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Cognitive impairment in Parkinson's disease: Impact and identification of comorbid disease mechanisms.

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Abstract

Cognitive impairment is a common and debilitating feature of Parkinson's disease (PD). While it is primarily caused by cerebral propagation of α-synuclein protein, evidence of comorbid diseases is frequently found in autopsy samples. This includes tau and amyloid-β pathologies – the hallmarks of Alzheimer's disease (AD) – and cerebrovascular damage. Comorbid diseases may influence cognition in PD over and above the effects of α-synuclein alone, and this influence may interfere with the results of clinical trials of next-generation medical treatments that target α-synuclein.

The primary aims of this thesis were to define the extent and the effects of comorbid disease mechanisms in PD, and to identify viable clinical strategies for detecting coexistent disorders *in vivo*. Methods included a systematic review of autopsy studies; a factor analysis of the Montreal Cognitive Assessment (MoCA); a regression analysis of two genes; and a cross-sectional neuropsychological study of 45 patients.

The systematic review found significant tau pathology in around one-third of PD patients at death. Significant amyloid-β pathology affected over half, and conferred a worse prognosis. Other pathologies (e.g. cerebrovascular disease) were less common, and did not contribute to dementia in PD. The factor analysis showed that the MoCA has limited value for distinguishing cognitive profiles in PD, suggesting that it should be used only for screening. The genetic project found that variation in the *APOE* gene influenced cognitive decline in early PD; the effect varied between men and women. Variation in *MAPT* did not affect cognitive decline. Finally, the neuropsychological study found that over half of cognitively impaired PD patients could be clinically diagnosed with a coexistent cognitive disorder, with AD being the most common.

Collectively, the results of this thesis show that comorbid diseases, particularly AD, are common in PD, and these contribute to the cognitive phenotype. Consequently, a clinical assessment incorporating selected neuropsychological tests can be used to identify comorbid diseases in PD patients. It is important to consider the potentially confounding impact of multimorbidity in the design and analysis of clinical trials that aim to modulate neurodegeneration in PD by targeting α-synuclein.

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List of Conference Presentations

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Abbreviations

AD	Alzheimer's disease
ApoE	Apolipoprotein E
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
DLB	Dementia with Lewy bodies
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
FET	Fused in sarcoma, Ewing's sarcoma, and TATA-binding protein-associated factor 15
FP-CIT	[^{123}I]-*N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane
FTD	Frontotemporal dementia
IQCODE	Informant Questionnaire for Cognitive Decline in the Elderly
IWG	International Working Group
LEDD	Levodopa equivalent daily dose
MCI	Mild cognitive impairment
MDS	Movement Disorder Society
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NHS	National Health Service
NIA	National Institute on Aging
NIA-AA	National Institute on Aging and Alzheimer's Association
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PPA	Primary progressive aphasia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RBD	Rapid eye movement sleep behaviour disorder
RNA	Ribonucleic acid
SD	Standard deviation
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
TDP-43	Transactive response DNA-binding protein 43
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
VASCOG	International Society for Vascular Behavioural and Cognitive Disorders
VCD	Vascular cognitive disorder

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Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or at any other institution.

Callum Smith

1 General introduction

Parkinson's disease (PD) is a chronic, incurable degenerative disorder of the central nervous system. PD is a movement disorder, defined clinically by a cardinal motor syndrome ("parkinsonism"). However, there is increasing recognition of the disease's significant non-motor element. Cognitive impairment, including dementia, is one of the most common long-term complications of PD, and one of the most consequential for the patient's quality of life. Current and future treatment strategies are challenged by the frequency of comorbid disease processes in people with PD and cognitive impairment. The primary aim of this thesis was to define the frequency and effects of comorbid diseases in this patient group, and to discuss methods for identifying them clinically. The treatment implications of comorbid diseases in PD are also discussed.

1.1 Parkinson's disease

PD is a common neurodegenerative disorder whose incidence is influenced by several known genetic and environmental factors. At autopsy, the disease is identifiable by two pathological hallmarks. In clinic, a diagnosis is made based on the cardinal motor signs, but numerous non-motor features frequently contribute to disease severity.

1.1.1 Epidemiology

PD is the second most common neurodegenerative disorder after Alzheimer's disease (AD; Nussbaum & Ellis, 2003). The strongest risk factor is advancing age (Reeve, Simcox, & Turnbull, 2014). The incidence of PD increases sharply between the fifth and seventh decades of life, with 60 being the median age of onset (Lees, Hardy, & Revesz, 2009). PD affects approximately 0.5-1% of the population over this age, and 2-4% of over-80s (Pringsheim, Jette, Frolkis, & Steeves, 2014; Tysnes & Storstein, 2017). In the United Kingdom (UK), the projected 2018 prevalence of PD was almost 150 000 people. The medical, social, and financial costs of PD are consequently formidable, and these are projected to grow still higher in the next 50 years, given the current trend towards an ageing population (Parkinson's UK, 2017).

PD is typically idiopathic: the precise causal mechanisms are not well defined. The incidence of the disease is around 1.5 times as high in men compared to women, and men tend to have more severe motor impairment (K. M. Smith & Dahodwala, 2014). Around 5-10% of cases are directly attributable to a known monogenic mutation: variants of the *SNCA*, *LRRK2*, and *Parkin* genes account for most of these. However, the vast majority of cases are caused by the cumulative action and interaction of numerous genetic and epigenetic factors with lifestyle and environmental exposures. The strongest genetic susceptibility factor is a mutation in *GBA*, the gene that encodes the lysosomal enzyme β-glucocerebrosidase. *GBA* mutations increase the risk of PD by more than fivefold (Sidransky et al., 2009). In addition, results of a recent, very large genome-wide association study implicated 90 independent risk signals spanning 78 genetic loci (Nalls et al., 2019). Lifestyle and environmental factors that increase PD susceptibility include pesticide exposure, higher dairy consumption, and a history of traumatic brain injury. Variables associated with reduced risk include higher physical activity, higher serum urate concentration, and the use of nicotine, caffeine, or non-steroidal anti-inflammatory drugs (Ascherio & Schwarzschild, 2016). Each of these factors has a relatively modest effect size, and many influencing variables remain unknown (Lill, 2016).

1.1.2 Neuropathology

PD is pathologically defined by two hallmarks. One is the depletion of dopaminergic neurons in the substantia nigra pars compacta in the midbrain. The most severely affected area is the ventrolateral tier, a region that projects to the dorsal putamen in the striatum via the nigrostriatal pathway. Deprivation of dopamine from the striatum leads to the emergence of the core motor syndrome. This feature is common to all other parkinsonian disorders, including multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. In PD, there is already moderate to severe loss of dopaminergic neurons in the substantia nigra by the onset of the motor signs. Striatal dopamine loss is profound within a few years of diagnosis (Kordower et al., 2013). Sections of brainstem in PD autopsy cases show a marked reduction in the normally dark pigmentation of the substantia nigra, reflecting the loss of

neuromelanin-laden neurons. Similar degeneration and depigmentation are also seen in the locus coeruleus (Dickson, 2012).

The other PD hallmark is α-synuclein pathology, and the disease can therefore be classified as an α-synucleinopathy. In PD, the ordinarily soluble α-synuclein protein misfolds into insoluble aggregates within neuronal perikarya ("Lewy bodies") and processes ("Lewy neurites"). The distribution of Lewy pathology in people with PD varies dramatically. The vulnerable neurons of the substantia nigra are universally affected. Lewy aggregates are almost always present in the dorsal nucleus of the vagus nerve (cranial nerve X), raphe nuclei, locus coeruleus, pontine tegmentum, and nucleus basalis. Less well-defined aggregates are sometimes observable higher up the neuraxis, including in the amygdala and the neocortex (Dickson, 2018). Lewy pathology may also be found in the peripheral nervous system, particularly in the sympathetic and enteric ganglia (Wakabayashi, Mori, Tanji, Orimo, & Takahashi, 2010). The extent of the pathology parallels the duration and clinical severity of the disease. A scheme for staging PD based on the distribution of Lewy aggregates has been published by Braak et al. (2003), and this will be reviewed in Chapter 2.

In addition to the two defining hallmarks, PD is characterised by various less specific pathological changes. Reactive gliosis and microgliosis of astrocytes and microglia occur in areas of cell death, prominently including the midbrain. The resulting chronic neuroinflammation promotes oxidative stress on neurons, leading to further cell loss (Kalia & Lang, 2015; Tansey & Goldberg, 2010). Intracellular iron accumulates in the substantia nigra, and this also increases oxidative damage (Belaidi & Bush, 2016). Furthermore, dysfunction of non-dopaminergic neurotransmitter systems occurs in PD. Early degeneration of the basal forebrain and its ascending pathways leads to a pronounced cholinergic deficit in frontotemporal brain regions. Serotonergic and noradrenergic dysfunction also occurs as a result of damage to the raphe nuclei and the locus coeruleus, respectively (Kehagia, Barker, & Robbins, 2010). Disequilibrium of these systems contributes to various clinical features of PD, and they are therefore potentially important targets for treatment (Brichta, Greengard, & Flajolet, 2013).

1.1.3 Clinical features

During a patient's lifetime, the clinical diagnosis of PD requires careful consideration of both motor and non-motor features. The current clinical diagnostic criteria for PD were published by the Movement Disorder Society (MDS) in 2015 (Postuma et al., 2015). The MDS criteria summarise the signs and symptoms that define or support a diagnosis of PD *in vivo*, as well as features that reduce the probability of a diagnosis, or exclude it. A recent validation study indicated that these criteria have excellent specificity (88.5%) and sensitivity (94.5%) against the gold standard of clinical diagnosis by an expert neurologist (Postuma et al., 2018), and they have been adapted to diagnose early PD – defined by a disease duration of less than five years – with a specificity of 95.4% and a sensitivity of 69.8% (Berg et al., 2018).

The MDS criteria define parkinsonism as bradykinesia plus rigidity and/or rest tremor. Bradykinesia is slowness in the initiation and execution of movement: limb bradykinesia is essential for a PD diagnosis. Rigidity refers to muscular resistance to passive movement – for example, when a clinician manipulates a patient's limb. Rest tremor is an involuntary, rhythmic, oscillating motion of a fully resting limb; in PD, this is of a relatively low frequency, typically around 4-6 Hz. A fourth feature of parkinsonism is postural instability, but this is not a prerequisite for PD by the MDS criteria due to its limited diagnostic specificity and its rarity outside of late disease. The motor signs usually have unilateral onset in PD, but spread to both sides of the body with disease progression (Gelb, Oliver, & Gilman, 1999; Postuma et al., 2015).

The probability of genuine PD is increased in the presence of four supportive features. The first is excellent response to medications based on L-3,4-dihydroxyphenylalanine (levodopa), the precursor of dopamine; these have been the standard method for managing the motor signs since the 1960s (Cotzias, Van Woert, & Schiffer, 1967). The second supportive feature is the emergence of medication-induced dyskinesia – a disabling hyperkinetic disorder characterised by involuntary writhing movements, which develops in response to prolonged dopamine therapy with levodopa and similar drugs (Heumann et al., 2014). Thirdly, rest tremor of a limb on clinical examination is also a supportive criterion. Finally, a diagnosis is supported by either a) clear loss of

olfactory function or b) cardiac sympathetic denervation, two non-motor features with over 80% specificity for PD (Postuma et al., 2015).

Features that are clearly diagnostic of another parkinsonian disorder (multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, etc.) are absolute exclusion criteria for PD. These include unequivocal signs of cerebellar dysfunction and downward supranuclear gaze palsy. Normal functional imaging of the presynaptic dopamine system is also exclusionary: scans of striatal dopamine transporters with the [^{123}I]-*N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane (FP-CIT) radioligand and single photon positron emission tomography (SPECT) are universally abnormal in degenerative parkinsonian disorders (Benamer et al., 2000; Cummings et al., 2014). Features that lower the probability of PD without ruling it out are labelled "red flags": these include early and severe bulbar or autonomic dysfunction, bilateral motor onset, and either long-term stability or rapid early progression of the motor signs. Clinically established PD is diagnosed when there are no red flags and at least two supportive criteria. Clinically probable PD may be diagnosed when up to two red flags are present, but there must be at least as many supportive criteria. The presence of more than two red flags, or any absolute exclusion criterion, rules out a diagnosis of PD (Postuma et al., 2015).

Variation in the clinical presentation of PD has led to the identification of disease subtypes based on the dominant motor signs. Most patients have either prominent postural instability and gait disorder, or a tremor-dominant phenotype. The former is associated with an older age of onset – usually greater than 65 years – and a more rapid disease progression. The tremor-dominant subtype tends to have a younger onset, with a more gradual progression. Patients who do not clearly fit either subtype may be classified as indeterminate or mixed (Jankovic et al., 1990). Recent cluster analysis has identified additional subtypes that are also characterised by variation in non-motor symptomatology (Lawton et al., 2018; Thenganatt & Jankovic, 2014).

In addition to the cardinal motor signs, PD is closely associated with a long list of non-motor symptoms, including sensory, autonomic, sleep-related, psychiatric, and cognitive features. Having several non-motor symptoms is the norm. Their incidence increases with disease progression; indeed, having none by five years is a diagnostic

red flag. However, some may precede emergence of the motor signs, often by several years (Barone et al., 2009; Goldman & Postuma, 2014). Non-motor symptoms have a significant detrimental impact on quality of life, in some cases even overshadowing the burden of the motor impairment (Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & The NMSS Validation Group, 2011). Despite this, these symptoms are often underappreciated in clinic, and consequently, they are frequently undertreated. Increasing recognition of non-motor symptoms has led to their becoming the focus of steadily more scientific attention over the last 30 years (D. Weintraub & Burn, 2011).

One of the most common non-motor symptoms is a decline in olfactory function (hyposmia), which occurs in more than 80% of people with PD (Doty, 2012), and is generally appreciable prior to or shortly after motor onset. Pain affects a similar proportion; this is normally musculoskeletal or dystonic in nature, and is of moderate to severe intensity in around 40% of all patients (Silverdale et al., 2018). Autonomic dysfunction is also common: around half of people with PD experience constipation (Chen et al., 2015), and the same proportion report urinary dysfunction, including urgency, nocturia, and incontinence (Winge, 2015). Around a third, particularly later in the disease, have orthostatic hypotension – a drop in blood pressure on standing that can cause dizziness, visual disturbance, and even loss of consciousness. Other autonomic symptoms include excessive sweating, reduced salivation, anorgasmia in women, and erectile dysfunction in men (Malek et al., 2017; Sveinbjornsdottir, 2016).

Around two-thirds of people with PD report sleep disorders. Fragmented sleep (brief arousals throughout the night) is the most common of these. Hypersomnia, typically manifesting as excessive daytime fatigue, affects around half. PD is also closely associated with rapid eye movement sleep behaviour disorder (RBD), a condition defined by the loss of natural muscle atonia during sleep. This leads to abnormal motor and vocal behaviours – kicking, thrashing, shouting, laughing, etc. – due to the acting out of dreams. RBD is the strongest known prodromal marker for PD and other α-synucleinopathies (Goldman & Postuma, 2014; Mehta, Morgan, & Sethi, 2008).

Psychiatric features are prevalent at all stages of PD. Clinically significant depressive symptoms are present in over a third of patients, and 17-19% fulfil criteria for major depressive disorder, according to one large meta-analysis (Reijnders, Ehrt, Weber,

Aarsland, & Leentjens, 2008). Both anxiety and apathy are clinically significant in approximately a third (Dujardin et al., 2007; Leentjens et al., 2011). In addition to affective symptoms, up to a fifth of PD patients develop impulse control disorders, commonly involving compulsive gambling, buying, eating, or sexual behaviours. These behaviours are usually iatrogenic, being strongly related to treatment with dopamine agonists, and to a lesser extent with levodopa medications. Other risk factors for these include being unmarried or relatively young, or having a personal or family history of addictive or affective disorders (D. Weintraub & Claassen, 2017).

Psychotic symptoms are also common in PD, with their severity ranging from mild illusions (e.g. senses of presence or passage) to persistent, detailed hallucinations or delusions. Visual hallucinations involving clear images of people, animals, and other complex stimuli occur in around a third of people with PD. Typically, insight into the falsity of these hallucinations is retained. Hallucinations in other sensory modalities (auditory, olfactory, gustatory, and tactile) are reported less frequently. Delusions affect only around 5% of patients, generally in late-stage disease. When they do occur, they tend to be of a paranoid, persecutory nature (Friedman, 2013).

Cognitive impairment is one of the most common long-term non-motor features of PD, and one of the most consequential for quality of life (Duncan et al., 2014).

1.2 Cognitive impairment

Cognitive impairment is defined as a clinically significant decline in cognition from a previous level of functioning. Cognition comprises a range of mental operations. Operations that are psychologically and neurologically similar may be grouped into discrete cognitive domains, though the number and nomenclature of these domains varies to an extent in the scientific literature.

The current, fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) distinguishes six cognitive domains. *Memory* involves the encoding, storage, and retrieval of information. *Attention* refers to processing speed and the ability to selectively assign and maintain concentration on

a particular stimulus, to the exclusion of competing stimuli. *Executive function* includes higher-order operations such as reasoning, planning, abstract thinking, error monitoring, cognitive flexibility, response inhibition feedback utilisation, judgement, and problem solving. *Visuospatial skills* relate to visual and spatial perception, coordination, and construction. *Language* refers to the production and comprehension of speech and writing. Finally, *social cognition* covers abilities such as theory of mind, emotion recognition, and social conduct. Some neuropsychological test batteries include additional cognitive domains, such as praxis – the ability to execute skilled or learned movements, like dressing or using tools (J. E. Park, 2017).

Lesion and neuroimaging studies support the theory that each cognitive domain corresponds to a distinct neurological substrate, largely involving different neural structures and networks. Neuropsychological tests may be used to ascertain the functioning of these substrates. Selective impairment by certain tests may indicate clinically significant damage to a specific brain region or network, as occurs in neurodegenerative diseases (Burrell & Piguet, 2015).

In the early stages of a degenerative cognitive disorder, clinical deficits are minor and often restricted to a single domain, reflecting relatively mild pathology confined to a specific neurological locus. This stage is termed “mild cognitive impairment” (MCI; Petersen et al., 2009; Petersen et al., 1999), or “mild neurocognitive disorder” in the DSM-5. With disease progression, the deficits become more severe, and other domains are gradually involved. Marked multiple-domain cognitive impairment is diagnostic of dementia (“major neurocognitive disorder” in the DSM-5). Functional impairment secondary to the cognitive symptoms is also required for a dementia diagnosis. This manifests as significant difficulties engaging in normal occupational, social, and recreational activities. The definition of MCI requires independence to be retained, though subtle interference from the cognitive problems may still be appreciable (American Psychiatric Association, 2013; Knopman & Petersen, 2014).

The cognitive impairment related to PD is heterogeneous in several respects (Litvan et al., 2011), similar to other features of the disease. The major distinction in terms of severity is between PD-MCI and PD dementia (PDD). The MDS has published clinical diagnostic criteria for both (Emre et al., 2007; Litvan et al., 2012), and these

will be reviewed in detail in Chapter 4. The rate of cognitive decline in PD varies, with some people experiencing a fluctuating course. One analysis of newly diagnosed patients who were followed over three years, for example, indicated that about 40% declined, a quarter remained cognitively stable, and the remainder either fluctuated or, in some cases, improved (Lawson, Yarnall, Duncan, et al., 2017). The differences in neuropathological burden that underlie this variation remain poorly understood.

The neuropsychological profile of PD-associated cognitive impairment is traditionally considered to be characterised by dominant deficits to the executive and attentional domains, with relative preservation of memory (Emre et al., 2007). This profile is consistent with dysfunction of subcortical and frontal brain structures. An amnestic (memory-dominant) profile pointing to medial temporal lobe damage affects a smaller proportion – around a third, according to one cluster analysis (Janvin et al., 2006). Findings are comparable for PD patients with MCI. A single-domain, non-amnestic (typically frontal-dysexecutive) profile is the most common individual presentation, but substantial heterogeneity exists, and many patients have deficits to two or more domains (Caviness et al., 2007; Kalbe et al., 2016).

1.2.1 Epidemiology of cognitive impairment in PD

Cognitive impairment is common at all stages of PD, although it is more closely associated with advanced disease. Most research indicates that the point prevalence of MCI is approximately a quarter (Aarsland et al., 2010; Litvan et al., 2011), and the point prevalence of dementia is approximately a third (Aarsland, Zaccai, & Brayne, 2005). In the long term, dementia affects the vast majority of people with PD; one large longitudinal study reported that it developed in 80% of those who survived for 20 years after diagnosis (Hely, Reid, Adena, Halliday, & Morris, 2008).

There are several known risk factors for cognitive decline in PD. Increasing age and disease duration are independently associated with the onset of dementia, though the predictive value of disease duration is muted in the oldest age groups (over 85 years of age). Male sex is more closely linked to dementia in PD, even after controlling for the increased incidence of PD in men; this contrasts with non-PD populations, where

female sex is more often associated with dementia (Cereda et al., 2016). MCI is a very strong predictor of a further decline to dementia, though a small percentage of people with PD-MCI may revert to normal cognition in the short term (Pedersen, Larsen, Tysnes, & Alves, 2013). As in other dementia disorders, some people with PD seem to be capable of withstanding a higher degree of neuropathology before it clinically manifests as cognitive impairment, due to individual differences in neural and cognitive networks. This "cognitive reserve" results from, and is measured by, signs of intellectual development, such as educational and occupational attainment (Poletti, Emre, & Bonuccelli, 2011).

Several motor and non-motor features predict cognitive decline in PD. The postural instability and gait disorder phenotype is linked to a faster cognitive decline and a higher incidence of dementia than the tremor-dominant phenotype. Tremor-dominant patients generally transition to postural instability and gait disorder, or to a mixed profile, before cognitive symptoms emerge (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006). Longitudinal analyses indicate that visual hallucinations and RBD are risk factors for cognitive decline in PD (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sørensen, 2003; Sinforiani et al., 2008). Depression and apathy both appear to be linked to dementia in PD, but it remains unclear whether they constitute genuine risk factors, or whether they are a consequence of cognitive problems (Marinus, Zhu, Marras, Aarsland, & van Hilten, 2018).

Genetically, cognitive impairment in PD is a highly complex trait, influenced by numerous genetic variations often with small individual effect sizes. Polymorphisms of multiple genes, including *APOE*, *MAPT*, *SNCA*, *GBA*, and *COMT*, have been linked to cognitive decline and dementia in PD (Fagan & Pihlstrøm, 2017). *APOE* is the most significant genetic factor underlying AD. Coding variants of this gene result in three alleles, ε2, ε3, and ε4: the last has been strongly linked to higher AD risk, as well as poorer cognitive outcomes in various other medical conditions (Y. Huang & Mahley, 2014). Similarly, the H1 haplotype of the *MAPT* gene has been linked to several neurodegenerative diseases characterised by cognitive decline and, often, parkinsonism, including progressive supranuclear palsy and corticobasal degeneration (Zhang, Xing, Tan, Tan, & Yu, 2016). Both *APOE* ε4 and *MAPT* H1 have also been associated with cognitive decline in PD, though results are mixed, particularly for

MAPT. Chapter 7 presents a novel analysis of these two genes in a large prospective cohort, with the aim of clarifying the relationships that they have to cognitive function throughout the course of early PD.

The prognostic implications of cognitive impairment in PD are significant. Dementia is associated with earlier mortality and a shorter time to nursing home placement (Parashos, Maraganore, O'Brien, & Rocca, 2002). Functional independence declines in parallel to worsening cognition, even in the absence of overt dementia (Rosenthal et al., 2010). Furthermore, cognitive impairment predicts significantly poorer quality of life for both the patient (Lawson et al., 2014) and for caregivers (Lawson, Yarnall, Johnston, et al., 2017). The substantial burden of cognitive impairment means that effectively managing it is a top priority for many people with PD and their families.

1.2.2 Other causes of cognitive impairment

There are numerous potential aetiologies for dementia. PD accounts for under 4% of the total figure (Aarsland, Zaccai, et al., 2005). Most cases are caused by another neurodegenerative disease. At least 60% of total dementia cases are caused by AD. Dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) account for smaller percentages (American Psychiatric Association, 2013). In addition to neurodegenerative disease, cognitive problems can be induced by acquired brain injury: cerebrovascular diseases account for most such cases. Cerebrovascular disease is a generic term for pathology of the brain's blood vessels. Cognitive impairment that results from such pathologies is referred to as vascular cognitive disorder (VCD), which includes both vascular MCI and vascular dementia (Farooq & Gorelick, 2013).

Each of these dementia disorders is defined by a characteristic neuropathology, generally affecting different brain structures. This neuropathology is described by post-mortem diagnostic criteria, which are used to confer a diagnosis after direct examination of the brain at autopsy. Abnormal protein aggregation is thematic in the neurodegenerative diseases, with pathology of different proteins being associated with different disorders (Kalia & Kalia, 2015). For PD, DLB, and AD, staging schemes use the topography of specific protein pathologies to define disease severity at autopsy.

Chapter 2 will describe the neuropathology associated with PD and each of these dementia disorders in detail, along with a summary of current post-mortem diagnostic criteria and staging schemes. In brief, DLB is another Lewy body disease, defined by the same intraneuronal α-synuclein inclusions that characterise PD (Lewy bodies and Lewy neurites). At autopsy, DLB is often indistinguishable from PDD: the distinction is purely a clinical one, defined by the "one-year rule." According to this rule, PDD is diagnosed when cognitive symptoms emerge in established PD (one year or more after diagnosis), whereas DLB is diagnosed where cognitive symptoms either emerge prior to or contemporaneously with the onset of the motor signs (Emre et al., 2007; McKeith et al., 2005). The validity of the one-year rule will also be discussed in detail later in the thesis, when the clinical diagnostic criteria for the dementia disorders are reviewed in Chapter 4.

Like PD, AD is pathologically defined by two hallmarks: intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau protein, and extraneuronal plaques consisting primarily of amyloid-β peptide (Thal, Walter, Saido, & Fändrich, 2015). FTD is pathologically heterogeneous. The characteristic feature is degeneration of the frontal and temporal lobes. In the vast majority of cases, this is associated with pathology of either the tau protein, or of transactive response DNA-binding protein 43 (TDP-43; Mackenzie & Neumann, 2016). The pathologies that underlie VCD are also varied. Infarcts, haemorrhages, and small vessel disease are the major pathologies that are implicated in vascular dementia (Rodríguez García & Rodríguez García, 2015).

During life, the different dementia disorders are associated with different clinical phenotypes as a result of differences in the nature and the location of the underlying neuropathology. Clinical diagnostic criteria describe the characteristics of each disorder, including the typical neuropsychological profile, associated non-cognitive symptoms, and indicative biomarkers (specific biochemical or anatomical correlates of disease progression that can be quantified *in vivo*). The diagnostic criteria will be covered in detail in Chapter 4, but the major clinical characteristics of each disorder are outlined here for an overview.

Neuropsychologically, DLB is similar to PDD, as is to be expected given the degree of pathological overlap. Deficits to executive function, attention, and visuospatial

skills predominate, consistent with frontostriatal dysfunction. The clinical profile also includes parkinsonism, cognitive fluctuations, RBD, and visual hallucinations (McKeith et al., 2017). AD is characterised by initial prominent episodic memory impairment resulting from degeneration of the medial temporal lobe, including the hippocampus and the entorhinal cortex. Measures of language function, including verbal fluency and object naming, may also be impaired at the early stages (Dubois et al., 2014; McKhann et al., 2011). The pathological heterogeneity of FTD results in clinical variation, but abnormalities in language, social cognition, and/or behaviour are consistently prominent (Bang, Spina, & Miller, 2015). VCD is also varied. Executive dysfunction is most common, and there may also be deficits to processing speed, attention, and visuoconstructional abilities. Careful history-taking, ideally complemented by neuroimaging, is very valuable for the differential diagnosis of VCD from other dementia disorders (S. Weintraub, Wicklund, & Salmon, 2012).

Currently, the diagnostic criteria for each dementia disorder demand exclusive disease processes: signs that implicate an alternative aetiology are typically exclusionary. However, multimorbidity is a common phenomenon in people with dementia. Neurodegenerative disease pathologies commonly overlap with one another (Irwin, Lee, & Trojanowski, 2013); cerebrovascular diseases and the associated lesions are also frequently present (Toledo et al., 2013). In PD, coexistent pathologies may influence a patient's neuropsychological presentation during life. Therefore, the assumption of PDD in a patient with PD and emerging dementia may be invalid, and may misdirect treatment approaches. Consideration of possible comorbidities is becoming increasingly important, as treatments currently in development are targeted directly at specific pathologies, rather than solely at symptom management.

1.2.3 Current treatment strategies

Current treatment options for cognitive decline, both in neurodegenerative disease and acquired brain injury, are limited. Strategies are targeted at either a) ameliorating the symptoms or b) managing factors that contribute to further decline. At present, true disease-modifying therapies that would slow or halt cognitive decline by impeding of reducing neuropathological burden are not available (O'Hara, Kalia, & Kalia, 2018).

The main medications currently used for cognitive disorders are acetylcholinesterase inhibitors (namely rivastigmine, donepezil, and galantamine), which are used for mild to moderate dementia, and memantine, an *N*-methyl-D-aspartate receptor antagonist used for moderate to severe dementia. The acetylcholinesterase inhibitors prevent the enzymatic breakdown of acetylcholine, whereas memantine targets glutamatergic overactivity. All of these drugs are licensed for AD, but only rivastigmine is licensed for PDD and DLB, and none are licensed for VCD or FTD (Broadstock, Ballard, & Corbett, 2014; Olney, Spina, & Miller, 2017). Randomised placebo-controlled trials indicate that acetylcholinesterase inhibitors also improve cognition and global functional status in PDD (Dubois et al., 2012; Rolinski, Fox, Maidment, & McShane, 2012), but the evidence for the efficacy of memantine in the α-synucleinopathies is weaker; a meta-analysis of clinical trials found that memantine conferred no benefit to cognition, behavioural symptoms, or functional independence in PDD and DLB (H. F. Wang et al., 2015). Thus, the best current method of ameliorating cognitive symptoms in PD is by targeting the cholinergic deficit.

All of these medications have several disadvantages. Crucially, they are effective only for slowing the rate of cognitive decline over a relatively short period of time. For example, one large study found that donepezil delayed the progression of MCI to dementia over a 12-month period, but after 36 months, there was no difference between the treatment and the placebo groups (Petersen et al., 2005). Moreover, neither acetylcholinesterase inhibitors nor memantine improve cognitive function at the MCI stage (Tricco et al., 2013). One study reported that global cognition in PD patients without dementia improved with atomoxetine, a selective norepinephrine reuptake inhibitor usually used in the treatment of attention deficit hyperactivity disorder (D. Weintraub et al., 2010); however, no medications have yet shown sufficient efficacy to be licensed for MCI of any aetiology. Certain behavioural interventions, aerobic exercise, mental exertion, and regular social interaction may reduce the risk of further decline in MCI, though effect sizes are typically small and results are often inconsistent (Langa & Levine, 2014). Finally, a limitation of the acetylcholinesterase inhibitors is the burden of the side effects, which include dizziness, nausea, gastrointestinal dysfunction, and sleep disturbance (Zemek et al., 2014). As discussed, all of these symptoms can occur naturally in PD; medication use

can exacerbate them significantly, and optimally titrating the dosage can therefore be very challenging with some patients.

In addition to cholinergic medications, dopaminergic treatments (levodopa, dopamine agonists, and monoamine oxidase B or catechol-*O*-methyltransferase inhibitors) used to treat motor impairment in PD may also affect cognition, though the relationship is complex. These medications may impair some aspects of executive function (e.g. rule learning), but improve others (e.g. planning and cognitive flexibility). The "dopamine overdose hypothesis" suggests that this disparity may be explained by the fact that dopaminergic medications, which are intended to boost depleted dopamine activity in the dorsal striatum, simultaneously overdose the ventral striatum, which is relatively preserved in the early stages of PD. Therefore, functions that rely on dorsolateral and frontostriatal circuits (which pass through the dorsal striatum) may be improved, but functions that are mediated by limbic and orbitofrontal circuits (which pass through the ventral striatum) may be impaired. The hypothesis is supported by several studies (Dirnberger & Jahanshahi, 2013), and emphasises the need to consider cognitive as well as motor function when prescribing dopaminergic medications in PD.

The second major strategy for managing cognitive impairment involves targeting modifiable risk factors that may contribute to further cognitive decline. Late-life depression is an established risk factor for dementia (Diniz, Butters, Albert, Dew, & Reynolds, 2013). Vascular risk factors – diabetes, hypertension, hyperlipidaemia, obesity, smoking, etc. – are strongly implicated in the pathogenesis of VCD, and also confer an increased risk of developing AD (Hasnain & Vieweg, 2014). Additionally, vascular comorbidity contributes to cognitive decline in PD (Malek et al., 2016), particularly to attentional and executive dysfunction (Pilotto et al., 2016). Depression and many of the vascular risk factors (e.g. hypertension, obesity, smoking) are potentially modifiable by medication, behavioural interventions, lifestyle changes, or other means, and these therefore represent realistic targets for treatment programmes.

Studies that have sought to medicate these factors to reduce the incidence of dementia have so far reported generally disappointing results. Longitudinal studies have provided equivocal evidence for the benefit of antihypertensive drugs in lowering the long-term incidence of dementia (Peters et al., 2008). Cholesterol-lowering therapy

and diabetes management do not appear to slow cognitive decline (Tariq & Barber, 2018). These results are probably due to the interventions being applied too late: neurodegenerative disease pathologies typically originate many years before symptom onset, so neural damage may be quite substantial by the time cognitive decline manifests clinically. Effectively employing vascular treatments to counteract cognitive decline may therefore require earlier intervention over longer time scales.

Introducing true disease-modifying strategies that target the underlying pathologies to slow or halt cognitive decline in the long term represents an urgent unmet need for people with neurodegenerative disorders. Many such treatments are currently in development, and some have shown promising results in preclinical and early clinical trials (Medina, 2018; van Dyck, 2018; Zella et al., 2019). The design and analysis of trials in cognitively impaired PD cohorts requires a clear and accurate understanding of the pathology that underlies cognitive impairment in PD, in order to ensure appropriate interpretation and implementation of results. A detailed discussion of disease-modifying therapies is presented in Chapter 9, in relation to the original research findings in this thesis.

1.3 Aims and structure of the thesis

This thesis explores the contribution of coexistent disease mechanisms, such as AD pathologies and cerebrovascular disease, to cognitive impairment in PD. Additionally, the thesis aims to identify viable methods by which coexistent disease mechanisms may be detected *in vivo*.

Four novel studies were undertaken to fulfil these aims. The objectives of these were:

- To define the extent and the effects of the neuropathological heterogeneity underlying dementia in PD by systematically reviewing existing literature;
- To assess the value of the Montreal Cognitive Assessment (MoCA), for distinguishing different cognitive profiles in PD patients;

- To clarify the link between cognitive decline in PD and variation in the *APOE* and *MAPT* genes, both of which are implicated in susceptibility to other neurodegenerative diseases;
- To ascertain the proportion of people with PD and cognitive impairment who meet clinical diagnostic criteria for different cognitive disorders (e.g. AD), and to identify clinical tests with value for differential diagnosis.

Various essential background topics are reviewed to contextualise the novel analyses. A literature review is used to describe a) the pathologies associated with PD and the main dementia disorders, and the post-mortem diagnostic criteria and staging systems used to evaluate their severity; b) clinical diagnostic criteria used to confer a diagnosis *in vivo*; and c) neuropsychological assessment strategies used to quantify the severity of impairment in different cognitive domains.

The remainder of the thesis is divided into eight chapters, as follows:

- **Chapter 2** describes the neuropathology of PD and the dementia disorders, including DLB, AD, VCD, and FTD. The post-mortem diagnostic criteria for the main dementias are reviewed. Staging schemes for the different dementia pathologies are also described in this chapter. These are designed to quantify the severity of the pathology based on its global density and topographical distribution. This chapter illustrates the ways in which the dementia disorders differ from one another pathologically.

- **Chapter 3** presents a systematic review of autopsy studies of dementia in PD. Five databases were searched for English-language studies involving human subjects with dementia and PD. The main objective was to describe the neuropathology underlying dementia in PD. The results primarily focus on the severity and distribution of Lewy and Alzheimer pathologies, and define the extent to which these are associated with dementia in PD. The more modest contributions of cerebrovascular and other pathologies (e.g. TDP-43) to dementia in PD are also assessed.

- **Chapter 4** is a critical review of the clinical diagnostic criteria for the main dementia disorders. These criteria are used to generate a probabilistic statement about the pathological cause of a patient's cognitive impairment based on their clinical presentation. The contentious distinction between PDD and DLB (currently made clinically on the basis of the one-year rule) is also assessed in this section. This chapter illustrates the ways in which the dementia disorders differ from one another *in vivo*.

- **Chapter 5** describes the neuropsychological assessment of MCI and dementia. This includes screening tests, which are designed to provide a brief impression of a patient's global cognition, and domain-focused evaluation, which provides more detailed data about a patient's function in specific cognitive domains. Methods of contextualising raw scores by comparison to normative data or estimated premorbid function are discussed. Challenges pertaining specifically to the neuropsychological assessment of people with PD are also considered.

- **Chapter 6** is a novel statistical analysis of the MoCA, one of the most widely used clinical instruments for screening dementia and MCI. Previous research in PD, AD, and other disorders has shown evidence of a factor structure in the MoCA. Such a structure suggests that the test has the potential to describe variation in the function of different cognitive domains, which ordinarily requires detailed neuropsychological testing. This could be used to distinguish meaningful cognitive profiles in PD. MoCA data were drawn from a large cohort study, the Tracking Parkinson's study (n = 1738), and various previously reported models were tested with factor analysis.

- **Chapter 7** is a novel analysis of the contribution of *APOE* and *MAPT* variants to cognitive decline in early PD. Both genes have been associated with other neurodegenerative diseases, and with cognitive decline in PD, but results are not always consistent. This analysis again used data from the Tracking Parkinson's study. MoCA data were drawn from baseline and 18 and 36-month follow-up visits. The study outcomes were the relationships

between *APOE* and *MAPT* genotypes and cognitive scores and cognitive status at each visit, as well as the rate of cognitive decline between visits.

- **Chapter 8** presents the results of a cross-sectional clinical study examining the heterogeneity of cognitive impairment in PD, which was conducted in two health boards in Scotland. Forty-five people with PD and evidence of cognitive impairment were recruited to the project, and all completed a detailed neuropsychological assessment designed to test multiple cognitive domains. Both the participant and a relative completed questionnaires on cognition and other non-motor symptoms. Medical notes were accessed for medical histories, medication plans, and neuroimaging results. The collated data were evaluated by the author together with a panel of experts in neurology, psychiatry, and clinical neuropsychology, to determine which disease underlay each participant's cognitive decline. Tests with the best value for distinguishing different cognitive profiles were identified.

- **Chapter 9** is a general discussion of all the work presented in the thesis. Disease-modifying therapies for neurodegenerative disorders are discussed, and results from the studies above are used to make recommendations for trialling these treatments in PD cohorts.

2 Neuropathology of PD and dementia disorders

At autopsy, the main dementia disorders are distinguished from one another by the underlying neuropathology. In neurodegenerative diseases, this pathology is defined by misfolded, insoluble aggregates of characteristic proteins. With time, these pathologies become more concentrated, and insidiously affect additional brain areas. During a patient's lifetime, this process is reflected by a gradual worsening of the clinical features, including motor and cognitive impairment in PD.

The mechanism by which pathological protein aggregates spread through the brain is hypothesised to resemble that of infectious prion particles, which propagate via direct cell-to-cell transfer (Goedert, Clavaguera, & Tolnay, 2010; Henderson, Trojanowski, & Lee, 2019). In most cases, the pathologies that define PD, DLB, and AD follow a reasonably predictable path through the brain. These paths form the basis of staging schemes, which describe hierarchical disease stages that are distinguished by the topographical distribution of the characteristic lesions. Staging schemes are used to quantify disease severity at autopsy. Post-mortem diagnostic criteria generally require certain severity thresholds to be reached before a diagnosis can be conferred. These criteria are most often used to retrospectively verify a clinical diagnosis.

This chapter describes the pathological hallmarks of PD and the main dementia disorders (DLB, AD, FTD, and VCD), including current theories for explaining their pathogenic mechanisms, as well as methods for measuring the pathologies both at autopsy, and *in vivo* using biomarkers. Staging schemes and post-mortem diagnostic criteria are also reviewed. This background is an essential foundation to Chapter 3, in which a systematic review of autopsy studies of dementia in PD is presented.

2.1 Lewy pathology

PD is pathologically defined by degeneration of the dopaminergic nigrostriatal system and by the propagation of aggregated α-synuclein protein in the form of Lewy bodies

and Lewy neurites into surviving neurons (Dickson, 2012). Nigrostriatal degeneration is the main substrate of the parkinsonian syndrome, but Lewy pathology is the more relevant hallmark for understanding cognitive decline in PD (Emre et al., 2007).

The α-synuclein protein is an isoform of the synuclein family, a group of small, ordinarily soluble, presynaptic proteins that also includes β-synuclein and γ-synuclein. In PD, α-synuclein misfolds initially into soluble pathogenic oligomers and, later, into larger, insoluble aggregates within neurons (Burré, Sharma, & Südhof, 2018). These inclusions exist in several morphological variations (Figure 2-1). Brainstem-type (or classical) Lewy bodies occur primarily in brainstem nuclei. They typically have a dense, spherical core and a halo of radiating fibrils. Cortical-type Lewy bodies are more amorphous, generally lacking a distinct core or halo (Ikeda, Ikeda, Yoshimura, Kato, & Namba, 1978; Wakabayashi et al., 2013). Their predilection sites include the amygdala and the neocortex.

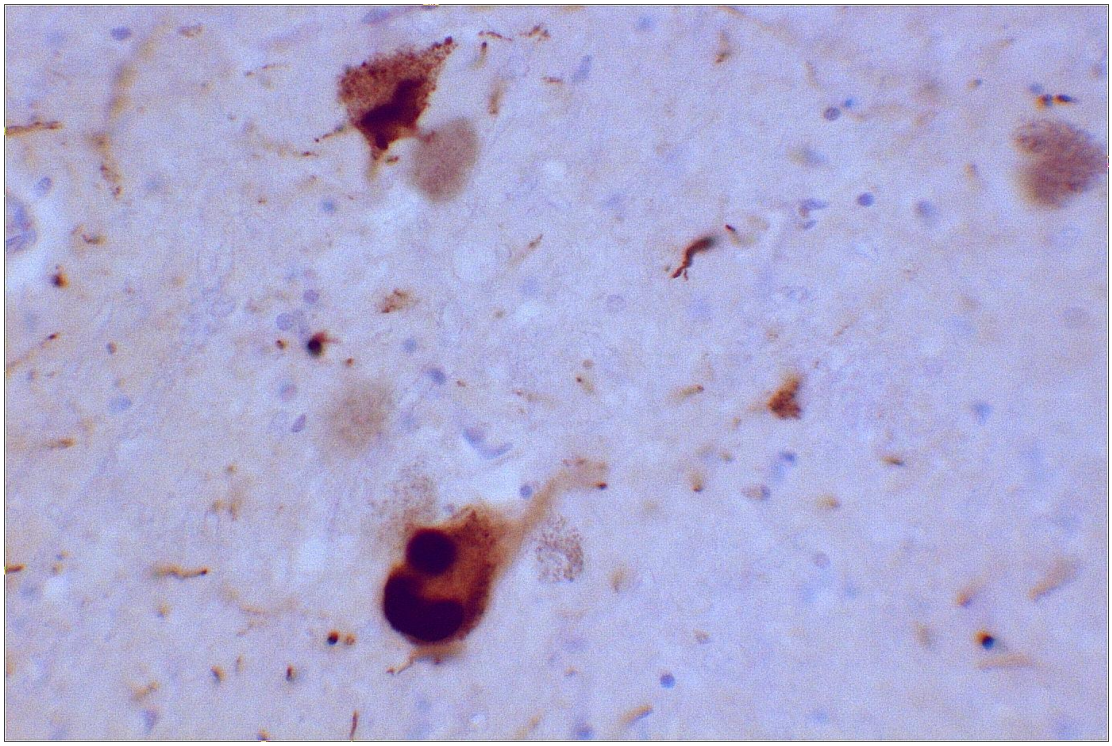


Figure 2-1. Lewy bodies and Lewy neurites.

Photomicrograph of Lewy inclusions (brown) in the substantia nigra of an individual with Parkinson's disease, stained with a mouse monoclonal α-synuclein antibody and Mayer's haematoxylin counterstain. Source: WikiMedia Commons.

Cortical-type Lewy bodies are thought to be progenitors of classical Lewy bodies, and indeed, some severely affected PD cases show mature brainstem-type Lewy bodies in higher brain structures at autopsy, particularly in the amygdala and other limbic areas (Dickson, 2012). Lewy bodies are accompanied by Lewy neurites in neuronal processes, most commonly in axons. Other α-synuclein aggregates are observable throughout the neuropil, where they typically have a thin thread-like or dot-like structure (Kalia & Kalia, 2015).

