Cognitive features of familial Alzheimer's disease

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SIGNED DECLARATION

I, Yuying Liang confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Familial Alzheimer's disease (FAD) is considered a pathological model for sporadic Alzheimer's disease (SAD) due to their similarities. The studies described in this thesis aim to address the issue of improving our knowledge of the cognitive features of FAD at early stages of the disease. This is important from the point of view of a better understanding of the pathophysiology of AD and for trial planning.

A longitudinal cohort study aimed to provide analysis of the timing and temporal progression of neuropsychological changes in FAD. It found that a paired associative learning task was one of the earliest neuropsychological tests to decline in the asymptomatic phase of the disease. There was evidence of increased year-to-year fluctuations in select neuropsychological tests after the onset of symptoms in some FAD mutation carriers. A prospective study using a novel experimental paradigm for investigating short-term visual memory found that asymptomatic mutation carriers had a specific impairment in object identity and localization binding despite intact memory for object identity and localization *per se*. The asymptomatic mutation carriers also had normal long-term and short-term memory performance as measured by standard neuropsychological tests. Performance on the binding task showed a significant correlation with total mean hippocampal volume, consistent with the view that

the hippocampus is involved in relational binding, regardless of the memory duration.

A case study detailing the longitudinal clinical, neuropsychological and structural imaging findings in an individual with a *MAPT* mutation yielded important insight into the role of the medial temporal lobe (MTL) in memory functions and highlighted the pitfalls in the differential diagnosis of progressive amnestic syndrome.

This thesis therefore provides psychological data in the early stages of FAD and offers insights into the role of the MTL in memory functions in AD and related dementia.

IMPACT STATEMENT

The results of the longitudinal neuropsychological study contribute to our knowledge of the timing and sequence of objective cognitive changes in early stages of FAD. The results, when interpreted in the context of the dynamics of other biomarkers, provide empirical support for the current biomarker model of AD and the validity of FAD as a pathological model for SAD.

An intra-individual approach was taken to characterize the changes in cognitive functions in the FAD cohort. This included using a change point modelling approach to determine the time point when mutation carriers and controls diverged in their individual cognitive trajectories. I also investigated the presence of year-to-year intraindividual variability in neuropsychological performance in the FAD mutation carriers. These methodological approaches have not been previously applied to studies on cognition in FAD. The findings of practice effect and increased variability in select cognitive tests amongst some mutation carriers have important implications for the diagnosis of AD and the design of clinical trials.

I demonstrated the practicality of using a novel, computerized visual short-term memory binding task in FAD mutation carriers. The results contribute to the existing literature on the role played by the medial temporal lobe, and in

particular, the hippocampus in relational binding. The findings also have implications for understanding the symptomatology of AD. The signal in asymptomatic mutation carriers suggests that the task may be useful in detecting AD at an early stage, along with other, established methods for diagnosis.

The case report of a *MAPT* mutation individual who presented with progressive amnesia provided a useful reminder to clinicians that amnesia with medial temporal lobe atrophy is not specific for AD. An important clinical lesson is to consider frontotemporal lobe dementia (more specifically *MAPT* mutations) where there may be semantic knowledge impairment together with episodic memory loss. The case also illustrates the usefulness of longitudinal structural imaging and CSF biomarkers in the differential diagnosis of dementia.

My research provides insight into the intra-individual cognitive trajectories in FAD, and indirectly the pathophysiology of AD. It has implications for the early and accurate diagnosis of AD and the design of treatment trials.

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ABBREVIATIONS

Aβ	amyloid-beta
AD	Alzheimer's disease
APP	amyloid precursor protein
BSI	boundary shift integral
CDR	Clinical Dementia Rating
CPAL	Camden Paired Associate Learning
CSF	cerebrospinal fluid
DIAN	Dominantly Inherited Alzheimer Network
EAO	expected age of symptom onset
FAD	familial Alzheimer's disease
FTD	fronto-temporal dementia
GDAT	Graded Difficulty Arithmetic Test
GDST	Graded Difficulty Spelling Test
GNT	Graded Naming Test
IIV	Intra-individual variability
IIV-D	Intra-individual variability-dispersion
IIV-I	Intra-individual variability-inconsistency
IWG	International Working Group
MAPT	microtubule-associated protein tau
MCs	mutation carriers

MCI	mild cognitive impairment
MCST	Modified Card Sorting Test
MTL	medial temporal lobe
NART	National Adult Reading Test
NFT	neurofibrillary tangles
NIA-AA	National Institute on Aging and Alzheimer's Association
NCs	non-mutation carriers
PAL	paired associate learning
PSEN 1	presenilin 1
PET	positron emission tomography
p-tau	phosphorylated tau
QD	questionable dementia
RMT	recognition memory test
STM	short-term memory
t-tau	total tau
UCL	University College London
VOSP	Visual Object and Spatial Perception battery
VSTM	visual short-term memory
WMS-R	Wechsler Memory Scale-Revised

Chapter 1 GENERAL INTRODUCTION

It is estimated that around 50 million individuals have dementia worldwide (World Health Organization, 2020). The number is projected to reach 82 million in 2030 and 152 million in 2050 (World Health Organization, 2020). Dementia is a major source of disability and mortality: 9% of all deaths registered in England and Wales in 2019 was due to dementia (Office for National Statistics, 2019). In addition to the devastating impact on the person and their family, it is also associated with enormous economic cost. In the UK, cost of dementia in 2019 was estimated to be around £34.7 billion (Wittenberg, Hu, Barraza-Araiza, & Rehill, 2019). In recognition of the health and social impact of dementia, the World Health Organization called for dementia to be given global public health priority (World Health Organization, 2012) .

AD is the most common form of dementia, accounting for 50%–75% of all dementia (Prince, Albanese, Guerchet, & Prina, 2014). Although disease-modifying treatments are currently not available, accurate and timely diagnosis are important in order for individuals to access support and symptomatic treatment. Secondary prevention trials aimed at delaying or preventing symptom onset in individuals at-risk of AD are currently underway (Bateman et al., 2017; Mills et al., 2013; Reiman et al., 2011; Sperling et al., 2014). The success of these trials requires high degree of accuracy in terms of recruiting individuals

with AD pathology and reliable methods in tracking clinical and pathological progress.

1.1 Familial Alzheimer's disease

Although less than 1% of all cases of AD is inherited in an autosomal dominant pattern (Bateman et al., 2011) - referred to as familial Alzheimer's disease (FAD) - much of what we know about AD pathogenetic mechanisms have been informed by the study of individuals with pathological mutations or duplications in amyloid precursor protein (*APP)* gene, presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2)* genes. Many of these pathological mutations lead to a relative increase in toxic forms of Aβ with some causing a reduction in the clearance of Aβ (Scheuner et al., 1996) whilst duplication in the APP locus cause overproduction of all Aβ species. On the other hand, an *APP* missense mutation A673T confers protective effects against AD by decreasing APP cleavage by β-secretase (Jonsson et al., 2012). The clear functional consequences on Aβ due to many of the FAD mutations have given support to the "amyloid hypothesis" which postulates that the abnormal accumulation of Aβ is the initial step in triggering the pathophysiological cascade that eventually leads to AD (Selkoe & Hardy, 2016).

1.2 Sporadic AD

The vast majority of AD cases occurs in a sporadic fashion (SAD). It is now thought that numerous interconnected genetic and environmental factors are implicated in the aetiology of SAD. In contrast with the monogenetic nature of FAD, it is estimated that up to 60-80% of SAD is genetically determined with underlying genetic risk factors that are of relatively high frequency but low penetrance (Bertram, Lill, & Tanzi, 2010) (Gatz et al., 2006). The APOE gene, which has three variants, ε2, ε3 and ε4, is the single biggest risk for sporadic AD.

1.3 Pathological features of AD

The core pathological features of AD- both SAD and FAD- are extra-cellular deposits of amyloid-β (Aβ) protein in the form of amyloid plaques and intra-cellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011) (Hyman et al., 2012).

Aβ, a 38–43 amino acid peptide, is produced in neurons by sequential proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretase (Selkoe, 2001). In healthy persons, excess Aβ is cleared from the brain. However, in AD, Aβ misfolds and aggregates to form higher order species such

as soluble oligomers and insoluble fibrils. Amyloid plaque deposition appears to occur preferentially in the "default-mode network", a set of brain regions that exhibits elevated metabolic activity in the resting state (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner et al., 2009, 2005). Fibrillary Aβ can also deposit in the wall of arterioles in the leptomeninges and penetrating vessels, resulting in cerebral amyloid angiopathy (Johnson et al., 2007).

NFTs, the other major proteinopathy in AD, are chiefly composed of paired helical filaments composed of hyperphosphorylated tau. Unlike Aβ pathology which begins in the neocortex and appear later in the hippocampus, NFTs first appear in the brainstem (particularly the locus coeruleus) then the transentorhinal cortex before spreading to the hippocampus, the adjacent medial-basal temporal cortex, followed by the cortical association areas and last to primary sensory-motor and visual areas (Braak & Braak, 1991) in a stereotypic topographic progression pattern.

Neuronal loss and therefore atrophy, is more closely associated with NFT topographically than with β-amyloid distribution (Serrano-Pozo et al., 2011). In keeping with this, clinico-pathology correlation studies show a much stronger correlation between NFT and cognitive impairment both spatially and

temporally than between amyloid and cognitive impairment (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Bierer et al., 1995).

Greater degrees of amyloid burden, NFTs and cerebral amyloid angiopathy have been observed in FAD compared to SAD (Cairns et al., 2015; Ringman et al., 2016). In addition, it is not uncommon for AD pathology to co-exist with other neuro-pathologies: Lewy body pathology being the most common in both SAD and FAD (Revesz et al., 1997; Cairns et al., 2015). Vascular disease, argyrophilic grain disease, TDP-43 proteinopathy and hippocampal sclerosis has been observed to co-exist with AD pathology in SAD but not FAD (Cairns et al., 2015). As a result, clinical presentations of AD may be modulated by the presence of other pathologies which may in turn make accurate diagnosis more challenging.

1.4 Clinical features and phenotypical variants of AD

The most common clinical presentation of SAD is an amnestic syndrome where the leading symptoms are insidious, progressive difficulties in episodic memory. This is also the case in FAD. A large retrospective study found that 84% of individuals with *PSEN1* and 97% of *APP* mutation carriers presented with the classic amnestic syndrome (Ryan et al., 2016).

Both SAD and FAD can also present with non-amnestic phenotypes initially (Alladi et al., 2007). Around one third of individuals with early onset SAD (defined as <65 year at the age of onset) have a non-amnestic presentation (Koedam et al., 2010) such as posterior cortical atrophy, logopenic aphasia and the frontal variant of AD (Dubois et al., 2014; Lam, Masellis, Freedman, Stuss, & Black, 2013). In FAD, non-amnestic presentation is more likely to be associated with *PSEN1* mutation (Ryan et al., 2016).

It is currently not known why some individuals with SAD or FAD develop an amnestic syndrome whilst others develop a language or frontal variant. Understanding the pathophysiological processes that lead to the multitude of clinical phenotypes clearly has importance implications for treatment.

1.5 FAD as a pathological model for SAD

FAD and SAD share many similarities in terms of pathology (see section 1.3), pathophysiology (see section 1.6), clinical and cognitive features (see section 1.4) despite differences in probable aetiology (predominantly increased Aβ production in FAD versus reduced Aβ clearance in SAD). As a result, FAD has come to be regarded as a useful pathological model for SAD.

It is now established that cerebral pathology of AD predates clinical diagnosis by many years to decades (McDade et al., 2018; Palmqvist et al., 2019; Villemagne et al., 2013; Yau et al., 2015). This knowledge, combined with the failure of phase-3 trials in symptomatic patients (Doody *et al*., 2014; Green *et al*., 2009; Salloway *et al*., 2014; Samson, 2010) has led to an increasing interest in prevention trials in asymptomatic individuals at risk of developing AD such as those who are carriers of pathological FAD mutations (Bateman et al., 2017; Reiman et al., 2011) as it is thought that by the time individuals are symptomatic, a multitude of more downstream pathological processes such as inflammation and mitochondrial dysfunction are already established, and may not be reversible.

Understanding how the pathophysiological processes unfold during the preclinical period is key for the development of therapeutic interventions. Identifying and recruiting sufficient number of individuals at-risk of SAD for observational studies and prevention trials is logistically difficult. In contrast, given the certainty of the underlying pathology and the reasonably predictable age of symptom onset in FAD (Ryman et al., 2014), it is much more feasible to conduct longitudinal studies to assess the temporal order of pathological events in FAD mutation carriers (Bateman et al., 2011).

As the ultimate aim of any AD prevention trials is to prevent or delay the onset of cognitive and behavioural impairments associated with AD, knowledge of the earliest cognitive features of FAD is crucial, not only from the point of view of improved understanding of the pathophysiology of AD but also for trial planning. Furthermore, it is important to develop cognitive tests that are sensitive to cognitive decline at the earliest clinical stages of the disease, and which can be used to track the progression of AD clinically or in a trial setting.

In section 1.8, I will review the literature on objective cognitive changes in the early stages of FAD. Given the evidence that objective cognitive changes can be detected in the asymptomatic stage of AD (Fox et al., 1998; Godbolt et al., 2005), I will present a brief overview of current concepts of preclinical and early clinical stages of AD. Before doing so, it is useful to review currently established biomarkers of AD given their role in the conceptualization of preclinical AD.

1.6 Biomarkers in AD

A biomarker is a physiological, biochemical, or anatomic parameter that can be objectively measured as an indicator of normal biological or pathological processes, or responses to a therapeutic intervention (Jack et al., 2018). As *in vivo* markers of underlying pathophysiology, biomarkers are a powerful tool in

studying the natural history of AD, particularly the period before the individual develops symptoms, namely the preclinical phase. The knowledge gained through biomarker studies have revolutionised our conceptualization of AD from a clinico-pathological entity to encompassing the spectrum of underlying pathophysiological disease process. Biomarkers are also invaluable in clinical practice by providing positive support for the diagnosis of AD (see Chapter 3). Here, I will review established AD biomarkers and their applications in clinical practice and research that are relevant for my study.

Currently AD biomarkers fall into three main categories: those of Aβ pathology, fibrillary tau and neurodegeneration (Jack et al., 2018). The two major modalities are imaging and cerebrospinal fluid (CSF) based biomarkers. CSF biomarkers measure the concentrations of proteins in the CSF that reflect the net result of rates of production and clearance. As such, they are best considered as markers of pathological states. Imaging measures, on the other hand, represent the cumulative effects of pathologic burden or damage over time (Jack et al., 2018).

