 Diagnostic groups

At the time of data locking, participants had been followed-up for a mean of 1.9 years (*SD* = 1.1, Min = 0, Max = 5, Median = 2).

Table 4.1. Clinical features of LewyPro baseline diagnostic groups.

	MCI-AD (*n* = 23)	**Poss. MCI-LB (*n* = 12)**	**Prob. MCI-LB (*n* = 41)**
Parkinsonism	0 (0%)	0 (0%)	19 (46%)
Cognitive Fluctuations	0 (0%)	4 (33%)	23 (56%)
REM Sleep Behaviour Disorder	0 (0%)	5 (42%)	20 (49%)
Complex Visual Hallucinations	0 (0%)	0 (0%)	12 (29%)
Abnormal FP-CIT SPECT	0 (0%)	3 (25%)	26 (67%)[a]

[a]Two participants did not consent to FP-CIT SPECT, but had sufficient clinical symptomatology to receive a probable MCI-LB diagnosis without confirmatory biomarkers

Thirty-two participants (42%) had transitioned to dementia; seven MCI-AD (30%), five possible MCI-LB (42%), and 20 (49%) probable MCI-LB. Fourteen transitioned within the first year, 12 in the second, five in the third, and one in their fourth. All seven cases of AD dementia had been previously diagnosed with MCI-AD. Of five possible DLB, three had been diagnosed as MCI-AD but subsequently developed LB symptoms, and two had baseline diagnoses of possible MCI-LB. All 20 cases of probable DLB had been diagnosed as probable MCI-LB. In comparison with MCI-AD, a Fisher's exact test did not find diagnosis of possible MCI-LB to be significantly associated with an eventual diagnosis of possible DLB rather than AD (exact $p = .152$). Probable

MCI-LB diagnosis was significantly associated with eventual diagnosis of probable DLB versus AD (exact $p < .001$).

Clinical diagnoses, demographics and baseline scores have been reported in detail previously (Donaghy *et al.*, 2018) and are summarised in **Table 4.1, Table 4.2, and Table 4.3**. Diagnostic groups did not differ in age, education, or baseline global cognitive function. Probable MCI-LB presented with greater functional impairment than MCI-AD (lower IADL score), though all subjects had minimal impairments, as reflected by their MCI diagnosis; IADL scores were correlated (Spearman's ρ) with UPDRS-III ($\rho = -0.28$, $p = .023$) but not ACE-R total scores ($\rho = 0.12$, $p = .344$) suggesting that these related to motor, not cognitive, impairments. MCI-AD were mostly female, and probable MCI-LB mostly male. Higher daytime sleepiness (ESS), motor impairment (UPDRS-III), and neuropsychiatric symptomatology (NPI, GDS-15, NEVHI, CAF, and DCFS) were found in probable MCI-LB; this was expected as these relate to the symptoms used for differential diagnosis, as was a higher rate of self-reported hyposmia.

Table 4.2. Baseline demographic and clinical measures for LewyPro cohort.

Demographics and clinical measures	**MCI-AD (*n* = 23)**	**Poss. MCI-LB (*n* = 12)**	**Prob. MCI-LB (*n* = 41)**	*p*
Female	15 (65%)	5 (42%)	14 (34%)	.055
Male	8 (35%)	7 (58%)	27 (66%)	-
Age	78.2 (7.5)	75.3 (7.3)	75.5 (7.6)	.335
Years in Education	11.9 (3.0)	10.8 (2.1)	11.4 (2.8)	.531
CDR Total (Median)	0.5 (0)	0.5 (0)	0.5 (0)	.206
IADL Total (0-8)	7.2 (0.9)	6.6 (1.6)	6.1 (1.7)	.038
CIRS-G Total	9.2 (4.0)	12.1 (5.2)	9.1 (4.1)	.097
MSQ Q1 'Yes'	3 (13%)	2 (17%)	20 (49%)	.095
ESS	4.2 (3.7)	6.8 (4.9)	10.4 (5.0)	<.001
GDS	2.4 (2.2)	2.9 (2.7)	4.4 (3.6)	.039
UPDRS-III	15.0 (7.1)	14.0 (7.8)	26.2 (16.2)	.001
NPI Total	5.8 (7.0)	12.9 (13.2)	13.7 (9.8)	.021
NEVHI	1.0 (2.8)	1.3 (3.4)	3.4 (4.4)	.031
CAF	0.3 (1.0)	2.0 (2.5)	2.4 (2.9)	.019
DCFS	5.6 (1.6)	7.4 (2.3)	8.9 (3.2)	<.001
Lost Sense of Smell	4 (17%)	2 (17%)	19 (46%)	.026

Table 4.3. Baseline cognitive measures in LewyPro cohort.

Cognitive measures	**MCI-AD**	**Poss. MCI-LB**	**Prob. MCI-LB**	*p*
MMSE	26.5 (2.3)	26.2 (2.9)	26.5 (2.0)	.901
ACE-R Total	79.5 (11.70)	79.3 (14.1)	79.3 (8.3)	.996
ACE-R Att./Orient.	17.0 (1.4)	16.6 (2.1)	16.8 (1.4)	.745
ACE-R Memory	15.7 (5.8)	15.8 (5.9)	17.4 (4.4)	.356
ACE-R Fluency	9.7 (2.7)	8.2 (3.3)	7.9 (2.8)	.041
ACE-R Language	22.9 (3.3)	24.1 (2.9)	23.6 (2.1)	.385
ACE-R Visuospatial	14.2 (1.9)	14.7 (1.9)	13.5 (2.1)	.125
FAS Fluency	36.2 (13.1)	26.5 (16.3)	29.0 (14.5)	.093
Rey Delayed Recall	3.1 (4.3)	2.5 (2.6)	3.9 (3.1)	.438
Rey Recognition	12.0 (2.3)	10.3 (3.6)	11.7 (2.3)	.184
Rey % Trial 5 Recalled	35.2 (39.0)	37.5 (40.0)	53.9 (50.6)	.253
GNT	16.5 (6.8)	20.3 (5.9)	17.6 (5.7)	.223
SRT Mean (ms)	406 (149)	410 (177)	403 (155)	.993
CRT Mean (ms)	678 (131)	747 (355)	730 (250)	.642
DVT Mean (ms)	555 (75)	534 (72)	584 (72)	.074
Motion Task Score	0.70 (0.28)	0.67 (0.28)	0.65 (0.28)	.784

4.3.2 Longitudinal change: global cognitive function

To test the hypothesis that LB symptomatology would have a faster decline than AD, a model was developed incorporating diagnosis as a fixed effect (**Figure 4.1**) predicting ACE-R total score; this did not improve fit under either criteria. This full model, and alternate best-fitting model, are reported (**Table 4.4)**. Diagnostic groups did not significantly differ in their initial global cognition, or their decline.

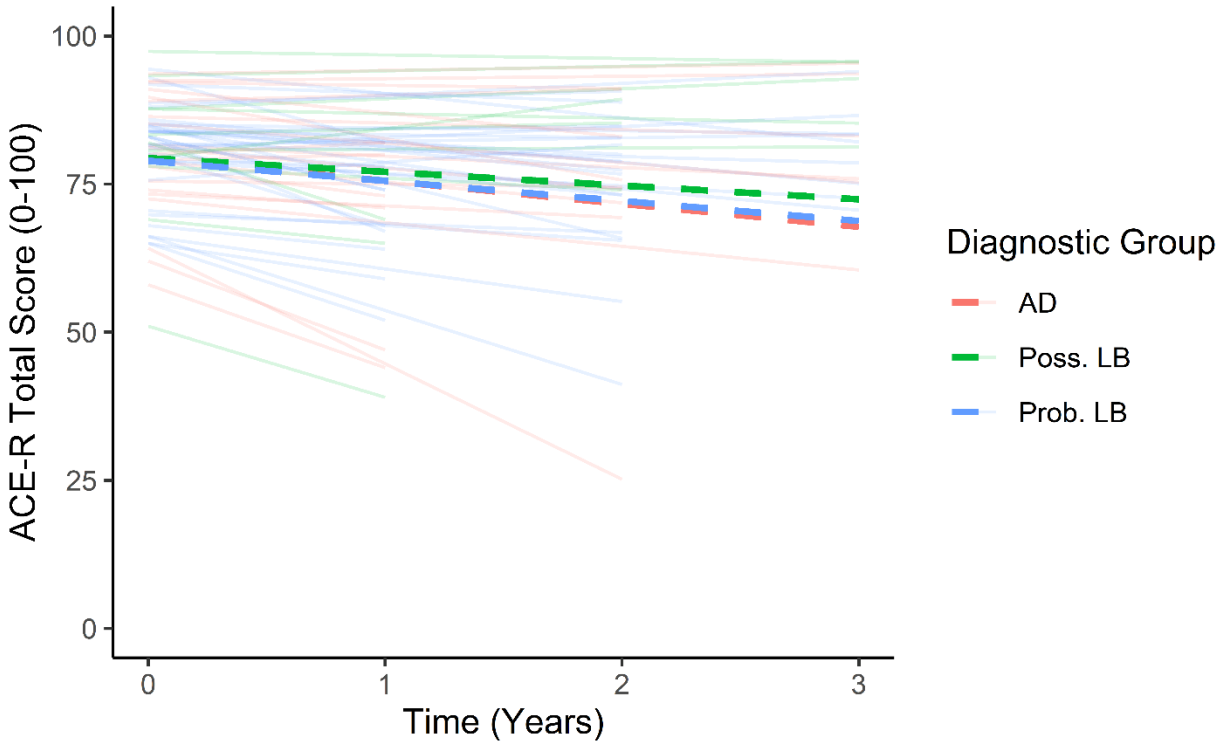


Figure 4.1. Longitudinal observed individual (solid lines) and predicted diagnostic-specific (dashed lines) trajectories of global cognitive decline in LewyPro.

4.3.3 Domain-specific function

This method was repeated for domain-specific measures. Estimates for ACE-R sub-scores are reported in **Table 4.4**, including diagnosis (full model), interacting with time where appropriate. Best-fit models are also reported in when diagnosis was not observed to have an effect, or as indicated by the more parsimonious Bayesian criterion. Age, gender, and education were included as covariates in all cases.

Attentional functions (ACE-R Attention & Orientation) significantly declined over time, but there was no effect of diagnosis, with no improvement in model fit.

Overall memory (ACE-R Memory) did not decline over time; incorporating diagnosis did not improve model fit, and diagnoses did not differ in their initial profiles or time-trajectories. Verbal fluency significantly declined in MCI. In the full model, probable MCI-LB was associated with poorer verbal fluency (ACE-R Fluency) than MCI-AD. However, including diagnosis did not improve fit sufficiently to include in the best-fit model with BIC.

Speech and language (ACE-R Language) declined significantly over time. Including diagnosis did not improve fit; there were no differences between groups in initial language impairment or declines thereafter.

For visuospatial functions (ACE-R Visuospatial), including diagnosis as a fixed effect interacting with time provided best fit under AIC (**Table 4.4**). Although probable MCI-LB had a lower baseline visuospatial sub-score, the error term around this was quite large. MCI-AD patients did not significantly decline in visuospatial performance over time, however probable MCI-LB had a significantly more rapid decline in comparison to MCI-AD (**Figure 4.2**). Possible MCI-LB did not significantly differ in baseline visuospatial performance or rate of decline compared to MCI-AD. Using BIC, the simplest model without diagnosis was favoured; this parsimonious model is also reported.

Table 4.4. Fixed effects coefficients for linear mixed-effects models for ACE-R total and domain scores in LewyPro.

	Intercept[a]	**Change from intercept**					*Time*	*Interaction with time*	
ACE-R Total	**MCI-AD**	**Possible MCI-LB**	**Probable MCI-LB**	**Education**	**Age**	**Gender Male**	*MCI-AD*	*Possible MCI-LB*	*Probable MCI-LB*
Best fit[b]	**83.4** (10.60), *< .001*	No difference from MCI-AD		**0.6** (0.31), *.041*	**-0.15** (0.13), *.257*	**-0.4** (1.96), *.856*	**-3.2** (0.55), *< .001*	No difference from MCI-AD	
Full model	**85.3** (11.25), *< .001*	**-2.0** (2.97), *.500*	**-1.1** (2.25), *.630*	**0.6** (0.32), *.064*	**-0.16** (0.13), *.243*	**-0.05** (2.06), *.981*	**-3.2** (0.55), *< .001*	No difference from MCI-AD	
ACE-R Attention & Orientation									
Best fit	**16.1** (1.91), *< .001*	No difference from MCI-AD		**0.06** (0.06), .292	**0.001** (0.02), *.961*	**-0.2** (0.35), *.623*	**-1.2** (0.19), *< .001*	No difference from MCI-AD	
Full model	**16.3** (2.0), *< .001*	**-0.3** (0.53), *.616*	**-0.2** (0.40), *.686*	**0.06** (0.06), *.349*	**0.00005** (0.02), *.999*	**-0.1** (0.37), *.721*	**-1.5** (0.19), *< .001*	No difference from MCI-AD	
ACE-R Memory									
Best fit	**22.6** (6.60), *.001*	No difference from MCI-AD		**0.2** (0.18), .397	**-0.1** (0.08), *.189*	**0.4** (1.21), *.756*	**-0.1** (0.22), *.807*	No difference from MCI-AD	
Full model	**21.2** (6.83), *.003*	**0.4** (1.81), *.810*	**1.6** (1.36), *.251*	**0.2** (0.19), *.353*	**-0.1** (0.08), *.222*	**0.01** (1.26), *.991*	**-0.1** (0.22), *.785*	No difference from MCI-AD	
ACE-R Verbal Fluency									
Best fit	**7.2** (3.52), *.044*	No difference from MCI-AD		**0.3** (0.10), *.002*	**-0.03** (0.04), *.518*	**-0.6** (0.65), *.368*	**-0.2** (0.12), *.043*	No difference from MCI-AD	
Full model	**8.8** (3.56), *.015*	**-0.9** (0.95), *.322*	**-1.5** (0.71), *.032*	**0.3** (0.10), *.004*	**-0.04** (0.04), *.403*	**-0.2** (0.66), *.734*	**-0.2** (0.12), *.044*	No difference from MCI-AD	
ACE-R Language									
Best fit	**26.3** (3.05), *< .001*	No difference from MCI-AD		**0.15** (0.09), *.088*	**-0.06** (0.04), *.110*	**-0.04** (0.56), *.942*	**-0.5** (0.14), *< .001*	No difference from MCI-AD	
Full model	**25.4** (3.14), *< .001*	**1.3** (0.83), *.130*	**0.5** (0.63), *.465*	**0.18** (0.09), *.051*	**-0.06** (0.04), *.134*	**-0.2** (0.58), *.716*	**-0.5** (0.14), *< .001*	No difference from MCI-AD	
ACE-R Visuospatial									
Best fit	**12.3** (2.66), *< .001*	No difference from MCI-AD		**0.1** (0.08), *.096*	**-0.003** (0.03), *.912*	**0.5** (0.49), *.332*	**-0.5** (0.14), *< .001*	No difference from MCI-AD	
Full model	**12.8** (2.72), *< .001*	**-0.04** (0.72), *.955*	**-1.0** (0.54), *.081*	**0.1** (0.08), *.130*	**-0.003** (0.03), *.933*	**0.7** (0.50), *.166*	**-0.2** (0.23), *.420*	**-0.1** (0.37), *.830*	**-0.6** (0.28), *.036*

[a]**Estimate** (*SE*), *p value*

[b]Best fit models fit for parsimony with diagnosis parameter/interaction excluded when indicated by model fitting criterion

As overall ACE-R memory score is a composite of various tasks; we also examined specific scores to explore memory patterns in-depth. Diagnostic groups did not differ in their registration or un-cued recall of information; performance in these sub-domains was not predicted by age, education, or gender, and did not significantly decline over time. In recognition of learned information, there was a significant difference at baseline between probable MCI-LB, and MCI-AD, with the former performing better in the full model (**Table 4.5**). Incorporating diagnosis improved fit under AIC, but not BIC, so an alternate best-fit model is also reported. Recognition memory did not display any clear time trend overall, nor any group differences in decline.

To explore visuospatial decline more clearly, ACE-R visuospatial totals were decomposed into visuo-constructional (pentagon and cube copying, and clock drawing), and perceptual scores (letter identification and dot-counting), each marked out of eight. There was no significant time trend in visuo-perceptual performance, no effect of age, education, or gender, and no influence of diagnostic status; none of these improved model fit. Visuo-constructional performance was significantly influenced by diagnosis (**Table 4.5**); probable MCI-LB performed poorer at baseline, and deteriorated at a faster rate than MCI-AD. AIC favoured this full model and BIC favoured a more parsimonious model without interaction term; this best-fit model is also reported in **Table 4.5**. After controlling for baseline function post hoc, without interaction with time (as indicated by AIC and BIC), the pattern of faster decline in probable MCI-LB remained (B = -0.7, SE = 0.30, p = .026), suggesting that the declining trend was not just an artefact of the lower starting function in probable MCI-LB.

To adequately assess visuo-perception, a secondary model examined line-angle task performance, which showed utility in a previously reported cross-sectional study using the baseline data from this same study (Donaghy *et al.*, 2018), and was administered repeatedly at subsequent follow-ups. Higher values reflect poorer angle discrimination (in degrees) and therefore worse performance. LAT performance was best predicted by the inclusion of diagnosis, without time-interaction, under both criteria (**Table 4.5**). Genders significantly differed in performance, with males better able to discriminate angle differences than females, but did not differ in their progressions. Probable MCI-LB was associated with significantly poorer angle judgement than MCI-AD at baseline. There was no significant time trend in LAT performance,

and no interaction of time with other effects. There were few repeated observations (n = 132), limiting the ability to estimate changes over time.

Repeated measurements were also available for FAS verbal fluency; in the full model, probable MCI-LB had significantly poorer performance at baseline after controlling for covariates (**Table 4.5**). There was no significant time effect, or interaction with diagnosis. Diagnostic status improved fit under AIC, but not BIC, so the alternate parsimonious model is also reported. As with the LAT, repeated measures were taken but observations were limited (n = 130).

For TMT-A, completion time was best predicted by models incorporating age and education as non-interacting effects (**Table 4.5)**; including diagnosis improved fit under AIC, but not BIC. Diagnostic effects were non-significant. For TMT-B there was no effect of diagnostic group. In both, higher education was associated with faster- and higher age with slower completion.

Mean and *SD* of correct response times in both simple and choice reaction tests, and digit vigilance task, were not significantly predicted by age, education, or gender. Incorporating diagnosis did not improve model fits. Reaction times did not clearly improve or worsen over time and there were no differences in profiles or trajectories between the diagnostic groups.

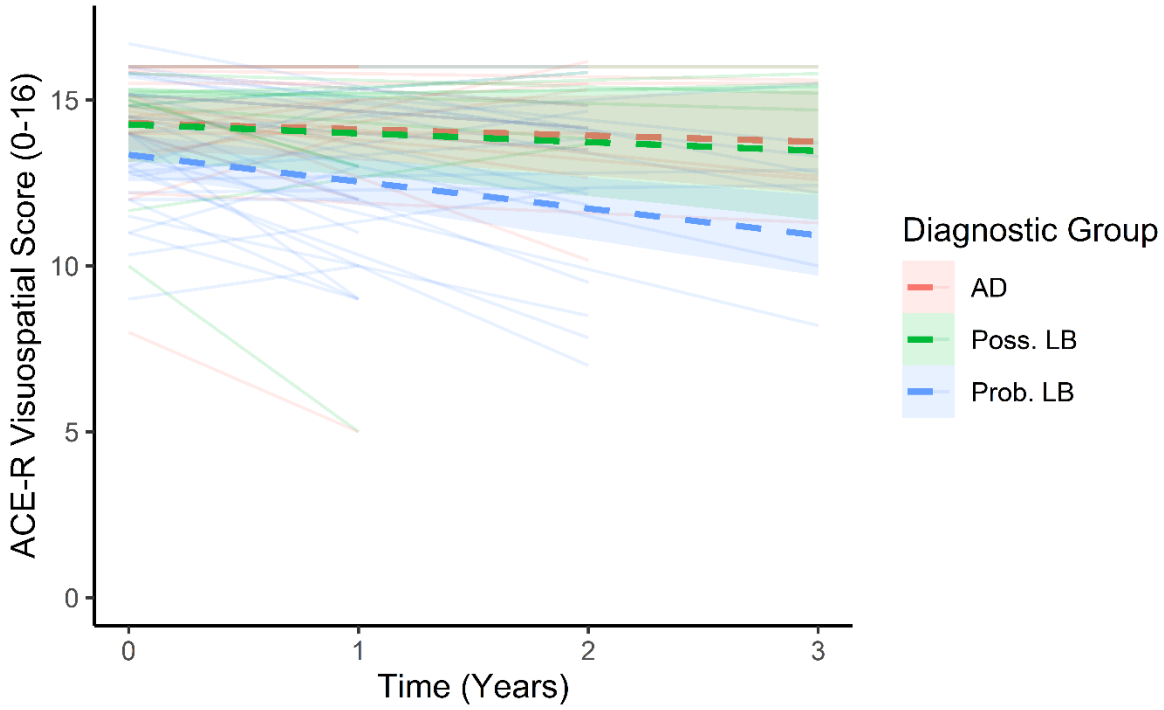


Figure 4.2. Observed individual (solid) and predicted diagnostic-group (dashed) trajectories of cognitive decline in visuospatial domain in LewyPro.

Table 4.5. Fixed effect coefficients for linear mixed-effects models for supplementary cognitive tests in LewyPro.

	Intercept[a]	**Change from intercept**					*Time*	*Interaction with time*	
ACE-R Visuo-Construction	**MCI-AD**	**Possible MCI-LB**	**Probable MCI-LB**	**Education**	**Age**	**Gender Male**	*MCI-AD*	*Possible MCI-LB*	*Probable MCI-LB*
Best fit[b]	**5.3** (2.30), *.025*	**0.28** (0.61), *.642*	**-1.1** (0.46), *.022*	**0.1** (0.07), *.118*	**-0.003** (0.03), *.904*	**0.8** (0.42), *.071*	**-0.4** (0.11), *.001*	No difference from MCI-AD	
Full model	**5.3** (2.29), *.024*	**0.3** (0.61), *.623*	**-0.9** (0.46), *.045*	**0.1** (0.07), *.134*	**-0.004** (0.03), *.875*	**0.8** (0.42), *.054*	**-0.1** (0.19), *.713*	**-0.1** (0.31), *.739*	**-0.6** (0.24), *.018*
ACE-R Recognition Memory									
Best fit	**3.9** (1.12), *< .001*	No difference from MCI-AD		**0.05** (0.03), *.158*	**-0.01** (0.01), *.540*	**0.05** (0.20), *.824*	**0.1** (0.07), *.420*	No difference from MCI-AD	
Full model	**3.5** (1.13), *.003*	**0.0** (0.29), *.993*	**0.5** (0.22), *.035*	**0.1** (0.03), *.108*	**-0.01** (0.01), *.670*	**-0.1** (0.21), *.759*	**0.1** (0.07), *.429*	No difference from MCI-AD	
LAT									
Best fit	**32.9** (18.58), *.081*	**-4.5** (4.92), *.360*	**9.9** (3.66), *.008*	**-0.9** (0.56), *.120*	**-0.01** (0.22), *.971*	**-9.9** (3.41), *.005*	**3.0** (2.17), *.178*	No difference from MCI-AD	
TMT-A									
Best fit	**-56.2** (41.24), *.178*	No difference from MCI-AD		**-3.6** (1.25), *.005*	**2.1** (0.50), *<.001*	**14.7** (7.57), *.057*	**10.9** (5.10), *.040*	No difference from MCI-AD	
Full model	**-54.2** (41.67), *.198*	**-21.7** (10.85), *.050*	**2.3** (8.23), *.785*	**-3.9** (1.23), *.002*	**2.1** (0.50), *<.001*	**15.4** (7.56), *.046*	**10.9** (5.20), *.044*	No difference from MCI-AD	
TMT-B									
Best fit	**-72.1** (105.60), *.498*	No difference from MCI-AD		**-12.8** (3.30), *<.001*	**4.9** (1.30), *<.001*	**31.9** (19.72), *.113*	**1.2** (6.34), *.851*	No difference from MCI-AD	
Full model	**-98.0** (112.2), *.387*	**2.6** (26.91), *.922*	**18.4** (22.99), *.428*	**-12.2** (3.42), *<.001*	**5.0** (1.33), *<.001*	**28.0** (20.59), *.181*	**0.6** (6.36), *.920*	No difference from MCI-AD	
FAS Total									
Best fit	**14.4** (16.91), *.399*	No difference from MCI-AD		**2.2** (0.50), *< .001*	**-0.1** (0.20), *.605*	**-1.4** (3.12), *.662*	**0.2** (0.68), *.725*	No difference from MCI-AD	
Full model	**24.2** (17.05), *.160*	**-9.0** (4.50), *.050*	**-7.2** (3.40), *.037*	**2.0** (0.49), *<.001*	**-0.2** (0.20), *.439*	**0.5** (3.15), *.879*	**0.3** (0.67), *.688*	No difference from MCI-AD	

[a]**Estimate** (*SE*), *p value*

[b]Best fit models fit for parsimony with diagnosis parameter/interaction excluded when indicated by model fitting criterion

4.4 Discussion

There was no clear difference in rates of global cognitive decline between diagnostic subgroups, contrary to our hypothesis, but as hypothesised, probable MCI-LB was associated with a faster deterioration in aspects of visuospatial function as assessed by the ACE-R. We did not observe different rates of decline in attentional or executive functions between groups.

Overall memory performance did not differ between groups, either in initial impairment or decline thereafter. In exploratory analyses MCI-AD displayed poorer recognition memory than probable MCI-LB, but these did not differ in their progressions.

The more severe pattern of visuo-spatial impairment in probable MCI-LB aligns with previous findings in dementia (Ferman *et al.*, 2006; Metzler-Baddeley, 2007; Wood *et al.*, 2013a), Parkinson's disease (Weil *et al.*, 2016) and MCI (Ferman *et al.*, 2013; Yoon *et al.*, 2015), and may reflect disruption to cortical (Minoshima *et al.*, 2001; Fujishiro *et al.*, 2013) and sub-cortical (Delli Pizzi *et al.*, 2014) visual systems in DLB. Furthermore, the faster decline of visuo-constructional skills in MCI-LB is consistent with recent observations of faster declining visuospatial functions in DLB and PDD in comparison to AD (Smirnov *et al.*, 2020).While the ACE-R appears insensitive to visuo-perceptual decline in MCI, group differences are evident at baseline with the line angle discrimination task, suggesting that relatively pure perceptual tests might be valuable in assessing earlier visuospatial impairments in MCI.

Probable MCI-LB did not deteriorate more quickly in global cognitive function than MCI-AD, consistent with some (Walker *et al.*, 2012), but not all (Rongve *et al.*, 2016) findings from the respective dementia stages, which did not support our hypothesis; this could suggest that an accelerated decline occurs in DLB later than at the MCI stage. Alternatively, total score in the ACE-R may not account for global cognitive decline in MCI-LB and MCI-AD equally given their different patterns of domain-specific cognitive impairment; ACE-R sub-scores are not equally weighted towards total score, or equally sensitive to dysfunction, and so may underestimate the relative contributions of some domains to global cognitive impairment. Further exploration may establish whether MCI-LB also has a comparable rate of dementia onset as

MCI-AD, or if the faster expected decline manifests in faster loss of independent function after onset of cognitive impairment. Furthermore, our subject numbers are modest, and longer follow-up may be required to identify differences in decline.

These results help resolve some of the previously reported inconsistencies between two different tests of verbal fluency (Donaghy *et al.,* 2018); after controlling for relevant covariates and undertaking repeated measurement, ACE-R verbal fluency sub-score and FAS letter-fluency were consistent in finding greater impairments of verbal fluency in probable MCI-LB than in MCI-AD.

It was expected that MCI-LB would be associated with less memory impairment than MCI-AD. This hypothesis was only partially supported; while overall memory scores did not show this pattern, recognition-specific memory was worse in AD than probable MCI-LB. These results partially reflect previously observed patterns of memory impairments in AD and DLB, as assessed with dedicated verbal learning tests (Salmon *et al.,* 1996; Ferman *et al.,* 2006), with DLB displaying difficulties with encoding and recall but relatively preserved recognition, in comparison with the rapid 'forgetting' associated with AD.

The unexpected lack of progressive decline in memory may be partially explained by floor effects, or repeated practice and familiarity with common screening tests, such as the ACE-R. Comparison with a healthy control cohort may clarify whether practice effects are contributing, and if observed declines in language and attention are related to neurodegenerative processes, or normal aging. This would also afford the opportunity to characterise cognitive profile categorically, for example as amnestic or non-amnestic (Ferman *et al.,* 2013), in comparison to healthy normative data.

Intended for dementia screening, ACE-R sub-scores may be insensitive to domain-specific decline in MCI. More sensitive and less familiar tests may be suitable for this purpose, such as computerised testing batteries. While the RAVLT was administered to a subset of those who entered a follow-up study, there were insufficient repeated observations to develop a longitudinal

model; repeated assessment with a suitable memory test may better demonstrate how memory progresses over the course of MCI.

Using multiple domain-specific tests, these results are limited by the use of independent tests without adjustment for multiple comparisons, and limited improvement of model fit under the more conservative criterion; there is a need for replication of these findings, and future research with larger samples may benefit from the use of multivariate methods to succinctly describe multi-domain change.