While there are several methods for studying the extent and distribution of Lewy pathology at autopsy, there are currently no established biomarkers. A cerebrospinal fluid (CSF) signature of lower total α-synuclein levels with increased oligomeric and phosphorylated levels has been reported in PD, but the diagnostic accuracy of this is insufficient for it to be considered a valid disease biomarker (Blennow, Biscetti, Eusebi, & Parnetti, 2016). Levels of α-synuclein in blood and plasma samples have similarly limited diagnostic value. Some studies report that solid tissue biopsies (e.g. from the submandibular and labial salivary glands and the colonic mucosa) have high sensitivity and specificity for detecting PD, although sample sizes are typically very small (Malek et al., 2014). A potentially viable alternative to these methods would be α-synuclein neuroimaging, which would involve the injection of a radioactive ligand with a specific binding affinity for pathological α-synuclein aggregates, followed by a positron emission tomography (PET) scan. At present, valid α-synuclein radiotracers are still in their infancy (Harada, Okamura, Furumoto, & Yanai, 2018).

In contrast to *in vivo* methods, post-mortem tools for studying Lewy pathology are well established. Brainstem-type Lewy bodies are readily detectable at autopsy with conventional haematoxylin-eosin staining, though this method is insensitive to Lewy neurites and cortical-type Lewy bodies. Immunohistochemical methods offer greater sensitivity, as they exploit antibodies that selectively bind to the target protein. A second stain (counterstain) may then be applied to highlight the target protein against the surrounding tissue, facilitating visualisation of the pathological aggregates.

Traditional immunohistochemical stains for Lewy pathology relied on antibodies to ubiquitin, a small regulatory protein that is abundant in Lewy inclusions (Kuzuhara, Mori, Izumiyama, Yoshimura, & Ihara, 1988). A limitation of these stains is that they

do not reliably differentiate Lewy inclusions from AD-related neurofibrillary tangles, in which ubiquitin is similarly abundant (McKeith et al., 2005). The discovery that α-synuclein is the core constituent of Lewy bodies (Spillantini et al., 1997) led to the development of more sensitive immunostaining methods that relied on antibodies raised against the amino- and carboxyl-terminal sequences of that protein (Spillantini, Crowther, Jakes, Hasegawa, & Goedert, 1998). Immunohistochemistry for α-synuclein remains the optimal method for detecting Lewy pathology at autopsy, with several antibodies showing excellent sensitivity and specificity (Beach et al., 2008).

2.1.1 Pathological staging and diagnosis of Lewy body disease

Susceptibility to α-synuclein aggregation and the development of clinical PD may be mediated by multiple molecular pathways and mechanisms, including α-synuclein proteostasis, mitochondrial function, calcium homeostasis, and oxidative stress and neuroinflammation. For example, Lewy body disease may be caused by genetic mutations that trigger an overproduction of α-synuclein; increase the propensity of intraneuronal α-synuclein to misfold; or interfere with neuronal functions designed to degrade misfolded α-synuclein (Poewe et al., 2017). Additionally, numerous studies indicate that Lewy pathology may spread via a prion-like mechanism that involves direct transfer from affected to unaffected neurons, a process that correlates with clinical progression (Brundin & Melki, 2017).

According to the prion hypothesis for PD, pathological α-synuclein is secreted from affected neurons into the extracellular space (El-Agnaf et al., 2003), and subsequently taken up by other vulnerable neurons in synaptically-connected regions, where it seeds pathological misfolding and aggregation of endogenous α-synuclein. The validity of this model is supported by several *in vitro* studies (Volpicelli-Daley et al., 2011) and murine models of PD (Luk, Kehm, Carroll, et al., 2012; Luk, Kehm, Zhang, et al., 2012). Compellingly, it is also supported by long-term studies of a small number of PD patients who had experimental therapy, involving a graft of foetal mesencephalic dopamine neurons being implanted into their striata. Within the relatively short span of 11-16 years, Lewy bodies appeared in the young grafted

neurons, suggesting that they had been corrupted by diseased neurons endogenous to the host brain (Kordower, Chu, Hauser, Freeman, & Olanow, 2008; Li et al., 2008).

Autopsy studies by Braak and colleagues indicate that the hypothetical prion-like propagation of Lewy pathology through the PD brain follows a reasonably consistent, caudal-to-rostral trajectory. The Braak-PD model divides this path into six stages of increasing severity (Braak et al., 2003). Stage 1 is defined by pathology confined to specific nuclei of the medulla oblongata, specifically the dorsal vagal nucleus and sometimes the intermediate reticular zone. In stage 2, the pathology spreads to higher brainstem structures, including the caudal raphe nuclei and the locus coeruleus. Stage 3 is defined by midbrain involvement; the substantia nigra is affected at this point. At stage 4, subcortical structures are affected, including various nuclei of the basal forebrain, thalamus, amygdala, and claustrum. Finally, stages 5 and 6 involve the neocortex, with the prefrontal, anterior cingulate, and sensory association cortices affected most prominently at stage 5, and the entire neocortex by stage 6. In later publications, Braak and colleagues hypothesised that the earliest pathogenic event in PD is the induction of a neurotropic pathogen, such as a virus, via a nasal and/or gastrointestinal route. The pathology could then spread to the central nervous system via the olfactory tract or vagus nerve (Hawkes, Del Tredici, & Braak, 2007).

As an autopsy study, the Braak-PD model was based on cross-sectional data; there was no direct evidence for a temporal order to the pathological stages that mapped to clinical progression. However, the hypothesised correlation between pathological stages and clinical milestones is consistent with data from longitudinal cohort studies. Early pathology of the olfactory and gastrointestinal systems could underlie features such as hyposmia and constipation, which are recognised prodromal markers that often occur several years before motor onset (Berg et al., 2015; Rey, Wesson, & Brundin, 2018; Stokholm, Danielsen, Hamilton-Dutoit, & Borghammer, 2016). Involvement of the substantia nigra at stage 3 may lead to emergence of the motor syndrome, which is known to occur only when nigrostriatal degeneration is relatively advanced (Kordower et al., 2013). Finally, limbic and neocortical pathology at stages 5-6 may underlie the cognitive decline that emerges in late PD (Braak et al., 2003).

Nevertheless, several criticisms of the Braak-PD model have also emerged. The preselection of cases with Lewy pathology in the dorsal vagal nucleus for the original study may have resulted in a non-representative PD sample (Kalaitzakis, Graeber, Gentleman, & Pearce, 2008a). Subsequent studies demonstrated that about 7% of PD cases had no involvement of this nucleus despite Lewy pathology in higher areas, suggesting that the sequentiality of the Braak-PD stages is not universally consistent (Kalaitzakis, Graeber, Gentleman, & Pearce, 2008b). Additionally, the model does not consider other pathological features that are essential to the clinical expression of PD, such as neuron loss and neurotransmitter dysfunction. The "incidental Lewy body disease" entity, discussed below, clearly indicates that Lewy pathology alone is often insufficient for motor and cognitive impairment, and the Braak-PD model may therefore be criticised for focusing purely on this hallmark (Kalaitzakis et al., 2008a).

Despite these criticisms, most research to validate the model in PD has largely supported it. One autopsy study of 53 PD cases found that all had Lewy pathology of the medulla, pons, and substantia nigra, and all could be assigned to one of stages 4-6 (Jellinger, 2003). A later study involving 21 PD cases and six neuropathologists indicated that the model has very high interrater and intrarater reliability at all stages (Müller et al., 2005). Thus, the Braak-PD scheme is a valid and reliable measure for describing the propagation of Lewy pathology in those clinically diagnosed with PD.

Given the degree of pathological overlap between PD and DLB, it is unsurprising that a large percentage of DLB cases are also assignable to one of the Braak-PD stages. Jellinger's (2003) study, for example, found that all 22 DLB cases had Lewy pathology of the brainstem, entorhinal and cingulate cortices, and in some cases, the neocortex. All cases were therefore classified as stages 5 or 6. Similarly, the main criteria for describing the distribution of Lewy pathology in DLB – the McKeith criteria by the DLB Consortium (McKeith et al., 1996) – are equally applicable to PD.

In grading the severity of Lewy pathology, the McKeith criteria recommend that 10 regions from the brainstem, limbic lobe, and neocortex should be examined at autopsy. The burden of Lewy bodies and neurites in each region is scored on a semiquantitative ordinal scale (0-4, corresponding to absent, mild, moderate, severe, and very severe). The topographical distribution of these lesions forms the basis of a

classification model, whereby cases can be assigned to brainstem-predominant, limbic (or transitional), or diffuse neocortical categories (McKeith et al., 2005; McKeith et al., 1996). The most recent iteration of the criteria added olfactory bulb only and amygdala-predominant categories. These are not associated with clinical DLB, but they have potential utility for identifying prodromal disease (McKeith et al., 2017), and they may also describe the distribution of incidental α-synuclein inclusions in other neurodegenerative diseases, such as AD.

In conferring a diagnosis of DLB, the McKeith protocol requires the burden of coexistent AD lesions to be assessed. This procedure was recommended based on previous observations that the clinical expression of the DLB syndrome is muted in patients with severe comorbid AD (Del Ser, Hachinski, Merskey, & Munoz, 2001). The relative extent of Lewy and Alzheimer pathologies is used to confer a post-mortem diagnosis of DLB in the form of a probability statement. High likelihood DLB may be diagnosed only when there is limbic or neocortical Lewy pathology, and coexistent Alzheimer lesions are absent, mild, or moderate (McKeith et al., 2017).

In addition to PD and DLB, a third category of subjects with Lewy pathology may be observed in autopsy studies. These are elderly cases with Lewy inclusions but without a clear clinical history of neurological abnormality, including motor and cognitive impairment. These cases are termed “incidental Lewy body disease” (Gibb & Lees, 1988). Such cases are reasonably common: one autopsy study of 1720 cases who were positive for α-synuclein pathology reported that approximately half of those with neocortical Lewy bodies had been free of both parkinsonism and dementia during life. The vast majority of these cases could be assigned to a Braak-PD or McKeith stage (Parkkinen, Pirttilä, & Alafuzoff, 2008).

The nature of incidental Lewy body disease is contentious. It may be a non-specific, age-related development, with minimal implications for an individual’s neurological health. However, most evidence indicates that the condition is in fact a prodromal stage of PD/DLB, which would have emerged clinically had the subject survived for longer. One study found that Lewy aggregates in incidental Lewy body disease were distributionally similar to early PD (brainstem-predominant) or DLB (with neocortical involvement), but significantly sparser (Frigerio et al., 2011). Other studies have

demonstrated that the nigrostriatal dopamine deficiency (DelleDonne et al., 2008; Dickson et al., 2008) and neuron loss in the substantia nigra (Iacono et al., 2015) in incidental Lewy body disease cases are intermediate between controls and PD cases. These pathological changes are known to be reasonably severe by the time the motor signs emerge in PD (Kordower et al., 2013), pointing to a clinically silent period of pathological spread and neurodegeneration leading up to this event. Finally, limited data suggest that some mild but relevant clinical abnormalities can be detected in patients diagnosed with incidental Lewy body disease post-mortem. These include minor parkinsonian signs, subtle executive dysfunction, and hyposmia, all of which are strongly related to prodromal PD and DLB (Adler et al., 2010). Together, these results suggest that incidental Lewy body disease represents a preclinical stage of PD or DLB, where the pathology is insufficiently severe to cause significant problems.

2.2 Tau and amyloid-β pathology

Like PD, AD is pathologically defined by two hallmarks: in this case, neurofibrillary tangles and amyloid-β plaques (Figure 2-2). Neurofibrillary tangles are intraneuronal aggregates consisting of hyperphosphorylated tau protein. The microtubule-associated protein tau has six major isoforms, ranging up to 441 amino acids in length, all of which derive from the *MAPT* gene (Goedert, Spillantini, Jakes, Rutherford, & Crowther, 1989). Tau is expressed primarily in axons. Normally, it is highly soluble. However, in AD, tau undergoes hyperphosphorylation and misfolds into insoluble bundles of fibres. These neurofibrillary tangles are typically flame-shaped and consist ultrastructurally of straight or paired helical filaments (Grundke-Iqbal et al., 1986; Iqbal & Grundke-Iqbal, 2008) in a β-pleated sheet structure. Similar filamentous tau structures are also found in axons and dendrites throughout the neuropil, where they are referred to as neuropil threads (Braak, Braak, Grundke-Iqbal, & Iqbal, 1986). Hyperphosphorylation of tau protein is not unique to AD: it is also the defining pathological feature of the primary tauopathies, a group of neurodegenerative diseases that includes progressive supranuclear palsy and corticobasal degeneration.

Amyloid-β plaques are the other AD hallmark. These are microscopic, extraneuronal structures consisting primarily of amyloid-β peptide. Like the α-synuclein and tau

proteins, amyloid-β is normally soluble. It is derived from the amyloid precursor protein following sequential cleavage by β-secretase and then γ-secretase enzymes. The major isoforms have 40 or 42 amino acid residues. The $A\beta_{40}$ variant is the more abundant in the central nervous system (about 80-90% of total amyloid-β); the longer, less common form is more neurotoxic and more prone to pathological aggregation into insoluble plaques (Murphy & LeVine, 2010).

The two main types of amyloid-β deposits associated with AD are neuritic and diffuse plaques. Neuritic plaques have a dense, fibrillar core of amyloid-β configured in a β-sheet structure, typically between 10μm and 160μm in diameter, and containing both $A\beta_{40}$ and $A\beta_{42}$ isoforms. The core is encircled by pathologically altered processes (dystrophic neurites). These contain tau filaments in a paired helical configuration, indistinguishable both morphologically and biochemically from neurofibrillary tangles and neuropil threads (Dickson, 1997). Diffuse amyloid-β plaques are less well-circumscribed, lacking a β-sheet structure, a dense core, and dystrophic neurites

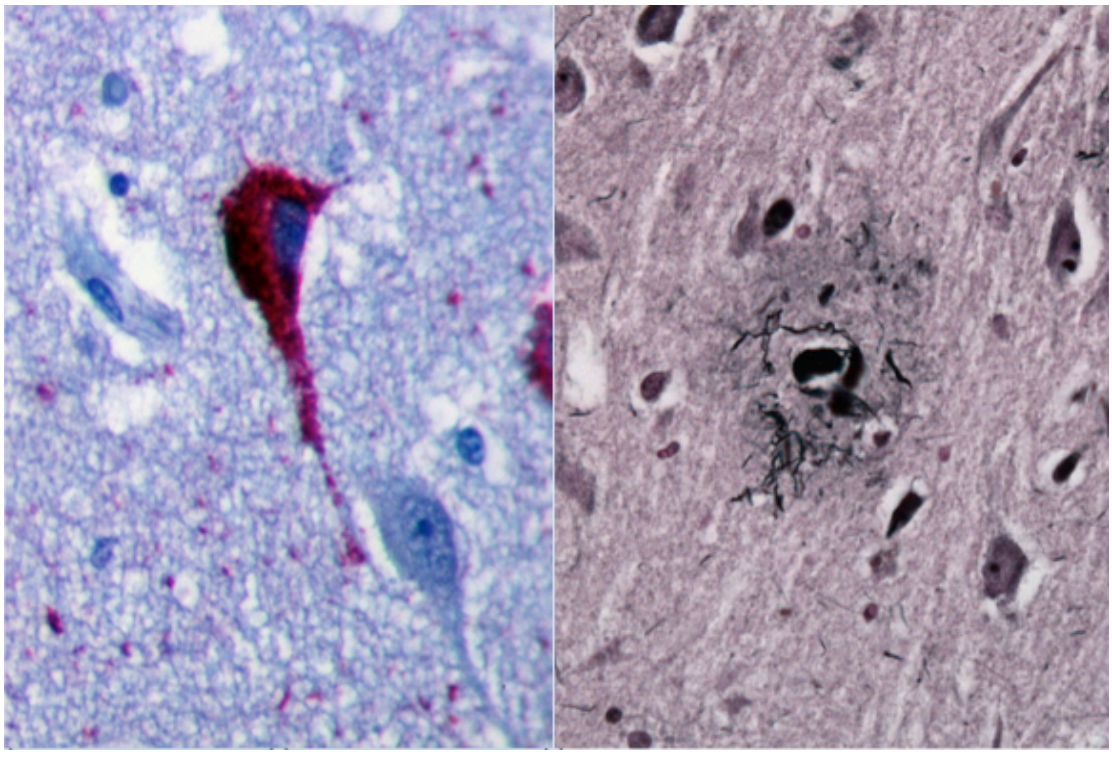


Figure 2-2. Neurofibrillary tangles and amyloid-β plaques.

Left: A neurofibrillary tangle stained with a tau antibody. Right: a neuritic amyloid-β plaque stained with the Gallyas silver technique. Source: WikiMedia Commons.

(Ikeda, Haga, Kosaka, & Oyanagi, 1989). They consist almost entirely of $A\beta_{42}$, with virtually no colocalised $A\beta_{40}$ (Iwatsubo, Saido, Mann, Lee, & Trojanowski, 1996).

As with α-synuclein, evidence indicates that tau and amyloid-β pathologies seed from neuron to neuron in the manner of infectious prion particles. The two pathologies propagate independently of one another, both temporally and spatially (L. C. Walker, 2018). According to the seminal amyloid cascade hypothesis (Hardy & Higgins, 1992), amyloid-β aggregation is the critical pathogenic event in AD, preceding tau pathology and antedating clinical onset by up to 15 years (Benzinger et al., 2013). Accumulating amyloid-β pathology disrupts intraneuronal calcium homeostasis, inducing tau hyperphosphorylation and aggregation (Baudier & Cole, 1987). Neuron and synapse loss and clinical dementia occur thereafter (Hardy & Higgins, 1992). In light of the recent, repeated failures of drugs targeting amyloid-β (e.g. solanezumab, bapineuzumab) to improve cognitive outcomes in phase 3 clinical trials involving early stage AD patients (Doody et al., 2014; Salloway et al., 2014; Vandenberghe et al., 2016), the amyloid cascade hypothesis has been criticised as fundamentally flawed (Herrup, 2015). A full discussion of the arguments for and against the hypothesis is beyond the scope of this thesis. Despite the controversy, it remains the dominant model for explaining AD chronology and for directing the development of novel treatments for the disease (Selkoe & Hardy, 2016).

One putative weakness of the hypothesis that is relevant here is the relatively poor correlation observed between amyloid-β plaque burden and dementia severity in AD. Neurofibrillary tangles and, particularly, the degree of neuron and synapse loss show significantly stronger associations (Giannakopoulos et al., 2003; Gómez-Isla et al., 1997; Terry et al., 1991). Indeed, approximately one third of healthy elderly controls are positive for amyloid-β plaque pathology despite showing no signs of cognitive impairment, though longitudinal follow-up does suggest that these individuals are at an increased risk of conversion to MCI or dementia (Villemagne et al., 2011). These findings have led some authors to argue that amyloid-β acts as the trigger in AD pathogenesis, and tau as the bullet (Bloom, 2014). In other words, tau pathology may be the mechanism by which amyloid-β indirectly exerts neurotoxic and synaptotoxic effects, an argument that is consistent with the amyloid cascade hypothesis.

Additional downstream effects of amyloid-β and tau aggregation are diverse and less specific. Massive neuron and synapse loss by late disease is reflected by marked cortical atrophy on gross inspection, with enlarged ventricles and shrunken gyri (Apostolova et al., 2012). This is readily apparent *in vivo* with structural scanning, such as computed tomography (CT) or magnetic resonance imaging (MRI). Severe loss of neurons in the nucleus basalis results in profound disruption of the cholinergic system, and modulating this process remains the best available method for slowing the progression of dementia symptoms (Ferreira-Vieira, Guimaraes, Silva, & Ribeiro, 2016). Reactive gliosis occurs in response to the neural damage; as in PD, this mainly involves astrocytes and microglia, and it is primarily centred on neuritic plaques (Fakhoury, 2017; Itagaki, McGeer, Akiyama, Zhu, & Selkoe, 1989). Finally, cerebral amyloid angiopathy (amyloid-β deposition within blood vessel walls) is a common autopsy finding in AD cases, with capillaries being the most susceptible vessels (Thal, Griffin, de Vos, & Ghebremedhin, 2008).

Methods for studying tau and amyloid-β lesions *in vivo* are currently superior to their equivalents for α-synuclein. A CSF signature of increased total and phosphorylated tau with decreased $A\beta_{42}$ has excellent sensitivity and specificity (both 85-90%) for AD dementia (Blennow et al., 2016). PET imaging with radiotracers for amyloid-β, such as thioflavin or stilbene derivatives and ^{11}C-Pittsburgh Compound B (Anand & Sabbagh, 2017), is a well-established tool in selected clinical and research settings. Development of a tau neuroimaging agent has been more challenging due to the diversity of the protein's possible ultrastructural conformations, as well as its relative scarcity in the brain; in AD, tau levels are typically 5-20 times lower than amyloid-β levels (Villemagne & Okamura, 2014). Quinoline derivatives that bind clearly to tau aggregates have been employed in clinical research, but the validity of these tracers is uncertain, as they are subject to some off-target binding. The development and validation of superior, second-generation tau tracers is ongoing (Harada et al., 2018; Schöll et al., 2019).

At autopsy, various staining techniques are available to visualise plaques and tangles. The argyrophilic properties of tau and amyloid-β mean that they respond positively to silver impregnation methods. Silver stains such as the modified Bielschowsky and Gallyas techniques have been recommended in older consensus statements, as have

the Congo red and thioflavin S dyes, which recognise β-sheet structures (Hyman & Trojanowski, 1997; Mirra et al., 1991). Such methods are superior to traditional haematoxylin-eosin staining; however, newer immunohistochemical methods offer the greatest sensitivity. These include the AT8 antibody for tau and the 4G8 antibody for amyloid-β, which were introduced more recently and remain the preferred staining methods for Alzheimer lesions (Alafuzoff et al., 2006).

2.2.1 Pathological staging and diagnosis of AD

Staging systems exist for both tau and amyloid-β pathologies in AD. The Braak-tau model (Braak & Braak, 1991) distinguishes six stages of pathology, including both neurofibrillary tangles and neuropil threads. At stages I and II (mild pathology), tau lesions are mostly confined to the superficial pre-α layer of the transentorhinal cortex and the CA1 sector of the hippocampus, both located in the medial temporal lobe. In stages III and IV (moderate pathology), there is severe involvement of the pre-α layers of both the transentorhinal and the entorhinal cortices, and progressively more hippocampal involvement. Finally, stages V and VI (severe pathology) are marked by the extension of tau aggregates to the entirety of the hippocampal formation and to the neocortex, culminating in the primary motor field in the frontal lobe. Gradually more severe involvement of certain subcortical nuclei (including the anterodorsal thalamus, amygdala, and claustrum) occurs as the disease progresses, particularly between stages III and VI (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Braak & Braak, 1991, 1995).

The original study by Braak and Braak (1991) also attempted to stage neuritic plaque progression, but the high variability of these deposits meant that the model was less clear and consistent than the equivalent system for tau pathology. However, later work by Thal and colleagues established a five-phase model of amyloid-β deposition in AD (Thal, Rüb, Orantes, & Braak, 2002; Thal et al., 2000), covering all forms of amyloid-β pathology. The first Thal phase is defined by diffuse plaques distributed throughout the neocortex. These spread to superficial (mainly pre-β and pre-γ) layers of the entorhinal cortex in phase 2. At the same time, there is deposition of “fleecy” amyloid – amorphous clouds of amyloid-β (Thal et al., 1999) – in the internal layers

of the entorhinal cortex (pri-α, pri-β, and pri-γ) and in the CA1 sector of the hippocampus. Phase 3 is marked by amyloid-β deposition in numerous subcortical structures, including the basal forebrain, dorsal striatum, thalamus, claustrum, hypothalamus, and white matter. The final two phases are defined by further caudal proliferation, affecting the substantia nigra and the reticular formation in phase 4, and the locus coeruleus, raphe nuclei, and cerebellum in phase 5 (Thal et al., 2002).

Much like the equivalent model for Lewy pathology, the Braak-tau scheme does not apply universally (Gertz et al., 1998). Nonetheless, its validity is strongly supported by clinicopathological studies, which also show a clear correlation between the pathological stages and dementia severity (P. T. Nelson et al., 2012). Suboptimal reliability was a limitation of the original 1991 model, which was based upon unconventionally thick brain sections (100μm) and used a relatively unreliable silver stain for tau. A later study used 5-15μm sections with the sensitive AT8 antibody, a protocol that made the staging scheme significantly more reliable (Braak et al., 2006). This Braak-tau model still showed relatively low interrater reliability for mild pathology – stages I-II had only 50% absolute agreement for 25 observers – though ratings were much more consistent for more advanced pathology (Alafuzoff et al., 2008). A similar study reported that Thal phases had very high interrater reliability, with approximately 80% absolute agreement found between 26 observers across the spectrum of amyloid-β pathology (Alafuzoff et al., 2009).

Early criteria for the post-mortem diagnosis of AD relied primarily on the extent of amyloid-β rather than tau lesions. The Khachaturian criteria suggested a diagnosis of AD if the number of amyloid-β plaques in a $1mm^2$ section of neocortical tissue exceeded an age-adjusted minimum (Khachaturian, 1985). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria emphasised neuritic plaques specifically. By these criteria, neuritic plaques were scored ordinally (absent, sparse, moderate, or frequent), and then adjusted for age to generate a score of A, B, or C, corresponding to increasing probability of AD (Mirra et al., 1991). The age adjustments of both systems were valuable, given the increasing incidence with age of plaque pathology without clinical manifestation (Wolf et al., 1999). However, both sets of criteria were limited by the exclusion of tau pathology – an important omission, given the correlation between tau lesions and dementia severity in AD.

This limitation was addressed by the National Institute on Aging (NIA) and Ronald and Nancy Reagan Institute of the Alzheimer's Association (NIA-Reagan) consensus criteria for AD, which incorporated indices of both tau and amyloid-β pathology into the diagnostic algorithm. The original NIA-Reagan criteria defined the likelihood of dementia resulting from Alzheimer pathology as low, intermediate, or high, based on various permutations of Braak-tau and CERAD scores (Hyman & Trojanowski, 1997). The current, significantly updated NIA and Alzheimer's Association (NIA-AA) criteria use an "ABC" model that also includes Thal phases in the diagnostic algorithm. Rather than describing the likelihood that AD underlies dementia, the new criteria simply describe the severity of Alzheimer lesions as absent, low, intermediate, or high (Hyman et al., 2012; Montine et al., 2012).

As in incidental Lewy body disease, it is reasonably common for autopsy studies to detect individuals who are neurologically normal despite the presence of Alzheimer lesions. One autopsy analysis of 188 elderly, community-dwelling individuals with no cognitive impairment during life found that more than a third fulfilled NIA-Reagan criteria for a post-mortem diagnosis of AD, the vast majority with intermediate likelihood (Schneider, Aggarwal, Barnes, Boyle, & Bennett, 2009). Moreover, another study involving 2332 unselected autopsy cases found that tau pathology was ubiquitous, though generally very mild, after the age of 40. Almost 80% of those over the age of 60 could be assigned a Braak-tau stage. Amyloid-β pathology was also common, albeit not universal. Increasing prevalence and severity was observed from age 40 onwards, but until the age of 80, less than half were affected. Even in the oldest age groups (90 and older), approximately a quarter of cases remained free of amyloid-β pathology (Braak, Thal, Ghebremedhin, & Del Tredici, 2011).

Results such as these suggest that tau and amyloid-β lesions do not universally cause manifest dementia, as is also true for α-synuclein in the case of incidental Lewy body disease. In contrast to α-synuclein, it is probable that incidental tau pathology is not always a marker of prodromal AD, given that it is universally present by middle age and, in most cases, remains clinically silent even for several decades thereafter. It is more likely that mild tau changes are a natural consequence of normal senescence, which generally do not approach the threshold for clinical significance during the average human lifespan. The combination of tau with amyloid-β pathology in the

ageing brain is a more pernicious occurrence that probably does constitute prodromal AD, in line with the amyloid cascade hypothesis.

2.3 Pathology associated with FTD

The primary feature of FTD is frontotemporal lobar degeneration, defined by selective and progressive neuron loss and reactive gliosis in the frontal and temporal lobes. Various proteins are associated with this neurodegenerative process. TDP-43 and tau underlie 85-90% of cases. TDP-43 is the most common molecular substrate of FTD, accounting for around half of the total figure. TDP-43 inclusions associated with frontotemporal lobar degeneration are typically spherical or crescent-shaped, and surrounded by dystrophic neurites of varying length and number. They are most commonly observed in the neuronal cytoplasm, though they may also occur in the nucleus, particularly in familial cases. Immunohistochemical methods for detecting TDP-43 inclusions are available; these also stain ubiquitin, but are negative for tau and other neurodegenerative disease proteins (Mackenzie & Neumann, 2016). Autopsy studies using antibodies to TDP-43 demonstrate that these lesions are reasonably common in individuals who do not have dementia. One meta-analysis involving a cumulative total of 1196 cognitively normal elderly adults found that almost a quarter had incidental TDP-43 pathology (Nascimento et al., 2018).

Tau pathology in FTD exists in several morphological variations. Pick's disease is a tauopathy defined by swollen neurons with spherical, tau-positive, intracytoplasmic inclusions ("Pick bodies"). These are biochemically and structurally distinct from AD lesions, being composed mainly of the 3-repeat tau isoform, whereas neurofibrillary tangles comprise both 3-repeat and 4-repeat isoforms (Olney et al., 2017). Aggregates of mainly 4-repeat tau also occur in FTD. These include argyrophilic grains – small, comma-shaped structures in neuronal processes (Rodriguez & Grinberg, 2015) – and large, globular inclusions in oligodendrocytes and astrocytes (Ahmed et al., 2013).

Most of the remaining cases of frontotemporal lobar degeneration relate to a family of RNA/DNA-binding proteins derived from three oncogenes: namely, the fused in sarcoma, Ewing's sarcoma, and TATA-binding protein-associated factor 15 genes.

Collectively, these are referred to as FET proteins (Mackenzie & Neumann, 2016). A very small percentage of FTD cases have inclusions that are immunoreactive for ubiquitin, but not for TDP-43, tau, or FET proteins (Holm, Isaacs, & Mackenzie, 2009). The rarity of FTD associated with any of these proteins means that they remain poorly characterised and poorly understood.

Currently, there are no validated biomarkers or staging schemes for FTD-associated protein pathologies. *In vitro* evidence suggests that these proteins may also spread via a prion-like, cell-to-cell mechanism, similar to α-synuclein in PD and tau and amyloid-β in AD (Smethurst et al., 2016). Therefore, equivalent staging schemes are plausible. Two staging models for TDP-43 pathology are available. The first is for incidental TDP-43 pathology in the context of AD (Josephs et al., 2014; Josephs et al., 2016), and the second for a newly defined disease entity – limbic-predominant age-related TDP-43 encephalopathy – that is associated with hippocampal sclerosis and often overlaps with AD and FTD (P. T. Nelson et al., 2019). In both diseases, TDP-43 inclusions originate in the amygdala, then spread to medial temporal lobe structures such as the hippocampus, and finally, to frontal cortical areas. Incidental TDP-43 lesions in DLB spread via a similar pathway (McAleese et al., 2017).

At present, no staging scheme has been validated specifically in cases of FTD caused by TDP-43 pathology. In the behavioural variant of FTD, a key model has identified four distinct distribution patterns of TDP-43 pathology (Brettschneider et al., 2014). However, evidence of a sequential order to these patterns was lacking, and therefore, the model does not constitute a true hierarchical staging scheme. Further research is needed to better characterise the trajectories of TDP-43 and other proteins in FTD, and to identify valid staging schemes.

2.4 Cerebrovascular pathology

Cerebrovascular disease refers to a diverse group of pathologies affecting the brain's blood vessels. While the diseases are chronic, they often induce cognitive impairment after one or more acute events, such as a cerebrovascular accident (otherwise known as a stroke). This occurs when the blood supply to a region of the brain is interrupted,

either due to obstruction (ischaemic stroke) or rupture (haemorrhagic stroke) of a blood vessel. Various types of neurological lesion may result from cerebrovascular disease. As the lesions do not proliferate through the brain in any predictable manner, the concept of hierarchical staging schemes does not apply in this context.

The main cerebrovascular diseases that are implicated in the pathogenesis of VCD are atherosclerosis, cerebral amyloid angiopathy, and cerebral small vessel disease (Grinberg & Thal, 2010; McAleese et al., 2016). Atherosclerosis is a degenerative disease that affects large and medium-sized arteries. It is defined by the gradual accumulation of proteins and lipids (e.g. cholesterol) into calcified plaques, which adhere to the arterial wall and result in a narrowing of the lumen. Rupture of these plaques is a major cause of blood clots (thrombosis) and subsequent stroke (Jackson, 2011). Cerebral amyloid angiopathy – a common pathology in AD, as well as VCD – is defined by the deposition of amyloid-β peptide within the walls of leptomeningeal and intracortical arteries, arterioles, capillaries, and sometimes veins, which results in the degradation of smooth muscle cells (McAleese et al., 2016). Finally, cerebral small vessel disease comprises a set of disorders that affect the brain's arterioles, capillaries, venules, veins, and small arteries. This includes arteriolosclerosis and a number of genetic and inflammatory small vessel diseases (Pantoni, 2010).

Cerebrovascular diseases can damage neural tissue in various ways. The most common cerebrovascular lesions are infarcts, haemorrhages, and white matter lesions. Infarcts are areas of necrotic tissue resulting from constricted blood supply. Large macroinfarcts are typically linked to atherosclerosis; cavitating lacunar infarcts to small vessel disease; and small microinfarcts to either small vessel disease or cerebral amyloid angiopathy (Grinberg & Thal, 2010). Cerebral haemorrhages are areas of bleeding in the brain. In cortical areas, they are often related to amyloid angiopathy, whereas in subcortical and brainstem nuclei or the white matter, they are more often related to small vessel disease (McAleese et al., 2016). Finally, white matter lesions – referred to as leukoaraiosis or white matter hyperintensities when observed by neuroimaging – involve demyelination, axon loss, and reactive gliosis in the brain's white matter. Generally, this damage is the result of degeneration of the blood-brain barrier and chronic hypoperfusion of the white matter, both of which occur as a consequence of small vessel disease (Grinberg & Thal, 2010).

Currently, criteria for evaluating the contribution of cerebrovascular lesions to cognitive impairment are limited. For research purposes, the NIA criteria for AD include diagnostic and reporting recommendations for cerebrovascular diseases and vascular brain injuries. These criteria require a minimum of six brain sections from the neocortex, basal nuclei, and thalamus to be assessed for microvascular lesions. It is recommended that the location, age, and number of these lesions, along with any macroscopic infarcts and haemorrhages, should be reported. A standardised reporting format is described in the criteria (Hyman et al., 2012).

As with neurodegenerative protein pathologies, cerebrovascular lesions are often found in tissue samples from cases who had been cognitively normal during life. An analysis of 210 cases without cognitive impairment or neurodegenerative disease found some kind of cerebrovascular pathology in just over two-thirds. Atherosclerosis was the most common pathology, affecting almost a quarter of cases. Microinfarcts, macroinfarcts, lacunar infarcts, and cerebral amyloid angiopathy were all observed in 10-20% of cases. Finally, haemorrhages and arteriosclerotic white matter lesions were found in less than 5% (Toledo et al., 2013). Thus, incidental cerebrovascular lesions are reasonably common in elderly autopsy samples, and often clinically silent.

2.5 Chapter summary

The most common dementia disorders affect the brain in different ways. The pathology of neurodegenerative diseases is defined by aberrant protein aggregates, including α-synuclein in PD and DLB, tau and amyloid-β in AD, and tau, TDP-43, FET proteins, and ubiquitin in FTD. The post-mortem identification of these proteins has been facilitated by recent advances in staining techniques that rely on sensitive immunohistochemical antibodies over traditional methods. Autopsy studies indicate that neurodegenerative and cerebrovascular lesions are common in cognitively intact elderly cases, as well as in dementia cases. In some cases, incidental pathology may constitute a prodromal disease that will manifest clinically if given sufficient time, but in many other cases, the lesions are clinically silent for the duration of the lifespan.

Typically, protein aggregates associated with neurodegenerative diseases follow characteristic paths through the brain. Numerous variables may contribute to the propagation of these protein pathologies, including disruption of proteostasis, mitochondrial dysfunction, and oxidative stress and neuroinflammation. Numerous studies also point to a prion-like mechanism of direct cell-to-cell transmission. The predictability of these paths has allowed for the creation of staging schemes that quantify pathological severity, including the Braak-PD model for α-synuclein, the Braak-tau model for neurofibrillary tangles, and Thal phases for amyloid-β. While these schemes do not apply universally, their validity and reliability are strongly supported. The extent of Lewy and Alzheimer pathologies may also be quantified by the McKeith criteria for DLB and the NIA models for AD. At present, comparable models are not available for most of the protein inclusions that underlie FTD. The concept of staging models does not apply in the same way to cerebrovascular diseases, given the heterogeneity of lesions that arise in this context.

3 Systematic review of autopsy studies of dementia in PD[1]

3.1 Introduction

According to Braak theory, the cognitive decline associated with advanced PD is driven primarily by the propagation of pathological α-synuclein aggregates into limbic and neocortical areas (Braak et al., 2003). Brief literature reviews to date support this hypothesis, but also note the high prevalence of comorbidity in people with PD (Emre et al., 2007). Coexistent pathologies, particularly those associated with AD, may influence a PD patient's cognition over and above the effect of Lewy pathology alone. Pathologies associated with frontotemporal lobar degeneration and cerebrovascular disease may also contribute to the clinical presentation. This chapter presents a novel systematic review of autopsy studies of PD cases with dementia. The main objective was to describe the relationship between each of these pathologies and the presence of dementia in PD.

Direct examination of tissue with an autopsy remains the most definitive method for studying brain pathology. In AD, autopsy examination is more sensitive than any established *in vivo* biomarker (Jack et al., 2018). In PD, valid *in vivo* biomarkers for α-synuclein are limited or unavailable, as reviewed in the previous chapter. Therefore, direct visualisation and quantification of α-synuclein aggregates requires an autopsy. An additional advantage of the procedure is that it allows for post-mortem verification of the clinical PD diagnosis. This is very valuable, given the relatively high estimates of the clinical diagnostic error rate (Adler et al., 2014; Rizzo et al., 2016).

As discussed, lesions associated with neurodegenerative and cerebrovascular diseases are frequent incidental findings in autopsy cases who did not have a corresponding diagnosis *in vivo*. For example, some degree of tau pathology, with no overt clinical

[1] The author acknowledges the contributions of Drs. Naveed Malek and Katherine Grosset to data collection for the work described in this chapter. Prof. Steve Gentleman contributed expertise in neuropathology to the final text.

manifestation, invariably develops by middle age (Braak et al., 2011), and more than a third of elderly individuals without dementia may be assigned a post-mortem diagnosis of AD (Schneider et al., 2009). Based on these results, it is unsurprising that autopsy studies consistently point to a high degree of comorbidity in these diseases. Up to half of PD cases with dementia may have enough tau and amyloid-β pathology to fulfil post-mortem diagnostic criteria for AD. These lesions also occur in PD cases without dementia, though here they tend to be less common and less severe, more similar to healthy controls (Irwin et al., 2013). In AD, Lewy bodies were observed in just under half of one autopsy sample (n = 347). In around 40% of the α-synuclein-positive AD cases, Lewy bodies were more or less restricted to the amygdala, but the remaining 60% had a pathological profile consistent with comorbid DLB (Uchikado, Lin, DeLucia, & Dickson, 2006). Recent evidence also points to a high degree of coexistent TDP-43 pathology in these diseases: TDP-43 inclusions were observed in almost three-quarters of pure AD cases, a third of pure DLB cases, and over half of mixed AD/DLB cases, compared to less than 20% of controls (McAleese et al., 2017).

In addition to these findings, cerebrovascular pathology commonly coexists with neurodegenerative diseases. A very large autopsy study by Toledo et al. (2013) found comorbid cerebrovascular disease in a third of cases with pathological AD (n = 4629, 85.7% with dementia) and a fifth of cases with an α-synucleinopathy (n = 323, 80.5% with dementia). Moderate to severe cerebral amyloid angiopathy was present in around 40% of the AD group, and around 10% of the α-synucleinopathy group. Furthermore, coexistent cerebrovascular pathology appeared to lower the threshold required for Alzheimer and Lewy pathologies to manifest clinically as dementia. Combined, these results show that neurodegenerative and cerebrovascular diseases frequently co-occur, especially in dementia cases. This phenomenon is clearest in the context of AD, where TDP-43 and cerebrovascular pathologies are significantly more prevalent than in the α-synucleinopathies (McAleese et al., 2017; Toledo et al., 2013).

Several variables contribute to the overlap between these pathologies. Firstly, neurodegenerative and cerebrovascular diseases share many risk factors. Increasing age is the strongest risk factor for most of these diseases (Guerreiro & Bras, 2015; Portegies, Koudstaal, & Ikram, 2016; Reeve et al., 2014). Autopsy studies involving large numbers of cases stratified by age group indicate that the prevalence of

comorbid conditions increases linearly with age; in the oldest age groups, multiple pathology is the norm (Jellinger & Attems, 2010b; Kovacs, Alafuzoff, et al., 2008). Vascular risk factors and depression also contribute to all-cause dementia risk. The contributions to VCD and AD are strongest, but these factors also increase the risk of dementia in PD (Diniz et al., 2013; Hasnain & Vieweg, 2014; Pilotto et al., 2016).

In addition to shared risk factors, disruption of essential molecular pathways and mechanisms may also explain the frequency of multimorbidity in elderly individuals. For example, disrupted proteostasis, neuroinflammation, and oxidative stress are all closely linked to the pathogenesis of multiple neurodegenerative diseases, including both PD and AD (Chen, Zhang, & Huang, 2016; Klaips, Jayaraj, & Hartl, 2018). Compellingly, research from cellular and animal studies also suggests that different protein pathologies may directly interact to promote one another's aggregation. In transgenic mice, overexpression of human α-synuclein promotes the formation of tau fibrils (Giasson et al., 2003). Similarly, tau provokes the aggregation and toxicity of α-synuclein *in vitro* (Badiola et al., 2011), suggesting that the relationship between the two is bidirectional. Similarly, an interaction between α-synuclein and amyloid-β (particularly the more neurotoxic $A\beta_{42}$ isoform) has been shown *in vitro* (Mandal, Pettegrew, Masliah, Hamilton, & Mandal, 2006) and in a murine model (Tsigelny et al., 2008). Thus, the development of one neurodegenerative disease may increase the probability of developing a second.

Cellular and animal models have also explored the effect of pathological protein interaction on cognition within the context of neurodegenerative diseases. In one study, the colocalisation of α-synuclein, tau, and amyloid-β in transgenic mice resulted in a markedly accelerated cognitive decline (Clinton, Blurton-Jones, Myczek, Trojanowski, & LaFerla, 2010). This finding has implications for the differential diagnosis of PDD and DLB, which currently rests on the relative timing of motor versus cognitive onset, as per the one-year rule (Emre et al., 2007; McKeith et al., 2005). If the finding that multiple pathology accelerates cognitive decline in murine models holds true in humans, then the onset timing of dementia within the context of an α-synucleinopathy may be mediated by the burden of coexistent Alzheimer pathology. This would imply that PDD and DLB are pathologically dissociable to some extent, with DLB having a higher degree of AD comorbidity.

The primary objective of this novel systematic review was to synthesise the scientific evidence to describe the relationship between various cerebral pathologies and dementia in PD. In addition to α-synuclein pathology, the frequency of coexistent tau and amyloid-β pathologies in PD was defined, and the effects of these comorbidities on cognitive status were described. The potential role of cerebrovascular lesions was also assessed, as was the influence of the less common protein pathologies associated with FTD. Secondary objectives were a) to establish the extent to which PDD is pathologically dissociable from DLB, and b) to explore the autopsy evidence for a possible additive or interactive effect between multiple coexisting pathologies, as described in cellular and animal models.

3.2 Methods

3.2.1 Protocol and registration

This systematic review was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009) at www.prisma-statement.org. The protocol was predefined and registered with the International Prospective Register of Systematic Reviews at www.crd.york.ac.uk/prospero/ on 13/02/18 (registration code CRD42018088691). The protocol was not amended at any stage after it was uploaded, though the procedure for the risk of bias assessment was modified as described below.

3.2.2 Eligibility criteria

Report and study characteristics. Only autopsy studies were eligible for the review. Studies were required to include cases with clinically diagnosed and/or pathologically verified PD, including cases with dementia diagnosed either prospectively or retrospectively. The minimum sample size was five, including comparators. Only full text papers in English with original data were included.

Types of comparators. The presence of a comparator group (e.g. healthy controls) was not mandatory. Many studies compared PD cases with dementia to other disease populations, including PD without dementia, DLB, and AD.

Types of outcome measures. The primary outcome was the presence of dementia during life, defined by clinical diagnosis or by objective cognitive testing. Studies limited to PD with MCI were not included.

3.2.3 Information sources

Search criteria were designed for the Ovid databases Medline and Embase, with articles from 1946 (Medline) or 1974 (Embase) to 26/01/2018 considered.

The search terms and syntax were then copied to and adapted for the following databases, all to 26/01/2018: *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (provided by BIREME), Cumulative Index to Nursing and Allied Health Literature (provided by EBSCO), and the Cochrane Library (provided by John Wiley & Sons). In order to identify additional relevant reports, reference lists within included articles and relevant reviews were hand searched, and the "cited by" function was applied to all included reports.

3.2.4 Search strategy

The search strategy was designed with reference to the Peer Review of Electronic Search Strategies checklist (McGowan et al., 2016). The literature search relied on medical subject headings combined with Boolean operators. Truncation of the words "dementia" and "cognition" was used to ensure that all potentially relevant lexical variations (e.g. "demented" or "cognitive") were captured.

The search terms were initially piloted for sensitivity by confirming that they identified five preselected key articles.

Searches were filtered to include only human subjects. Language filters were not applied, and duplicate results were removed. The search strategies for each database are provided in Appendix 1.