Current biomarkers of Aβ pathologies are positive amyloid positron emission tomography (PET) (Klunk et al., 2004; Villain et al., 2012) and abnormally low CSF $A\beta_{42}$ level (Fagan et al., 2007; Mattsson et al., 2009). The latter is

indicative of a pathologic state that is associated with amyloid plaque formation whereas amyloid PET reflects amyloid plaque load over time (Jack et al., 2018). As mentioned in section 1.3, in AD, tau is hyperphosphorylated and misfolded. High levels of phosphorylated tau (p-tau) and total-tau (t-tau) have consistently been found in the CSF of AD patients (Olsson et al., 2016). While CSF t-tau is considered a non-specific biomarker of neuronal injury, p-tau is likely to reflect AD-related tau pathology in the brain (Jack et al., 2018). The combination of decreased CSF $A\beta_{42}$ together with increased t-tau and p-tau have been validated as the biomarker profile of AD (Barthélemy et al., 2020; Janelidze et al., 2020; Sato et al., 2018). This CSF biomarker profile has also proven useful in distinguishing AD from frontotemporal lobar dementia such as behavioural variant fronto-temporal dementia (FTD) and semantic dementia (Lleó et al., 2018; Paterson et al., 2018) (see Chapter 3).

Aβ and tau related biomarkers are considered pathophysiological (Dubois et al., 2014). Both are required for a neuropathological diagnosis of AD. In the 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) research framework, the presence of one or more Aβ biomarkers alone (CSF $A\beta_{42}$ and amyloid PET) also determines whether or not an individual is in the Alzheimer's continuum (Alzheimer's pathological change but not AD) (Jack et al., 2018). In contrast, neurodegenerative biomarkers- raised CSF t-tau (Blennow, 2017), hypometabolism on FDG PET (Jagust, 2010) and atrophy on

structural MRI (Desikan et al., 2009; Dickerson & Wolk, 2012; Fox, Warrington, Freeborough, et al., 1996; Vemuri et al., 2009)- are not specific for AD.

1.6.1 Structural imaging in AD

In both FAD and SAD, the typical pattern of atrophy involves the medial temporal lobes (MTL), paralimbic and temporo-parietal cortices. However, each clinical phenotype has its corresponding topographic signatures. Hence PCA is associated with a diffuse pattern of atrophy, particularly affecting the parietal and temporal cortices compared to greater MTL atrophy in amnestic cases (Frisoni et al., 2007; Harper et al., 2017; Möller et al., 2014). Within FAD, *APP* mutations tend to show more prominent medial temporal lobe atrophy whereas *PSEN1* mutations are more likely to demonstrate greater neocortical loss (Scahill et al., 2013) including parietal lobe involvement (Harper et al., 2017).

Visual rating scales that quantify the degree of MTL atrophy have shown to provide around 80% sensitivity and specificity in distinguishing individuals with AD from those without cognitive impairment, with slightly lower sensitivity and specificity for diagnosing individuals with amnestic MCI (DeCarli et al., 2007; Duara et al., 2008; Scheltens et al., 1992). However, as we shall see in Chapter 3, MTL atrophy alone is not specific for AD.

Although several structures- such as the amygdala, entorhinal cortex and parahippocampal gyrus- in the MTL show evidence of atrophy in the early stages of AD, the boundaries of the hippocampus are the easiest for human operators or automated algorithms to recognize (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Schott et al., 2003). Automated algorithms allows the hippocampus to be segmented much more efficiently compared to manual approach which is both labour intensive and operator dependent (Barnes et al., 2007; Jorge Cardoso et al., 2013; Leung et al., 2010). In Chapter 3, I used an automated segmentation method (STEPS) (Jorge Cardoso et al., 2013) to estimate the hippocampal atrophy rate. In Chapter 4, I used the same method to estimate hippocampal volume and examine the relationship between participants' performance on a visual short-term memory task and their hippocampal volume.

1.6.2 Temporal sequence and dynamics of biomarker changes

One of my research questions is to understand when objective cognitive changes occur in FAD. This has many parallels with biomarker studies that seek to elucidate the temporal sequence of various AD pathological processes. I will review these studies and discuss some of the methodological issues which are also relevant for my research.

The hypothetical model of AD biomarkers in an individual with pure AD is an extension of the hypothetical model of AD pathogenesis based on the amyloid hypothesis. It predicts that biomarkers related to amyloid pathology become abnormal first (CSF $A\beta_{42}$ and Pib PET), followed by those associated with tau-related neurodegeneration (CSF t-tau, FDG-PET and atrophy on MRI scan) and last by overt clinical symptoms and cognitive impairment (Jack et al., 2013).

The general sequence of biomarker progression proposed by the hypothetical model appears consistent with empirical findings in elderly individuals (Palmqvist et al., 2019; Villemagne et al., 2013) and in carriers of FAD mutations (McDade et al., 2018; Yau et al., 2015) albeit that here is evidence that the temporal progression of amyloidosis, metabolic decline and atrophy can be variable rather than strictly linear across the various regions of the cortex (Gordon et al., 2018).

It is notable that the length of follow-up in most multi-modal longitudinal cohort studies in FAD is typically two to three years (Gordon et al., 2018) (McDade et al., 2018). Ideally, we need multi-modal biomarker studies that are decades-long and span the entire disease -from the preclinical phase through to clinical stages.

Second, most of the biomarker studies on FAD relate the biomarker dynamics to expected age of symptom onset (EAO) (Benzinger et al., 2013; Gordon et al.,

2018; McDade et al., 2018; Yau et al., 2015) rather than actual age of symptoms as the latter is usually unknown. This approach is based on the assumption that there is a good correlation between an individual's age of symptom onset and the parental or mutation-specific age of symptom onset drawn from different kindreds with the same mutation (Ryman et al., 2014). However, there is likely to be imprecision in determining the parental age of symptom onset retrospectively (Godbolt et al., 2005). Variability between an individual's age of onset and parental age of onset has also been observed (Yau et al., 2015). Using prospectively confirmed age of symptom onset would introduce less uncertainly. This is the approach I used for my study presented in Chapter 2.

1.7 Research diagnostic frameworks and current conceptualization of early stages of AD

As my research focuses on the earliest cognitive changes in FAD, it is helpful to review the way in which early stages of AD are conceptualized in current research diagnostic frameworks of AD.

For many years, AD was considered a clinical-pathological entity. It was diagnosed in life as possible or probable AD and definitively at autopsy (McKhann et al., 1984). As a result, the term AD was taken to mean two different entities: archetypical clinical syndromes without neuropathologic

confirmation and AD neuropathology. More recently, in recognition of evidence supporting the likely existence of a long period where pathologies accumulate before the clinical diagnostic criteria are met, there has been a shift towards viewing both the pathophysiological process of AD and its clinical symptomatology as a continuum (Dubois et al., 2016; Jack Jr. et al., 2018; Sperling et al., 2011). To reflect this shift in the conceptualization of AD, both the NIA-AA (Albert et al., 2001; Jack Jr. et al., 2018; Sperling et al., 2011) and the International Working Group (IWG) (Dubois et al., 2010, 2014, 2016) have made recommendations for research diagnostic criteria of AD spanning the preclinical period up to dementia.

In the latest iterations of the NIA-AA and IWG research frameworks (Dubois et al., 2016; Jack Jr et al., 2018), preclinical AD is defined as cognitively normal individuals with biomarker evidence of abnormal amyloid *and* tau. In the IWG framework (2016), cognitively normal individuals who carry a pathogenic mutation for FAD (presymptomatic AD) are not considered as preclinical AD but may precede it, as are cognitively normal individuals with biomarker evidence of abnormal amyloid or tau but not both. The latter are considered as asymptomatic at risk for AD (Dubois et al., 2016).

The recently updated NIA-AA research framework (Jack et al., 2018) incorporates both a biomarker-based system (A/T/N) and a clinical staging

system related to the severity of cognitive impairment (Jack Jr et al., 2018; Jack, Hampel, Universities, Cu, & Petersen, 2016). The A/T/N biomarker classification system denotes the presence and absence of pathological evidence for Aβ, pathological tau and neurodegeneration. Two types of clinical staging systems are proposed: a syndrome categorical cognitive staging and a numeric clinical staging scheme. The former scheme divides the cognitive continuum into three categories- clinically unimpaired, MCI and dementia. In the latter scheme, a distinct transitional stage between asymptomatic and mildly impaired stage is proposed. Asymptomatic stage (stage 1) denotes clinically unimpaired individual who does not have objective or subjective evidence of subtle decline. Clinically unimpaired individual who has subjective or objective evidence of subtle decline is labelled stage 2. MCI is equivalent to stage 3. Mild, moderate and severe AD are assigned stage 4-6.

By combining both biomarker and clinical (behavioural) data, this approach is highly granular and may increase in the power of observational studies or treatment trials. It is intended to form the basis of personalized treatment where interventions are stratified according to the biomarker and clinical information available.

In practice, clinical research studies in FAD commonly classify participants based on symptomatology, for example, asymptomatic vs. symptomatic

mutation carriers (Cash et al., 2013; Liang et al., 2016; Ryan et al., 2013) or using Clinical Dementia Rating (CDR) (Morris, 1993). As symptoms of AD usually progress in a very gradual fashion, it is often challenging to date precisely when individuals transition from one clinical stage to the next, for example, from asymptomatic to symptomatic, or from symptomatic to MCI (see Chapter 2).

1.8 Cognition in AD: from general neuropsychology to experimental psychology

In the following sections, I am going to review the literature on the patterns of neuropsychological changes in FAD before turning to a specific aspect of memory function, visual short-term memory (VSTM). I will also briefly review the literacy on intra-individual variability as a potential early marker of cognitive dysfunction in AD.

1.8.1 Neuropsychological studies

Neuropsychology tests have the advantage of being widely available. As many tests have been standardized, their use allows for comparisons across different studies. A number of studies-most of them cross-sectional in nature- have been conducted using neuropsychology batteries to gain a broad picture of the pattern of cognitive changes in FAD.

In one of the earliest natural history studies in FAD, Fox et al. (Fox et al., 1998) followed a cohort of asymptomatic individuals who were at risk of developing FAD and who were within 5 years of the average age at which affected family members became affected. Ten of 63 at-risk individuals developed symptoms during the study. The most common presenting symptom was very mild episodic memory difficulties. Baseline neuropsychology tests (performed between 1 to 5 years before the onset of symptoms) showed that those who went on to develop symptoms already had, on average, lower scores on Recognition Memory Test (RMT) for words and performance IQ compared to those who did not. Two individuals performed in the impaired range ($<5^{th}$ percentile) in RMT for words (Warrington, 1984) at baseline. These findings led the authors to conclude that certain cognitive changes were detectable approximately 2-3 years before the onset of symptoms and 4-5 years before meeting diagnostic criteria for probable AD.

In a separate study, Ringman *et al.*, stratified mutation carriers (MCs) according to how close they were to the median age of dementia diagnosis in their family (Ringman et al., 2005). The study included 30 MCs and 21 non-mutation carriers (NCs) from 10 Mexican families with two distinct PSEN1 mutations. Some of the MCs had symptoms although the severity of which did not affect normal daily activities. As a whole, MCs were worse than NCs on a range of cognitive tests including the Mini-Mental State Examination (MMSE), Trail

Making test Part A & B, delayed recall of 10-word list and WAIS block design test. However, when the MCs were separated into three age groups in relation to the expected age of dementia diagnosis in the family, MCs were not worse than NCs on any test in the youngest 2 groups. This suggests that the differences between MCs and NCs group as a whole were mainly driven by those who were closest to expected age of dementia diagnosis. In the study, the mean age of those in the oldest group was on average 5.6 years younger than the medium age at dementia diagnosis in the family. Although the design of the study did not allow a more precise estimate of when cognitive impairment in MCs had started, the findings were in agreement with the study by Fox *et al*. in terms of the time frame when cross-sectional differences in neuropsychological tests performance are detectable between MCs and NCs.

In another early cross-sectional study investigating cognitive features of FAD MCs, Ardila *et al.* studied 40 MCs and 82 NCs from a large PSEN1 E280A kindred (Ardila et al., 2000). Again, some of the MCs had subjective memory symptoms but all were functioning normally. The two groups performed similarly on a broad range of neuropsychological tests. However, when MCs were separated into those with or without subjective memory complaints, the former performed significantly worse than the latter at a group level on a wide range of tests including the MMSE, naming of low frequency words, Wechsler Memory Scale, Rey Complex Figure, Digit Symbol test and “A” cancellation

tests. These findings suggest that wide ranging changes in cognition are already present even when individuals are only mildly symptomatic. This is corroborated by the findings of a recent cross-sectional study from the Dominantly Inherited Alzheimer Network (DIAN), discussed in further detail below (Storandt, Balota, Aschenbrenner, & Morris, 2014).

Due to the rarity of FAD, studies from individual research centres usually have relatively small samples sizes. In addition, lack of standardization in terms of clinical staging across different studies makes it difficult to directly compare results between studies.

DIAN was launched in 2009 as a multinational collaborative study of individuals at risk of FAD. Participants are carefully characterized using standardized clinical and biomarker measures across the participating research centres and undergo comprehensive longitudinal clinical, cognitive, imaging and other biochemical tests (Bateman et al., 2012).

The initial cross-sectional study from DIAN related baseline clinical, cognitive, imaging, CSF and blood biomarker results of 128 at-risk individuals with their expected age of symptom onset (EAO) (Randall J. Bateman et al., 2012). It found significant impairment in the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R) in MCs who were on average 10 years before

their EAO. However, as MCs already had impaired Clinical Dementia Rating (CDR) on average 5 years before their EAO, it is likely that the onset of objective decline in neuropsychological performance is much closer to the actual age of symptom onset.

Subsequently, DIAN published a more detailed paper on its baseline, cross-sectional neuropsychology results. It showed that on the whole, asymptomatic MCs (CDR 0) (n=89) performed significantly worse than NCs (n=96) in the delayed recall condition of the Logical Memory test and in semantic categorization accuracy (Storandt et al., 2014). Consistent with Ringman *et al.*'s findings discussed earlier (Ringman et al., 2005), there was a relationship between scores in a number of neuropsychology tests (Logical Memory, Digit Symbol and reaction time on an attention switch task) and EAO such that the closer an individual was to EAO, the worse their performance was. Given that the asymptomatic MCs group contained individuals who were at various temporal distance from developing symptoms, it is possible that the cross-sectional differences were mainly driven by those who were closer to developing symptoms. Echoing Ardilla et al.'s earlier findings (Ardila et al., 2000), widespread cognitive impairment was evident even when MCs were only mildly affected (CDR 0.5). Importantly, the pattern of cognitive impairment was similar to the typical profile of cognitive impairments seen in SAD

(Bäckman, Jones, Berger, Laukka, & Small, 2005; Chen et al., 2001) which lends support to using FAD as a pathological model for SAD.

To date, few studies have investigated individual trajectories of cognitive changes in FAD. In an early study, Godbolt *et al.* followed 19 FAD at-risk individuals from various clinical stages through to dementia diagnosis (Godbolt et al., 2004). Eight participants- who were also included in the current study- had presymptomatic neuropsychological assessments at least 6 months before onset of symptoms. At the initial presymptomatic assessment, impairments of cognition (defined as scores ≤ the 5^{th} percentile) were restricted to general intelligence and memory in 2 of the 8 individuals. At the first symptomatic assessment, 14 of 19 participants showed deficits in intelligence, 14 of 18 in memory and 5 of 17 were dyscalculic. The relative timings of the onset of symptoms and impaired scores in various cognitive tests were analyzed in a pairwise fashion, using the binomial exact test. Timing of the appearance of deficits in memory tests and IQ were not significantly different to that of the onset of symptoms. This implied that neuropsychological deficits were unlikely to have occurred significantly before individuals became symptomatic. However, as the sample size was small, it may have lacked the power to detect small differences in the timings.