The characteristics of possible MCI-LB remain unclear as they did not differ from MCI-AD in cognitive performance. Given the limited sample size, there may be a lack of statistical power to identify any real differences from MCI-AD or probable MCI-LB. Further exploration may establish how LB symptomatology develops over time in this cohort, how this affects progression, and where possible MCI-LB diagnoses fit into this picture, as ‘possible’ diagnoses may include early-stage low-symptomatic MCI-LB cases, or atypical presentations of MCI-AD such as those with false-positive FP-CIT imaging.

While some MCI cases demonstrate a clear cognitive decline towards dementia over the course of this study, others remain stable for many years; this could be explained by the existence of sub-groups with differing progressions. Specific clinical features, demographics, medical history, health anxiety or biomarkers may be associated with steeper or flatter trajectories of cognitive decline. Although differences were found between diagnostic groups in some cognitive domains, in only a handful of analyses was diagnostic status found to be a valuable predictor of function under the more parsimonious model-fitting criteria.

While the differences between AD and DLB in verbal fluency, visuospatial functions, and recognition memory may already be observed in their respective MCI stages, with visuospatial functions also declining faster in the latter, expected differences in other executive functions, memory encoding and recall, attention, and global decline are not yet apparent at this stage and require further exploration. Repeated testing with appropriately sensitive visuospatial, recognition

memory, and fluency tests may therefore be appropriate in the assessment of cognitive decline in MCI-LB.

4.5. Chapter summary

On average, rates of global cognitive decline do not differ between MCI-LB and MCI-AD. Patterns of cognitive impairment do differ however, with probable MCI-LB featuring worse visuospatial function and verbal fluency, and MCI-AD worse recognition memory. Probable MCI-LB also may feature a faster decline in complex visuospatial functions. Any broad differences between groups are mild however, and diagnostic group does not consistently predict a difference in cognitive performance.

The use of methods which average across the whole population within heterogeneous diagnostic groups may limit the ability to adequately describe the cognitive progressions experienced by people with MCI and may also limit statistical power. Latent class methods were considered as a suitable next step to explore cognitive decline in MCI.

Chapter 5. LewyPro: Latent Classes of Cognitive Decline

These results are adapted from a published manuscript (Hamilton *et al.*, 2020b).

Within a broad MCI population there is heterogeneity in the pattern of cognitive impairments and in the rate and pattern of decline, with some emerging over time as a non-declining stable MCI (Geslani *et al.*, 2005). There is a need to identify whether an individual with MCI is likely to decline towards dementia or remain stable over a longer period. A stable MCI may be a consequence of non-degenerative causes (Stone *et al.*, 2015), but some of this heterogeneity may still reflect the complex biological processes underlying cognitive impairment in neurodegenerative diseases such as DLB and AD.

Predicting rate of decline may be complicated by heterogeneity within clinical syndromes as well as between them: within population studies and prospective cohorts, patterns of underlying neuropathology (Zaccai *et al.*, 2015) and emergent symptomatology (Donaghy *et al.*, 2017) vary greatly. While individual trajectories of decline may differ due to as-yet unaccounted-for biological differences, such as an undiagnosed mixed aetiology (Malek-Ahmadi *et al.*, 2019), these may also be associated with different patterns of clinical symptomatology, biomarkers, or imaging findings that are already evident in MCI.

Previous findings from the dementia stages may provide a starting point for identifying hypothesised predictors of decline; findings are mixed as to whether any particular clinical symptom or imaging abnormality is associated with faster decline in DLB, or dementia in general. For example, presence of abnormal dopaminergic imaging has shown an association with faster cognitive decline (Kramberger *et al.*, 2017). Neuropsychiatric symptoms such as delusions and hallucinations have also been implicated as predictors of faster cognitive decline in AD (Scarmeas *et al.*, 2005b; D'Antonio *et al.*, 2019), and faster conversion from MCI to dementia (Mauri *et al.*, 2012), which may reflect a greater underlying cholinergic deficit responsible for these symptoms and decline (O'Brien *et al.*, 2005). However, some symptoms of neurodegeneration are known to precede cognitive decline by many years in various syndromes, such as RBD and PD (Williams-Gray *et al.*, 2007; Claassen *et al.*, 2010; Aarsland, 2016), and do not appear to be predictive of a faster decline in dementia (Chwiszczuk *et al.*, 2017).

5.1. Aims and hypotheses

We aimed to explore the heterogeneity in cognitive trajectories in greater depth by using LCMM to identify latent classes in an MCI cohort with distinct profiles of cognitive progression such as a faster or slower decline, stable progression without deterioration, or improvement, and to identify early-stage predictors of eventual trajectories.

Based on the above we hypothesised that within an MCI cohort there would be a group of stable/very slow decliners, a group of rapid decliners (largely with LB disease) and an in-between group with slow but clear progression. We hypothesised that faster decline would be more likely in MCI-LB in MCI featuring visual hallucinations, and in those with abnormal dopaminergic imaging findings.

5.2. Methods

5.2.1. Participants and diagnoses

Seventy-six participants were included from the LewyPro cohort, as in the previous analysis (**Chapter 4**), with clinical feature consensus, FP-CIT imaging, and consequent differential diagnoses operationalised in the same way.

Additionally for this analysis, participant deprivation level was derived from publicly-available (Department for Communities and Local Government, 2011) English Index of Multiple Deprivation (IMD) score of their home neighbourhood at the time of study entry, sorted into nationally ranked deciles, as in previous studies (Stephens *et al.*, 2014), with higher decile rank indicating greater local deprivation.

5.2.2. Analysis

Total score in the ACE-R at each observation was modelled as the cognitive outcome of interest. LCMM was used to identify subgroups with distinct cognitive trajectories using the *lcmm* package (Proust-Lima *et al.*, 2017) for *R* statistical software. This method allows for data-driven identification of classes and their respective characteristics (intercept, slope, and curvilinearity). As an extension of LMM methods, the suitability of any models with latent classes may be

compared to a typical single-class mixed model by familiar model fitting criteria, allowing for the possibility that identifying latent classes may not improve the model.

Selection of mixed model components and number of latent classes was based on BIC; a lower BIC value reflects better model fit, with a penalty for extra parameters, therefore favouring parsimony. Models were fit by maximum likelihood (ML) methods.

All models controlled for age, education, gender, and deprivation as fixed effect covariates. Quadratic trajectories of decline were assessed for suitability but did not improve model fit over a linear-only time term in these data, and so were not retained in the final models.

Predictive value of diagnostic group, clinical features, and FP-CIT imaging for each distinct trajectory class, were assessed by two multinomial logistic regression models; latent class was the three-level categorical outcome in both cases, with the intermediate trajectory as the reference. In the first model, diagnostic group was included as a three-level predictive factor, with probable MCI-LB as the reference due to being the largest group. In the second model, all five DLB diagnostic characteristics were included as baseline predictors initially; however, this number of predictors would not be supported by the assumptions of logistic regression given the sample size, and so backwards elimination of predictors was used to result in a best-fit model also reported, using BIC to assess changing model fit. Additional assumptions of logistic regression were checked after selection of the best-fitting model to confirm suitability.

Alpha level was defined as $p < .05$; no corrections were made for multiple comparisons due to the exploratory nature of this analysis, with the use of BIC for conservative model fitting to favour parsimony and retain only the best-supported predictive factor(s).

5.3. Results

At the time of analysis, participants had been followed-up for a mean of 2.4 years ($SD = 1.21$) after consent at baseline, with a maximum of 5 years. Baseline characteristics of the overall MCI group, and diagnostic subgroups, were as reported previously in **Chapter 4**. These are briefly summarised again in **Table 5.1**, including deciles of multiple deprivation.

Table 5.1. Baseline characteristics of MCI diagnostic groups.

	MCI-AD (*n* = 23)	**Poss. MCI-LB (*n* = 12)**	**Prob. MCI-LB (*n* = 41)**	***P*[a]**
Female – n (%)	15 (65%)	5 (42%)	14 (34%)	.055
Male – n (%)	8 (35%)	7 (58%)	27 (66%)	-
Age – mean (SD)	78.2 (7.5)	75.3 (7.3)	75.5 (7.6)	.335
Years in Education – Mean (SD)	11.9 (3.0)	10.8 (2.1)	11.4 (2.8)	.531
IADL Total – Mean (SD)	10.3 (2.3)	10.5 (3.2)	14.3 (4.7)	.002
Deprivation Decile – Median (IQR)	5 (6.00)	7 (3.25)	6 (5.00)	.709
MMSE – Mean (SD)	26.5 (2.3)	26.2 (2.9)	26.5 (2.0)	.901
ACE-R Total – Mean (SD)	79.5 (11.70)	79.3 (14.1)	79.3 (8.3)	.996

[a]χ^2 tests for gender, ANOVA/Kruskal-Wallis for all others

IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination – Revised; Prob. MCI-LB, probable mild cognitive impairment with Lewy bodies; MCI-AD, mild cognitive impairment due to Alzheimer's disease; Poss. MCI-LB, possible mild cognitive impairment with Lewy bodies.

5.3.1. Identification of latent classes

Five models were developed to explore; the initial longitudinal mixed model, without accounting for latent classes, provided a BIC value of 1612.07. A two-class model proved better-fitting (BIC = 1593.69), with the first latent class identified being too small to be meaningfully identified (n = 10). A three-class model also maintained an improved fit (BIC = 1604.61), but identified larger, well-defined classes (n = 31 & 35) in addition to the small class. Within each competing model, subjects were assigned *a posteriori* to the class to which they had the highest membership probability (posterior probability > 0.5). Any additional groups identified in four- and five-class models were small (n < 10) and indistinct from existing classes.

The three-class model was taken forward due to its identification of three clear clinically- and research-relevant groups with distinct trajectories, while maintaining an improved fit over the standard mixed model (**Table 5.2, Figure 5.1**).

Table 5.2. Fixed effects on total ACE-R score in longitudinal model.

Class Effects	**Intercept**[a]	**Time Slope**	**Intercept vs. Class 3**
Class 1 (fast decline) n = 10	**42.9** (8.79), < *.001*	**-12.0** (1.38), < *.001*	**-1.3** (0.37), < *.001*
Class 2 (intermediate) n = 31	**61.3** (8.48), < *.001*	**-3.6** (0.37), < *.001*	**-0.2** (0.31), *.603*
Class 3 (slow/stable) n = 35	**69.9** (8.21), < *.001*	**-0.6** (0.37), *.088*	-
Covariates			
Age at baseline	**-0.07** (0.09), *.416*	-	-
Years in education	**1.29** (0.20), < *.001*	-	-
Male gender	**2.7** (1.32), *.038*	-	-
Deprivation	**0.99** (0.23), < *.001*	-	-

[a]**Estimate** (SE), *p value*

5.3.2. Class characteristics

The first identified class (*n* = 10, 13%) represented a rapid declining MCI; they were characterised by a lower baseline cognitive function (*B* = 42.9, SE = 8.79) and a steep decline (*B* = -12.0, *SE* = 1.38) in cognition.

The second class (*n* = 31, 41%) began with an intermediate level of baseline functioning (*B* = 61.3, *SE* = 8.48) and a significant, but less aggressive, trajectory of deterioration thereafter (*B* = -3.6, *SE* = 0.58). This class was treated as the reference group going forward as they approximated the mean decline in the overall MCI group.

The final and largest group (*n* = 35, 46%) began with the highest level of baseline functioning (*B* = 69.9, *SE* = 8.21), and did not significantly decline year-on-year over the observed time period (*B* = -0.6, *SE* = 0.37).

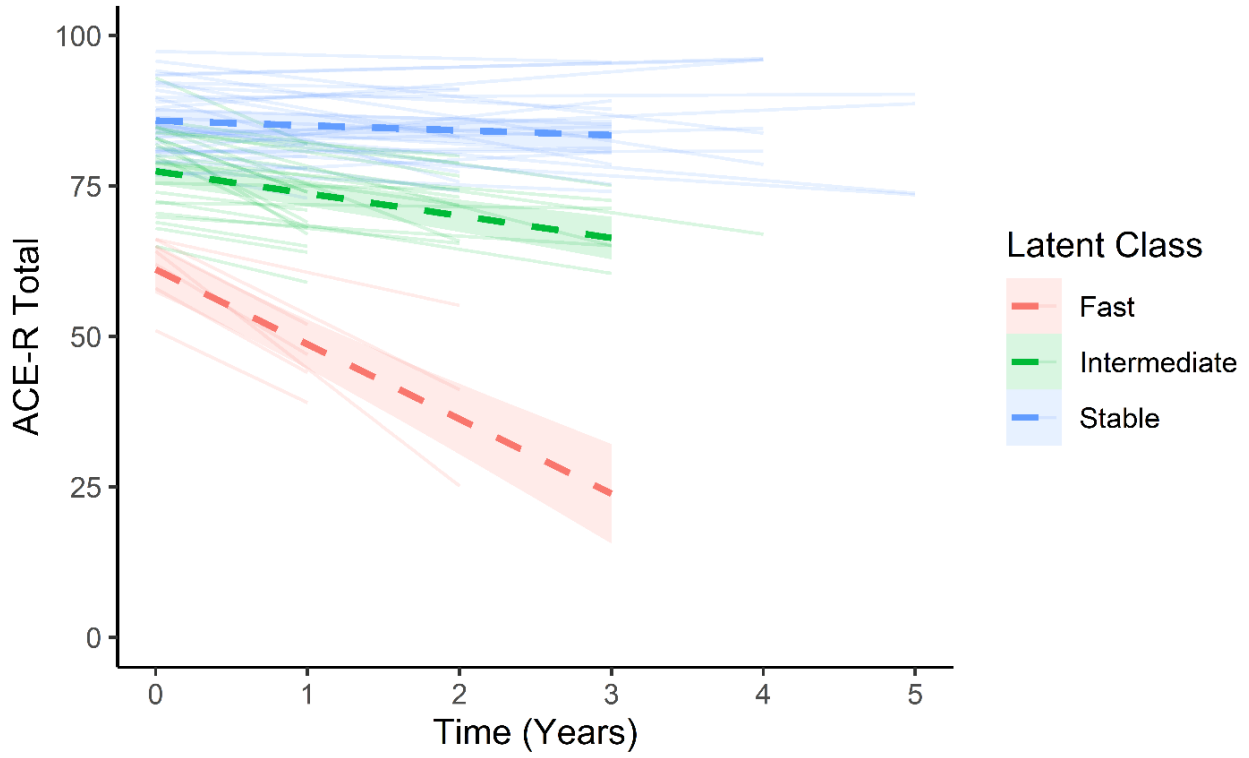


Figure 5.1. Observed subject-specific (solid) and predicted class-specific (dashed) linear trajectories of global cognitive change, with latent trajectories predicted up to three years from baseline.

Since baseline function was related to rate of decline in each group, we sought to examine the influence of impairment level at study entry. When controlling for baseline in the full sample, the mixed model without allowance for latent classes was the best-fitting (BIC = 1417) compared with two- (BIC = 1430), three- (BIC = 1417) and four-class (BIC = 1456) alternatives. We were therefore unable to identify any clear latent classes in the baseline-adjusted model.

5.3.3. Clinical MCI diagnoses in latent classes

In MCI-AD, 61% progressed with a slow/stable course, 22% had an intermediate trajectory, and 17% a fast decline. In possible MCI-LB, 67% followed a slow/stable trajectory, 17% an intermediate decline, and 17% a fast decline. In probable MCI-LB, 32% demonstrated a slow/stable progression, 59% intermediate decline, and 10% fast decline.

In comparison to probable MCI-LB, possible MCI-LB (OR = 7.38, 95% CI: 1.36 – 40.02), and MCI-AD (OR = 5.17, 95% CI: 1.52 – 17.58), were significantly more likely to demonstrate a

slowed decline relative to the intermediate trajectory (**Table 5.3**). Possible MCI-LB and MCI-AD were also overrepresented in the rapid declining group, but neither significantly predicted rapid decline, with wide confidence intervals likely reflecting the low overall prevalence of rapid decline (n = 10).

Table 5.3. Latent trajectories observed in each diagnostic group, and multinomial logistic regression for diagnosis as predictor of prospective trajectory with probable MCI-LB and intermediate trajectory as the respective reference groups.

	Diagnostic Group		
***Class Counts** (%)*	**Prob. MCI-LB**	**MCI-AD**	**Poss. MCI-LB**
Slow/Stable	13 (32%)	14 (61%)	8 (67%)
Intermediate	24 (59%)	5 (22%)	2 (17%)
Faster	4 (10%)	4 (17%)	2 (17%)
Logistic Model[a]			
Faster vs Intermediate	**0.17** [0.06, 0.48] *< .001*	**4.80** [0.89, 25.96] *.069*	**6.00** [0.65, 55.67] *.115*
Slow/Stable vs Intermediate	**0.54** [0.28, 1.06] *.075*	**5.17** [1.52, 17.58] *.009*	**7.38** [1.36, 40.02] *.020*

[a]**Odds Ratio** [95% Confidence Interval] *p value*

Prob. MCI-LB, probable mild cognitive impairment with Lewy bodies; MCI-AD, mild cognitive impairment due to Alzheimer's disease; Poss. MCI-LB, possible mild cognitive impairment with Lewy bodies.

5.3.4. Time course differences – time to dementia

We further explored the effects of time-to-dementia and baseline function to assess whether trajectory differences between classes could be explained by individuals being at different stages of decline upon study entry (i.e. rapid decliners being simply later-stage MCI than intermediate decliners), by running the LCMM analysis with time zeroed on their study end-stage (observed conversion to dementia, death, or withdrawal) rather than baseline assessment date, on the sub-group where this was available (n = 39). In this manner, individual time trajectories were recoded to align at the intercept by their end-point rather than their start; a similar method of zeroing time to the point of dementia transition has previously shown utility in a model of decline in preclinical AD (Verlinden *et al.*, 2016).

The best-fit model featured two classes, being an improvement over the null mixed model without latent classes (BIC: 687 < 696); these resembled the two declining trajectories observed from the full-sample model. The first and smallest (n = 7) group had a lower estimated function at the intercept (B = 23.0, SE = 12.36) and faster decline leading up to this (B = -12.7, SE = 1.64). The second group (n = 32) had higher estimated zero-point function (B = 54.1, SE = 12.34, p < .001) and a slower, but significant, decline to this (B = -3.8, SE = 0.80, p < .001).

While a three-class model was also a better fit than the traditional mixed model (BIC: 691 < 696), the only further group identified was too small to draw meaningful conclusions from (n = 2).

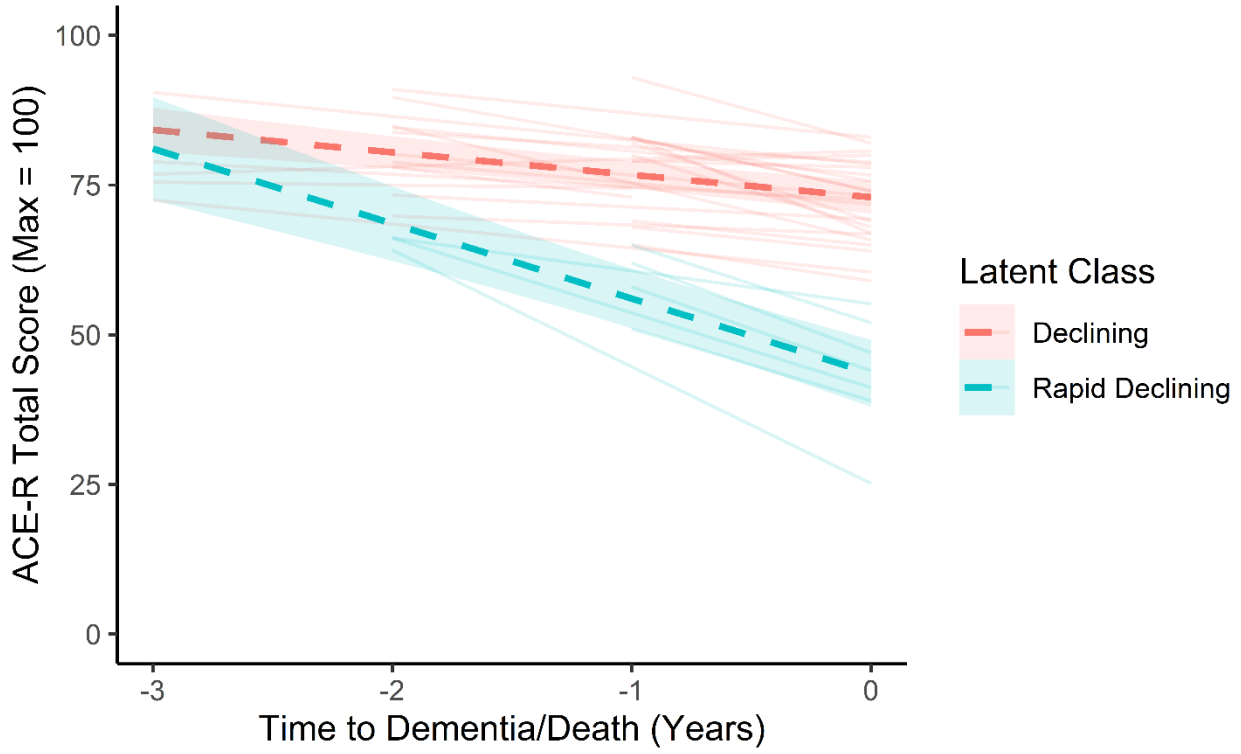


Figure 5.2. With time re-oriented to conversion to dementia or death, two declining groups with different rates of cognitive progression remain.

The numbers in these observed two classes were considered too small to attempt to investigate further with a logistic regression. All seven of the rapid decliners had been classified as rapid decliners with time zeroed to the first observation (100% agreement). Twenty-four of 32

intermediate decliners had been classified as intermediate decliners in the earlier investigation (75%), and the remaining eight had been classified as slow/stable decliners (25%). There was no apparent stable group identified, likely due to the required observation of dementia or death in this second investigation.

5.3.5. Clinical symptomatology and imaging

In the second logistic model, the predictive value of specific symptoms and FP-CIT imaging was also explored in the three-class model. The presence at baseline of RBD, parkinsonism, or cognitive fluctuations as clinical symptoms in MCI was not associated with any particular cognitive trajectory (**Table 5.4**). Abnormal dopaminergic imaging was also not significantly associated with any particular trajectory of cognitive progression.

In the full initial model, and after backwards removal of predictors to reach a best-fitting model under BIC (**Table 5.4**), the presence of complex visual hallucinations at baseline was associated with reduced likelihood of slow/stable, rather than intermediate, decline (OR = 0.06, 95% CI: 0.01 – 0.52) but was not predictive of fast versus intermediate decline.

Table 5.4. Full and reduced best-fit multinomial logistic regression models for included predictors of faster or slower cognitive trajectory in MCI, relative to the intermediate course of decline

		Symptom/Biomarker Present				
Full Model	**Intercept**[a]	**Vis. Halls.**	**RBD**	**Cog. Flucs.**	**Park.**	**Abnormal FP-CIT**
Faster vs Intermediate	**0.46** [0.14, 1.52] *.203*	**0.45** [0.07, 3.07] *.417*	**0.50** [0.08, 3.13] *.460*	**2.62** [0.51, 13.39] *.247*	**2.18** [0.34, 13.80] *.409*	**0.25** [0.04, 1.48] *.127*
Slow/Stable vs Intermediate	**2.33** [1.00, 5.40] *.049*	**0.09** [0.01, 0.79] *.031*	**1.16** [0.36, 3.74] *.798*	**1.23** [0.37, 4.12] *.734*	**0.72** [0.17, 2.97] *.645*	**0.36** [0.11, 1.18] *.091*
Reduced Model						
Faster vs Intermediate	**0.38** [0.17, 0.86] *.020*	**0.52** [0.09, 2.94] *.463*	-	-	-	-
Slow/Stable vs Intermediate	**1.62** [0.94, 2.79] *.083*	**0.06** [0.01, 0.52] *.010*	-	-	-	-

[a]**Odds Ratio** [95% Confidence Interval] *p value*

Vis. Halls, complex visual hallucinations; RBD, REM sleep behaviour disorder; Cog. Flucs., cognitive fluctuations; Park., parkinsonism.

5.4. Discussion

Prospectively-identified MCI develops in a heterogeneous manner. Our analysis identified three patterns of decline; some people deteriorate at a much faster rate than their peers, others decline slowly or remain stable for several years, and some follow an intermediate trajectory which is comparable to the overall mean. People with probable MCI-LB were less likely to have a slow/stable course of progression compared with MCI-AD, and the majority declined at the intermediate rate. The majority of those meeting criteria for MCI-AD declined at a slower rate or remained stable. Possible MCI-LB did not clearly differ from MCI-AD in their likelihood of a faster or slower decline.

Overall, the presence of visual hallucinations at baseline was specifically associated with intermediate decline rather than a slow/stable cognitive trajectory. Contrary to our hypothesis and previous research findings, abnormal FP-CIT imaging was not associated with a declining trajectory, which did not support the findings of Kramberger *et al.* (2017) from DLB. These findings may suggest that individually-differing patterns of pathophysiology underlying MCI may contribute to differing risks of progression; the patterns of LB pathology in an MCI syndrome featuring complex visual hallucinations may contribute to a greater risk of decline than in MCI-LB cases without visual hallucinations (e.g. in individuals with parkinsonism and FP-CIT imaging abnormalities).

Poorer baseline function makes some contribution to decline, as controlling for baseline cognitive function performance limits the ability to identify distinct time-courses. Since the time of consent into any research study is randomly variable, people will enter at different stages of their natural decline. However, different trajectories may not be due only to observations being at different stages of MCI, as distinct class trajectories are still evident after directly controlling for time to dementia conversion. The lower baseline functions estimated here benefit from the availability of subsequent repeated measures, and the ability to control for numerous covariates; while the group estimates show clear separation, the overall outcome measurement uncertainty at the intercept is much larger. More objective baseline predictors of progression (presence or absence of specific symptoms or biomarkers) may therefore have greater prognostic utility in clinical settings than baseline cognitive scores alone.

Abnormal FP-CIT imaging was under-represented in the stable group with a low odds ratio, but with large confidence intervals this was not significant as a predictor of decline. Repeated and quantitative measurement of dopaminergic function may clarify the extent of any relationship, if one exists, and the value of FP-CIT imaging in predicting prospective decline. While dopaminergic imaging alone does not appear to be sufficiently predictive of decline, other imaging methods, diagnostic biomarkers, or a combination of these, may provide early signs of a prospective decline. Differing rates of decline may reflect different stages of disease course within the MCI stage, or individual burden of neurodegenerative processes, which a combined biomarker approach may be more sensitive to. Dopaminergic deficiencies are only one aspect of LB pathophysiology, and so other mediating effects (e.g. region-specific or wider cortical

degeneration) may account for differing risks observed for progressive higher-level cognitive decline.

The delineation between a stable progression and slow decline was not entirely clear; within the slow/stable latent class identified some cases may be at an early stage of cognitive decline with undetectably slow progression, prior to any 'turning-point' previously observed (Rajan *et al.*, 2017), while others may continue with a long-term stable course – possibly suggesting a non-neurodegenerative cause of apparent MCI. Despite the rigorous assessment involved in this cohort, with all participants having a diagnosis of MCI within the health service and having this confirmed according to NIA-AA criteria within this study, it remains plausible that some of these purported MCI cases may not have any neurodegenerative disease. Cognitive impairment secondary to depression, anxiety, or being functional or subjective in nature, may be causes of non-decline (Stone *et al.*, 2015). Being able to identify non-degenerative MCI cases prospectively within clinical settings has many potential benefits for both clinicians and patients, and future research may look to more effectively separate these from slow-declining neurodegenerative cases. The inclusion of a healthy control group for comparison may allow for clearer separation of slow decline from non-decline, as the latter may be expected to display a cognitive trajectory indistinguishable from that of normal ageing.

The early identification of slow/stable, progressive, and rapidly progressive MCI groups within MCI-AD and MCI-LB has important implications in clinical practice and research. Namely, limiting healthcare costs and individual burden due to diagnostic false-positives in the former, and appropriate stratification of samples in research and clinical trials. Lower baseline cognitive function and presence of visual hallucinations in MCI may warn of prospective decline.

5.5. Chapter summary

Individual cases of MCI vary in their progression of global cognitive scores. Latent class modelling methods identified three distinct sub-groups characterised, respectively, by stable/slow progression, intermediate decline, and rapid decline. The presence of diagnostic features for DLB in an MCI syndrome was predictive of a progressive decline, not stability, in comparison to MCI-AD. Visual hallucinations in particular were predictive of decline. Rapid declining MCI cases could still be distinguished after controlling for time-to-dementia, suggesting that they were not

simply later-stage MCI. However, with a small sample size, a predictive model for rapid decline did not identify any consistent risk factors.

This analysis demonstrates the statistical and conceptual value of characterising sub-groups within neurodegenerative conditions by data-driven methods; previously utilised in explorations of cognitive trajectories in AD and normal ageing, this is a novel application of latent class modelling to analysing the cognitive progression in the context of Lewy body disease.

While these results suggest that patterns of domain-specific cognitive decline, and rates of cognitive stability or progressive decline may differ in MCI-LB from MCI-AD, it is unclear whether this translates into different rates of functional decline and prognosis of transition to dementia, which is not defined by cognitive decline alone.