3.2.5 Study selection process

Preliminary screening relied on title and/or abstract screening, and potentially relevant articles were then read in full. Both selection stages were independently conducted by two investigators (CS and NM), with a third (KG) resolving discrepancies.

3.2.6 Data collection

A data extraction form was developed, containing one column for each item of interest. As a calibration exercise, data extraction was initially performed by the author (CS) for five randomly selected articles, and the form was then refined.

3.2.7 Data items

Data describing the type, location, and severity of pathological findings, as well as staining methods and diagnostic or staging criteria, were extracted. Demographic information (age at death, sex, disease duration, education) was recorded where provided for PD cases with dementia and for any comparison groups. Statistical comparison methods and results were noted. Study funding sources and conflicts of interest were also recorded.

3.2.8 Risk of bias assessment

The initial plan to assess risk of bias with a modified version of the Newcastle-Ottawa Scale (Wells et al., 2009), which was documented in the protocol, was revised after further reading identified significant problems with the scale's validity (Stang, 2010), and with the use of strict quantitative scales and checklists for this purpose generally (Higgins & Altman, 2009; Liberati et al., 2009). Risk of bias was therefore assessed with an adapted version of the semiquantitative Cochrane tool (Higgins & Altman,

2009). Reports were evaluated for potential bias in selection, detection, and reporting. Bias was defined as "a systematic error, or deviation from truth" sufficient to meaningfully interfere with the results or conclusions (Higgins & Altman, 2009).

The risk of bias assessment was performed by the author (CS), who was not blinded to any aspect of the included reports. Eligible reports were included in the review regardless of risk level.

3.2.9 Methods of analysis

Given the methodological and analytical heterogeneity of the target studies, no plans were made to conduct a meta-analysis.

Some reports used the same cases; in determining the sample size of all studies combined, these cases were only counted once. Partial overlap between studies was not subjected to any adjustment. In generating the bar charts to describe the severity of Alzheimer pathology, it was sometimes necessary to impute data where categories in the original report (e.g. absent and mild) had been collapsed, provided that this information could not be obtained from the report's authors. Values for imputation were based on average values when all studies were combined. Aggregation for each bar chart was based on raw numbers.

A Pearson chi-square test was used to assess whether cerebrovascular pathology was more common in PD cases with dementia compared to those without.

3.3 Results

3.3.1 Study selection and characteristics

The electronic search strategy retrieved 1552 records. Fourteen more were identified from hand searching. Excluding duplicates and non-human studies, 1519 records underwent preliminary screening. Six potentially relevant articles were found in languages other than English: these were not included, but the titles are listed in

Appendix 2. Eighty-four potentially relevant articles were read in full, and 40 of these were discarded. Half of the discarded articles were deemed to have little or no relevant detail; these are listed in Appendix 3. Ultimately, 44 articles involving 41 studies were included (Figure 3-1).

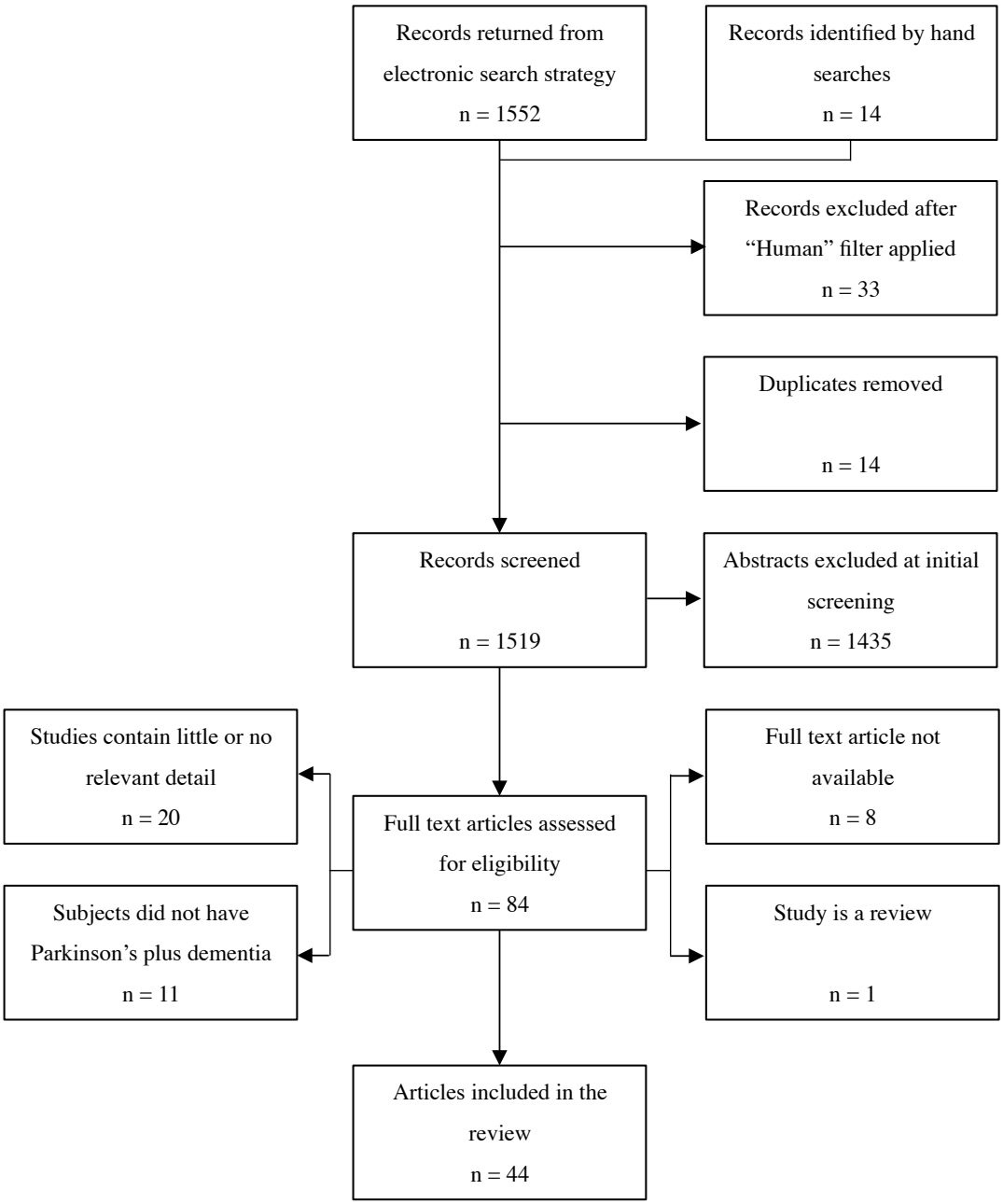


Figure 3-1. PRISMA flow diagram showing stages in the selection of studies.

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Interrater agreement was 96.8% at initial screening, and 92.9% at the full text stage. Four authors were contacted for missing information about the severity of tau and amyloid-β pathology in PD cases with dementia; none responded, and data were therefore imputed in the bar charts.

The 44 reports involved 2002 cases with clinically diagnosed and pathologically verified PD, 1145 (57.2%) of whom had dementia. Dementia was primarily a clinical diagnosis, generally referencing the most recent version of the DSM, but standard neuropsychological tests were often applied. In 32 reports (72.7%), the diagnosis of dementia was based on retrospective review of clinical notes; in the other 12 reports (27.3%), dementia was established prospectively. Comparison groups included PD without dementia, healthy controls, DLB, AD, and various others (Table 3-1).

Seven studies excluded cases that reached a specified threshold of coexistent tau pathology (Churchyard & Lees, 1997; Colosimo, Hughes, Kilford, & Lees, 2003; Halliday, Song, & Harding, 2011; Harding & Halliday, 2001; Kalaitzakis, Walls, Pearce, & Gentleman, 2011; Kövari et al., 2003; Wills et al., 2010), and one study required cases to meet post-mortem criteria for both AD and Lewy body disease (L. Walker et al., 2015). Differential diagnosis of PDD versus DLB generally relied on the conventional one-year latency rule (Emre et al., 2007; McKeith et al., 2005), but a longer range of 2 to 5 years was sometimes applied (Apaydin, Ahlskog, Parisi, Boeve, & Dickson, 2002; Harding & Halliday, 2001; Hurtig et al., 2000; Irwin et al., 2012; Kövari et al., 2003; Tsuboi, Uchikado, & Dickson, 2007).

Table 3-1. Characteristics of reports included in the systematic review.

Author (year)	PD total	PD with dementia (n, %)	Definition of dementia	Comparison groups
Aarsland et al. (2005)	22	18 (81.2)	DSM-III-R	None
Apaydin et al. (2002)	22	13 (59.1)	DSM-III-R	None
Ballard et al. (2006)	28	28 (100)	DSM-III-R	DLB
Bancher et al. (1993)[a, b]	28	12 (42.9)	MMSE<17	None
Braak and Braak (1990)	11	10 (90.9)	Clinical	Controls, AD, trisomy 21
Braak et al. (2005)	88	79 (89.8)	MMSE<21	None
Churchyard and Lees (1997)	27	17 (63.0)	DSM-III	Controls
Colosimo et al. (2003)	38	21 (55.3)	DSM-III-R	None
Compta et al. (2011)[c]	56	29 (51.8)	DSM-IV	None
de la Monte et al. (1989)	10	4 (40.0)	Clinical	Controls and AD
de Vos et al. (1995)	18	12 (66.7)	DSM-III-R / MMSE<20	Controls
Fujishiro et al. (2010)	13	13 (100)	Clinical	DLB
Gaspar and Gray (1984)	32	18 (56.3)	Clinical	Controls
Halliday et al. (2011)	19	12 (63.2)	Clinical	Controls and DLB
Harding and Halliday (2001)	41	16 (39.0)	CDR>0.5	DLB
Horvath et al. (2013)	155	109 (70.3)	Clinical	None
Howlett et al. (2015)[d]	34	34 (100)	Clinical	DLB
Hughes et al. (1993)	100	31 (31.0)	DSM-III / MMSE<20	None
Hurtig et al. (2000)	42	22 (52.4)	DSM-IV	None
Irwin et al. (2012)	140	92 (65.7)	DSM-IV	None
Jellinger et al. (1991)[a, b]	26	9 (34.6)	MMSE<17	Controls
Jellinger et al. (2002)[b]	200	66 (33.3)	MMSE<20	None
Jellinger and Attems (2006)[b]	17	17 (100)	Clinical	DLB
Jellinger and Attems (2008)[b]	68	32 (47.1)	MMSE<20	DLB
Jendroska et al. (1996)	50	23 (46.0)	DSM-III-R	Controls
Kalaitzakis et al. (2009)	32	12 (37.5)	DSM-IV / ICD-10	DLB
Kalaitzakis et al. (2011)	93	41 (44.1)	DSM-IV / ICD-10	Controls, DLB, MSA, PSP
Kempster et al. (2010)[c]	129	69 (53.5)	DSM-IV	None
Kotzbauer et al. (2012)	32	32 (100)	Clinical	None
Kövari et al. (2003)	22	10 (45.5)	CDR>0.5	None
Libow et al. (2009)	18	18 (100)	DSM-IV	None
Mattila et al. (1998)[e]	44	35 (79.5)	GDS>1	None
Mattila et al. (1999)[e]	45	35 (77.8)	GDS>1	None
Mattila et al. (2000)[e]	45	35 (77.8)	GDS>1	None
Nakashima-Yasuda et al. (2007)	90	21 (23.3)	Clinical	Controls and DLB
Perry et al. (1985)	11	7 (63.6)	Clinical	Controls and AD
Ruffmann et al. (2016)	104	55 (52.9)	DSM-IV / MDS	DLB
Sabbagh et al. (2009)	51	51 (100)	DSM-IV	None
Sierra et al. (2016)	20	10 (50)	MDS	Controls, AD, DLB
Tsuboi et al. (2007)	7	7 (100)	Clinical	DLB
Vermersch et al. (1993)	24	16 (66.6)	Clinical	Controls and AD
Walker et al. (2015)[d]	3	3 (100)	MDS	AD and DLB
Whitehouse et al. (1983)	9	5 (55.6)	Clinical	Controls and PEP
Wills et al. (2010)[f]	35 18	18 (51.4) 7 (38.9)	Clinical	Controls

[a] These reports were based on the same sample.

[b] There was potential overlap between these samples.

[c] There was potential overlap between these samples.

[d] There was potential overlap between these samples.
[e] These reports were based on the same sample.
[f] This study obtained striata from 35 cases and inferior frontal gyri from 18.
AD = Alzheimer's disease, CDR = Clinical dementia rating, DLB = Dementia with Lewy bodies, DSM = Diagnostic and Statistical Manual of Mental Disorders, GDS = Global Deterioration Scale, ICD = International Classification of Diseases, MDS = Movement Disorder Society, MMSE = Mini-Mental State Examination, MSA = Multiple system atrophy, PD = Parkinson's disease, PEP = Postencephalitic parkinsonism, PSP = Progressive supranuclear palsy.

3.3.2 Risk of bias

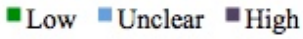
Studies were evaluated for risk of selection, detection, and reporting bias, which were then combined to generate an impression of overall risk (Table 3-2). Overall, 77.3% of reports had low risk of bias. Nine had an unclear risk, and only one report (Libow, Frisina, Haroutunian, Perl, & Purohit, 2009) had a high risk of bias. Risk of selection bias, introduced by procedures for case recruitment, was low in 65.9% of reports. Two reports had high risk. The cases in one study (Libow et al., 2009) were primarily hospital residents, whose health is likely to be considerably poorer than most PD samples (either due to PD or due to comorbid conditions). The second study recruited cases from NIA-funded AD centres, potentially leading to an overrepresentation of PD cases with comorbid AD (Nakashima-Yasuda et al., 2007). 13 reports had an unclear risk of selection bias; in all of these, the recruitment procedure and/or the source of the autopsy cases was not provided.

Risk of detection bias, related to the ways in which study outcomes were determined, was low in 45.5% reports, and unclear in 52.5%. All instances of unclear risk were due to omission of information regarding the neuropathological assessment procedures, including whether the pathologists were blinded to clinical data, what antibodies were used, and what guidelines or diagnostic criteria were consulted.

Assessment of reporting bias relied on comparison of the report's method section to its results and discussion sections, in order to identify selective outcome reporting. One study (Libow et al., 2009) had a high risk of reporting bias, due to the omission of crucial information from the results section, including neuropsychological and medical data pertaining to the vast majority of the autopsy cases. All other studies had low risk of reporting bias.

Table 3-2. Risk of bias in each report in the systematic review.

Author (year)	Selection	Detection	Reporting	Overall risk
Aarsland et al, (2005)				
Apaydin et al. (2002)				
Ballard et al. (2006)				
Bancher et al. (1993)				
Braak & Braak (1990)				
Braak et al. (2005)				
Churchyard and Lees (1997)				
Colosimo et al. (2003)				
Compta et al. (2011)				
de la Monte et al. (1989)				
de Vos et al. (1995)				
Fujishiro et al. (2010)				
Gaspar and Gray (1984)				
Halliday et al. (2011)				
Harding and Halliday (2001)				
Horvath et al. (2013)				
Howlett et al. (2015)				
Hughes et al. (1993)				
Hurtig et al. (2000)				
Irwin et al. (2012)				
Jellinger and Attems (2006)				
Jellinger and Attems (2008)				
Jellinger et al. (1991)				
Jellinger et al. (2002)				
Jendroska et al. (1996)				
Kalaitzakis et al. (2009)				
Kalaitzakis et al. (2011)				
Kempster et al. (2010)				
Kotzbauer et al. (2012)				
Kövari et al. (2003)				
Libow et al. (2009)				
Mattila et al. (2000)				
Mattila et al. (1999)				
Mattila et al. (1998)				
Nakashima-Yasuda et al. (2007)				
Perry et al. (1985)				
Ruffmann et al. (2016)				
Sabbagh et al. (2009)				
Sierra et al. (2016)				
Tsuboi et al. (2007)				
Vermersch et al. (1993)				
Walker et al. (2015)				
Whitehouse et al. (1983)				
Wills et al. (2010)				



A summary of risk of bias in each category across all studies is shown in Figure 3-2.

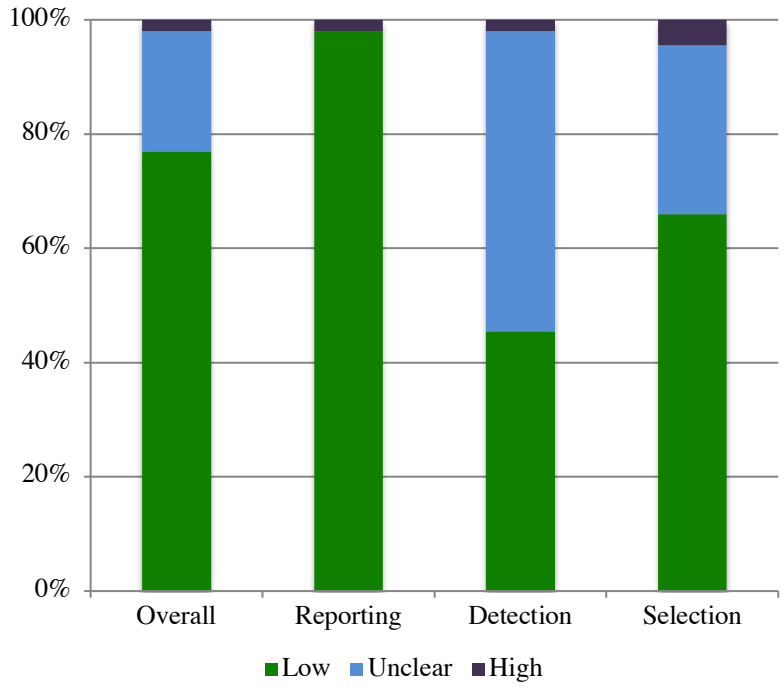


Figure 3-2. Summary of risk of bias in the included reports.

Reports were evaluated for risk of selection, detection, and reporting bias, each graded as "low", "unclear", or "high". These were combined for an impression of overall risk.

3.3.3 Lewy pathology

Lewy pathology was detected by routine staining or antibodies to ubiquitin in earlier studies, while antibodies to α-synuclein were widely used following their introduction in 1998 (Spillantini et al., 1998). Two early studies found leading causes of dementia in PD to be comorbid AD, cortical Lewy bodies, and cerebrovascular disease, though no identifiable aetiology was reported for a significant percentage (Hughes, Daniel, Blankson, & Lees, 1993; Jendroska, Lees, Poewe, & Daniel, 1996), probably due to the reliance on older staining methods.

Dementia was linked to Braak-PD or McKeith stage in four studies with a cumulative total of 480 cases. In dementia cases, Lewy pathology almost invariably extended to the limbic lobe or the neocortex (85.3-100% of cases); neocortical involvement was

consistently more frequent than in PD cases without dementia (Compta et al., 2011; Horvath, Herrmann, Burkhard, Bouras, & Kövari, 2013; Irwin et al., 2012; Kempster, O'Sullivan, Holton, Revesz, & Lees, 2010). Insoluble cortical α-synuclein levels were particularly overexpressed, though soluble levels were also raised, according to an analysis of the inferior frontal gyrus (Wills et al., 2010). Limbic and neocortical Lewy body counts were around 10 times higher in dementia cases (Apaydin et al., 2002). A moderate total cortical Lewy body score had excellent sensitivity (90.9%) and specificity (90.0%) for detecting dementia in PD (Hurtig et al., 2000). The severity of cognitive impairment correlated strongly with Braak-PD stage (Braak, Rüb, Jansen Steur, Del Tredici, & de Vos, 2005), and with Lewy body densities in the frontal, straight, cingulate, middle temporal, and angular gyri, particularly when cases with coexistent Alzheimer pathology were excluded (Mattila, Rinne, Helenius, Dickson, & Röyttä, 2000; Mattila, Röyttä, Torikka, Dickson, & Rinne, 1998).

PD cases with dementia also showed higher Lewy pathology in subcortical regions relative to those without dementia. In the amygdala and hippocampus, studies relying on ubiquitin stains found no association of Lewy bodies to dementia (Churchyard & Lees, 1997; de Vos, Jansen, Stam, Ravid, & Swaab, 1995; Mattila, Rinne, Helenius, & Röyttä, 1999), but studies using α-synuclein stains found significantly higher Lewy body densities in these regions, which correlated with dementia severity (Apaydin et al., 2002; Halliday et al., 2011; Mattila et al., 2000). Parahippocampal α-synuclein scores had excellent sensitivity (91-93%) and specificity (84-88%) for separating dementia cases from cognitively healthy PD cases (Harding & Halliday, 2001). However, in the nucleus basalis and the midbrain, including the substantia nigra, there were no differences in α-synuclein burden between PD without dementia, PDD, and DLB (Apaydin et al., 2002; Sierra, Gelpi, Martí, & Compta, 2016).

In the striatum, one study found that insoluble α-synuclein levels were twice as high in PDD as in PD without dementia (Wills et al., 2010). Another study differentiated PDD from DLB on the basis of striatal α-synuclein. Lewy pathology of the striatum affected only 29.4% of 17 PDD cases, compared to 76.5% of 17 DLB cases (Jellinger & Attems, 2006). Additionally, in the claustrum, there was a progressive and significant trend towards greater Lewy pathology from PD without dementia to PDD to DLB (Kalaitzakis, Pearce, & Gentleman, 2009). DLB groups tended towards

greater global α-synuclein than PDD groups, but differences were usually not statistically significant (Fujishiro et al., 2010; Halliday et al., 2011; Ruffmann et al., 2016; Sierra et al., 2016).

The strong association between extensive Lewy pathology and dementia was challenged by some observations. Various large samples found that between 15.2% and 44.7% of 181 cognitively healthy PD cases had severe, neocortical-type pathology (Compta et al., 2011; Horvath et al., 2013; Irwin et al., 2012; Kempster et al., 2010). One study described 17 PD cases with no dementia despite limbic and/or neocortical pathology, and concluded that no clear threshold of Lewy body burden can distinguish PD cases with and without dementia (Colosimo et al., 2003).

The opposite phenomenon, dementia cases with modest Lewy pathology, was also reported, albeit rarely. One study described three PD cases with dementia despite no Lewy bodies outside of the brainstem, and only absent or mild Alzheimer or cerebrovascular pathology. In one of the cases, the dementia may have been due to a vitamin B12 deficiency (Libow et al., 2009), but insufficient detail is provided in the report to explain the other two; partly as a result of this, the report was deemed to have a high risk of bias. However, studies with low risk of bias sporadically found other dementia cases with brainstem-type pathology. These accounted for 14.7% of one large (n = 109) dementia group (Horvath et al., 2013); smaller studies reported the figure as 12.5% (Harding & Halliday, 2001) and 3.8% (Compta et al., 2011). In all other studies that reported Braak-PD or McKeith stage, no such cases were found.

3.3.4 Coexistent Alzheimer pathology

Coexistent tau and amyloid-β pathologies of varying severity were common in PD cases. Tau pathology was universally scored with Braak-tau staging. A third of cases with dementia had moderate or severe tau pathology (Figure 3-3). There was more heterogeneity in the methods used to quantify amyloid-β lesions. Most studies used CERAD criteria, and therefore considered neuritic plaque burden only. Moderate to severe amyloid-β pathology affected just over half of PD cases with dementia (Figure 3-4). Thus, amyloid-β pathology was typically more prominent than tau pathology.

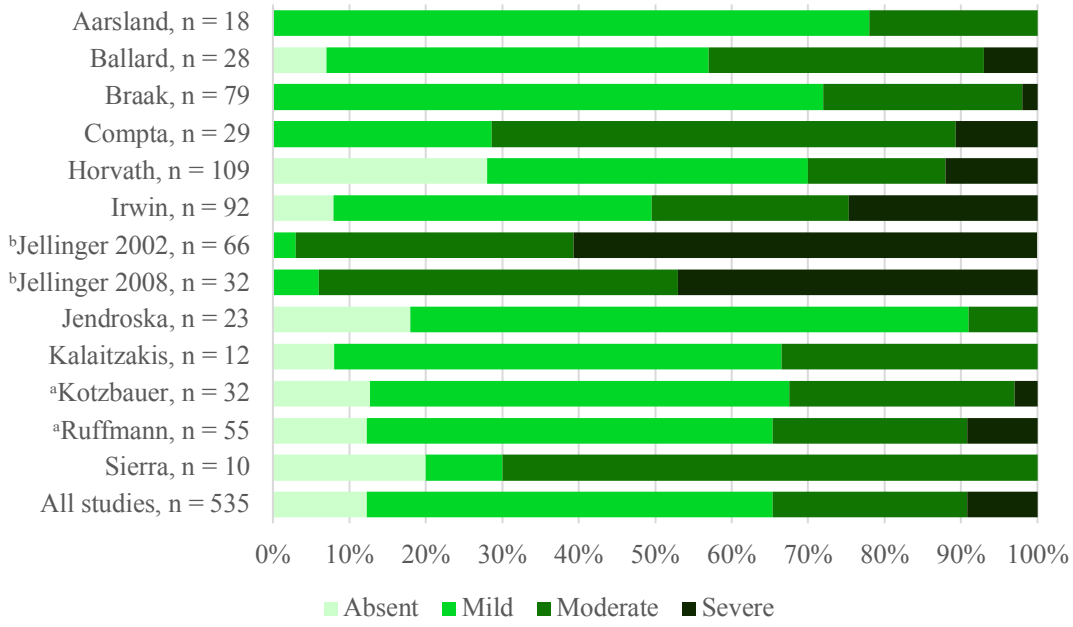


Figure 3-3. Severity of tau pathology in PD cases with dementia.

The severity of tau pathology was universally scored with Braak-tau staging. [a] Data were imputed for two or more categories. [b] There was potential overlap between these samples. PD = Parkinson's disease.

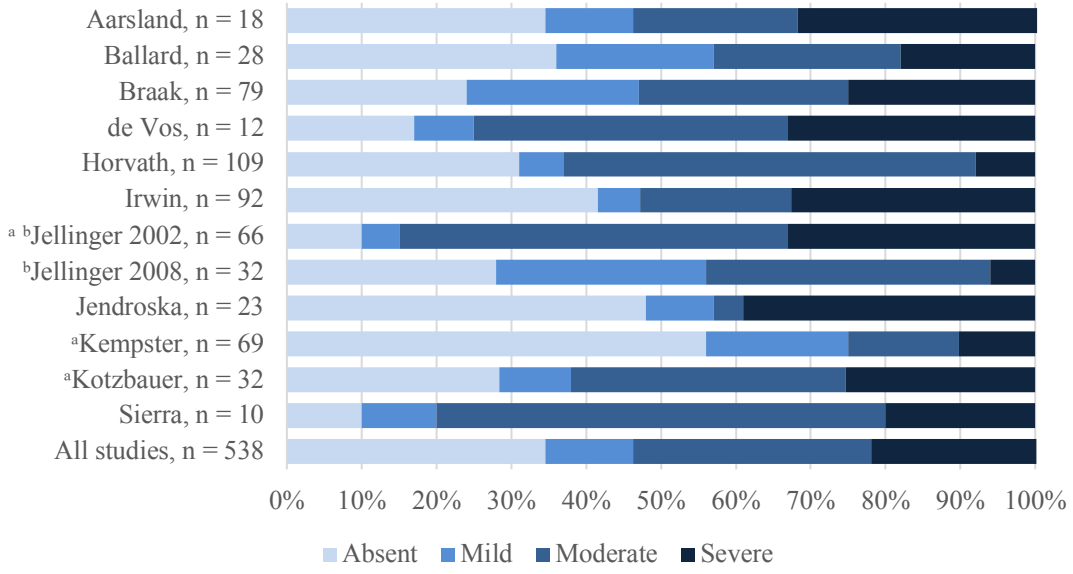


Figure 3-4. Severity of amyloid-β pathology in PD cases with dementia.

Amyloid-β scored by CERAD criteria, except for Horvath et al. (Thal phases), and Braak et al. (semiquantitative scoring ranging from mild to severe). For Thal phases, phase 1 was defined as mild, phases 2-3 as moderate, and phases 4-5 as severe. [a] Data were imputed for two or more categories. [b] There was potential overlap between these samples. CERAD = Consortium to Establish a Registry for Alzheimer's Disease, PD = Parkinson's disease.

There was significant heterogeneity in the criteria used to diagnose comorbid AD. Many studies used Khachaturian or CERAD criteria, which rely on neuritic plaque pathology only. Partially as a result of the use of different criteria, the percentage of PD cases diagnosed with comorbid AD varied markedly. The four largest studies that defined AD as intermediate or high probability by NIA criteria – thereby accounting for tangles as well as plaques – were reasonably consistent: comorbid AD was diagnosed in 19.3% (Braak et al., 2005), 20.0% (Horvath et al., 2013), 28.6% (Irwin et al., 2012), and 31.5% (Jellinger, Seppi, Wenning, & Poewe, 2002) of all PD cases. When only PD cases with dementia were considered, there was much more variability, with one large study (Jellinger et al., 2002) finding considerably more cases of comorbid AD than most other studies (Figure 3-5).

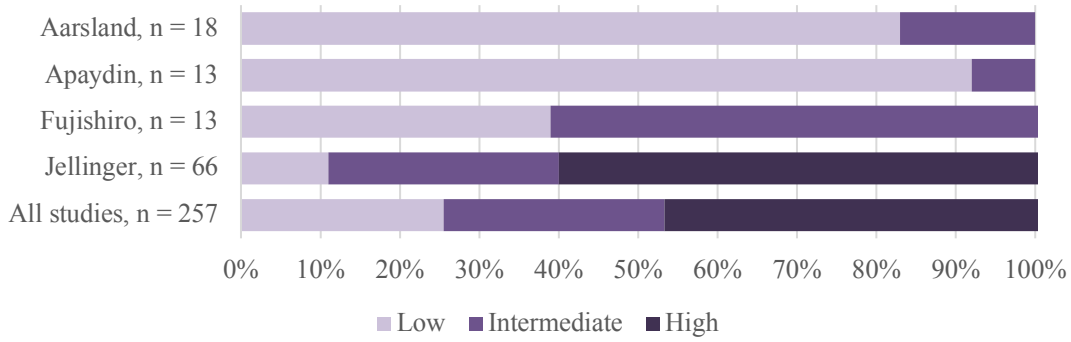


Figure 3-5. Likelihood of AD in PD cases with dementia (NIA-Reagan).

The NIA-Reagan criteria define the likelihood that dementia is due to Alzheimer pathology using an algorithm that combines CERAD scores with Braak-tau stages, therefore considering both plaque and tangle pathology. AD = Alzheimer's disease, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, NIA = National Institute on Aging, PD = Parkinson's disease.

Early studies linked dementia in PD to dysfunction of the cholinergic system resulting from degeneration of basal forebrain neurons (Gaspar & Gray, 1984; E. K. Perry et al., 1985; Whitehouse, Hedreen, White, & Price, 1983), which is also a prominent feature of AD. Comorbid AD was associated with greater cortical and amygdala atrophy in PD cases with dementia, but the striatum was severely atrophic regardless of AD comorbidity (de la Monte, Wells, Hedley-Whyte, & Growdon, 1989).

Tau and amyloid-β pathologies in PD cases with dementia were typically moderate to severe only in the entorhinal cortex, and mild in the hippocampus, according to two descriptive studies. The neocortex was generally unaffected by tau and variably affected by amyloid-β (Braak & Braak, 1990; de Vos et al., 1995). The prefrontal cortex was more affected by tau pathology than the temporal cortex in PDD cases – a rare pattern in AD. The occipital and cingulate cortices were rarely affected in these cases (Vermersch, Delacourte, Javoy-Agid, Hauw, & Agid, 1993).

Two reports based on the same samples described considerably more advanced Alzheimer pathology in PD cases with severe dementia, and concluded from this that dementia in PD was due to comorbid AD (Bancher, Braak, Fischer, & Jellinger, 1993; Jellinger, Braak, Braak, & Fischer, 1991). Later studies from the same research group supported this (Jellinger & Attems, 2008; Jellinger et al., 2002). Alzheimer pathology was substantially higher in these studies than in other series.

Amyloid-β pathology in the striatum had value for differentiating PDD and DLB. In one study, all of 17 DLB cases had moderate to severe striatal amyloid-β, compared to only 17.6% of 17 PDD. This was a statistically significant difference (Jellinger & Attems, 2006). A study excluding cases with substantial neurofibrillary pathology similarly found higher striatal amyloid-β in DLB, which correlated with dementia severity, and had 100% sensitivity and 66.7% specificity for differentiating the 10 DLB cases from the 12 PDD cases (Halliday et al., 2011). In another study, 92.9% of 14 DLB cases had dense-core plaques in the striatum, which were entirely absent in 41 PDD cases. The higher frequency of severe striatal amyloid-β in DLB was not significant in this analysis (Kalaitzakis et al., 2011).

Claustrum amyloid-β was comparable between PDD and DLB, but exceeded levels in PD without dementia, while tau was negligible in all three groups (Kalaitzakis et al., 2009). Midbrain and cerebellar amyloid-β was higher in DLB than PDD in one study (Fujishiro et al., 2010), but not in another, possibly because the latter study involved PDD cases that were approximately seven years younger on average, and therefore likely to have less advanced amyloid-β pathology than the other group (Sierra et al., 2016). In both of these studies, subtentorial tau was comparable in PD (regardless of dementia) and DLB. Finally, in a sample of cases with comorbid Lewy and Alzheimer

pathologies, those clinically diagnosed with DLB had greater global amyloid-β (significant in the temporal and cingulate cortices) and tau (significant in the frontal and cingulate cortices) than those with PDD. Global amyloid-β load was comparable for DLB and AD clinical groups (L. Walker et al., 2015).

3.3.5 Coexistent TDP-43 and cerebrovascular pathology

Only one study focused on TDP-43 pathology. Hippocampal and entorhinal sections were positive for TDP-43 in 3.0% of healthy controls, 7.2% of PD cases without dementia, 19.0% of PDD, 31.3% of DLB plus AD, and none of the DLB cases without comorbid AD. Statistical differences were found only when a dementia group was compared to a non-dementia group, and when a disease group was compared to controls (Nakashima-Yasuda et al., 2007). The risk of bias assessment suggested that this study might have artificially selected cases with more advanced AD pathology, but the clear demarcation of groups with and without pathological AD means that this procedure did not affect the results, and they can be accepted as valid.

Two studies examined argyrophilic grain disease, which was found in approximately 5% of total PD cases (n = 88 and n = 140), with no relationship to dementia (Braak et al., 2005; Irwin et al., 2012). No studies reported results for other forms of tau pathology, nor for any of the other FTD pathologies (i.e., FTD-specific tau inclusions, ubiquitin, or FET proteins).

Cerebrovascular pathology affected 16.7-28.6% of PD cases without dementia, and 15.6-44.4% of those with dementia (Aarsland, Perry, Brown, Larsen, & Ballard, 2005; Horvath et al., 2013; Irwin et al., 2012; Ruffmann et al., 2016). The percentage was sometimes higher for dementia cases, but no study detected a statistically significant difference. To assess if this observation was due to limited sample sizes, the four samples were combined and tested together with a chi-square test. The total sample size was 421; 274 had dementia, of whom 59 (21.5%) had cerebrovascular disease and 215 (78.5%) did not. Of the 147 without dementia, 31 (21.1%) had cerebrovascular disease and 116 did not (78.9%). The chi-square test confirmed that

cerebrovascular pathology was not significantly more common in PD cases with dementia ($\chi^2 = 0.01$, $p = 0.92$).

Unlike other cerebrovascular pathologies (infarcts, haemorrhages, etc.), cerebral amyloid angiopathy was significantly more common in PD cases with dementia (Compta et al., 2011; Irwin et al., 2012). The most comprehensive study of amyloid angiopathy found that it affected various types of blood vessel in PD cases with dementia, including parenchymal capillaries as well as meningeal and cortical vessels. Capillary amyloid angiopathy was severe in more than half of the dementia cases; generalised amyloid angiopathy, affecting meningeal and cortical vessels, was severe in a quarter, and moderate in around a third. In contrast, three-quarters of PD cases without dementia were completely unaffected. Consistently significant differences between the two groups were observed (Jellinger & Attems, 2008).

3.3.6 Relative contribution of α-synuclein, amyloid-β, and tau

Multiple indices of α-synuclein, amyloid-β, and (less consistently) tau were significant predictors of dementia in PD based on univariable regressions (Horvath et al., 2013; Irwin et al., 2012; Ruffmann et al., 2016). One study of 22 PD cases found that most of the variance in cognitive scores was accounted for by Lewy pathology in the entorhinal, anterior cingulate, and temporal cortices, with smaller contributions of entorhinal and temporal amyloid-β (Kövari et al., 2003). The predictive values of amyloid-β and tau were typically muted in multivariable regressions (Table 3-3). A measure of tau pathology remained independently associated in one analysis (Horvath et al., 2013), but Lewy pathology was consistently the best predictor. The predictive values of amyloid-β and tau were lost from another model when cortical Lewy bodies were added; strong collinearity of these pathologies precluded further multivariable analysis in this study (Compta et al., 2011).

Table 3-3. Predictors of dementia in PD by multivariable regression.

Author (year); method	Variable	OR (95% CI)	*p*-value
Horvath et al. (2013)	Lewy body score >6[a]	4.2 (1.7-10.6)	0.002
Multivariable logistic regression	Braak-tau stage	1.6 (1.1-2.3)	0.009
Irwin et al. (2012)	Total cortical Lewy score	4.1 (1.9-8.8)	<0.001
Stepwise-selection model	*APOE* ε4 genotype	4.2 (1.3-13.8)	0.018
Ruffmann et al. (2016)	Mean cortical Lewy score	4.2 (2.2-9.0)	<0.001
Multivariable logistic regression			

[a] By 1996 McKeith criteria (McKeith et al., 1996).
CI = confidence interval, OR = odds ratio.

One study of 104 cases used receiver operating characteristic curves to predict dementia in PD, and found that mean cortical Lewy body score alone was the best predictor (area under the curve [95% confidence interval, CI]: 0.80, [0.72, 0.88]) (Ruffmann et al., 2016). However, another study of 56 cases indicated that a combination of α-synuclein, amyloid-β, and tau was superior to any single measure (0.95, [0.88, 1.00]) (Compta et al., 2011).

A multivariable regression with dementia severity as a continuous dependent variable indicated that anterior cingulate and entorhinal Lewy body densities jointly accounted for approximately 60% of the variance in cognitive scores; values for tau and amyloid-β were non-significant in this model (Kövari et al., 2003). Another study using linear regression again found the best results for cingulate Lewy pathology; additionally, neurofibrillary tangle load in the temporal lobe was a marginally significant predictor ($p = 0.047$). When cases with severe amyloid-β load were excluded, frontal α-synuclein was the sole significant predictor (Mattila et al., 2000).

Only one study (n = 22) found that cognitive scores could not be predicted by any measure of α-synuclein, amyloid-β, or tau, though Lewy body score could predict the annual rate of cognitive decline (Aarsland, Perry, et al., 2005). The best predictor of annual decline was a summated score incorporating both Lewy and Alzheimer

pathologies of the prefrontal cortex, according to a later study that used multiple backward regressions (Howlett et al., 2015).

None of the studies that assessed the predictive value of cerebrovascular pathology for dementia found a significant association, including for cerebral amyloid angiopathy, in either univariable or multivariable analyses (Compta et al., 2011; Horvath et al., 2013; Irwin et al., 2012; Ruffmann et al., 2016).

3.3.7 The motor-cognitive interval and mortality

The latency from motor to cognitive onset in PD was studied in four survival analyses (Ballard et al., 2006; Kotzbauer et al., 2012; Ruffmann et al., 2016; Sabbagh et al., 2009) with a cumulative total of 166 PD cases with dementia; three of these studies (Ballard et al., 2006; Ruffmann et al., 2016; Sabbagh et al., 2009) associated higher amyloid-β with a shorter motor-cognitive interval. Moderate to severe plaque pathology reduced this interval by 4.7 years on average (Sabbagh et al., 2009). Additionally, a multivariable regression model established cortical amyloid-β as the only significant predictor of a shorter motor-cognitive interval (Ruffmann et al., 2016). No associations of α-synuclein or tau were found in any of these studies.

In another study (n = 28), a longer time to dementia correlated moderately with reduced plaque pathology, and more weakly with reduced α-synuclein, but not with Braak-tau stage. A significant correlation ($r = –0.37$, $p = 0.04$) was also observed with measures of choline acetyltransferase in the temporal cortex, indicating that cholinergic activity in this area is reduced in cases with a longer duration of motor decline preceding cognitive onset (Ballard et al., 2006).

Other studies explored the association of pathology with mortality. Kaplan-Meier survival curves in one study (n = 32) linked increased amyloid-β pathology to a higher mortality rate (Kotzbauer et al., 2012). A larger study (n = 200) additionally found a weaker association of tau to mortality; comorbid AD decreased life expectancy by a mean of 4.5 years. A multivariable regression found that dementia,

tau pathology, and particularly neuritic plaque pathology all predicted lower survival (Jellinger et al., 2002).

3.3.8 Intercorrelations between different pathologies

Moderate positive correlations were reported between Braak-tau stage and cortical and striatal amyloid-β load (Compta et al., 2011; Halliday et al., 2011) and Thal phase (Horvath et al., 2013). Alzheimer lesions also correlated positively with α-synuclein burden. Braak-tau stage correlated weakly with Braak-PD stage, global Lewy body score, and global, cortical, and striatal Lewy neurite score (Compta et al., 2011; Halliday et al., 2011; Horvath et al., 2013). Generally stronger correlations were found between α-synuclein and amyloid-β. Global Lewy body score correlated better with Thal phases than with Braak-tau stages, though the coefficient was still modest (Horvath et al., 2013). Moderate correlations were found between multiple indices of α-synuclein (Braak-PD stage, cortical Lewy body score, and striatal and hippocampal Lewy neurites) and cortical and striatal amyloid-β (Compta et al., 2011; Halliday et al., 2011). Another study demonstrated moderate positive correlations between striatal α-synuclein and cortical and hippocampal plaques, but not with hippocampal tangles (Tsuboi et al., 2007).

Cerebral amyloid angiopathy correlated moderately with tau pathology, and more modestly with cortical amyloid-β load (Compta et al., 2011). TDP-43 pathology correlated strongly with Braak-tau stage (Nakashima-Yasuda et al., 2007), but unfortunately, the potential association of TDP-43 with amyloid-β was not analysed.

3.3.9 Genetic results

The genetics underlying dementia in PD were not the focus of this review, but data pertaining to genetic differences were recorded where present. A higher percentage of *APOE* ε4 carriers were consistently found in PD cases with dementia compared to those without. In two studies, this was not statistically significant (Compta et al., 2011; Ruffmann et al., 2016), but another study with fewer ε4 carriers in the cases without dementia did detect a significant difference (Irwin et al., 2012). A stepwise

regression model in this study also found that the ε4 allele was strongly related to dementia in PD, with an odds ratio of 4.2, comparable to the odds ratio for total cortical Lewy body score (Table 3-3). Another study based on cases with mixed Alzheimer and Lewy pathologies found that those clinically diagnosed with PDD, DLB, and AD could not be differentiated by ε4 frequency (L. Walker et al., 2015).

The *APOE* ε4 allele was linked to some pathology scores. One study found that it was associated with higher parietal, temporal, and entorhinal amyloid-β, and higher total, entorhinal, and occipital amyloid angiopathy. However, there was no relationship of ε4 to cortical Lewy pathology or to tau (Compta et al., 2011). In contrast, other studies found that ε4 was associated with increased global Lewy pathology in the cortex, which was significant in the precentral, angular, and temporal gyri (Mattila et al., 2000). In a combined PDD/DLB sample, ε4 was again associated with higher global cortical α-synuclein, and linear regressions showed that it predicted higher Lewy body density in the frontal, parietal, and temporal cortices (Ruffmann et al., 2016). In the only other study that examined amyloid angiopathy and *APOE*, no ε4 carriers were identified in the PDD group. In the limited number of cases of DLB and PD without dementia, no association of ε4 to generalised or capillary amyloid angiopathy scores was observed (Jellinger & Attems, 2008).

The only other genetic results concerned *MAPT*. No association of *MAPT* status to dementia was found in any study that carried out the analysis. Additionally, linear regression found that no *MAPT* genotype was associated with any clinical or pathological outcome (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016).

3.4 Discussion

The results of the systematic review show that limbic and neocortical Lewy pathology is present in virtually all cases of PD with dementia. Coexistent pathologies that contribute to dementia, most notably Alzheimer-related changes, are common. Of the studies that defined pathological AD by NIA-Reagan criteria, between a fifth and a third of all PD cases fulfilled that diagnosis (Braak et al., 2005; Horvath et al., 2013; Irwin et al., 2012; Jellinger et al., 2002). In the PD cases with dementia, tau pathology

was moderate or severe in around a third, and amyloid-β pathology was moderate or severe in just over half. Thus, even taking into account the differences across studies, both tau and amyloid-β pathologies are common in PD cases at autopsy, particularly in those with dementia.

The relative contribution of Alzheimer versus Lewy pathologies was more difficult to define, due to variation between studies. Studies from one research group found advanced Alzheimer pathology in most cases of PD with dementia (Bancher et al., 1993; Jellinger & Attems, 2008; Jellinger et al., 1991; Jellinger et al., 2002). In other studies, Alzheimer lesions were universally less frequent and less severe. These differences were not explicable by systemic differences in dementia severity, age, disease duration, or case selection procedures. While global tau independently predicted dementia in PD in one study (Horvath et al., 2013), two other studies found no such association (Irwin et al., 2012; Ruffmann et al., 2016). One possible explanation for this was the lower α-synuclein burden in the first study compared to the other two, which might have allowed the independent contribution of tau to emerge. Another factor may be differences in the distribution of tau pathology, as involvement of some areas correlated more closely and consistently with dementia than others. For example, neurofibrillary tangles in the temporal lobe showed a particularly strong linear association with dementia severity (Mattila et al., 2000).