More recently, DIAN published a longitudinal analysis of clinical, cognitive and biomarker data of 217 individuals with baseline results and repeated measures (McDade et al., 2018). The participants had an average of 2.7 visits with a mean follow-up period of 2 years. General linear Models were used for estimating rates of change in measures such as composite cognitive scores and hippocampal atrophy relative to his or her EAO at baseline. In MCs, the rate of change relative to baseline EAO showed linear association with 2 splines, i.e. 2 different linear phases, for the cognitive composite. The time point when the rates of change became significantly different between MCs and NCs was estimated to be -24 years for $CSF_{A\beta,}$ -2 years for the cognitive composite, -1 year for hippocampal volume and 0 for CDR sum of boxes with respect to EAO. The use of a composite cognitive score means that it is not possible to delineate the timing of pathological change of individual neuropsychological test. Nonetheless, the results suggest that, broadly speaking, measurable cognitive decline was likely to be detectable close to the EAO. Although the sample size in this study was relatively large, the average length of follow-up was still limited. This means that, for each participant, it was only possible to capture a fraction of his/her individual trajectory.

In another recent study examining longitudinal trajectory of neuropsychological function of FAD mutation carriers (Almkvist et al., 2019), the authors modelled the cognitive performance of 11 PSEN1 and 23 APP mutation carriers with

respect to EAO using a curvilinear mixed effect modelling approach (by including EAO and EAO^2 as fixed effect terms and producing trajectories with curved spline). Interestingly, for some cognitive tests including Rey Auditory Verbal Learning test, Digit symbol, Corsi block and block design, PSE1 and APP mutation carriers differed significantly in terms of their trajectories of cognitive change. The former group showed relatively rapid objective cognitive decline close to the EAO whereas the latter demonstrated much more gradual but earlier decline (Almkvist et al., 2019).

In both McDade and Almkvist's studies, EAO was an estimate based on the average parental age at symptom onset and previous reports of the age of symptom onset for the specific mutations in the literature. The actual age at which symptoms eventually occur in the MCs is likely to be different to the estimates due to variabilities both between kindreds and between individuals. In addition, the estimation of parental age of symptom onset may be subject to recall bias. In a case report of an *APP* mutation carrier (Godbolt et al., 2005), the author noted that when the individual eventually sought medical advice regarding his memory difficulties, he and his wife dated his cognitive difficulties back only two to three years, despite having previously commented on a decline of his memory six years earlier (as documented in prospectively collected research records).

In order to accurately determine the timing and order of the earliest cognitive changes, ideally, studies need to recruit asymptomatic at-risk individuals and follow them prospectively through to symptom onset and AD dementia.

1.8.2 Binding in Alzheimer's disease

In the previous section, I reviewed natural history studies which investigated the nature and timing of cognitive changes in FAD as measured by standard neuropsychological tests. Such observational studies can offer valuable insight into the pathophysiology of AD, particularly when combined with other biomarkers. As discussed in section 1.5, sensitive cognitive markers for AD are needed for screening and early diagnosis of AD and for tracking responses to treatments in clinical trials. However, standard neuropsychology tests may not be sufficiently sensitive in detecting cognitive decline due to AD during the earliest stages of the disease and may also be insufficiently sensitive to changes over time which is important for tracking disease progression and response to therapeutic interventions. However, novel psychological tests, informed by cognitive neuroscience research, may provide new inroads in the development of useful cognitive markers.

1.8.2.1 Concepts in binding research

In the following sections, I will review the concepts of binding in cognitive neuroscience and the evidence for binding failures in AD. I will also consider the neural mechanisms that are thought to underpin the impaired binding functions in AD and the potential clinical applications of cognitive tests based on binding research.

It is generally assumed that different object features such as shape, identity and location are separately represented in distributed neural structures. Similarly, memory entries related to time, place, people and actions of an event are sets of separate features. Binding refers to the cognitive process where stimulus features or memory traces come together and form associations. As a result, elements belonging to the same cognitive "event" are bound and separated from other features belonging to a different "event". Binding is a basic cognitive process which occur in all levels of cognition, from thinking to remembering to semantic knowledge representation. By the same token, some form of binding is also required in all aspects of memory, from encoding, consolidation to retrieval (Zimmer, Mecklinger, & Lindenberger, 2006).

An unresolved question in the field of binding research is whether qualitatively different types of binding exist and whether they are served by different neural structures. In one view, distinction of different types of binding are made. Treisman proposed that object features representing specific objects are bound

in an object file or object token which become the units of both working memory and long-term memory (Kahneman, Treisman, & Gibbs, 1992). Such intra-item binding of features such as colour and shape is called conjunctive binding.

Binding between objects is required when there are multiple objects. This involves the binding of object files themselves. Where relational information between items or item and context is relevant, this form of binding is called "relational binding". Relational binding may include binding of a wide range of features including cross-modal information such as spatial or temporal relational information.

Strictly speaking however, all forms of memory may be considered relational. Hence the distinction between relational memory and item memory is only a matter of degree (Cabeza, 2006). Nonetheless, different levels of the binding hierarchy may be associated with different neural mechanisms. Binding at a low level (e.g. perceptual level) may be provided by the activities of the feature-selective neurons themselves, with relatively little additional neural support. Higher, complex between-item binding may rely more on the support of a well-functioning prefrontal cortex (Cabeza, 2006). Individuals with selective bilateral hippocampal atrophy has been shown to have a selective deficit in association

memory tests (a form of relational memory) but largely intact memory for intra-item associations (conjunctive binding) (Mayes et al., 2004).

1.8.2.2 Examples of binding failures in AD

Decline in episodic memory is a cardinal feature of AD in the majority of individuals (Greene et al., 1996; Hodges, 2000) (see section 1.4). Episodic memory refers to the process whereby memory traces related to time, place, people and actions of an event form associations in order to constitute distinctive episodes. Episodic memory is regarded as a type of relational memory (Underwood, 1969). It is thought that the MTL, and in particular, the hippocampus, plays a key role in relational memory (Cashdollar, Duncan, & Duzel, 2011; Watrous, Tandon, Conner, Pieters, & Ekstrom, 2013). As the MTLs are one of the earliest regions to be affected by pathology of AD (see section 1.3), it is therefore unsurprising that episodic memory difficulty is a common early feature of AD.

Recently, Parra *et al*. showed that individuals with both SAD and FAD had a specific deficit in binding intra-item object features such as colour and shape in short-term memory (Parra et al., 2009, 2010). This type of binding deficits in visual short-term memory (VSTM) was also detectable in asymptomatic FAD mutation carriers who performed normally on standard neuropsychology tests.

Unlike associative or relational memory, intra-item object features binding is considered to be relatively independent of the functions of the MTL (Mayes et al., 2004; Parra et al., 2014; Parra et al., 2015). These findings raise the question of whether binding deficits in general is an early feature of AD, regardless of whether the MTL was involved.

In the following sections, I shall review the literature on cognitive tests which have been developed to probe relational binding and conjunctive binding function in AD.

1.8.2.2.1 Associative (relational) learning tasks

Associative learning tasks involve learning the associations between stimuli. Examples include the CANTAB Paired Associates Learning (PAL) test which requires learning the association between objects and location (Sahakian et al., 1988) and verbal paired associate learning tasks which involve learning the association between two words, for instance those in Weshsler Memory Scale (Wechsler, 1987) and the Camden Paired Learning (CPAL) test (Warrington, 1996). Associative learning is thought to dependent on functional integration in the MTL structures, particularly the hippocampus, and cortical regions (Mayes et al., 2007; Murre et al., 2006). It has been suggested that these tasks may be useful for detecting memory changes in the early stages of AD (Fowler et al.,

1995; Fowler et al., 1997; Fowler et al., 2002; Lee et al., 2003; Lowndes & Savage, 2007; Pike et al., 2013; Swainson et al., 2001). As my study in Chapter 4 investigated object-location binding in visual short-term memory (VSTM), I will therefore limit my review of associative learning tasks to one in the visual domain, i.e. the CANTAB PAL task.

The CANTAB PAL test

In an early study investigating visuospatial memory and learning in AD, Sahakian and colleagues compared a group of 12 patients with probable AD (McKhann et al., 1984) with age and IQ-matched normal controls, as well as individuals with Parkinson's disease (Sahakian et al., 1988). In a matching-to-sample test, participants were shown a complex abstract pattern (the sample) in the centre of the screen and were required to match it to 1 of 4 choice patterns. Individuals with AD were not impaired at the simultaneous-matching-to-sample condition compared to controls. However, their performance declined rapidly as a function of increased delay, resulting in performance at chance level at 16 seconds. The discrepancy in the simultaneous and delayed conditions suggests that whilst the AD individuals were able to process the abstract visual pattern, their ability to retain the pattern in VSTM is impaired.

In the CANTAB PAL test, the participants were also required to learn a set of pattern-location associations varying in number (of locations) from 1 to 8. AD patients were severely impaired in the test both in terms of the total trials taken to criterion scores and the errors made.

Following these findings of impaired learning of pattern-location associations, a series of studies investigated the utility of the CANTAB PAL test in diagnosing AD (Fowler, K. S., Saling, M. M., Conway, E. L., Semple, J. M., Louis, 1997; K S Fowler et al., 1995; Kylie S. Fowler et al., 2002; Lee et al., 2003; Swainson et al., 2001).

Swainson (Swainson et al., 2001) compared groups of individuals with clinically probable AD, questionable dementia (QD) (similar to current definition of MCI in their characteristics), major depression and healthy controls on a number of tests of memory, attention and executive function. Scores on the visuo-spatial PAL test accurately classified individuals as belonging to either the AD or the combined depression/control group with only 7% overlap (compared with 27% for logical memory recall).

Interestingly, the PAL 6-pattern score (error and number of trials to criteria) clearly detected two distinct sub-groups of participants with QD: those who performed similarly to probable AD individuals and those whose performance

were more like that of control subjects. The authors concluded that it was likely that those QD individuals who performed poorly on the PAL were at the early stages of AD. In contrast, although the QD cohort and combined depression/control group differed significantly in their mean scores in several other tests such as the delayed matching-to-sample test, Logical memory recall, category fluency and Alzheimer's Disease Assessment Scale-Cognitive Subscale, there was considerable overlap of scores at the individual level. However, as it was a cross-sectional study, one could not be certain of the eventual clinical outcome of the QD sub-group who performed similarly to the probable AD individuals.

To address this issue, Fowler *et al*. followed 21 individuals with QD every 6 months over 2 years along with 19 controls and 16 participants with early AD. The participants were assessed on the CANTAB PAL task, the match-to-sample tests and standard neuropsychology batteries. Most of the QD individuals performed similarly to controls at baseline. However, results of repeated assessments over time demonstrated two sub-groups of QD individuals from the 6 months' mark: those who clearly declined on the PAL in a progressive fashion ("deteriorating" group) and those who continue to perform similarly to controls ("stable" group). By the end of the 2-year study period, the individuals in the QD-deteriorating subgroup all fulfilled clinical diagnostic criteria for probable AD and there was no significant difference between them and the early AD

group on the PAL test. Importantly, unlike many other neuropsychology tests included in the study, there was little overlap in the performance of the QD-deteriorating group with either the age-matched normal controls or the QD-stable group at the individual level. Further, the PAL test appeared to be sensitive to change over time for individuals progressing from MCI to mild AD, raising the possibility that it may have utility in tracking responses to treatment intervention in the MCI stage (Fowler et al., 2002).

Of note, in this study, other PAL tests were not as discriminative as the CANTAB PAL test in differentiating between the QD -stable and -deteriorating subgroups. For example, the two subgroups did not differ in the visual paired associate learning subtest of the Wechsler Memory Scale Revised (WMS-R) until at the 24 month mark (Fowler et al., 2002). It is clear, therefore, the sensitivity and specificity of different associative learning tests are not equivalent.

The neural basis of the CANTAB visuospatial PAL task has been examined in a functional MRI study (de Rover et al., 2011) which included individuals with MCI and healthy controls. Activation of the hippocampus was demonstrated during the encoding phase of the task (involving association of an object with a location). People with MCI had decreased hippocampal activation with increasing memory load, whereas healthy controls showed the opposite pattern.

In a separate study, impaired performance on the CANTAB PAL correlates with hippocampal volume loss in MCI (Kéri, Szamosi, Benedek, & Kelemen, 2012). Another neuroimaging study also found that MTL structures play an important role in associating different stimuli (in this case objects and scenes) when retrieving them from memory (Staresina, Cooper, & Henson, 2013). Together, these findings suggest that the MTL regions make an important contribution to performance on PAL tasks.

1.8.2.2.2 Conjunctive binding in short-term memory

In contrast with *relational association* tasks such as the CANTAB PAL which require learning associations between items, *conjunctive binding* refers to tasks which involve binding information such as colour, orientation and shape into integrated representations or unified objects. Unlike relational association, conjunctive association may rely less on medial temporal lobe structures and depend more on the interactions between neocortical regions (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000).

Parra and colleagues have studied conjunctive binding in AD extensively (Parra et al., 2009, 2010; Parra, Saarimäki, et al., 2015). One of their earliest studies investigated object-colour binding in the verbal domain in short-term memory (STM). Compared with healthy controls, individuals with AD were significantly

poorer in the binding condition than in conditions assessing memory for objects or colours alone or objects and colours unbound. This was the case even after controlling for memory load across conditions and allowing for differences in overall memory capacities between the groups (Parra et al., 2009).

In a follow up study, the authors went on to show that deficits in shape-colour conjunctive association could also be identified in the visual domain in both symptomatic and asymptomatic mutation carriers for the *PSEN1* E280A mutation. Asymptomatic carriers performed similarly to healthy controls in the shapes-only and colours-only conditions. However, they could not remember the binding condition as well as the controls. On average, asymptomatic carriers and healthy controls did not differ significantly in scores on any of the standard neuropsychological tests, including the PAL task (David Wechsler, 1945). It is noteworthy, however, that the PAL and the shape-colour binding tasks were the two tests in which the greatest proportion of asymptomatic carriers showed an impairment (Parra et al., 2010).

To be a useful biomarker for AD, it is important that the biomarker has high specificity. Della Sala et al. reported that colour-shape conjunctive binding was specifically affected by AD relative to other dementias such as frontotemporal dementia and Lewy body dementia. This deficit was observed even when memory for single features, namely colour and shape, was at a similar

level across individuals with different types of dementia (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012). STM colour-shape conjunctive binding also appears to be relatively insensitive to the effects of aging and depression (Brown et al., 2017; Brown & Brockmole, 2010).