Chapter 6. LewyPro: Clinical Conversion to Dementia

6.1. Aims and hypotheses

DLB is known to have a worse prognosis than AD, with increased risk of hospitalization (Mueller *et al.*, 2018), shorter time to death (Mueller *et al.*, 2019), and features a faster cognitive decline in some (Rongve *et al.*, 2016) but not all (Walker *et al.*, 2012) longitudinal studies; prognosis is especially poor in pathologically-confirmed mixed AD/DLB (Malek-Ahmadi *et al.*, 2019). Additionally, it has been found that as the DLB clinical profile increases in complexity (e.g. with more clinical features observed), healthcare costs also increase progressively (Espinosa *et al.*, 2020). However, it remains unclear as to whether this also manifests as a faster transition to dementia in the respective MCI stages. We therefore first aimed to explore whether the presence of diagnostic characteristics of DLB (core clinical features and biomarkers) in MCI would confer greater risks of dementia onset in comparison with MCI-AD, and if these risks would increase in more clinically complex cases.

AD (Scheltens *et al.*, 2016) and DLB (Morenas-Rodríguez *et al.*, 2018) are heterogeneous in their pathological and clinical presentation. Different subtypes of AD may vary in their prognosis (Ferreira *et al.*, 2017), but it is unclear whether particular subtypes of DLB, or its cognitive prodrome in MCI, also differ in this manner. We also aimed to ascertain whether particular clinical presentations would be associated with a different prognosis. REM sleep behaviour disorder and Parkinson's disease may remain as stable diagnoses without cognitive decline for many years (Claassen *et al.*, 2010; Aarsland, 2016) and so MCI cases with sleep or motor symptoms may not be associated with increased conversion to dementia. Psychiatric symptoms in an amnestic MCI syndrome are associated with a faster conversion to dementia (Mauri *et al.*, 2012), and poorer outcome with faster decline in AD (Scarmeas *et al.*, 2005b; D'Antonio *et al.*, 2019). In DLB, the presence of cognitive fluctuations has been associated with higher healthcare resource utilisation and economic costs of any core clinical feature, followed by visual hallucinations (Espinosa *et al.*, 2020). MCI cases with neuropsychiatric symptoms of DLB (visual hallucinations or cognitive fluctuations) may therefore be associated with faster conversion to dementia.

Socio-economic background was anticipated to be a confounding variable; local-community deprivation has been directly associated with cognitive dysfunction in older age, and indirectly via other deprivation-related factors associated with increased risk of conversion to dementia from MCI (Xue *et al.*, 2017).

We hypothesised that MCI-LB would have a worse prognosis than MCI-AD, featuring a greater risk of clinical conversion to dementia over time. We also hypothesised that specific diagnostic characteristics of DLB, reflecting different patterns of underlying neurodegeneration, would influence risk of conversion to dementia, specifically that cognitive fluctuations and visual hallucinations would be associated with conversion to dementia whereas RBD and parkinsonism would not.

6.2. Methods

6.2.1. Participants and diagnosis

Seventy-six participants were suitable for inclusion from the LewyPro cohort; MCI or dementia diagnoses, clinical review of DLB core features, and rating of FP-CIT imaging, were operationalised as previously reported.

6.2.2 Analysis

A competing risks multi-state model was estimated with the *msm* package for *R* software (Jackson, 2011). Three states were defined: MCI, dementia, and death. Dementia and death were treated as competing absorbing states with no subsequent transitions allowed; as participants ceased involvement in the study after conversion to dementia, no further information was available after clinical conversion. Exact dates were recorded for all deaths, but whether the participant had, or had not, developed dementia in the intervening time since last assessment was not known. Cause of death was not differentiated.

All MCI diagnoses were included under the same MCI state. Likewise, all dementia diagnoses were included within a single dementia state. At each observation, participants could either remain as MCI, with or without some change in any covariates, or progress to dementia or death.

The emergence of diagnostic features later in the MCI course, and their association with subsequent dementia transitions, could therefore be assessed in this model in a flexible manner.

Covariates theorised to have an association with clinical conversion were included to assess the association of DLB features and other demographic variables with risk of death or dementia: age, deprivation, gender, education, and number of DLB diagnostic characteristics (core clinical features and biomarkers, combined). MCI cases with no DLB characteristics (MCI-AD) were treated as the reference for the latter variable. An additional analysis included the same, with each of five specific diagnostic characteristics included as individually present or absent: complex visual hallucinations, cognitive fluctuations, parkinsonism, RBD, and FP-CIT abnormality.

Model fit was assessed by Akaike Information Criterion (AIC) with a lowered AIC value indicating better model fit, with a penalty for inclusion of additional parameters. Covariates were chosen by backwards selection leading to the best-fitting models reported here.

6.3 Results

6.3.1 Demographics and baseline

Baseline demographic and clinical information were as in previous chapters, summarised for convenience in **Table 6.1**. Thirty-three participants had converted to dementia at the time of data locking; the mean follow-up time had been 2.4 years (*SD* = 1.47) from baseline, with a maximum of 6.1 years. Participants had a median of 3 observations each. None of the possible MCI-LB were in receipt of cholinesterase inhibitors. While many of the MCI-AD and probable MCI-LB group were in receipt of cholinesterase inhibitors at baseline, there was no significant difference between these two groups (χ^2= 2.54, p = .111). Those receiving cholinesterase inhibitors did not significantly differ in global cognitive function from those who were not receiving this treatment (Welch's $t(46.1) = 1.83$, p = .074).

Observed state-to-state transitions are summarised in **Table 6.2**. As no information was available on participants after the onset of dementia, dementia to death transitions could not be included.

Table 6.1. Baseline descriptive statistics for overall MCI group, and diagnostic sub-groups.

	MCI overall	MCI-AD	Possible MCI-LB	Probable MCI-LB
Age, mean (SD)	76.0 (7.5)	78.2 (7.5)	75.3 (7.3)	75.5 (7.6)
Number (% of total MCI group)	76 (100%)	23 (30%)	12 (16%)	41 (54%)
Female, count (%)	34 (45%)	15 (65%)	5 (42%)	14 (34%)
Clinical Dementia Rating, median (IQR)	0.5 (0)	0.5 (0)	0.5 (0)	0.5 (0)
Mini-Mental State Examination, mean (SD)	26.4 (2.2)	26.5 (2.3)	26.2 (2.9)	26.5 (2.0)
ACE-R total, mean (SD)	79.4 (10.3)	79.5 (11.7)	79.3 (14.1)	79.3 (8.3)
IADL, mean (SD)	13 (4.4)	10 (2.3)	11 (3.2)	14 (4.7)
Years of education, mean (SD)	11 (2.8)	12 (3.0)	11 (2.1)	11 (2.8)
Deprivation decile, median (IQR)	5.5 (5)	5 (6)	7 (3)	6 (5)
Prescribed cholinesterase inhibitors, count (%)	25 (33%)	6 (26%)	0 (0%)	19 (46%)

ACE-R, Addenbrooke's Cognitive Examination – Revised; IADL, Instrumental Activities of Daily Living; IQR, interquartile range; MCI, mild cognitive impairment; SD, standard deviation.

Table 6.2. State transition table from LewyPro cohort.

	to MCI	to Dementia	to Death
from MCI	124	33	5

6.3.2 Overall DLB feature and biomarker count

The best-fitting model included age and DLB clinical feature/biomarker count as non-interacting covariates (**Table 6.3**). Higher age was associated with an increased risk of death, and a small non-significant increase in dementia per year. In comparison to MCI-AD, each DLB diagnostic characteristic observed conferred an increasing risk of transition to dementia or death (modelled

as a linear dose-dependent relationship). An increasingly Lewy body-like clinical profile in MCI was therefore associated with worse prognosis as evidenced by an increased annual risk of conversion to dementia and to death.

Table 6.3. Associations between age and presence of Lewy body diagnostic characteristics in transitions from mild cognitive impairment (MCI) to death or dementia in the LewyPro cohort. Reduced models after backwards elimination of predictors.

Baseline Transition Probabilities from MCI[a]		***Covariates[b]***		
Model 1. Overall Feature Count		**Age[c]**		**Lewy Body Characteristics (0-5)**
to MCI	**0.88** [0.79, 0.93]	-		-
to Dementia	**0.11** [0.07, 0.19]	**1.05** [0.99, 1.10]		**1.37** [1.07, 1.75]
to Death	**0.01** [0.001, 0.05]	**1.20** [1.05, 1.37]		**1.86** [1.03, 3.37]
Model 2. Specific Characteristics		**Age**	**Visual Hallucinations**	**Cognitive Fluctuations**
to MCI	**0.89** [0.81, 0.94]	-	-	-
to Dementia	**0.10** [0.06, 0.17]	**1.06** [1.01, 1.12]	**2.26** [1.02, 5.00]	**3.06** [1.42, 6.57]
to Death	**0.01** [0.001, 0.04]	**1.21** [1.06, 1.39]	**7.79** [1.47, 41.22]	**3.78** [0.69, 20.57]

[a]**Transition Probability for One Year** [95% Confidence Interval]

[b]**Hazard Ratio** [95% Confidence Interval]

[c]Mean-centred, hazard per year

6.3.3 Specific DLB features

The best fitting model favoured inclusion of age, visual hallucinations, and cognitive fluctuations as covariates (**Table 6.3**), without interaction. Increased age was associated with an increased hazard of both dementia and death. The presence of visual hallucinations was associated with

increased hazard of both dementia and death, while cognitive fluctuations were associated with increased hazard of dementia, and an increased risk of death but with wide confidence intervals. The full model, prior to backwards removal of covariates, is reported in **Table 6.4**. Presence of parkinsonism, RBD, and abnormal FP-CIT imaging were not associated with an increased transition risk of dementia or death compared to MCI-AD. Male gender was associated with increased risk of transition to dementia in the full model, but not in reduced models including this factor; its inclusion in the best-fit final model was also not supported by the model fitting criteria.

Table 6.4. Full multi-state model for clinical transition in LewyPro, prior to backwards elimination.

Baseline Transition Probabilities from MCI[a]		***Covariates[b]***							
		Age[c]	**Male Gender**	**Deprivation Decile[c]**	**Visual Hallucinations**	**Cognitive Fluctuations**	**Parkinsonism**	**REM Sleep Behaviour**	**Abnormal FP-CIT Imaging**
to MCI	**0.91** [0.81, 0.95]	-	-	-	-	-	-	-	-
to Dementia	**0.08** [0.04, 0.16]	**1.06** [1.00, 1.12]	**2.81** [1.13, 7.01]	**1.02** [0.89, 1.17]	**2.46** [1.01, 5.95]	**3.29** [1.30, 8.37]	**1.46** [0.57, 3.76]	**0.46** [0.19. 1.11]	**0.54** [0.21, 1.40]
to Death	**0.01** [0.001, 0.07]	**1.17** [0.98, 1.39]	**0.66** [0.05, 8.74]	**0.89** [0.62, 1.29]	**6.19** [0.99, 38.52]	**2.81** [0.37, 21.22]	**2.29** [0.24, 22.05]	**0.42** [0.03, 7.20]	**1.49** [0.20, 11.29]

[a]**Transition Probability for One Year** [95% Confidence Interval]

[b]**Hazard Ratio** [95% Confidence Interval]

[c]Mean-centred, hazard per year

6.4. Discussion

We hypothesised that an MCI syndrome presenting with diagnostic characteristics of DLB would have a worse prognosis than those without, and therefore meeting criteria for MCI-AD, increasing with greater clinical complexity. We found that, in comparison to cases with MCI alone, the presence of any DLB diagnostic characteristic in MCI was associated with an increased hazard of transition to dementia; this risk further increased as more core features or biomarkers were observed and was especially high for those experiencing complex visual hallucinations or cognitive fluctuations. The data therefore supported the hypotheses that an MCI with diagnostic characteristics of DLB would be associated with a worse prognosis than MCI-AD, that this prognosis would be worse in the more clinically complex cases, and that specific DLB diagnostic characteristics are associated with different rates of clinical progression.

These results mirror recent findings on the prognosis of DLB or AD: it appears that in both MCI and dementia (Price *et al.*, 2017), the presence of DLB-specific characteristics is associated with a worse prognosis, and that more complex cases with more diagnostic characteristics may have a worse prognosis, as in dementia (Espinosa *et al.*, 2020). DLB features increased hospitalisation (Mueller *et al.*, 2018), shorter time to full-time care, and shorter survival time (Mueller *et al.*, 2019), and worse quality of life for patients and carers than AD (Wu *et al.*, 2018a). While our results here indicate that MCI-LB also has a greater annual risk of developing dementia than MCI-AD, with this risk increasing as more features or biomarkers of DLB are observed; this could suggest that MCI-LB cases with a greater number of diagnostic characteristics have more extensive neurodegeneration and therefore a worse prognosis. Alternatively, risks of clinical transition may be more specifically associated with particular symptoms (as discussed below), and more clinically complex cases may simply be more likely to feature those particular symptoms (and associated pattern of pathophysiology which may mediate these associations).

The specific association between cognitive fluctuations and visual hallucinations, and a poorer prognosis in MCI, may indicate that these are symptomatic of a more aggressive clinical phenotype. Both fluctuations (O'Dowd *et al.*, 2019) and visual hallucinations (Erskine *et al.*, 2019) are hypothesised to reflect particular patterns of neurodegeneration within Lewy body disease which may share a link in the cholinergic deficit which often occurs in DLB (O'Brien *et*

al., 2005) alongside other pathophysiological changes (e.g. dopaminergic dysfunctions). This could underlie the associations of these features with a progressive clinical decline, with greater cholinergic dysfunction leading to faster onset of dementia from MCI in some cases; this naturally requires exploring with biomarkers specific to the cholinergic system, such as EEG markers of NBM integrity (Schumacher *et al.*, 2020b).

6.5 Chapter summary

An increasingly DLB-like clinical profile in an MCI syndrome is associated with greater annual risk of conversion to dementia, according to clinical criteria. Presence of cognitive fluctuations or visual hallucinations is particularly associated with increased risk of conversion annually. Parkinsonism, RBD, and FP-CIT SPECT abnormality are not individually associated with increased risk of conversion to dementia in comparison to MCI-AD however; higher dementia transition risks in more clinically complex cases may reflect that an increasingly manifest DLB-like clinical profile is simply more likely to feature at least one of the two highest-risk clinical features of cognitive fluctuations or visual hallucinations, and therefore to decline to dementia. These results are consistent with the increased risk of global cognitive decline found in MCI-LB, and in MCI with visual hallucinations specifically. These results align with, and extend, previous findings that DLB has a shorter survival time (Price *et al.*, 2017; Mueller *et al.*, 2019), increased risk of hospitalisation (Mueller *et al.*, 2018), and shorter time to nursing home admission than AD (Mueller *et al.*, 2017).

6.6 LewyPro Section Summary

In comparison to probable MCI-AD, probable MCI-LB features an early pattern of cognitive impairment similar to that found in DLB, with more prominent executive and visuospatial dysfunction. Complex visuospatial skills may progressively decline over the time-course of MCI-LB, and impairments in recognition memory are less severe than those in MCI-AD. These findings are consistent with the expected profiles of these syndromes as the respective cognitive prodromes of AD and DLB.

While the average course of global cognitive decline does not differ between MCI-AD and MCI-LB, exploration of cognitively declining and stable subgroups has suggested that MCI-LB is less

likely to remain cognitively stable than MCI-AD. Cases of MCI featuring complex visual hallucinations, a finding highly specific to DLB (Lin *et al.*, 2018), were particularly unlikely to remain stable.

Finally, consistent with the increased risk of global cognitive decline in MCI-LB, the presence of DLB diagnostic characteristics in MCI were associated with an increased annual risk of conversion to dementia, further increasing with each additional feature observed. Visual hallucinations and cognitive fluctuations in particular were associated with an increased risk.

Taken together, the past literature and these results argue that the apparent presence of Lewy bodies in a neurodegenerative syndrome may be associated with a poorer prognosis; there is a greater risk of cognitive decline and clinical progression to dementia in MCI, and an increased risk of hospitalisation, full-time care and death, in dementia. These findings lend support to the value in identifying cases of possible or probable LB disease in the context of an MCI syndrome, as early features of DLB may differentiate those at risk of decline from stable MCI.

In these cases, the presence of DLB features in an MCI syndrome does not necessarily indicate the absence of any AD co-pathology; indeed, pathological studies have suggested that a mixed DLB with AD may be the norm, rather than the exception (Selvackadunco *et al.*, 2019). An unknown number of these MCI cases may feature an undiagnosed mixed pathology at this stage. At the dementia stage, an apparently mixed AD-DLB syndrome (based on CSF biomarker profile or neuropathological assessment) is associated with worse prognosis than either single disease with greater cognitive decline in some studies (Abdelnour *et al.*, 2016; Blanc *et al.*, 2017) and further increased nursing home admittance and mortality risk than DLB alone (Lemstra *et al.*, 2017); such cases could therefore account for the poorer prognosis in our MCI-LB groups.

The improved identification of mixed AD-DLB, and by extension, a potentially mixed aetiology MCI may benefit from the post-mortem neuropathological diagnosis of longitudinal cohorts such as these. This would aid in the characterisation of pure AD, LB, and mixed AD-LB cases in dementia and MCI; a necessary step in developing effective interventions.

Identification of these risk factors at the MCI stage may be of benefit in clinical settings to help guide treatment and management. However, these findings were limited by the small sample size and lack of healthy control group to provide further context; there was therefore a need for validation of these results.

These results were also limited in their ability to answer one aspect of the research question at hand, specifically in regards to characterising cognitive sub-types as in Ferman *et al.* (2013); without a comparable healthy control cohort, there were no meaningful normative data to appropriately characterise MCI as single- or multi-domain, amnestic or non-amnestic.

In response to this, a follow-up study was undertaken to validate the findings from the LewyPro cohort, with the addition of another biomarker and healthy control cohort.

Chapter 7. SUPErB Study Background

Following up on the LewyPro cohort, the SUPErB study cohort was recruited to assess the utility of MIBG scintigraphy in the prodromal stages of DLB, compared with both MCI-AD and healthy controls to provide further context and normative data.

For this work, the intention was to assess whether the development models from the LewyPro study would be validated with a comparable independent cohort.

7.1 Study recruitment and assessment

Both MCI patients (inclusion/exclusion criteria as in LewyPro) and healthy controls were recruited for inclusion in the SUPErB study cohort (see below for details on each group). Ethical approval for this study was given by the National Research Ethics Service Committee North East – Newcastle and North Tyneside 2 (Research Ethics Committee No. 15/NE/0420). All prospective participants provided written, informed consent to participate prior to baseline assessment.

As in the LewyPro study, participants underwent detailed baseline assessment over several visits, and subsequently were followed-up approximately annually unless they withdrew, converted to dementia or other serious illness, or died. Due to postponement of follow-up assessments from March of 2020 as a result of the COVID-19 pandemic, datasets were locked for analysis with all available follow-up observations in April 2020. Mean follow-up time was 1.1 years (*SD* = 0.87), with a median of 2 total observations per participant.

As in the LewyPro cohort, local deprivation level was assessed for each participant based on their community's ranking of score in the 2019 English Indices of Deprivation; in this instance, scoring was inverted in the statistical release in comparison to previous indices, with a low score rank, and consequently low decile rank (e.g. of 1), corresponding to high local deprivation, while a high score rank, and consequently high decile rank (e.g. of 10) corresponding to low local deprivation.

7.1.1 MCI patient group

Participant recruitment for the SUPErB study ran from March 2016 to September 2019. Patients were recruited from local healthcare trusts in North-East England, were aged 60 years or older, and had a health service diagnosis of MCI. As in the LewyPro cohort, participants were identified from health service records if they reported any symptoms or signs which may be associated with prodromal DLB (but could be present in AD) including any suggestive features of DLB, visual disturbance, hyposmia, mood change, or autonomic dysfunction. Any core features of DLB were also a reason for approach to consent. Exclusion criteria for this group were the presence of dementia or lack of cognitive impairment at baseline, possible frontotemporal or vascular aetiology, or an established history of PD for more than one-year preceding onset of cognitive impairment.

Eighty-nine new potential patients were assessed for inclusion, in addition to all remaining participants of the LewyPro cohort (excluding those contraindicated for MIBG imaging, those who had withdrawn, developed dementia, or died). Of these 89, seven were excluded due to having dementia at baseline, three were excluded due to absence of objective cognitive impairment, and four withdrew before completing baseline assessment.

Including 28 LewyPro patients, 103 participants were deemed suitable for inclusion in the SUPErB MCI group at baseline. To maintain independence of the discovery and validation cohorts, these 28 LewyPro participants were removed from the following analysis of SUPErB data (**Chapter 8**). There were therefore 75 participants included in the patient group who were independent of the LewyPro sample and eligible for inclusion after baseline assessment.

7.1.2 Healthy control group

Thirty-four prospective participants were recruited for a healthy control group from friends or family members of patient-participants, or the Join Dementia Research volunteer network. Healthy controls were aged 60 years or older. Exclusion criteria were evidence of cognitive impairment or other major illness.

Three controls failed to complete baseline assessment; two died during the course of the baseline assessment due to unrelated emergent illness, and one withdrew. Thirty-one healthy control participants therefore completed all assessments at baseline and 28 were consequently followed up with at least one annual re-assessment.

Data availability at each observation year, and any known loss to follow-up or censoring, are detailed in **Figure 7.1.**

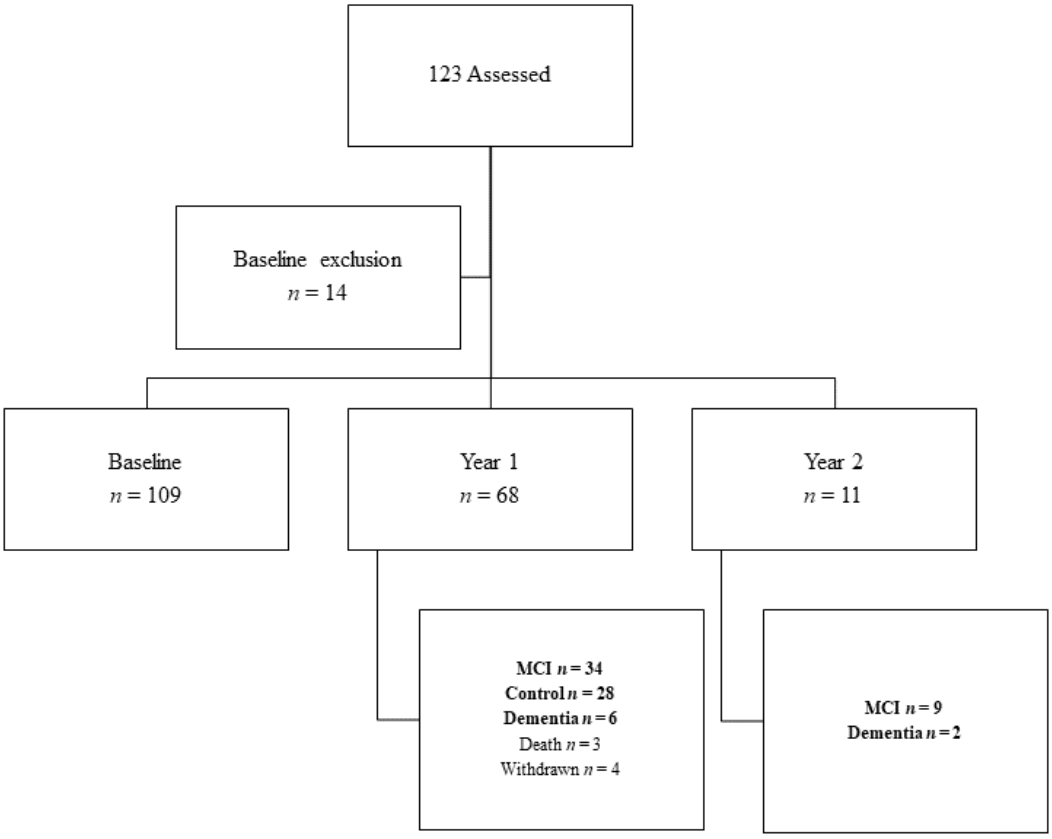


Figure 7.1. Data available (bold) or lost to follow-up in the SUPErB study cohort at the point of data locking.

7.2 Diagnosis

7.2.1 Neurocognitive syndrome

As in the LewyPro study, patients were annually rated on the presence of neurocognitive impairment, either MCI or dementia, independently by the same panel of experienced old age psychiatrists. MCI diagnoses were made in accordance with NIA-AA criteria (Albert *et al.*, 2011), while dementia was determined according to McKhann *et al.* (2011) 'all-cause dementia' criteria, with the latter being a cause for exclusion (baseline) or an end to follow-up (repeat).

7.2.2 Clinical symptoms

Clinical symptomatology, including DLB core and supportive symptoms, were annually assessed by clinical interview, and quantified with a range of scales. At each annual visit the participant was administered the UPDRS-III (Ballard *et al.*, 1997), NEVHI (Mosimann *et al.*, 2008), ESS (Johns, 1991), and GDS (Yesavage *et al.*, 1983). Informants of patients were also administered the IADL scale (Lawton and Brody, 1969), a modified scoring of which (Cromwell *et al.*, 2003) is also reported in this research, the NPI (Cummings *et al.*, 1994), MSQ (Boeve *et al.*, 2011a), CAF (Walker *et al.*, 2000b), and DCFS (Lee *et al.*, 2014). Based on review of clinical notes, the CIRS-G (Miller and Towers, 1991) and CDR (Morris, 1993) were also completed.

7.2.3 Biomarkers

Data on several indicative and supportive biomarkers were available for each participant. These were administered to both patients and controls.

FP-CIT SPECT dopaminergic imaging was performed at baseline assessment as in LewyPro and as previously published (Thomas *et al.*, 2019), and repeated at the first annual follow-up. Images were rated as normal or abnormal by an experienced panel trained in image analysis, blind to clinical information. In cases where there was change or inconsistency in repeat images (i.e. abnormal at baseline, but normal at follow-up) these were reviewed to result in a 'definitive' imaging result.

Participants also undertook MIBG scintigraphy at baseline assessment to examine any wider denervation of the sympathetic nervous system, providing an additional indicative biomarker in accordance with current criteria for DLB. Images were taken both shortly after intravenous injection of the MIBG ligand, and after a ~ 4-hour (± 30 min) delay. Early images were used for comparison with delayed images outside of this work, whereas delayed images are the current standard use in diagnosis (Kane *et al.*, 2019; Roberts *et al.*, 2019). Delayed images were processed by two medical physicists blind to clinical information, allowing for quantification of heart:mediastinum uptake ratio values. Values of greater than two standard deviations below mean uptake in controls were rated as 'abnormal', with values above this threshold rated as 'normal'. Results of both MIBG and FP-CIT imaging were incorporated into differential diagnoses as discussed below.

Structural and resting state functional MRI, and resting state EEG recordings were also collected at baseline. Blood samples were taken during medical review at baseline. All participants were offered a lumbar puncture to provide cerebrospinal fluid samples, though uptake was low. Results of these assessments were used as research outcomes (not in this work) and were not included in differential diagnoses, though structural MRI scans were able to provide further context to other clinical or imaging findings; one participant was found to have a striatal infarct on MRI, and so their FP-CIT imaging results were not included in diagnosis.

7.2.4 Differential diagnosis

After diagnosis of MCI or dementia, differential diagnosis of aetiology was operationalised in a manner consistent with the LewyPro study at baseline and follow-ups, but with the addition of MIBG imaging results from baseline. The same three-person expert panel of old age psychiatrists reviewed clinical notes taken at each annual visit, using clinical judgement of notes to rate the presence or absence of four core DLB clinical features: RBD, parkinsonism, complex visual hallucinations, and fluctuating cognition, providing a consensus decision on their presence or absence. These decisions were taken independently of and blind to the imaging results.
These four clinical features, alongside the two indicative biomarkers (MIBG and FP-CIT imaging) provided a maximum of six possible DLB diagnostic characteristics which were

incorporated into MCI or DLB diagnoses: patients with MCI and no DLB diagnostic characteristics (no core clinical DLB features, and both imaging methods rated normal) received a diagnosis of MCI-AD, those with MCI and one DLB diagnostic characteristic (one core feature, or imaging abnormality) received a diagnosis of possible MCI-LB, and those with two or more DLB diagnostic characteristics (two or more core features, or one core feature with imaging abnormality) received a diagnosis of probable MCI-LB, in line with contemporary criteria for diagnosis of MCI-LB in research settings (McKeith *et al.*, 2020), and mirroring current DLB consensus clinical criteria (McKeith *et al.*, 2017). Diagnosis of probable MCI-LB could not be made based on the presence of two biomarkers alone; at least one core clinical diagnostic feature was also required for this.

As with MCI or dementia diagnosis, core feature presence or absence, and consequent differential diagnoses, were reassessed after each follow-up to reflect the emergence of new diagnostic features, or new information coming to light (e.g. from an informant who was not previously available).

7.3 Neuropsychological assessment

The neuropsychological tests used in LewyPro were also administered in SUPErB, with the addition of other supplementary assessments. As in LewyPro, neuropsychological outcomes were not incorporated into differential diagnoses.

7.3.1 Global cognition

Total score on the ACE-R (Mioshi *et al.*, 2006) was used to measure global cognitive functioning, from which MMSE was also derived.