Combined, these results indicate that tau contributes to dementia in a subset of PD cases, particularly when α-synuclein levels are relatively low or tau levels relatively high. Amyloid-β, in contrast, was not independently related to dementia in any study. Thus, tau has a closer relationship with cognitive status in PD than amyloid-β, which is consistent with observations in AD (P. T. Nelson et al., 2012). These findings have implications for clinical trials of novel disease-modifying therapies in PD that target α-synuclein. Specifically, testing for tau (e.g. using CSF assays) will be beneficial for studies that include cognitive function as a key outcome, either as part of the selection criteria or as a stratification factor for sub-group analysis.

While amyloid-β pathology was not associated with the presence of dementia in PD, moderate to severe plaque deposition was strongly linked to a more rapid cognitive decline (Ballard et al., 2006; Halliday et al., 2011; Ruffmann et al., 2016; Sabbagh et

al., 2009), and to earlier mortality (Jellinger et al., 2002; Kotzbauer et al., 2012). Longitudinal biomarker studies measuring amyloid-β *in vivo* support its association with the rate of cognitive decline in PD, showing that higher amyloid-β predicts a greater decrease in cognitive scores over time (Gomperts et al., 2013; Siderowf et al., 2010). Therefore, testing for amyloid-β as well as tau is also likely to become relevant in longitudinal studies of disease-modifying treatments for PD. Analyses of the rate of cognitive decline should include a measure of amyloid-β as a covariate.

The consistent association of amyloid-β with the motor-cognitive interval in both autopsy and biomarker studies indicates that it is a key factor distinguishing DLB from PDD. The most striking differences between these two groups were found in the striatum. Moderate to severe striatal amyloid-β had good specificity (66.7-82.4%) for DLB versus PDD (Halliday et al., 2011; Jellinger & Attems, 2006), and dense-core striatal plaques were present only in DLB (Kalaitzakis et al., 2011). While neuroimaging findings are similar (Edison et al., 2008), it is not clear how early these differences emerge; further studies of this would help to refine the diagnostic criteria for prodromal PD. These criteria rely on features such as RBD, hyposmia, and autonomic dysfunction (Berg et al., 2015), all of which also frequently precede DLB, such that the criteria often capture cases who progress to DLB rather than PD (Fereshtehnejad et al., 2017). Amyloid-β biomarkers, which are already incorporated into criteria for prodromal and preclinical AD (Dubois et al., 2014; Sperling et al., 2011), may also have a place in the prediction of a motor-dominant PD phenotype versus a cognitive-dominant DLB phenotype in at-risk individuals.

As expected, the relationship between α-synuclein and dementia was strong, but again there was some variation between studies. Global cortical α-synuclein was generally the best predictor of dementia (Horvath et al., 2013; Irwin et al., 2012; Kövari et al., 2003; Mattila et al., 2000; Ruffmann et al., 2016), though cingulate or frontal scores had the best correlations in one study (Mattila et al., 2000), and the addition of tau and amyloid-β measures improved predictive accuracy for dementia in another (Compta et al., 2011). Neocortical, limbic, and paralimbic α-synuclein was almost universally more severe in dementia cases, and this had excellent sensitivity and specificity for distinguishing these cases from cognitively healthy PD cases (Harding & Halliday, 2001; Hurtig et al., 2000). While the findings strongly support Braak theory (Braak et

al., 2003) and the role of extensive α-synuclein as the primary substrate of dementia in PD, some exceptions to the rule were observed.

Firstly, significant α-synuclein deposition in limbic or neocortical areas was often found in PD cases who did not have a history of cognitive impairment. Such cases accounted for around 15-45% of the cognitively healthy PD group in the largest studies (Compta et al., 2011; Horvath et al., 2013; Irwin et al., 2012; Kempster et al., 2010). Other large autopsy studies have also reported relatively severe α-synuclein, as well as tau and amyloid-β pathologies, in many elderly cases with neither motor nor cognitive impairment in life (Parkkinen, Kauppinen, Pirttilä, Autere, & Alafuzoff, 2005; Parkkinen et al., 2008; Schneider et al., 2009). Higher cognitive reserve may explain the variance between pathological and clinical severity in AD (W. Xu, Yu, Tan, & Tan, 2015), and this may also apply to PD (Hindle, Martyr, & Clare, 2014). Unfortunately, too few studies reported proxy measures of cognitive reserve, such as educational or occupational attainment, to allow a test of this as part of the systematic review. Neural plasticity, genetics, and environmental exposures could also explain the observations; all of these are worthy of further study in the context of PD.

Secondly, a rare but intriguing finding was the occurrence of dementia cases with relatively modest, brainstem-type Lewy pathology. The cognitive impairment in these cases is presumably due to a pathology distinct from the primary condition. Comorbid AD probably accounts for the majority of these, but some individual cases may have had other problems, including vascular dementia or FTD. Alternatively, cholinergic dysfunction originating in the basal forebrain, which was related to cognitive function in several studies (Gaspar & Gray, 1984; E. K. Perry et al., 1985; Whitehouse et al., 1983), might be sufficient to independently cause dementia in a small number of cases. A focus on these apparently anomalous cases in future research would be useful for further explaining the pathological variation that underlies dementia in PD.

Several other pathologies were assessed for a link with dementia in PD. TDP-43 did not contribute to dementia in the only study that assessed this. TDP-43 was correlated strongly with tau pathology (Nakashima-Yasuda et al., 2007), but the association with amyloid-β was not evaluated. Animal models indicate that amyloid-β induces TDP-43 misfolding and aggregation (Herman, Khandelwal, Stanczyk, Rebeck, & Moussa,

2011); the potential for this in PD could be examined in future research. Similarly, argyrophilic grain disease was rare and not associated with dementia in PD (Braak et al., 2005; Irwin et al., 2012). It is possible that this pathology is more common than indicated by these two studies, as it is often overlooked at autopsy (Das & Ishaque, 2018), but the current results suggest that argyrophilic grain disease is an incidental, age-related finding that does not contribute to the incidence of dementia in PD.

Cerebral amyloid angiopathy was significantly more common in dementia cases, and correlated with coexistent Alzheimer pathology (Compta et al., 2011; Irwin et al., 2012; Jellinger & Attems, 2008). Other cerebrovascular pathologies were not more common in dementia (Aarsland, Perry, et al., 2005; Horvath et al., 2013; Irwin et al., 2012; Ruffmann et al., 2016), even when the studies were combined. This finding seemingly contrasts with some prospective studies, which have reported a correlation between increasing vascular risk factors and cardiovascular disease, and poorer cognitive scores in PD (Malek et al., 2016), particularly in the domains of executive function and attention (Pilotto et al., 2016). Differences in disease duration and overall pathological burden may explain the discrepancy. Participants in the prospective studies were one to five years into the disease on average. In contrast, the autopsy cases represented end-stage PD, when the extensive burden of Lewy and Alzheimer pathologies probably masked any independent role of vascular factors.

Finally, previous cellular and animal studies have indicated that α-synuclein, tau, and amyloid-β may promote one another's aggregation to accelerate neurodegeneration and dementia (Badiola et al., 2011; Clinton et al., 2010; Giasson et al., 2003; Mandal et al., 2006; Tsigelny et al., 2008). Multiple studies in the systematic review found correlations that support this theory in humans with PD (Apaydin et al., 2002; Compta et al., 2011; Halliday et al., 2011; Horvath et al., 2013; Mattila et al., 2000). An exacerbating role of amyloid-β on α-synuclein or tau may be the mechanism by which this pathology accelerates the rate of cognitive decline in PD. Additionally, the intercorrelations between these pathologies suggests that disease-modifying therapies targeted against one may actually inhibit the proliferation of another, increasing the overall benefit. This effect has already been demonstrated in a murine model, in which transgenic mice overexpressing α-synuclein were protected from cognitive and

motor impairment after treatment with an antibody for tau (Gerson et al., 2018). How this would translate to clinical research involving humans remains to be evaluated.

3.4.1 Role of *APOE* and *MAPT* genotypes

Genetic analysis of autopsy cases focused exclusively on two genes: *APOE* and *MAPT*. *APOE* ε4, the strongest genetic risk factor for AD (Pimenova, Raj, & Goate, 2018), was consistently overrepresented in PD cases with dementia compared to those without (Compta et al., 2011; Ruffmann et al., 2016; L. Walker et al., 2015), though the differences were only statistically significant in one study (Irwin et al., 2012). A multivariable regression in this last study additionally found that ε4 had strong predictive value for dementia, with an odds ratio similar to that reported in AD samples (Andreasson et al., 2014). Studies involving living subjects have produced similarly inconsistent results for *APOE* ε4, likely a product of small sample sizes and heterogeneous cognitive measures. According to a recent review, most evidence supports a link between ε4 status and cognitive decline in PD (Fagan & Pihlstrøm, 2017), with a faster progression to dementia in ε4 carriers compared to non-carriers (Morley et al., 2012; Schrag, Siddiqui, Anastasiou, Weintraub, & Schott, 2017).

The link between *APOE* ε4 and pathology scores could explain the mechanisms by which the allele influences cognition in PD. No study reported an association of ε4 with tau. However, several studies found that ε4 exacerbated amyloid-β and (less consistently) Lewy pathology, particularly in neocortical areas (Compta et al., 2011; Irwin et al., 2012; Mattila et al., 2000; Ruffmann et al., 2016). Previous research has indicated that the exacerbatory effects of ε4 on amyloid-β pathology may promote the development of comorbid AD in Lewy body diseases. However, separate mechanisms that are unrelated to amyloid-β (e.g. disruption of neuroplasticity or mitochondrial function) may also contribute to the development of pathologically "pure" PDD or DLB (Tsuang et al., 2013). Recent research indicates that ε4 may have direct pathogenic effects on α-synuclein (Emamzadeh, Aojula, McHugh, & Allsop, 2016), which could also explain the allele's association with pure PDD and DLB. Together, these findings show that ε4 confers a significantly worse prognosis in PD by

increasing the probability of dementia, either due to comorbid AD or due to advanced Lewy pathology.

The included studies agreed that *MAPT* status was unrelated to dementia and to any pathology scores (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016). This is consistent with some cohort studies (Mata et al., 2014; Morley et al., 2012), but contrasts with others that reported an association of the H1 haplotype with cognition (Nombela et al., 2014; Williams-Gray, Evans, et al., 2009). Again, the discrepancy may be partially explicable by limited sample sizes leading to underpowered analysis, or by heterogeneity in cognitive measurement methods and sample characteristics. It has been suggested that *MAPT* H1 is related to cognitive decline in early PD, but that this association is muted in later disease (Collins & Williams-Gray, 2016; Morley et al., 2012). Because the studies included in this review involved autopsy subjects, they naturally tended to involve older cases with advanced PD: in the three studies that reported results for *MAPT*, mean disease durations were in the 13-15 year range (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016). At present, this explanation remains speculative; further research is required to establish whether different genetic mechanisms mediate early versus late cognitive decline in PD.

The association of *APOE* and *MAPT* with cognition in PD will be considered in further detail in Chapter 7, in which a novel analysis of these genes in a large PD cohort is presented. This will clarify some of the inconsistencies that have been observed in previous research, including the autopsy studies in this review.

3.4.2 Limitations

Strengths of the review were the comprehensiveness of the search strategy, the large sample size of over 2000 pathologically-confirmed PD cases, and the low risk of bias in almost all of the included studies. However, various methodological limitations were found in the studies assessed. Ascertainment of dementia was retrospective in 32 reports (72.7%), and therefore derived from non-standardised medical notes that may have been incomplete or superficial. In particular, distinguishing PDD from DLB based purely on retrospective review may be difficult (Lippa et al., 2007), though

some studies controlled for this by requiring a longer motor-cognitive interval in order to exclude ambiguous cases. Secondly, several studies used a short screening test to assess cognition; many of these have limited sensitivity and specificity for dementia in non-AD samples, including PD (Zadikoff et al., 2008). Thirdly, many of the included studies had a small sample size, and none reported power calculations. Finally, many studies did not report relevant information pertaining to the source of autopsy cases or the procedures followed during the pathological assessment. Ideally, two neuropathologists should conduct each assessment, in order to control for the subjectivity that is inherent in semiquantitative rating scales. Pathologists should also be blinded to clinical data, in order to minimise the risk of observer-expectancy bias.

The review itself may have been limited by aspects of the electronic search strategy. There was some potential for publication bias: eight possibly relevant unpublished articles could not be retrieved online. Furthermore, the exclusion of articles in languages other than English may have led to the omission of some relevant detail.

3.4.3 Conclusions

Several disease processes, particularly Alzheimer-related, often coexist with PD, and these are frequently severe enough to affect cognition, thereby adding to the effects of Lewy pathology alone. Tau pathology contributes to dementia in a subset of cases, and amyloid-β confers a worse prognosis, characterised by an accelerated cognitive decline and earlier mortality. A reciprocal interaction between α-synuclein, tau, and amyloid-β means that they promote one another's aggregation, leading to a more aggressive disease course. Accordingly, both tau and amyloid-β should be assessed in clinical trials of new disease-modifying therapies targeting α-synuclein, particularly when cognition is a study outcome. This will improve the chance of showing efficacy, and reduce the risk of a false negative finding caused by coexistent pathologies.

4 Clinical diagnostic criteria for dementia disorders

Dementia disorders are distinguishable at autopsy by pathological differences: either aberrant protein aggregations in neurodegenerative diseases, or cerebrovascular damage in vascular dementia. The pathological variation means that each disorder is associated with a characteristic clinical profile *in vivo*. Features of these profiles (cognitive, behavioural, neurological, etc.) are described in clinical diagnostic criteria. These guidelines form the framework for diagnosis, especially in research settings where it is important for study samples to be clearly and consistently defined. In most criteria, particular combinations of core and supportive features are used to specify the level of diagnostic confidence. This chapter describes and critically reviews the current diagnostic criteria for the main dementia disorders (AD, PDD, DLB, FTD, and VCD). Where available, research criteria for the predementia stages of each disorder are also considered.

In most sets of diagnostic criteria, dementia is defined consistently with the DSM-5: a decline in cognition from a previous level, evidenced by concern on the part of the patient, a knowledgeable informant, and/or a clinician, and supported by objective neuropsychological testing. The decline should affect a minimum of two cognitive domains. The symptoms should not occur purely in the context of drug intoxication or delirium, and should not be attributable to another disorder, such as major depression or encephalitis. The decline should be of sufficient magnitude to interfere with social and occupational function. Importantly, the functional impairment must result from cognitive deficits, rather than from motor or sensory deficits (e.g. parkinsonism or post-stroke paralysis). MCI is distinguished from dementia by a more modest decline, sometimes affecting only one domain, which is insufficient to significantly interfere with function (American Psychiatric Association, 2013). In this chapter, it will be noted where the diagnostic criteria deviate from the DSM definition.

4.1 Clinical diagnostic criteria for AD dementia

Two major sets of AD diagnostic criteria are currently in use. The first was published by the International Working Group (IWG) for New Research Criteria for AD (Dubois et al., 2007), and subsequently updated as the IWG-2 criteria (Dubois et al., 2014). The other criteria were published by the NIA-AA. Separate sets of clinical NIA-AA criteria were published for AD dementia (McKhann et al., 2011), AD-MCI (Albert et al., 2011), and preclinical AD (Sperling et al., 2011); these were recently collated into an overarching research framework (Jack et al., 2018).

Both the IWG and the NIA-AA dementia criteria define typical AD by a gradual and relatively long-term decline in episodic memory (Dubois et al., 2007; McKhann et al., 2011). The IWG criteria also specify that the memory deficit does not benefit from cueing (Dubois et al., 2007). This is a useful addition, as a lack of a cueing benefit points to a genuine encoding problem reflecting hippocampal dysfunction, as opposed to an information retrieval problem mediated by frontostriatal circuits. This feature has value for distinguishing AD from other dementias, such as DLB and PDD, in which a retrieval deficit is prominent (Economou, Routsis, & Papageorgiou, 2016).

The IWG-2 criteria distinguish three atypical AD variants, defined by focal cortical damage and a relatively spared hippocampus, resulting in a primarily non-amnestic presentation. Posterior-variant AD is defined by occipitotemporal or bilateral parietal atrophy, leading to visuospatial deficits (e.g. object or face recognition). Frontal-variant AD presents clinically as the behavioural variant of FTD, with marked frontal lobe atrophy leading to behavioural changes and a dysexecutive cognitive syndrome. Logopenic-variant AD also presents clinically as an FTD subtype, with a progressive language impairment that primarily affects word retrieval (Dubois et al., 2014). The anatomical substrate of logopenic AD is atrophy of the posterior temporal and inferior parietal lobes of the left hemisphere (Henry & Gorno-Tempini, 2010). The NIA-AA distinguish the same atypical variants, albeit with different terminology (visuospatial, executive, and language presentations) that reflects the primary neuropsychological deficit (McKhann et al., 2011).

The inclusion of atypical variants gives the current criteria greater validity than previous criteria, which required memory impairment (McKhann et al., 1984). This is a significant development, given that large clinicopathological studies have found that 6-25% of autopsy-confirmed AD cases had a non-amnestic profile *in vivo* (Lopez et al., 2000; Murray et al., 2011). However, the description of atypical variants introduces potential for confusion with other dementias, particularly FTD. Most cases with a posterior or logopenic syndrome have AD at autopsy (Migliaccio et al., 2009), but the frontal syndrome is more often associated with pathological FTD (Mendez, Joshi, Tassniyom, Teng, & Shapira, 2013). Future criteria would benefit from more detailed guidelines for the differential diagnosis of atypical AD and FTD (especially behavioural-variant FTD). Altered food preferences and neuropsychiatric disturbances appear to have the most value for this purpose (Chare et al., 2014), but further studies are needed to more clearly delimit the atypical AD phenotypes.

Various exclusionary items are already included in the diagnostic criteria to rule out other causes of dementia. By the IWG-2 criteria, core features of other dementias (e.g. early behavioural abnormalities or hallucinations) exclude an AD diagnosis (Dubois et al., 2014). These items reduce diagnostic confidence by the NIA-AA criteria, but do not rule out a diagnosis (McKhann et al., 2011). Rigorously applying these items results in high specificity against other dementias, but may lead to lower sensitivity. One clinicopathological study, for example, found prominent behavioural changes in many AD cases that often compromised diagnostic sensitivity (Harris et al., 2015). Moreover, hallucinations are not uncommon in early AD (Ruiz et al., 2018), though they are typically much less severe and less complex than in disorders such as PDD and DLB. Therefore, these exclusionary items may need to be applied stringently only when very high specificity is required. Again, further studies are needed to clarify how behavioural and neuropsychiatric symptoms may differ qualitatively as well as quantitatively in AD versus the other dementias.

Finally, a very significant feature of current criteria is their incorporation of AD biomarkers into the diagnostic algorithm. In the NIA-AA and original IWG criteria, these are a) medial temporal lobe atrophy by MRI, b) reduced temporoparietal glucose metabolism by PET, c) a CSF signature defined by increased total and phosphorylated tau with reduced $A\beta_{42}$, or d) the presence of an autosomal dominant

mutation with essentially full penetrance on the amyloid precursor protein (*APP*) or presenilin (*PSEN1* or *PSEN2*) genes (Dubois et al., 2007; McKhann et al., 2011).

The more recent IWG-2 criteria are stricter, specifying only three AD biomarkers: the AD CSF signature, a pathogenic mutation, or evidence of amyloid-β pathology using a PET scan with a validated radioligand (Dubois et al., 2014). These are more specific biomarkers than medial temporal lobe atrophy and reduced temporoparietal glucose metabolism, both of which may be observed in older individuals who have neither Alzheimer pathology nor dementia (Wirth et al., 2013). While each of the biomarkers are continuous measures, the NIA-AA research framework recommends applying standardised cutoffs (positive/negative) in clinical trials (Jack et al., 2018). However, cutoff values are not suggested. Identification and implementation of the values that best balance sensitivity and specificity should be considered a priority, as this would enable standardisation of research projects across varied settings and populations.

4.1.1 AD-MCI and preclinical AD

The current diagnostic criteria extend to the stages of AD that precede overt dementia, including the prodromal stage (encompassing MCI) and the presymptomatic or preclinical stage (Dubois et al., 2010). The NIA-AA has separate guidelines for AD-MCI (Albert et al., 2011) and preclinical AD (Sperling et al., 2011). AD-MCI is defined by a lower cognitive performance than would be expected based on the person's age, education, etc., preferably with documented evidence of a progressive decline, and typically affecting episodic memory. Functional independence must be preserved. High likelihood AD-MCI is defined by positive biomarkers for both neurodegeneration (e.g. decreased hippocampal volume or reduced temporoparietal glucose metabolism) and amyloid-β pathology. Intermediate likelihood AD-MCI is diagnosed if only one of these is positive. Caution is recommended in the presence of features such as hallucinations, parkinsonism, or high vascular risk, but these are not exclusionary (Albert et al., 2011).

The NIA-AA definition of preclinical AD is characterised by the presence of AD biomarkers without clinical manifestation. This category was divided into three

stages. Stage 1 is defined by amyloid-β pathology by CSF or PET, stage 2 when there is also tau pathology and AD-type neurodegeneration, and stage 3 by additional subtle cognitive and/or behavioural changes that do not reach criteria for AD-MCI (Sperling et al., 2011). The last stage may include subjective cognitive decline reported by individuals who are within the normal range on neuropsychological tests (Jessen et al., 2014). The three stages follow a temporal sequence, consistent with the amyloid cascade hypothesis: thus, amyloid-β aggregation occurs first, and this is followed by tau, neurodegeneration, and dementia (Hardy & Higgins, 1992; Jack et al., 2010). This definition of preclinical AD is firmly grounded in current theory and practice, but there is still a significant need for its validation, given the controversy surrounding the hypothetical chronology of AD pathogenesis (Garrett & Valle, 2016).

In characterising predementia AD, the IWG favour a more unified approach, whereby a single set of criteria describes the entire clinical and pathological continuum of symptomatic AD, regardless of severity. No cutoff is proposed to separate prodromal AD from AD dementia; both require one of the core clinical phenotypes with at least one positive biomarker (Dubois et al., 2007). Preclinical AD, as defined in the IWG-2 criteria, encompasses asymptomatic at risk and presymptomatic AD. Patients are asymptomatic at risk if they have the AD CSF signature or a positive PET scan for amyloid-β, but do not meet criteria for one of the clinical AD phenotypes (Dubois et al., 2014). This is slightly more specific for AD than the NIA-AA stage 1 criteria, which do not require evidence of tau pathology in the CSF (Dubois et al., 2016). Individuals who are positive for a pathogenic *APP*, *PSEN1*, or *PSEN2* mutation are classified as presymptomatic AD, reflecting the fact that these individuals will invariably develop clinical AD given sufficient survival time (Dubois et al., 2014).

4.2 Clinical diagnostic criteria for Lewy body dementias

As described in Chapter 2, PDD and DLB are Lewy-type α-synucleinopathies that are often indistinguishable at autopsy. There are separate diagnostic criteria for both, but the term “Lewy body dementias” may be used to capture both diseases if required (Lippa et al., 2007).

4.2.1 PDD and DLB

The MDS diagnostic criteria for PDD define the two core features as a diagnosis of PD, and a dementia with insidious onset and gradual decline that develops within established PD (i.e. one year or more after motor onset). PDD may be distinguished from AD by greater executive and visuospatial impairment and fluctuating attention. Free recall may be impaired, but cued recall is relatively preserved, as is language. Hallucinations (generally complex and visual), delusions, and sleep disturbances, including excessive daytime fatigue and RBD, are also more common in PDD than in AD. Mood disorders, such as apathy and depression, are less specific changes that are associated with all forms of dementia (Emre et al., 2007).

The MDS criteria recommend a diagnosis of probable PDD when there is impairment in two of the four core cognitive domains (attention, executive function, visuospatial skills, and free recall), and at least one psychiatric or behavioural symptom. Possible PDD is diagnosed where there is an atypical cognitive profile or a lack of psychiatric and behavioural changes, or where the interval between motor and cognitive onset cannot be firmly established (Emre et al., 2007).

At present, the criteria do not recommend any biomarkers. Compared to AD, PDD has significantly reduced frontal, cingulate, and parietal glucose metabolism by PET, but this is insufficiently sensitive to be considered a valid biomarker (Emre et al., 2007). Later research has identified some potential biomarkers that, subject to further validation, may be incorporated into the next iteration of the diagnostic criteria. These include serum butyrylcholinesterase activity (M. X. Dong et al., 2017) and nucleus basalis degeneration (Schulz, Pagano, Fernández Bonfante, Wilson, & Politis, 2018), both of which are markers of cholinergic change. Direct measures of α-synuclein pathology (e.g. by PET or CSF analysis) will have utility as biomarkers when they are feasible, and if required, AD biomarkers are useful for establishing the extent of coexistent Alzheimer pathologies.

The McKeith criteria for DLB define the disorder by prominent executive, attentional, and visuospatial deficits, similar to PDD. There are four core clinical features. In

addition to dementia, these are cognitive fluctuations affecting attention and alertness; recurrent, complex visual hallucinations; RBD; and spontaneous parkinsonism. In patients with parkinsonism, dementia must have occurred prior to or within one year of the motor onset. Supportive clinical features include severe sensitivity to neuroleptic medications, repeated falls, syncope, autonomic dysfunction, delusions, excessive daytime fatigue, hyposmia, and mood changes (McKeith et al., 2017).

The most recent McKeith criteria incorporate biomarkers as an adjunct to clinical examination, paralleling developments in AD diagnosis. A distinction between indicative and supportive biomarkers is made; supportive biomarkers do not enter the diagnostic algorithms, but may help with the diagnostic evaluation. Probable DLB is diagnosed if there are two or more of the four core clinical features, or one of these features plus one or more indicative biomarkers. Possible DLB is diagnosed if there is one core clinical feature with no biomarker support, or where there is indicative biomarker evidence but no core features. The indicative biomarkers for DLB are reduced dopamine transporter uptake in the basal nuclei by FP-CIT SPECT; cardiac sympathetic denervation by metaiodobenzylguanidine myocardial scintigraphy; and polysomnographic verification of RBD. Supportive biomarkers are little or no atrophy of the medial temporal lobe by CT or MRI; hypometabolism of the occipital lobe with relative sparing of the cingulate gyrus (the “cingulate island sign”) by PET or SPECT; and a characteristic electroencephalography signature defined by prominent abnormalities at posterior derivations (McKeith et al., 2017). The supportive biomarkers are particularly valuable for distinguishing DLB from AD, even at the MCI stage (Bonanni et al., 2016; Chiba, Fujishiro, Iseki, Kasanuki, & Sato, 2018).

4.2.2 PD-MCI and MCI-LB

The MDS criteria for PD-MCI were designed to be consistent with the PDD criteria and with concepts established in the AD literature. PD-MCI requires a gradual and modest cognitive decline, insufficient to interfere with functional independence, which develops within the context of PD. Two certainty levels may be used for a diagnosis. Level I is based on abbreviated neuropsychological testing: cognitive decline may be identified by either a short screening test, or by impaired performance

on at least two tests within a limited assessment battery. Level II requires detailed testing, comprising at least two tests of each of the five core cognitive domains (attention, executive function, visuospatial skills, memory, and language). A diagnosis requires at least two of the tests to be impaired at 1-2 standard deviations (SDs) below appropriate norms, or evidence that performance has declined substantially from a previous level that has been either estimated or established by serial testing. The level I criteria are intended for resource-restricted clinical settings, while level II criteria offer greater sensitivity and the ability to subtype different presentations of PD-MCI (Litvan et al., 2012).

The sensitivity and specificity of the MDS criteria for PD-MCI, particularly the level II criteria, have been supported by subsequent research (Goldman et al., 2013). Both levels of testing have clear independent predictive ability for PDD (Hoogland et al., 2017; Hoogland et al., 2019). The level II criteria also have good reliability (Broeders et al., 2013). The reliability of the level I criteria is lower: marked variation in the proportion of PD cases diagnosed with MCI is introduced by the use of different cutoff values and screening tests. The incorporation of a formal measure of premorbid cognitive function may improve the consistency of the criteria, particularly when they are based on abbreviated testing (Szeto et al., 2015).

At present, diagnostic criteria for the MCI equivalent of DLB ("MCI-LB") are not available. Studies investigating this stage of the disease have relied on *ad hoc* definitions formed by analogy with MCI in other diseases. Initial studies suggest that MCI-LB can be differentiated from AD-MCI by a cognitive profile that is similar to but milder than overt DLB, with prominent executive and visuospatial decline, and a higher frequency of neuropsychiatric symptoms (Cagnin et al., 2015; Donaghy et al., 2018; Sadiq et al., 2017; Yoon, Kim, Moon, Yong, & Hong, 2015). Prodromal forms of DLB that initially present as an affective or psychotic disorder, or as delirium, have been identified (McKeith, Taylor, Thomas, Donaghy, & Kane, 2016).

As with AD, the incorporation of DLB biomarkers may be an especially useful complement to clinical review for detecting prodromal DLB. The validity of FP-CIT SPECT for this purpose is supported (Thomas et al., 2019); data regarding other DLB biomarkers are not yet available. It is anticipated that the DLB Consortium will

collate this evidence in the near future, and release consensus criteria for prodromal DLB that are comparable with those for prodromal PD and AD.

4.2.3 The one-year rule for differential diagnosis of PDD and DLB

Current clinical diagnostic criteria for PDD and DLB distinguish them on the basis of the one-year rule: PDD is diagnosed if dementia occurs more than one year after PD diagnosis, whereas DLB is diagnosed if the cognitive symptoms emerge prior to or within one year of motor onset (Emre et al., 2007; McKeith et al., 2005). Several authors have argued that the arbitrary one-year cutoff should be abandoned, and the two dementias treated as a single disease entity (Friedman, 2018; Postuma et al., 2016), but this is controversial; other authors have emphasised the differences between the disorders to justify a maintenance of the *status quo* (Boeve et al., 2016).

Pathologically, PDD and DLB are often indistinguishable. Both are characterised by extensive limbic and neocortical α-synuclein pathology. This may be more severe in DLB, where there is also usually a higher amyloid-β load (particularly in the striatum) and a lower cholinergic deficit (Ballard et al., 2006; Halliday et al., 2011; Jellinger & Attems, 2006, 2008; Kalaitzakis et al., 2011). Additionally, DLB generally has less severe neuron loss in the substantia nigra (Tsuboi & Dickson, 2005), leading to milder striatal dopamine depravation. Clinically, these differences are reflected by worse global cognition (K. W. Park et al., 2011; Takemoto et al., 2016; Yoon, Lee, Yong, Moon, & Lee, 2014) and more frequent neuropsychiatric disturbances (Chiu, Tsai, Chen, Chen, & Lai, 2016) in DLB. Parkinsonism is usually milder, with less tremor, though the levodopa response, which is typically excellent in PD, is muted in DLB (Goldman, Goetz, Brandabur, Sanfilippo, & Stebbins, 2008). Around a quarter of DLB patients never develop parkinsonism (W. S. Kim, Kågedal, & Halliday, 2014).

While the differences in means are often statistically significant, none of these variables can distinguish PDD and DLB consistently. Moreover, there are numerous other ways in which the two dementias are more similar than different. Many autonomic, sleep-related, and psychiatric features are common to both disorders.

Features such as RBD, constipation, orthostatic hypotension, and hyposmia are established prodromal markers of both PD and DLB (Donaghy & McKeith, 2014; Gibbons & Freeman, 2015), and the research criteria for prodromal PD also have predictive value for DLB (Fereshtehnejad et al., 2017). Furthermore, prodromal biomarkers (e.g. degeneration of the dopaminergic nigrostriatal system by FP-CIT SPECT) are comparable for both (Berg et al., 2015; Thomas et al., 2019).

Additionally, problems with the basic validity of the one-year rule have emerged. Neuropsychological studies have indicated that 20-40% of PD patients have MCI at the time of diagnosis (Lawson et al., 2014; Yarnall, Rochester, & Burn, 2013), and cognitive decline not reaching the threshold for clinical significance precedes PD diagnosis in many patients, often by several years (Darweesh et al., 2017). Thus, cognitive decline is not necessarily a later feature of PD, as the one-year rule implies. Finally, distinguishing PDD and DLB has limited value for clinical practice. The two have very similar responses to current dementia drugs (H. F. Wang et al., 2015), and disease-modifying therapies targeting α-synuclein will be equally useful for both.

In summary, despite some statistically significant differences in mean clinical or pathological scores, PDD and DLB are more similar than different, and there is no empirical basis for the one-year rule. The two dementias are best considered as different points on a continuum, ranging in severity from incidental Lewy body disease to PD without dementia, and then to PDD, DLB, and DLB with comorbid AD (Jellinger & Korczyn, 2018). The current criteria for PDD and DLB are of high quality, well validated, and in widespread use, but there is a need for future versions to decisively address this issue. Increased communication between the organisations involved in PD research and those involved in DLB should facilitate the development of harmonised diagnostic criteria that have greater validity across the spectrum of Lewy body diseases.

4.3 Clinical diagnostic criteria for FTD

FTD is defined by degeneration of the frontal and temporal lobes, often asymmetrical, with heterogeneous molecular pathology; tau, TDP-43, FET, and ubiquitin proteins

may underlie this dementia. The pathological diversity is reflected *in vivo* by variability in cognitive and behavioural presentation. Current criteria distinguish a behavioural variant (Rascovsky et al., 2011), and three types of primary progressive aphasia (PPA; Gorno-Tempini et al., 2011). FTD often overlaps clinically and pathologically with degenerative motor disorders, including progressive supranuclear palsy, corticobasal degeneration, and amyotrophic lateral sclerosis (Olney et al., 2017); the diagnosis of these diseases is beyond the scope of this thesis.

Neuroanatomically, behavioural-variant FTD is usually characterised by bilateral atrophy of the frontal lobes (Neary et al., 1998). The clinical diagnostic criteria describe a gradual onset and progression of behavioural and cognitive change. Given the potential for a loss of insight on the part of the patient, history should be provided by an informant. Both probable and possible diagnoses require at least three of six core clinical features: behavioural disinhibition, apathy, loss of sympathy or empathy, compulsive or stereotyped behaviours, hyperorality and dietary changes, and a neuropsychological profile characterised by a primarily dysexecutive syndrome, with relative preservation of memory and visuospatial function (Rascovsky et al., 2011).

Probable behavioural-variant FTD may only be diagnosed where there is significant functional impairment and neuroimaging evidence of atrophy, hypoperfusion, or hypometabolism of the frontal and/or temporal lobes. Possible behavioural-variant FTD should be diagnosed in the absence of functional impairment or neuroimaging support. A definite diagnosis may be conferred either with post-mortem verification, or *in vivo* if there is a known pathogenic mutation. For all FTD variants, pathogenic mutations are on the *MAPT* or granulin (*GRN*) genes (Rascovsky et al., 2011).

The diagnostic criteria for PPA (Gorno-Tempini et al., 2011) distinguish three subtypes: nonfluent, semantic, and logopenic. In each, the impairment has a gradual onset and progression, and primarily affects language. Marked early impairment to memory, visual perception, or behaviour is not consistent with PPA (Mesulam, 2001).

Nonfluent PPA is characterised by a progressive agrammatism with speech dyspraxia, resulting in slow and effortful speech. Two of three supportive features – impaired comprehension of complex sentences, spared single-word knowledge, and spared

object knowledge – are also required. Semantic PPA, in contrast, has impaired single-word knowledge and impaired object naming, particularly for low-frequency words and objects. Three of four supportive features – impaired object knowledge, dyslexia or dysgraphia, spared sentence repetition, and spared speech production – are required. Language is typically fluent and grammatically correct in semantic variant PPA (Gorno-Tempini et al., 2011).

As discussed above (section 4.1.1), logopenic PPA is generally an atypical AD variant (Dubois et al., 2014). The core features are impaired single-word retrieval (e.g. object naming) and impaired sentence or phrase repetition. Three of four supportive features – phonological errors in speech, spared single-word comprehension, spared motor speech, and spared grammatical knowledge – are required for a diagnosis. Speech is slowed, as in nonfluent PPA, but it is grammatically correct and normally inflected (Gorno-Tempini et al., 2011).

Confidence in a diagnosis of any of the three PPA variants is increased if there is supportive structural (CT or MRI) or functional (PET or SPECT) neuroimaging. This should show marked atrophy or hypometabolism in the fronto-insular region for nonfluent PPA; in the anterior temporal lobe for semantic PPA; and in the left temporoparietal area for logopenic PPA. As with behavioural-variant FTD, a definite diagnosis for any of the PPA syndromes can be made if there is either post-mortem confirmation, or a pathogenic mutation in the *MAPT* or *GRN* genes (Gorno-Tempini et al., 2011).

The diagnostic criteria for both behavioural and PPA variants of FTD have several strengths. Autopsy studies show excellent sensitivity and very good specificity against AD (Harris et al., 2013). The description of the logopenic syndrome is useful for capturing clinically atypical, language-dominant AD cases. The inclusion of several features such as object agnosia, phonological errors, altered food preferences, and neuropsychiatric dysfunction is also useful for differential diagnosis, as studies show that these items are specific markers of FTD syndromes over AD (Chare et al., 2014).

Further strengths of the criteria is that they allow for a diagnosis relatively early in the disease, and they incorporate biomarkers; both features are essential for long-term

clinical trials that require early identification of FTD and an objective measure of disease progression. The validity of the imaging profile for PPA has been supported by a large meta-analysis, though for nonfluent and semantic variants, the regional overlap between atrophy and hypometabolism is not total. This suggests that future diagnostic criteria should specify different guidelines for structural and functional scans (Bisenius, Neumann, & Schroeter, 2016).

Clinicopathological analysis has also revealed some limitations with the criteria. A subset of cases (10-30%) diagnosed with non-logopenic FTD variants had a post-mortem diagnosis of AD (Chare et al., 2014), suggesting that FTD remains a relatively common clinical misdiagnosis for atypical AD. Moreover, the specificity of the criteria against non-AD dementias and psychiatric disorders remains to be determined. Evidence so far indicates that the criteria for possible behavioural-variant FTD have low specificity against psychiatric disorders, such as schizophrenia, though the more stringent neuroimaging-based criteria for probable disease have good specificity (Kerssens et al., 2016; Vijverberg et al., 2016).

Finally, the current criteria have limited ability to distinguish the various molecular pathologies (tau, TDP-43, etc.) that underlie FTD, which will be essential for clinical trials of disease-modifying therapies. AD biomarkers are valuable for the differential diagnosis of AD and FTD associated with tau pathology, particularly in early disease. Valid neuroimaging and CSF biomarkers for TDP-43 pathology are not yet available, but they are in development (Steinacker, Barschke, & Otto, 2019). Additionally, the different molecular pathologies have been linked to subtly different symptom profiles (D. C. Perry et al., 2017); further characterisation of these would also be useful for the next generation of FTD diagnostic criteria.

4.4 Clinical diagnostic criteria for VCD

Like FTD, VCD is characterised by marked clinical and pathological heterogeneity. Several sets of diagnostic criteria have been published, often for subtypes of VCD such as multi-infarct dementia, ischaemic vascular dementia, and subcortical vascular dementia (Chui et al., 1992; Erkinjuntti et al., 2000; Hachinski et al., 1975; Román et

al., 1993). The most recent criteria subsume all kinds of cognitive decline associated with cerebrovascular disease (Gorelick et al., 2011; Sachdev et al., 2014), and incorporate standardised protocols for the clinical assessment (Hachinski et al., 2006) and neuroimaging (Wardlaw et al., 2013) of VCD.

The latest diagnostic criteria were published by the International Society for Vascular Behavioural and Cognitive Disorders (VASCOG; Sachdev et al., 2014). Two possible cognitive onset patterns are described. Firstly, the onset may be temporally related to a documented stroke or series of strokes, and therefore has an abrupt onset (typically within three months) followed by a stepwise or fluctuating course. Relevant focal neurological signs (lower facial weakness, dysarthria, hemiparesis, hemianopsia, etc.) can be considered evidence of a stroke. The second onset pattern is more gradual; this type is generally related to subcortical ischaemic disease (O'Brien et al., 2003). The criteria allow for a diagnosis in this case if neuropsychological testing points to a classic subcortical ischaemic profile. This is defined by prominent deficits to speed of information processing, complex attention, and executive function, in addition to early gait disturbance or urinary dysfunction, or personality and mood changes such as abulia, depression, or emotional incontinence (Sachdev et al., 2014).

A diagnosis of probable VCD requires neuroimaging evidence of cerebrovascular disease, which is more sensitive than any clinical test. Relevant imaging includes multiple large infarcts; a single strategically placed infarct (e.g. in the thalamus or basal nuclei); multiple lacunar infarcts; extensive white matter lesions; or one or more intracerebral haemorrhages. A single infarct may be sufficient to cause mild VCD. Evidence of one of the rare genetic cerebrovascular disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, also supports a diagnosis of probable VCD, even in the absence of neuroimaging (Sachdev et al., 2014).

Additional exclusion criteria were added to the VASCOG criteria to facilitate differential diagnosis from other disorders. In particular, an early and progressive memory decline with aphasia, agnosia, or apraxia is exclusionary, unless there are explanatory focal lesions or vascular events. Clear and early parkinsonism is also an exclusion criterion. Comorbid AD is not an exclusion criterion for VCD, given the

frequency of overlap between these dementias. However, AD biomarkers may be used to select cases with a relatively pure cerebrovascular disorder for clinical trials if this is required (Sachdev et al., 2014).

The VASCOG criteria have various strengths. They are comprehensive; compatible with the DSM-5, AD diagnostic criteria, and previous standardisation protocols; and they allow for a diagnosis of VCD before overt dementia has emerged. Several ongoing developments are likely to contribute to future iterations of the diagnostic criteria for VCD. The development of biomarkers is difficult, given the heterogeneity of cerebrovascular pathologies, but various potential CSF markers – including measures of sulfatide, neurofilament, matrix metalloproteinases, and the serum albumin ratio – may increase diagnostic certainty in some cases (Hachinski et al., 2006). Additionally, established biomarkers for AD may be useful for distinguishing pure VCD from AD with coexistent cerebrovascular disease (Janelidze et al., 2016).

Improved biomarkers could also form part of a diagnostic strategy aimed at detecting preclinical VCD. This is a more complex procedure than identifying preclinical AD, as some subtypes of vascular dementia (e.g. abrupt-onset caused by post-stroke infarction) can develop immediately after an acute event, without an intervening preclinical or MCI stage (Meyer, Xu, Thornby, Chowdhury, & Quach, 2002). However, other subtypes with more insidious onset (e.g. small vessel disease) may be detectable with MRI in the preclinical and MCI stages (Lambert et al., 2018; Sudo et al., 2015). Large-scale prospective longitudinal studies are needed to facilitate the identification of additional predictive variables, as well as genetic and environmental risk factors, that can be used to inform clinical trials in the future.

Finally, a major challenge for the clinical diagnosis of VCD is the frequent overlap with AD. Pure vascular dementia is rare; tau and amyloid-β pathologies are present with varying severity in the clear majority of cases, particularly in the oldest age groups (Jellinger & Attems, 2010a; Thal, Grinberg, & Attems, 2012). Similarly, cerebrovascular pathology is frequently found in AD cases, and contributes to poorer cognition (Toledo et al., 2013). The current criteria allow for a diagnosis of possible VCD with AD, or possible AD with cerebrovascular disease, in cases with both types of pathology (Sachdev et al., 2014). A useful addition to future diagnostic criteria

would be a refined protocol for identifying cases with probable dual pathology, which again would allow clinical trials the option of selecting relatively pure cases of VCD.

4.5 Chapter summary

Current clinical diagnostic criteria have multiple strengths. Increasing recognition of the diversity of pathologies that may underlie cognitive decline has led to better characterisation of the clinical profiles associated with each disorder. The focus on biomarkers has facilitated the preclinical detection of degenerative pathologies, raising the prospect of disease-modifying therapies at an early stage. As a result of these developments, the current criteria show excellent sensitivity and specificity, and are therefore valid and reliable methods for the differential diagnosis of dementias.

Several ongoing challenges face the development of the next generation of diagnostic criteria. Eventual harmonisation of the NIA-AA and IWG criteria for AD is essential for consistency across diverse research settings. A major rethinking of the traditional division between PDD and DLB is required, given the problems with the one-year rule. In FTD, the focus should be on identifying valid biomarkers for the range of molecular pathologies associated with frontotemporal lobar degeneration. Finally, in VCD, there is a need to further clarify the relationship to AD and the numerous risk factors associated with various kinds of cerebrovascular disease. Overcoming these challenges will require constant dialogue between the various organisations involved in each of these disorders. This will enable the creation of shared research objectives, a standardised language, and consistent diagnostic criteria and testing methods across all of the various disorders that can cause cognitive decline.

5 Neuropsychological assessment of cognition

Current diagnostic criteria for MCI and dementia require objective evidence that a clinically significant decline in cognition has taken place. Neuropsychological assessment is used to establish this. Numerous tests of cognition are available for this purpose, including short cognitive screening tests and more detailed domain-focused tests. Screening tests are designed to identify patients with probable MCI or dementia as efficiently as possible. Domain-focused tests are typically performed as part of a comprehensive neuropsychological evaluation. This is a considerably longer and more resource-intensive procedure, but it provides much more detail about the nature and severity of a patient's cognitive impairment, which may be used to assist differential diagnosis and inform the planning of effective clinical management.