Evidence for the neural mechanisms supporting the STM conjunctive binding have come from both behavioural data and imaging studies. Parra *et al*. reported a case of an individual with right hippocampal damage due to stroke who showed significant relational STM binding deficits but preserved performance on conjunctive binding. The results suggest that relational and conjunctive binding functions dissociate in short-term memory and that conjunctive binding does not require an intact hippocampus (Parra, Fabi, et al., 2015). This is in keeping with the existing body of literature on binding (Baddeley et al., 2010, 2011; Piekema et al., 2010).

An fMRI study which investigated the brain regions supporting the encoding and maintenance of object features (colours or shapes) and bindings of colour and feature in healthy volunteers appear to support such behavioural data. Regions within the parietal, temporal and occipital cortex, but not within the prefrontal cortex or the medial temporal lobe, appear to correlate with the integrated object binding function (Parra et al., 2014).

Colour-shape conjunctive binding in the visual STM and associative memory tests for words have also been shown to have different neural correlates in a diffusion tensor MRI study involving individuals with FAD, asymptomatic mutation carriers and non-carrier controls (Parra, Saarimäki, et al., 2015). White matter integrity in frontal regions and in the anterior part of corpus callosum accounted for a significant proportion of variance of colour-shape binding performance whereas white matter integrity in frontal region and in the hippocampal part of cingulum bundle accounted for a significant proportion of variance in performance on the PAL task in the symptomatic FAD individuals.

Taking these studies together, AD is characterized by deficits in both relational and conjunctive binding. The former is likely to be underpinned by dysfunction of the medial temporal lobe. However, studies investigating relational binding in AD have usually been conducted using a delay of minutes. Recent research suggests that the MTL and hippocampus in particular, are critical in relational binding in both short-term and long-term. Therefore, one would predict that relational binding in STM would also be impaired in AD. This is the subject of my study in Chapter 4 where I investigate whether FAD mutation carriers show a deficit in object-location binding in VSTM.

1.8.3 Intra-individual variability

Traditionally, measuring cognitive functioning in neurodegeneration has focused on changes in individuals' mean level of performance. There is, however, also an interest in using qualitative measures such as intra-individual variability (IIV) to capture changes in cognitive function (Costa, Dogan, Schulz, & Reetz, 2019). Greater inconsistency, particularly in reaction time (RT) has also been found to correlate with lower levels of cognitive performance such as general intelligence (Rabbitt, Osman, Moore, & Stollery, 2001), working memory, episodic memory and crystallized abilities (Hultsch, MacDonald, & Dixon, 2002). On the other hand, IIV appears to be a marker of cognitive functioning independent of the level of performance (Anderson et al., 2016; Hultsch et al., 2002; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Li, Aggen, Nesselroade, & Baltes, 2001).

As a result, there has been considerable interest in exploring the use of this qualitative measure as an early marker of cognitive decline in neurodegeneration (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Christ, Combrinck, & Thomas, 2018; Costa et al., 2019; Dixon et al., 2007; Gamaldo, An, Allaire, Kitner-Triolo, & Zonderman, 2012; Lu et al., 2020; MacDonald, Hultsch, & Dixon, 2003; Tales et al., 2012). The two main types of IIV are dispersion (IIV-D) and inconsistency (IIV-I). The former refers to variation across different cognitive domains within a single individual at a given time (Holtzer, Verghese, Wang, Hall, & Lipton, 2008; Kälin et al., 2014) and

the latter is defined as variability within a single person across multiple trials in one session or over time (Costa et al., 2019; Stuss et al., 2003).

As my study in Chapter 2 investigated year-to-year variability in cognitive performance in FAD mutation carriers, I will limit my review to literature on IIV-I only. Most studies that investigated IIV-I in the context of aging and AD have based the measurement on repeated trials of a task administered in one session or across short intervals, referred to henceforth as short-term IIV-I. Variability in reaction time (RT) is most widely studied (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Christ et al., 2018; Hultsch et al., 2000; Lu et al., 2020; MacDonald et al., 2003; Tales et al., 2012), followed by accuracy scores on tests probing memory (Burton et al., 2006; Christ et al., 2018; Hultsch et al., 2000), attention (Duchek et al., 2009) and executive functions (Bielak et al., 2010; Stuss et al., 2003). In general, individuals with AD or mild cognitive impairment (MCI) show increased short-term IIV-I compared to cognitively normal controls (Burton et al., 2006; Christ et al., 2018; Lövdén, Li, Shing, & Lindenberger, 2007; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007). The degree of inconsistency has also been shown to correlate with measures of severity of impairment (Burton et al., 2006).

Increased IIV-I at baseline has been shown to have predictive value for cognitive deterioration in community-dwelling older individuals over and above

RT performance level *per se* (Bielak et al., 2010; Kochan et al., 2016; MacDonald et al., 2003) and the progression of individuals with MCI to dementia (Haynes, Bauermeister, & Bunce, 2017; Tales et al., 2012). In the study by Tales *et al*., high IIV-I appears related to an increased probability that an individual with amnestic MCI will become demented within 2.5 years, rather than to amnestic dysfunction *per se* (Tales et al., 2012). Recent studies have also found associations between increased short-term IIV-I in cognitive performance and biomarker evidence of AD. For example, in a population based study, cognitively normal Aβ-positive participants had more variable RTs than Aβ-negative individuals, despite having similar mean RTs (cross-sectionally) (Lu et al., 2020).

Is important to note that increased IIV is not specific to AD. Increased IIV-I has also been associated with non-AD dementia (Murtha, Cismaru, Waechter, & Chertkow, 2002), head injury (Stuss et al., 1994) and attention deficit hyperactivity disorder (Kuntsi *et al*., 2012). This suggests that it may be a non-specific marker of cognitive impairment. Several potential neural mechanisms have been proposed including impaired executive control (Hultsch *et al*., 2002; Stuss *et al*., 2003), reduced dopamine neurotransmitter levels and compromised coordination of neural networks as reflected in impaired deactivations of the default mode activity (Kelly *et al.*, 2008; MacDonald *et al*., 2009). All of these

processes have also been described in AD (Greicius *et al*., 2004; Mann *et al*., 1987; Nedjam *et al*., 2004; Ringman *et al*., 2005; Zhang *et al*., 2010).

As most longitudinal natural history studies investigating cognitive changes in aging and AD assess participants at yearly intervals, it is useful to ascertain if increased variability on a longer time scale (for instance annually) is also associated with cognitive decline in individuals in preclinical or very early stages of AD. In a case-control study from the Baltimore Longitudinal Study of Aging, Gamaldo *et al.* found that year-on-year fluctuations in several cognitive tests were present around five years before individuals developed cognitive impairment due to SAD (Gamaldo *et al*., 2012). As it is possible to follow FAD mutation carriers from an asymptomatic stage, it would be particularly interesting to investigate whether increased IIV-I is also a feature of cognitive decline in FAD and if so, the relationship between IIV-I and the onset of objective cognitive decline. To my knowledge, there have been no systematic investigations into IIV-I at yearly intervals in FAD individuals transitioning from healthy cognition to dementia.

1.9 Objectives of the thesis

The overarching objective of this thesis is to explore the earliest cognitive features of FAD with particular emphasis on memory functions.

Specific thesis aims:

1. Assess the timing and qualitative changes of neuropsychological decline in FAD across a broad range of cognitive domains using a well characterised longitudinal cohort with a focus on changes in the preclinical and early clinical stages of the disease.

2. Assess visual short-term memory in FAD mutation carriers using a novel experimental paradigm probing the binding of object identity and location. Additionally, to investigate the association between binding performance and hippocampal volumes.

3. Describe an individual with a novel *MAPT* mutation. This case report illustrates the diagnostic challenges of a progressive amnestic syndrome and highlights the clinical, neuropsychological and structural imaging features that help with the differential diagnosis.

Chapter 2. COGNITIVE FUNCTION IN INDIVIDUALS AT RISK OF FAMILIAL ALZHEIMER'S DISEASE

2.1 Introduction

As discussed in section 1.7, convergent evidence supports the notion of a long presymptomatic period where pathologies of AD accumulate (Dubois et al., 2010; Sperling et al., 2011). There is also increasing interest in prevention trials in asymptomatic individuals who either already have evidence of AD pathology or are at risk of developing AD such as those who are carriers of pathological mutations responsible for FAD (Mills., 2013; Reiman et al., 2011; Sperling 2014). Delineating the earliest cognitive changes in FAD is not only important for understanding the pathophysiology of AD but also crucial for trial planning. The main objective of this study is to determine the timing and sequence of objective cognitive decline in FAD mutation carriers with respect to the onset of symptoms, the earliest clinical manifestation of the disease (see Ardila et al., 2000).

Most previous studies investigating cognitive functions in FAD have taken a cross-sectional approach, typically comparing performance of mutation carriers with controls before they manifest symptoms or develop dementia (Acosta-Baena et al., 2011; Arango-Lasprilla, Cuetos, Valencia, Uribe, & Lopera, 2007; Ardila et al., 2000; Randall J. Bateman et al., 2012; N. Fox et al., 1998; J M

Ringman et al., 2005; Storandt et al., 2014) (see section 1.8.1). These studies have demonstrated the presence of objective cognitive impairment in cohorts of asymptomatic and mildly symptomatic FAD mutation carriers. However, group differences between mutation carriers and controls could be due to the characteristics of those who were close to symptom development (or who were already symptomatic) rather than the entire mutation carriers' group. In order to ascertain the timing of objective cognitive changes with greater certainty, longitudinal studies following asymptomatic mutation carriers through symptom onset and the diagnosis of dementia are needed. To date, only a small number of such studies have been conducted (Almkvist et al., 2019; Godbolt et al., 2005; Godbolt et al., 2004) (see section 1.8.1).

In my clinical practice, I have observed that some mutation carriers appear to experience fluctuating subjective cognitive symptoms and/or show fluctuations in objective cognitive performance in the early symptomatic phase. These observations echo the longitudinal clinical and neuropsychological findings of an *APP* mutation carrier who had been followed up for over a decade (Godbolt et al., 2005). The authors noted learning effects as well as year-to-year fluctuations in the individual's performance on several cognitive tests. In a cross-sectional study conducted by Acosta-Baena et al., 450 FAD mutation carers were categorised to 4 clinical stages (asymptomatic pre-MCI, symptomatic pre-MCI, MCI and dementia) according to whether they had subjective memory

complaints and impairment in activities of daily living (Acosta-Baena et al., 2011). The affected cognitive domains showed some variability in the early stages. For example, individuals who met the criteria for asymptomatic pre-MCI performed worse than controls in memory, language and abstract reasoning. However, those who met the criteria for the next clinical stage, symptomatic pre-MCI, showed better performance in these domains than those in the asymptomatic pre-MCI stage. Although the findings were not based on intra-individual longitudinal results, they hinted at non-linear trajectories of cognitive changes in FAD. In a case-control study from the Baltimore Longitudinal Study of Aging, Gamaldo *et al* found that year-on-year fluctuations in several cognitive tests were present around 5 years before individuals developed cognitive impairment (Gamaldo et al., 2012). All these findings raise the possibility that year-on-year fluctuations in cognitive performance may be an early marker of cognitive decline in FAD. As discussed in section 1.8.3, most research on IIV-I in aging and neurodegeneration has focused on short-term fluctuations in performance. However, most longitudinal natural history studies assess individuals at longer intervals, commonly yearly. The second aim of the study is therefore to investigate whether increased year-to-year fluctuations in neuropsychology performance is a marker of cognitive decline in FAD.

In this retrospective study, I was careful to ensure that only participants who were cognitively well at baseline were recruited (see section 2.2.1). I used

prospectively collected collateral information to determine when mutation carriers started manifesting symptoms to increase the confidence of this estimate.

To evaluate the timing of pathological cognitive decline, we used a change point model (Hall et al., 2000) to estimate the time when the rates of change in a given neuropsychology test diverged between mutation carriers and controls relative to symptom onset. The model allows us to control for any baseline differences in cognitive abilities between mutation carriers and controls, variable numbers of observations and practice effects associated with multiple assessments (see Godbolt et al., 2005). It is relatively simple to apply and has been widely used to examine patterns of cognitive decline (Grober et al., 2008; Hall et al., 2000; Howieson et al., 2008; Wilson et al., 2012).

2.2 Methods

2.2.1 Participants

Participants for the study were recruited from an ongoing longitudinal FAD study at the Dementia Research Centre, University College London (UCL) which receives referrals from across the UK (Fox et al., 1998). Individuals were recruited into the observational study if they had at least two family members in two different generations, including a first-degree relative, affected with AD.

Pathological genetic mutations in *PSEN1* or *APP* genes were confirmed in all pedigrees and at least one affected member of each family had undergone confirmatory post-mortem neuropathological examination. Fifty-six individuals were included in the current study. Of these, 19 individuals were asymptomatic at baseline and developed symptoms due to AD during the course of the study and had confirmatory positive genetic results. Henceforth they are referred to as converters. Thirty-seven at-risk individuals were included as controls. These consisted of 31 participants who had negative genetic tests and six whose genetic status could not be confirmed but who had remained well for at least 10 years after the mean age of symptom onset in the family and were therefore considered extremely unlikely to be mutation carriers. In these six individuals, research genetic blood sample was either unavailable or failed to yield a result on technical grounds (most likely due to the age of the samples). See section 2.2.5 Genetic testing. Also see Table 2.1 for detailed descriptive information of the cohort. All participants had at least two assessments with converters having had at least one assessment before and at least one after they developed symptoms. All participants in the longitudinal FAD observational study were included in the current study if they fulfilled the criteria outlined above for converters and controls. Data included in the current study were collected from 1990 to 2013.

Written informed consent was obtained from all participants and the study received ethical approval from the local ethics committee (University College London/University College London Hospital).

2.2.2 Protocol

Participants were assessed annually in most cases. Each assessment consisted of semi-structured interviews with the participant and an informant, a neurological examination, neuropsychological assessments and a structural MRI scan. Interviews were undertaken with the participants and their informants separately to probe for the presence of any decline in participants' cognition and behaviour.

2.2.3 Definition of "onset of symptoms" and clinical "Alzheimer's disease"

Date of onset of clinically relevant symptoms in converters was determined through consensus decision after notes review by two neurologists (NF, YL) and a psychologist (SC). The onset of symptoms was defined as the time point when progressive cognitive symptoms attributable to AD were reported to occur by either the participants or their informants, whichever was earlier. A range of symptoms were accepted as clinically significant when they occurred in a progressive manner. Examples include repetitiveness, difficulty in learning new information and topographical disorientation. Care was taken to date the onset of

symptoms to when they became persistent and progressive in order to reduce the noise of non-specific symptoms. Contemporaneous research neuropsychology results did not play any part in determining the timing of the onset of symptoms for the purpose of this study. Thus, I avoid the circularity of using neuropsychological assessment to define symptom onset and then attempting to determine the timing of cognitive decline in relation to the onset of symptoms. Date of dementia diagnosis, different to date of symptom onset, was taken as the date when the individual received a clinical diagnosis of AD according to established diagnostic criteria (McKhann et al., 1984).