7.3.2 Attention and executive functions

ACE-R and FAS verbal fluency (Baldo *et al.*, 2006), and TMT-B assessed executive functioning. Raw and cognitive processing speeds were again measured with simple (SRT) and binary-choice (CRT) reaction time tasks. Higher level processing speed was assessed with TMT-A, as well as three digit-symbol substitution tests (DSST); digit-symbol coding, symbol copy, and error checking.

Sustained and selective attention were also assessed with the computerised continuous performance task (CPT).

Stroop Colour (Stroop C) and Colour-Word (Stroop CW) interference tasks were administered as repeated measures to assess selective attention and executive functions.

7.3.3 Memory and learning

ACE-R memory sub-scores were available at each annual visit, and the RAVLT was administered at baseline. Additionally, a 15-minute delayed un-cued recall of the Rey-Osterrieth (ROCF; baseline) or Modified Taylor Complex Figure (MTCF; alternate form for follow-up) was utilised to assess visuospatial episodic memory at each visit. Scores for the complex figure copies were ratified by a second marker who second-marked a randomly-selected subset of 20% of the figure copy and recall sheets, blind to the first marker's scores; the same two markers were used for assessing all MTCF images. ROCF images were marked by a second pair of markers in the same manner.

7.3.4 Visuospatial functions

The LAT was administered as a repeated measure (Wood *et al.*, 2013a), and ACE-R visuospatial sub-scores were also available from each year. At baseline, computerised Corsi block-tapping and visual patterns (VPT) tests were administered on a touchscreen-capable study laptop to assess visuospatial working memory. These were supplemented by the addition of the complex figure copy test (ROCF or MTCF) at baseline and follow-up, to provide further sensitivity to higher-level visuo-constructional deficits. The Pareidolia Test (Mamiya *et al.*, 2016) was administered as a repeated measure to assess susceptibility to visual illusions and misperception of faces in ambiguous visual stimuli, having shown previous utility in assessing these in DLB.

7.3.5 Speech, language, and intelligence

The GNT (Bird and Cipolotti, 2007) and NART (Nelson and Willison, 1991) were completed by all participants at baseline to assess language and pre-morbid intelligence. Annually repeated ACE-R language sub-scores assessed change in speech and language function over time.

Auditory forwards and backwards digit span tests were repeated at each annual visit to assess attention and working memory.

7.4 Procedure

A longitudinal repeated-measures design was again utilised. Measures were taken at baseline, and again at approximately annual follow-ups, to track differences in within-subject progression between diagnostic groups in a mixed design.

7.4.1 Baseline testing

Visits were arranged as follows:

1) Screening, consent, and neuropsychological testing
2) Medical review
3) FP-CIT SPECT
4) MIBG scintigraphy
5) EEG, MRI, and computerised testing
6) (Optional) lumbar puncture

FP-CIT and MIBG imaging were spaced out by a minimum of one week to prevent interference; visits were otherwise scheduled as close together as could be. Median delay between first and fifth visit was two months.

7.4.2 Follow-up testing

Neurocognitive assessment and clinical review were undertaken within a single session at each annual follow-up. After developing dementia, patients were not assessed further. Where participants were lost to follow-up due to a clinically relevant reason, such as conversion to dementia or death, this was recorded as appropriate. At each follow-up visit, healthy controls were assessed for any change in status. One control participant had developed a non-neurodegenerative cognitive impairment at follow-up, and this observation was excluded from analysis.

Patient recruitment closed in October 2019, and all participants had completed their baseline assessments in December 2019. Follow-up data collection was arrested in March 2020.

7.5 Analysis

The same methods as used in LewyPro were repeated with this cohort to validate findings from the discovery cohort: domain-specific longitudinal patterns of cognitive function were assessed with simple LMM, while LCMM explored heterogeneity in trajectories of cognitive decline Finally, MSM methods were again applied to analysis of transitions from MCI to dementia, or death. These are described in depth in **Chapter 8** with the respective results.

7.6 Chapter summary

The SUPErB study built on the conceptualisation of MCI-LB that resulted from the LewyPro cohort and offered the opportunity to assess the validity of the longitudinal findings from LewyPro in an independent cohort. This cohort was bolstered by the addition of a healthy control group, and the use of an additional biomarker sensitive and specific to Lewy body disease (MIBG imaging).

Chapter 8. SUPErB Study Validation Analyses

8.1. Baseline information

Recruitment for the SUPErB study closed in the Autumn of 2019, with the final baseline visit occurring in December 2019. Twenty-eight participants with MCI who had previously contributed to the LewyPro study were consented into the SUPErB study. These participants were excluded from validation analyses in this chapter to ensure independence of the cohorts. After clinical review, 75 new patients and 34 controls were included in the SUPErB cohort, with baseline characteristics presented in this section. Pairwise comparisons are reported in-text for baseline-only assessments; omnibus tests are reported for longitudinal measures, which are reported in depth in the longitudinal analysis which follows. Unless otherwise stated, for continuous measures where the mean is reported, group differences were assessed with one-way ANOVA with pairwise *t*-tests; where the median is reported, Kruskal-Wallis with pairwise Dunn's tests were applied. Pairwise comparisons included Holm correction of *p* values in both parametric and non-parametric methods. For categorical outcomes, χ^2 or Fisher's exact tests were utilised, as appropriate. Significance level was set as $p < .05$ for all comparisons.

8.1.1 Demographics

Demographic data are presented in **Table 8.1**. As in the LewyPro cohort, there was a gender disparity with MCI-AD being more likely to be female, and probable MCI-LB being more likely to be male. The groups did not significantly differ in their mean ages, but controls had spent significantly more years in education than had patients ($p = .017$). Pairwise comparisons did not find any significant educational differences between the patient groups, however. The possible MCI-LB group had a lower median decile of deprivation than controls ($p = .026$), but MCI-AD ($p = .806$) and probable MCI-LB ($p = .872$) did not. Correspondingly the possible MCI-LB group had lower estimated premorbid function as accessed with the NART ($p = .002$) than controls, but MCI-AD ($p = .135$) and probable MCI-LB ($p = .135$) did not.

Table 8.1. Demographic data for SUPErB participants.

	Control (n=34)	MCI-AD (n=30)	Possible MCI-LB (n=17)	Probable MCI-LB (n=28)	*p*[a]
Gender					
Female	10 (29.4%)	18 (60.0%)	9 (52.9%)	1 (3.6%)	< .001
Male	24 (70.6%)	12 (40.0%)	8 (47.1%)	27 (96.4%)	
Baseline Age	74.2 (7.45)	75.2 (7.12)	73.5 (8.41)	74.6 (5.72)	.888
Years in Education	14.4 (3.82)	12.7 (3.43)	12.6 (4.66)	11.6 (2.39)	.016
Missing	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	
IMD Decile	6.50 [1.00, 10.0]	6.00 [1.00, 10.0]	3.00 [1.00, 10.0]	5.50 [1.00, 10.0]	.042
NART Estimated Full-Scale IQ	114 (8.64)	108 (12.5)	103 (12.2)	108 (9.02)	.003
Missing	1 (2.9%)	2 (6.7%)	0 (0%)	1 (3.6%)	

Count (%), Mean (SD), or Median [Min, Max].

[a]Omnibus tests; corresponding post-hoc tests with adjustment in-text

8.1.2 Clinical symptomatology

In the probable MCI-LB group, the most common differential diagnostic characteristics were RBD and abnormal FP-CIT imaging results, each being present in 75% of cases (see **Table 8.2**). For the possible MCI-LB group, FP-CIT abnormality and visual hallucinations were the commonest DLB diagnostic characteristics. One MCI-AD patient reported experiencing visual hallucinations associated with advanced eye disease; these were interpreted by the diagnostic panel as symptomatic of Charles Bonnet syndrome and therefore did not contribute to a diagnosis of MCI-LB. For this same case, and in any others with significant non-cortical visual impairment, cognitive assessments with a visual component were excluded from analysis.

Table 8.2. Diagnostic characteristics for dementia with Lewy bodies present at baseline in diagnostic groups, diagnosis based on most recent follow-up.

Symptom Present, Count (%).	**Control (n=34)**	**MCI-AD (n=30)**	**Possible MCI-LB (n=17)**	**Probable MCI-LB (n=28)**
Parkinsonism	0 (0%)	0 (0%)	0 (0%)	10 (35.7%)
Cognitive Fluctuations	0 (0%)	0 (0%)	1 (5.9%)	13 (46.4%)
REM Sleep Behaviour Disorder	0 (0%)	0 (0%)	1 (5.9%)	21 (75.0%)
Visual Hallucinations	0 (0%)	1 (3.3%)[a]	4 (23.5%)	7 (25.0%)
Abnormal FP-CIT	2 (5.9%)	0 (0%)	5 (29.4%)	21 (75.0%)
Missing	2 (5.9%)	4 (13.3%)	3 (17.6%)	0 (0%)
Abnormal Delayed MIBG	2 (5.9%)	0 (0%)	3 (17.6%)	17 (60.7%)
Missing	2 (5.9%)	0 (0%)	2 (11.8%)	1 (3.6%)

[a]One case of MCI-AD with Charles Bonnet syndrome due to eye disease-related visual impairment, visual hallucinations were interpreted by the clinical panel as not symptomatic of Lewy body disease.

8.1.3 Clinical scores

Due to their direct relationship with the differential diagnostic features which formed these groups, the diagnostic groups were anticipated, and indeed observed, to differ in their scores on a number of clinical rating scales, which are presented in **Table 8.3**. With issues of circularity in mind these were not considered as primary results of this work but are presented to provide context for the severity of clinical symptoms in each group.

As not all patients had informants available, there were missing data in a number of clinical assessments requiring the presence of an informant to complete (IADL, NPI, CAF and DCFS) and greater missingness in the MSQ, which required an informant to also live with the patient. However these variables were not included in subsequent analyses, being used only to contextualise the clinical profile of this cohort.

Table 8.3. Baseline clinical characteristics of groups in SUPErB cohort.

	Control (n=34)	MCI-AD (n=30)	Possible MCI-LB (n=17)	Probable MCI-LB (n=28)	*p*
CDR	0 [0, 0]	0.5 [0.5, 0.5]	0.5 [0.5, 0.5]	0.5 [0, 0.5]	< .001
IADL	-	8 [2, 8]	7 [3, 8]	7 [4, 8]	.027
Missing	-	8 (26.7%)	2 (11.8%)	1 (3.6%)	
CIRS	5.29 (3.29)	5.92 (3.29)	7.53 (2.72)	8.38 (4.58)	.008
MSQ Question 1 'Yes'	-	0 (0%)	0 (0%)	22 (78.6%)	< .001
Missing	-	16 (53.3%)	10 (58.8%)	3 (10.7%)	
ESS	5 [0, 12]	4 [0, 13]	6 [1, 14]	8 [0, 16]	.005
GDS	1 [0, 9]	3 [0, 11]	3 [1, 12]	3 [0, 13]	< .001
UPDRS	5.55 (4.3)	15.4 (14.8)	16.4 (11.2)	23.3 (14.2)	< .001
NPI	-	6 [0, 34.0]	3 [0, 44]	15 [0, 52]	.045
Missing	-	8 (26.7%)	2 (11.8%)	1 (3.6%)	
NEVHI	0 [0, 3]	0 [0, 7]	0.5 [0, 15]	0 [0, 16]	< .001
CAF	-	0 [0, 9]	0 [0, 6]	3 [0, 16]	.003
Missing	-	8 (26.7%)	3 (17.6%)	1 (3.6%)	
DCFS	-	7 [4, 11]	8 [4, 15]	8 [4, 17]	.360
Missing	-	8 (26.7%)	2 (11.8%)	1 (3.6%)	
Lost Sense of Smell	5 (14.7%)	8 (26.7%)	8 (47.1%)	15 (53.6%)	.007
Missing	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	
MMSE	28.5 (1.13)	26.8 (2.10)	25.6 (3.02)	26.3 (2.37)	< .001
ACE-R Total	92.7 (4.27)	82.3 (8.06)	76.4 (11.5)	82.4 (9.65)	< .001

Count (%), Mean (*SD*), or Median [Min, Max].

All controls had a CDR of 0, and all patients a CDR of 0 or 0.5. While all patients had minimal impairment of independent function, reflective of their MCI diagnostic status, probable MCI-LB had slightly lower scores on the IADL scale (p = .043) than MCI-AD.

Only the probable MCI-LB group had more concurrent illness than controls (higher CIRS-G; p = .009); MCI-AD (p = .894) and possible MCI-LB (p = .166).

Reflecting the presence of RBD in their diagnoses, informants for probable MCI-LB cases were more likely to answer 'yes' in response to question 1 of the MSQ: 'Have you ever seen the patient appear to "act out his/her dreams" while sleeping? (punched or flailed arms in the air, shouted or screamed)'. Accordingly, probable MCI-LB patients also reported higher daytime sleepiness on the ESS than controls (p = .004) while MCI-AD (p = .440) and possible MCI-LB (p = .473) did not.

All patient groups reported higher levels of depression at the time of assessment than controls, according to self-completion of the GDS (MCI-AD & probable MCI-LB p < .001, possible MCI-LB p = .009).

All MCI groups were found to feature greater motor impairment than controls (MCI-AD vs controls, p = .006) on the UPDRS-III. Consistent with the presence of parkinsonism, probable MCI-LB also featured significantly higher motor impairment than MCI-AD (p = .038), though possible MCI-LB did not (p = .785).

While probable MCI-LB appeared to feature higher neuropsychiatric symptom severity (NPI total score), any pairwise differences between MCI groups were non-significant (probable MCI-LB vs MCI-AD, p = .066; possible MCI-LB vs MCI-AD, p = .832), Similarly, MCI groups reported significantly higher visual hallucination symptomatology (NEVHI total score) than controls (MCI-AD, p = .023), but possible (p = .767) and probable MCI-LB (p = .862) did not significantly differ from MCI-AD.

Due to the diagnostic presence of cognitive fluctuations, probable MCI-LB featured greater levels of carer-reported fluctuating confusion or consciousness than MCI-AD (CAF total score; p = .003) while possible MCI-LB did not (p = .487). The DCFS was not sensitive to any differences between MCI-AD and possible (p = .896) or probable (p = .461) MCI-LB.

MCI-AD (exact $p = .352$) were no more likely than controls to report a lost sense of smell, though possible (exact $p = .019$) and probable (exact $p = .002$) MCI-LB were.

8.2. Baseline cognitive scores

8.2.1 Global cognitive function

As expected, MCI-AD featured poorer MMSE ($p = .010$) and ACE-R ($p < .001$) scores at baseline than controls, and possible ($p = .202$) and probable ($p = .603$) MCI-LB did not differ from MCI-AD in their baseline MMSE, nor in their ACE-R total scores ($p = .057$ and $p = .965$, respectively). These are reported alongside clinical data in **Table 8.3.**

8.2.2 Attention and executive functions

Reported in **Table 8.4**, the patient group broadly differed from controls with poorer attention and executive functions, including worse scores on the ACE-R attention and orientation, and fluency sub-scores, fewer words produce in the FAS verbal fluency test, slower reaction times in simple, choice and continuous-performance response tasks, and produced fewer words at baseline in both Stroop test conditions. Administered at baseline alone, MCI was associated with slower completion of TMT-A ($p < .001$) but did not significantly differ from one-another (possible MCI-LB vs MCI-AD, $p = 1$; probable MCI-LB vs MCI-AD, $p = 1$). Similarly in the TMT-B, MCI-AD was associated with slower completion than in healthy controls ($p = .008$), but the groups did not significantly differ (possible MCI-LB vs MCI-AD, $p = .979$; probable MCI-LB vs MCI-AD, $p = .272$). Only probable MCI-LB demonstrated a significantly different ratio of performance between tasks to healthy controls ($p = .012$), both MCI-AD ($p = .979$) and possible MCI-LB ($p = 1$) did not. Detailed performance differences in repeated measures are addressed later in this work.

Table 8.4. Baseline attention and executive functions.

	Control (n=34)	MCI-AD (n=30)	Possible MCI-LB (n=17)	Probable MCI-LB (n=28)	*p*
ACE-R Attention	17.8 (0.59)	17.1 (1.17)	16.8 (1.29)	16.9 (1.45)	.005
ACE-R Fluency	11.9 (1.50)	8.90 (2.66)	7.65 (2.98)	8.57 (2.60)	< .001
FAS Total	43.4 (9.70)	33.3 (10.8)	26.5 (11.4)	31.5 (12.0)	< .001
Simple Reaction Time	340 (67.6)	441 (164)	550 (331)	423 (130)	.002
Missing	3 (8.8%)	1 (3.3%)	2 (11.8%)	2 (7.1%)	
Choice Reaction Time	507 (131)	691 (272)	861 (495)	649 (180)	.001
Missing	7 (20.6%)	3 (10.0%)	3 (17.6%)	2 (7.1%)	
CPT Reaction Time	376 (55.6)	422 (79.3)	417 (76.2)	441 (97.6)	.018
Missing	3 (8.8%)	4 (13.3%)	7 (41.2%)	4 (14.3%)	
Trail Making Test - A	30.5 [17.3, 63.1]	45.2 [27.3, 166]	55.2 [17.8, 239]	47.4 [25.0, 496]	< .001
Missing	0 (0%)	1 (3.3%)	2 (11.8%)	0 (0%)	
Trail Making Test - B	61.7 [32.1, 161]	89.6 [53.3, 304]	95.2 [48.2, 206]	112 [64.0, 417]	< .001
Missing	0 (0%)	10 (33.3%)	9 (52.9%)	5 (17.9%)	
Trail Making Test Ratio	0.485 [0.261, 0.835]	0.458 [0.235, 0.738]	0.428 [0.196, 0.597]	0.363 [0.153, 1.06]	.018
Missing	0 (0%)	10 (33.3%)	9 (52.9%)	5 (17.9%)	
Stroop C Items	86.5 [54, 112]	74[23, 104]	48 [21, 93]	62 [33, 95]	< .001
Missing	2 (5.9%)	3 (10.0%)	3 (17.6%)	5 (17.9%)	
Stroop CW Items	32 [19, 52]	20 [0, 29]	12 [6, 33]	19.5 [2, 45]	< .001
Missing	2 (5.9%)	3 (10.0%)	5 (29.4%)	4 (14.3%)	
Stroop Interference	55.7 (17.7)	55.7 (17.7)	39.3 (20.1)	41.6 (11.2)	.001
Missing	2 (5.9%)	3 (10.0%)	5 (29.4%)	5 (17.9%)	

Count (%), Mean (*SD*), or Median [Min, Max].

Processing speed

Reported in **Table 8.5**, three DSST processing speed subtests were administered at baseline. Post-hoc tests indicated that all MCI groups had slower symbol copying than controls (all $p < .001$) and neither possible ($p = 1$) nor probable ($p = 1$) MCI-LB differed from MCI-AD.

In the DSST 'original' task, after controlling for baseline symbol copying speed, MCI-AD ($p = .021$) and probable ($p = .012$) MCI-LB also experienced more interference from the task than controls, though possible MCI-LB did not ($p = .284$). The same pattern was found in the 'error check' task, with MCI-AD ($p = .005$) and probable MCI-LB ($p = .013$) experiencing more interference than controls, after controlling for copy speed, but not possible MCI-LB ($p = .536$).

The omnibus test indicated that the number of errors made on the 'original' task was uneven between groups, but there were no significant differences between controls and possible MCI-LB ($p = .076$), probable MCI-LB ($p = 1$) or MCI-AD ($p = .055$). This may reflect the low number of errors made overall, with a median in all groups of 0.

Table 8.5. Digit symbol substitution test scores and errors at baseline.

	Control (n=34)	MCI-AD (n=30)	Possible MCI-LB (n=17)	Probable MCI-LB (n=28)	*p*
DSST Symbol Copy	95.5 (18.0)	67.1 (23.1)	68.7 (26.8)	62.3 (22.4)	< .001
Errors	0 [0, 10]	0 [0, 1]	0 [0, 3]	0 [0, 4]	.720
Missing	0 (0%)	2 (6.7%)	3 (17.6%)	3 (10.7%)	
DSST Original	45.7 (10.6)	29.3 (11.4)	26.8 (10.9)	26.0 (8.67)	< .001
Errors	0 [0, 2]	0 [0, 3]	0 [0, 3]	0 [0, 1]	.015
Missing	0 (0%)	2 (6.7%)	2 (11.8%)	3 (10.7%)	
DSST Error Check	48.1 (9.54)	37.1 (11.9)	31.8 (13.2)	29.6 (10.2)	< .001
Errors	0 [0, 3]	0 [0, 1]	0 [0, 4]	0 [0, 3]	.467
Missing	0 (0%)	3 (10.0%)	5 (29.4%)	8 (28.6%)	
DSST Original Interference	-49.8 (13.5)	-37.8 (17.3)	-40.5 (19.8)	-36.3 (15.6)	.006
Missing	0 (0%)	2 (6.7%)	3 (17.6%)	3 (10.7%)	
DSST Error Check Interference	-47.3 (15.4)	-31.9 (16.2)	-38.6 (23.0)	-32.4 (17.1)	.002
Missing	0 (0%)	3 (10.0%)	5 (29.4%)	8 (28.6%)	

Count (%), Mean (*SD*), or Median [Min, Max].

8.2.3 Memory

Table 8.6. Simple baseline memory task performance in SUPErB cohort.

	Control (n=34)	**MCI-AD (n=30)**	**Possible MCI-LB (n=17)**	**Probable MCI-LB (n=28)**	***p***
ACE-R Memory	22.6 (2.93)	18.4 (4.98)	16.1 (5.04)	19.1 (4.68)	< .001
Rey Delayed Recall	8 [2, 15]	1 [0, 12]	2 [0, 13]	5 [0, 10]	< .001
Missing	0 (0%)	1 (3.3%)	0 (0%)	1 (3.6%)	
Rey Cued Recognition	14 [9, 15]	12 [6, 15]	11 [5, 14]	12 [6, 15]	.006
Missing	0 (0%)	3 (10.0%)	2 (11.8%)	1 (3.6%)	
Rey Recall % of Max	73.9 [25, 108]	12.5 [0, 225]	30 [0, 100]	50 [0, 90]	< .001
Missing	0 (0%)	1 (3.3%)	0 (0%)	1 (3.6%)	
Complex Figure % Recall	48.5 (16.7)	27.1 (16.2)	22.4 (15.1)	35.5 (15.2)	< .001
Missing	1 (3%)	4 (13%)	1 (6%)	2 (7%)	

Count (%), Mean (*SD*), or Median [Min, Max].

As reported in **Table 8.6**, MCI was associated with poorer retention of words from the RAVLT, in both free recall and cued recognition trials. After adjustment for the maximum number of words learned over the trials, recall was poorer than controls for MCI-AD ($p < .001$); possible MCI-LB ($p = .804$) and probable MCI-LB ($p = .358$) did not significantly differ from MCI-AD. Both MCI-AD ($p = .021$) and possible MCI-LB ($p = .018$) had poorer cued recognition than controls, but probable MCI-LB did not ($p = .169$).

8.2.4 Visuospatial

At baseline (**Table 8.7**), MCI groups had poorer performance in ACE-R visuospatial and construction tasks, poorer visuospatial working memory in the Corsi task, and worse copy and incidental recall of a complex figure. They did not show broad group impairments in visuo-perception as assessed with the LAT, however.

In the baseline-only tests, post-hoc comparisons of the Corsi task with Dunn's tests indicated that probable MCI-LB ($p = .012$) and MCI-AD ($p = .047$) had impaired visuospatial working memory relative to the controls, but possible MCI-LB ($p = .301$) did not. MCI was associated with poorer performance overall on the VPT than in controls ($p < .001$), but probable ($p = 1.00$) and possible ($p = 1.00$) MCI-LB did not significantly differ from MCI-AD.

Table 8.7. Baseline performance in visuospatial tasks in SUPErB cohort.

	Control (n=34)	**MCI-AD (n=30)**	**Possible MCI-LB (n=17)**	**Probable MCI-LB (n=28)**	***p***
ACE-R Visuospatial	16 [13, 16]	15 [8, 16]	14 [5, 16]	14 [11, 16]	.004
ACE-R VisuoConstruction	8 [5, 8]	7 [2, 8]	6 [1, 8]	6.5 [3, 8]	.010
LAT Discrimination	8 [5.12, 16.2]	10.5 [5.12, 88.4]	12.1 [5.19, 37.7]	11.5 [5.39, 83.2]	.088
Missing	10 (29.4%)	7 (23.3%)	7 (41.2%)	7 (25.0%)	
Corsi Block Span	5 [3, 8]	5 [3, 6]	5 [2, 5]	4 [2, 6]	.009
Missing	3 (8.8%)	6 (20.0%)	7 (41.2%)	1 (3.6%)	
Complex Figure Copy	35 [30, 36]	32 [8, 36]	30.75 [6.5, 36]	32 [13, 36]	< .001
Missing	1 (3%)	2 (7%)	1 (6%)	2 (7%)	
Complex Figure Recall	16.7 (5.73)	8.5 (5.53)	6.6 (4.83)	10.8 (5.33)	< .001
Missing	1 (3%)	4 (13%)	1 (6%)	2 (7%)	
VPT Score	29.4 (5.40)	20.4 (8.50)	21.6 (4.80)	21.0 (7.58)	< .001
Missing	7 (20.6%)	13 (43.3%)	8 (47.1%)	5 (17.9%)	
Pareidolia Task Correct	40 [35, 40]	39 [24, 40]	36 [20, 40]	38 [26, 40]	.002
Missing	0 (0%)	1 (3.3%)	3 (17.6%)	1 (3.6%)	
Pareidolia False Positive	0 [0, 5]	1 [0, 16]	3.5 [0, 20]	1 [0, 14]	.005
Pareidolia False Negative	0 [0, 1]	0 [0, 2]	0 [0, 3]	0 [0, 2]	.373

Count (%), Mean (*SD*), or Median [Min, Max].

8.2.5 Speech and language

As reported in **Table 8.8**, MCI was associated with poorer performance than controls in ACE-R language sub-scores, and poorer auditory working memory span on both forward and backward tasks. In the GNT, administered at baseline only, MCI-AD ($p < .001$), probable ($p = .030$) and possible ($p = .002$) MCI-LB all featured poorer semantic memory compared to controls, but did not significantly differ from each other.

Possible MCI-LB had significantly shorter forward digit span than controls ($p = .009$) but MCI-AD ($p = .143$) and probable MCI-LB ($p = .826$) did not. All MCI groups had impaired backwards digit span relative to controls (MCI-AD, $p = .008$; possible MCI-LB, $p = .014$; probable MCI-LB, $p = .019$) but did not significantly differ from each other.

Probable MCI-LB had a significantly higher backwards task cost than controls ($p = .038$), while MCI-AD ($p = .647$) and possible MCI-LB ($p = .931$) did not.

Table 8.8. Baseline speech, language, and auditory working memory scores in SUPErB cohort.

	Control (n=34)	**MCI-AD (n=30)**	**Possible MCI-LB (n=17)**	**Probable MCI-LB (n=28)**	***p***
ACE-R Language	25 [21, 26]	24 [18, 26]	23 [15, 26]	24.5 [20, 26]	< .001
GNT	24 [12, 30]	20 [7, 25]	20 [0, 25]	21 [7, 28]	< .001
Missing	0 (0%)	1 (3.3%)	0 (0%)	1 (3.6%)	
Digit Span Forward	9 [4, 14]	7 [4, 13]	6 [3, 10]	9 [5, 11]	.004
Missing	0 (0%)	1 (3.3%)	0 (0%)	1 (3.6%)	
Digit Span Back	6.50 [2, 13]	5 [2, 10]	5 [2, 7]	5 [3, 11]	.002
Missing	0 (0%)	1 (3.3%)	0 (0%)	1 (3.6%)	

Count (%), Mean (*SD*), or Median [Min, Max].

8.3 Validation analyses of longitudinal models from LewyPro

At the point of data locking for this work in April 2020, the mean follow-up time in the SUPErB cohort was 1.1 years (*SD* = 0.87), up to a maximum of 3.7 years from baseline, though 32 participants had not undertaken at least one follow-up visit at this time with three of these having died after baseline assessment. Validation analyses were undertaken as planned with the data available, with all previous LewyPro participants excluded to maintain independence of the two cohorts.

8.4.1 Domain-specific cognitive progressions

Validation analyses of the domain-specific LMM models developed from the primary outcomes of LewyPro were run with the data available from the independent SUPErB cohort to date, including healthy controls as an additional diagnostic group. These were again undertaken with the *lme4* and *lmerTest* packages for *R* software. Each cognitive measure was included as a separate outcome predicted by time, diagnosis, and where previously indicated, time x diagnosis interaction in an LMM with random slope and intercept. Continuous covariates were mean-centred to aid interpretation. Parameters indicated by the development cohort were included for this validation cohort. These models are presented in **Table 8.9**. Corresponding models, including time x diagnosis interactions in all cases, are displayed in **Figure 8.1**.

Visuospatial functions

The LewyPro cohort (**4.3 Results**) identified that probable MCI-LB featured worse visuospatial functions than MCI-AD and possible MCI-LB including poorer perception in the LAT, and that complex visuoconstruction task performance also progressively declined over time in the former group, while in the latter two these functions did not.