This chapter gives a brief overview of methods employed in the neuropsychological assessment of cognition, with reference to some of the most widely used and well validated test paradigms for both screening and domain-focused testing. Challenges that must be addressed during the application and interpretation of these tests, such as motor or language impairment, are discussed. Available strategies for assessing the degree of functional interference resulting from cognitive decline, and for estimating premorbid cognitive ability, are also described.

5.1 Cognitive screening tests

5.1.1 Patient-directed measures

Time pressure and resource constraints in clinical settings, particularly in primary care, means that there is generally a need to identify potential cognitive impairment as efficiently as possible. Short cognitive screening tests are very frequently used for this purpose. The quality of a screening test can be measured by various criteria, some of which are mutually exclusive. This section will summarise these criteria and describe two of the most widely used screens: the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the MoCA (Nasreddine et al., 2005).

Naturally, screening tests should be short; 10 minutes is generally the maximum acceptable administration time, but in primary care settings a five minute maximum is desirable (Carnero-Pardo, 2014). They should be easy to use and score reliably for a variety of clinical practitioners, and easy for patients with a wide range of medical conditions to tolerate without undue distress or discomfort. Additionally, the tests should be applicable to a diverse patient population, and therefore, they should not be biased by socioeconomic or cultural factors. Ease of remote administration (e.g. online or by telephone) and adaptability to different languages is extremely useful (Carnero-Pardo, 2014). Psychometrically, screening tests should have high sensitivity, specificity, and positive predictive value for cognitive impairment of any aetiology; this requires the assessment of multiple cognitive domains, so that the clinical profiles of different dementia disorders are captured (Cullen, O'Neill, Evans, Coen, & Lawlor, 2007). Finally, sensitivity to the mild stages of these disorders, including MCI, is very valuable (Lorentz, Scanlan, & Borson, 2002).

Until recently, the MMSE was the ubiquitous screening test in clinical practice. The MMSE takes 5-10 minutes and is scored out of 30, with a score above 23 usually indicating normal function. Approximately two-thirds of the items assess memory, language, and orientation to time and place; attention and calculation items amount to five points, and executive-visuospatial function is assessed by a single item requiring the patient to copy a drawing of two interlocking pentagons (Folstein et al., 1975).

Despite its widespread use, the popularity of the MMSE has declined markedly due to multiple limitations. Its reliability is compromised by a lack of standardisation; for example, the words that a patient must learn in the recall task may vary, such that some versions of the test are objectively more difficult than others (Carnero-Pardo, 2014). The test lacks adequate sensitivity for MCI and mild dementia (G. Xu, Meyer, Thornby, Chowdhury, & Quach, 2002), and also for non-AD dementias as a result of its emphasis on memory, language, and orientation items. Finally, the MMSE was removed from the public domain and made subject to copyright in 2001, making it an expensive option for routine clinical administration.

The MoCA was explicitly designed to overcome these limitations. The test is formally divided into six cognitive domains: short-term recall; attention, concentration, and

working memory; executive function; visuospatial skills; language; and orientation to time and place, with approximately equal allocation of points to each. As a result of the balanced coverage of executive and visuospatial domains, the MoCA is sensitive to various non-AD dementias, including DLB (C. S. Wang et al., 2013), VCD (Y. Dong et al., 2010), and behavioural-variant FTD (Freitas, Simões, Alves, Duro, & Santana, 2012). It is also superior to the MMSE for evaluating cognitive impairment in PD (Biundo et al., 2016); this will be discussed more fully in the next chapter. The MoCA has less of a ceiling effect than the MMSE, and consequently, it is more sensitive to MCI (Nasreddine et al., 2005). The test is in the public domain and three standardised, English-language parallel versions are freely available online, as are versions in other languages (www.mocatest.org). The MoCA takes approximately as much time to administer as the MMSE, and it is also scored out of 30 (Nasreddine et al., 2005). The MoCA is highly adaptable: an abbreviated version (Horton et al., 2015) and a telephone version (Wong et al., 2015) have been published. Because of these features, the MoCA has become one of the most popular and valuable screening tests currently in clinical practice.

5.1.2 Informant-rated measures

Informant-rated cognitive measures are usually questionnaires that are completed by a knowledgeable informant (e.g. a relative or friend). A widely used example is the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 1994; Jorm, Scott, Cullen, & MacKinnon, 1991), a 10-minute questionnaire in which the informant is asked to rate the patient's level of performance on a series of everyday tasks relative to their performance 10 years earlier. Scoring for each item is based on a five-point scale ranging from "much worse" to "much better"; the final score is the mean value across all items.

Informant-rated measures have the advantage of being unaffected by any potential confounders that are intrinsic to the patient, such as their baseline cognitive ability, education, or physical or language impairments (Jorm et al., 1996). The format of these methods means that they can be completed remotely, and they are therefore adaptable to large scale community screening projects (Cullen et al., 2007). However,

they may be biased by unmeasured personal characteristics of the informant, such as the quality of their relationship with the patient, and their capacity for sensitive observation (Jorm et al., 1996). Some potential informants may be unwilling to candidly report on the patient's deteriorating cognition due to personal or cultural factors. In many cases, elderly patients may be unable to identify someone who knows them sufficiently well (Lorentz et al., 2002). Finally, informant-rated scales often provide little or no information about decline in specific cognitive domains, and their usefulness for differential diagnosis is therefore extremely limited. Because of these weaknesses, informant-rated measures are best employed as an adjunct to clinician-administered, patient-directed cognitive testing.

5.2 Domain-focused neuropsychological tests

Short cognitive screening tests are very useful in time-restricted settings where there is a need to identify possible cognitive impairment quickly and efficiently. However, their brevity means that these screening tests do not offer a comprehensive assessment of each cognitive domain, which is an essential component of the diagnostic process. Full domain-focused evaluation is longer, often lasting several hours, and is usually conducted in secondary care settings by a clinical neuropsychologist. A patient's performance is generally compared against established norms, which are adjusted for age and/or education as appropriate.

Most mental operations rely on input from several cognitive domains. As described in the introduction, the six cognitive domains described in the DSM-5 are memory, attention, executive function, visuospatial skills, language, and social cognition (American Psychiatric Association, 2013). Performance on any individual cognitive test requires a base level of attention, orientation, and language function, so that the patient can understand and adhere to the instructions (Burrell & Piguet, 2015). Domain-focused cognitive tests are designed to isolate a primary component of a single cognitive domain to the greatest extent that is possible, although no test provides a completely pure assessment of a particular domain. The most important diagnostic information is derived from the pattern of deficits across all of the tests in

the neuropsychological evaluation (Palta, Snitz, & Carlson, 2016). Some of the most popular test paradigms for each cognitive domain are briefly described below.

Memory. A broad distinction can be made between explicit memory for facts, events, and other specific items of information, versus implicit memory for skills and routines. Explicit memory may be further divided into semantic memory (general knowledge, ideas, and concepts of the world) and episodic memory (experiences and biographical events). Most clinical tests of memory target episodic memory, as this is characteristically impaired in neurodegenerative disorders such as AD (Machado et al., 2009), in which there is damage to medial temporal lobe structures including the hippocampus and the adjacent entorhinal, perirhinal, and parahippocampal cortices (Squire & Wixted, 2011). The common tests of episodic memory usually involve presenting a series of verbal or visual stimuli, often belonging to certain semantic categories, and asking the patient to recall as many as possible, either immediately or after a delay. For example, verbal episodic memory may be tested with a word list learning paradigm, such as the Hopkins Verbal Learning Test (Brandt, 1991). Recall may be either free or cued. Cueing involves the presentation of a clue (e.g. semantic or phonemic) relevant to one or more stimuli from the learning trial. A cueing benefit during data retrieval is a useful feature for distinguishing PDD and DLB from AD, as this generally points to a frontostriatal attentional problem, as opposed to a genuine hippocampal encoding deficit (Economou et al., 2016).

Attention, processing speed, and working memory. These abilities have a complex neural basis that includes the dorsolateral and anterior prefrontal cortex, the anterior cingulate cortex, the inferior parietal lobe, and various subcortical structures, such as the caudate nucleus and the cerebellum (Joyce & Hrin, 2015). Tests of attention and/or speed generally require a response to target stimuli, often while working as quickly as possible and ignoring task-irrelevant stimuli. The trail-making task Part A (Reitan, 1944) is a common test of processing speed that involves presenting a patient with circled numbers distributed randomly across a page, and asking the patient to draw a trail between these in ascending order, as quickly as possible. The Symbol Digit Modalities Test (A. Smith, 1982) is another speed test in which patients must use a reference key to pair as many abstract symbols with a corresponding number as they can in 90 seconds. Orientation is a component of attention referring to the

individual's ability to place themselves appropriately in time and space; asking the patient to provide the date or to name the building that they are in may be used to assess this. Working memory is another component of attention (though it also taps memory and executive function), which involves the temporary storage and manipulation of a limited amount of data. A classic test of working memory is the digit span task (Wechsler, 1981), in which the patient is read consecutive number lists of increasing length, and then immediately asked to recite them in the same order (forward digit span) or in reverse (backward digit span).

Executive function. Like attention, executive function has a complex neural basis; the frontal lobes, subcortical nuclei, and white matter connections are all centrally involved (Bettcher et al., 2016). "Executive function" is an umbrella term for various cognitive operations including reasoning, planning, cognitive flexibility, response inhibition, and problem solving, and a range of tests are available for testing these abilities. Fluency tasks, such as the Controlled Oral Word Association Test (Benton, de Hamsher, & Sivan, 1983), require the patient to list as many words as possible that start with a given letter (phonemic fluency) or fit within a given semantic category (semantic fluency). Cognitive flexibility may be assessed by a set-shifting paradigm, in which patients must alternate between two competing sets of rules. An example is Part B of the trail-making task, in which patients are asked to draw a line that alternates between ascending numbers and ascending letters. Problem-solving abilities may be assessed by complex puzzles, or by presenting patients with a series of hypothetical problems and asking them to identify an appropriate course of action. Response inhibition is another component of the executive system necessary for selectively suppressing prepotent responses to stimuli. This can be assessed with a classic Stroop colour/word interference task, in which patients are presented with a series of colour words printed in an incongruently coloured ink (e.g. the word "red" printed in blue ink) and asked to name the ink colour for each word as quickly as possible (Stroop, 1935). Set shifting may be incorporated into the Stroop task, so that patients alternate between naming the ink colour and reading the word.

Visuospatial skills. Visuospatial skills are mediated primarily by the parietal lobe and the parieto-occipital junction (Thiyagesh et al., 2009). Assessment of these skills is based on the patient's ability to interpret or produce visual information. Basic visual

perception may be assessed by asking patients to identify letters that have been partially destroyed, or objects from their silhouette. Various tasks involving the production of a simple line drawing are commonly used to test visuoconstructional ability: this includes the shape copying and clock drawing tasks on the MoCA, and the interlocking pentagons copying task on the MMSE. The Rey-Osterrieth Figure Test requires the patient to reproduce a substantially more complex, abstract line drawing (Osterrieth, 1944). Finally, a common test of spatial perception is the judgement of line orientation task, in which the patient is asked to identify which of many angled lines in a diagram have the same orientation as the target lines (Benton, Varney, & Hamsher, 1978).

Language. Neurologically, language is situated mainly in the left hemisphere, including Broca's area in the inferior frontal lobe and Wernicke's area in the posterior temporal lobe (Hickok, 2009). Various aspects of language, including comprehension, expressive language production, grammar, prosody, and motor speech function, may be assessed in routine conversation with the patient. Formal tests of language production that are useful in the diagnosis of aphasia are confrontation naming tasks, such as the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), in which the patient is presented with a series of drawings depicting objects, and asked to name the objects. Asking the patient to repeat a list of single words or sentences is useful for identifying certain subtypes of PPA-variant FTD. Language comprehension can be assessed by asking the patient to follow commands or answer questions. For each of these tasks, stimuli of varying levels of complexity may be employed.

Social cognition and behaviour. These aspects of cognition are mediated by widely distributed neural regions, most importantly including the prefrontal cortex, cingulate gyrus, fusiform gyrus, amygdala, and the insula (Patin & Hurlemann, 2015). Tests of social cognition do not often feature in neuropsychological assessment batteries, but numerous tests are available. The Edinburgh Social Cognition Test is used for the assessment of theory of mind: patients are asked to describe images that portray social interactions (Baksh, Abrahams, Auyeung, & MacPherson, 2018). The Ekman 60 is a test of emotion recognition that involves the sequential presentation of 60 faces, each expressing one of six basic emotions; the patient is asked to identify the emotion (Ekman & Friesen, 1976). Assessment of pathological behavioural changes is more

challenging within the confines of a formal clinical or research setting. Because patients with social cognition disorders (e.g. behavioural-variant FTD) often have impaired insight (Desmarais, Lanctôt, Masellis, Black, & Herrmann, 2018), information is generally sourced from a reliable informant. For example, the widely used Neuropsychiatric Inventory relies on a structured interview with an informant to probe various behavioural disturbances that are common in cognitive disorders, such as apathy, anxiety, depression, disinhibition, and impulsivity (Cummings et al., 1994).

5.3 Assessment of functional impairment

The severity of functional interference that results from cognitive impairment is an essential feature to evaluate during a neuropsychological assessment, as it has important implications for diagnosis and patient management. Most functional scales probe the patient's ability to handle everyday activities and affairs, such as mobility, washing, dressing, shopping, and managing financial matters or medications. Input from an informant is usually necessary. For example, the Clinical Dementia Rating scale, developed for and validated in AD, relies on a semi-structured interview with both the patient and an informant (Morris, 1997).

5.4 Neuropsychological assessment in PD

In neuropsychological evaluation, it is essential to ensure the validity of cognitive test scores by minimising the effects of potential confounders. The motor impairment that characterises PD may be a significant confounder in tests that require motor dexterity or speed, including those that involve writing or complex drawing. Circumnavigating this problem requires careful selection of tests that are suitable for the individual patient or the target population. The MDS has published a list of tests that minimise the need for a motor response, and are therefore appropriate for evaluating cognition in PD. Furthermore, the MDS recommend that people with PD be tested in their "optimal motor state", typically meaning that they are responding to anti-Parkinson medications at the time (Litvan et al., 2012). Currently, a standardised cognitive battery for use in PD research that tests all cognitive domains with suitable methods is not available, though efforts are underway (Hoogland et al., 2018).

Similar problems relate to the assessment of functional impairment due to cognitive decline in PD. Many functional rating scales validated in other neurodegenerative disease groups (e.g. the Clinical Dementia Rating scale) rely on information about personal care and hygiene, such as dressing and washing, which may be impaired in PD purely as a result of motor rather than cognitive dysfunction. An informant-rated functional rating scale has been published specifically for use in PD (Kulisevsky et al., 2013), and this exclusively includes items that are minimally affected by motor impairment. Therefore, the questionnaire provides a valid index of the degree of functional interference that results directly from cognitive problems in PD.

5.5 Normative scores and premorbid ability

Even once an appropriate task has been selected and administered correctly, a raw test score in isolation is not particularly informative. A meaningful interpretation requires comparison to a baseline or reference standard that, at a minimum, defines the cutoff between normal and impaired function. In the context of a neurological or psychiatric disorder, the ideal option would be to compare a patient's test scores before and after diagnosis, but this is rarely an option, due to the rarity of routine neuropsychological testing in healthy individuals. Therefore, comparisons are generally to a normative score and/or an index of estimated premorbid function.

Normative scores are typically obtained from large samples of cognitively healthy individuals, usually stratified by age group, education level, and other potential covariates. These normative studies define the range of test scores that characterises the healthy population. Raw test scores obtained from a patient become meaningful once they are transformed into the appropriately adjusted standardised score, such as percentile ranks, scaled scores, z-scores, and T-scores, all of which indicate how typical the patient's score is in comparison to their peer group. Impaired performance is usually defined by a score more than two SDs below the mean, corresponding to the second percentile or lower (Palta et al., 2016).

A complementary approach is to compare a patient's score to their estimated level of cognitive function prior to the onset of their disorder. This may be particularly

informative for patients who were previously at the high or low extremes of cognitive function, as comparison to population reference scores alone may be misleading for these individuals. For example, scores in the average range may represent a clinically significant decline, with substantial implications for occupational and social function, for a person who was previously at the high end of the cognitive spectrum.

The simplest way of estimating premorbid function is based on demographic factors such as educational and occupational attainment. The duration of education remains correlated with cognitive scores into old age (Ritchie, Bates, Der, Starr, & Deary, 2013), and has the advantage of being relatively easy to measure, regardless of the patient's current level of function. A more formal method is to test a "crystallised" cognitive ability, such as reading, which is often relatively spared in the mild to moderate stages of dementia (McGurn et al., 2004). Reading tests used for this purpose (H. E. Nelson & Willison, 1991; Wechsler, 2001, 2009) involve the presentation of a series of low-frequency words with irregular grapheme-phoneme mappings or stress patterns (e.g. "naive"). The patient is asked to read each word aloud; the proportion of correct answers correlates with lifelong capacity for learning and knowledge. These tests provide a reasonably accurate index of premorbid cognition, although again, they are less valid for people who were previously high or low functioning (Bright & van der Linde, 2018).

5.6 Chapter summary

Neuropsychological assessment is a complex but essential procedure for investigating cognitive disorders. An extensive range of tests is available both for dementia screening and detailed, domain-focused evaluation. The optimal test for a particular situation depends on the characteristics of the patient or group under examination; sensitivity to specific factors, such as motor impairment in PD, is required in order to produce meaningful scores. Interpretation of these scores also requires a normative or comparative baseline, so that the magnitude of any decline can be contextualised. The neuropsychological information can then be combined with other clinical data (neurological, radiological, etc.) so that a diagnosis can be conferred and an effective clinical management plan can be decided upon.

6 Factor structure of the MoCA in PD

6.1 Introduction

As stated in the previous chapter, the MoCA (Nasreddine et al., 2005) is one of the most widely used screening tests currently used for cognitive screening in clinical and research settings. It is a brief, clinician-administered assessment that surpasses many of the limitations of the older MMSE (Folstein et al., 1975), having greater utility for detecting MCI, and better coverage of different cognitive domains. Some studies have assessed the construct validity of the MoCA in AD and other dementia groups, and found evidence of a factor structure that maps to the different cognitive domains. This indicates that the MoCA may be a brief method of obtaining domain-specific cognitive profiles that are useful for differential diagnosis and clinical management. This chapter presents a novel factor analysis of the MoCA designed to explore the extent to which previously reported factor structures are valid in people with PD.

Several studies have supported the value of the MoCA for detecting and quantifying cognitive impairment in PD. The test has consistently shown greater sensitivity for both PD-MCI and PDD than other screens (Dalrymple-Alford et al., 2010; Hoops et al., 2009; Zadikoff et al., 2008), largely due to its inclusion of executive and visuospatial items. Very good test-retest and interrater reliability statistics in PD have been demonstrated, and the MoCA correlates well with a full neuropsychological assessment battery (Gill, Freshman, Blender, & Ravina, 2008). As a result of its strong psychometric properties, the MDS has recommended the test for the global assessment of cognition in PD: an impaired MoCA score may be used for a level I diagnosis of PD-MCI (Litvan et al., 2012).

Although the MoCA was designed to provide an indication of global cognitive function, it was explicitly structured around six cognitive domains: short-term recall; attention, concentration, and working memory; executive function; visuospatial skills; language; and orientation to time and place (Nasreddine et al., 2005). A fuller test of these domains is possible with detailed, domain-focused neuropsychological assessment, which is then used to identify distinct cognitive profiles. However, such

testing is time-consuming, resource-intensive, and rarely available in retrospective studies that rely on review of patients' medical notes. Identification of cognitive subtypes would be greatly facilitated if a brief screening test could adequately distinguish and quantify function in the different cognitive domains. To test if the MoCA is capable of this, its internal structure has been assessed more rigorously to test whether the domain-specific sections map to statistically independent factors.

When applied to a heterogeneous dementia group, one factor analysis indicated that the MoCA comprised two distinct factors: namely, memory and attentional-executive function (Duro, Simões, Ponciano, & Santana, 2010). The memory factor included the short-term recall, language, and orientation subtests, and the attentional-executive function included attention, executive, and visuospatial subtests. A later factor analysis focused on a more specific clinical group (AD and MCI) and tested several models (Freitas, Simões, Marôco, Alves, & Santana, 2012). While the previously reported two-factor model had a good fit to the observed data, confirmatory factor analysis indicated that the six-factor structure postulated by Nasreddine et al. (2005) had the best fit. Additionally, one second-order factor ("cognition") was tested. This comprised all six first-order factors and had a good fit to the data, supporting the unidimensionality of the MoCA as a measure of global cognitive function (Freitas, Simões, Marôco, et al., 2012).

At present, there has been limited exploration of the construct validity of the MoCA in PD. One study found that the executive, visuospatial, and memory subsections showed high sensitivity against a detailed neuropsychological test of these domains, though specificity and diagnostic accuracy were only adequate for the executive subsection (Hendershott, Zhu, Llanes, & Poston, 2017). So far, only a single factor analysis of the MoCA in PD has been published. In this study, the cohort were highly educated, with a short average disease duration, and a high mean MoCA score of 26.4. As a result, some items (primarily belonging to the language and orientation subsections) showed clear ceiling effects, being correct in more than 95% of cases. Because of the lack of variance, these items were omitted from the exploratory factor analysis, which suggested a three-factor model comprising executive function, memory, and verbal attention (Benge et al., 2017). This model has not yet been independently tested with confirmatory factor analysis.

The objective of this analysis was to extend previous research by exploring the factor structure of the MoCA in a very large cohort of people with PD, including patients with possible MCI and dementia, in order to test whether it could validly distinguish different cognitive domains in this population. Previously reported models based on PD, AD, and other dementia cohorts formed the basis of the analysis.

6.2 Methods

The analysis used data from the Tracking Parkinson's study, a long-term prospective observational project involving 2000 recent-onset PD patients at 72 sites (Malek et al., 2015). The study was conducted in compliance with the Helsinki Declaration (World Medical Association, 1967), and approved by the multicentre research ethics committee (reference code 11/AL/0163) and local National Health Service (NHS) research and development departments (reference code GN11NE062). Patient recruitment took place between February 2012 and June 2014. The study is ongoing, with visits every six months, including in-depth assessments at baseline and every 18 months subsequently. Funding for the study was provided by Parkinson's UK (grant number J1101), a registered charity in England and Wales (charity number 258197) and in Scotland (charity number SC037554).

6.2.1 Participants

All participants in the Tracking Parkinson's cohort had PD diagnosed fewer than 3.5 years before study enrolment by a specialist movement disorder neurologist in local clinics. Exclusion criteria included age below 18 or over 90; a diagnosis of an alternative parkinsonian disorder; or a severe comorbid illness that would preclude full study participation. Patients with a clinical diagnosis of dementia at baseline were excluded, but cognitive function was not otherwise part of the eligibility criteria.

For this analysis, participants were excluded if they had incomplete MoCA data or blank values for education (n = 262). The analysis was initially applied to the full sample (n = 1738). Due to possible ceiling effects (which may obscure a meaningful factor structure), analysis was also conducted on two sub-samples defined by a MoCA

score lower than 26, encompassing probable MCI and more severe levels of cognitive impairment (n = 797), and lower than 21, indicative of moderate to severe impairment (n = 157). These cutoff values have good sensitivity and specificity (Dalrymple-Alford et al., 2010) and have been used in previous analyses of the Tracking Parkinson's cohort (Malek et al., 2015).

6.2.2 Materials

For this analysis, baseline study data were used. The primary measure was the MoCA version 7.1. The test was conducted by local clinical and/or research staff (generally a research nurse). The MoCA takes around 5-10 minutes to administer, and includes tests of word recall, figure copying, clock drawing, trail-making, phonemic fluency, verbal abstraction, picture naming, sentence repetition, forward and backward digit spans, vigilance, serial subtractions, and temporal and spatial orientation.

The highest possible MoCA score is 30; higher scores indicate better cognitive function. A single bonus point is added for participants with fewer than 13 years of education, and an education-adjusted score above 25 indicates normal cognition. For this analysis, some MoCA items were only available as ordinal values: the contour, hands, and numbers on the clock drawing task had been collapsed into a single item (scored 0-3), as had the serial subtractions (also 0-3). Item scores used for the factor analysis were not adjusted for education level, but the bonus point was included when reporting total scores, and when defining the MoCA<26 and MoCA<21 sub-samples.

Education was recorded dichotomously as more than 12 years of education versus fewer than 13 years of education. Item 1.1 of the MDS Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess the degree of functional impairment resulting from cognitive problems. This scale was completed by the clinician on a five-point scale (none, slight, mild, moderate, severe); these scores were analysed as numeric values (0-4). Motor severity was scored with a modified Hoehn and Yahr scale (Hoehn & Yahr, 1967; Jankovic et al., 1990), and anti-Parkinson medications were converted to levodopa equivalent daily dose (LEDD) using an established formula for dose equivalence (Tomlinson et al., 2010).

6.2.3 Statistical analysis

Statistical analysis used Stata version 13 (StataCorp, 2013). The factor structure of the MoCA was assessed using factor analysis, a test that groups observed variables based on common variance into a smaller number of latent factors. Confirmatory factor analysis with maximum likelihood estimation was used to test previously reported factor structures of the MoCA. Exploratory factor analysis (principal factors with oblique rotation) was used to identify possible alternative models. Because the MoCA item scores are not continuous, these analyses were based on summary statistics from correlation matrices. The exploratory factor analyses, and subsequent confirmatory analyses of the resulting model, were conducted on randomly-selected subgroups of the full sample; the similarity of these groups was confirmed using between-group comparisons (t-test or Mann-Whitney U test) for sex, education, age, disease duration, etc. The normality of the distributions was evaluated by inspecting a histogram.

Each model generated by confirmatory factor analysis was tested for goodness-of-fit to the observed data using various standard indices. Approximate cutoff values that indicated a good fit were those suggested by Acock (2013). The indices (with cutoff values indicating a good fit in parentheses) were: χ^2 / *df* (2-3), root mean square error of approximation (<0.05), comparative fit index (>0.95), Tucker-Lewis index (>0.95), and standardised root mean square residual (<0.08).

The Stata syntax for the analysis is available online on the Open Science Framework [https://osf.io/x7d8p/].

6.3 Results

6.3.1 Descriptive statistics

Descriptive statistics for the full sample and the MoCA<26 and MoCA<21 sub-samples are presented in Table 6-1. For each, functional impairment secondary to the cognitive symptoms was minimal. The ratio of men to women was typical of PD (K. M. Smith & Dahodwala, 2014), and was more pronounced in the MoCA<26 and

MoCA<21 sub-samples. The distribution of responses for each item is provided in Appendix 4 (Table A1). The highest percentage of correct answers was consistently provided for the orientation items; values for the recall items were typically lowest.

Table 6-1. Descriptive statistics for the full sample and the sub-samples.

Item	Full sample	MoCA<26	MoCA<21
Sample size (n)	1738	797	157
Male sex (n, %)	1123 (64.6)	564 (70.8)	117 (74.5)
Age in years	67.6 (9.2)	69.9 (8.5)	73.4 (7.3)
Disease duration in years	3.2 (3.1)	3.0 (2.7)	3.5 (4.1)
>12 years education (n, %)	1176 (67.6)	492 (61.7)	76 (48.4)
Hoehn and Yahr (median, IQR)	2 (1-2)	2 (1-2)	2 (1.5-2.5)
LEDD	291 (206)	301 (202)	315 (200)
MoCA	25.3 (3.4)	22.4 (2.7)	17.9 (2.2)
MDS UPDRS 1.1	0.5 (0.7)	0.7 (0.8)	0.9 (1.0)

Data are mean (standard deviation) unless otherwise specified. In the full sample, disease duration was missing for 46 participants; UPDRS for 5; Hoehn and Yahr for 4; and LEDD for 14. IQR = interquartile range, LEDD = levodopa equivalent daily dose, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating Scale.

6.3.2 Confirmatory factor analysis

Because some MoCA items were only available as ordinal values, polychoric correlation matrices were generated, as these accommodate both dichotomous and ordinal scores. Initially, these matrices had multiple blank values due to lack of variance in the data, precluding further analysis. Therefore, similar items were collapsed into additional ordinal variables, as follows: the lion, rhinoceros, and camel into a single "animals" item (scored 0-3); date, month, year, and day into a "temporal" [orientation] item (0-4); and place and city into a "spatial" [orientation] item (0-2).

The polychoric correlation matrix was used to create a summary statistics dataset, which formed the basis of the confirmatory factor analysis models. Factor-indicator

correspondences used standard reflective measurement. Four models based on previous research were tested: a two-factor model, a six-factor model, a one-factor second-order model, and a three-factor model based on 20 out of the 30 MoCA items Table 6-2).

Table 6-2. Summary of models tested with confirmatory factor analysis.

Item	2-factor model	6-factor models	3-factor model
Trail-making	Attentional-executive	Executive	Executive
Phonemic fluency	Attentional-executive	Executive*	Executive
Abstraction 1	Attentional-executive	Executive	Executive
Abstraction 2	Attentional-executive	Executive	Executive
Animals	Memory	Language	Not included
Repetition 1	Memory	Language	Verbal attention
Repetition 2	Memory	Language	Verbal attention
Recall 1	Memory	ST Recall	ST Recall
Recall 2	Memory	ST Recall	ST Recall
Recall 3	Memory	ST Recall	ST Recall
Recall 4	Memory	ST Recall	ST Recall
Recall 5	Memory	ST Recall	ST Recall
Digits forward	Attentional-executive	ACWM	Verbal attention
Digits backward	Memory	ACWM	Executive
Vigilance	Attentional-executive	ACWM	Not included
Subtractions	Attentional-executive	ACWM	Executive†
Cube	Attentional-executive	Visuospatial	Executive
Clock	Attentional-executive	Visuospatial	Executive
Temporal	Memory	Orientation	Not included
Spatial	Memory	Orientation	Not included

*Phonemic fluency was cross-loaded onto the language factor in the six-factor model. †Subtractions was cross-loaded onto the Verbal Attention factor. ACWM = attention, concentration, and working memory; ST = short term.

The two-factor model included memory and attentional-executive function (Duro et al., 2010). Factor loadings for the two-factor model in the full sample were varied, but all were statistically significant (Table A2).

The six-factor model comprised short-term recall, visuospatial abilities, executive function, attention, language, and orientation (Freitas, Simões, Marôco, et al., 2012), The model initially failed to converge. After noting that the "spatial" variable loaded perfectly onto the Orientation factor, that variable's error variance was constrained to zero, enabling an admissible solution model to converge. Factor loadings were again universally significant (Table A3). Phonemic fluency was loaded onto two factors (executive function and language): for both, the coefficients were weak.

The six-factor model formed the basis of a one-factor second-order model, again replicating Freitas, Simões, Marôco, et al. (2012). Again, the error variance for the "spatial" variable was constrained to zero. All of the first-order factors loaded strongly onto the higher-order factor ("cognition"), with the exception of orientation, which loaded more weakly. All loadings were statistically significant (Table A4).

The three-factor model excluded 10 items that were also previously excluded in the original factor analysis (Benge et al., 2017) due to clear ceiling effects (specifically, the orientation, naming, and vigilance items). The subtractions test was cross-loaded onto both the executive and the verbal attention factors. All loadings were significant and coefficients were high, except for the loading of subtractions on verbal attention (Table A5).

Fit statistics were computed for all of the above models (Table 6-3); none had a good fit, according to the previously defined cutoff values. When tested in the MoCA<26 subgroup, correlation coefficients and fit statistics in the two-factor and three-factor models were generally poorer (Appendix 4, Tables A6-A8). The six-factor models failed to converge. With the MoCA<21 sub-group, all tested models failed to converge, possibly due to the limited sample size (n = 157). In each model, various strategies were explored with the aim of achieving convergence (e.g. examining modification indices and specifying better starting values), but the possible respecifications could not be justified theoretically, or did not lead to convergence.

Table 6-3. Goodness-of-fit statistics for the confirmatory factor analyses.

Statistic	2-factor model	6-factor model	1-factor model	3-factor model
χ^2_M	4031.53	2753.84	2994.20	1623.26
df_M	169	155	164	101
p	<0.001	<0.001	<0.001	<0.001
$p_{close\text{-}fit\ H0}$	<0.001	<0.001	<0.001	<0.001
χ^2 / df	23.86	17.77	18.26	16.07
RMSEA (90% CI)	0.12 (0.11-0.12)	0.10 (0.10-0.10)	0.10 (0.10-0.10)	0.09 (0.09-0.10)
CFI	0.62	0.74	0.72	0.81
TLI	0.57	0.69	0.68	0.77
SRMR	0.09	0.07	0.08	0.06

All models were tested in the full sample (n = 1738). CFI = comparative fit index, CI = confidence interval, RMSEA = root mean square error of approximation, SRMR = standardised root mean square residual, TLI = Tucker-Lewis Index.

6.3.3 Exploratory factor analysis

In order to determine whether the MoCA's items mapped to a different factor structure in this cohort, a novel exploratory factor analysis was conducted. The full sample was split randomly into two subgroups of approximately equal size (subgroup 1, n = 856; subgroup 2, n = 882). The exploratory factor analysis was applied to subgroup 1, and then tested with confirmatory factor analysis in subgroup 2. Between-group comparisons found no significant differences between the subgroups in any of the tested variables (age, disease duration, education, etc.).

The exploratory factor analysis was constrained to six factors after examining a screeplot. Factors identified were short-term memory (comprising recall items 1-5), executive-visuospatial function (cube, clock, trail-making, and subtractions), attention and working memory (repetition 1, digit spans forward and backward, vigilance, and phonemic fluency), verbal-executive function (abstraction 1 and 2 and phonemic fluency), orientation (temporal and spatial) and expressive language (repetition 2 and animals). Table 6-4 contains loadings for every item on every domain.

Table 6-4. Loadings for each item by factor using exploratory factor analysis.

Item	Memory	Visuospatial-executive	Attention	Verbal-executive	Orientation	Expressive language
Trail-making	0.03	**0.60**	0.03	0.04	0.13	–0.07
Phonemic fluency	0.03	0.08	**0.22**	**0.23**	0.13	0.06
Abstraction 1	–0.02	0.11	–0.08	**0.59**	0.14	0.02
Abstraction 2	0.06	0.06	–0.08	**0.68**	0.07	0.23
Animals	0.00	0.40	–0.06	0.13	–0.18	**0.45**
Repetition 1	0.04	0.00	**0.55**	0.09	–0.15	0.27
Repetition 2	0.06	–0.13	0.13	0.22	0.29	**0.53**
Recall 1	**0.35**	0.10	0.02	0.23	–0.10	–0.22
Recall 2	**0.65**	0.05	0.02	0.13	–0.11	–0.18
Recall 3	**0.69**	0.04	–0.01	0.06	–0.01	–0.05
Recall 4	**0.74**	–0.02	–0.01	–0.07	0.05	0.23
Recall 5	**0.74**	–0.05	–0.02	-0.05	0.04	0.19
Digits forward	–0.02	0.06	**0.72**	–0.12	–0.10	–0.07
Digits backward	–0.05	0.18	**0.48**	–0.18	0.27	0.18
Vigilance	0.05	–0.13	**0.32**	0.17	0.27	–0.06
Subtractions	–0.08	**0.33**	0.12	0.11	0.13	–0.03
Cube	–0.07	**0.53**	–0.06	0.24	0.05	0.08
Clock	0.08	**0.59**	0.15	-0.01	–0.18	0.08
Temporal	0.16	0.29	–0.08	–0.28	**0.45**	–0.09
Spatial	–0.05	–0.04	–0.08	0.17	**0.84**	0.08

Values are correlation coefficients. For each item, the strongest loading is in bold text. This analysis was run on the full sample, subgroup 1.

The new model did not converge when tested with confirmatory factor analysis in subgroup 2. Again, various strategies designed to achieve convergence were explored, but no appropriate respecifications emerged. Therefore, it was not possible to validly

compare the fit of the new model to previously tested ones. The model was not retained for further interpretation.

A second exploratory factor analysis replicating Benge et al. (2017), constrained to three factors and excluding the orientation, naming, and vigilance items, was also conducted in subgroup 1. The resulting model was almost identical to that reported by Benge et al. (2017), the sole exception being backward digit span, which loaded strongly onto the verbal attention factor rather than the executive factor. Subjecting this revised model to confirmatory factor analysis in subgroup 2 again found poor fit statistics (Table A9).

6.4 Discussion

In a large PD cohort, no clear factor structure in the MoCA was found. Six-factor and one-factor second-order models reported in AD and MCI samples (Freitas, Simões, Marôco, et al., 2012), and a two-factor model reported in a varied dementia group (Duro et al., 2010), were not replicated in this cohort. Additionally, there was a poor fit for a three-factor model previously suggested as appropriate for PD (Benge et al., 2017). Finally, new exploratory factor analyses did not identify any better structures to fit the observed data.

The discrepancy between these results and some previous models may be explicable by different cognitive score distributions in the samples tested. In this sample, the mean MoCA score was 25.3, and 941 (54.1%) were in the normal range. In contrast, the samples in previous analyses had much lower cognitive scores, with overall means of 14.4 (Duro et al., 2010) and 22.4 (Freitas, Simões, Marôco, et al., 2012) in the cognitively impaired patients – in the latter study, the controls had a mean score of 24.7, below the recommended cutoff for healthy cognition. In both studies, the MCI groups would have been considered moderately to severely impaired in this analysis, as they had means of 19.6 (Duro et al., 2010) and 18.3 (Freitas, Simões, Marôco, et al., 2012). Moreover, over two-thirds of the Tracking Parkinson's cohort had more than 12 years of education, compared to only around 10% of one previously tested

sample (Duro et al., 2010). In the other study, the mean number of education years was only 7.8 (Freitas, Simões, Marôco, et al., 2012).

The exploratory factor analysis previously conducted in PD (Benge et al., 2017) was based on a cohort much more similar to the Tracking Parkinson's group; mean MoCA score, disease duration, education, and the ratio of men to women were all similar, though the other cohort was slightly younger. The present analysis found a poor fit for their model, showing that promising models generated by exploratory factor analysis do not necessarily have a good fit when tested in independent samples with confirmatory factor analysis. This was also the case for the new models generated by exploratory factor analysis in this project. Similar to Benge et al. (2017), the orientation, object naming, and digit span items had clear ceiling effects, reflecting their relative ease. Executive and memory items showed much greater variance, as was also the case for the AD group in Freitas et al.'s (2012) study. Therefore, screening tests designed to be even shorter than the MoCA (i.e. five minutes or less) should minimally include sensitive tests of these two domains.

Combined, these results imply that a clear factor structure to the MoCA may emerge in cohorts that are characterised by more severe cognitive impairment, where a consistent and theoretically reasonable pattern of errors might emerge. However, this factor structure is obscured in cognitively normal or mildly impaired samples, where by definition most participants will provide correct responses to the majority of the MoCA's items. Attempts were made to test this hypothesis in a subset of the Tracking Parkinson's cohort with more severe impairment (MoCA<21), but the model failed to converge, probably due to the small sample size. Future research with a larger cohort of moderately or severely impaired PD patients would be useful to establish whether the factor structure reported in other dementias is evident in this context. Further follow-up of the Tracking Parkinson's cohort could potentially explore this.

The major strength of the present analysis was the very large sample size (n = 1738), which permitted a well-powered sub-group analysis with a MoCA<26 sub-group (n = 797). A limitation was the relatively large number of participants (n = 262) who were excluded due to missing data. Additionally, the cohort was not fully representative of

the PD population at large, given the eligibility criteria requiring diagnosis 3.5 years or fewer before study enrolment, and the high education level.

The current results suggest that the MoCA should be reserved for screening purposes, or for assessment of global level of cognitive function, as is suggested by the MDS (Litvan et al., 2012). The MoCA is a reliable and valid instrument for these purposes. Its coverage of multiple cognitive domains makes it particularly useful for screening non-AD dementias, even at the early stages of mild impairment, while also retaining the brevity of less sensitive assessments, such as the MMSE. However, detailed neuropsychological testing remains the gold standard for accurately measuring multiple cognitive domains and subsequently describing a patient's cognitive profile.

6.4.1 Conclusions

These results do not support the existence of a clear factor structure to the MoCA in a large cohort of PD patients with overall normal or mildly impaired cognition. Comparisons to previous studies suggest that a clinically significant factor structure may emerge in samples with moderate to severe dementia. The MoCA may be useful for identifying meaningful subtypes in such cases, but the evidence suggests that it cannot do so in more mildly impaired patients, including those with PD-MCI. Therefore, for the present, subtyping people with PD-MCI should rely on the established procedure of detailed neuropsychological testing. The MoCA should be used for either screening purposes or for assessing global cognitive function in PD.

7 The influence of *APOE* and *MAPT* on cognitive decline in early PD

7.1 Introduction

Cognitive decline in PD and other neurodegenerative disorders is a highly polygenic trait, influenced by numerous genetic variants of modest individual effect size. Two of the genes that have been most extensively studied in relation to cognitive decline in PD are *APOE* and *MAPT*, though results have often been inconsistent, particularly for *MAPT*. This chapter presents a new, detailed analysis of *APOE* and *MAPT*, again using data from the Tracking Parkinson's project, with the MoCA as the measure of cognitive function. The aim is to take advantage of the study's large sample size, longitudinal design, and detailed genetic data to clarify the nature of the relationship between *APOE* and *MAPT* variants and cognition through the course of early PD.

7.1.1 *APOE*: structure, function, and role in AD susceptibility

Of the more than 30 genetic loci that have been implicated in AD susceptibility, *APOE* is by far the most significant (Pimenova et al., 2018). This gene is located at chromosome 19q13, consists of four exons, and encodes apolipoprotein E (apoE), the major apolipoprotein in the central nervous system. Mature human apoE consists of 299 amino acid residues. A cysteine / arginine alternation at residues 112 and 158 distinguishes three protein isoforms: apoE2, apoE3, and apoE4 (Zhong & Weisgraber, 2009). These isoforms correspond to three alleles of the *APOE* gene – ε2, ε3, and ε4 – which are defined by two exonic single nucleotide polymorphisms (SNPs), rs429358 and rs7412 (Rasmussen, 2016). These alleles have different frequencies in the population. One large meta-analysis reported a frequency in Caucasians of 8.4% for ε2, 77.9% for ε3, and 13.7% for ε4; ε3/ε3 homozygotes constituted almost two-thirds of healthy controls (Farrer et al., 1997).

The three *APOE* alleles have different implications for AD susceptibility. The most common allele, ε3, is neutral with respect to AD risk. The ε4 allele is the major

genetic risk factor for AD. The effect size increases in a dose-dependent manner: the probability of AD is increased by approximately three times in individuals with a single copy of ε4 relative to individuals with no ε4 alleles, and by approximately eight times in ε4 homozygotes. This allele also reduces the average age of dementia onset by 9-16 years, and the average age of death by 5-6 years (Corder et al., 1993). The rarer ε2 allele is a protective factor against AD, and is about half as common in AD patients compared to healthy controls (Chartier-Harlin et al., 1994). Again, the magnitude of the effect depends on dosage. Thus, in order of AD susceptibility from lowest to highest risk, the *APOE* genotypes are as follows: ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4 (Pimenova et al., 2018).

The mechanisms by which *APOE* influences AD risk are incompletely understood, partly due to the multifunctionality of the apoE protein. The protein's central role is in the transportation of cholesterol and triglycerides, but it also has isoform-specific effects on amyloid-β metabolism that are more relevant for AD pathogenesis (Y. Huang & Mahley, 2014). ApoE4 is less efficient at amyloid-β clearance than the other isoforms (Castellano et al., 2011), and also increases fibrillar amyloid-β deposition (Reiman et al., 2009). Both of these contribute to plaque formation, and subsequently to the neurotoxic cascade that ultimately leads to AD dementia. ApoE4 is also associated with heightened tau phosphorylation, reduced mitochondrial function, increased neuroinflammation, and decreased neurogenesis in regions such as the hippocampus (Y. Huang, 2010), all of which may further contribute to AD risk.

7.1.2 *MAPT*: structure, function, and role in tauopathies

The *MAPT* gene encodes the microtubule-associated protein tau, and it is therefore strongly linked to neurodegenerative tauopathies. The gene is located on chromosome 17q21 and spans 134kb of nucleotide sequence. As a result of an ancient inversion of an approximately 900kb region, including the entire *MAPT* gene, there are two major haplotypes, H1 and H2, which are differentiated by a defined set of SNPs and an intron deletion in H2. The H2 haplotype is almost exclusive to European populations, in which it has a frequency of around 20% (Stefansson et al., 2005). Subsequent evolutionary processes led to multiple subhaplotypes that are unique to H1, and a

small number that are unique to H2. A classification system introduced by Pittman et al. (2005) identified 24 subhaplotypes, designated H2a-H1x in descending order of frequency, which capture more than 95% of the diversity at the locus.

Like apoE, tau is a multifunctional protein. Its primary role is in maintaining the structural integrity of neurons by regulating axonal transport, promoting neurite outgrowth, and assembling and stabilising microtubules in the cytoskeleton (Zhang et al., 2016). The protein is subject to numerous post-translational modifications, of which phosphorylation is the most relevant for neurodegenerative diseases. All tauopathies are defined by abnormally phosphorylated (usually hyperphosphorylated) tau. This impairs the protein's normal function, thus compromising the structural integrity of neurons. Additionally, there may be a gain of neurotoxic function, as hyperphosphorylation of the tau protein promotes its pathological oligomerisation and aggregation into neurofibrillary tangles (Johnson & Stoothoff, 2004).