2.2.4 Neuropsychology

Neuropsychological assessments were performed on the same day as clinical assessments as part of the research protocol. The tests included a short version of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) consisting of four verbal subtests (vocabulary, arithmetic, digit span and similarities) and three performance subtests (block design, picture completion and picture arrangement) from 1990 until 2007 and subsequently the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) consisting of two verbal subtests (vocabulary and similarities) and two performance subtests (block design and matrix reasoning); the Recognition Memory Test (RMT) (Warrington, 1984); the Camden Paired Associate Learning (CPAL) (Warrington, 1996); digit span (Wechsler, 1987);

the Graded Difficulty Arithmetic Test (GDAT) (Jackson and Warrington, 1986); the Graded Difficulty Spelling Test (GDST) (Baxter and Warrington, 1994); the Graded Naming Test (GNT) (McKenna and Warrington, 1983); the synonym comprehension test (Warrington et al., 1998); silhouettes and cube analysis from the Visual Object and Spatial Perception battery (VOSP) (Warrington and James, 1991); "O" cancellation and number copying from the Psychomotor Speed Tests (Willison and Warrington, 1992). The National Adult Reading Test (NART) (Nelson, 1991) was administered to obtain an estimate of pre-morbid intellectual functioning. Over the 20-year period, a variety of different tasks sensitive to executive dysfunction were used but none consistently. These included Cognitive Estimates (Shallice and Evans, 1978), phonological verbal fluency test (Spreen and Strauss, 1998), Modified Card Sorting Test (MCST) (Nelson, 1976) and the Hayling test (Burgess and Shallice, 1997). The MCST, which was administered most consistently, was not felt to be sufficiently sensitive to longitudinal changes once the participants have learned the solutions (Bird et al., 2004; Burgess, 1997; Lezak, 1995; Wilson et al., 2000). Therefore, MCST was included in the analysis of baseline results only (see 2.2.6 statistical methods). Administration of the CPAL was limited to the years between, and inclusive of 1994 and 2008 due to changes in the neuropsychology assessment battery used and 42 (out of a total of 56) participants had more than one assessment that included the CPAL. We therefore analysed this subgroup separately in terms of demographic and neuropsychological characteristics (Table 2.1).

2.2.5 Genetic testing

Participants who became symptomatic during the study were reviewed in a specialist cognitive disorders clinic and underwent confirmatory clinical genetic testing. As part of the study protocol, all participants donated blood samples for research. Research genetic testing was performed in at-risk individuals who remained asymptomatic for the duration of the study. Individuals who were found to be gene-negative were eligible to be controls. See section 2.2.1 for further details. Participants and researchers were blinded to the results of research genetic testing except for the study statistician (JN) who did not have contact with the participants and was blinded to their identity.

2.2.6 Statistical analysis

2.2.6.1. Cross-sectional analysis

Cross-sectional comparisons between controls and converters were made for all neuropsychology tests undertaken at the baseline visit. Apart from the MCST, comparisons were also made between converters at the first visit after symptom onset and controls at matched time since baseline assessment; and between converters at the first visit after diagnosis of AD and controls at matched time since baseline assessment. Unpaired t-tests were used for these cross-sectional

analyses, with Satterthwaite's adjustment for unequal variance where necessary. In the converters group, the association at baseline between each neuropsychological score and temporal distance to development of symptoms was evaluated using Spearman's rank correlation coefficient since it was expected that the association might not follow a linear trend. P-values are reported uncorrected for multiple comparisons, as this interpretation was considered most appropriate in light of the strong *a priori* expectation of differences in cognition between controls and converters.

2.2.6.2 Longitudinal analysis: change point estimation

Longitudinal change in each neuropsychological test was evaluated using linear mixed models with a change point, which allowed controls, and converters to follow a different trajectory for change over time. In this model, controls and converters initially share a common rate of change in neuropsychological test score for each additional year of age. After a point in time relative to symptom onset, converters transition to a different rate of change, reflecting the start of cognitive decline. The time at which they transition to a new rate of decline is called the change point and is estimated from the data using a profile likelihood method (Hall *et al*., 2000). This method involves fitting a maximum likelihood linear mixed model at each potential change point every 0.1 years between 7 years before symptom onset to 7 years after symptom onset, covering the period

when most assessments took place in converters. The time point with greatest likelihood is taken as the maximum likelihood estimate of the change point and the coefficient values for the predictor variables are the maximum likelihood estimates for these parameters. The 95% confidence interval for the change point is taken from models with likelihood ratio above the critical value. Scores for "O" cancellation and digit copying were right skewed, so the inverse was used for modelling. All other neuropsychological test scores were examined on the original scale. Predictor variables were age (centred on mean at baseline), an indicator variable for affected group membership, time to change point and sex. NART IQ at baseline (as a proxy for premorbid IQ) was used as a predictor in models for Verbal and Performance IQ. All models included a random intercept for participant to take into account the correlation in score between different visits in the same individual. Random coefficients for age, time to change point and affected group membership were also fitted where data permitted. Our longitudinal modelling approach included all assessments where the participants completed the neuropsychological test of interest and assumed that data were missing at random rather than completely at random. Hence it was assumed that missing scores depended on scores in that participant at other time points, their age and sex, participant group status and time from symptom onset (in converters).

2.2.6.3 Longitudinal analysis: intra-individual variability

The initial change point model allowed for one common residual variance, which assumes that IIV-I in scores remains constant over time. To explore whether IIV-I in score changes as participants approached symptom onset, a further change point model was estimated for each neuropsychological test. This model allowed residual variance to differ between three time periods: controls and converters more than two years before symptom onset, converters less than two years before symptom onset, and converters following symptom onset. These three residual variances reflect the variance not accounted for by the random and fixed effects included in each model. A likelihood ratio test was used to assess evidence of heterogeneous variance by comparison to the simple change point model with shared residual variance. Where residual variance is higher, this reflects a wider dispersion of observed scores around the fitted line for change in score over time and suggests possible increased IIV. This approach has been used previously in sporadic Alzheimer's disease to assess IIV (Gamaldo et al., 2012).

To examine whether results were sensitive to the inclusion of participants close to symptom onset at baseline, analyses were repeated excluding any converters who were within one year of symptom onset at the baseline assessment.

2.3 Results

2.3.1 Participant characteristics

Fifty-six at-risk individuals fulfilled the entry criteria and were recruited into the study. Participant characteristics are given in Table 2.1: 19 were converters and 37 were controls. Baseline data of six of the 19 converters and 26 of the 37 controls have previously been reported (Fox et al., 1998). Longitudinal data of eight converters – some of whom were amongst the six individuals whose baseline data had been published- have previously been reported (Godbolt et al., 2004). All converters presented with amnestic symptoms initially. The baseline assessment for converters was on average 5.0 ± 4.8 (mean ± S.D.) years before onset of symptoms and 8.4 ± 5.6 years before AD diagnosis (Table 2.1). A substantial proportion of converters had multiple assessments in the period leading up to symptom onset and in the years following symptom onset, with a quarter having at least one assessment more than 7 years before symptom onset and a quarter having at least one assessment more than 6 years after symptom onset. Half of all converters had at least one assessment more than 3 years before and 4 years after symptom onset. At their baseline assessment, three of the 19 converters were within one year of symptom onset.

The subgroup of 42 participants (28 controls and 14 converters) who completed the CPAL on more than one visit had a similar proportion of male participants and was of similar age at baseline in comparison to the sample as a whole.

Converters in this subgroup were at a similar temporal distance to symptom onset at baseline compared to converters in the whole sample (Table 2.1).

The distribution of the mutations in the 19 converters is as follows: 4 *APP* V717G, 4 *APP* V717I, 4 *PS1* M139V, 2 *PS1* Intron 4 and 1 each of *APP* V717L, *PS1* E280G, *PS1* F283L, *PS1* L171P and *PS1* L250S.

Table 2.1: Characteristics of participants.

	Controls	Converters
All participants	N=37	N=19
Number (%) male	15 (41%)	9 (47%)
Age at initial assessment (years) Mean ±SD, range	42.9 ±8.4, 29.3 to 55.5	39.8 ±6.6, 26.9 to 50.5
Number of assessments Mean ±SD, range	5.9 ±4.1, 2 to 19	8.5 ±3.8, 3 to 15
Length of follow-up (years) Mean ±SD, range	8.1± 6.4, 0.59 to 22.7	10.0 ± 5.2, 3.1 to 20.7
Time from initial assessment to onset of symptoms (years) Mean ±SD, range		5.0 ± 4.8, 0.4 to 18.8
Time from initial assessment to AD diagnosis (years) Mean ±SD, range		8.4 ± 5.6, 1.2 to 21.3
Time between symptom onset and AD diagnosis (years) Mean ±SD, range		3.4 ±1.8, 0.8 to 7.5
CPAL subgroup	N=28	N=14
Number (%) male	11 (39%)	7 (50%)
Age at initial assessment (years) Mean ±SD, range	42.1 ±8.2, 29.3 to 56.8	40.9 ±7.0, 26.9 to 52.3
Number of assessments Mean ±SD, range	5.5 ±3.0, 2 to 12	6.9 ±2.5, 3 to 11
Time from initial assessment to onset of symptoms (years) Mean ±SD, range[a]		5.0 ±4.8, -1.7 to 16.3
Time from initial assessment to AD diagnosis (years) Mean ±SD, range[b]		8.6 ±5.5, -0.1 to 18.7
Time between symptom onset and AD diagnosis (years) Mean ±SD, range		3.6 ±1.8, 1.1 to 7.5

Legend

a and b: Time from initial assessment to onset of symptoms or to AD diagnosis was coded as a negative value if the assessment was conducted after the onset of symptoms or AD diagnosis respectively.

2.3.2 Cross-sectional neuropsychological results

At baseline, there was a trend for a lower mean score on RMT for words in the converters than controls (44.3 versus 46.7 out of 50, p=0.07) but there were no other differences between the groups (Table 2.2). Once the three converters within one year of symptom onset were excluded, the trend towards differing RMT for words at baseline was less apparent (45.3 versus 46.7, p=0.23). For a number of tests, there was an association between neuropsychological scores and temporal distance to symptom onset, indicating that converters who were closer in time to symptom onset tended to have worse performance (Table 2.2) (Figure 2.1). This correlation was statistically significant for verbal IQ, performance IQ, RMT for words, "O" cancellation, GDAT, MCST, and CPAL. This relationship did not appear to be linear. For example, in the case of RMT for words, lower scores were only apparent in participants who were within 5 years of symptom onset (Figure 2.1).

Table 2.2a: Neuropsychological scores for controls and converters at initial assessment.

Test	Maximum score	Controls (N=37)		Converters (N=19)		P value controls versus converters	Correlation between scores and time from symptom onset[a]	P-value correlation
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing			
Verbal IQ		99 ±12	0 (0)	101 ±13	0 (0)	0.72	-0.49	0.032
Performance IQ		103 ±16	0 (0)	101 ±15	0 (0)	0.76	-0.52	0.023
NART FIQ		101 ±12	1 (2.7)	104 ±12	1 (5.3)	0.37	-0.16	0.518
RMT words	50	46.7 ±3.5	0 (0)	44.3 ±4.8	0 (0)	0.07	-0.66	0.002
RMT faces	50	43.8 ±3.4	0 (0)	43.1 ±5.0	0 (0)	0.62	-0.45	0.052
Digit copying (s)		42.4 ±14.9	3 (8.1)	35.9 ±6.6	2 (10.5)	0.11[b]	0.34	0.184
"O" Cancellation (s)		49.9 ±16.8	4 (10.8)	47.8 ±14.6	2 (10.5)	0.82[b]	0.77	<0.001
GNT	30	20.9 ±6.4	0 (0)	22.7 ±3.5	0 (0)	0.19	0.07	0.780
GDAT	24	12.4 ±5.8	1 (2.7)	13.6 ±4.7	1 (5.3)	0.45	-0.53	0.024
GDST	30	18.9 ±6.7	2 (5.4)	20.1 ±6.7	2 (10.5)	0.56	-0.03	0.922
Cube analysis	10	9.2 ±1.1	1 (2.7)	9.1 ±1.6	1 (5.3)	0.72	-0.06	0.813
Silhouettes	30	22.9 ±4.7	2 (5.4)	23.1 ±2.9	1 (5.3)	0.81	-0.04	0.863
Digit span[c]	20	9.7 ±2.3	0 (0)	10.1 ±2.8	1 (5.3)	0.62	-0.26	0.289
MCST	6	5.6 ±1.0	3 (8.1)	5.8 ±0.6	4 (21.1)	0.36	-0.59	0.020
Wisconsin errors		5.7 ±6.3	5 (13.5)	5.7 ±4.2	4 (21.1)	0.96	0.27	0.338
Synonyms concrete	25	20.9 ±2.9	2 (5.4)	21.8 ±2.4	3 (15.8)	0.25	0.03	0.926
Synonyms abstract	25	20.4 ±2.5	3 (8.1)	21.3 ±2.3	3 (15.8)	0.24	-0.10	0.717
MMSE	30	30 ±0.7	7 (18.9)	30 ±0.7	3 (15.8)	0.58[d]	0.11	0.676

Table 2.2b: Neuropsychological scores for CPAL for a subset of participants at initial assessment.

Test	Maximum score	Controls (N=28)		Converters (N=14)		P value controls versus converters	Correlation between scores and time from symptom onset[a]	P-value correlation
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing			
CPAL	48	39.3 ±7.4	0 (0)	36.3 ±8.7	0 (0)	0.29	-0.64	0.014

Legend
a. Spearman's rank correlation for converters only. Time from symptom onset was coded as a negative value if baseline assessment was conducted before symptom onset.
b. p value from t-test comparing speed (1/s) between groups
c. Raw scores converted into scaled scores with a mean of 10, standard deviation of 3
d. p value from Wilcoxon rank-sum test

RMT: Recognition Memory Test

GNT: Graded Naming Test

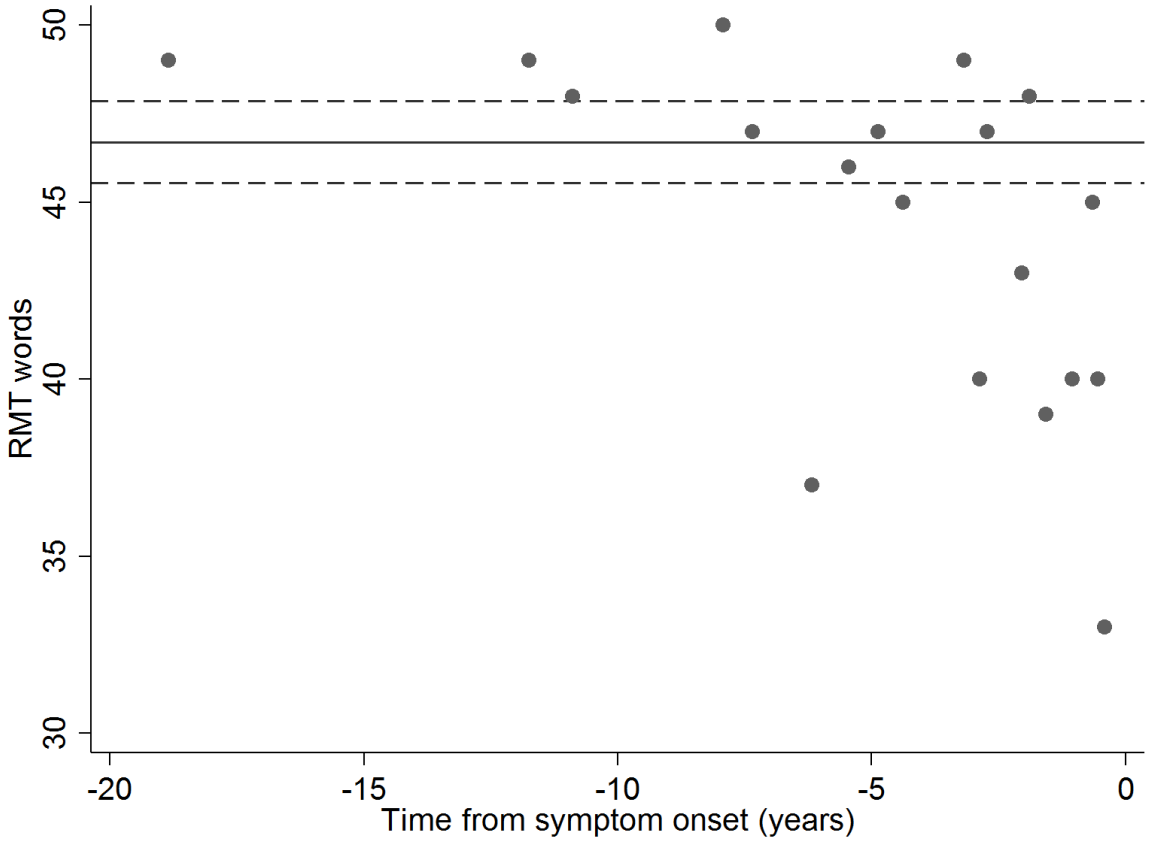
GDAT: Graded Difficulty Arithmetic Test

GDST: Graded Difficulty Spelling Test

CPAL: Camden Paired Associative Learning

MCST: Modified Card Sorting Test

Figure 2.1: Baseline scores for Recognition Memory Test for words.