In the SUPErB study (**Table 8.9**), broad visuospatial functions as assessed with the ACE-R did not significantly decline over time in MCI-AD. Neither possible nor probable MCI-LB had significantly poorer estimated visuospatial functions at baseline than MCI-AD but appeared to differ in their decline in these. The interaction between time and diagnosis was significant for possible, but not probable, MCI-LB indicating a significant decline over time in the former group. In the latter group the size of the negative effect was comparable to that identified in the

same diagnostic group in the LewyPro cohort, with an additional loss of ~ 0.6 points per year in overall visuospatial functions, though possibly underpowered in this instance. Providing further context, healthy controls did not differ from MCI-AD in either initial visuospatial functions, or in their time trajectories. This suggests that MCI-AD did not only feature relatively less visuospatial impairment than MCI-LB, but that they typically featured no clear visuospatial impairment relative to controls at this stage.

In performance in more complex visual construction tasks specifically assessed by the cube, pentagons, and clock drawing tests only of the ACE-R, similar patterns of initial function and non-decline were observed for both MCI-AD and healthy controls. Possible, but not probable, MCI-LB featured significantly poorer initial performance. Both MCI-LB groups then demonstrated comparable loss of function over time in these tasks; the point estimate ($B = – 0.66$ and $B = – 0.64$, respectively) in both being comparable to the findings from LewyPro ($B = – 0.6$, $SE = 0.24$); however this difference was only significant in probable MCI-LB, which may reflect the small number of possible MCI-LB, or high heterogeneity in this measure.

In lower-level simple visual perception assessed with the LAT, no significant differences were identified between MCI-AD and controls, nor MCI-LB and MCI-AD, with no significant time trend. This was inconsistent with the findings from LewyPro. However, given the modest effects in each direction, it appears that probable MCI-LB may have poorer discrimination of line angles than controls, with MCI-AD and possible MCI-LB occupying the middle ground between these groups, though with large variation. Furthermore, this variable had a greater level of missingness than other measures (**see Table 8.7**), being mistakenly excluded for a number of participants initially.

Verbal fluency

In the LewyPro study (**4.3 Results**), probable MCI-LB had worse verbal fluency than MCI-AD in both the ACE-R subscale and FAS fluency task. All MCI groups progressively declined, but with no difference in rates of decline.

In the validation models (**Table 8.9**), controls performed better than MCI-AD in both tests of verbal fluency, while possible MCI-LB produced fewer words on average than other MCI-AD; this difference only being significant in the FAS expanded phonemic task. Contrary to the findings from LewyPro, a probable MCI-LB diagnosis was not associated with poorer fluency on either task. Furthermore, verbal fluency did not significantly decline over time in either task in any group.

Memory

In the LewyPro study (**4.3 Results**), MCI-AD had poorer recognition memory than probable MCI-LB. Contrary to these findings, in the validation model (**Table 8.9**) recognition memory in the ACE-R was found to be significantly poorer in possible MCI-LB than MCI-AD. Neither controls nor probable MCI-LB performed better than MCI-AD. There was a significant, slight improvement over time in scores (see **Figure 8.1**), which likely reflect practice effects in this measure.

Section summary

Of the differences in cognitive profile and progressions observed in LewyPro, only the progressive decline in visuoconstruction performance was replicated in the SUPErB cohort based on data available so far. While limited by the number of observations due to disruption to follow-up schedule, taken at face value this represents a partial validation of the development model in an independent sample, suggesting that differences in this particular aspect of visuospatial dysfunction may be a consistent characteristic of probable MCI-LB.

Table 8.9. Validation analyses of LewyPro models of domain-specific cognitive decline in independent SUPErB cohort.

	Intercept (MCI-AD)	Control	Poss. MCI-LB	Prob. MCI-LB	Age	Education	Male Gender	Time	Time x Control	Time x Poss. LB	Time x Prob. LB
ACE-R Visuospatial	**14.6** [13.94, 15.27] *<.001*	**0.61** [-0.32, 1.54] *.198*	**-1.0** [-2.08, 0.08] *.069*	**-0.65** [-1.71, 0.40] *.226*	**-0.05** [-0.10, -0.00] *.036*	**0.08** [-0.02, 0.18] *.121*	**0.61** [-0.21, 1.43] *.147*	**0.24** [-0.24, 0.71] *.328*	**-0.33** [-0.91, 0.25] *.266*	**-1.04** [-1.83, -0.25] *.014*	**-0.55** [-1.13, 0.04] *.066*
ACE-R VisuoConstruction	**6.84** [6.31, 7.36] *<.001*	**0.43** [-0.31, 1.17] *.252*	**-0.9** [-1.75, -0.04] *.040*	**-0.44** [-1.28, 0.40] *.304*	**-0.04** [-0.07, 0.00] *.072*	**0.09** [0.01, 0.16] *.030*	**0.48** [-0.17, 1.13] *.146*	**0.21** [-0.22, 0.64] *.347*	**-0.19** [-0.72, 0.34] *.484*	**-0.66** [-1.37, 0.06] *.072*	**-0.64** [-1.18, -0.11] *.018*
ACE-R Fluency	**8.99** [8.11, 9.87] *<.001*	**2.4** [1.17, 3.62] *<.001*	**-1.27** [-2.71, 0.16] *.082*	**-0.2** [-1.59, 1.18] *.773*	**-0.05** [-0.12, 0.01] *.111*	**0.15** [0.02, 0.28] *.028*	**-0.11** [-1.20, 0.97] *.838*	**-0.16** [-0.47, 0.15] *.303*		As MCI-AD	
FAS Fluency	**33.71** [29.84, 37.59] *<.001*	**8.84** [3.44, 14.24] *.001*	**-7.91** [-14.23, -1.58] *.014*	**-0.52** [-6.63, 5.60] *.869*	**-0.03** [-0.32, 0.25] *.811*	**0.94** [0.37, 1.51] *.001*	**-1.31** [-6.10, 3.49] *.593*	**-0.04** [-1.06, 0.98] *.937*		As MCI-AD	
ACE-R Recognition	**4.25** [3.97, 4.52] *<.001*	**0.32** [-0.04, 0.67] *.079*	**-0.58** [-1.00, -0.15] *.008*	**-0.12** [-0.52, 0.28] *.565*	**-0.02** [-0.04, -0.00] *.045*	**-0.01** [-0.05, 0.02] *.501*	**0.02** [-0.29, 0.34] *.879*	**0.14** [0.01, 0.27] *.039*		As MCI-AD	
Line Angle Task Discrimination (º)	**15.23** [10.41, 20.05] *<.001*	**-4.13** [-10.76, 2.50] *.222*	**1.0** [-7.36, 9.37] *.814*	**4.47** [-3.16, 12.09] *.251*	**0.36** [0.00, 0.72] *.048*	**-0.61** [-1.31, 0.08] *.084*	**-3.25** [-9.37, 2.87] *.298*	**-0.02** [-2.35, 2.31] *.988*		As MCI-AD	

Estimate [95% Confidence Interval] *p value*

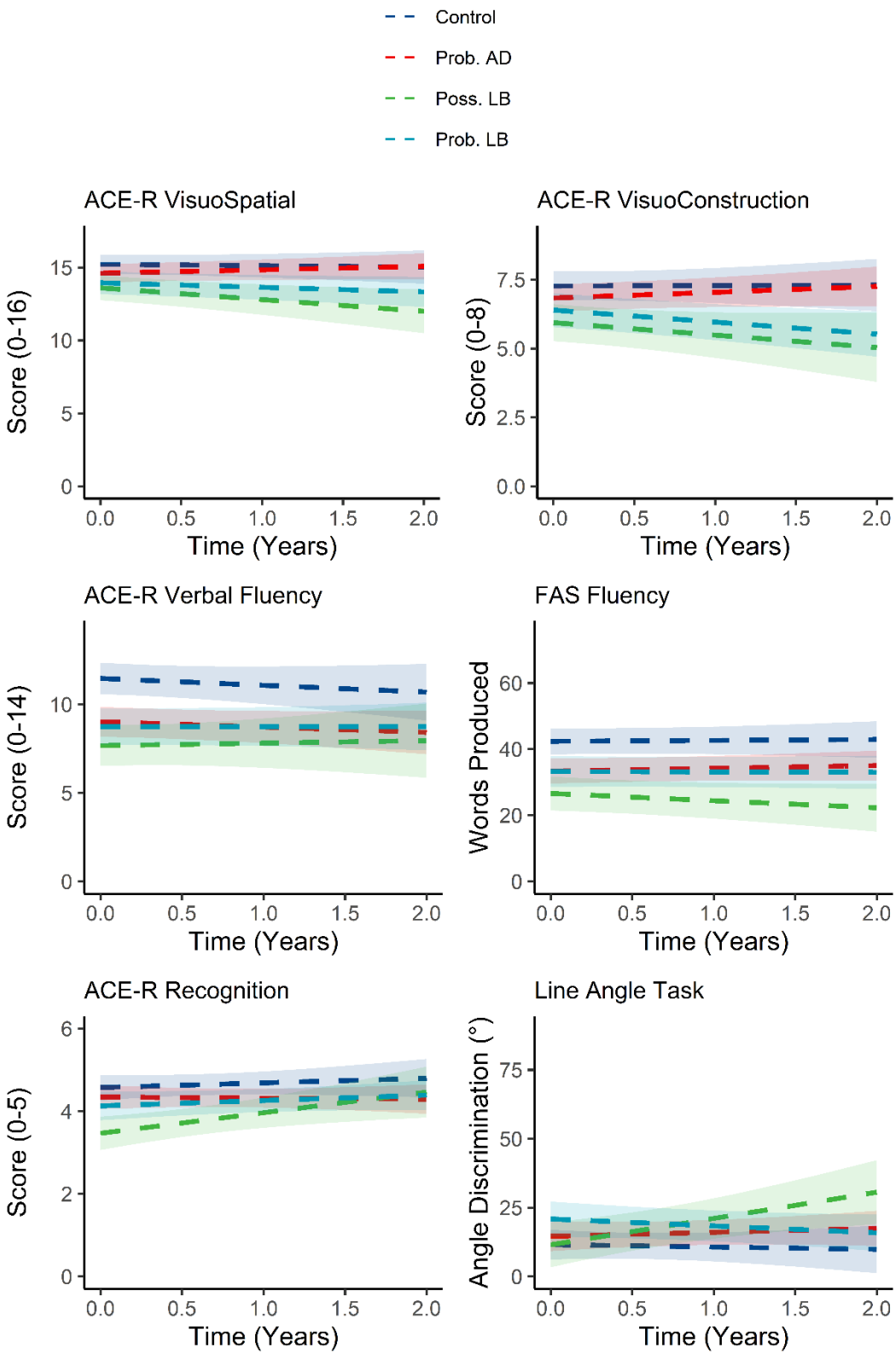


Figure 8.1. Predicted trajectories for each diagnostic group. Shaded area is 95% confidence interval for diagnostic effects only.

8.4.2 Latent classes of decline

The LewyPro development cohort identified three latent classes with distinct cognitive trajectories (**5.3. Results**): slow or stable progression, intermediate decline, and rapid decline. A probable MCI-LB diagnosis was found to predict a greater chance of decline, rather than stable progression, as was the presence of complex visual hallucinations as a clinical feature in MCI. A validation model was therefore conducted, with the same specifications of the underlying LMM, though latent classes were freely identified.

In the validation model with time zeroed on study entry as in LewyPro, no latent classes were identifiable in the SUPErB data available to date, failing to validate this model; this may be a consequence of the limited number of follow-up observations to date causing any trajectory differences to be indistinguishable from noise. In an alternative model with time centred for each individual to maximise differences at the intercept, including only those with two or more observations (n = 77), a two-class model was identified, though this did not improve model fit over the standard mixed model (BIC 580 > 563), which was reasonably well-defined by its posterior classification probabilities (means ≥ .9 for both classes). These two classes; one declining, one stable, are described in **Table 8.10**.

Table 8.10. Latent classes identified in two-class model for SUPErB cohort; intercept centred in time (midpoint in observations for each individual).

Class	**Intercept**[a]	**Time**
Declining (n = 28, 36%)	**68** (2.87), < *.001*	**-10** (2.75), < *.001*
Stable/slow decline (n = 49, 64%)	**90** (2.11), < *.001*	**-0.5** (2.60), *.847*
Covariates		
Age	**-0.28** (0.09), *.001*	
Education	**0.89** (0.20), < *.001*	
Gender (Male)	**0.23** (1.62), *.888*	
Deprivation	**0.33** (0.26), *.197*	

[a]**Estimate** (*SE*), *p value*

Diagnostic predictors of cognitive decline

The presence of each diagnostic group within these latent classes is presented in **Table 8.11**. All but two controls were classified as stable progressors, and so this trajectory was considered as a control-like cognitive progression. As in LewyPro, MCI-AD was treated as the reference group for a logistic regression, also presented in **Table 8.11**. While controls were naturally more likely to remain cognitively stable, no significant differences were apparent yet in cognitive prognosis between MCI groups.

Table 8.11. Distribution of diagnostic groups across latent cognitive classes and logistic regression model with MCI-AD as reference group.

		Diagnostic Group		
Class Counts (%)	**Control (n = 30)**	**MCI-AD (n = 14)**	**Poss. MCI-LB (n = 9)**	**Prob. MCI-LB (n = 24)**
Slow/Stable	28 (93%)	7 (50%)	3 (33%)	11 (46%)
Declining	2 (7%)	7 (50%)	6 (67%)	13 (54%)
Logistic Model[a]				
Decline vs. Stability	**0.07** [0.01 – 0.42], *.004*	**1.00** [0.35 – 2.85], *.999*	**2.00** [0.35 – 11.36], *.434*	**1.18** [0.32 – 4.42], *.804*

[a]**Odds Ratio** [95% Confidence Interval], *p value*

Visual hallucinations as a predictor of cognitive decline

The logistic model including visual hallucinations as a predictor of cognitive decline was repeated as in LewyPro, though this did not improve fit over the intercept-only model; controls were excluded from this analysis due to the necessary absence of hallucinations in this group (see **Table 8.12**). The presence of visual hallucinations was not a significant predictor of cognitive decline, in reality being under-represented (non-significantly) in the declining group. However, out of twelve participants with visual hallucinations at baseline, only six had been assessed with at least one follow-up visit, limiting the utility of this as a predictor at this time.

Table 8.12. Distribution of visual hallucinations between declining and non-declining latent classes, and logistic model predicting decline.

	Visual Hallucinations	
Class Counts (%)	**Absent (n = 41)**	**Present (n = 6)**
Slow/Stable	17 (41%)	4 (67%)
Declining	24 (59%)	2 (33%)
Logistic Model[a]		
Decline vs. Stability	**1.41** [0.76 – 2.63], *.277*	**0.35** [0.06 – 2.16], *.260*

[a]**Odds Ratio** [95% Confidence Interval], *p value*

Section summary

The findings from the LewyPro LCMM analysis could not be validated with the data available from the SUPErB study so far; the development model did not identify any latent classes in the validation cohort, likely given the limited number of repeated observations in the MCI group at this time. A version of this model modified post-hoc to centre time trajectories for each individual was capable of differentiating those with a healthy control-like cognitive trajectory from those with a declining trajectory, suggesting that this method may be an effective means of objectively characterising non-degenerative cases with a fuller dataset, but no predictors of decline or non-decline were observed in the logistic models indicated by the development cohort.

8.4.3 Clinical prognosis in SUPErB study cohort

Two multi-state transition models were derived from the LewyPro cohort (**6.3 Results**), finding a dose-effect of the increasing presence of core clinical features and biomarkers of DLB being associated with an increased risk of onset of dementia in MCI. When considering these features and biomarkers separately, cognitive fluctuations and visual hallucinations specifically were associated with increased risk of transition to dementia.

These models were therefore specified in the same manner for the SUPErB data to date, using the *msm* package for *R* software. Only MCI cases were included; while the rate of conversion of healthy ageing to mild cognitive impairment could be a useful addition to these models, and healthy controls were assessed for any emergent cognitive impairment, no apparent cases of neurodegenerative disease had emerged within the control group to date, though some degree of normal age-related cognitive decline may have been observed (as evidenced by two controls being categorised within the poorer performing latent class in previous analysis).

As previously, all cases of mild cognitive impairment were included under the same state, with diagnostic and demographic features included as covariates moderating the hazard of transitioning to the absorbing state of dementia. State transitions are summarised in **Table 8.13**.With only one patient death in the first year of assessment, and this occurring soon after baseline assessment, including death as an outcome resulted in non-estimable models. This case was therefore censored, and only dementia transitions were modelled to facilitate convergence.

Table 8.13. State-to-state transition table in the SUPErB study cohort.

	to MCI	**to Dementia**	**to Death**
from MCI	43	8	1

Both validation models are reported in **Table 8.14**. As in the LewyPro cohort, there was an apparent increased hazard of transition to dementia from MCI with increasing age, and the increasing presence of DLB diagnostic characteristics, with confidence intervals overlapping with those from the development model in both cases, validating these effects.

In the second model exploring specific diagnostic characteristics, the presence of cognitive fluctuations was again associated with an increased risk of developing dementia; though with wide confidence intervals lending uncertainty as to the magnitude of this effect, there was overlap with the estimates from the development model, validating this result.

However, contrary to the findings of the development model (**6.3 Results)**, visual hallucinations were not a meaningful predictor of dementia in this model, with effects not estimable. Of eleven participants with complex visual hallucinations at baseline (one case of Charles Bonnet syndrome excluded), five had not undertaken any follow-up visit at the time of data locking, limiting the utility of this parameter at this time.

Table 8.14. Validation of multi-state models for SUPErB cohort, incorporating overall Lewy body diagnostic characteristic count, or specific features as covariates.

Baseline Transition Probabilities from MCI[a]		***Covariates[b]***		
Model 1. Overall Feature Count		**Age**		**Lewy Body Characteristics (0-6)**
to MCI	**0.94** [0.78, 0.98]	-		-
to Dementia	**0.06** [0.02, 0.22]	**1.14** [1.00, 1.30]		**1.38** [0.99, 1.91]
Model 2. Specific Features		**Age**	**Visual Hallucinations**	**Cognitive Fluctuations**
to MCI	**0.95** [0.82, 0.99]	-	-	-
to Dementia	**0.05** [0.01, 0.18]	**1.12** [0.99, 1.26]	**Not estimable**	**16.21** [3.11, 84.34]

[a]**Transition Probability for One Year** [95% Confidence Interval]

[b]**Hazard Ratio** [95% Confidence Interval]

[c]Death transitions fixed to initial value to facilitate model convergence.

8.5 Discussion

The aims of this chapter were to present the baseline characteristics of the SUPErB study cohort, and to utilise this group, including the addition of a healthy control cohort, to assess whether the models developed from the LewyPro study (**Chapters 4-6**) would be validated in an independent cohort.

The MCI stage of DLB was again found to feature a progressive decline in complex visuoconstructional skills relative to MCI-AD, who followed a control-like trajectory without clear decline. This represents a deterioration in complex visually-guided copying tasks, including several tasks common in clinical screening tests, and previously indicated as sensitive to dysfunction in DLB, including clock, cube and overlapping-pentagon drawing tasks. This result is consistent with the same finding from the LewyPro cohort (**Chapter 4**), and also with recent research conducted in parallel suggesting that visuospatial dysfunctions continue to progress at a faster rate over the course of dementia in DLB and PDD in comparison to AD (Smirnov *et al.*, 2020). MCI-LB also featured poorer visuo-perception than controls, as assessed with the LAT, though there was overlap with the MCI-AD group occupying the middle-ground; this was inconsistent with the findings from the LewyPro study, where the separation between MCI-AD and MCI-LB was much clearer with a larger effect in the same direction.

Verbal fluency appeared to be more impaired in the possible, but not probable, MCI-LB group, contrary to earlier findings. Unexpectedly, recognition memory was also more impaired in the possible MCI-LB group than in MCI-AD, suggesting that more appropriate selection of memory testing methods may be required.

When attempting to identify latent classes of global cognitive decline, the development model as previously specified in **Chapter 5** (Hamilton *et al.*, 2020b) was unable to identify any distinct classes, which may reflect the lack of clear separation in trajectories to date. Adapting this model to maximise differences at the intercept by centring each individual's growth curve allowed for the identification of two distinct trajectories; a non-declining class characteristic of all but two of the controls as well as a number of patients, and a cognitively impaired, declining class. None of

the predictors of decline identified in the LewyPro cohort were clearly supported in this altered model, and indeed the development model itself was unable to identify any distinct latent classes, suggesting that more longitudinal data may be required to observe clearer separation in global functioning. As it stands with the current data availability, this represents a failure to validate the findings of the development model, which previously identified an association between probable MCI-LB diagnosis, visual hallucinations, and progressive cognitive decline. However, this does demonstrate the prospective utility of this method in objectively classifying cases of MCI with a non-declining cognitive profile comparable to healthy controls.

Finally, there was an indication that the presence of LB diagnostic characteristics in MCI were again associated with an increasing risk of transition to dementia, as was increased age. Specifically, cognitive fluctuations were again associated with particularly increased risk of transition to dementia, though visual hallucinations were not; the former being consistent with the development cohort, but the latter was not, with few hallucinators having been available for follow-up to date. This again represents a partial validation of the respective findings from the LewyPro cohort (**Chapter 6**), suggesting that MCI-LB may have an increased annual risk of developing dementia compared to MCI-AD, and that this risk increases in individuals with a more clear DLB-like clinical profile. However, with low death rates in the SUPErB study so far, it was not suitable to account for death as a competing risk.

Chapter 9. Supplementary Analysis of the SUPErB and LewyPro Cohorts

Additional data were available from the SUPErB study which were not available in the LewyPro study, including repeated measures data using the Stroop, digit span, and pareidolia tasks. These measures were not administered in LewyPro, and so no development models were available to validate. The following models were therefore developed from the ground-up, retaining all participants from the SUPErB study, including those who originated in LewyPro in contrast with the previous validation analyses. An additional final analysis was undertaken with both cohorts combined to describe the available repeat cognitive data as fully as possible.

9.1 SUPErB-only repeat cognitive tests

9.1.1 Analysis

Continuous outcome measures were converted to z-scores based on the mean and SD of performance in the healthy control group at baseline; error rates in the pareidolia task were not standardised in this manner, as this was considered likely to reduce, rather than improve, their interpretability with a median error rate of 0 in controls. LMM were utilised as in the LewyPro development and validation models, with the addition of NART-estimated IQ as a covariate to approximate premorbid functioning. A generalised LMM with log link function was considered in the analysis of error counts following a Poisson distribution. Linear and non-linear terms were assessed for continuous predictors, with diagnostic group included as a predictive factor in all cases, and suitability of time x diagnosis interactions assessed in each model. Models were fit and compared by AIC. As in previous analyses, effects were considered as statistically significant when $p < .05$, after controlling for relevant covariates.

9.1.2 Results

In all cases, no non-linear relationships were supported between any continuous predictors (including time) and any outcomes. There was no improvement to any model by the inclusion of a time x diagnosis interaction, except in the pareidolia task.

Stroop test

Stroop C (colour) and CW (colour-word) task performances are presented in **Table 9.1**. In both tasks there was a declining trend for performance, with fewer words correctly recited over time. Additionally, MCI groups showed poorer performance in both Stroop tasks than controls, with estimated performance over 1 SD poorer in simple reading speed, and approximately 2 SDs below healthy performance in the CW interference task. Compared to MCI-AD, possible and probable MCI-LB had slower word-reading speed, though this difference was only significant for possible MCI-LB. MCI-LB did not differ in performance from MCI-AD in the Stroop CW task; after controlling for baseline reading speed (C – CW) to provide a measure of the interference caused by the CW task, both MCI-LB groups appeared to experience less interference than MCI-AD.

Digit span task

MCI groups did not show impairment in forward digit span relative to controls (**Table 9.1**) but did show mildly poorer performance in the backwards span task, which may reflect the greater complexity in the latter measure. There was no difference in performance between MCI diagnostic groups, and no significant time trend.

Pareidolia test

In analysis of false positive 'pareidolias' and false negative 'missed' error rates in the pareidolia task, a log-link function offered a substantial improvement in model fit over the general LMM, with models presented in **Table 9.2**. MCI-LB groups generally produced more false positive 'pareidolia' responses compared to MCI-AD and controls, with incident rate ratios of 3.93 in possible MCI-LB, and 3.05 in probable MCI-LB, though this increased error rate subsided over time in the former group. Higher premorbid functioning was associated with lower incidence of pareidolia responses.

Only increasing age was associated with incidence of false negatives (missed true faces in stimuli) across all groups.

MCI-AD did not significantly differ from controls in either production of false positives, or false negatives in the pareidolia task.

To test whether pareidolia production was related to the presence of visual hallucinations, an additional generalised LMM was constructed including this clinical feature as a predictor; this was not found to be a significant predictor of false positive pareidolia perceptions (Incidence rate ratio = 0.73, 95% CI = 0.31 – 1.73). Finally, a repeated measures correlation analysis did not identify any clear association between the production of false positives and false negatives ($r(149) = -0.08$, $p = .326$).

Table 9.1. Supplementary linear mixed models for SUPErB-only outcome measures. All outcome measures as z-scores in reference to healthy control baseline performance.

Measure (z-scored)	**Intercept MCI-AD[a]**	**Control**	**Poss. MCI-LB**	**Prob. MCI-LB**	**Age**	**Education**	**IMD**	**NART IQ**	**Male Gender**	**Time**
Digit Span	**-0.75**	**0.32**	**-0.23**	**0.32**	**-0.02**	**0.01**	**-0.02**	**0.03**	**0.01**	**-0.03**
Forwards	[-1.07, -0.44] *<.001*	[-0.04, 0.68] *.077*	[-0.65, 0.19] *.278*	[-0.03, 0.67] *.077*	[-0.03, 0.00] *.089*	[-0.03, 0.05] *.508*	[-0.06, 0.03] *.476*	[0.02, 0.05] *<.001*	[-0.28, 0.30] *.941*	[-0.11, 0.05] *.509*
Digit Span	**-1.00**	**0.40**	**-0.12**	**-0.00**	**-0.03**	**0.02**	**0.01**	**0.02**	**0.12**	**-0.04**
Backwards	[-1.28, -0.73] *<.001*	[0.09, 0.72] *.012*	[-0.48, 0.25] *.529*	[-0.31, 0.31] *.988*	[-0.04, -0.01] *.001*	[-0.01, 0.06] *.240*	[-0.03, 0.05] *.639*	[0.01, 0.04] *<.001*	[-0.13, 0.38] *.335*	[-0.12, 0.03] *.254*
Stroop C	**-1.20**	**0.79**	**-1.02**	**-0.52**	**-0.01**	**0.02**	**-0.01**	**0.04**	**-0.21**	**-0.34**
Words	[-1.70, -0.69] *<.001*	[0.23, 1.35] *.006*	[-1.70, -0.35] *.003*	[-1.08, 0.04] *.070*	[-0.04, 0.02] *.486*	[-0.05, 0.08] *.623*	[-0.09, 0.06] *.709*	[0.02, 0.06] *<.001*	[-0.6, 0.25] *.375*	[-0.47, -0.22] *<.001*
Stroop CW	**-2.05**	**1.65**	**-0.25**	**0.19**	**-0.06**	**0.01**	**-0.02**	**0.02**	**0 .00**	**-0.27**
Words	[-2.49, -1.62] *<.001*	[1.16, 2.13] *<.001*	[-0.84, 0.35] *.417*	[-0.30, 0.68] *.457*	[-0.09, -0.04] *<.001*	[-0.05, 0.07] *.666*	[-0.09, 0.04] *.497*	[0.00, 0.04] *.016*	[-0.39, 0.39] *.998*	[-0.37, -0.16] *<.001*
Stroop Interference (C – CW)	**0.15** [-0.32, 0.63] *.526*	**-0.21** [-0.37, 0.05] *.009*	**-1.11** [-1.76, -0.46] *.001*	**-0.76** [-1.29, -0.23] *.005*	**0.03** [0.00, 0.06] *.023*	**0.01** [-0.05, 0.08] *.731*	**-0.02** [-0.09, 0.05] *.641*	**0.03** [0.01, 0.05] *.008*	**-0.31** [-0.74, 0.11] *.148*	**-0.21** [-0.37, -0.05] *.009*

[a]**Estimate** [95% Confidence Interval] *p value*

Table 9.2. Linear and generalised linear mixed models for error counts in the pareidolia task.