Approximately 60 *MAPT* variants have been linked to neurodegenerative diseases (Zhang et al., 2016). Various mutations in the gene are pathogenic for autosomal dominant FTD (Rascovsky et al., 2011). The H1 haplotype is a major risk factor for primary tauopathies including progressive supranuclear palsy (Conrad et al., 1997; Höglinger et al., 2011), corticobasal degeneration (Houlden et al., 2001), and argyrophilic grain disease (Kovacs, Pittman, et al., 2008). Recent analysis of H1 subhaplotypes indicated that they do not confer equal risk: for example, the strongest risk factors for progressive supranuclear palsy are the H1c, H1d, H1g, and H1o subhaplotypes (Heckman et al., 2019). The H2 haplotype is associated with reduced susceptibility to these disorders (Zhang et al., 2017). As a secondary tauopathy, AD is not as closely associated with *MAPT* as the primary tauopathies; however, genome wide association studies show that H1 increases AD risk and H2 decreases AD risk by small but statistically significant margins (Allen et al., 2014; Gerrish et al., 2012).

7.1.3 Effects of *APOE* and *MAPT* in PD

Given the associations of *APOE* and *MAPT* variants with neurodegenerative diseases, many researchers have assessed the potential link to PD susceptibility. For *APOE*,

results have often been inconsistent. Two meta-analyses found no overall link between ε4 and PD susceptibility; instead, ε2 – the protective allele with respect to AD – was implicated as a modest PD risk factor (X. Huang, Chen, & Poole, 2004; Williams-Gray, Goris, et al., 2009). Frequently small sample sizes, heterogeneity of odds ratios, and probable publication bias suggested that these conclusions should be interpreted with caution (Williams-Gray, Goris, et al., 2009). For *MAPT*, results have been more consistent: the link between H1 and PD has been clearly supported by genome wide association studies (Nalls et al., 2011), which found that the H1/H1 genotype increases the risk of developing PD by around 50% relative to H1/H2 and H2/H2 (Zabetian et al., 2007).

In addition to a potential role in PD pathogenesis, both *APOE* and *MAPT* have been studied as candidate genes for cognitive decline in PD. The autopsy studies presented in the systematic review in this thesis all found that ε4 carriers were over-represented in PD cases with dementia relative to those without, although statistical comparisons were not always significant (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016; L. Walker et al., 2015). These findings are consistent with large meta-analyses of clinical studies, which have reported that the presence of an ε4 allele in PD increases the risk of dementia by approximately 60-70% (Pang, Li, Zhang, & Chen, 2018; Williams-Gray, Goris, et al., 2009). The ε4 allele also induces a more rapid cognitive deterioration in PD (Morley et al., 2012). Neuropsychological studies have suggested that the ε4 allele causes PD patients to express an amnestic cognitive phenotype similar to that of pure AD, characterised by poorer information encoding and semantic fluency associated with reduced activity in temporoparietal circuits (Mata et al., 2014; Nombela et al., 2014). While these data imply that ε4 promotes amyloid-β pathology and comorbid AD in PD, clinicopathological studies have also shown that ε4 increases the incidence of dementia in α-synucleinopathies with minimal coexistent Alzheimer lesions. This suggests that the gene may have direct effects on the propagation of Lewy pathology (Tsuang et al., 2013), consistent with some studies in the systematic review (Mattila et al., 2000; Ruffmann et al., 2016).

Evidence for an effect of *MAPT* on cognitive decline in PD is more mixed. The H1 haplotype has been linked to poorer memory (Morley et al., 2012) and visuospatial function (Nombela et al., 2014) in PD patients without overt cognitive impairment.

Another study (n = 512) reported that H1 was a strong predictor of dementia within five years of diagnosis (Williams-Gray, Evans, et al., 2009). However, several other studies have found no association of *MAPT* with cognition in PD. This included all of the autopsy studies in the systematic review that analysed this gene (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016), as well as the largest prospective study to date, which reported no link between *MAPT* and any cognitive measure in a total of 1079 patients with a mean of 6.6 years disease duration (Mata et al., 2014).

It has been suggested that *MAPT* may influence cognition in early PD, but that this effect is muted in cases with longer disease durations (Collins & Williams-Gray, 2016; Morley et al., 2012). While this could potentially explain much of the variation between studies, some authors reported an association of H1 with dementia even in cases with long disease durations (Setó-Salvia et al., 2011). Analysis of individual *MAPT* subhaplotypes might provide a more plausible explanation for the variability. The H1p subhaplotype has been linked to dementia in PD (Setó-Salvia et al., 2011), and H1g has been associated with DLB (Labbé, Heckman, Lorenzo-Betancor, Soto-Ortolaza, et al., 2016). Another study linked various subhaplotypes (H1e, H1j, and H1x) to multiple system atrophy (Labbé, Heckman, Lorenzo-Betancor, Murray, et al., 2016), another neurodegenerative α-synucleinopathy. Each of these studies found that the majority of *MAPT* subhaplotypes were neutral with respect to disease risk.

The main objective of this analysis was to conduct a detailed assessment of the role of *APOE* and *MAPT* in cognitive decline in early PD. Data were again drawn from the Tracking Parkinson's cohort. The analysis uses cognitive data collected over three years, and detailed genetic data that enabled estimation of 24 *MAPT* subhaplotypes.

7.2 Methods

7.2.1 Participants

Basic information about the Tracking Parkinson's study, including eligibility criteria, was provided in the previous chapter (section 6.2.1). This analysis used data from the baseline, 18-month, and 36-month follow-up visits, when participants completed an

in-depth assessment that included cognitive testing with the MoCA. Participants were excluded if they were missing genetic data for *APOE* or *MAPT*, or if full MoCA data were not available at each of the three timepoints. Additionally, only participants who self-reported white British ancestry were included, in order to limit confounding by ancestry (Lander & Schork, 1994). Following these procedures, the total sample size for the main analysis was 986. Further details on participants who were excluded, including the main reasons for exclusion, are provided in Appendix 5.

7.2.2 Materials

The primary outcome measure was the MoCA version 7.1. Scores were adjusted for education, to a maximum of 30, as described previously. The rate of cognitive decline was calculated by subtracting a later MoCA score from an earlier one (e.g. a participant with a MoCA of 29 at baseline and 24 at 36 months had a 0-36 month decline of 5 points). A higher change indicated greater cognitive decline; zero indicated no change, and a negative value indicated improvement. The MoCA score at each timepoint was used to define probable cognitive status in three categories: normal (MoCA 26-30), MCI (21-25), and dementia (<21). These cutoffs have good psychometric properties and have been used previously (Dalrymple-Alford et al., 2010; Malek et al., 2015).

As in Chapter 6, functional impairment resulting from cognitive deficits was assessed with the MDS UPDRS 1.1; Hoehn and Yahr stage was used to quantify the degree of motor impairment; and all anti-Parkinson medications were converted into LEDD. Education was recorded dichotomously as more than 12 years of education versus fewer than 13 years of education. For each analysis, age and disease duration were converted to binary variables based around a median split, in order to facilitate examination of statistical interactions.

7.2.3 Genotyping

Blood samples were collected from each participant at baseline. An ethylene diamine tetra-acetic acid sample was used for DNA extraction, and transferred to the genetics

laboratory at the Medical Research Council Centre for Neuropsychiatric Genetics and Genomics at Cardiff University for analysis.

SNP array genotyping was performed using the Illumina HumanCore Exome array. Over half a million SNPs, including approximately 27 000 custom variants previously associated with neurological or psychiatric disorders, were analysed (Malek et al., 2015). Genotypes were aligned to the Haplotype Reference Consortium panel (hg19 / GRCh37) using perl script (http://www.well.ox.ac.uk/~wrayner/tools/) for imputation. Pre-imputation haplotype phasing was performed with Eagle, and imputation with Minimac3 (Das et al., 2016) using the 1000 Genomes Phase 3 v5 panel (Auton et al., 2015), a mixed population reference panel.

PHASE 2.1 (Stephens & Donnelly, 2003) was used for reconstructing genotypes. The SNPs for determining *APOE* status were not directly genotyped, but were imputed to a high quality (INFO >0.98 for rs429358 and rs7412). *MAPT* H1 and H2 haplotypes were distinguished by rs9468. The subhaplotypes specified for the analysis were the 24 originally defined by Pittman (2005).

7.2.4 Statistical analysis

Statistical analysis used Stata version 15 (StataCorp, 2017). A chi-square was used to test whether *APOE* and *MAPT* allele frequencies deviated from the Hardy-Weinberg equilibrium; significant deviations may reflect population stratification, genotyping errors, or other factors that might lead to bias (Namipashaki, Razaghi-Moghadam, & Ansari-Pour, 2015). The test used the user-written “genhw” command (Cleves, 1999).

Linear regression was used with continuous dependent variables (MoCA score and rate of cognitive decline). The robust estimator of variance was used to calculate the standard errors. Standard assumptions of linear regression (including normality and homoscedasticity of the residuals) were checked for each model. When MoCA score was the dependent variable, normality plots indicated that the residuals were somewhat skewed, but given the large sample size and the robustness of linear regression models, no data transformations were applied. Ordered logistic regression

was used with the categorical dependent variable (cognitive status). The assumption of proportional odds was tested, and if this was violated, generalised ordered logistic regression using the "gologit" command (Williams, 2006) was used.

Separate analyses were run with the primary independent variable as *APOE* genotype (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4) and *MAPT* genotype (H1/H1, H1/H2, and H2/H2); reference categories were set as ε3/ε3 in the *APOE* analyses and H1/H1 in the *MAPT* analyses. Secondary analyses used the number of *APOE* ε4 alleles (0, 1, or 2), *APOE* ε4 status (positive/negative), and *MAPT* H2 status (positive/negative) as the main independent variables. Each analysis was initially unadjusted, then adjusted for sex and age (partially adjusted), and finally adjusted for sex, age, disease duration, and education (fully adjusted). Due to some missing data for disease duration or education, the sample size for the fully adjusted models was 969 at baseline and at 36 months, and 966 at 18 months. The *APOE* analyses were not adjusted for *MAPT* status, and *vice versa*. As described above, age, disease duration, and education were dichotomised. In fully adjusted models, genotypes were tested for interactions with each of the other predictor variables, and stratified analysis (e.g. sex-stratified, age-stratified) was conducted subsequently if a significant interaction was found.

Further analysis of *MAPT* subhaplotypes used logistic regression with the user-written "haplologit" command (Marchenko, Carroll, Lin, Amos, & Gutierrez, 2008), a semiparametric profile-likelihood method that uses phased and unphased SNP data to estimate subhaplotype effects. The binary outcome measure was normal cognition versus dementia. Participants with probable MCI (MoCA 21-25) were excluded. Only data from the 36-month visit were used, as this timepoint had the highest raw number and the highest percentage of participants with dementia.

Because subhaplotypes were unphased, their frequencies were not directly observed; therefore, they were estimated using haplologit's expectation-maximisation algorithm. An additive model was used, allowing for the effect of an extra copy of a given haplotype to be assessed. The reference category was the subhaplotype with the highest estimated frequency in participants without dementia, combined with all rare subhaplotypes, which were defined by a frequency lower than 2 divided by the total

sample size. The analysis was adjusted for sex and age category. Power calculations were run with G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009).

The Stata syntax for the analysis is available online on the Open Science Framework [https://osf.io/wh6k4/].

7.3 Results

7.3.1 Descriptive statistics

The distribution of *APOE* and *MAPT* genotypes is shown in Table 7-1. Observed genotype frequencies did not significantly deviate from Hardy-Weinberg expected frequencies (*APOE* $\chi^2 = 7.3$, $p = 0.06$; *MAPT* $\chi^2 = 0.007$, $p = 0.93$).

Table 7-1. Distribution of *APOE* and *MAPT* genotypes (n = 1002).

***APOE* genotype**	**n (%)**
ε2/ε2	9 (0.9)
ε2/ε3	128 (13.0)
ε2/ε4	37 (3.8)
ε3/ε3	592 (60.0)
ε3/ε4	199 (20.2)
ε4/ε4	21 (2.1)
***MAPT* genotype**	
H1/H1	639 (64.8)
H1/H2	309 (31.3)
H2/H2	38 (3.9)

Table 7-2 provides descriptive statistics for the Tracking Parkinson's cohort in the present analyses at the baseline, 18-month, and 36-month timepoints. The mean

change in MoCA score was –0.2 (SD 2.7) from baseline to 18 months, with 37.4% of participants declining, and the remainder either staying the same or improving. The mean change was 0.4 (SD 2.8) from 18-36 months (with 45.3% declining), and 0.4 (SD 3.3) from baseline to 36 months (with 42.1% declining).

Table 7-2. Descriptive statistics for the analysis sample at each timepoint.

	Baseline	18 months	36 months
Sample size (n)	986		
Male sex (n, %)	625 (63.4)		
Age in years	66.7 (8.9)	68.3 (8.9)	69.9 (9.1)
Disease duration in years	1.3 (0.9)	2.9 (0.9)	4.4 (2.2)
>12 years education (n, %)	683 (69.3)		
Hoehn and Yahr (median, IQR)	1.5 (1-2)	2 (1.5-2.5)	2 (1.5-2.5)
LEDD	280 (207)	421 (253)	558 (293)
MoCA	25.9 (3.0)	25.9 (3.3)	25.5 (3.9)
Normal cognition (n, %)	608 (61.7)	620 (62.9)	581 (58.9)
MCI (n, %)	327 (33.2)	295 (30.0)	299 (30.3)
Dementia (n, %)	50 (5.1)	70 (7.1)	105 (10.6)
MDS UPDRS 1.1	0.4 (0.7)	0.6 (0.7)	0.7 (0.9)

Data are mean (standard deviation) unless otherwise specified. Across all visits, full data on disease duration were missing for 4 participants; UPDRS for 9; Hoehn and Yahr for 42; LEDD for 21; and education for 18. Cognitive status was determined based on MoCA score: normal = 26-30, MCI = 21-25, dementia = 0-20. IQR = interquartile range, LEDD = levodopa equivalent daily dose, MCI = mild cognitive impairment, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating Scale.

7.3.2 *APOE*

The results of all unadjusted, partially adjusted, and fully adjusted regression models are provided in Appendix 6. The fully adjusted linear regression models found no associations between *APOE* genotype and cross-sectional MoCA score at any timepoint, though at 36 months, deleterious effects of the ε3/ε4 (unstandardised

coefficient [95% CI]: –0.6 [–1.2, 0.0], $p = 0.06$) and ε4/ε4 (–1.6 [–3.4, 0.2], $p = 0.09$) genotypes relative to ε3/ε3 approached statistical significance.

There was a significant interaction between *APOE* genotype and sex at each timepoint. Subsequent sex-stratified analyses found significant associations between *APOE* genotype and cognitive outcome that varied by sex. Relative to male ε3 homozygotes, male ε2 homozygotes had higher cognitive scores at all timepoints; in contrast, male ε4 homozygotes had lower cognitive scores at 18 and 36 months. The ε2/ε3 genotype was marginally deleterious in men at baseline only. In women, ε4 homozygosity was protective at 18 and 36 months, and there was a marginal protective effect of ε2/ε3 at 18 months, but not at baseline or 36 months (Table 7-3).

No significant interactions between *APOE* genotype and age, disease duration, or education were observed at any timepoint.

Unadjusted, partially adjusted, and fully adjusted logistic regression models to predict cognitive status found no significant associations at any timepoint. Moreover, there were no significant interactions with any of the other predictors. However, based on the interaction that had been observed in the linear regression results for MoCA score, a sex-stratified analysis was conducted. This found that in men only, ε4 homozygosity was significantly associated with higher odds of worse cognitive status at 18 (2.9 [1.0, 8.4], $p = 0.04$) and 36 months (odds ratio [95% CI]: 3.9 [1.3, 11.7], $p = 0.02$).

The next analyses used the magnitude of MoCA change between study visits as the outcome variable. Fully adjusted models found no effect of *APOE* genotype on change from baseline to 18 months or 18 to 36 months. However, the ε2/ε3 genotype was marginally protective from baseline to 36 months (unstandardised coefficient [95% CI]: –0.6 [–1.2, 0.0], $p = 0.04$) relative to the ε3/ε3 reference genotype.

Table 7-3. Effect of *APOE* genotype on cognition, stratified by sex.

Men (n = 614)	**Baseline**	**18 months**	**36 months**
ε2/ε2	2.5 (1.2, 3.8) $p < 0.001$*	3.1 (2.7, 3.5) $p < 0.001$*	2.8 (2.0, 3.7) $p < 0.001$*
ε2/ε3	–0.9 (–1.8, –0.2) $p = 0.05$*	–0.6 (–1.5, 0.3) $p = 0.22$	–0.3 (–1.2, 0.6) $p = 0.48$
ε2/ε4	0.3 (–1.3, 1.3) $p = 0.97$	–0.3 (–2.4, 1.7) $p = 0.74$	–0.6 (–2.6, 1.5) $p = 0.59$
ε3/ε4	–0.3 (–1.0, 0.3) $p = 0.30$	0.2 (–0.4, 0.9) $p = 0.49$	–0.5 (–1.3, 0.3) $p = 0.24$
ε4/ε4	–1.0 (–2.4, 0.4) $p = 0.16$	–2.2 (–4.0, –0.5) $p = 0.01$*	–3.3 (–5.7, –0.8) $p = 0.008$*
Women (n = 355)			
ε2/ε2	–0.6 (–2.7, 1.6) $p = 0.60$	–0.1 (–1.5, 1.2) $p = 0.84$	0.2 (–1.4, 1.9) $p = 0.79$
ε2/ε3	0.5 (–0.4, 1.4) $p = 0.30$	0.8 (0.0, 1.6) $p = 0.05$*	0.9 (–0.1, 1.9) $p = 0.06$
ε2/ε4	–0.1 (–1.6, 1.3) $p = 0.78$	0.2 (–1.8, 2.3) $p = 0.82$	–1.0 (–3.8, 1.8) $p = 0.50$
ε3/ε4	0.1 (–0.6, 0.8) $p = 0.81$	–0.2 (–1.1, 0.6) $p = 0.58$	–0.8 (–1.7, 0.2) $p = 0.13$
ε4/ε4	0.7 (–0.2, 1.7) $p = 0.60$	1.2 (0.2, 2.3) $p = 0.02$*	1.8 (0.4, 3.1) $p = 0.001$*

Data are unstandardised regression coefficient (95% CI); significance level. The dependent variable is MoCA score. The reference category is *APOE* ε3/ε3. Positive values indicate a higher MoCA score than the mean score in the ε3/ε3 group, and negative values indicate a lower MoCA than ε3/ε3. Age, disease duration, and education category were covariates. *$p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

The MoCA change model from baseline to 36 months showed significant interactions between *APOE* and sex, age, and disease duration (separately). Sex-stratified analysis indicated that ε4 homozygosity was associated with cognitive decline over this period only in men (2.5 [0.8, 4.2], $p = 0.004$). Age-stratified analysis showed that the ε2/ε3 genotype was protective only in older participants (–1.4 [–2.4, –0.4], $p = 0.008$); the ε2/ε4 genotype was marginally deleterious only in younger participants (1.3 [0.0, 2.6],

$p = 0.05$). Finally, when the analysis was stratified by disease duration, ε2/ε2 and ε2/ε3 were protective (–1.7 [–3.2, –0.3], $p = 0.02$ and –1.3 [–2.1, –0.6], $p < 0.001$, respectively) only in participants with a longer disease duration, whereas ε3/ε4 and particularly ε4/ε4 were deleterious (0.8 [0.0, 1.5], $p = 0.04$ and 3.2 [0.9, 5.5], $p = 0.007$, respectively) in those with a shorter disease duration. Over the shorter intervals (baseline to 18 months and 18-36 months), no significant interactions were observed. Secondary analyses used different indices of *APOE* status as the predictor. When the number of *APOE* ε4 alleles was used, the results were almost identical to the above. When ε4 positivity was used, most previously observed results, including all interactions, were no longer evident. These results are summarised in Appendix 7.

7.3.3 *MAPT*

Unadjusted, partially adjusted, and fully adjusted linear regression models found no statistically significant relationships between the three major *MAPT* groups (H1/H1, H1/H2, and H2/H2) and MoCA scores at any timepoint (Appendix 6). Similarly, no associations were found when logistic regression was used to examine the relationship with cognitive status, nor when the magnitude of MoCA decline was the dependent variable. There was no significant interaction between *MAPT* genotype and any of the other predictors in any analysis. The results were almost identical when the analysis was simplified to a comparison of H2 carriers with non-carriers (Appendix 7).

For the subhaplotype analysis, participants with MCI (n = 299) were excluded, leaving a sample size of 686 (581 with normal cognition and 105 with dementia). The expectation-maximisation algorithm estimated that the most common subhaplotype was H2a, which had a frequency of 20.6%, comparable to previous studies (Labbé, Heckman, Lorenzo-Betancor, Soto-Ortolaza, et al., 2016; Pittman et al., 2005). The reference category was formed by combining H2a (allele sequence: AGGCCG) with subhaplotypes that had an estimated frequency lower than 0.3%, of which there were two: H1k (AAACTG) and H2w (GGGCCG). Three participants had constituent haplotype frequencies below 0.3%, and these were excluded from further analysis. Odds ratios were therefore computed in 683 participants for 21 subhaplotypes (Table 7-4), adjusted for sex and age category. The unadjusted model is included in

Appendix 8. As shown, no *MAPT* subhaplotypes were significantly associated with dementia.

Table 7-4. Effect of *MAPT* subhaplotypes on odds of dementia in PD.

Subhaplotype	Allele sequence	Estimated frequency (%)	OR (95% CI)	*p*-value
H1b	GGGCTA	17.9	0.7 (0.4, 1.2)	0.18
H1c	AAGTTG	15.1	0.8 (0.5, 1.4)	0.44
H1d	AAGCTA	7.5	0.7 (0.3, 1.5)	0.39
H1e	AGGCTA	6.8	0.9 (0.4, 1.8)	0.71
H1f	GGACTA	0.7	2.2 (0.3, 16.1)	0.42
H1g	GAACTA	1.2	0.8 (0.1, 5.4)	0.83
H1h	AGACTA	2.8	1.3 (0.5, 3.5)	0.58
H1i	GAGCTA	4.3	1.8 (0.9, 3.6)	0.12
H1j	AGGCTG	1.0	–*	0.99
H1l	AGACTG	4.8	1.2 (0.6, 2.4)	0.63
H1m	GAGCTG	2.3	1.5 (0.6, 3.8)	0.40
H1n	GGACTG	1.0	–*	1.00
H1o	AAACTA	1.1	1.3 (0.3, 5.8)	0.76
H1p	GGGTTG	0.04	3.7 (0.7, 19.6)	0.12
H1q	AAGTTA	1.3	0.4 (0.5, 3.3)	0.42
H1r	AGGTTG	1.6	1.0 (0.2, 4.0)	0.96
H1s	GGGCTG	1.1	–*	0.99
H1t	AGATTG	1.0	–*	0.99
H1u	AAGCTG	2.5	1.7 (0.7, 3.9)	0.24
H1v	GGATTG	1.7	0.9 (0.2, 3.9)	0.94
H1x	GAATTG	1.4	1.1 (0.2, 5.4)	0.93

For allele sequence, SNPs are in the following order: rs1467967, rs242557, rs3785883, rs2471738, rs9468 (H2-tagging), and rs7521. The reference category was H2a combined with all rare subhaplotypes (estimated frequency <0.3%). *OR very close to 0, with undefined upper CI limits and *p*-values very close to 1; therefore, results are not reported. CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

Power calculations indicated that the analysis was often underpowered for rarer subhaplotypes and smaller odds ratios (Appendix 9).

7.3.4 Sensitivity analysis

The sensitivity analysis repeated the main analysis, but included participants who had been excluded due to incomplete MoCA data (n = 781). The extent of missing data and the main reasons for it are summarised in Appendix 5, and the results of the sensitivity analysis are provided in Appendix 10. Statistically significant associations were slightly more frequent in the sensitivity analysis. For *APOE*, the mild deleterious effect of ε3/ε4 on MoCA score at 36 months crossed into significance in the fully adjusted model, and there were some additional marginally significant interactions. Sex-stratified effects of *APOE* on MoCA score were similar to the main analyses above. For *MAPT*, results were again very similar to the main analyses, with no significant results in any fully adjusted model.

7.4 Discussion

This study provides a detailed analysis of the influence of *APOE* and *MAPT* on cognitive decline in early PD, with full genotyping of both genes and a large sample size as important strengths of this work. The primary novel finding was that the effects of *APOE* ε4 homozygosity were significant only in men, with evidence of lower cognitive scores and higher odds of cognitive impairment at the 18 and 36 month timepoints, and an accelerated cognitive decline over the entire three-year period. Male ε2 homozygotes had consistently higher cognitive scores, though here there was no observable effect on rate of decline. Furthermore, in women only, there was an unexpected protective effect of ε4 homozygosity on cross-sectional MoCA score at 18 and 36 months. These results were independent of the potentially confounding effects of age, disease duration, and education, and they were supported by the sensitivity analysis, which had a larger sample size.

Interactions between *APOE* and sex are well established in the AD literature, but they are in the opposite direction. Meta-analyses have indicated that the protective effect of

ε2 and the deleterious effect of ε4 on AD risk are significantly greater in women than in men, particularly up to the age of around 75 (Farrer et al., 1997; Neu et al., 2017). Moreover, female ε4 carriers have a faster rate of cognitive decline than male ε4 carriers at the MCI stage (X. Wang et al., 2019). Multiple mechanisms for these sex differences have been suggested, including a complex interaction of apoE systems with oestrogenic changes in peri- and post-menopausal women (Riedel, Thompson, & Brinton, 2016), and an exacerbating effect of ε4 on tau pathology in women but not in men (Altmann, Tian, Henderson, Greicius, & ADNI Investigators, 2014).

In sharp contrast to AD, male sex is a risk factor for PD (K. M. Smith & Dahodwala, 2014), and men typically have a worse clinical progression (Haaxma et al., 2007), including a higher incidence of cognitive decline and dementia (Cereda et al., 2016; Miller & Cronin-Golomb, 2010). The current study suggests that a sexually dimorphic role of *APOE* – which was not examined in any of the studies above – may partially underlie the sex differences in the cognitive decline of PD versus AD. Biomarker and animal studies are needed to explore the biological mechanisms by which *APOE* interacts with sex to affect cognition in PD specifically. In addition, replication of this result in other large PD cohorts would also be useful, in order to verify that it is not a false positive result. Finally, this finding underscores the importance of considering sex as a covariate in future studies of *APOE* in PD.

In the cohort as a whole, there was no clear effect of *APOE* on cognitive scores cross-sectionally. Similarly, the link between *APOE* and the rate of cognitive decline over time was weak, with a significant effect only of the ε3/ε4 genotype between the 18 and 36-month follow-up visits. A potential reason for this is the relative instability of cognition in early PD. Other prospective studies with three-year follow-up of newly diagnosed PD patients have indicated that a substantial minority fluctuate or even improve over this period (Lawson, Yarnall, Duncan, et al., 2017). It may be that more robust associations of *APOE* with cognitive decline will emerge with time. The Tracking Parkinson's study is ongoing, and an update of this analysis will be useful when participants are in the middle to late stages of the disease, and the incidence of advanced cognitive dysfunction is appreciably higher.

Variants of the *MAPT* gene (including subhaplotypes) were not associated with any measure of cognition in this cohort. The historically inconsistent results relating the major *MAPT* haplotypes to cognitive decline in PD have been attributed to differences in disease duration; variation in *MAPT* has been suggested to be most relevant in early PD (Collins & Williams-Gray, 2016; Morley et al., 2012), although this hypothesis does not explain all of the discrepancies (Setó-Salvia et al., 2011). The present study provides further evidence against this hypothesis, as *MAPT* haplotypes were unrelated to cognition in the 4-5 years following PD diagnosis. These results are consistent with a similarly large-scale prospective study that had more detailed, domain-focused neuropsychological testing (Mata et al., 2014), and with all of the autopsy studies in the systematic review in this thesis that conducted an analysis of *MAPT* (Compta et al., 2011; Irwin et al., 2012; Ruffmann et al., 2016). The weight of these studies together indicates that *MAPT* H1 does not increase the risk of cognitive decline in PD.

Analysis of *MAPT* subhaplotypes is a relatively new area of research, particularly within the α-synucleinopathy spectrum. In the current study, no subhaplotypes approached statistical significance for distinguishing PD patients with dementia from those without. This included H1p and H1g, which have previously been found to be overrepresented in PDD or DLB relative to controls (Labbé, Heckman, Lorenzo-Betancor, Soto-Ortolaza, et al., 2016; Setó-Salvia et al., 2011). Variation in statistical methods, the definition of dementia, and demographics may partially explain the inconsistency. However, a more likely explanation is the rarity of most *MAPT* subhaplotypes combined with sub-optimal sample sizes. The current study, like the others above, had a relatively small sample size for a genetic association study, and the power analysis consistently showed limited power with rarer subhaplotypes. Thus, there was potential for a false-negative result, whereby a significant relationship between one or more subhaplotypes and dementia may have emerged with a larger PD sample. Future studies from other large cohorts and, in particular, meta-analyses of the accumulated results are needed to verify the present findings.

As stated, a limitation of the study was the sample size, which was larger than the vast majority of other studies of PD, but small for a genetic association study. A second limitation of this study was the reliance on the MoCA as the sole index of cognitive function. This test has good psychometric properties and is recommended by the

MDS for global cognitive assessment in PD (Litvan et al., 2012); however, it is designed as a brief dementia screening instrument, and does not offer comprehensive coverage of individual cognitive domains, as illustrated in the previous chapter. In addition, the MoCA is susceptible to practice effects with repeated administrations (Cooley et al., 2015), as was the case in this study. This may have contributed to the variability in cognitive progression seen in these participants, of whom a substantial proportion fluctuated or improved across the three-year study period. Future prospective studies should take advantage of the three different versions of the test if repeated administrations are to be performed over time.

Finally, the study had limited representativeness. Most of the participants in the cohort were relatively young and early in the disease course; high education was typical, and the analysis was restricted to those who self-reported white British ancestry. Further follow-up of the cohort will allow the effects of *APOE* and *MAPT* to be examined in the middle to late stages of the disease, when the proportion with significant cognitive dysfunction is higher. Additional cohort studies are needed to investigate whether these results are replicable in other populations.

7.4.1 Conclusions

A thorough analysis of the *APOE* and *MAPT* genes in a large prospective cohort of people with early PD found significant effects of both protective and deleterious variants of *APOE* in men only. This finding partly explains why the rate and severity of cognitive decline in PD is more marked in men, in contrast to AD, where women are more severely affected. Further research into the biological nature of the *APOE*-by-sex interaction in PD is warranted; moreover, stratifying by sex is important for future studies of *APOE* in PD. In contrast to *APOE*, variation in the *MAPT* gene was not associated with cognition in this cohort. These results provide further evidence refuting earlier observations that *MAPT* H1 is a significant risk factor for dementia in PD. Novel treatment strategies directed against *APOE*, which are discussed in Chapter 9, may be useful for managing cognitive decline in a subset of PD patients.

8 Distinct disease syndromes in cognitively impaired PD patients[2]

8.1 Introduction

The evidence presented in this thesis thus far shows that the pathology underlying cognitive decline in PD is complex. As shown in the systematic review in Chapter 3, Lewy pathology is the primary substrate of dementia in PD, but there is frequently a contribution from comorbid Alzheimer pathologies. Coexistent cerebrovascular and TDP-43 lesions do not have a major independent contribution to dementia in PD, though they are present to varying degrees in many autopsied cases, and may affect the rate or the neuropsychological presentation of cognitive decline. Because new treatments for cognitive decline in PD are targeted against the underlying pathology, there is an important need to define the extent of coexistent pathologies in people with PD *in vivo*. This chapter presents an observational study that aimed to achieve this.

The most important development in the treatment of neurodegenerative disorders in recent years has been the move towards disease-modifying therapies. Current medications for motor impairment in PD (e.g. levodopa) and cognitive impairment across the spectrum of dementia disorders (acetylcholinesterase inhibitors and memantine) are purely symptomatic. Disease-modifying therapies, in contrast to these medications, are targeted against a specific neurotoxic protein pathology. As a result, these therapies could potentially slow or halt the progression of a neurodegenerative disorder, preventing further neuron death and the associated worsening of the clinical features (O'Hara et al., 2018).

Naturally, a prerequisite for effective implementation of disease-modifying therapies is that they are used against the appropriate protein pathology. For example, in PD, treatments that target α-synuclein might ameliorate cognitive decline in a patient with a relatively pure α-synucleinopathy, but they would be less efficacious if there are

[2] The author acknowledges the contribution of Dr. Katherine Grosset to the conception, planning, and design of the work presented in this chapter.

coexistent AD changes also acting on cognition. As these therapies enter large-scale, long-term, and expensive clinical trials, this is an important element to consider. As shown, a high frequency of multiple pathology is to be expected in PD cohorts (Irwin et al., 2013), and this may confound the results of a trial by increasing the probability of a false negative finding. Therefore, it is essential to identify coexistent pathologies in prospective cohorts, and to consider their potential impact during data analysis.

Objectively identifying and measuring a given protein pathology *in vivo* has been facilitated by the development of specific biomarkers, including CSF assays and neuroimaging methods (Blennow et al., 2016). Biomarkers are valuable methods of monitoring disease progression in longitudinal studies, and for quantifying outcome measures in clinical trials of disease-modifying therapies, as has already been done in Phase 3 trials of drugs that target amyloid-β aggregation (Vandenberghe et al., 2016). However, at present, biomarkers for neurodegenerative disorders other than AD are not well established. This includes PD, for which a valid α-synuclein CSF signature or radioligand has not yet been introduced (Blennow et al., 2016; Harada et al., 2018).

Because established biomarkers for cognitive decline in PD are currently unavailable, characterising the severity and the nature of a patient's cognitive impairment relies on clinical evaluation. As reviewed in Chapter 4, the current diagnostic criteria are valid and reliable methods of identifying cognitive disorders *in vivo*, and they are widely used in research. In clinical care settings, a heuristic diagnosis by an expert clinician is the usual procedure, though the diagnostic criteria may be consulted as an aid in specific cases (Jack et al., 2018).

The objective of this study was to use a structured clinical assessment to ascertain the proportion of cognitively impaired PD patients who meet criteria for a diagnosis of different cognitive disorders. A secondary objective was to identify specific tests that have value for differential diagnosis.

8.2 Methods

The study had a cross-sectional, observational design, and was conducted in compliance with the Declaration of Helsinki (World Medical Association, 1967). A

favourable ethical opinion was granted by the local NHS research ethics committee (reference code 17/NS/0049) and by the Health and Social Care research and development departments at NHS Greater Glasgow and Clyde and NHS Lanarkshire (reference code GN17NE086). Recruitment took place between October 2017 and February 2019. Funding was given by the Neurosciences Foundation, a registered charity based in Scotland (charity number SCO11199). Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross-sectional studies (Vandenbroucke et al., 2007; von Elm et al., 2007).

8.2.1 Participants

All participants had PD diagnosed by a specialist neurologist in movement disorder clinics in Glasgow and Lanarkshire, Scotland, in addition to cognitive problems either self-reported or documented in the medical notes. Further inclusion criteria were age between 18 and 90 (inclusive), capacity to provide informed consent, and objective evidence of potentially significant cognitive impairment on screening, defined by a) a score below 27 on the MoCA (Nasreddine et al., 2005), b) a score above 3.3 on the IQCODE (Jorm, 1994), or c) functional impairment resulting from cognitive problems reported on the MDS UPDRS 1.1 (Goetz et al., 2008).

Each participant nominated one person to complete informant-rated questionnaires. The informant had to have known the participant for 10 years or more, to be aged between 18 and 90 (inclusive), and to have capacity to provide informed consent.

8.2.2 Materials

Potentially eligible patients were screened, and eligible participants then completed a multi-domain neuropsychological assessment incorporating selected subtests from various test batteries that are suitable for people with PD (Table 8-1). The assessment lasted around 90 minutes, and included at least two tests in each cognitive domain, in line with MDS guidelines (Litvan et al., 2012).

Table 8-1. List of neuropsychological tests by cognitive domain.

Cognitive domain	Test
Memory	KBNA word lists (free recall, delayed recall, and recognition); KBNA picture recognition
Executive function	KBNA phonemic and semantic fluency; KBNA practical problem-solving and conceptual shifting; DKEFS color-word interference
Attention and speed	WAIS-IV digit span forwards and backwards; SDMT (spoken version)
Visuospatial skills	RBANS line orientation; VOSP incomplete letters; VOSP object decision; interlocking pentagons
Language	KBNA picture naming; KBNA auditory comprehension
Praxis	KBNA praxis test

DKEFS = Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), KBNA = Kaplan-Baycrest Neurocognitive Assessment (Leach, Kaplan, Rewilak, Richards, & Proulx, 2000), RBANS = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, Tierney, Mohr, & Chase, 1998), SDMT = Symbol Digit Modalities Test (A. Smith, 1982), VOSP = Visual Object and Space Perception Battery (Warrington & James, 1991), WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition (Wechsler, 2008).

Participants also completed several questionnaires to explore various other diagnostic features. Hyposmia was defined by a score below 23 on the Hyposmia Rating Scale (Millar Vernetti, Perez Lloret, Rossi, Cerquetti, & Merello, 2012). Anxiety and depression were measured with the Hospital Anxiety and Depression Scale (Stern, 2014; Zigmond & Snaith, 1983): scores of 0-7 were normal, 8-10 indicated mild impairment, and greater than 10 indicated marked impairment. A positive response to items 6-10 on the Psychosis and Hallucinations Questionnaires for PD (Shine et al., 2015) indicated the presence of visual, auditory, tactile, olfactory, and gustatory hallucinations, respectively; a positive response to any of items 11-13 indicated delusions. RBD was defined by a score above 5 on the RBD screening questionnaire (Stiasny-Kolster et al., 2007) and excessive daytime fatigue by a score above 9 on the Epworth Sleep Scale (Johns, 1991).

Height and weight were recorded and converted to body mass index. Constipation was defined by self-report as fewer than one bowel movement per day or the use of

laxatives. Urinary incontinence, falls, syncope, smoking history, and demographics were also self-reported.

Participants' medication plans, medical histories, motor scores, and neuroimaging data were retrieved from electronic medical records. These were used to fill in missing data if possible, and to corroborate self-reported items. Anti-Parkinson medications were converted to LEDD, as previously (Tomlinson et al., 2010).

Informants completed three questionnaires concurrently with the patient assessment. The PD Cognitive Functional Rating Scale identified functional impairment due to cognitive decline; a score of 2-8 indicated mild impairment, and a score above 8 indicated marked impairment, consistent with MCI and dementia respectively (Kulisevsky et al., 2013; Ruzafa-Valiente et al., 2016). Cognitive fluctuations were identified by a positive answer to three of the four discriminating items on the Dementia Cognitive Fluctuation Scale (D. R. Lee et al., 2014). Behavioural changes (disinhibition, apathy, loss of empathy, stereotypy, and hyperorality) were evaluated with the Cambridge Behavioural Inventory (Wear et al., 2008); total scores for each variable were divided into percentage ranks (0-25% normal, 26-50% mild, 51-75% moderate, 76-100% severe) based on a previously published method (Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011).

8.2.3 Procedure

Anonymised data were transferred to a panel with expertise in movement disorders neurology, psychiatry, and clinical neuropsychology. Each participant was evaluated with reference to diagnostic criteria for various dementia disorders (Albert et al., 2011; Emre et al., 2007; Gorno-Tempini et al., 2011; Litvan et al., 2012; McKeith et al., 2017; McKhann et al., 2011; Rascovsky et al., 2011; Sachdev et al., 2014). Participants reporting cognitive decline prior to or contemporaneously with motor onset were classified as DLB. MCI-LB was defined analogously to PD-MCI, except with cognitive onset preceding or co-occurring with motor onset. Multiple diagnoses were permitted in a single participant. Diagnoses were conferred with two levels of confidence: probable and possible. Final diagnoses were by consensus.

To obtain an indication of the panel's diagnostic accuracy against autopsy, three pathologically-confirmed cases with various forms of dementia were identified from published reports that presented detailed neuropsychological workup on individual subjects (Eratne et al., 2018; Gurd et al., 2000; Price et al., 1993). Motor scores were fabricated so that the cases appeared to have PD (and thereby met inclusion criteria), but cognitive and other clinical data were not modified. These cases were included randomly with the participants in the study in a blinded fashion.

8.2.4 Data analysis

Results are reported as descriptive statistics and proportions. 95% confidence intervals (CI) were calculated using the formula

$$p \pm 1.96 \sqrt{\frac{p(1-p)}{n}}$$

where p is the sample proportion and n is the sample size.

8.3 Results

The screening and eligibility assessment process is provided in Figure 8-1. Consensus clinical diagnosis was correct for each of the pathologically-confirmed dementia cases drawn from previously published reports.

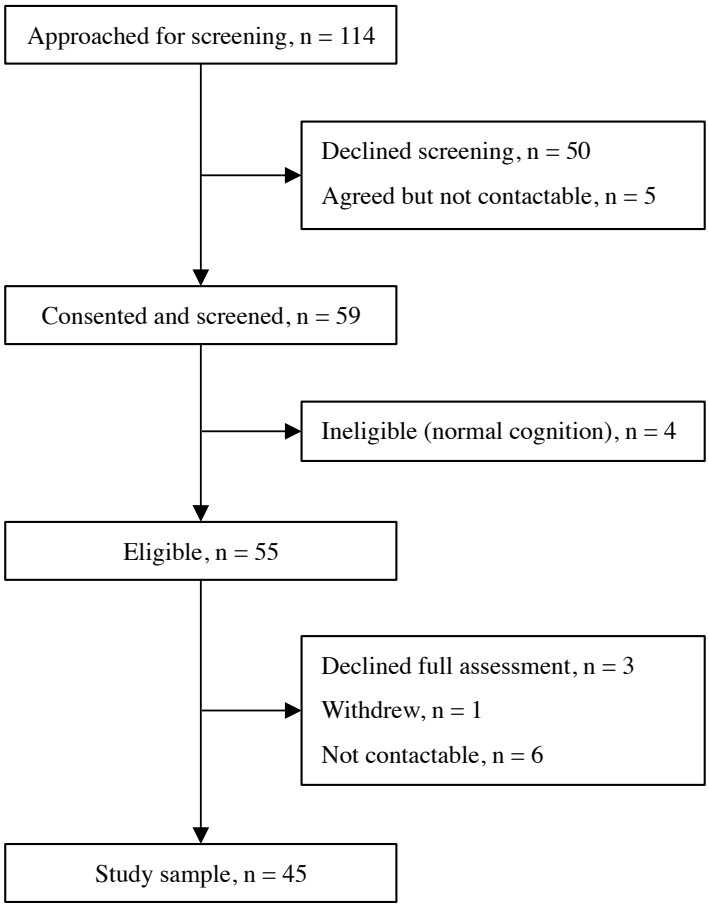


Figure 8-1. Flow diagram showing the recruitment process.

8.3.1 Descriptive statistics

Table 8-2 provides descriptive statistics for the 45 participants in the study. All had a diagnosis of idiopathic PD by a movement disorder neurologist. Thirty-nine (86.7%) had clinically established PD by MDS diagnostic criteria (Postuma et al., 2015), and the remaining six (13.3%) had probable PD. The sample was well educated, and 24 (53.3%) were or had been professionals, according to a standardised classification scheme (International Labour Organization, 2012).

In 16 participants (35.6%), the clinical diagnosis of PD was supported by FP-CIT SPECT; in the remaining 29 (64.4%), no functional scans had been performed. Eleven participants (24.4%) had had a structural brain scan: MRI only in seven, CT only in two, and both in two.

Table 8-2. Descriptive statistics for the observational sample.

Variable	Value
Sample size	45
Male sex (n, %)	33 (73.3%)
Age in years	69.1 (8.3)
Disease duration in years	8.9 (6.0)
Education in years	13.2 (2.9)
LEDD	567 (318)
MoCA	21.9 (3.6)
IQCODE	3.5 (0.7)
MDS UPDRS 1.1	1.9 (0.9)
PD-CFRS	2.4 (1.7)

Data are mean (standard deviation) unless otherwise specified. The IQCODE was missing for 9 participants, and PD-CFRS for 7. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, LEDD = levodopa equivalent daily dose, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, PD-CFRS = Parkinson's Disease Cognitive Functional Rating Scale, UPDRS = Unified Parkinson's Disease Rating Scale.

Core DLB features were common, with cognitive fluctuations in 27 patients (60.0%), RBD in 24 (53.3%), and visual hallucinations in 14 (31.1%). Other non-motor features were hyposmia in 28 patients (62.2%), constipation in 25 (55.6%), excessive daytime fatigue in 23 (51.1%), one or more falls in the previous three months in 19 (42.2%), hallucinations in a non-visual modality in 14 (31.1%), clinically significant anxiety in 12 (26.7%), depression in nine (20.0%), and urinary incontinence in seven (15.6%). Two (4.4%) were current smokers, and seven (15.6%) were ex-smokers.

8.3.2 Consensus panel diagnoses

The consensus panel diagnosed MCI in 26 (57.7%), and dementia in 19 (42.2%). Cognitive status, clinical diagnosis, and other key findings are in Table 8-3.

Table 8-3. Clinical features and diagnoses for individual participants.