Scores for converters are represented by dots (•) according to years from symptom onset at baseline. The solid and dashed lines represent the mean value and 95% confidence intervals of baseline scores for the control group respectively. X-axis refers to temporal distance to onset of symptoms at baseline such that the further an individual was from symptom onset, the greater the absolute value. Y-axis refers to scores for RMT for words (max 50).

At the first visit after symptom onset (on average 5.8 years from baseline assessment), converters had significantly lower mean performance IQ, RMT for

words and CPAL in comparison to controls of similar duration of follow-up (on average 6.6 years from baseline assessment) but there were no other differences between the groups (Table 2.3).

At the first visit after the diagnosis of AD (on average 8 years from baseline assessment), converters had significantly worse performance than controls of similar follow-up duration (on average 7.2 years from baseline assessment) on verbal IQ, performance IQ, RMT for words, "O" Cancellation, GDAT, digit span and CPAL (Table 2.4).

Table 2.3: Neuropsychological scores for converters at first assessment after symptom onset and controls at matched duration from initial assessment.

Test	Maximum score	Controls (N=37)		Converters (N=19)		p value controls versus converters
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing	
Verbal IQ		106 ±13	1 (2.7)	99 ±16	0 (0.0)	0.10
Performance IQ		112 ±17	1 (2.7)	102 ±21	0 (0.0)	0.04
NART FIQ		103 ±12.9	3 (8.1)	105 ±12	3 (15.8)	0.65
RMT words	50	47.3 ±3.3	0 (0.0)	38.0 ±8.3	1 (5.3)	<0.001
RMT faces	50	43.7 ±3.8	0 (0.0)	41.6 ±5.9	1 (5.3)	0.17
Digit copying (s)		43.2 ±10.5	8 (21.6)	45.3 ±16.0	6 (31.6)	0.91[a]
"O" Cancellation (s)		49.10 ±13.5	8 (21.6)	65.6 ±41.4	5 (26.3)	0.38[a]
GNT	30	22.6 ±6.8	0 (0.0)	22.8 ±4.0	1 (5.3)	0.89
GDAT	24	13.5 ±6.0	1 (2.7)	11.9 ±6.9	1 (5.3)	0.41
GDST	30	17.2 ±7.2	10 (27.0)	19.3 ±8.0	4 (21.1)	0.41
Cube analysis	10	9.6 ±1.0	8 (21.6)	7.8 ±3.4	4 (21.1)	0.06
Silhouettes	30	24.6 ±3.3	9 (24.3)	24.0 ±4.1	4 (21.1)	0.64
Digit span[a]	20	10.9 ±3.1	0 (0.0)	10.3 ±3.6	1 (5.3)	0.55
Synonyms concrete	25	21.2 ±3.5	12 (32.4)	20.8 ±3.0	7 (36.8)	0.72
Synonyms abstract	25	20.7 ±4.1	12 (32.4)	21.2 ±3.5	7 (36.8)	0.71

Test	Maximum score	Controls (N=28)		Converters (N=14)		p value controls versus converters
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing	
CPAL subgroup						
CPAL	48	41.7 ±6.0	3/28(10.7)	28.3 ±15.6	3/14 (21.4)	0.02

Legend
a. p-value from t-test comparing speed (1/s) between groups

Table 2.4: Neuropsychological scores for converters at first assessment after diagnosis of Alzheimer's disease and controls at matched duration from initial assessment

Test	Maximum score	Controls (N=37)		Converters (N=19)		p value controls versus converters
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing	
Verbal IQ		106 ±13	1 (2.7)	87 ±19	3 (15.8)	<0.001
Performance IQ		113 ±17	0 (0.0)	89 ±21	3 (15.8)	<0.001
NART FIQ		100 ±22	4 (10.8)	102 ±13	7 (36.8)	0.74
RMT words	50	47.2 ±3.3	0 (0.0)	34.9 ±6.4	5 (26.3)	<0.001
RMT faces	50	43.7 ±3.8	0 (0.0)	41.1 ±6.6	5 (26.3)	0.18
Digit copying (s)		43.4 ±10.3	8 (21.6)	56.8 ±17.9	11 (57.9)	0.10[a]
"O" Cancellation (s)		50.4 ±18.3	8 (21.6)	86.0 ±43.4	10 (52.6)	0.002[a]
GNT	30	22.7 ±6.7	0 (0.0)	21.3 ±5.1	3 (15.8)	0.38
GDAT	24	12.8 ±5.5	1 (2.7)	6.2 ±5.8	4 (21.1)	<0.001
GDST	30	17.6 ±7.1	9 (24.3)	13.6 ±8.8	8 (42.1)	0.22
Cube analysis	10	9.5 ±1.1	8 (21.6)	7.0 ±3.9	9 (47.4)	0.07
Silhouettes	30	24.4 ±3.3	8 (21.6)	23.0 ±4.7	8 (42.1)	0.38
Digit span[a]	20	10.7 ±3.1	1 (2.7)	6.3 ±3.1	3 (15.8)	<0.001
Synonyms concrete	25	21.4 ±3.5	11 (29.7)	20.6 ±3.4	10 (52.6)	0.54
Synonyms abstract	25	20.5 ±4.1	11 (29.7)	20.4 ±3.6	10 (52.6)	0.97

Test	Maximum score	Controls (N=28)		Converters (N=14)		p value controls versus converters
		Mean ±SD	N (%) missing	Mean ±SD	N (%) missing	
CPAL subgroup						
CPAL	48	41.7 ±5.5	1 (3.6)	26.7 ±8.7	7 (50.0)	0.003

Legend
a. p value from t-test comparing speed (1/s) between groups

2.3.3 Longitudinal analysis: change point estimation

A significant change point for converters was detected in verbal and performance IQ, RMT for words and faces, CPAL, digit copying, GNT, GDAT, GDST, digit span and the concrete synonym comprehension test (Table 2.5).

The cognitive tests with change point significantly before the onset of symptoms were RMT for words and CPAL (1.8 and 2.3 years before symptom onset respectively). The GNT was estimated to have the latest change point: 4.1 years after symptom onset. For all other cognitive tests, the start of cognitive decline was estimated to occur around the time of symptom onset (performance IQ, RMT for faces, digit copying, GDAT and synonyms concrete) or shortly after symptom onset (verbal IQ, GDST and digit span). It was not possible to provide a lower limit to the 95% confidence interval for "O" cancellation because the likelihood for models at all earlier change points did not differ significantly from 0.5 years. Results are not presented for VOSP cube analysis due to a very strong ceiling effect. Results are also not presented for VOSP silhouettes and the abstract synonym comprehension test since the best-fitting model found no significant post-change-point decline, meaning that no evidence of a change point was identified. For all analyses, findings were similar when participants who were within one year of symptom onset were excluded, so results are presented for analysis of all participants.

Table 2.5: Change point, control rate of change, and post-change-point rate of decline in converters

Test	Number of participants (% of total)	Number of assessments (% of total)	Change point (years from symptom onset (95% CI)	Control rate of change per year increase in age (95% CI)	Post-change point decline per year relative to controls (95% CI)
Verbal IQ	54 (96)	359 (94)	1.5 (0.9 to 2.0)	0.56 (0.34 to 0.77)	-6.82 (-9.00 to -4.64)
Performance IQ	54 (96)	358 (94)	1.1 (-0.1 to 3.2)	0.72 (0.42 to 1.01)	-6.27 (-7.88 to -4.66)
RMT words	55 (98)	367 (96)	-1.8 (-2.8 to -1.1)	0.01 (-0.05 to 0.06)	-2.08 (-2.72 to -1.44)
RMT faces	55 (98)	367 (96)	-1.4 (-5.2 to 0.1)	0.06 (0.00 to 0.12)	-0.91 (-1.33 to -0.49)
Digit copying (1/s)	52 (93)	296 (77)	-0.7 (-2.9 to 0.7)	-0.02 (-0.03 to -0.01)	-0.16 (-0.23 to -0.08)
"O" cancellation (1/s)	52 (93)	306 (80)	0.5 (NA to 1.6)	-0.02 (-0.03 to 0.00)	-0.15 (-0.24 to -0.06)
GNT	56 (100)	361 (95)	4.1 (3.0 to 4.5)	0.17 (0.13 to 0.22)	-3.13 (-5.04 to -1.21)
GDAT	56 (100)	341 (89)	0.2 (-2.0 to 2.0)	0.07 (-0.03 to 0.16)	-1.61 (-2.16 to -1.07)
GDST	51 (91)	293 (77)	1.8 (0.3 to 2.7)	0.10 (0.04 to 0.17)	-2.34 (-3.86 to -0.82)
Digit span	56 (100)	355 (93)	1.2 (0.2 to 1.9)	0.10 (0.06 to 0.15)	-1.31 (-1.76 to -0.87)
Synonyms concrete	52 (93)	268 (70)	-1.3 (-6.1 to 1.4)	0.11 (0.05 to 0.16)	-0.40 (-0.65 to -0.14)
CPAL subgroup (Participants N=42; assessments N=252)					
CPAL	42 (100)	234 (93)	-2.3 (-4.8 to -1.2)	0.21 (0.07 to 0.36)	-2.52 (-3.99 to -1.41)

Legend:
Unit for change point estimates: number of years from symptom onset. Negative change point estimates mean change occurred before onset of symptoms
Unit for rate of change: point (on neuropsychology test) per year or number of digits copied or "O" cancelled per second per year

Before the change points, scores for most neuropsychological tests either remained stable with increasing age (RMT for words and faces, and GDAT) or improved with each year of increasing age (performance and verbal IQ, CPAL, GNT, GDST, digit span and synonyms concrete), most likely due to practice effects. Only measures of psychomotor speed (digit copying and "O" cancellation) showed a slight decline over time when participants were asymptomatic. There was no effect of group in the final change point model for all but one of the tests, which indicates that differences in scores between controls and converters were in most cases accounted for by the change point model. For concrete synonyms, scores in converters were estimated to be on average 1.4 points higher (0.1 to 2.7, p=0.035) than in controls before the estimated change point. This suggests either that there were true baseline differences in scores or that the model for longitudinal change was unable to fully account for the observed group differences.

2.3.4 Longitudinal analysis: intra-individual variability

For most neuropsychological tests, there was no evidence that intra-individual variability (IIV) differed between the following periods: more than two years before symptom onset, within two years prior to symptom onset or after symptom onset (see Figure 2.2 for the example of verbal IQ). However, there were significant differences in residual variance for RMT for words and faces,

GNT, GDAT and synonyms concrete (Table 2.6). For all these tests the residual variance was similar during the years before symptom onset but increased substantially after symptom onset. The most dramatic increase in variance during the post-symptomatic period was seen for RMT for words (Figure 2.3) and faces (Figure 2.4). There was a somewhat smaller increase in variance for GNT, GDAT and synonyms concrete. These results indicate that each individual's neuropsychological test scores showed increased variability around his or her predicted trajectory after symptom onset, in comparison to the pre-symptomatic period. Although we did not assess the precise timing of increased IIV after symptom onset, visual inspection of the figures showing observed scores over time suggest that it occurred soon after the onset of symptoms. On visual inspection, it also appears that this increased IIV is more apparent in some individuals than in others (Figure 2.3 and 2.4).