	Intercept MCI-AD	**Control**	**Poss. MCI-LB**	**Prob. MCI-LB**	**Age**	**Education**	**IMD**	**NART IQ**	**Male Gender**	**Time (MCI-AD)**	**Time x Control**	**Time x Poss. MCI-LB**	**Time x Prob. MCI-LB**
Pareidolia Correct[a]	**37.06** [35.53, 38.60] *<.001*	**0.77** [-1.09, 2.63] *.417*	**-2.76** [-4.96, 0.55] *.014*	**-1.05** [-2.89, 0.78] *.261*	**-0.10** [-0.19, -0.02] *.017*	**0.00** [-0.20, 0.20] *.992*	**-0.10** [-0.31, 0.11] *.346*	**0.08** [0.02, 0.15] *.011*	**0.49** [-0.83, 1.81] *.470*	**-0.35** [-1.35, 0.65] *.490*	**0.12** [-1.32, 1.56] *.866*	**1.87** [0.33, 3.40] *.017*	**0.00** [-1.21, 1.22] *.995*
Pareidolia False Positives[b]	**0.74** [0.34, 1.62] *.451*	**0.79** [0.30, 2.09] *.631*	**3.93** [1.42, 10.88] *.008*	**3.05** [1.23, 7.60] *.016*	**1.07** [1.03, 1.12] *.002*	**1.03** [0.94, 1.15] *.507*	**1.06** [0.96, 1.19] *.254*	**0.95** [0.92, 0.98] *.004*	**0.63** [0.31, 1.25] *.184*	**1.30** [0.76, 2.21] *.338*	**0.80** [0.39, 1.65] *.551*	**0.36** [0.16, 0.81] *.014*	**0.88** [0.49, 1.58] *.669*
Pareidolia False Negatives[b]	**0.28** [0.12, 0.67] *.004*	**As MCI-AD**			**1.05** [1.00, 1.10] *.037*	**1.03** [0.93, 1.15] *.552*	**0.96** [0.85, 1.08] *.509*	**0.97** [0.94, 1.00] *.093*	**0.91** [0.45, 1.84] *.795*	**0.72** [0.34, 1.52] *.390*	**As MCI-AD**		

[a]**Estimate** [95% Confidence Interval] *p value*

[b]**Incidence Rate Ratio** [95% Confidence Interval] *p value*

9.1.3 Discussion

There was no apparent loss of simple auditory working memory capacity measured by digit span in any MCI group, though there was mild impairment of backwards digit span relative to healthy older adults; the greater difficulty of the latter task may make it more sensitive to identify dysfunction, or this may reflect interference from impairment other domains, such as executive dysfunctions.

MCI-LB featured less apparent interference in the Stroop task, this may reflect their slower reading speeds in the non-interference CW condition; their task completion may be so slow as to prevent any automatic interference effects from colour-word incongruency. While the Stroop task may therefore be an effective measure of processing speed impairment in MCI-LB, it may be insensitive to dysfunction of executive functions such as error detection, response inhibition, and attention direction. These findings are not consistent from past research from the dementia stages, where DLB were seen to perform worse than AD, and AD worse than controls, in a Stroop task (Calderon *et al.*, 2001); such differences, if true, may only become apparent further into the dementia stages. However, these results were based on findings from a particularly small cohort (DLB $n = 10$, AD $n = 9$), which may not be representative of the wider population of DLB or AD.

The pareidolia task has shown utility in previous research, with ‘pareidolia’ false positive responses (false perception of faces within ambiguous visual noise) being interpreted as phenomena analogous to visual hallucinations in DLB (Uchiyama *et al.*, 2012; Mamiya *et al.*, 2016), and being associated with cognitive impairments and conversion to DLB or PD in idiopathic RBD (Honeycutt *et al.*, 2020). Those with an MCI-LB diagnosis were more likely to falsely report the presence of faces in visual stimuli, though this should not be taken to imply a clear separation between groups as pareidolia rates were low even in this group. Visual hallucinators were not shown to be more likely to produce pareidolic responses, and so it is unclear that these false positives reflect true hallucination-like experiences in LB disease; other processes could account for apparent misperceptions in DLB and MCI-LB, including a lower threshold for the perception of faces, a misunderstanding of task instructions, or application of a

biased task strategy (e.g. falsely reporting seeing faces when unsure, to avoid a perceived 'low score'), though each of these would implicate different processes and could differ between individuals. While these are speculative examples for other potential causes of false positive answers, there is evidence that experimentally induced negative mood can increase the rate of false positive misidentifications in this task in DLB (Watanabe *et al.*, 2018), suggesting that face misidentifications in this group may be a consequence of emotionally-moderated perceptual biases, rather than an expression of primary visuospatial cognitive deficits. Meanwhile in this study (**Table 9.2**), higher premorbid functioning was associated with a lower rate of false positives, which could be interpreted as lending support to cognitive-mediated explanations of the mechanisms underlying pareidolias, though more exploration is clearly warranted.

Only age appeared to be associated with false negative rate in the pareidolia tasks (missed true faces), though of marginal significance, which may reflect age-related perceptual decline (e.g. visual acuity loss) rather than any cognitive or psychiatric process. False negative errors were also not significantly associated with production of false positive pareidolia responses, supporting the distinction drawn between these two error types. These results suggest that the false positive 'pareidolia' error rate may be the more pertinent score to assess for the intended purpose than the false negative 'miss' rate or overall correct identification score, and that this test may be sensitive to differences at the MCI stages as in dementia, though the mechanisms underlying this and their relationships to other aspects of MCI-LB are not entirely clear.

9.2 Combined cohort analysis – domains of cognitive impairment

To provide the best characterisation of MCI-LB with the data available, data from both cohorts were combined, including key outcome and predictor measures that were uniform across both studies. Deprivation deciles were updated for LewyPro participants to be consistent in direction with the SUPErB study; lower deciles (e.g. one) correspond to more community deprivation (Noble *et al.*, 2019). Observation times were centred on the first observation point (i.e. LewyPro baseline assessment) for cross-study participants. Diagnoses were based on the most up-to-date clinical information for each individual at the time of writing; there were therefore changes to diagnoses in some cases (e.g. where new information had come to light, or new clinical features or biomarker findings had emerged).

9.2.1 Analysis

Continuous outcomes were centred and scaled into z-scores in reference to baseline performance in the healthy control group. LAT discrimination was log-transformed prior to scaling to reduce skewness; after scaling, z-scores in this measure were linear transformed by -1(x) to reverse value signs so that negative values indicated poorer performance, consistent with other outcomes. As previously, MCI-AD was treated as the reference group. Linear mixed models were fit controlling for key covariates as in **Chapters 4 and 8**, while assessing the suitability of non-linear terms for continuous predictors (non-improvement in all cases). Model fit was assessed by improvements in AIC. Significance was considered as $p < .05$.

9.2.2 Results

Results of the mixed models with the full cohort are reported in **Table 9.3.** As expected, the three MCI groups had global cognitive impairment relative to controls (95% CI: 1.3 to 3.1 *SD*s below control performance). Probable MCI-LB did not significantly differ from MCI-AD, though the possible MCI-LB group were slightly worse at baseline. While the MCI groups had significant global decline over time, controls did not. No difference was indicated in rate of decline between MCI groups.

In the overall ACE-R memory subscale, controls performed better than MCI, with no significant diagnostic group differences within MCI. While MCI sub-groups did not clearly decline over time, this may reflect the counteracting effects of learning effects as healthy controls showed slight, but significant improvement in performance relative to MCI-AD. In the pooled analysis there were sufficient observations for analysis of the Rey AVLT, reflecting the delayed recall as a percentage of each participant's best number of words recited on trial 5, as by Ferman *et al.* (2013). MCI-AD had significantly poorer retention of learned words than controls, being approximately two standard deviations below healthy performance in this sample. While possible MCI-LB did not clearly differ from MCI-AD, probable MCI-LB showed significantly less memory impairment than MCI-AD.

Verbal fluency was impaired relative to controls, with both ACE-R subtest and FAS fluency measures, in all MCI groups, and significantly more-so in possible MCI-LB than MCI-AD. Probable MCI-LB had poorer performance in both tests than MCI-AD, but this was non-significant in both cases. While the ACE-R verbal fluency measure was sensitive to decline over time, the FAS task was not. To explore these inconsistencies more comprehensively, a post-hoc model was constructed including both verbal fluency measures as a composite outcome measure; in this case, probable MCI-LB was associated with non-significantly poorer verbal fluency (B = -0.42, SE = 0.22, p = .058) while possible MCI-LB had significantly poorer fluency (B = -0.89, SE = 0.27, p = .001). This model also indicated that there was a significant decline in verbal fluency over time (B = -0.08, SE = 0.03, p = .015), but no group differences in time trend.

In both overall ACE-R visuospatial score, and the visuoconstructional sub-score previously identified, probable MCI-LB had poorer baseline performance than MCI-AD and controls. Both possible and probable MCI-LB featured progressive decline in this domain, while MCI-AD and controls remained stable. In the LAT, all MCI groups were impaired relative to controls, and probable MCI-LB had significantly more visual-perceptual dysfunction than MCI-AD. There was no clear time effect on any group.

MCI groups had poorer language skills than controls, though the diagnostic groups did not differ from each other. There was a slight deterioration in speech and language over time across groups, with no interaction between time and diagnosis supported.

9.2.3 Discussion

Understandably, the findings from the combined cohorts largely mirror the profiles of cognitive decline observed in the separate development (**Chapter 4**) and validation (**Chapter 8**) cohorts which comprise this dataset. However, these provide the strongest evidence yet that the profiles of cognitive decline in MCI-LB and MCI-AD may match those of their eventual dementia syndromes, with MCI-AD featuring worse retention of learned information, and MCI-LB featuring worse executive and visuospatial dysfunction, with the latter progressively worsening as the MCI progresses, in contrast to typical MCI-AD and healthy controls and consistent with observations from DLB (Smirnov *et al.*, 2020). With sufficient repeated measurements available

in the combined cohort, the Rey AVLT assessment also showed sensitivity to different patterns of memory dysfunction in MCI-AD and MCI-LB, to which the ACE-R memory scale was not sensitive. While probable MCI-LB had worse retention of learned words than the healthy comparison group, both possible MCI-LB and MCI-AD had notably worse performance than probable MCI-LB.

The addition of controls provides further context as to the magnitude of cognitive impairments in all groups showing that, despite the differences observed between groups, all three MCI groups were typically impaired relative to controls in most domains (**Figure 9.1**). These group differences are therefore not clear-cut, even at the mild stage. The cognitive domain with the clearest dissociation between MCI-AD and controls, and MCI-LB, is the visuospatial domain.

Table 9.3. Combined LewyPro-SUPErB cohort longitudinal cognitive performance. Outcomes z-scored on healthy control performance at baseline.

	Intercept (MCI-AD)[a]	Control	Poss. MCI-LB	Prob. MCI-LB	Age	Education	Male Gender	Time (MCI-AD)	Time x Control	Time x Poss. LB	Time x Prob. LB
ACE-R Total	**-2.71** [-3.35, -2.08] *<.001*	**2.24** [1.31, 3.17] *<.001*	**-1.21** [-2.18, -0.24] *.014*	**-0.10** [-0.88, 0.68] *.806*	**-0.06** [-0.10, -0.02] *.004*	**0.12** [0.05, 0.20] *.001*	**-0.04** [-0.69, 0.60] *.896*	**-0.47** [-0.73, -0.21] *<.001*	**0.48** [0.05, 0.90] *.028*	**0.08** [-0.34, 0.51] *.698*	**0.01** [-0.31, 0.32] *.974*
ACE-R Memory	**-1.79** [-2.26, -1.32] *<.001*	**1.74** [1.05, 2.44] *<.001*	**-0.65** [-1.37, 0.08] *.080*	**0.29** [-0.30, 0.87] *.337*	**-0.05** [-0.08, -0.02] *.001*	**0.02** [-0.04, 0.07] *.593*	**-0.01** [-0.49, 0.46] *.952*	**-0.16** [-0.35, 0.03] *.108*	**0.34** [0.01, 0.67] *.041*	**0.28** [-0.03, 0.58] *.078*	**0.09** [-0.14, 0.31] *.464*
Rey AVLT Recall	**-1.91** [-2.41, -1.42] *<.001*	**2.03** [1.30, 2.77] *<.001*	**0.20** [-0.56, 0.96] *.601*	**0.84** [0.23, 1.45] *.007*	**-0.02** [-0.05, 0.01] *.197*	**-0.01** [-0.08, 0.06] *.779*	**-0.14** [-0.66, 0.37] *.584*	**0.22** [-0.14, 0.58] *.229*		As MCI-AD	
ACE-R Verbal Fluency	**-1.97** [-2.51, -1.43] *<.001*	**1.3** [0.52, 2.08] *.001*	**-1.03** [-1.86, -0.21] *.014*	**-0.61** [-1.28, 0.06] *.072*	**-0.04** [-0.07, -0.00] *.048*	**0.14** [0.08, 0.21] *<.001*	**-0.06** [-0.62, 0.49] *.822*	**-0.2** [-0.30, -0.10] *<.001*		As MCI-AD	
FAS Verbal Fluency	**-1.02** [-1.38, -0.65] *<.001*	**0.71** [0.18, 1.24] *.008*	**-0.98** [-1.55, -0.42] *.001*	**-0.37** [-0.82, 0.09] *.113*	**-0.01** [-0.03, 0.01] *.444*	**0.1** [0.05, 0.14] *<.001*	**-0.03** [-0.41, 0.36] *.890*	**-0.01** [-0.08, 0.07] *.878*		As MCI-AD	
ACE-R Visuospatial	**-1.49** [-2.12, -0.87] *<.001*	**0.57** [-0.28, 1.42] *.189*	**-0.74** [-1.69, 0.21] *.125*	**-0.97** [-1.74, -0.20] *.014*	**-0.03** [-0.08, 0.01] *.097*	**0.12** [0.04, 0.20] *.004*	**0.63** [-0.02, 1.27] *.056*	**0.01** [-0.33, 0.35] *.951*	**-0.11** [-0.67, 0.45] *.703*	**-0.64** [-1.18, -0.1] *.021*	**-0.48** [-0.88, -0.08] *.019*
ACE-R Vis.Cons.	**-1.41** [-2.00, -0.83] *<.001*	**0.57** [-0.28, 1.42] *.189*	**-0.60** [-1.49, 0.28] *.181*	**-1.02** [-1.73, -0.30] *.006*	**-0.03** [-0.07, 0.01] *.092*	**0.09** [0.02, 0.17] *.014*	**0.76** [0.17, 1.36] *.012*	**0.11** [-0.21, 0.44] *.496*	**-0.11** [-0.65, 0.43] *.691*	**-0.50** [-1.03, 0.03] *.063*	**-0.55** [-0.94, -0.16] *.005*
Line Angle Task	**-1.88** [-2.40, -1.35] *<.001*	**0.88** [0.14, 1.62] *.019*	**0.07** [-0.76, 0.90] *.870*	**-1.06** [-1.69, -0.42] *.001*	**-0.04** [-0.07, -0.01] *.02*	**0.11** [0.04, 0.18] *.003*	**0.83** [0.30, 1.37] *.002*	**-0.03** [-0.22, 0.16] *.778*		As MCI-AD	
ACE-R Language	**-1.22** [-1.78, -0.67] *<.001*	**0.83** [0.02, 1.64] *.045*	**-0.76** [-1.62, 0.09] *.081*	**0.16** [-0.53, 0.85] *.652*	**-0.07** [-0.11, -0.04] *<.001*	**0.08** [0.02, 0.15] *.013*	**0.05** [-0.53, 0.63] *.877*	**-0.16** [-0.25, -0.07] *.001*		As MCI-AD	

[a]**Estimate** [95% Confidence Interval] *p value*

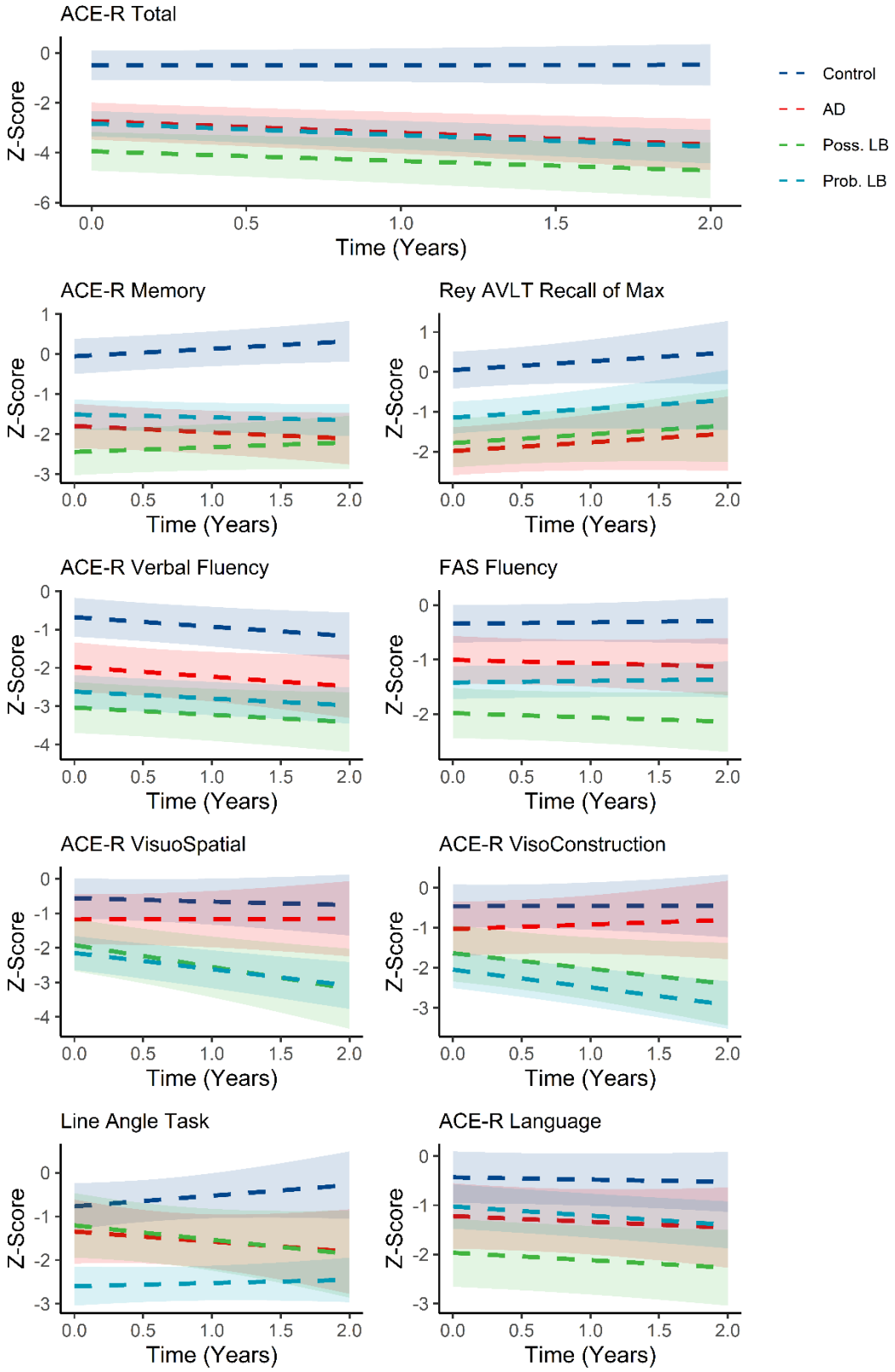


Figure 9.1. Two-year predicted neuropsychological test performance in combined LewyPro-SUPErB cohort.

9.3 Pooled LCMM

Analysis of the full dataset was undertaken as in **Chapter 5**, exploring the presence of latent classes with distinct trajectories of cognitive decline.

9.3.1 Analysis

Total scores on the ACE-R were centred and scaled to z-scores in reference to baseline performance in the healthy control group. As previously, a random intercept and slope model was fit with the *lcmm* package for *R* software, assessing the suitability of any non-linear terms (non-significant in all cases). The number of latent classes was decided by an improvement in model fit according to BIC over the single-class alternative, while maintaining well-defined and clinically relevant sub-groups based on their sizes and posterior classification probabilities. Models with between one and five classes were specified for initial consideration. More complex models (i.e. six or more classes) were to be considered if progressive improvements in fit were sustained up to the five-class model.

As previously, predictors of cognitive trajectory class were examined with logistic regression, with diagnostic status, core clinical features of DLB, and imaging results considered as predictors in these.

9.3.2 Results

A three-class model was the best characterised, maintaining an improved fit over the one, two, four, and five-class alternatives, and with clearly defined subgroups. These classes included slow declining, intermediate declining, and small rapid declining groups (**Table 9.4, Figure 9.2**). Nearly all healthy subjects were characterised by high starting point with slow progression (**Table** 9.5), though one appeared with a relatively lower level of cognitive function so as to be classified within the intermediate declining group.

In the logistic model including diagnostic group as a predictor of cognitive trajectory, with probable MCI-LB and the slow trajectory as reference categories for the predictor and outcome, respectively, controls were significantly more likely to follow a slow progressing cognitive

trajectory, as expected. The only difference in prognosis within MCI groups was a non-significant increased risk of rapid decline within the possible MCI-LB group; in all other cases, MCI-LB and MCI-AD did not significantly differ in their cognitive prognosis. In the second model including specific diagnostic characteristics as predictors (MIBG and FP-CIT imaging abnormalities, complex visual hallucinations, RBD, parkinsonism, and cognitive fluctuations), only cognitive fluctuations improved model fit (

Table 9.5). As expected, controls had a considerably lower rate of intermediate cognitive decline than MCI. While the point estimates suggested an increased risk of intermediate or rapid cognitive decline in MCI cases with cognitive fluctuations, these were not statistically significant with wide confidence intervals, particularly in the latter.

Table 9.4. Estimated intercept and time effects for ACE-R Total z-score for each class, and covariates.

Class	**Intercept**[a]	**Time**
Slow Decline	**-1.53** (0.24),	**-0.13** (0.06),
(n = 109, 60%)	< *.001*	*.021*
Intermediate Decline	**-4.24** (0.31),	**-0.66** (0.12),
(n = 59, 32%)	< *.001*	*.002*
Rapid Decline	**-7.77** (0.46),	**-2.02** (0.31),
(n = 14, 8%)	< *.001*	< *.001*
Covariates		
Age	**-0.07** (0.02), < *.001*	
Education	**0.19** (0.03), < *.001*	
Gender (Male)	**0.25** (0.27), *.183*	
Deprivation	**0.03** (0.04), *.529*	

[a]**Estimate** (SE), *p value*

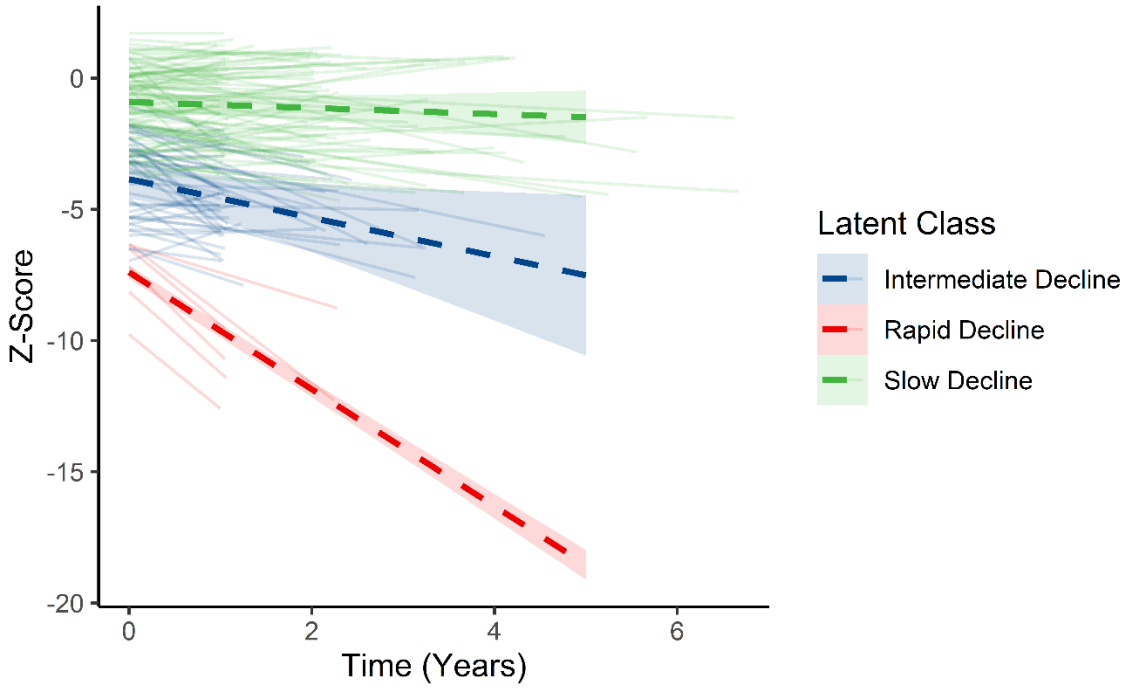


Figure 9.2. Latent classes with distinct trajectories (dashed) identified within the combined LewyPro-SUPErB cohorts, with shaded 95% confidence intervals reflecting uncertainty in the fixed effects for class estimates only, and solid lines for individual observed trajectories.

Table 9.5. Diagnostic group versus latent class, and multinomial logistic models, probable MCI-LB and intermediate declining trajectory as reference categories in model 1, MCI without cognitive fluctuations as reference in model 2.

	Diagnostic Group			
Class Counts (%)	**Prob. MCI-LB (n=71)[a]**	**Control (n=34)**	**MCI-AD (n=49)**	**Poss. MCI-LB (n=28)**
Slow Decline	35 (49.3%)	33 (97.1%)	27 (55.1%)	14 (50%)
Intermediate Decline[a]	32 (45.1%)	1 (2.9%)	18 (36.7%)	8 (28.6%)
Rapid Decline	4 (5.6%)	0 (0%)	4 (8.2%)	6 (21.4%)
Logistic Model 1[b]	**(Intercept)**			
Intermediate vs. Slow	**0.91** [0.57, 1.48], *.714*	**0.03** [0.00, 0.26], *.001*	**0.70** [0.33, 1.51], *.365*	**0.67** [0.25, 1.83], *.439*
Rapid vs. Slow	**0.11** [0.04, 0.32], *< .001*	*Not estimable*	**1.25** [0.29, 5.45], *.766*	**4.04** [0.98, 16.65], *.053*
Logistic Model 2[b]	**MCI without Fluctuations[a]**	**Controls**	**MCI with Fluctuations**	
Intermediate vs. Slow	**0.62** [0.42, 0.93], *.022*	**0.05** [0.01, 0.37], *.004*	**2.14** [0.98, 4.68], *.057*	
Rapid vs. Slow	**0.16** [0.08, 0.32], *< .001*	*Not estimable*	**1.63** [0.45, 5.91], *.459*	

[a]Reference group

[b]**Odds Ratio** [95% Confidence Interval], *p value*

9.3.3 Discussion

These results extend previous findings (**Chapter 5**), similarly identifying three distinct cognitive trajectories in MCI, and suggesting that MCI patients with a slow cognitive decline follow a trajectory comparable to that of cognitively healthy older adults. However, while the majority of healthy controls were classified as cognitively slow progressing, one was included within the intermediate declining class; the distinctions are therefore not clear-cut. With the limited follow-

up available to date in the SUPErB cohort, class allocations may be largely indicative of differences at the intercept (i.e. cognitive function at baseline) in the model as specified, rather than any subsequent decline which may require longer follow-up. With more data available, those with a declining trend may separate more clearly from those with only a low initial function, but overall stability.

However, the finding of the logistic models predicting cognitive trajectories were not consistent with the results of the LewyPro-only cohort. In this analysis, cognitive fluctuations were the only DLB symptom predictive of a declining trajectory, though this was non-significant. MCI-AD and probable MCI-LB did not significantly differ in their odds of developing in a stable, slow declining, or rapid manner. This was in contrast to the LewyPro study, which identified that a probable MCI-LB diagnosis, and the presence of visual hallucinations, were predictive of progressive decline. Possible MCI-LB may feature a poorer prognosis, with a disproportionate number following a rapidly-declining trajectory, though non-significant as a predictor; with small relative numbers in both groups, this could merely be an artefact of the small sample, or as discussed previously (**Chapter 5**), could suggest that greater cognitive impairment may obscure the presence of DLB features, and that these may be cases with a greater mixed pathological burden.

9.4 Transitions from MCI to dementia or death in combined LewyPro-SUPErB cohorts

The MSM analysis of transitions from MCI to dementia was repeated as in **Chapters 6 & 8** including the full combined LewyPro-SUPErB cohort and covariates common to both cohorts. This provided 111 patients with at least two observations, over which time there were 6 deaths and 38 diagnoses of dementia. Mean (SD) follow-up time was 2.26 (1.38) years, with a maximum of 6.67 years after baseline. This section has been adapted from a manuscript under peer review.

9.4.1 Analysis

Using the *msm* package for *R* software, a three-state model was specified, including MCI, and the two absorbing states of dementia or death, with death times being exact and freely estimated. Healthy controls were excluded from analysis. As previously, two models were fit: one including

DLB core clinical feature and indicative biomarker count, and one including specific DLB core clinical features and indicative biomarker presence or absence separately. Additional covariates common across cohorts were also assessed in both models, with continuous variables mean- or median-centred as appropriate: age, education, gender, and deprivation decile. Parameters were selected by backwards elimination based on improved model fit assessed by AIC.

9.4.2 Results

Results from both models are reported in **Table 9.6.**

Lewy body characteristic count

Increasing age was associated with increasing hazard of transition to dementia, or of death. Additionally, the presence and increasing number of diagnostic characteristics of DLB in MCI was associated with a progressively increasing hazard of transition to dementia. There was a non-significant effect whereby DLB diagnostic characteristics were also associated with increased hazard of the competing risk of death.

Specific Lewy body characteristics

In addition to age as previously noted, the best-fit model favoured inclusion of visual hallucinations and cognitive fluctuations as covariates. Cognitive fluctuations were a significant risk factor for progression to dementia, with a large effect of non-significance for death. The presence of visual hallucinations meanwhile was significantly associated with increased hazard of death, though with wide confidence intervals reflecting the lower numbers, and a large but non-significant effect on risks of transition to dementia.

Table 9.6. Multi-state models for transitions from MCI to dementia or death in combined LewyPro-SUPErB cohort.