Diagnosis	Status	Case	PD duration (years)	MDS UPDRS 3	MoCA	Memory	Attention	Executive	Visuospatial	Language	Praxis	Behaviour	Vascular	DLB features
Probable Lewy-related pattern														
No coexistent diagnosis	MCI	1	20+	NA	21	+	–	–	+	–	–	–	+	1
		2	4	26	22	+	–	–	–	–	–	–	–	1
		3	20+	15	23	–	–	–	+	–	–	++	++	2
		4	11	32	23	–	+	–	–	–	–	NA	+	1
		5	2	NA	23	–	–	–	–	–	–	NA	–	NA
		6	4	20	24	–	–	–	–	–	–	–	–	1
		7	8	36	24	–	–	+	–	–	–	++	+	3
		8	11	28	25	–	–	–	–	–	+	–	–	1
		9	9	NA	25	–	++	+	+	+	–	+	+	3
		10	1	NA	26	–	–	–	–	–	–	–	+	2
		11	10	30	27	–	–	–	–	–	–	–	–	2
		12	2	NA	27	–	–	+	–	–	–	–	–	1
	Dementia	13	7	19	13	++	++	+	++	–	–	NA	–	1
		14	14	25	18	–	+	+	–	–	–	–	–	3
		15	9	33	19	+	++	–	++	–	–	–	–	1
		16	17	30	20	++	+	+	+	+	–	NA	–	2
		17	18	NA	22	–	–	+	++	+	+	–	+	2
		18	15	NA	23	+	–	–	++	–	–	–	+	3
		19	4	45	23	+	++	++	+	–	–	–	+	1
Coexistent AD	MCI	20	4	19	21	+	–	++	–	–	–	–	–	2
		21	11	37	23	–	–	–	–	+	–	+	–	2
		22	2	44	23	–	+	+	–	+	–	–	+	2
		23	6	29	23	++	–	++	–	+	–	++	–	2
		24	10	31	24	+	–	+	–	–	–	–	+	1
		25	10	39	24	–	–	+	–	–	–	NA	+	1
	Dementia	26	7	NA	13	++	–	–	–	+	–	++	+	3
		27	9	48	13	++	–	+	++	+	+	++	++	2
		28	15	NA	14	+	–	++	+	+	+	NA	+	NA
		29	6	NA	18	+	+	++	++	++	–	–	–	1
		30	4	NA	20	++	++	–	+	–	–	NA	–	0
		31	10	44	20	–	+	+	++	++	+	–	–	3
		32	15	33	21	+	–	++	–	+	+	++	–	1
		33	12	25	23	+	–	+	–	++	–	–	–	1
Coexistent vascular	MCI	34	17	26	22	–	–	–	–	–	–	–	+	0
		35	1	36	23	+	–	–	–	–	–	+	++	2
		36	2	NA	23	–	–	++	+	+	–	–	++	2
		37	20+	NA	23	–	++	+	+	–	–	NA	++	NA
		38	8	25	26	–	–	–	–	–	–	+	++	1
		39	6	NA	26	–	–	+	+	–	–	++	++	3
Coexistent AD + vascular	MCI	40	8	29	22	+	–	++	+	++	–	–	++	1
Possible Lewy-related pattern														
AD	MCI	41	8	19	25	+	–	–	–	+	–	+	–	0
		42	1	22	27	–	–	–	–	–	–	–	+	0
	Dementia	43	6	28	19	–	–	+	–	++	–	–	+	2
AD + vascular	Dementia	44	5	29	19	++	++	++	–	+	–	–	++	1
FTD	Dementia	45	4	16	22	–	–	–	–	–	–	++	–	2

Behavioural features are disinhibition, apathy, loss of empathy, stereotypy, and hyperorality. Vascular burden is derived from vascular risk factors and medical history. The three core DLB features are cognitive fluctuations, visual hallucinations, and RBD. For cognitive features: – no impairment, + mild impairment (1-2 SDs below the mean), ++ marked impairment (2+ SDs below the mean). AD = Alzheimer's disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MCI = mild cognitive impairment, MDS = Movement Disorder Society, MoCA = Montreal Cognitive Assessment, NA = not available, PD = Parkinson's disease, RBD = rapid eye movement sleep behaviour disorder, SD = standard deviation, UPDRS = Unified Parkinson's Disease Rating Scale.

Forty of the 45 participants (88.9%, [95% CI: 79.7, 98.1]) had probable Lewy-related cognitive decline, which developed within established PD in 37, and before or around the time of motor onset in three (Figure 8-2).

The cognitive profile was Lewy-type, without comorbid disease, in 19 participants (42.2% [27.7, 56.6]). Neuropsychological impairments were to visuospatial abilities in nine, executive function in eight, memory in seven, and attention in seven. Three showed language deficits, and three had possible ideomotor apraxia. RBD, cognitive fluctuations, and hallucinations affected 11 participants each; the hallucinations were primarily visual in eight. Behavioural symptoms were mild or absent, except for moderate apathy and/or loss of empathy in three participants.

In the remaining 21/45 participants (46.7% [32.1, 61.3]) with a probable Lewy-related cognitive pattern, there were additional features indicating other disease processes. AD was the most common, being present in 15 (33.3% [19.5, 47.1]), of whom seven had MCI and eight had dementia. The primary deficits were in memory, language, and executive function. Semantic fluency was universally worse than phonemic fluency. Four had RBD, four were moderately depressed, three had fluctuations, and two had prominent psychosis.

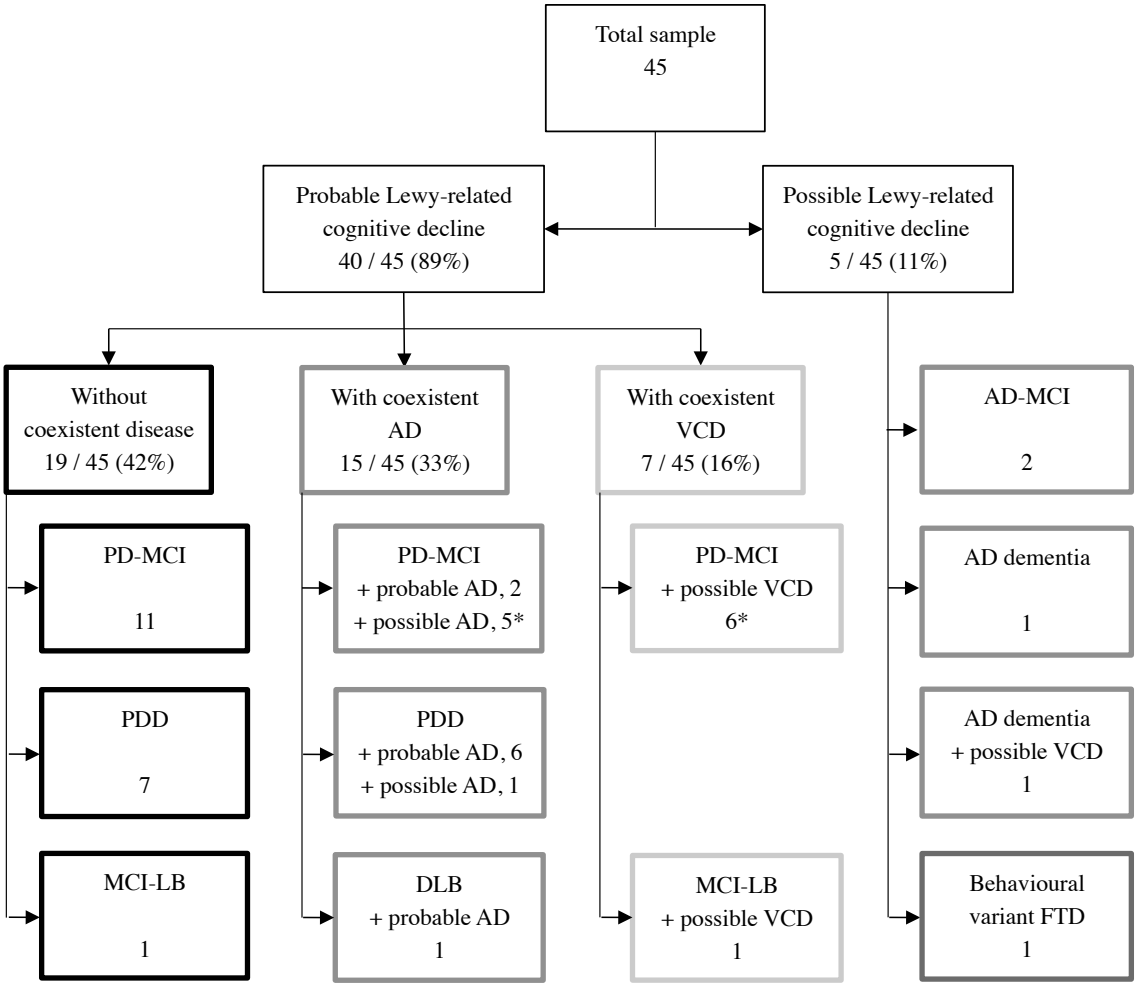


Figure 8-2. Consensus clinical diagnoses in each disease category.

Lewy body disease was a probable cause of cognitive decline in 40 patients. Nineteen of these cases had no comorbidity; 15 had coexistent AD; and 7 had coexistent VCD. Lewy body disease was not a primary cause of cognitive impairment in 5 patients, of whom 4 had AD and one had behavioural variant FTD.
***One patient had PD-MCI plus possible AD and possible VCD. AD = Alzheimer's disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MCI = mild cognitive impairment, PD = Parkinson's disease, PDD = Parkinson's disease dementia, VCD = vascular cognitive disorder.**

In the seven participants with comorbid probable AD, cognitive deficits were typically global, and there was also substantial non-cognitive morbidity. Memory was universally affected, and none benefited significantly from cueing, indicating a hippocampal encoding deficit (Economou et al., 2016). Posterior cortical deficits were common: six had impaired object naming, and three showed signs of ideomotor apraxia. Semantic fluency was consistently poor, and in the impaired range in four.

Five had cognitive fluctuations, four had hallucinations, and one had delusions. Five reported excessive daytime fatigue, though only one had RBD. Behavioural symptoms were also common: three of these participants had moderate or severe apathy and loss of empathy, and two showed signs of disinhibition, stereotypy, and/or hyperorality. Five reported multiple recent falls, and all had autonomic dysfunction (constipation in six, urinary incontinence in two, and orthostatic hypotension in one).

In 5/45 participants (11.1% [1.9, 20.3]), the cognitive profile was such that the panel rated Lewy-related cognitive decline as possible, rather than probable. In four, an AD pattern was identified. All had a clear amnestic profile, with limited or no cueing benefit. Semantic fluency was much worse than phonemic fluency, and three had impaired language. Typical features of Lewy body dementia were relatively infrequent: two had RBD, one had cognitive fluctuations, and none had hallucinations in any sensory modality.

Possible VCD was diagnosed in 8/45 participants (17.8% [6.6, 29.0]), of whom seven had probable Lewy-related cognitive decline, and one had an AD pattern. All had characteristic deficits in areas of executive function and attention, including processing speed, cognitive flexibility, and response inhibition. Vascular morbidity was frequent in this subgroup, and included one or more vascular events in five, hypertension in five, diabetes in three, obesity in two, long-term smoking history in two, and hypercholesterolaemia in one. Neuroimaging data were available for two; both showed evidence of small vessel disease. In all of these patients, cerebrovascular disease was not considered to be the primary cause of the cognitive symptoms.

Finally, the panel diagnosed probable behavioural-variant FTD in a single participant (2.2% [0.0, 6.5]) who had marked behavioural change, including severe disinhibition, apathy, loss of empathy, stereotypy, and hyperorality. Neuropsychological scores were generally in the average to high average range, consistent with education and work history. However, most executive tests, as well as processing speed and line orientation, were low average.

The percentage of the sample meeting probable and possible diagnoses for each cognitive disorder is shown in Figure 8-2.

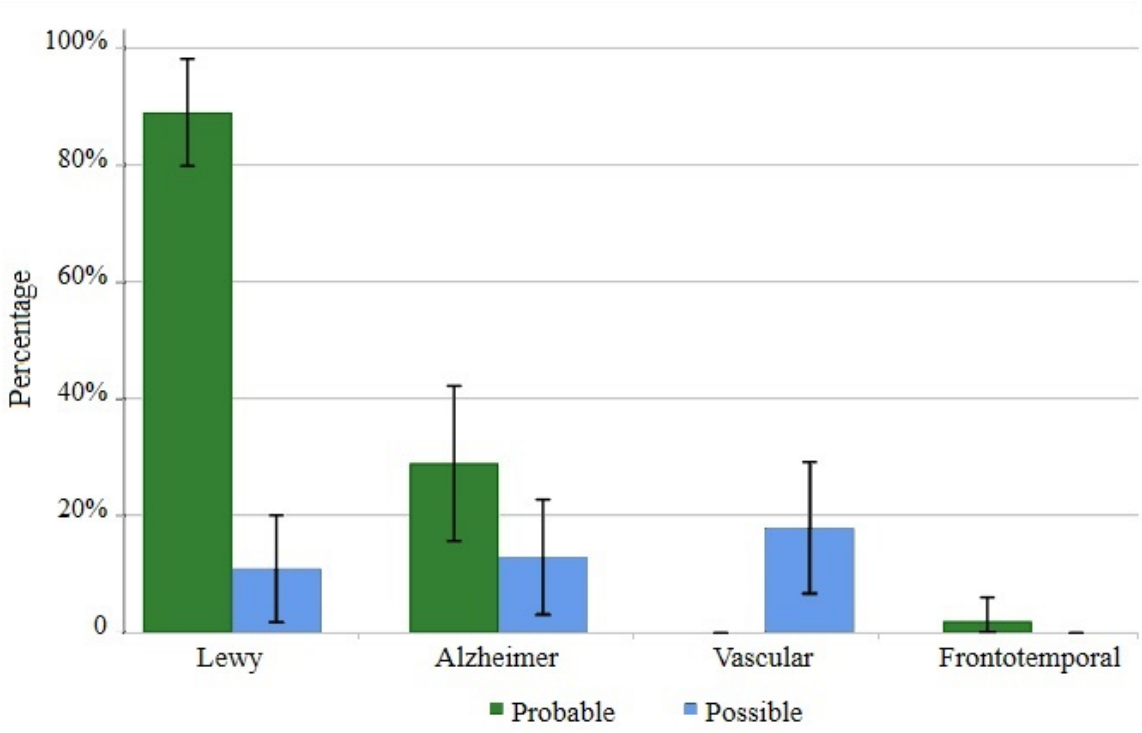


Figure 8-3. Frequency of different cognitive disorders in PD.

Disease categories are not exclusive; participants could be counted in more than one. Data are percentages with 95% confidence intervals. PD = Parkinson's disease.

8.4 Discussion

This study demonstrates that neuropsychological assessment is a practical method of identifying distinct disease profiles in people with PD and cognitive impairment. Most participants had a Lewy-type clinical and cognitive profile, but more than half of patients had features fulfilling the clinical criteria for other cognitive disorders. Almost 45% had signs of coexistent AD, graded probable in around 30%, and possible in around 15%. Possible VCD was diagnosed in just under a fifth of participants. These proportions are comparable to autopsy studies (Irwin et al., 2013; Toledo et al., 2013), though these have sometimes reported higher figures, presumably due to the advanced age and disease duration of autopsy samples leading to a higher incidence of multiple pathology (Jellinger & Attems, 2010b; Kovacs, Alafuzoff, et al., 2008). This study, in conjunction with pathological reports, indicates

that cognitive impairment in PD is frequently multifactorial. Other disorders contribute in approximately half of patients, and in around 10%, another disorder may be the primary explanation for cognitive impairment in PD.

AD was the most common secondary diagnosis, consistent with autopsy studies (Irwin et al., 2013), and various factors emerged as useful clinical indicators of AD comorbidity in PD. Cognitively, participants with comorbid AD consistently had poorer semantic fluency than phonemic fluency, as well as a free recall deficit that did not improve with cueing. Both of these are indicative of temporal lobe dysfunction and characteristic of AD (Economou et al., 2016; Glikmann-Johnston, Oren, Hendler, & Shapira-Lichter, 2015). A language deficit, generally manifesting as impaired object naming, was also frequent. Along with semantic fluency, this is a typical feature of early AD (Verma & Howard, 2012), and in α-synucleinopathy cases with dementia, object naming is significantly worse in those with pathological AD compared to those without (Coughlin et al., 2019). In the current study, poorer semantic fluency and naming were both seen in the context of MCI as well as dementia, indicating that they are useful AD markers at an early stage of cognitive decline. In the dementia group alone, comorbid AD was linked to a higher frequency of falls, behavioural disturbances, and possible ideomotor apraxia.

These results suggest that coexistent AD is detectable in PD even at the MCI stage by a neuropsychological evaluation comprising free recall, semantic fluency, and object naming items. Selective impairments to these tests are indicative of comorbid AD, particularly in participants who lack key features of the Lewy-type cognitive profile. Furthermore, these findings show that establishing the coexistence of AD at an early stage has important prognostic implications, as AD comorbidity is associated with more widespread cognitive deficits, as well as falls and behavioural changes. Considering the clinicopathological evidence that coexistent amyloid-β and tau induce a more rapid cognitive decline and earlier mortality in PD (discussed in the systematic review in Chapter 3), the markers of coexistent AD identified in our study are likely to be predictors of a worse prognosis.

These findings have implications for ongoing clinical trials of disease-modifying therapies that target α-synuclein. Even if these are effective at reducing α-synuclein

pathology in PD, they may not attenuate cognitive decline in patients with coexistent tau and amyloid-β changes. Potential AD comorbidity is therefore an important variable to consider during data analysis, particularly when cognitive function is a study outcome. The incorporation of domain-focused neuropsychological assessment into these trials would be useful for excluding or stratifying participants according to the likelihood of comorbid AD. Therapies targeting α-synuclein have the greatest chance of showing efficacy if they are applied in a relatively homogeneous group of patients, without significant comorbidity.

Cerebrovascular pathology was not the primary cause of cognitive decline in any participant in this study, though it played a contributory role in almost a fifth. This is consistent with the studies presented in the systematic review in Chapter 3, which found that cerebrovascular pathology was not a major independent cause of dementia in PD. Prospective studies have reported that cardiovascular disease and increasing vascular risk are linked to lower executive and attentional scores in PD (Pilotto et al., 2016), which is also consistent with the current results. Again, it is possible that cerebrovascular lesions influence the rate and/or presentation of cognitive impairment in the early stages of PD, but by the later stages, this is obscured by the burden of extensive Lewy and/or Alzheimer lesions.

A single participant was diagnosed with behavioural-variant FTD. This diagnosis was based on severe behavioural changes and a possible dysexecutive neuropsychological profile, covering all six key features of this disorder (Rascovsky et al., 2011). The coexistence of PD and FTD has not been the subject of much research, and is clearly an uncommon event. However, this participant illustrates that attention to behavioural as well as motor and cognitive change in PD is important to consider in clinic.

Strengths of this project included the detailed neuropsychological assessment, the use of questionnaires that are well validated in PD populations, and the reliance on an interdisciplinary panel comprising four expert clinicians. The primary limitation was the lack of biomarker assessment, which would provide a more objective measure of coexistent disease processes. As discussed, biomarkers for α-synuclein and tau are currently limited (Blennow et al., 2016; Harada et al., 2018), and the comparatively well-established biomarkers for amyloid-β are subject to limitations including high

cost and restricted accessibility (de Almeida et al., 2011; S. A. Lee, Sposato, Hachinski, & Cipriano, 2017; Shi et al., 2018). The lack of structural neuroimaging for all patients in the study was another limitation; this would have allowed for a more accurate assessment of the degree of cerebrovascular comorbidity. As a result of these limitations, replication of these findings using AD biomarker measurement or autopsy follow-up would be very useful. Large, well-funded clinical trials of new disease-modifying therapies in PD should consider incorporating amyloid-β biomarkers as an adjunct to detailed neuropsychological testing.

8.4.1 Conclusions

This study extends previous autopsy findings by showing that pathological variation underlying cognitive impairment in PD is detectable *in vivo* using clinical assessment. A quarter of this sample had a diagnosis of probable AD, identifiable by early and marked amnestic and linguistic deficits and behavioural changes. Smaller percentages of the sample met criteria for possible AD or vascular cognitive disorder, and one participant had behavioural-variant FTD. The presence of coexistent diseases is an essential feature to consider when designing and analysing trials of disease-modifying therapies in PD, as the probability of misleading negative findings could be increased significantly in unstratified samples. A clinical assessment comprising selected neuropsychological and behavioural items is a practical method of distinguishing different disease processes *in vivo*, and this should be incorporated into new drug studies of PD when cognitive function is included as a study outcome.

9 General discussion

This thesis has used several methods to explore the contribution of comorbid disease mechanisms to cognition in PD. The accumulated results show that PD is a highly complex neurodegenerative disorder that varies substantially between different patients in terms of its underlying neuropathology, its clinical manifestation, and its genetic influences. This heterogeneity has major implications for basic and applied research, as well as clinical practice. The most important implications are for ongoing clinical trials of disease-modifying therapies, which represent the best hope for impeding the progression of PD, including the decline in cognition that ultimately leads to dementia.

This chapter synthesises the findings presented in this thesis and discusses the ways in which they can inform current treatment strategies and clinical trials of new therapies for PD. Firstly, a brief review of disease-modifying therapies for amyloid-β, tau, and α-synuclein pathologies to date is provided. The results in the thesis are then used to make recommendations for trialling new therapies, and for implementing them in clinic once efficacy has been demonstrated. Strategies for managing the contribution of cerebrovascular pathologies to cognitive function in PD are then discussed. Gene therapies, which may benefit PD patients whose cognition is affected by variation in the *APOE* gene, are described. Finally, a general conclusion summarises the major themes of this thesis.

9.1 Disease-modifying therapies for amyloid-β, tau, and α-synuclein

The current generation of treatments for neurodegenerative diseases provides only symptomatic relief. This includes levodopa-based drugs for motor impairment in PD, and acetylcholinesterase inhibitors and memantine for cognitive impairment in dementia disorders. As discussed in Chapter 1, these drugs have various crucial limitations: they are only effective for a reasonably short period of time (typically fewer than three years); they are not effective for treating MCI; and they may

exacerbate autonomic and sleep-related symptoms that occur naturally in PD and similar disorders (Petersen et al., 2005; Tricco et al., 2013; Zemek et al., 2014). Disease-modifying therapies would be significantly more useful, as these could impede the progression of neurotoxic protein pathologies, thereby preventing further neurological and clinical deterioration (O'Hara et al., 2018).

Multiple mechanisms of action have been suggested for disease-modifying therapies. These include inhibiting the target protein's production or aggregation; promoting its degradation in and around neurons; and reducing its uptake from the extracellular space by unaffected neurons (Brundin, Dave, & Kordower, 2017). Immunotherapies are a class of promising disease-modifying treatments that exploit antibodies in order to target specific proteins. These may be divided into active immunotherapies, whereby the body's innate immune system is stimulated to produce antibodies against a target (i.e. a vaccine), and passive immunotherapies, whereby antibodies are administered directly to patients (O'Hara et al., 2018). Several drugs based on these mechanisms have been developed to target amyloid-β, tau, and α-synuclein. Many of these have been or are being tested in large-scale phase 2 and 3 clinical trials involving AD or PD cohorts. These novel treatments will be briefly reviewed here.

9.1.1 Summary of clinical trials to date

So far, disease-modifying therapies targeting amyloid-β are the most extensively trialled. Several trials with very large sample sizes and biomarker assessments have shown that various passive immunotherapies, including aducanumab, solanezumab, bapineuzumab, crenezumab, and gantenerumab, are well tolerated, and some reduce cerebral amyloid-β pathology in patients across the spectrum of clinical AD (Blennow et al., 2012; Farlow et al., 2012; Ostrowitzki et al., 2012; Salloway et al., 2018; Sevigny et al., 2016). However, phase 3 trials of all of these treatments failed to show efficacy at the primary endpoint of impeding cognitive decline (Cummings et al., 2018; Honig et al., 2018; Ostrowitzki et al., 2017; Selkoe, 2019; Vandenberghe et al., 2016). The sole exception is aducanumab; trials of this therapy were initially to be abandoned following a futility analysis, but according to a recent press release, later analyses of larger datasets indicated that the drug is effective for reducing clinical

decline in AD. Consequently, the manufacturer intends to submit a regulatory filing to the Food and Drug Administration to license aducanumab for clinical practice (Biogen, 2019).

Other putative AD-modifying treatments have targeted amyloid-β pathology by inhibiting cleavage of the amyloid precursor protein by the β-secretase enzyme, thereby reducing amyloid-β production. These include atabecestat, lanabecestat, and verubecestat. Again, these universally failed in phase 2 and 3 trials in large AD cohorts (Panza et al., 2018). Indeed, the use of some of these agents was actually associated with more cognitive decline, in addition to various adverse events affecting liver metabolism, mood, and sleep (Henley et al., 2019).

Because the dominant amyloid cascade hypothesis suggests that tau pathology occurs downstream of amyloid-β aggregation in AD, tau has attracted less attention as a target for disease-modifying therapy. However, some tau treatments have reached phase 2 and 3 trials (Logroscino et al., 2019; Panza et al., 2019). Leuco-methyl thioninium, a methylene blue derivative that inhibits tau aggregation, reached phase 3, but here it failed to improve cognitive outcomes in both AD (Gauthier et al., 2016) and behavioural-variant FTD cohorts (TauRx Pharmaceuticals, 2016). One active immunotherapy, AADvac1 (Axon Neuroscience SE, NCT02579252), and two passive immunotherapies – ABBV-8E12 (AbbVie, NCT02880956) and BIIB092 (Biogen, NCT03352557) – are currently in phase 2 trials in AD. BIIB092 is also in a phase 1 trial (NCT03658135) involving patients with various primary tauopathies, and a phase 2 trial (NCT03391765) in a cohort of patients with progressive supranuclear palsy. All of these trials have estimated end dates between 2019 and 2024.

Several disease-modifying therapies that target α-synuclein in PD are being trialled. Two passive immunotherapies – prasinezumab (Prothena/Roche; NCT03100149) and BIIB054 (Biogen; NCT03318523) – are currently in phase 2 trials, after safety was demonstrated in phase 1 (Brys et al., 2019; Jankovic et al., 2018; Schenk et al., 2017). Both are projected to end in 2021. Another passive immunotherapy, MEDI1341 (AstraZeneca, NCT03272165), is currently in phase 1. Two active immunotherapies, PD01A and PD03A (Affiris, NCT02267434) have been well tolerated in phase 1, and secondary analysis showed that most participants began producing serum antibodies

against both oligomeric and fibrillar α-synuclein. Although the latter study was not powered to assess clinical efficacy, motor scores for the immunised PD patients were stable over a four-year period, according to conference data (Poewe, 2018).

Additionally, several therapies that exploit non-immunological mechanisms of action are currently being tested. NPT200-11 (Neuropore, NCT02606682), a small molecule inhibitor of α-synuclein, is in phase 1. Various other non-immunological therapies target α-synuclein indirectly. Increased α-synuclein aggregation has been associated with underactivity of the β-glucocerebrosidase enzyme (Schapira, Chiasserini, Beccari, & Parnetti, 2016), overactivity of c-Abl, a tyrosine kinase (Karuppagounder et al., 2014; Simuni et al., 2019), and oxidative damage caused by excess intracellular iron in the substantia nigra (Moreau et al., 2018). Ambroxol (NCT02914366) and ibiglustat (Sanofi/Genzyme, NCT02906020) are two drugs designed to modulate the activity of β-glucocerebrosidase to reduce α-synuclein aggregation. The ambroxol trial includes PDD patients, while the ibiglustat trial only includes patients with a mutation in *GBA*, the β-glucocerebrosidase gene, which is an established genetic risk factor for PD and for rapid motor and cognitive progression in PD. Nilotinib (NCT03205488), a licensed drug for certain forms of leukaemia, is a c-Abl inhibitor. Finally, deferiprone (NCT02655315; NCT02728843) is an iron-chelating drug that translocates iron from cells in which iron is overexpressed to cells where it is underexpressed. All of these therapies are currently in phase 2 trials in PD cohorts. Numerous additional candidates for α-synuclein therapy are being tested in preclinical trials (O'Hara et al., 2018; Savitt & Jankovic, 2019).

9.1.2 Recommendations for clinical trials in PD cohorts

The increasing number of disease-modifying therapies against α-synuclein represents an encouraging step towards the introduction of much more effective treatments for motor and cognitive progression in PD. However, there are lessons to be learned from the failures of equivalent therapies in AD. The reasons for the lack of efficacy of amyloid-β therapies in AD despite target engagement are numerous, and have been extensively reviewed (Mullane & Williams, 2018a, 2018b). One hypothesis, which can generalise to PD, is that monotherapy is probably insufficient to impede further

deterioration in diseases that are characterised by such extensive and diverse neuropathology (Selkoe, 2019). As a result of this, achieving disease modification in AD is likely to require combination therapy, in which multiple treatments are targeted against several different pathophysiological targets, minimally including both amyloid-β and tau (Cummings, Tong, & Ballard, 2019; Tomaszewski, Gauthier, Wimo, & Rosa-Neto, 2016).

Results in Chapters 3 and 8 of this thesis show that PD is frequently complicated by tau and amyloid-β comorbidities, and these are major contributors to cognitive decline. Therefore, an immediate recommendation for clinical trials of α-synuclein therapies is that they are designed to control for potential confounding by coexistent Alzheimer pathologies whenever cognitive function is included as an outcome. As shown in Chapter 8, a detailed clinical assessment that includes domain-focused neuropsychological testing can be used to identify comorbid AD in PD cohorts. Well-funded studies should also employ AD biomarkers for this purpose. A recent clinicopathological study showed that the ratio of total tau to $A\beta_{42}$ in the CSF had 100% specificity and 90% sensitivity for distinguishing Lewy body disorder cases with comorbid AD from those without (Irwin et al., 2018). CSF collection is therefore a very valuable procedure to add into the design of a clinical trial of a PD cohort. Typically, ongoing trials in PD cohorts (e.g. of prasinezumab and BIIB054) do not included detailed cognitive assessments or AD biomarkers, reflecting their focus on motor decline in PD. However, the design of the ongoing ambroxol trial could be used as a model for future studies. This trial incorporates a number of well-validated tests spanning multiple cognitive domains, as well as structural neuroimaging and CSF measures of tau and amyloid-β.

Sensitivity to the potential effect of comorbid AD is also important during data analysis of clinical trials in PD cohorts. Stratifying the cohort into those with a high versus low probability of comorbid AD is likely to be beneficial, as these subgroups can be expected to respond differently to the same treatment. Specifically, participants with a significant burden of tau and/or amyloid-β are likely to have more severe cognitive impairment and a more rapid cognitive decline than those without, even if a novel therapy is successful in attenuating cerebral Lewy pathology. Trials of α-synuclein therapies therefore have the greatest chance of showing efficacy if they are

based on well-defined, homogeneous samples comprising participants with minimal tau and amyloid-β comorbidity. Additionally, clinical trials of aducanumab in PD cohorts may now be justified, given the recent announcement of that drug's efficacy in AD. Naturally, such trials should include PD patients who have moderate to high amyloid-β comorbidity. Future clinical trials that plan to stratify PD cohorts by the degree of comorbid AD should ensure that the sample size is adequately powered to permit appropriate subgroup analyses.

A very valuable task for the future would be to develop and validate a brief cognitive test that has high sensitivity and specificity for distinguishing PD patients with comorbid AD from those without. This would minimise the need to rely on biomarker methods, which are often expensive and difficult to access. Efforts to create a universal cognitive assessment battery for use in PD are underway (Hoogland et al., 2018), and this battery should be able to distinguish these groups, for the reasons outlined above. As shown in Chapter 6, the MoCA is not suitable for this purpose, primarily due to its lack of variance outside of moderately or severely impaired patients. Therefore, the MoCA should be reserved for screening MCI and dementia in PD, without making any statements about aetiology. A new test designed to identify the presence of comorbid AD in PD should comprise relatively difficult measures of free recall, cued recall and language, including semantic fluency and object naming items. Well-validated executive, attentional, and visuospatial measures should also be incorporated. Combining such a test with brief questionnaires that probe additional diagnostic features (e.g. RBD and hallucinations) is likely to have good sensitivity and specificity for comorbid AD, potentially to the extent where this could substitute for biomarker assessment in clinical trials if necessary.

Once disease-modifying therapies begin to show efficacy in trials, and subsequently enter routine clinical settings, the results in this thesis can be used to guide their effective implementation. Successful disease modification in PD will probably require combination therapy, given the extent of neuropathological heterogeneity. Many patients will need a combination of α-synuclein, tau, and amyloid-β therapies in order to preserve their cognitive abilities throughout the disease – although, given the interactions between these pathologies (discussed in Chapter 3), it is possible that attending to one may inhibit propagation of the others. Continuing research in human

cohorts, more so than animal models and cell cultures, is essential to identify the best way to exploit these interactions therapeutically.

9.2 Targeting cerebrovascular comorbidity in PD

The accumulated results in this thesis show that, in contrast to α-synuclein, tau, and amyloid-β pathologies, cerebrovascular diseases are not a major independent cause of dementia in people with PD. However, they are relatively common, affecting approximately a fifth of patients with and without dementia. Importantly, none of the studies in the systematic review in Chapter 3 evaluated the extent to which comorbid cerebrovascular pathology might have influenced the rate or expression of cognitive impairment in PD *in vivo* – for example, by causing a faster decline, as was the case for amyloid-β, or by causing a selective decline in some cognitive domains, while leaving others relatively intact.

Results from the clinical study in Chapter 8 indicated that, while vascular factors are not a frequent cause of dementia in PD, they do contribute to the neuropsychological expression of a significant minority of patients. The most common effects of vascular comorbidity were deficits in specific components of executive function and attention, such as processing speed and response inhibition. Such deficits are closely associated with cerebrovascular pathologies, including infarcts, haemorrhages, and white matter lesions (Prins et al., 2005; Tullberg et al., 2004; Uiterwijk et al., 2016). Additionally, previous research has shown that vascular comorbidity exacerbates both motor and cognitive progression in PD. White matter leukoaraiosis and vascular risk factors – particularly hypertension – lead to more marked axial and gait impairment and a higher rate of conversion from the tremor dominant to the postural instability and gait disorder phenotype (Malek et al., 2016; Schwartz, Halliday, Soh, Cordato, & Kril, 2018). White matter leukoaraiosis is also associated with greater cognitive decline and cortical atrophy – particularly in the frontal lobe – in PD patients (Dadar et al., 2018). Executive function and attention are prominently affected as a result (Pilotto et al., 2016). Finally, in all elderly individuals, vascular factors are aetiologically related to leading causes of death, such as heart disease and stroke (Brown, Allik, Dundas, & Leyland, 2019; Patel, 2017).

Despite the impact of vascular comorbidity in PD, there is evidence that these factors are underrecognised and undertreated in routine care. One combined analysis of the Tracking Parkinson's and Oxford PD Centre cohorts (n = 2909) found that almost two-thirds of PD patients had medium or high vascular risk (Swallow et al., 2016), for which statin usage is indicated (Rabar, Harker, O'Flynn, Wierzbicki, & Guideline Development Group, 2014). However, statins were prescribed in only a quarter of the at-risk group. Even in patients with established cardiovascular disease, only three-quarters were prescribed statins, and statin non-use was linked to significantly lower MoCA scores in this group. Potential reasons for low statin use include interference from muscle cramps and the reduced rate of smoking in PD populations, which may mislead a clinician conducting a vascular risk assessment (Swallow et al., 2016).

Together, these findings indicate that attention to vascular factors in PD should be emphasised in clinical care settings. Estimating a patient's long-term risk of a vascular event is a relatively simple procedure due to the introduction of validated predictive algorithms (e.g. the QRISK3-2018 calculator) that have been recommended in consensus statements (Hippisley-Cox, Coupland, & Brindle, 2017; Rabar et al., 2014). Routine application of algorithms such as these, and appropriate clinical decision-making with patients at a medium or high risk, has the potential to improve motor and cognitive prognosis in PD. In research settings (e.g. clinical trials), it may be beneficial to stratify participants into those with low versus high likelihood of cerebrovascular disease, but this should not be essential for most projects.

The ability to impede cognitive decline resulting from cerebrovascular pathology is currently limited, as is also the case for α-synuclein, tau, and amyloid-β. Vascular treatments do not consistently lower the incidence of all-cause dementia in at-risk patients (Peters et al., 2008; Tariq & Barber, 2018). In PD specifically, data on this topic are limited, though some ongoing clinical trials are exploring the potential utility of vascular medications to impede PD progression. One ongoing phase 2 trial (NCT02787590) is examining the value of simvastatin for ameliorating motor and cognitive decline in moderate PD (Carroll & Wyse, 2017). The results of this study, which is due to end in 2020, will be useful for further characterising the extent to which targeting vascular morbidity is beneficial in PD.

In addition to prescribing treatments for symptomatic elderly patients, long-term preventative methods have an important role in reducing the burden of vascular pathologies. A modest reduction in modifiable vascular factors, such as midlife hypertension and obesity, smoking, diabetes, and physical inactivity, could reduce the number of new dementia cases by several million globally (Barnes & Yaffe, 2011; Baumgart et al., 2015). The value of national policies and guidelines for improving outcomes in dementia is clear from large-scale epidemiological studies in the UK, which show a significant and sustainable increase in the rate of diagnosis and the quality of care following the introduction of new public health policies (Donegan et al., 2017; Mukadam, Livingston, Rantell, & Rickman, 2014). Based on this, new strategies targeting people in midlife and aiming to promote healthier lifestyles are likely to be valuable for reducing the risk, and ultimately the incidence, of vascular diseases at a population level.

9.3 Targeting *APOE* in PD

Gene therapy is a relatively recent innovation that could be very useful for moderating the effects of certain genetic variants that increase susceptibility to neurodegenerative diseases, or cause poorer outcomes in those diseases. *APOE* is an important target for emerging gene therapies, given its strong association with AD. Chapter 3 showed that, in PD samples, the *APOE* ε4 allele is associated with increased deposition of both amyloid-β and α-synuclein pathology, particularly in neocortical areas. As a result, it increases the risk of both comorbid AD and pathologically pure PDD in these samples (Tsuang et al., 2013). Chapter 7 indicated that, in early PD, *APOE* ε4 is related to lower cognitive scores and faster cognitive decline in men only. Further follow-up is needed to see if comparable effects will emerge in women at greater disease duration, as may be expected from the AD literature. Overall, the results of this thesis show that novel gene therapies targeting *APOE* are likely to be valuable not just for lowering the incidence of AD, but also for preserving cognitive function in PD.

Emerging gene therapies that target *APOE* are all in the preclinical stages, but some encouraging results have been found. Many target the relationship between ε4 and amyloid-β metabolism. For example, immunotherapies using anti-apoE antibodies

have been used to reduce amyloid-β pathology in murine models (J. Kim et al., 2012; Liao et al., 2014). Another study administered a synthetic peptide to transgenic ε4 mice that blocked the interaction between apoE4 and amyloid-β, and thereby reduced amyloid-β accumulation and memory deficits (Pankiewicz et al., 2014). Based on the results of clinical trials that have targeted amyloid-β directly, it is uncertain if these methods will show efficacy in humans. An alternative approach would be to induce expression of the protective ε2 gene and the corresponding apoE2 protein isoform, in order to offset the deleterious effects of ε4. This has been safely accomplished in mice and non-human primates by administering a viral vector directly into the brain (Hu et al., 2015; Rosenberg et al., 2018). Further in the future, genome editing of *APOE* ε4 to ε2 or ε3 may be a realistic treatment option (Zhao, Liu, Qiao, & Bu, 2018).

In addition to suggesting potential utility of *APOE*-based therapies for PD, the results of this thesis have immediate implications for clinical trials. Specifically, determination of *APOE* status is important for trials where cognitive function in PD is an outcome, as both the ε2 and ε4 alleles may act as confounders in these analyses (at least in men). Controlling for *APOE* is particularly important in light of findings from clinical trials in AD cohorts, which have sometimes shown different drug effects in ε4 carriers versus non-carriers. For example, retrospective analyses of bapineuzumab trials found that the drug reduced biomarker indices of tau and amyloid-β in ε4 carriers only, but it was also related to a higher incidence of amyloid-related imaging abnormalities in this group (Salloway et al., 2014; Sperling et al., 2012). Therefore, stratifying by *APOE* status should be considered for future trials of amyloid-β therapies. Given the associations between *APOE* and α-synuclein reported in Chapter 3, *APOE*-based stratification might also be valuable for trials of α-synuclein therapies, though at present, the implications of doing so are uncertain.

Finally, one of the most interesting findings in Chapter 7 was that the effects of *APOE* were markedly different in men and women. Furthermore, the sex-based effects were opposite to those seen in AD, in that *APOE* ε4 had a more pronounced deleterious effect in men rather than women. Indeed, ε4 was actually associated with some higher cross-sectional cognitive scores in women, showing that *APOE* may have no value as a therapeutic target in women with PD. Again, further follow-up and replication is needed to assess the robustness of this novel finding. It was not possible to identify

the biological basis of these sex differences in this thesis, but this would be a very valuable goal for future studies. These results indicate that stratifying by sex is important for studies focused on *APOE*, as the gene's effects are not identical in men and women. This reinforces the need to consider sex as an important biological variable in biomedical and neuroscientific research, as has been recommended in consensus guidelines (National Institutes of Health, 2015).

9.4 General conclusions

A major contributor to the difficulty in treating cognitive decline in PD is the marked heterogeneity that it shows. The results of this thesis indicate that the majority of cognitively impaired PD patients have an advanced α-synucleinopathy. However, a significant number have additional tau and amyloid-β changes that often justify a secondary diagnosis of AD. Current clinical diagnostic criteria are valid, reliable, and efficient methods of identifying the different cognitive disorders in PD patients *in vivo*. At present, most brief cognitive screening tests are inadequate for distinguishing different disease profiles. The development of a standardised assessment battery for PD that is valid for identifying comorbid AD is very important for future research.

As a result of the frequent coexistence of AD, it is also important that clinical trials of disease-modifying therapies for PD are designed and powered in such a way that the cohorts can be stratified by the presence of comorbid AD. Therapies that target α-synuclein have the greatest chance of showing efficacy if they are trialled in a well-defined, homogeneous group in which participants are without significant comorbid disease. Patients with comorbid AD will ultimately need complex combination therapy to target the additional burden of tau and amyloid-β pathologies. If and when tau and amyloid-β therapies show efficacy in AD cohorts, replicating these trials in a carefully selected PD group will be required.

In addition to tau and amyloid-β changes, cerebrovascular pathology is common in PD. Its contribution to overt dementia is modest, but evidence suggests that vascular morbidity is undertreated in clinic. The numerous benefits of appropriately managing vascular diseases, particularly in people with PD and other neurodegenerative

diseases, mean that greater attention to vascular factors should be emphasised in current clinical practice. Careful consideration of individual patient presentations will also facilitate the detection of rarer coexistent disease processes, such as FTD, which may impair cognition and behaviour in a small percentage of patients.

The move towards disease-modifying therapies for α-synuclein, tau, and amyloid-β is an exceptionally promising step towards a paradigm shift in the treatment of PD and other neurodegenerative diseases. Similar advancements in gene therapy mean that it might soon be possible to ameliorate the effects of deleterious variants of certain genes, such as *APOE*. Finally, increasing clinical and biomarker characterisation of the prodromal stages of these diseases means that they can frequently be identified before any clinically significant signs or symptoms have emerged. Together, these strategies can be used to refine a targeted medicine approach in the future, whereby new treatments are directed against specific biological disease mechanisms, rather than simply at symptom management. Ultimately, these emerging therapies represent a real hope that it will eventually become possible to slow, halt, or prevent motor and cognitive decline in PD.

Appendix 1: Systematic review search strategies

The following search strategies were used to identify relevant articles for the systematic review.

Medline / Embase

1. Parkinson disease/pa [Pathology]
2. Dement*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
3. Cogniti*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
4. 2 or 3
5. 1 and 4
6. limit 5 to humans
7. remove duplicates from 6

Literatura Latino-Americana e do Caribe em Ciências da Saúde

Parkinson* disease AND dement* OR cogniti*

Filters – LILACS, Humans

Cumulative Index to Nursing and Allied Health Literature

S1: (MH "Parkinson Disease/PA)

S2: "Dement*"

S3: "Cogniti*"

S4: SR OR S3

S5: S1 AND S4

Limiters – Human; Exclude MEDLINE records

Cochrane Library using advanced search

#1	MeSH descriptor: [Parkinson disease] explode all trees with qualifier(s): [Pathology – PA]
#2	dement*
#3	cogniti*
#4	#2 or #3
#5	#1 and #4

Appendix 2: Potentially relevant articles in other languages

The following articles were excluded from the systematic review during preliminary screening because they were not fully available in English.

Dubois, B., Hauw, J. J., Ruberg, M., Serdaru, M., Javoy-Agid, F., & Agid, Y. (1985). Dementia and Parkinson's disease: biochemical and anatomo-clinical correlation. *Revue Neurologique, 141*(3), 184-193. [French].

Iwatsubo, T. (1999). Parkinson's disease, dementia with Lewy bodies, multiple system atrophy and alpha-synuclein. *Rinsho Shinkeigaku – Clinical Neurology, 39*(12), 1285-1286. [Japanese].

Jansen, E. N., & de Vos, R. A. (1994). Dementia in Parkinson disease: Lewy body disease or Alzheimer's disease? *Nederlands Tijdschrift voor Geneeskunde, 138*(26), 1305-1309. [Dutch].

Kretzschmar, H. A., & Neumann, M. (2000). Neuropathological diagnosis of neurodegenerative and dementia diseases. *Pathologe*, *21*(5), 364-374. [German].