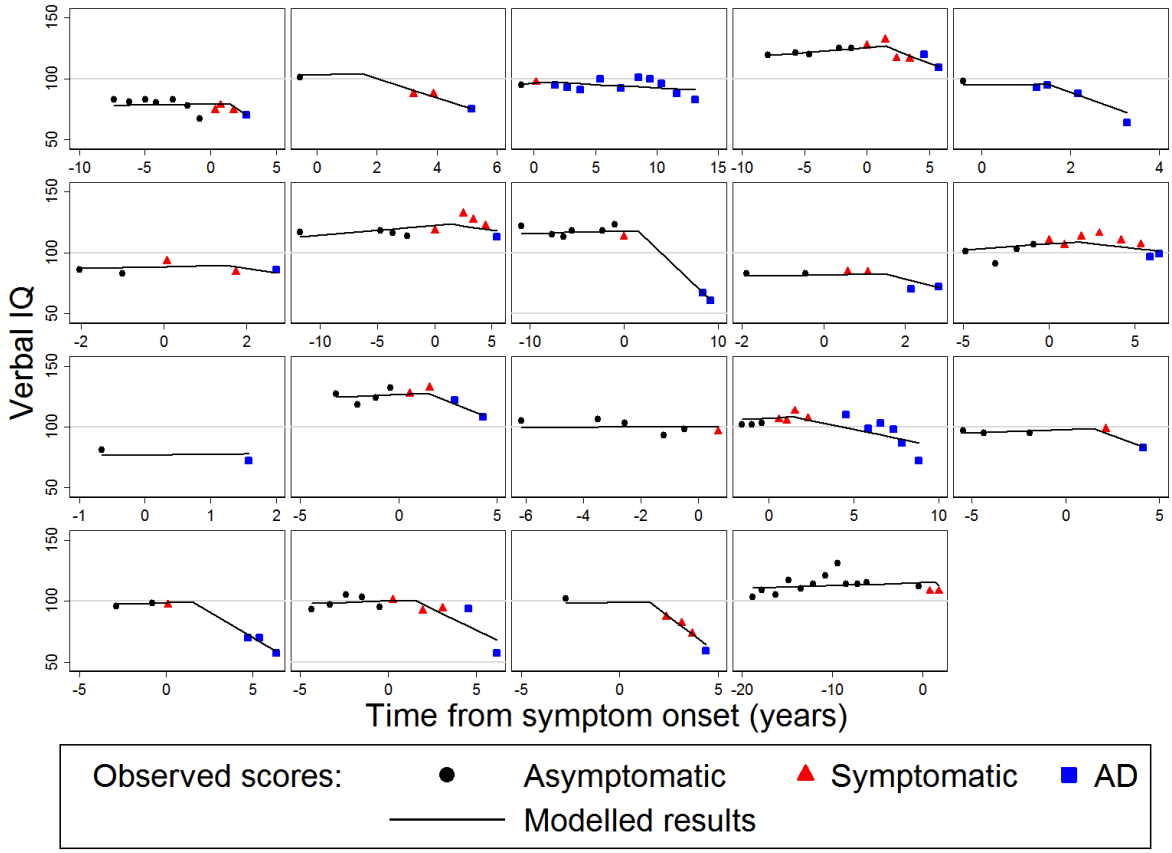
Table 2.6: Intra-individual variability (indexed by variance) in neuropsychological performance for converters

Test	Number of participants (% of total)	Number of assessments (% of total)	Residual variance in score from change point model with common variance	Residual variance in score for change point model with heterogeneity in variance			p value for test of heterogeneity in residual variance[a]
				Controls and converters more than 2 yrs before symptom onset	Converters within 2 years prior to symptom onset	Converters post symptom onset	
Verbal IQ	54 (96)	359 (94)	27.9	26.5	19.5	35.7	0.20
Performance IQ	54 (96)	358 (94)	69.1	66.8	70.0	76.8	0.83
RMT words	55 (98)	367 (96)	6.7	4.3	3.6	20.5	<0.001
RMT faces	55 (98)	367 (96)	8.5	6.5	7.5	17.5	<0.001
Digit copying (1/s)	52 (93)	296 (77)	0.07	0.07	0.02	0.07	0.12
"O" cancellation (1/s)	52 (93)	306 (80)	0.13	0.13	0.11	0.15	0.75
GNT	56 (100)	361 (95)	2.2	1.9	1.8	3.3	0.03
GDAT	56 (100)	341 (89)	6.6	6.0	2.1	10.3	0.001
GDST	51 (91)	293 (77)	2.8	2.4	5.0	3.5	0.066
Digit span	56 (100)	355 (93)	2.2	2.0	2.2	2.9	0.25
Synonyms concrete	52 (93)	268 (70)	1.9	1.8	0.8	3.0	0.04
CPAL subgroup (Participants N=42; assessments N=252)							
CPAL	42 (100)	234 (93)	12.2	11.2	7.1	20.4	0.065

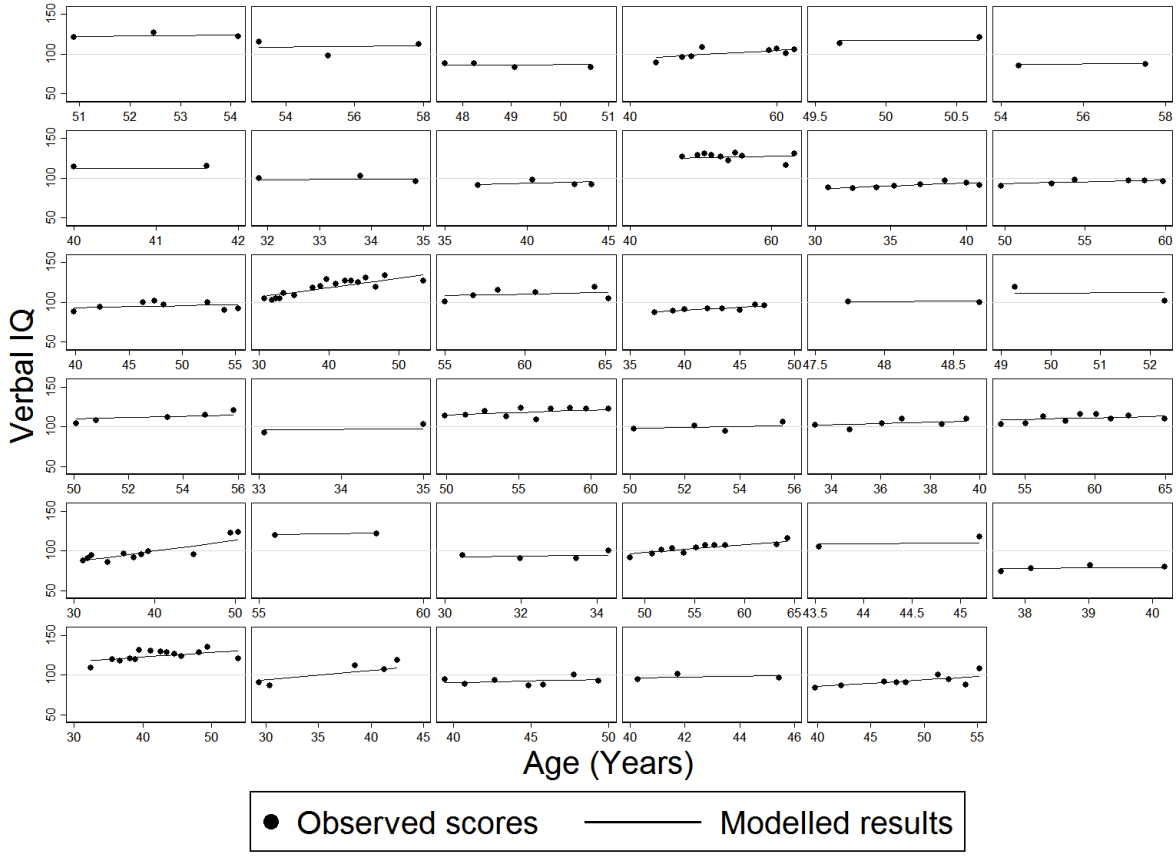
Legend:
a. P-value from likelihood ratio test comparing model with and without heterogeneity of residual variance

Figure 2.2: Longitudinal scores for verbal IQ in converters (A) and controls (B) showing little variability in scores over time

A



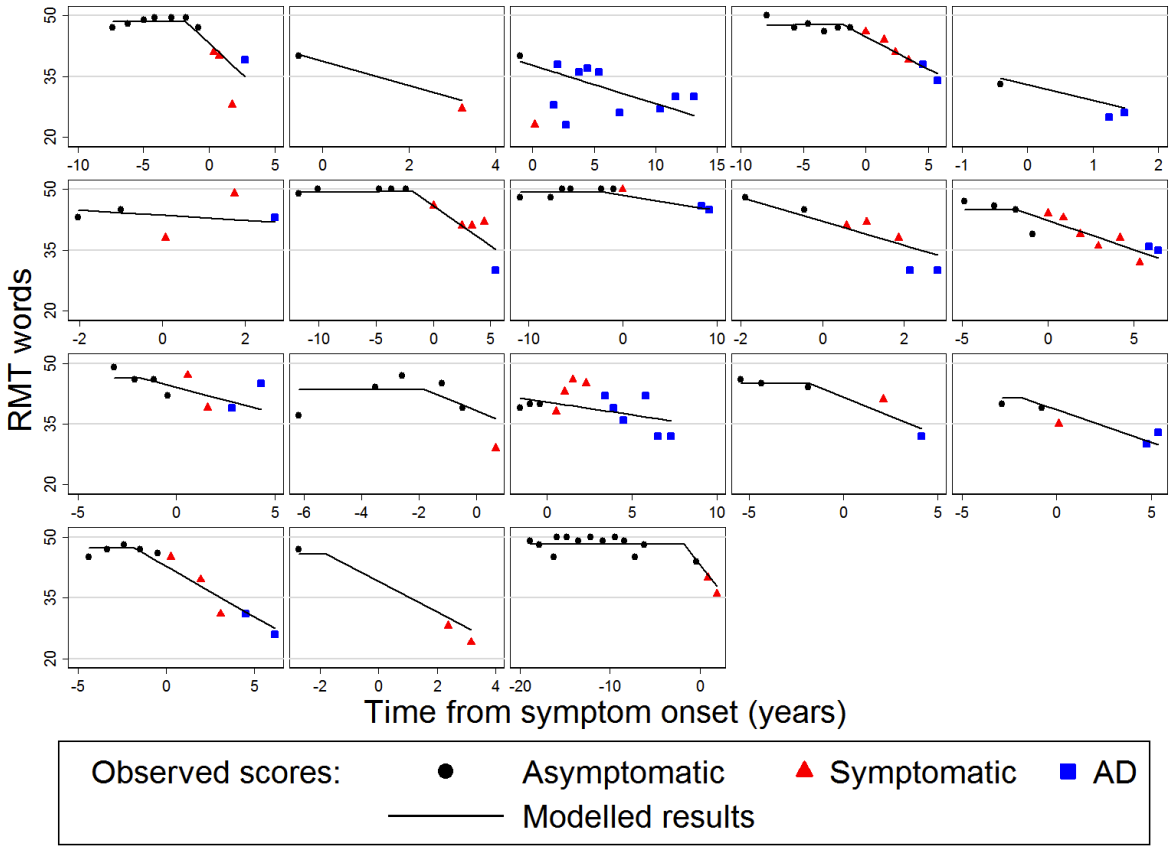
B



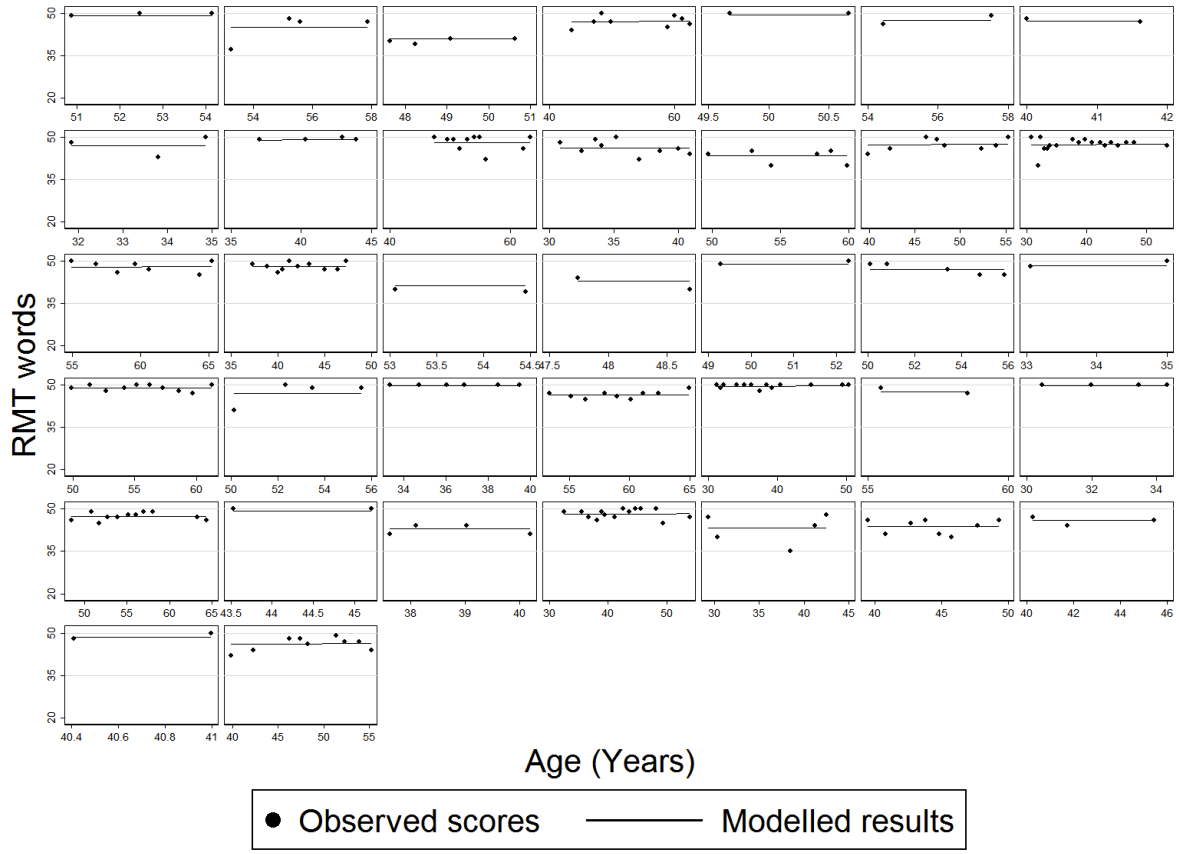
A: Each panel refers to a converter. Dot (●), triangle (▲) and square (■) represent scores obtained during the asymptomatic, symptomatic and AD phase respectively. Solid lines represent model based fit. Where the solid lines have two linear components, the first component represents the model-based fit in the period prior to the change point and the second in the period post change point. X-axis refers to the temporal distance from symptom onset when the assessment took place. Negative values are used when assessments took place prior to the onset of symptoms. Y-axis refers to scores for verbal IQ. B: Each panel refers to a control participant. X-axis refers to controls' age at the time of assessments. Y-axis refers to scores for verbal IQ.

Figure 2.3 Longitudinal scores for Recognition Memory Test for words in converters (A) and controls (B) showing increased fluctuations in scores in some converters after symptom onset but little variability in controls.