Baseline Transition Probabilities[a]	***Covariates***[b]		
Model 1. Overall Feature Count	**Age**		**Lewy Body Characteristics (0-6)**
to MCI	**0.89** [0.82 - 0.93]		
to Dementia	**0.10** [0.06 - 0.17]	**1.05** [1.00, 1.10]	**1.33** [1.11, 1.60]
to Death	**0.01** [0.001 - 0.04]	**1.24** [1.08, 1.42]	**1.39** [0.90, 2.14]
Model 2. Specific Characteristics	**Age**[c]	**Visual Hallucinations**	**Cognitive Fluctuations**
to MCI	**0.91** [0.85 - 0.95]		
to Dementia	**0.08** [0.05 - 0.14]	**1.06** [1.01, 1.11]	**1.98** [0.92, 4.29]	**3.99** [2.03, 7.84]
to Death	**0.01** [0.001 - 0.03]	**1.25** [1.09, 1.44]	**7.30** [1.53, 34.97]	**2.29** [0.49, 10.82]

[a]**Transition Probability for One Year** [95% Confidence Interval]

[b]**Hazard Ratio** [95% Confidence Interval]

[c]Mean-centred, hazard per year

9.4.3 Discussion

While conceptually comparable to the results from the respective separate cohorts (**Chapters 6 & 8**), these findings provide more precise estimates of the clinical and statistical significance of the associations between diagnostic characteristics of DLB in an MCI syndrome, and risks of converting to dementia while accounting for death as a competing risk. Even in the combined dataset however, death rates were low overall (n = 6); caution will be required when interpreting the large size of some effects given the low confidence in estimates of hazards for death.

These results arguably provide the strongest evidence within this work that an MCI with core clinical diagnostic features or indicative biomarkers of DLB (i.e. MCI-LB) has a poorer prognosis than MCI-AD, that the presence of more features or biomarkers is associated with worse prognosis, and that specific features differ in their associated risk. Specifically, features reflecting altered consciousness and perception (cognitive fluctuations, and complex visual hallucinations) are associated with a worse prognosis. These results are consistent with recent research which has suggested that more clinically complex cases of DLB, in particular those featuring fluctuating cognition, are associated with greater healthcare reliance and therefore economic burden (Espinosa *et al.*, 2020). While all findings naturally require further independent replication, the association between visual hallucinations and prognosis may require further exploration; while the effect of the association is fairly large in both dementia and death transitions, the confidence intervals are wide in both, and statistically non-significant in the former.

9.5 Chapter summary

In addition to its use in validating models developed from the LewyPro cohort, the SUPErB study included a number of additional supplementary cognitive assessments. Consistent with findings from DLB, MCI-LB was associated with an increased incidence of false-positive errors on the pareidolia task relative to MCI-AD and controls. Additional analysis was also undertaken with both cohorts combined, to provide comprehensive estimates of effects from the primary development and validation models with the full sample. Overall, MCI-LB featured a distinct declining visuospatial profile relative to MCI-AD and controls, while MCI-AD featured worse

amnestic memory impairment. MCI-LB also transitioned to dementia faster than MCI-AD, with a notably worse prognosis in those with more clinically apparent LB disease, and specifically in those experiencing cognitive fluctuations, or visual hallucinations. However, latent classes of cognitive progression were not as clearly distinguished in this combined cohort as in the LewyPro study alone, which may be due to the limited follow-up undertaken in the SUPErB cohort to date.

Chapter 10. Discussion

10.1 Summary of research question

The motivation of this research was to test the hypothesis that the cognitive prodromes of the two most common neurodegenerative dementias, DLB and AD, would feature different cognitive patterns, progressions, and prognosis. This research question was informed by the current understanding of the clinical and cognitive manifestations of dementia in the typical syndromes of DLB and AD, and comparable work from cross-sectional and retrospective MCI cohorts with differential neurodegenerative diagnoses.

10.2 Broad group differences in cognitive pattern and progression

It was hypothesised that the profile of cognitive decline in MCI-LB would manifest as an early reflection of the cognitive profile found in DLB, which in comparison to AD is typified by less memory impairment, and greater visuospatial, attention, and executive dysfunction. These were assessed by analysis of baseline group differences and longitudinal changes with linear mixed effects models (**Chapters 4, 8, and 9**).

10.2.1 Attention and executive functions

Background

Attention and executive dysfunctions are typically greater in DLB than AD (Metzler-Baddeley, 2007), being qualitatively characterised by more distractibility, intrusions and confabulation (Doubleday *et al.*, 2002), featuring poorer performance on Stroop, verbal fluency, and selective attention tasks (Calderon *et al.*, 2001), and slower reaction times in simple and two-choice response tasks (Ballard *et al.*, 2001b). It was therefore hypothesised that MCI-LB would feature a comparable, but milder, pattern of performance to DLB, with greater attention and executive dysfunction than in MCI-AD.

Summary of findings

While two tests of verbal fluency (ACE-R subscale and FAS fluency task) indicated poorer performance in MCI-LB than MCI-AD (**Chapter 4**), this was not consistently significant across

cohorts, or between MCI-LB groups (**Chapters 8 and 9**). With groups otherwise comparable in language abilities, differences in verbal fluency performance may be taken to reflect greater executive dysfunction, lending some tentative support to the hypothesis that these dysfunctions would be greater in MCI-LB than MCI-AD. While somewhat poorer in MCI-LB, impairments in this domain were not specific to this group as the MCI-AD group also featured poorer fluency than controls. Verbal fluency declined over time in MCI, but group trajectories did not clearly diverge nor converge, suggesting that these differences were not emerging over the course of MCI, but rather had already emerged earlier in the prodromal or preclinical stages; though, an alternate explanation is that any continuing separation was simply so small or inconsistent as to be undetectable over this time-course.

However, MCI-LB and MCI-AD did not appear to differ in their performance on a range of other tests of attention and executive functions, including simple and choice reaction times, or TMT-A and –B completion speeds; both of which have previously been sensitive to differences between DLB and AD (Ballard *et al.*, 2001b; Ferman *et al.*, 2006). Attention and executive functions being broad and multi-faceted domains, this inconsistency may reflect a different staging of deterioration in particular tests of attention and executive functions; some functions may deteriorate earlier and others later, or particular neuropsychological tests may have varying sensitivity to decline at different stages. This would not necessarily be inconsistent with the past literature; for instance, Breitve *et al.* (2018) identified that TMT-A completion speed declines faster in DLB than AD, suggesting that performance differences in this particular test may still be emerging later into the dementia stage than over the course of MCI. Both TMT measures (but particularly TMT-B) are complicated by completion failure being common, while the cause of these may not be comparable between individuals.

Due to the complexity and diversity inherent to these particular cognitive functions including inhibitory control, mental flexibility, abstract reasoning, a wider range of neuropsychological tests may be required to assess any impairments, which may differ between individuals, or a battery of tests similar to the Frontal Assessment Battery, which encompasses a number of relevant functions (Dubois *et al.*, 2000), though this specific battery may not be appropriate in

DLB, given the motor component, or in MCI, being intended for identifying a frontotemporal dementia.

Discussion

The attentional and executive system appears to be widely distributed both anatomically and functionally (Petersen and Posner, 2012), and there are a number of neurochemical systems which may contribute to normal attention and executive function, or dysfunction (Thiele and Bellgrove, 2018). One possible explanation for the greater observed impairments in DLB is the particular association of LB disease with dysfunction of the cholinergic basal forebrain (Perry *et al.*, 1995), which innervates, amongst others, areas of the frontal lobes and thalamus (Perry *et al.*, 1999), which may contribute to normal executive and attentional functions (van der Werf *et al.*, 2003). There is considerable evidence supporting the role of the cholinergic system in normal attentional functions (Thiele and Bellgrove, 2018). Attentional dysfunctions could therefore share a neural substrate with the fluctuating cognition characteristic of DLB; attention is the cognitive domain most typified by fluctuations in performance (Ballard *et al.*, 2001b), and cognitive fluctuations have been previously related to cholinergic dysfunction observed at autopsy (Ballard *et al.*, 2002), consistent with the role of the cholinergic system in modulation of wakeful brain states (Harris and Thiele, 2011).

However, the cholinergic system does not contribute to attention and executive functions in isolation; dopaminergic function plays an important role in normal attention and executive functions independently and in interaction with cholinergic functions (Robbins and Arnsten, 2009). In PD it has been hypothesised that at least some aspects of attentional and executive dysfunctions may be reflective of dopaminergic fronto-striatal dysfunctions (Dirnberger and Jahanshahi, 2013), though there may also be overlap with cholinergic dysfunctions (Kehagia *et al.*, 2013). Given that dopaminergic dysfunctions are typical to both DLB and PD, as evidenced by the commonly abnormal striatal dopamine uptake in DLB (O'Brien *et al.*, 2004) and MCI-LB (Thomas *et al.*, 2019), dopaminergic dysfunctions may also be a possible contributing factor to attention and executive dysfunctions in MCI-LB. There may naturally be further heterogeneity in this domain even within a given clinical syndrome; some individuals may have a more prominent cholinergic deficiency, while others may have a greater dopaminergic deficiency, with both

resulting in either qualitatively similar, or possibly differing presentations of attention and executive dysfunctions (e.g. impairments on different cognitive tests), requiring exploration.

Summary of attention and executive functions

While verbal fluency may be more impaired in MCI-LB than MCI-AD, as in the respective dementia syndromes, this difference is inconsistent between cohorts, and does not clearly extend to other assessments of attention or executive dysfunctions included. More suitable and in-depth tests may be required, given the variety inherent to executive and attentional functions, or any differences may be obscured by heterogeneity within MCI groups; this may be explored by considering the neuropsychological profiles present within each disease-characterised diagnostic group, as by Ferman *et al.* (2013). This could provide a clearer description of whether attention or executive dysfunctions are more common in MCI-LB than MCI-AD, and whether these differ in pattern (i.e. as a single-domain impairment, or within a multi-domain profile of cognitive impairment).

10.2.2 Episodic memory

Background

The typical pattern of cognitive impairment in AD is characterised by amnestic episodic memory impairment; while this may also occur in DLB, it is typically less severe. The presence of episodic memory dysfunction may reflect the effects of AD-related hippocampal atrophy within a mixed AD-DLB phenotype. Based on cognitive profile, an amnestic MCI syndrome is more likely to transition to an AD-type dementia while a non-amnestic syndrome more typically transitions to DLB (Ferman *et al.*, 2013), while retrospective analyses with clinical differential diagnosis have identified that memory dysfunction and decline may typically also be poorer in MCI-AD than MCI-LB (van de Beek *et al.*, 2020). It was therefore hypothesised that episodic memory functions would typically be less impaired cross-sectionally and longitudinally in prospectively identified MCI-LB than in MCI-AD.

Summary of findings

While broad memory functions as assessed with the ACE-R did not differ between MCI-LB and MCI-AD, in recognition memory specifically MCI-AD presented with more impairment in the

LewyPro cohort (**Chapter 4**), though this was not validated subsequently (**Chapter 8**). The RAVLT, anticipated to be more sensitive to memory dysfunction in the MCI stages than dementia screening scales, did not identify any baseline differences between groups in a simple analysis for LewyPro, and lacked sufficient repeated observations to develop a longitudinal model (**Chapter 4**), but after incorporating results from both cohorts (**Chapter 9**) a more complete model could be formed, demonstrating that MCI-AD does feature a poorer retention of words after delay in the RAVLT, as a percentage of best performance from the learning trials (demonstrating that this is not a failure of attention, but rather a failure of retention; a phenomenon comparable to amnestic forgetfulness). These results are consistent with the amnestic memory impairments typically found in AD, and with these being less severe (Ferman *et al.*, 2006) though still often present (Barber *et al.*, 1999), in DLB.

The lack of clear memory decline in MCI may be due to the influence of practice effects in mildly impaired patients, which will naturally have a greater effect in memory domains, or insensitivity of tests utilised to performance differences within individuals, and between groups; such practice effects in memory tests have been identified previously in amnestic MCI patients, even to the point of improvement in scores (Campos-Magdaleno *et al.*, 2017). Controls were seen to have significant improvement over time in the ACE-R memory domain, supporting the possibility of practice effects. A greater variety of tests, specifically those not in use in clinical settings and therefore more resistant to practice effects, or composite scores of these (e.g. van de Beek *et al.*, 2020) may be required to adequately describe intra-individual change in memory performance should these differ between disease groups; however recent longitudinal study in a neuropathologically-assessed cohort did not identify any clear differences in rate of memory decline between DLB and AD (Smirnov *et al.*, 2020), so it remains possible that any trajectory differences may likewise not be present in MCI.

Discussion

Amnestic memory impairment is a common cognitive feature of AD, being present in many, but not all AD-related clinical syndromes, but also occurring in other neurodegenerative conditions. Memory impairments often occur in DLB (Hamilton *et al.*, 2004; Metzler-Baddeley, 2007), and may reflect concurrent AD-related MTL atrophy. These findings support previous observations

that the prodromal stage of AD features episodic memory impairment relative to controls (Wilson *et al.*, 2011), and extends these to demonstrate that these impairments are generally worse than in the prodromal stage of DLB.

Memory impairments in both groups may reflect early MTL atrophy, which has been theorised to emerge prior to any clinical symptoms in AD (Jack *et al.*, 2010), and with this typically being greater in AD than DLB (Burton *et al.*, 2008). MTL integrity is an important contributor in normal learning and memorisation, and so likely mediates the associations between neurodegeneration and amnestic memory dysfunctions. This naturally warrants direct exploration with MRI in a differentially diagnosed MCI cohort to establish whether specific patterns of atrophy on MRI in MCI-LB are associated with amnestic memory dysfunctions (and possibly therefore AD co-pathology) with a sufficiently sensitive and specific cognitive assessment.

Assessing memory impairment in a quantitative manner may be complicated by the nature of this particular cognitive process: accurate recall of information in a memory test requires allocation of attention to the information, sufficient working memory capacity to incorporate the number of items to be memorised, appropriate encoding of information to long-term memory, and subsequent retrieval with or without cues. This provides numerous potential points of failure in a cognitive impairment syndrome, any of which may result in failed recall of information, but with only failures in the latter two representing episodic memory failures as typically described (e.g. amnestic complaints in AD), reflecting the key role of the MTL structure and activity in memory encoding (Kopelman *et al.*, 1998), recall (Tanaka *et al.*, 2014) and recognition (Bird, 2017). Complicating assessment, failure in the earlier steps will present as apparent memory dysfunction, which could account for inconsistencies between tests. Verbal learning tests such as the RAVLT may therefore more specifically assess episodic memory impairments, with the repeated learning trials limiting the influence of working memory capacity and attention on performance, explaining why this test may identify group differences that the more brief ACE-R sub-test does not reliably find (**Chapter 9**). In longitudinal research cohorts, the utility of the RAVLT may be limited by its length and difficulty being a barrier to some patients; shorter verbal learning tests such as the Hopkins verbal learning test (Benedict *et al.*, 1998) may be more agreeable to patients while incurring a smaller time burden.

In addition to verbal-oriented episodic memory assessments, tests may assess long-term memorisation of visuospatial information, such as in delayed recall of complex figures. Such tests have found comparable levels of performance in AD and DLB previously (Collerton *et al.*, 2003), suggesting that the primary visuospatial impairments may carry over into poorer visually-oriented memory performance. Selection of suitable episodic memory assessments should therefore consider the intended use: while visual episodic memory tests may be more sensitive in screening for cognitive impairments in DLB, they may not assess pure episodic memory impairments as specifically as a verbal learning test, since verbal skills are less typically impaired in DLB and AD.

Summary of episodic memory functions

While there is inconsistency between assessments, possibly due to the complexity of the underlying cognitive process, MCI-AD may feature worse episodic memory impairment than MCI-LB in keeping with their respective dementia syndromes, though the latter are not wholly unimpaired. Memory dysfunction in both syndromes may be presumed to reflect early MTL atrophy, though this remains unexplored at this stage.

10.2.3 Visuospatial

Background

DLB typically features greater impairment of simple visual perception and complex construction skills than AD; this manifests in less automatic 'pop-out' of visual features prior to the direction of visual attention (Cormack *et al.*, 2004), worse discrimination of visual features such as size, orientation, angles, form and motion (Mosimann *et al.*, 2004; Wood *et al.*, 2013a), and worse complex task performance such as copying of pictorial stimuli including clocks, cubes, and overlapping figures (Collerton *et al.*, 2003; Noe *et al.*, 2004). These findings suggest that patterns of LB pathology contribute to greater dysfunction in both simple visuo-perceptual tasks, and complex visuoconstruction tasks, than is typically found in AD; though while direct comparisons are rare, an AD phenotype manifesting in a PCA syndrome may be the natural exception to this (Metzler-Baddeley *et al.*, 2010).

People with DLB have also been shown to be more prone to making pareidolic misidentifications in response to ambiguous visual stimuli, for instance mistakenly perceiving human faces within visual noise; this has been interpreted as an example of a hallucination-like phenomenon (Mamiya *et al.*, 2016), though the precise aetiology remains unclear, and could be attributed to more general cognitive processes such as attention and executive dysfunctions.

Summary of findings

In this work, it was found that simple visuo-perception, assessed by a line angle discrimination task, was more impaired in probable MCI-LB than MCI-AD in the LewyPro cohort (**Chapter 4 and 9**); the effects were mild, with an effect size comparable to the gender differences observed in the same task. There was no apparent decline over time in any MCI group in visual perception; this could suggest an insensitivity of this test to change over the course of MCI, or a lack of sufficient repeated observations to estimate a meaningful time effect. The same model run with the SUPErB cohort alone failed to support these findings however (**Chapter 8**); while MCI-LB groups had poorer estimated discrimination sensitivity than MCI-AD, as in LewyPro, the size of the effect was less than that of the LewyPro group. The MCI-AD group appeared to have poorer performance on this task in SUPErB than the comparable group in LewyPro, and occupied the middle ground between controls and MCI-LB. In the combined analysis (**Chapter 9**), results were consistent with the LewyPro cohort in identifying worse visuo-perception in probable MCI-LB than MCI-AD, and also suggested that MCI-AD performed slightly worse than controls.

Two baseline-only assessments of visuospatial working memory were administered to the SUPErB cohort (**Chapter 8**); a touchscreen variant of the Corsi block-tapping task, and a computerised visual patterns test (VPT). While identifying poorer performance in MCI groups than healthy controls, these tasks did not capture any clear quantitative performance differences between MCI groups.

MCI-AD did not appear to feature a clear impairment or progressive deterioration in more complex visuoconstructional skills (i.e. figure copying) relative to healthy controls, but these were observed to decline over time in probable MCI-LB, with this being consistent across the cohorts (**Chapters 4, 8, and 9**).

Finally, MCI-LB was associated with an increased rate of false positive 'pareidolia' responses in the Pareidolia task (i.e. reporting the presence of human faces in visual noise stimuli when none were present) than MCI-AD, who did not differ from controls (**Chapter 9**), suggesting that respective findings from the dementia stages are already apparent at the milder stages.

Discussion

The visual domain showed a clearer separation between diagnostic groups than other cognitive domains. MCI-AD did not feature any clear dysfunction relative to controls in visuoconstructional tasks, nor progressive decline in these, while MCI-LB had poorer performance, and progressively declined in performance in these tasks. MCI-AD had similarly low rates of pareidolic misidentifications to healthy controls, while these had a higher incidence in MCI-LB. While MCI-AD had some impairment in visuo-perceptual discrimination, this was much more impaired in MCI-LB. These results are consistent with findings from DLB, and suggest that visuospatial impairments, and progressive decline in these, may be more typical in MCI-LB than in MCI-AD.

These results contextualise how the visuospatial deficits evident from the early stages of DLB (Hamilton *et al.*, 2012) might manifest over the course of MCI-LB, and are consistent with recent findings that DLB and PDD both feature a greater initial impairment and faster decline in visuospatial functions than in dementia due to AD (Smirnov *et al.*, 2020). Early deficits in lower-order perceptual cognitive functions (with LAT performance as only one possible example of these) may be evident at the early stages of MCI-LB (Donaghy *et al.*, 2018), but this does not appear to progressively decline further over the course of MCI (**Chapter 4**) or dementia (Wood *et al.*, 2013b), despite a pattern of decline being observed in more complex construction tasks in MCI-LB (**Chapter 4**) and DLB (Smirnov *et al.*, 2020). A possible explanation for this disparity is that performance in constructional tasks is multifaceted, requiring the integration of multiple forms of visual and spatial perceptual information (Possin *et al.*, 2011); dysfunction of, for example, line angle judgement alone may not be sufficient to cause clear dysfunction in complex tasks at the early stages. Deterioration in these constructional tasks may therefore reflect progressive loss of a greater range of the individual functions which comprise of visuospatial

functioning (e.g. orientation, shape, size, distance) which may not be reflected in longitudinal assessment of a single sub-domain such as the LAT (Wood *et al.*, 2013a). Additionally, complex functions may benefit more from remaining cognitive reserve in early MCI, e.g. using heuristics and semantic knowledge to help approximate the copying of a cube even in the absence of a consistent visual representation for the stimulus, thereby compensating for simple loss of visual perception. Such compensations could break down as MCI develops, manifesting in deterioration in more complex tasks over the course of MCI.

There was inconsistency between some tasks; MCI groups in general had impaired visual working memory, with no clear group differences (assessed at baseline only). Visual working memory capacity may therefore not be affected to a greater extent than MCI-AD in the early stages of MCI-LB; application of respective assessments as repeated measures could establish whether visual working memory performance diverges over time. An alternative explanation is that the tasks themselves and method of assessment incurred an additional barrier in these measures. While drawing from intact lower-level domain-specific resources (visual imagery or speech rehearsal), working memory functions are complex and closely entwined with domain-general executive functions and supportive coding from other modalities even in the prominent multi-component model (Chai *et al.*, 2018). This introduces additional potential points of failure (e.g. in those with executive dysfunctions) as well as potential mechanisms for compensation in those who can make effective use of multimodal strategies (Brown and Wesley, 2013), potentially obscuring domain-specific cognitive differences when task failures may represent different processes in different individuals.

Additionally, in contrast to other computerised tasks which required only a left or right response with handheld buttons (e.g. the LAT), these tasks required use of a mouse or touchscreen. While previous research suggested that there was minimal additional task demand in touchscreen block-tapping tasks compared with the traditional manual variant (Robinson and Brewer, 2016), this was based in a much younger sample (all aged < 50 years), which may be more familiar with touchscreen technology and therefore not comparable to either the cognitively impaired or healthy older adult groups in this work (all aged ≥ 60 years). These tasks could therefore be limited by the additional difficulty incurred by unfamiliar technology in cognitively impaired

groups, which could introduce additional measurement error and obscure any differences, should they exist.

While they did not clearly worsen over time, pareidolic misidentifications were more common in MCI-LB than MCI-AD and controls. However, these arguably represent a unique form of visual perceptual anomaly, which may arise through an interaction between uncertainty in visual input (experimentally induced with visual noise, but could reflect cognitive visual dysfunction in real-world settings) and an increased weighting towards prior expectations rather than bottom-up sensory perception; this reliance on prior knowledge is typically greater in cases of DLB with visual hallucinations (Zarkali *et al.*, 2019) and may be experimentally or emotionally induced (Watanabe *et al.*, 2018). Given the absence of either visual ambiguity or this shift to prior knowledge, pareidolias may not occur as consistently. Therefore, while pareidolia tasks may be a useful method of assessing and understanding visual hallucinations in DLB and PD, they may not be as sensitive in assessing visuospatial dysfunctions due to the moderating role of prior expectations in pareidolia production.

Adequate detection of early visuospatial deficits in MCI may be particularly important given their role as a risk factor in dementia. In addition to increasing risk of falls in AD and DLB (Kudo *et al.*, 2009) and nursing home admission in PD (Aarsland *et al.*, 2000), visuospatial dysfunctions in DLB are also associated with faster cognitive decline (Hamilton *et al.*, 2008); visuospatial cognitive impairments may therefore reflect a more aggressive underlying aetiology, in addition to being a particular risk factor in themselves. DLB has been previously associated with a greater degree of dysfunction in the occipital lobes, including hypometabolism (Imamura *et al.*, 1999) and hypoperfusion (Ishii *et al.*, 1999; Lobotesis *et al.*, 2001); while the occipital lobes are generally spared from the formation of cortical Lewy bodies (Gomez-Tortosa *et al.*, 1999; Harding *et al.*, 2002; Khundakar *et al.*, 2016), DLB features more severe occipital white matter spongiform changes and gliosis than AD, comparable to those found in CJD (Higuchi *et al.*, 2000), which has been theorised to be a pathological substrate of occipital dysfunction in DLB. Cognitive visual decline in DLB could therefore arise from physiological dysfunction of the primary visual- and visual association cortices of the occipital lobes.

However, complex cognitive functions (rather than perception alone) may rarely be isolated to specific cortical regions or lobes, and typically rely on widely distributed cortical networks for normal functioning. Other aspects of the pathology of DLB which could account for the typically greater presence of visuospatial dysfunction include the distinct cholinergic deficit typical of DLB which may underlie the presence of complex visual hallucinations (Perry *et al.*, 1999), while changes to the sub-cortical visual system in DLB could also contribute to visual dysfunctions, due to impaired regulatory functions of the pulvinar and superior colliculus (Erskine *et al.*, 2019).

While the pathology underlying this association remains uncertain, and could be heterogeneous, there remains a clear association between cognitive dysfunction in the visual domain, the clinical syndrome of DLB including its cognitive prodrome, and a more aggressive pathology.

Summary of visuospatial functions

The visuospatial domain shows the clearest separation between diagnostic groups, with those with MCI-AD often performing comparably to healthy controls across the course of MCI, while those with MCI-LB have poorer simple visual perception at the early stages, with progressive decline in more complex visual tasks over time, and higher rates of pareidolic misperceptions.

10.2.4 Speech and language

Background

AD and DLB are not characteristically associated with significant speech and language dysfunction; nor do they typically differ in their level of speech and language impairments, or semantic knowledge (Collerton *et al.*, 2003). The exception to this being particular atypical syndromes such as primary progressive aphasias which are clinically characterised by prominent speech and language dysfunction (Gorno-Tempini *et al.*, 2011). These may occur in AD, but may also rarely arise in apparent Lewy body disease (Caselli *et al.*, 2002; Teichmann *et al.*, 2013; Watanabe *et al.*, 2020); in both diseases though, aphasic syndromes are uncommon.

One aspect of speech and language production which may be variably affected in DLB and AD is auditory working memory, which may contribute to language comprehension and speech

preparation through the ‘phonological loop’ working memory component (Baddeley *et al.*, 1991). Retention and reproduction of verbal items may be impaired in both DLB and AD, though there is little evidence that this impairment is greater in DLB (Collerton *et al.*, 2003).

Summary of findings

Consistent with the past literature from their dementia stages, no differences were found in baseline function or longitudinal decline in vocabulary or semantic knowledge between MCI-AD or MCI-LB in this work, based on comparison of the GNT, ACE-R language domain score, and NART. This supports the utility of vocabulary tests such as the NART (Nelson and O'Connell, 1978; O'Carroll *et al.*, 1987) as estimates of premorbid functioning in prodromal DLB as in AD. General language skills were observed to decline over the course of MCI in the language domain score of the ACE-R (**Chapters 4 and 9**).

MCI groups had poorer semantic memory than controls, though not differing from each other, with poorer naming performance in the GNT (**Chapter 8**). However, auditory working memory was not meaningfully impaired in any MCI group relative to controls (**Chapter 9**), though backwards digit span performance was slightly poorer, reflecting only slight impairment. Neither showed clear deterioration over time to date.

Discussion

These results are conceptually consistent with the expected lack of difference in speech and language functions between prodromal AD and DLB syndromes, though there may be some early divergence from healthy controls. Given the observed slight deterioration in language skills, tests of premorbid function may provide better estimates at earlier stages of the neurodegenerative process than later, though these declines could be attributed to global cognitive deterioration.

Prominent speech dysfunctions are more generally associated with particular frontotemporal patterns of neurodegeneration affecting the widely-distributed language networks, resulting in an atypical aphasic-type syndrome, which may have widely varying presentations (Vinceti *et al.*, 2019); regions affected by structural or functional neurodegeneration may include the left-posterior perisylvian cortex and parietal lobe in logopenic variant PPA, the left-posterior fronto-

insular cortex in nonfluent or agrammatic PPA, or the anterior temporal lobe in semantic variant PPA (Gorno-Tempini *et al.*, 2011). While these patterns may arise in AD or DLB, they are clearly far from typical and may not be represented in a sample of this size.

Summary of speech and language functions

Some speech and language functions were mildly poorer in MCI than healthy controls, with slight deterioration over time of broadly-assessed language skills. The MCI diagnostic groups did not differ in their typical level of language impairment, however. Mild speech and language impairments may be a primary dysfunction in themselves, or may be secondary to dysfunction in other domains, or in domain-general global cognition.

10.2.5 Neuropsychological performance in MCI-AD and MCI-LB: a summary

The domain-specific patterns of cognitive decline in MCI-AD and MCI-LB were consistent with these being mild presentations of the cognitive patterns of their typical respective dementia syndromes. Relative to healthy ageing, memory, executive, and mild language dysfunctions were typical in both MCI types, but varied in their magnitude with greater episodic memory impairments in MCI-AD, and possibly greater executive dysfunction in MCI-LB. Visuospatial dysfunctions presented a clearer separation with MCI-AD being typically comparable to healthy controls in cross-sectional and longitudinal performance, while MCI-LB showed impairment in multiple aspects of visuospatial function, and further progressive decline.