Yoshimura, M. (1997). Diffuse Lewy body disease. *Rinsho Shinkeigaku – Clinical Neurology, 37*(12), 1134-1136. [Japanese].

Yoshimura, M., Mori, H., Tomonaga, M., Yamanouchi, H., & Kuzuhara, S. (1984). Loss of neurons in the nucleus basalis of Meynert in Parkinson disease with dementia, "diffuse Lewy body disease" and senile dementia of Alzheimer type. *Nihon Ronen Igakkai Zasshi, 21*(6), 580-587. [Japanese].

Appendix 3: Articles excluded from the systematic review

Twenty studies were judged to have little or no detail that would be relevant to the systematic review, and these were consequently excluded. A list of these articles is provided below.

Ala T.A., Yang K.H., Sung J.H., & Frey W.H. II (2000). Inconsistency between severe substantia nigra degeneration with Lewy bodies and clinical parkinsonism in dementia patients: a cliniconeuropathological study. *Acta Neuropathologica*, *99*(5), 511-516.

Arendt, T., Bigl, V., Arendt, A., & Tennstedt, A. (1983). Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans, and Korsakoff's disease. *Acta Neuropathologica*, *61*(2), 101-108.

Armstrong, R. A. (2017). Laminar degeneration of frontal and temporal cortex in Parkinson disease dementia. *Neurological Sciences*, *38*(4), 667-671.

Colloby S.J., McParland S., O'Brien J.T., & Attems J. (2012). Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. *Brain*, *135*(9), 2798-2808.

Gaspar P., & Gray F. (1984). Dementia in idiopathic Parkinson's disease. A neuropathological study of 32 cases. *Acta Neuropathologica*, *64*(1), 43-52.

Hishikawa N., Hashizume Y., Yoshida M., & Sobue G. (2003) Clinical and neuropathological correlates of Lewy body disease. *Acta Neuropathologica*, *105*(4), 341-350.

Horimoto, Y., Matsumoto, M., Nakazawa, H., Yuasa, H., Morishita, M., Akatsu, H., Ikari, H., Yamamoto, T., & Kosaka, K. (2003). Cognitive conditions of pathologically confirmed dementia with Lewy bodies and Parkinson's disease with dementia. *Journal of the Neurological Sciences*, *216*(1), 105-108.

Jellinger K.A. (2004). Lewy body-related alpha-synucleinopathy in the aged human brain. *Journal of Neural Transmission*, *111*(10-11), 1219-1235.

Jellinger K.A. (2007). Morphological substrates of parkinsonism with and without dementia: a retrospective clinico-pathological study. *Journal of Neural Transmission*, S72, 91-104.

Mastaglia F.L., Johnsen R.D., Byrnes M.L., & Kakulas, B. A. (2003). Prevalence of amyloid-beta deposition in the cerebral cortex in Parkinson's disease. *Movement Disorders*, *18*(1), 81-86.

Monsell, S. E., Besser, L. M., Heller, K. B., Checkoway, H., Litvan, I., Kukull, W. A.

(2014). Clinical and pathologic presentation in Parkinson's disease by apolipoprotein e4 allele status. *Parkinsonism and Related Disorders*, *20*(5), 503-507.

Neumann, J. (2009). Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain*, *132*(7), 1783-1794.

Papapetropoulos S., Lieberman A., Gonzalez J., & Mash D.C. (2005). Can Alzheimer's type pathology influence the clinical phenotype of Parkinson's disease? *Acta Neurologica Scandinavica*, *111*(6), 353-359.

Parkkinen L., Neumann J., O'Sullivan S.S., Holton J.L., Revesz T., Hardy J., & Lees A.J. (2011). Glucocerebrosidase mutations do not cause increased Lewy body pathology in Parkinson's disease. *Molecular Genetics*, *103*(4), 410-412.

Pedersen K.M., Marner L., Pakkenberg H., & Pakkenberg B. (2005). No global loss of neocortical neurons in Parkinson's disease: a quantitative stereological study. *Movement Disorders*, *20*(2), 164-171.

Pletnikova O., West N., Lee M.K., Rudow G.L., Skolasky R.L., Dawson T.M., Marsh L., & Troncoso J.C. (1994). Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases. *Neurobiology of Aging, 26*(8), 1183-1192.

Postuma, R. B., Adler, C. H., Dugger, B. N., Hentz, J. G., Shill, H. A., Driver-Dunckley, E., Sabbagh, M. N., Jacobson, S. A., Belden, C. M., Sue, L. I., Serrano, G., & Beach, T. G. (2015). REM sleep behaviour disorder and neuropathology in Parkinson's disease. *Movement Disorders*, *30*(10), 1413-1417.

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

Sugiyama, H., Hainfellner, J. A., Yoshimura, M., & Budka, H. (1994). Neocortical changes in Parkinson's disease, revisited. *Clinical Neuropathology*, *13*(2), 55-59.

Toledo J.B., Gopal P., Raible K., Irwin D.J., Brettschneider J., Sedor S., Waits K., Boluda S., Grossman M., Van Deerlin V.M., Lee E.B., Arnold S.E., Duda J.E., Hurtig H., Lee V.M., Adler C.H., Beach T.G., & Trojanowski J.Q. (2016). Pathological alpha-synuclein distribution in subjects with coincident Alzheimer's and Lewy body pathology. *Acta Neuropathologica*, *131*(3), 393-409.

Appendix 4: Supplementary tables for Chapter 6

Table A1. Distribution of responses for each MoCA item.

Item	Full sample	MoCA<26	MoCA<21
Trail-making	79.6	64.2	29.3
Phonemic fluency	67.8	52.8	30.6
Abstraction 1	79.8	66.8	37.6
Abstraction 2	82.0	70.6	44.6
Lion	99.5	99.0	97.5
Rhinoceros	91.2	86.2	72.6
Camel	98.9	97.9	94.9
Repetition 1	90.3	83.4	67.5
Repetition 2	82.5	70.8	51.6
Recall 1	50.9	29.2	9.6
Recall 2	64.2	40.8	19.1
Recall 3	54.9	29.3	8.3
Recall 4	41.9	18.9	5.1
Recall 5	54.3	29.4	10.2
Digits forward	95.3	91.3	84.1
Digits backward	90.6	83.8	67.5
Vigilance	88.5	79.9	65.0
Cube	76.6	60.0	29.3
Date	90.7	84.4	73.9
Month	99.3	98.9	97.5
Year	99.1	98.1	93.0
Day	98.4	96.7	91.7
Place	99.0	98.4	96.2
City	99.8	99.6	99.4

Table continues on next page.

Table A1 (continued).

Item	Full sample	MoCA<26	MoCA<21
Subtractions (0 correct)	2.4	5.0	12.7
Subtractions (1 correct)	7.2	13.4	25.5
Subtractions (2-3 correct)	26.4	33.8	36.3
Subtractions (4-5 correct)	64.1	47.8	25.5
Clock (0 elements correct)	0.9	2.0	5.7
Clock (1 element correct)	4.5	9.9	23.6
Clock (2 elements correct)	18.5	29.9	42.7
Clock (3 elements correct)	75.6	58.2	28.0

All values are percentages. For all items except subtractions and clock, values represent correct responses.

Table A2. Loadings for each item by factor (2-factor model).

Item	Memory	Attentional-Executive
Trail-making		0.63 (0.02)**
Phonemic fluency		0.41 (0.02)**
Abstraction 1		0.54 (0.02)**
Abstraction 2		0.53 (0.02)**
Animals	0.32 (0.02)**	
Repetition 1	0.38 (0.02)**	
Repetition 2	0.42 (0.02)**	
Recall 1	0.54 (0.02)**	
Recall 2	0.67 (0.02)**	
Recall 3	0.72 (0.01)**	
Recall 4	0.67 (0.02)**	
Recall 5	0.66 (0.02)**	
Digits forward		0.37 (0.02)**
Digits backward	0.33 (0.02)**	
Vigilance		0.43 (0.02)**
Subtractions		0.43 (0.02)**
Cube		0.64 (0.02)**
Clock		0.57 (0.02)**
Temporal	0.35 (0.02)**	
Spatial	0.22 (0.03)**	

This model was tested in the full sample (n = 1738). Values are correlation coefficient (standard error).
*$p < 0.05$, **$p < 0.001$.

Table A3. Loadings for each item by factor (6-factor model).

Item	Executive	Language	Recall	Attention	Visuospatial	Orientation
Trail-making	0.65 (0.02)**					
Phonemic fluency	0.29 (0.04)**	0.16 (0.05)*				
Abstraction 1	0.55 (0.02)**					
Abstraction 2	0.55 (0.02)**					
Animals		0.33 (0.03)**				
Repetition 1		0.63 (0.02)**				
Repetition 2		0.74 (0.02)**				
Recall 1			0.55 (0.02)**			
Recall 2			0.70 (0.02)**			
Recall 3			0.78 (0.01)**			
Recall 4			0.69 (0.02)**			
Recall 5			0.69 (0.02)**			
Digits forward				0.46 (0.02)**		
Digits backward				0.60 (0.02)**		
Vigilance				0.53 (0.02)**		
Subtractions				0.46 (0.02)**		
Cube					0.68 (0.02)**	
Clock					0.62 (0.02)**	
Temporal						0.37 (0.02)**
Spatial[†]						1.00 (8.8×10^{-18})**

This model was tested in the full sample (n = 1738). Values are correlation coefficient (standard error).
*$p < 0.05$, **$p < 0.001$. [†] Error variance constrained to 0.

Table A4. Loadings for each item by factor (1-factor model).

Item	Executive	Language	Recall	Attention	Visuospatial	Orientation
Cognition	0.99 (0.02)**	0.71 (0.03)**	0.60 (0.02)**	0.80 (0.02)**	0.85 (0.02)**	0.33 (0.02)**
Trail-making	0.62 (0.02)**					
Phonemic fluency	0.34 (0.05)**	0.12 (0.05)*				
Abstraction 1	0.57 (0.02)**					
Abstraction 2	0.56 (0.02)**					
Animals		0.34 (0.03)**				
Repetition 1		0.65 (0.02)**				
Repetition 2		0.70 (0.02)**				
Recall 1			0.54 (0.02)**			
Recall 2			0.69 (0.02)**			
Recall 3			0.78 (0.01)**			
Recall 4			0.69 (0.02)**			
Recall 5			0.69 (0.02)**			
Digits forward				0.46 (0.02)**		
Digits backward				0.60 (0.02)**		
Vigilance				0.53 (0.02)**		
Subtractions				0.46 (0.02)**		
Cube					0.70 (0.02)**	
Clock					0.60 (0.02)**	
Temporal						0.37 (0.02)**
Spatial†						1.00 (2.0×10^{-17})**

This model was tested in the full sample (n = 1738). Values are correlation coefficient (standard error).
*$p < 0.05$, **$p < 0.001$. † Error variance constrained to 0.

Table A5. Loadings for each item by factor (3-factor model).

Item	Executive	Recall	Verbal Attention
Trail-making	0.66 (0.02)**		
Phonemic fluency	0.40 (0.02)**		
Abstraction 1	0.54 (0.02)**		
Abstraction 2	0.54 (0.02)**		
Repetition 1			0.77 (0.02)**
Repetition 2			0.62 (0.02)**
Recall 1		0.54 (0.02)**	
Recall 2		0.70 (0.02)**	
Recall 3		0.78 (0.02)**	
Recall 4		0.69 (0.02)**	
Recall 5		0.69 (0.02)**	
Digits forward			0.47 (0.02)**
Digits backward	0.44 (0.02)**		
Subtractions	0.45 (0.02)**		0.00 (0.00)
Cube	0.65 (0.02)**		
Clock	0.57 (0.02)**		

This model was tested in the full sample (n = 1738). Values are correlation coefficient (standard error). *$p < 0.05$, **$p < 0.001$.

Table A6. Loadings for each item by factor (2-factor model, MoCA<26 sample).

Item	Memory	Attentional-Executive
Trail-making		0.56 (0.04)**
Phonemic fluency		0.15 (0.04)*
Abstraction 1		0.31 (0.05)**
Abstraction 2		0.35 (0.05)**
Animals	–0.06 (0.04)	
Repetition 1	–0.01 (0.04)	
Repetition 2	–0.01 (0.04)	
Recall 1	0.38 (0.04)**	
Recall 2	0.61 (0.03)**	
Recall 3	0.68 (0.03)**	
Recall 4	0.59 (0.03)**	
Recall 5	0.55 (0.03)**	
Digits forward		0.04 (0.04)
Digits backward	–0.15 (0.04)**	
Vigilance		0.16 (0.04)**
Subtractions		0.27 (0.04)**
Cube		0.41 (0.04)**
Clock		0.41 (0.04)**
Temporal	0.00 (0.04)	
Spatial	–0.13 (0.04)*	

Values are correlation coefficient (standard error). *$p < 0.05$, **$p < 0.001$.

Table A7. Loadings for each item by factor (3-factor model, MoCA<26 sample).

Item	Executive	Recall	Verbal Attention
Trail-making	0.59 (0.04)**		
Phonemic fluency	0.16 (0.04)**		
Abstraction 1	0.33 (0.05)**		
Abstraction 2	0.36 (0.05)**		
Repetition 1†			1.00 ($3.7x10^{-16}$)**
Repetition 2			0.44 (0.03)**
Recall 1		0.37 (0.04)**	
Recall 2		0.61 (0.03)**	
Recall 3		0.68 (0.03)**	
Recall 4		0.60 (0.03)**	
Recall 5		0.55 (0.03)**	
Digits forward			0.31 (0.03)**
Digits backward	0.28 (0.04)**		
Subtractions	0.28 (0.04)**		
Cube	0.61 (0.04)**		
Clock	0.40 (0.04)**		

Values are correlation coefficient (standard error). *$p < 0.05$, **$p < 0.001$. † Error variance constrained to 0. Repetition 1 loaded almost perfectly onto Verbal Attention, preventing the model from converging. Therefore, this item's variance was constrained to 0.

Table A8 Goodness-of-fit statistics for the confirmatory factor analyses (MoCA<26 sample).

Statistic	2-factor model	3-factor model
χ^2_M	1966.62	796.32
df_M	169	102
p	<0.001	<0.001
$p_{close\text{-}fit\ H0}$	<0.001	<0.001
χ^2 / df	11.64	7.80
RMSEA (90% CI)	0.12 (0.11-0.12)	0.09 (0.09-0.10)
CFI	0.35	0.64
TLI	0.27	0.58
SRMR	0.10	0.07

CFI = comparative fit index, CI = confidence interval, RMSEA = root mean square error of approximation, SRMR = standardised root mean square residual, TLI = Tucker-Lewis Index.

Table A9. Goodness-of-fit statistics for the new confirmatory factor analysis.

Statistic	New 3-factor model
χ^2_M	1613.51
df_M	101
p	<0.001
$p_{close\text{-}fit\ H0}$	<0.001
χ^2 / df	15.98
RMSEA (90% CI)	0.13 (0.13-0.14)
CFI	0.7
TLI	0.6
SRMR	0.1

This analysis was run on the full sample, subgroup 2. CFI = comparative fit index, CI = confidence interval, RMSEA = root mean square error of approximation, SRMR = standardised root mean square residual, TLI = Tucker-Lewis Index.

Appendix 5: Participants excluded from the analysis in Chapter 7

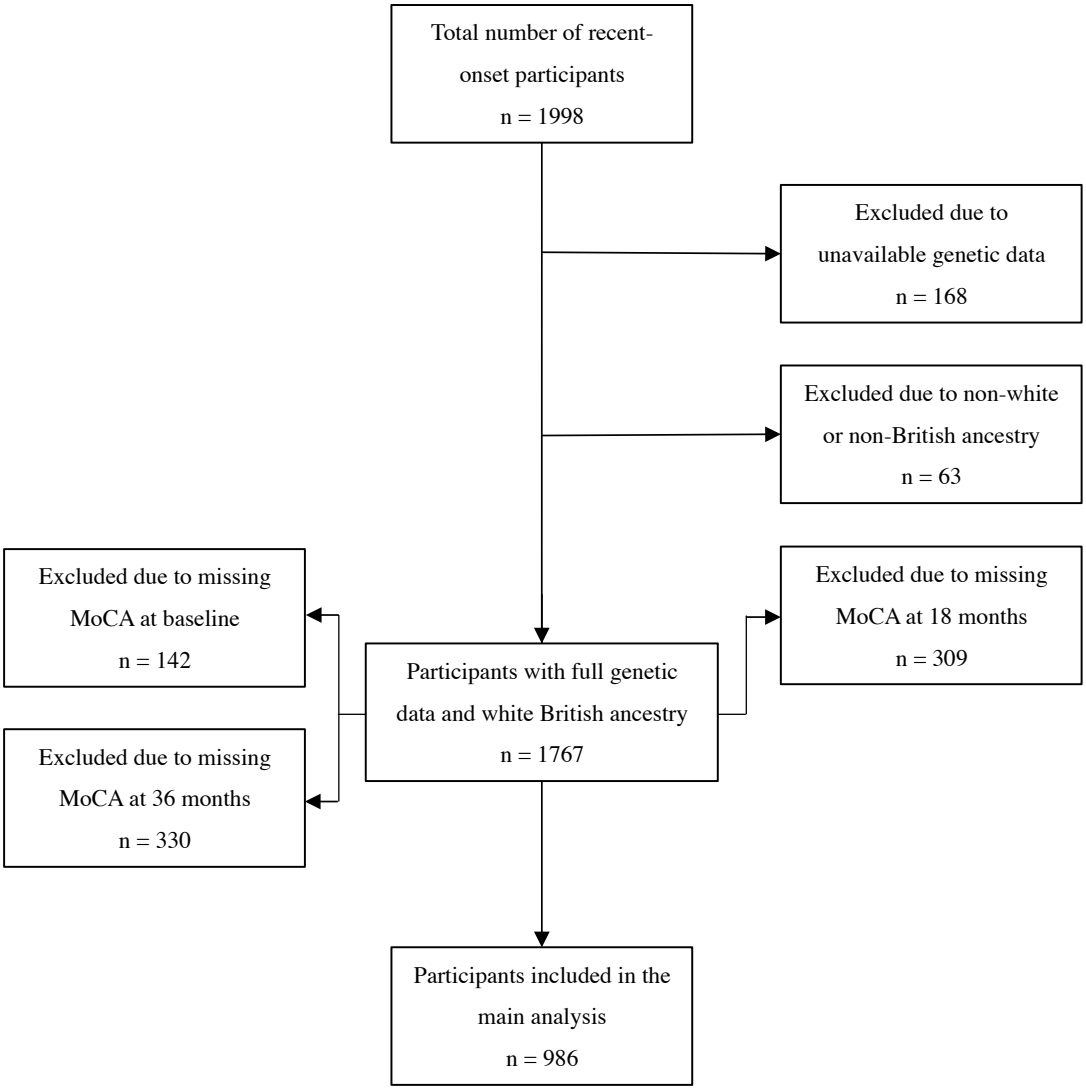


Figure A1. Flow diagram showing exclusions for the analysis in Chapter 7.

At baseline, 168 (8.4%) participants did not provide a DNA sample, and 63 (3.2%) were not of white British ancestry according to self-report. Excluding these participants reduced the sample size from 1998 to 1767.

Of the 1767 participants, 781 (44.2%) did not have MoCA data at all three relevant timepoints. The majority of these (455, 58.3%) had withdrawn before concluding the

three-year study period. The major reasons for withdrawals were patient choice (132, 29.0%), death (87, 19.1%), intercurrent illness (43, 9.5%), and site closure (31, 6.8%). Only nine participants (2.0%) had had their diagnosis changed from PD to another parkinsonian disorder.

A total of 326 (41.7%) participants had completed the three-year study period, but did not have MoCA data at all three timepoints; this included all 142 participants missing a baseline MoCA result. For all of these participants, one or more MoCA items were missing, and therefore, it was not possible to derive a total score.

Following exclusions of all participants missing MoCA data from the baseline, 18-month, or 36-month visits, the final sample size for the main analysis was 986.

Appendix 6: Linear and logistic regressions for Chapter 7

Table A10. Association of *APOE* genotype with MoCA score (linear regression).

Baseline	Unadjusted	Partially adjusted	Fully adjusted
ε2/ε2	0.8 (–1.0, 2.6) *p* = 0.38	0.0 (–2.0, 2.0) *p* = 0.99	0.0 (–2.0, 2.1) *p* = 0.97
ε2/ε3	–0.3 (–1.0, 0.4) *p* = 0.34	–0.4 (–1.1, 0.3) *p* = 0.23	–0.4 (–1.1, 0.2) *p* = 0.22
ε2/ε4	–0.1 (–1.1, 0.9) *p* = 0.87	0.0 (–1.0, 0.9) *p* = 0.95	0.0 (–1.0, 1.0) *p* = 0.97
ε3/ε4	–0.1 (–0.6, 0.4) *p* = 0.64	–0.2 (–0.7, 0.3) *p* = 0.42	–0.2 (–0.7, 0.3) *p* = 0.42
ε4/ε4	0.0 (–1.1, 1.1) *p* = 0.97	–0.3 (–1.3, 0.6) *p* = 0.50	–0.4 (–1.4, 0.6) *p* = 0.48
18 months			
ε2/ε2	1.4 (0.1, 2.7) *p* = 0.04*	0.5 (–1.0, 1.9) *p* = 0.55	0.5 (–1.0, 2.0) *p* = 0.54
ε2/ε3	–0.2 (–0.9, 0.5) *p* = 0.65	–0.1 (–0.8, 0.6) *p* = 0.78	–0.1 (–0.8, 0.6) *p* = 0.76
ε2/ε4	–0.4 (–1.8, 1.1) *p* = 0.64	–0.2 (–1.7, 1.3) *p* = 0.82	–0.2 (–1.7, 1.4) *p* = 0.84
ε3/ε4	0.0 (–0.5, 0.6) *p* = 0.89	0.0 (–0.5, 0.5) *p* = 0.93	0.0 (–0.5, 0.5) *p* = 0.94
ε4/ε4	–0.5 (–2.1, 1.0) *p* = 0.51	–1.0 (–2.4, 0.4) *p* = 0.15	–1.0 (–2.4, 0.3) *p* = 0.14
36 months			
ε2/ε2	1.6 (0.4, 2.8) *p* = 0.01*	0.7 (–0.8, 2.2) *p* = 0.36	0.7 (–0.8, 2.2) *p* = 0.36
ε2/ε3	0.2 (–0.5, 0.9) *p* = 0.56	0.1 (–0.5, 0.8) *p* = 0.70	0.1 (–0.5, 0.8) *p* = 0.70
ε2/ε4	–0.6 (–2.2, 0.9) *p* = 0.43	–0.7 (–2.3, 0.9) *p* = 0.39	–0.7 (–2.3, 0.9) *p* = 0.39
ε3/ε4	–0.6 (–1.2, 0.1) *p* = 0.09	–0.6 (–1.2, 0.0) *p* = 0.06	–0.6 (–1.2, 0.0) *p* = 0.06
ε4/ε4	–1.0 (–3.1, 1.1) *p* = 0.36	–1.5 (–3.4, 0.4) *p* = 0.12	–1.5 (–3.4, 0.4) *p* = 0.12

Data are unstandardised regression coefficient (95% CI); significance level. The dependent variable is MoCA score. The reference category is *APOE* ε3/ε3. Positive values indicate a higher MoCA score than ε3/ε3 and negative values indicate a lower MoCA score than ε3/ε3. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Table A11. Association of *APOE* genotype with cognitive status (logistic regression).

Baseline	Unadjusted	Partially adjusted	Fully adjusted
ε2/ε2	0.5 (1.0, 2.2) $p = 0.32$	0.7 (0.2, 3.6) $p = 0.71$	0.7 (0.1, 3.5) $p = 0.69$
ε2/ε3	1.2 (0.8, 1.7) $p = 0.42$	1.2 (0.8, 1.9) $p = 0.28$	1.3 (0.8, 1.9) $p = 0.27$
ε2/ε4	0.8 (0.4, 1.5) $p = 0.46$	0.7 (0.3, 1.5) $p = 0.39$	0.7 (0.3, 1.5) $p = 0.38$
ε3/ε4	1.0 (0.7, 1.4) $p = 0.82$	1.1 (0.8, 1.5) $p = 0.64$	1.1 (0.8, 1.5) $p = 0.63$
ε4/ε4	1.0 (0.4, 2.4) $p = 1.00$	1.3 (0.5, 3.2) $p = 0.58$	1.3 (0.5, 3.3) $p = 0.56$
18 months			
ε2/ε2	0.2 (0.0, 1.6) $p = 0.14$	0.4 (0.0, 2.9) $p = 0.33$	0.3 (0.0, 2.8) $p = 0.31$
ε2/ε3	0.9 (0.6, 1.3) $p = 0.61$	0.9 (0.6, 1.4) $p = 0.59$	0.9 (0.6, 1.4) $p = 0.65$
ε2/ε4	1.0 (0.5, 2.0) $p = 0.98$	0.9 (0.4, 1.9) $p = 0.76$	0.9 (0.4, 1.9) $p = 0.74$
ε3/ε4	1.0 (0.7, 1.4) $p = 0.93$	1.0 (0.7, 1.4) $p = 0.95$	1.0 (0.7, 1.4) $p = 0.97$
ε4/ε4	1.3 (0.5, 3.0) $p = 0.59$	1.7 (0.7, 4.1) $p = 0.25$	1.7 (0.7, 4.2) $p = 0.22$
36 months			
ε2/ε2	0.2 (0.0, 1.5) $p = 0.12$	0.3 (0.0, 2.4) $p = 0.25$	0.3 (0.0, 2.4) $p = 0.24$
ε2/ε3	1.1 (0.7, 1.5) $p = 0.80$	1.1 (0.8, 1.7) $p = 0.58$	1.1 (0.8, 1.7) $p = 0.56$
ε2/ε4	1.3 (0.7, 2.5) $p = 0.38$	1.3 (0.7, 2.6) $p = 0.43$	1.3 (0.7, 2.6) $p = 0.45$
ε3/ε4	1.3 (1.0, 1.8) $p = 0.09$	1.4 (1.0, 1.9) $p = 0.07$	1.4 (1.0, 1.9) $p = 0.07$
ε4/ε4	1.5 (0.6, 3.5) $p = 0.41$	2.0 (0.8, 4.9) $p = 0.14$	2.0 (0.8, 5.0) $p = 0.13$

Data are odds ratio (95% CI); significance level. The dependent variable is cognitive status, defined by MoCA score (normal = 26-30, MCI = 21-25, dementia = 0-20). The reference category is *APOE* ε3/ε3. Positive values indicate greater odds of worse cognition than ε3/ε3, and negative values indicate lower odds of worse cognition than ε3/ε3. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Table A12. Association of *APOE* genotype with MoCA change (linear regression).

0-18 months	Unadjusted	Partially adjusted	Fully adjusted
ε2/ε2	–0.6 (–1.9, 0.8) *p* = 0.40	–0.5 (–1.7, 0.8) *p* = 0.49	–0.4 (–1.7, 0.8) *p* = 0.50
ε2/ε3	–0.2 (–0.7, 0.4) *p* = 0.53	–0.3 (–0.8, 0.3) *p* = 0.39	–0.2 (–0.8, 0.3) *p* = 0.39
ε2/ε4	0.3 (–0.7, 1.3) *p* = 0.59	0.3 (–0.7, 1.4) *p* = 0.52	0.3 (–0.7, 1.4) *p* = 0.52
ε3/ε4	–0.2 (–0.6, 0.3) *p* = 0.49	–0.2 (–0.6, 0.3) *p* = 0.47	–0.2 (–0.6, 0.3) *p* = 0.46
ε4/ε4	0.5 (–0.6, 1.6) *p* = 0.36	0.7 (–0.4, 1.8) *p* = 0.20	0.7 (–0.4, 1.8) *p* = 0.20
18-36 months			
ε2/ε2	–0.2 (–1.0, 0.5) *p* = 0.53	–0.1 (–0.8, 0.7) *p* = 0.83	–0.1 (–0.8, 0.7) *p* = 0.87
ε2/ε3	–0.4 (–0.9, 0.1) *p* = 0.15	–0.4 (–0.9, 0.2) *p* = 0.18	–0.4 (–0.9, 0.2) *p* = 0.18
ε2/ε4	0.3 (–0.9, 1.4) *p* = 0.65	0.4 (–0.8, 1.6) *p* = 0.48	0.4 (–0.8, 1.6) *p* = 0.47
ε3/ε4	0.6 (0.1, 1.0) *p* = 0.01*	0.6 (0.1, 1.0) *p* = 0.01*	0.6 (0.1, 1.0) *p* = 0.01
ε4/ε4	0.5 (–0.6, 1.6) *p* = 0.42	0.6 (–0.6, 1.7) *p* = 0.32	0.6 (–0.6, 1.7) *p* = 0.34
0-36 months			
ε2/ε2	–0.8 (–1.7, 0.0) *p* = 0.06	–0.5 (–1.3, 0.2) *p* = 0.16	–0.5 (–1.3, 0.3) *p* = 0.21
ε2/ε3	–0.5 (–1.1, 0.0) *p* = 0.05*	–0.6 (–1.2, 0.0) *p* = 0.04*	–0.6 (–1.2, 0.0) *p* = 0.04*
ε2/ε4	0.5 (–0.8, 1.9) *p* = 0.42	0.8 (–0.6, 2.1) *p* = 0.27	0.8 (–0.6, 2.2) *p* = 0.27
ε3/ε4	0.4 (–0.1, 1.0) *p* = 0.13	0.4 (–0.1, 1.0) *p* = 0.13	0.4 (–0.1, 1.0) *p* = 0.13
ε4/ε4	1.0 (–0.5, 2.4) *p* = 0.19	1.3 (–0.1, 2.7) *p* = 0.08	1.3 (–0.2, 2.7) *p* = 0.09

Data are unstandardised regression coefficient (95% CI); significance level. The dependent variable is MoCA change. The reference category is *APOE* ε3/ε3. Positive values indicate a greater MoCA decline than ε3/ε3 and negative values indicate less MoCA decline than ε3/ε3. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Table A13. Association of *MAPT* genotype with MoCA score (linear regression).

Baseline	Unadjusted	Partially adjusted	Fully adjusted
H1/H2	0.1 (–0.3, 0.5) $p = 0.56$	0.0 (–0.4, 0.4) $p = 0.94$	0.0 (–0.4, 0.4) $p = 0.95$
H2/H2	0.4 (–0.6, 1.4) $p = 0.42$	0.2 (–0.7, 1.1) $p = 0.70$	0.2 (–0.7, 1.1) $p = 0.72$
18 months			
H1/H2	0.2 (–0.2, 0.7) $p = 0.32$	0.1 (–0.3, 0.6) $p = 0.57$	0.1 (–0.3, 0.6) $p = 0.59$
H2/H2	0.0 (–1.0, 1.1) $p = 0.94$	0.1 (–0.7, 1.0) $p = 0.76$	0.1 (–0.7, 1.0) $p = 0.78$
36 months			
H1/H2	0.3 (–0.2, 0.8) $p = 0.22$	0.2 (–0.3, 0.7) $p = 0.39$	0.2 (–0.3, 0.7) $p = 0.39$
H2/H2	0.8 (–0.4, 1.9) $p = 0.18$	0.7 (–0.4, 1.7) $p = 0.21$	0.7 (–0.4, 1.7) $p = 0.21$

Data are unstandardised regression coefficient (95% CI); significance level. The dependent variable is MoCA score. The reference category is *MAPT* H1/H1. Positive values indicate a higher MoCA score than H1/H1 and negative values indicate a lower MoCA score than H1/H1. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Table A14. Association of *MAPT* genotype with cognitive status (logistic regression).

Baseline	Unadjusted	Partially adjusted	Fully adjusted
H1/H2	0.9 (0.7, 1.2) $p = 0.43$	0.9 (0.7, 1.3) $p = 0.67$	0.9 (0.7, 1.3) $p = 0.68$
H2/H2	1.0 (0.5, 2.0) $p = 0.97$	1.2 (0.6, 2.3) $p = 0.66$	1.2 (0.6, 2.4) $p = 0.62$
18 months			
H1/H2	0.9 (0.7, 1.2) $p = 0.42$	0.9 (0.7, 1.3) $p = 0.70$	1.0 (0.7, 1.3) $p = 0.74$
H2/H2	1.0 (0.5, 1.9) $p = 0.93$	1.0 (0.5, 2.0) $p = 0.92$	1.0 (0.5, 2.0) $p = 0.95$
36 months			
H1/H2	0.9 (0.7, 1.1) $p = 0.29$	0.9 (0.7, 1.2) $p = 0.54$	0.9 (0.7, 1.2) $p = 0.55$
H2/H2	0.7 (0.3, 1.3) $p = 0.24$	0.8 (0.4, 1.6) $p = 0.45$	0.8 (0.4, 1.6) $p = 0.47$

Data are odds ratio (95% CI); significance level. The dependent variable is cognitive status, defined by MoCA score (normal = 26-30, MCI = 21-25, dementia = 0-20). The reference category is *MAPT* H1/H1. Positive values indicate greater odds of worse cognition than H1/H1, and negative values indicate lower odds of worse cognition than H1/H1. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Table A15. Association of *MAPT* genotype with MoCA change (linear regression).

0-18 months	Unadjusted	Partially adjusted	Fully adjusted
H1/H2	–0.1 (–0.5, 0.3) $p = 0.56$	–0.1 (–0.5, 0.3) $p = 0.63$	–0.1 (–0.5, 0.3) $p = 0.63$
H2/H2	0.4 (–0.5, 1.2) $p = 0.39$	0.3 (–0.6, 1.2) $p = 0.49$	0.3 (–0.6, 1.2) $p = 0.49$
18-36 months			
H1/H2	–0.1 (–0.5, 0.3) $p = 0.64$	–0.1 (–0.5, 0.3) $p = 0.72$	–0.1 (–0.5, 0.3) $p = 0.72$
H2/H2	–0.7 (–1.7, 0.3) $p = 0.17$	–0.8 (–1.8, 0.3) $p = 0.14$	–0.8 (–1.8, 0.2) $p = 0.13$
0-36 months			
H1/H2	–0.2 (–0.6, 0.2) $p = 0.37$	–0.2 (–0.6, 0.3) $p = 0.47$	–0.2 (–0.6, 0.3) $p = 0.46$
H2/H2	–0.3 (–1.4, 0.7) $p = 0.51$	–0.5 (–1.5, 0.6) $p = 0.39$	–0.5 (–1.5, 0.6) $p = 0.36$

Data are unstandardised regression coefficient (95% CI); significance level. The dependent variable is MoCA change. The reference category is *MAPT* H1/H1. Positive values indicate a greater MoCA decline than H1/H1 and negative values indicate less MoCA decline than H1/H1. The model was adusted for sex, and for age, disease duration, and education category. *Significant at $p < 0.05$. CI = confidence interval, MoCA = Montreal Cognitive Assessment.

Appendix 7: Secondary analysis for Chapter 7

Number of APOE ε4 alleles. When the number of ε4 alleles was the main predictor and cross-sectional MoCA score was the dependent variable, fully adjusted models found significant results only at 36 months, where one ε4 allele was deleterious (unstandardised coefficient [95% CI]: –0.7 [–1.2, –0.1], $p = 0.03$) relative to zero ε4 alleles.

There was an interaction between number of ε4 alleles and sex at 18 months and at 36 months but not at baseline. Sex-stratified analysis found that the deleterious effects of two ε4 alleles were confined to men (at 18 months, –2.1 [–3.9, –0.4], $p = 0.02$; at 36 months, –3.2 [–5.6, –0.8], $p = 0.009$). No other significant interactions were observed at any timepoint.

When ordered logistic regression was used to predict cognitive status (normal, MCI, or dementia), the only significant result was found in the sex-stratified analysis at 36 months, where the presence of two ε4 alleles was significantly associated with higher odds of worse cognitive status in men only (odds ratio [95% CI]: 3.9 [1.3, 11.7], $p = 0.02$). The interaction of ε4 dosage with sex was not statistically significant.

When the magnitude of MoCA change over time was the dependent variable, fully adjusted models found a deleterious effect of one ε4 allele on score change from 18-36 months (unstandardised coefficient [95% CI]: 0.6 [0.2, 1.1], $p = 0.004$); in contrast to the main analysis, a deleterious effect of one ε4 allele was also found on score change from baseline to 36 months (0.6 [0.1, 1.1] $p = 0.02$). The baseline to 36 months model showed a significant interaction between ε4 dosage and sex, but no significant interactions with age, disease duration, or education. Sex-stratified analysis found that decline over this period was associated with the presence of two ε4 alleles in men only (2.6 [0.9, 4.3], $p = 0.003$), and with the presence of one ε4 allele in women only (1.0 [0.1, 1.8], $p = 0.03$); the latter result was not encountered in the main analysis. The baseline to 18 months model also showed a significant interaction between ε4 dosage and sex; however, sex-stratified regressions returned no significant results.

APOE ε4 positivity. Fewer statistically significant results were observed when using the binary category of *APOE* ε4 carrier versus non-carrier as the main predictor. Fully adjusted models showed that ε4 carriers had lower MoCA scores than non-carriers at 36 months (–0.7 [–1.3, –0.2], $p = 0.01$). Ordered logistic regression with cognitive status as the dependent variable found a significant effect only at 36 months, such that ε4 positivity was associated with higher odds of worse cognitive status (odds ratio 95% CI]: 1.4 [1.0, 1.8], $p = 0.03$). Additionally, ε4 positivity was associated with MoCA decline from 18-36 months (unstandardised coefficient [95% CI]: 0.6 [0.2, 1.0], $p = 0.003$) and from baseline to 36 months (0.7 [0.2, 1.1], $p = 0.01$). No other significant results were seen, and none of the previously observed interaction effects were evident.

MAPT H2 positivity. When *MAPT* H2 carriers were compared to H1/H1, there were no significant results in any of the fully adjusted cross-sectional or longitudinal regression models. A marginally significant interaction between *MAPT* H2 positivity and education was observed in the logistic regression for cognitive status at 18 months, but education-stratified analysis did not show significant results. A corresponding result was not found in the main analysis, but it was seen in the sensitivity analysis (Appendix 10).

Appendix 8: Unadjusted analysis of *MAPT* subhaplotypes

Table A16. Effect of *MAPT* subhaplotypes on odds of dementia in PD (unadjusted for sex and age category).

ID	Allele sequence	Estimated frequency (%)	OR (95% CI)	*p*-value
H1b	GGGCTA	17.9	0.7 (0.4, 1.2)	0.18
H1c	AAGTTG	15.1	0.8 (0.5, 1.4)	0.44
H1d	AAGCTA	7.5	0.7 (0.3, 1.5)	0.39
H1e	AGGCTA	6.8	0.9 (0.4, 1.8)	0.71
H1f	GGACTA	0.7	2.2 (0.3, 16.1)	0.42
H1g	GAACTA	1.2	0.8 (0.1, 5.4)	0.83
H1h	AGACTA	2.8	1.3 (0.5, 3.5)	0.58
H1i	GAGCTA	4.3	1.8 (0.9, 3.6)	0.12
H1j	AGGCTG	1.0	7.3^{-6}*	0.99
H1l	AGACTG	4.8	1.2 (0.6, 2.4)	0.63
H1m	GAGCTG	2.3	1.5 (0.6, 3.8)	0.40
H1n	GGACTG	1.0	4.2^{-7}*	0.99
H1o	AAACTA	1.1	1.3 (0.3, 5.8)	0.76
H1p	GGGTTG	0.04	3.7 (0.7, 19.6)	0.12
H1q	AAGTTA	1.3	0.4 (0.1, 3.3)	0.42
H1r	AGGTTG	1.6	1.0 (0.2, 4.0)	0.96
H1s	GGGCTG	1.1	6.5^{-7}*	0.99
H1t	AGATTG	1.0	1.0^{-6}*	0.99
H1u	AAGCTG	2.5	1.7 (0.7, 3.9)	0.24
H1v	GGATTG	1.7	0.9 (0.2, 3.9)	0.94
H1x	GAATTG	1.4	1.1 (0.2, 5.4)	0.93

For allele sequence, SNPs are in the following order: rs1467967, rs242557, rs3785883, rs2471738, rs9468 (H2-tagging), and rs7521. The reference category was H2a combined with all rare subhaplotypes (estimated frequency <0.3%). *Confidence intervals were not generated for these subhaplotypes. CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

Appendix 9: Power calculations for the subhaplotype analysis

Table A17. Power to detect a significant association with dementia in PD.

Subhaplotype frequency	Odds ratio	Power
1%	1.5	10%
5%	1.5	18%
10%	1.5	27%
20%	1.5	40%
1%	2.0	17%
5%	2.0	42%
10%	2.0	63%
20%	2.0	84%
1%	2.5	25%
5%	2.5	64%
10%	2.5	86%
20%	2.5	98%
1%	3.0	32%
5%	3.0	79%
10%	3.0	95%
20%	3.0	99%

The total sample size was 686, of whom 15.3% had dementia. Power to detect significance at the 0.05 level was calculated. Calculations performed with G*Power software (Faul et al., 2009). PD = Parkinson's disease.

Appendix 10: Sensitivity analysis for Chapter 7

For the main analysis, cases with incomplete MoCA data at the baseline, 18-month, or 36-month visits were excluded (n = 781). As a sensitivity analysis, all models were rerun with all available data at each timepoints. The analysis sample was still restricted to those with genetic data who self-reported white British ancestry. At baseline, the total sample size was 1767; the distribution of *APOE* and *MAPT* genotypes for this sample is shown in Table A18. Genotype frequencies were comparable in the main and sensitivity samples. MoCA data were available for 1430 participants at 18 months and for 1155 at 36 months. The decline in sample size resulted from a combination of genuine withdrawals (see Appendix 5 for details) and the study being ongoing, meaning that some participants had not reached the 36-month visit when data were accessed.

Table A18. Distribution of *APOE* and *MAPT* genotypes in all participants with available MoCA data at baseline (n = 1767).

***APOE* genotype**	**n (%)**
ε2ε2	11 (0.6%)
ε2ε3	229 (13.0%)
ε2ε4	60 (3.4%)
ε3ε3	1050 (59.4%)
ε3ε4	378 (21.4%)
ε4ε4	39 (2.2%)
***MAPT* genotype**	
H1/H1	1169 (66.2%)
H1/H2	539 (30.5%)
H2/H2	59 (3.3%)

APOE. Fully adjusted models with MoCA score as the dependent variable and all six *APOE* genotypes as the predictor generally found no significant results, consistent

with the main analysis; the sole exception was a mild deleterious effect of ε3/ε4 at 36 months (unstandardised coefficient [95% CI]: –0.8 [–1.4, –0.2], $p = 0.006$). As with the main analyses, interactions of genotype with sex were found at each timepoint. The subsequent sex-stratified analysis showed the same protective effects of ε2 homozygosity and detrimental effects of ε4 homozygosity in men, though there were additional marginal effects of ε4/ε4 at baseline (–1.3 [–2.5, –0.1], $p = 0.04$), and of ε3/ε4 at 36 months (–0.8 [–1.6, 0.0], $p = 0.04$). Significant results for women were the same as the main analysis. Finally, two new significant interactions emerged in the sensitivity analysis. Genotype marginally interacted with age at baseline, and age-stratified analysis showed an effect of ε4 homozygosity only in the older participants (–2.9 [–5.1, –0.7], $p = 0.009$). There was also an interaction with education at 18 months, with education-stratified analysis showing effects of ε3/ε4 (–1.3 [–2.2, –0.4], $p = 0.007$) only in those with fewer than 13 years of education.

The logistic regressions found a significant effect of ε3/ε4 on worse cognitive status at 36 months (odds ratio [95% CI]: 2.0 [0.8, 4.7], $p = 0.01$), but no other significant results were observed. Again, sex-stratified analysis showed a deleterious effect of ε4/ε4 only in men. Unlike the main analysis, an interaction of genotype and education was observed at baseline; education-stratified analysis showed deleterious effects of ε3/ε4 and ε4/ε4 only in lower educated participants (1.6 [1.1, 2.5], $p = 0.02$ and 4.9 [1.4, 17.6], $p = 0.01$, respectively).

When MoCA change was the dependent variable, results were again similar to the main analysis. Fully adjusted models showed no associations between *APOE* genotype and change from baseline to 18 months, though there was some evidence for an interaction with disease duration. The ε3/ε4 genotype was weakly associated with decline from 18-36 months (unstandardised coefficient [95% CI]: 0.6 [0.1, 1.0], $p = 0.01$), and no interactions with other predictors were observed for this interval. Unlike the main analysis, fully adjusted models showed significant effects of ε2/ε3 and ε3/ε4 on change from baseline to 36 months (–0.6 [1.1, 0.0], $p = 0.03$ and 0.6 [0.1, 1.1], $p = 0.03$, respectively). For this interval, the interaction with sex crossed into non-significance ($p = 0.06$), but interactions with age and disease duration were again observed, and subsequent stratified regressions replicated the findings of the main analysis. In older participants, an additional deleterious effect of ε3/ε4 was observed

(1.1 [0.2, 2.0], $p = 0.02$); ε4/ε4 had a higher coefficient, but this was not statistically significant (3.1 [–0.3, 6.4], $p = 0.07$).

MAPT. Fully adjusted linear and logistic regression models replicated with main analysis, with no significant results found at any timepoint. However, there were two significant interactions of *MAPT* with other predictors. At 18 months, there was an interaction between *MAPT* genotype and education; the education-stratified analysis showed higher MoCA scores in the H2/H2 group than in the H1/H1 group (2.0 [0.9, 3.1], $p < 0.001$) only in participants with fewer than 13 years of education. At 36 months, this interaction was non-significant, but only marginally ($p = 0.0504$).

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