These differences may reflect the differing pathologies responsible for cognitive decline in the two groups; hippocampal atrophy may be more typical in MCI-AD, while a central cholinergic dysfunction, posterior hypometabolism, and fronto-striatal dopaminergic dysfunctions may be more characteristic of MCI-LB, with these contributing to their respective cognitive impairment patterns. The associations between these specific pathological patterns individually and in combination, or biomarkers for these, could provide further evidence in support of this and help to disentangle any heterogeneity within disease groups.

10.3 Heterogeneity in mild cognitive impairment

MCI is known to have a variable prognosis; while some cases progress cognitively and clinically to dementia, others remain stable or revert to apparent cognitive health. These associations were explored with approaches characterising latent trajectories of cognitive decline, and the clinical progressions of MCI to dementia, in **Chapters 5, 6, 8 and 9**.

10.3.1 Prognosis of progressive cognitive and clinical decline in MCI

Background

The *clinical* prognosis of MCI-AD has been reasonably well examined through both retrospective and prospective study, albeit with considerable variation in findings due to differing recruitment settings, diagnostic criteria, and lengths of follow-up. Observed percentages of MCI cases which transition to dementia over a 5-10 year period range from lows of 24-30% (Mitchell and Shiri-Feshki, 2009; Xue *et al.*, 2017) to highs of over 60% (Prichep *et al.*, 2006; Pagani *et al.*, 2010; Mauri *et al.*, 2012). Regardless of the 'true' figure, there is therefore a considerable amount of variability in the clinical prognosis of MCI, which remains largely unexplained and may be a source of uncertainty for people receiving a diagnosis of MCI with an indeterminate prognosis.

In assessing the *cognitive* prognosis of AD, heterogeneous trajectories have been identified in the lead-up to (Verlinden *et al.*, 2016), and after diagnosis of dementia (Leoutsakos *et al.*, 2015). However, such studies may not adequately describe the phenomenon of apparently stable MCI which are not observed to ever reach dementia, inconsistent with the presumed neurodegenerative disease underlying this syndrome; as highlighted previously, in some settings the majority of MCI cases do not clearly decline, which may reflect fundamental differences in how MCI is conceptualised (as the prodromal stage of dementia with a presumed neurodegenerative cause, or as an objective description of individual functioning without necessary presumption of underlying disease).

As an emerging concept at the time of this work, with only recently-published guidelines on its diagnosis in research settings (McKeith *et al.*, 2020), there was little in the way of evidence for the expected typical, and atypical, prognosis (either clinical or cognitive) of a prospective

diagnosis of MCI-LB, which this work aimed to address. In dementia, DLB and AD have been found to feature different prognoses, with the former having a shorter time to death (Mueller *et al.*, 2019), increased hospitalisation (Mueller *et al.*, 2018) and healthcare costs (Espinosa *et al.*, 2020), and greater dependence with less ability to live well for patients and carers (Wu *et al.*, 2018a). Prior to this work, it was unclear as to whether this poorer prognosis would already be evident in the MCI stage of DLB. Based on current understanding of the respective dementia stages, it was hypothesised that MCI-LB would have a poorer prognosis than MCI-AD, with a greater risk over time of cognitive decline and clinical transition to dementia.

An additional interest was in the varying prognosis within MCI-LB. The prodromal and manifest stages of LB disease are heterogeneous; some cases may present initially and for extended periods with isolated RBD or PD without apparent cognitive symptoms (Claassen *et al.*, 2010), while others may present with early cognitive or psychiatric symptoms leading to DLB (McKeith *et al.*, 2016; McKeith *et al.*, 2020). It was theorised that cases of MCI featuring core neuropsychiatric symptoms of DLB alongside cognitive impairment (complex visual hallucinations and cognitive fluctuations) would represent a more unstable clinical phenotype with greater risk of decline; either in global cognition, or in clinical transition to dementia. While RBD and parkinsonian signs may warn of long-term decline in previously healthy individuals, being symptomatic of a synucleinopathy in general, these were not anticipated to be associated with greater risks of decline over the short term in people already suspected to have a neurodegenerative disease (i.e. conferring no greater risk of progression than in AD).

Summary of findings

Three MCI sub-groups with distinct cognitive prognoses were identified in the LewyPro cohort after a mean of 2.4 years of follow-up; MCI with slow or stable cognitive progression (46% of cohort), MCI with intermediate cognitive decline comparable to the overall group mean (41%) and a small group (13%) of rapid-declining MCI cases; 54% of MCI cases therefore developed with a measurable cognitive decline over this brief time period (**Chapter 5**). Correspondingly, 42% of MCI cases transitioned to dementia over a similar period, with 58% remaining as MCI (**Chapter 6**). While these numbers are still emerging and derived from a shorter time period than past studies, with follow-up still ongoing, this does already identify a higher rate of cognitive

decline and clinical progression than found in some previous studies (Mitchell and Shiri-Feshki, 2009; Xue *et al.*, 2017), which may reflect the recruitment methods, detailed assessment, expert clinical panel review undertaken, and high proportion of LB disease in these cohorts.

In the SUPErB cohort, the slow or stable sub-group was populated mostly by healthy controls, but also included a number of apparent MCI cases, with 45% of MCI cases with at least two observations maintaining a control-like profile of cognitive progression (**Chapter 8**); while longer follow-up is clearly needed for this cohort, some of these could represent non-degenerative cases of MCI.

Crucially, differentially diagnosed MCI subtypes demonstrated markedly different clinical and cognitive prognoses: a probable MCI-LB diagnosis was associated with an increased risk of following an intermediate cognitive decline trajectory in comparison with MCI-AD and possible MCI-LB, which were more likely to remain cognitively stable (**Chapter 5**). Accordingly, an increasingly DLB-like clinical profile in MCI was also associated with an increased annual risk of clinical transition to either dementia or death (**Chapters 6, 8 & 9**), though death rates were low overall. Taken together, these results support the hypothesis that as the cognitive prodrome of DLB, MCI-LB may feature a poorer prognosis than MCI-AD with a greater risk of progressive cognitive decline, and greater annual risk of onset of dementia.

However, there was some inconsistency whereby probable MCI-LB diagnoses were underrepresented in the small rapidly-declining group (**Chapter 6**), despite over-representation in the intermediate declining class. Our data do not explain why some individuals decline faster; this could represent an artefact of the small size of this group, amounting to a sample of only ten, these could be cases of AD with particularly widespread neurodegeneration, or as discussed in the relevant section, this could reflect the non-emergence of diagnostic characteristics for DLB in cases who decline too quickly.

Specific core clinical features of DLB were associated with different prognoses: cases of MCI featuring complex visual hallucinations had a greater risk of cognitive and clinical decline (**Chapters 5 and 6**) in the LewyPro cohort, though these findings were not validated in the data

from the SUPErB study to date (**Chapter 8**). Those with MCI featuring fluctuating cognition and attention characteristic of DLB also had an increased annual hazard of dementia (**Chapter 6)**, a finding that was validated in the SUPErB study cohort (**Chapter 8**) and the combined cohort (**Chapter 9**), but did not feature a greater risk of measurable cognitive decline (**Chapters 5 & 8**) though there was a non-significant effect in this direction in the combined cohort (**Chapter 9**).

These findings suggest that within MCI-LB, a phenotype including neuropsychiatric core clinical features may be an early sign of a clinically or cognitively progressive syndrome. This is a novel finding, but in keeping with previously observed associations between neuropsychiatric symptoms and a poorer prognosis in AD, with increased risk of dementia from amnestic MCI (Mauri *et al.*, 2012) and greater cognitive decline after onset of dementia (D'Antonio *et al.*, 2019); hallucinations in AD are also associated with worse prognosis (Scarmeas *et al.*, 2005a), a finding that holds after exclusion of pathologically-confirmed DLB cases.

Discussion

The associations between DLB features in MCI and a poorer prognosis is consistent with the worse prognosis observed in DLB in comparison to AD (Mueller *et al.*, 2018; Mueller *et al.*, 2019), suggesting that this may already be apparent at the MCI stage.

The inconsistency in associations between fluctuating cognition and risks of progressing to dementia, but not with progressive cognitive decline, could suggest that the intra-individual cognitive variability in fluctuating patients may obscure any progressive linear decline in tests of global cognition; for example, if a baseline cognitive assessment takes place on a particularly low-functioning day for a patient who experiences fluctuations, while subsequent follow-up measures occur when the patient is relatively more lucid, this may underestimate their typical initial daily function, and any subsequent decline may not be evident due to the biased baseline measure. This disparity demonstrates the value in including conversion to dementia as a distinct outcome in longitudinal studies; cognitive assessments are limited in their ability to describe the real everyday cognitive difficulties encountered by individuals, who may be capable of sustaining brief periods of better-than-usual cognitive performance when faced with intense testing. Clinical progression to dementia does not reflect cognitive decline alone, but rather loss of independent

function due to multiple factors leading to an increased dependency on family and caregivers for everyday functioning, which may better reflect their true daily function (though with a loss of objectivity). This outcome may have greater clinical relevance, though lacks the ability to characterise progressive decline within an MCI syndrome with the granularity afforded by cognitive measures, and requires considerable clinical expertise to judge appropriately which may not be feasible in larger-scale studies; both types of outcome arguably have a part to play in understanding the prognosis of MCI.

The associations between LB disease and a poorer prognosis in MCI and dementia may reflect the particular combination of neuropathological processes found across the spectrum of LB disease; within this, the presence of visual hallucinations or cognitive fluctuations may also be symptomatic of a more aggressive clinical phenotype within DLB and MCI-LB. Though the pathological effects of LB disease are multifaceted, including dopaminergic denervation (Thomas *et al.*, 2017) amongst other processes, the pronounced cholinergic deficit often found in DLB (Lemstra *et al.*, 2003) has also been identified as a potential contribution to both visual hallucinations and cognitive fluctuations (O'Brien *et al.*, 2005; Delli Pizzi *et al.*, 2015). The worse prognosis identified may therefore be an outcome of a greater cholinergic dysfunction in these cases, of which visual hallucinations and cognitive fluctuations may also be symptomatic. Quantitative EEG has identified a loss of cholinergic drive in DLB relative to AD and controls (Schumacher *et al.*, 2020b), and so may be a useful biomarker to assess this in MCI-LB (Schumacher *et al.*, 2020a). These findings naturally warrant further exploration to establish whether markers for cholinergic denervation (e.g. reduced alpha reactivity on EEG, or quantified MRI analysis of NBM integrity) are similarly predictive of faster dementia onset or cognitive decline in MCI across diagnostic groups and within MCI-LB specifically, in contrast to FP-CIT imaging abnormalities, which were not (see **Chapters 5, 6, 8 & 9**).

The presence of a rapid declining sub-group was consistent with previous research suggesting that 20% of AD cases may present with particularly rapid deterioration (Nance *et al.*, 2019); in the LewyPro study (**Chapter 5**), 17% of MCI-AD and possible MCI-LB patients had a relatively more rapid declining cognitive trajectory. However, probable MCI-LB patients were unexpectedly under-represented in this latent trajectory, which may be an artefact of the small

group size. With a sufficiently sized sample or neuropathological study, it may be possible to better describe such rapid decliners in more depth, if indeed this group is consistently identified.

After a longer period of follow-up, MCI patients who continue to follow a healthy-like stable cognitive trajectory may be considered as non-degenerative cases, which may include subjective or functional cognitive disorders. Non-degenerative MCI cases would likely not benefit from disease-modifying therapies intended to treat neurodegenerative diseases, and so better prospective identification of such cases may have implications for the management of these syndromes, and in efforts to treat neurodegenerative causes of cognitive impairment.

Summary of clinical and cognitive prognosis

A probable MCI-LB syndrome is more likely to develop with progressive cognitive decline than MCI-AD. People with MCI and core clinical features or indicative biomarkers for LB disease are at greater annual risk of developing dementia, and this risk increases when more features or biomarkers are present. Not all symptoms or biomarkers are associated with an equal level of risk however; RBD, parkinsonism, and abnormal FP-CIT or MIBG imaging are not associated with increased individual risks of either cognitive decline or clinical progression from MCI, while fluctuating cognition and visual hallucinations are.

10.4 General discussion and future directions

These two cohorts represent some of the earliest attempts to prospectively characterise MCI-LB, a syndrome only recently studied in research settings, and requiring further large-scale study in order to reach sufficient maturity to apply in clinical settings (McKeith *et al.*, 2020). Wider work is ongoing to characterise the clinical and imaging findings in these cohorts, which do not lie within the scope of this thesis, but there is consequently considerable scope for further refinement of the diagnostic criteria and clinical characterisation of MCI-LB in future research.

10.4.1 Strengths and implications of this work

The cohorts characterised in this work underwent detailed, repeated assessment with clinical review by an experienced panel in accordance with the current gold standard criteria for

antemortem diagnosis (McKeith *et al.*, 1998), ensuring accurate judgement of clinical symptomatology, signs, and cognitive impairment, with appropriate consideration for competing diagnoses including subjective impairments and frontotemporal aetiologies, which were cause for exclusion. These studies also offered a comprehensive battery of imaging to all eligible participants regardless of diagnosis, including FP-CIT in both, and MRI and MIBG in SUPErB. FP-CIT imaging was repeated, and assessed by an experienced, trained panel blind to clinical information, providing more certainty in the abnormalities reported. This rigorous assessment is a particular strength of these cohorts, lending a great deal of confidence in the clinical ratings, imaging findings, and consequent diagnoses. The prospective nature of follow-up is more readily applicable to real-world clinical settings, providing an accurate reflection of the clinical symptoms, features and biomarkers present during the MCI stage, rather than at the dementia stage as in comparable, but retrospective, studies (van de Beek *et al.*, 2020).

These findings may help guide future research into the diagnosis and management of prodromal DLB, which first and foremost will require a clear and consistent characterisation of the clinico-cognitive syndrome of MCI-LB, and its prognosis. As in DLB (Taylor *et al.*, 2020), MCI-LB may have specific management and treatment needs in comparison to MCI-AD. Caregivers have previously identified a need for clear information on what to expect following diagnosis of DLB, and how to manage these challenges (Killen *et al.*, 2016), and earlier diagnosis has been associated with better outcomes for carers of people with dementia (Woods *et al.*, 2019). Early identification of the likely presence of LB disease in MCI may help prepare patients and caregivers to proactively recognise and manage any emergent symptoms and signs, with the potential to reduce patient and caregiver distress, e.g. through the recognition of newly emergent hallucinations or sleep disturbances as expected outcomes of the same underlying disease process, and to bring these to the attention of clinicians for management. Appropriate recognition of the presence or emergence of DLB symptoms in MCI (particularly visual hallucinations or cognitive fluctuations, given their apparent risks) may also help prepare diagnosticians for the nearing onset of dementia, reducing the diagnostic latency with potential benefits for clinical practice.

Early diagnosis of cognitive impairment may raise the risk of overdiagnosis (e.g. diagnosis of neurodegenerative MCI which has other, non-degenerative, causes) and so diagnosis must be not only early, but specific to avoid introducing unnecessary burden. In addition to their value in differential diagnosis (e.g. from MCI-AD), identifying the presence of biomarkers or clinical features of LB disease in MCI may also provide more certainty that a neurodegenerative disease is present, rather than any cognitive impairment due to major depression, subjective impairment, or a functional disorder.

Additionally, the differences in cognitive profiles, and decline in these, may have implications for the screening for mild cognitive impairments in clinical settings; given the declining trajectory of visuoconstructional skills, executive dysfunction, and less severe amnestic memory impairments found in MCI-LB, common screening tests such as the MMSE may be insensitive to mild and progressive cognitive decline in the context of LB disease.

The varied analytical approaches were able to characterise the progression of a cognitive impairment syndrome in a comprehensive manner, and are a strength of this work; individual trajectories of decline were described with LMM by incorporating all observations into a subject-specific curve, which may include multiple and unequally-timed observations, therefore being a more efficient and flexible alternative to traditional approaches to repeated measures (e.g. change scores or repeated measures ANOVA). These methods are also reasonably robust in incorporating missing data.

By applying latent class methods to this longitudinal data, the clinically-recognised heterogeneity within MCI could be appropriately described in a research setting; such considerations are often missing in contemporary MCI and dementia research, which often treat groups as homogeneous. While limited by the number of observations available in some analyses, this method demonstrated clear utility in describing the LewyPro cohort and is a particular strength of this work.

Utilising MSM methods to describe clinical transitions from MCI provides a flexible framework from which this work may be developed in the future; while such transitions may be adequately

described with a simple survival analysis, MSM approaches may be readily extended to include time-varying covariates as well as competing risks (though these do not separately require this approach), but may also be developed in future studies to account for other observable transitions (e.g. from normal cognition to MCI, or even reversion to healthy cognition).

10.4.2 Limitations and future directions

These cohorts are representative of the population from which they were drawn, reflecting prodromal cases of DLB and AD assessed in memory service settings in North-East England, UK. Findings from this broad area may not be mirrored in other areas of the United Kingdom; recognition of DLB in clinical settings is higher in the North-East of England than in other areas of the country (Kane *et al.*, 2018), which may reflect the influence of DLB research in the North-East on local medical education and service practice. The clinical profile of cases within these cohorts may therefore not reflect the spectrum of ostensible MCI-LB cases as diagnosed in other areas of the country. The identifiability, and consequent utility, of specific clinical features or biomarkers may vary in different areas with more or less familiarity with DLB. There may, as a hypothetical example, be a greater focus in some regions or services on biomarkers or clinical features which are clearly sensitive to a synucleinopathy (i.e. RBD, parkinsonism, and dopaminergic imaging) though these may not be specific to a declining MCI.

North-East England contains many of the most deprived areas of the United Kingdom (Department for Communities and Local Government, 2011; Noble *et al.*, 2019), a limitation of the localised recruitment in regards to wider generalisability. Deprivation may impact on apparent cognitive function through a number of mechanisms; more deprived individuals may have lower estimated premorbid functioning and cognitive reserve through reduced opportunities in education, attainment, and cognitive health-influencing behaviours through early and mid-life (Norton *et al.*, 2014; Clare *et al.*, 2017; Olivera *et al.*, 2018), while health inequalities may reduce access to memory services and anti-dementia treatment in later life (Cooper *et al.*, 2016). Increased deprivation is also associated with poorer quality of life after dementia diagnosis (Wu *et al.*, 2018b). In this research setting, both baseline cognitive scores and observed rates of decline are likely to reflect local effects of deprivation which may not generalise to other areas; note for instance that mean baseline ACE-R scores in MCI in these cohorts (**Chapters 4 and 8**)

fall below the 82-point cut-off found to be highly specific to dementia within a Cambridge, UK based sample (Mioshi *et al.*, 2006). Distributions of deprivation deciles of the cohorts are presented in **Figure 10.1**, which are uniformly distributed on a national scale by definition; while there were peaks at deciles three (moderately high deprivation) and nine (lower relative deprivation), there was no clear skew in deprivation in this sample, which may reflect the counteracting effects of greater local deprivation in the North-East (Basta *et al.*, 2007) and the previously-observed bias in research participation towards less-deprived communities (Gao *et al.*, 2015) resulting in an approximately evenly distributed sample.

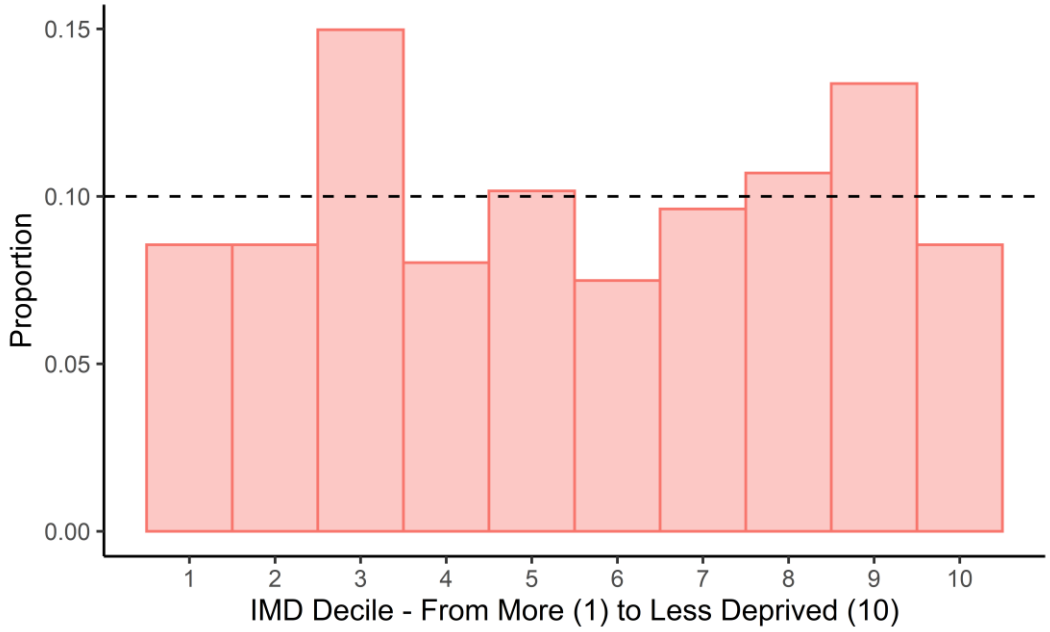


Figure 10.1. Distributions of English IMD deciles in LewyPro and SUPErB cohorts combined (n = 187), dashed line as reference for uniform distribution.

In an apparently heterogeneous condition such as DLB, or its prodromal stages, the clinical profiles observed in a research setting will to an extent reflect the healthcare services from which participants were recruited; those recruited from movement disorders service may naturally feature a more PD-like profile, while those recruited from memory services may feature a more AD-like presentation, though these differences may be difficult to quantify. This is of course complicated by the differing overlaps of service specialities and care pathways in different countries; the Amsterdam Dementia Cohort, for instance, identified much higher rates of

parkinsonism and FP-CIT imaging abnormalities in their prodromal DLB sample than observed in the LewyPro and SUPErB cohorts (van de Beek *et al.*, 2020), which may reflect intangible differences in culture between the services from which these cases are recruited leading to a more PD-like profile in MCI-LB in the former, with implications for direct comparisons between cohorts (e.g. resulting in a cohort with more typical dopaminergic dysfunction, and therefore different patterns of cognitive impairment).

To address these limitations, there may be a benefit in future work exploring differences in the cognitive and clinical presentations and progressions of MCI-LB nationally, across different services, and internationally, to establish if there exist any fixed (e.g. regional deprivation) or random (e.g. clinical culture in a particular service) effects which influence the presentation or prognosis of this syndrome.

While emerging evidence from these cohorts seems to support that MCI-LB transitions to clinically-diagnosed DLB in the short term (**Chapter 4**), it will eventually be necessary to demonstrate, when such data is available, that a prospective clinical diagnosis of MCI-LB is specifically associated with a neuropathological confirmation of the presence of LB disease, which may co-occur with AD pathology. Participants in these cohorts, including both controls and patients, have been provided information on volunteering as a donor to the Newcastle Brain Tissue Resource, but given the early stage of disease assessed in these studies, these data may take some time to reach fruition. By way of comparison, neuropathological follow-up of people with dementia has shown utility in identifying clinical symptoms associated with mixed neuropathologies (Thomas *et al.*, 2018), in assessing the accuracy of clinical diagnosis (Selvackadunco *et al.*, 2019), and in characterising the global cognitive trajectories of pure and mixed AD and DLB (Malek-Ahmadi *et al.*, 2019). Such confirmation of both the presence, and extent (i.e. pathological staging) of AD, LB, and other pathologies (e.g. TDP-43) in the brain could help to characterise the relative contributions and interactions of these on the domain-specific cognitive and clinical profiles, and progression of MCI. For example, the presence of greater AD-related pathology alongside prominent LB disease may cause greater amnestic memory impairment and less clearly manifest clinical features of MCI-LB, and this syndrome might also be expected to deteriorate at a faster rate relative to cases with less mixed pathology.

At various times throughout this work, it has been speculated that observed associations between DLB clinical features and cognitive or clinical progression may reflect shared patterns of neurodegeneration (e.g. central cholinergic deficiencies underlying both cognitive fluctuation symptoms and transition to dementia). Prior to the availability of pathological confirmation, it may be possible to build on this work using a combined biomarker approach to assess whether such patterns of neurodegeneration theorised to mediate the associations between underlying disease (AD or LB), the consequent clinical features (RBD, parkinsonism, visual hallucinations, and cognitive fluctuations) and cognitive profiles (e.g. amnestic, dysexecutive, visuospatial dysfunction) are evident. While both MIBG and FP-CIT are useful biomarkers for differential diagnosis of DLB from AD, neither appeared to predict cognitive decline or dementia onset in this work (**Chapter 9**), and so could reflect less aggressive phenotypes within LB disease (being respectively related to autonomic and dopaminergic dysfunctions). Various underlying mechanisms could mediate cognitive and clinical outcomes, with various corresponding biomarkers, for example: MTL atrophy (MRI), occipital activity reductions (perfusion or metabolism), dopaminergic dysfunctions (FP-CIT), and central cholinergic deficiencies (EEG) could vary in severity both within and across diagnostic groups, possibly with consequences for individual cognitive and clinical presentations as theorised throughout. Clarifying whether different patterns or combinations of biomarker findings are associated with different cognitive patterns and progressions, clinical feature presence, and rates of transition to dementia, could help explain some observed clinical and cognitive heterogeneity. If these speculated associations are observed, this could aid in prospective stratification of MCI cases.

This work largely focussed on the associations of core clinical features and indicative biomarkers of DLB with cognitive and clinical decline; while these characteristics are well-supported in differentiating DLB from AD (McKeith *et al.*, 2017), and MCI-LB from MCI-AD (McKeith *et al.*, 2020), it is possible that other features of LB disease such neuropsychiatric supportive features (Donaghy *et al.*, 2020), clinical features or biomarkers of neurodegenerative diseases in general, or other health factors, may be more predictive of a poorer prognosis within MCI.

While the analytical methods were flexible and appropriate for the longitudinal form of data, there remain limitations. Missing data were not imputed due to the complexity of incorporating

multiply-imputed datasets into less-widely supported *R* packages such as *lcmm* and *msm*. Data missingness due to censoring (dementia or death) was accounted for in models of discrete state transitions (MSM) or through adjusting for time to onset of dementia or death (LCMM), but not otherwise included as an additional competing outcome when assessing change in continuous outcomes (i.e. cognitive decline); with sufficient data, this could be incorporated into a joint cognitive trajectory and survival model.

While efforts were made to adjust for time-to-censoring, as well as to control for effects which may lead to delayed diagnoses, such as local deprivation, it remains likely that different individuals will have begun observation at different, arbitrary points following onset of cognitive symptoms. This could account for some observed differences in trajectories both between, and within, these groups. While the differential diagnostic groups were broadly similar in their global cognitive function on entry to these studies, as noted previously different underlying patterns of cognitive impairment may lead to incomparable raw scores on global cognitive assessments.

As anticipated, with relatively few observations per individual in both cohorts there was a limited ability to describe non-linear time effects in cognitive decline, which were routinely assessed as might be expected based on larger-scale (Yoo *et al.*, 2020) or longer-running studies (Muniz Terrera *et al.*, 2008). While this limits the accuracy with which the true latent cognitive trajectories may be described, this is in keeping with more comparable clinical studies (Rongve *et al.*, 2016; Breitve *et al.*, 2018; van de Beek *et al.*, 2020), though whether non-linear effects were assessed in these studies is not typically reported.

10.5 Conclusions

In comparison to MCI-AD, an MCI syndrome which features core clinical symptoms or signs of LB disease (RBD, parkinsonism, complex visual hallucinations, or fluctuating attention and cognition) or supportive biomarkers of LB disease (striatal dopaminergic imaging abnormalities, or reduced cardiac uptake of MIBG) may also feature greater executive dysfunction, greater and progressive decline in visuospatial functions, and less severe episodic memory impairment. This profile of cognitive decline is consistent with this syndrome being the cognitive prodrome of DLB, as this reflects the typical domain-specific impairments found in comparison with AD.

MCI-LB also has a greater risk of progressive global cognitive decline than MCI-AD, and a greater annual risk of progressing from MCI to dementia: this risk increases further as more clinical features or biomarkers of LB disease become apparent. However, not all clinical findings are equally hazardous; individuals experiencing complex visual hallucinations may be at more risk of progressive cognitive decline, while those experiencing fluctuations in attention and cognition appear to be at greater risk of developing dementia, while those with parkinsonism or RBD as slower-progressing core features do not appear to be at any greater risk of progression than MCI-AD (though likely retaining a greater risk of dementia than those without any neurodegenerative disease at all). Such findings could help inform future clinical trials in MCI-LB, for instance when balancing groups by clinical features which may be anticipated to have different rates of cognitive decline or transition to dementia.

As the clinical differential diagnosis of MCI is an emerging concept, further research is required to explore the mechanisms underlying these risk factors, cognitive impairments, and any worse prognosis, as these may have implications for potential future therapies. It must also be demonstrated that these differentially diagnosed clinical syndromes reliably progress to their respective dementia syndromes in other settings which may lack the diagnostic rigour afforded in this research project, and with neuropathological confirmation of diagnoses.

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