A



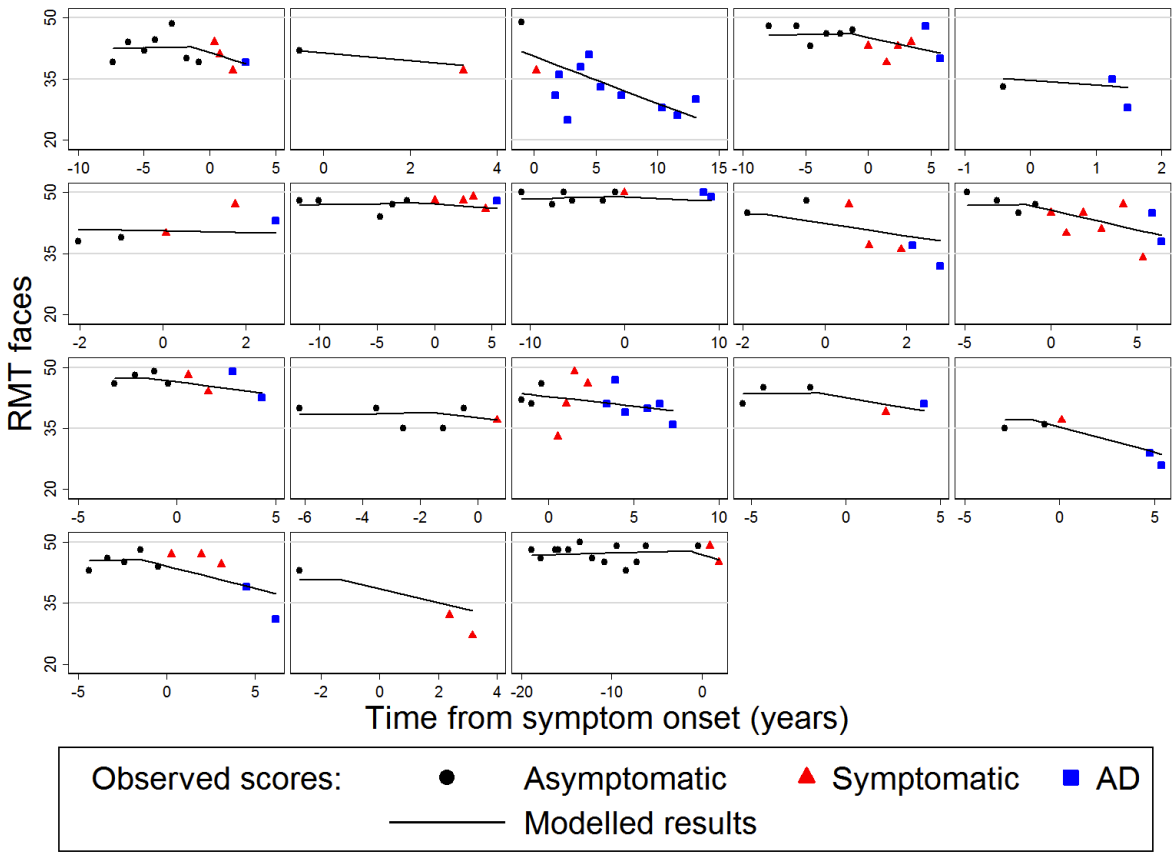
B



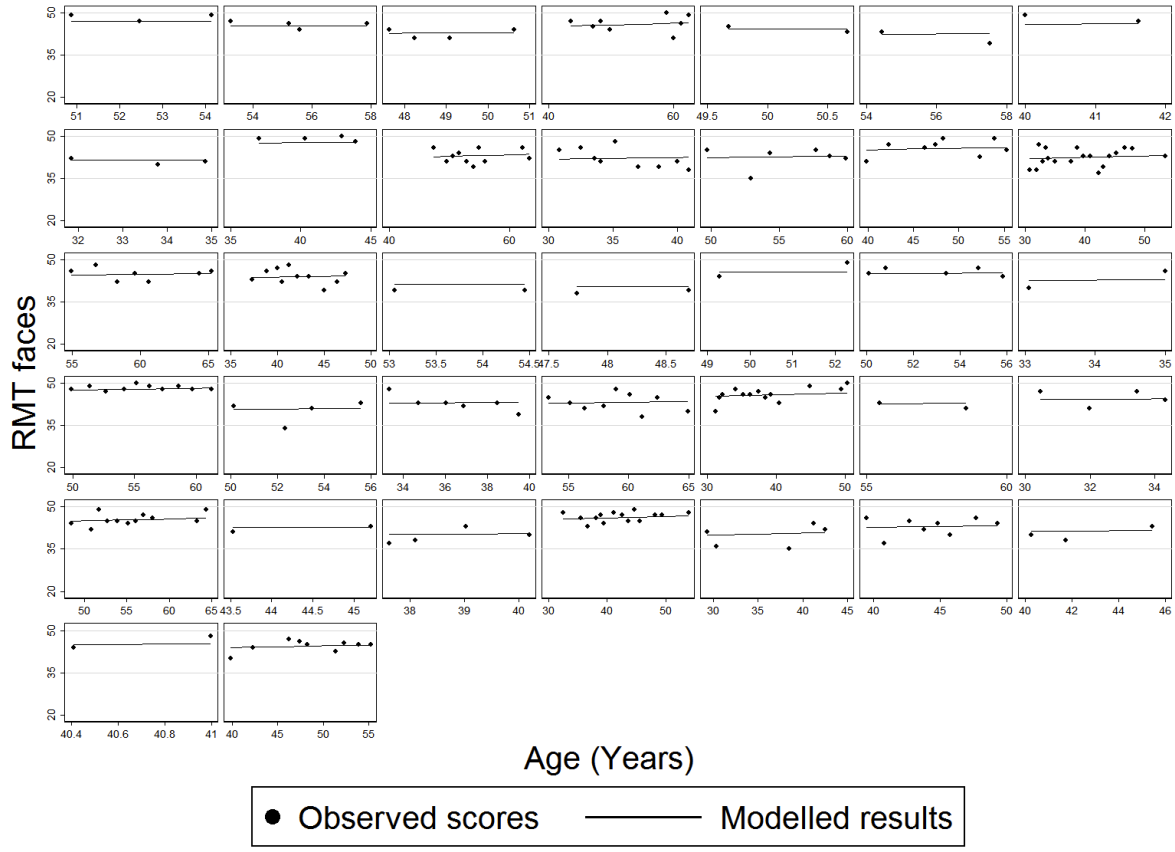
A: Each panel refers to an individual participant. Dot (●), triangle (▲) and square (■) represent scores obtained during the asymptomatic, symptomatic and AD phase respectively. Solid lines represent model based fit. Where the solid lines have two linear components, the first component represents the model-based fit in the period prior to the change point and the second in the period post change point. X-axis refers to the temporal distance from symptom onset when the assessment took place. Negative values are used when assessments took place prior to the onset of symptoms. Y-axis refers to scores for Recognition Memory Test for words (max 50). B: Each panel refers to a control participant. X-axis refers to controls' age at the time of assessments. Y-axis refers to scores for Recognition Memory Test for words (max 50).

Figure 2.4 Longitudinal scores for Recognition Memory Test for faces in converters (A) and controls (B) showing increased fluctuations in scores in some converters after symptom onset but little variability in controls.

A



B



A: Each panel refers to an individual participant. Dot (●), triangle (▲) and square (■) represent scores obtained during the asymptomatic, symptomatic and AD phase respectively. Solid lines represent model based fit. Where the solid lines have two linear components, the first component represents the model- based fit in the period prior to the change point and the second in the period post change point. X-axis refers to the temporal distance from symptom onset when the assessment took place. Negative values are used when assessments took place prior to the onset of symptoms. Y-axis refers to scores for RMT for faces (max 50). B: Each panel refers to a control participant. X-axis refers to controls' age at the time of assessments. Y-axis refers to scores for RMT for faces (max 50).

2.4 Discussion

This study provides a detailed account of the neuropsychological features of FAD in a cohort of at-risk individuals who were followed from an asymptomatic phase through to dementia diagnosis. I reported the results of cross-sectional cognitive assessments at three clinical stages of the disease, namely, presymptomatic, early symptomatic and Alzheimer's dementia. A change point modelling approach using longitudinal data provided robust but likely conservative estimates of the timing of decline in neuropsychological performance with respect to symptom development, the earliest clinical manifestation of the disease. I found that premorbid cognitive performance many years before the onset of symptoms was similar between mutation carriers and controls who shared a genetic and environmental background. I found that memory and learning-based tests declined on average 2 years before onset of symptoms in converters, approximately 5 years before a clinical diagnosis of AD. Most of the other neuropsychological tests showed pathological changes around the time of symptom onset. By the time the individual reached the stage of dementia diagnosis, pathological decline was present in nearly all cognitive domains. There was also evidence that increased year-to-year variability in performance on some tests accompanied cognitive decline in some individuals.

In my study, RMT was the only test to show a trend for poorer performance in asymptomatic MCs compared with controls at baseline. As discussed in the Introduction (see section 1.8.1), Storandt et al. reported significantly worse performance in asymptomatic MCs in Logical memory delayed recall and semantic categorization accuracy (Storandt et al., 2014). These differences may be due to differences in the MCs in terms of their temporal distance to symptom onset as well as the cognitive tests used. Storandt et al. reported that individuals with very mild symptoms (CDR 0.5) had impairment in a wide range of tasks that had previously been shown to be sensitive to SAD (Storandt et al., 2014). This is consistent with my findings that pathological decline in most cognitive tests occurred around the time of symptom onset.

Performances in several cognitive tests, such as concrete synonym tests, GDST, RMT for faces and VOSP silhouettes did not show cross-sectional differences from controls even after converters were diagnosed with AD clinically (Table 2.4), despite evidence that decline in test performance had begun earlier in the course of the disease (Table 2.5). This discrepancy illustrates the greater sensitivity of longitudinal analyses in detecting pathological decline compared to a cross-sectional approach.

Despite differences in methodologies, my finding that pathological decline in cognitive performance occurred around the time of symptom onset for most cognitive tests is broadly consistent with that reported by Godbolt (Godbolt et al., 2004) and the longitudinal results from DIAN (McDade et al., 2018). As there is some overlap in terms of research participants in my study and Godbolt et al.'s study, the similarity is perhaps unsurprising. McDade et al. estimated that the rates of change for a cognitive composite between MCs and controls started to diverge approximately 2 years before the EAO. As the cognitive composite represents the average of the Z scores of many tests, the finding cannot be extrapolated to specific cognitive tests. Nonetheless, this is broadly in keeping with my findings that RMT for words and CPAL declined approximately 2 years before symptom onset.

In contrast to the paucity of longitudinal neuropsychological studies in FAD, many more observational studies have followed cognitively-healthy older adults through to sporadic AD (Amieva *et al*., 2008; Grober *et al*., 2008; Johnson *et al*., 2009; Wilson *et al*., 2011, 2012). Those studies that used a comparable design to my study estimated the timing of decline in memory performance ranging from 2 years to 4 years before AD diagnosis for story recall from the logical memory subset of WMS-R and WMS associate learning respectively (Johnson, Storandt, Morris, & Galvin, 2009) to 5 years before diagnosis for a composite

episodic memory score (Wilson *et al*., 2011). These estimates are comparable to my findings and lend further support to the notion of FAD as a model for SAD.

It is helpful to consider the timing of cognitive decline in relation to changes in other biomarkers of AD. Longitudinal imaging studies have reported that differences in hippocampal and whole-brain atrophy rates between mutation carriers and controls could be detected approximately 5.5 and 3.5 years before the diagnosis of AD dementia respectively (Ridha et al., 2006). More recent studies have estimated that rate of structural decline between mutation carriers and controls started to diverge from 4.7 (S.D. 4.2) years (Gordon et al., 2018) to 1 year (McDade et al., 2018) before EAO. These estimates are comparable to the timing of the earliest neuropsychological decline shown in my study. Others, albeit cross-sectional studies have noted that accelerated appearance of volumetric declines coincided with the onset of the symptomatic phase (Benzinger et al., 2013; Yau et al., 2015). Taking these findings altogether, they suggest that structural atrophy is closely coupled with neuropsychological changes, thus providing empirical support for the current model of biomarker trajectories in Alzheimer's disease (Jack et al., 2013).

I found that, in some converters, performance on a number of tests such as the RMT, GNT and GDAT was less predictable after the onset of symptoms as

evidenced by increased residual variance unaccounted for by the change point model, in contrast with more stable and predictable performance in controls and in converters before they developed symptoms. This increased unpredictability is consistent with previous studies that directly or indirectly described unstable cognitive performance (when assessed on an annual basis) in individuals with FAD (Acosta-Baena et al., 2011; Godbolt et al., 2005). However, due to the relatively small sample size, we could not exclude the possibility that the increased variance is not entirely random and might have been accounted for by a more complex predictive model.

In one of the few studies that investigated year-to-year IIV-I in AD, Gamaldo found that older individuals who eventually developed SAD had greater performance variability on the Boston Naming Test, Trail Making Test and Category Fluency in the period between their baseline assessment and 5 years before the eventual onset of cognitive impairment (Gamaldo et al., 2012). In their study, the onset of cognitive impairment was determined by both objective cognitive testing and functional changes. Hence individuals who reached the criteria of cognitive impairment would have been at a clinically more advanced stage than the participants who fulfilled symptom development stage in my study. Therefore, it is difficult to make direct comparisons in terms of the timing of cognitive fluctuations. As was the case with my study, Gamaldo et al. also found that IIV-I was increased in select cognitive tests, rather than across

all tests. Tests based on confrontational naming showed increased IIV-I in both studies. Gamaldo et al. did not find any differences in IIV-I in the California Verbal Learning Test (CVLT) between the cases and controls. There was also no clear evidence of increased IIV-I in CPAL in converters in my study. Of note, the CVLT and CPAL are both tests based on associative memory. In contrast, RMT for words and faces showed the greatest variability in the current study. Recognition Memory Test has also been found to be sensitive in detecting short-term fluctuations in cognition in SAD (Burton et al., 2006; Christ et al., 2018; Hultsch et al., 2000; Murtha et al., 2002). Further research is needed to compare the degree of IIV-I shown by individuals at early stages of AD in different neuropsychological tests. So far, most literature in IIV-I focuses on short-term IIV-I. However, given that most observational studies in aging and dementia research assess participants on a yearly basis, more research is also needed to establish whether year-to-year variability is a useful marker of cognitive decline in AD.

Consistent with the literature that increased IIV can be a trait-like characteristic such that some individuals consistently show greater variability in cognition (Fuentes, Hunter, Strauss, & Hultsch, 2001; Hultsch et al., 2000; Rabbitt et al., 2001), I found that even amongst converters, some individuals demonstrated more variability than others.

The variability in cognitive performance and practice effects observed in some tests have implications for the design of secondary prevention trials. For example, preliminary reports from the DIAN-TU trial (AD/PD Conference, 2020) suggest that variance on certain tests, for example, MMSE, differed between asymptomatic and symptomatic mutation carriers and that asymptomatic mutation carriers showed practice effect on tests such as logical memory and digit-symbol substitution whereas symptomatic mutation carriers did not. These ran contrary to some of the assumptions which had been made when designing the trial including constant variance across asymptomatic and symptomatic participants and that performance on all tests would decline.

The present study has a number of strengths. The cohort was carefully characterized based on detailed clinical information. I used actual rather than predicted age of symptom onset. By using prospectively collected interview records with the participants and their informants and focusing on intra-individual decline, we could be more confident in our ability to date the onset of symptoms (Godbolt et al., 2005; Storandt et al., 2006). The use of a change point model allowed us to examine individual cognitive trajectories using all available assessments for each participant. Lastly, the average durations from the initial assessment to onset of symptoms and dementia diagnosis were 5 and 8.4 years respectively, offering us the opportunity to examine pre-dementia changes over a reasonable length of time. More specifically, a substantial

proportion of participants had follow-up visits several years before and after symptom onset.

Several limitations of the study warrant further discussion. First, although this is one of the largest longitudinal neuropsychological cohorts in FAD, as a single-centre study the sample size is inevitably small. This limited the flexibility with which we were able to model change over time in cognitive scores, only allowing for inclusion of the linear rate of change and a fixed change point with sharp transition from normal aging to cognitive decline. This may have underestimated the start of decline since the transition is likely to have occurred more gradually. Given the small sample size, we were unable to investigate potential differences in the cognitive trajectories of PSEN1 and APP carriers separately. As discussed in the Introduction (section 1.8.1), Almkvist et al. used a curvilinear modelling approach and demonstrated a much earlier start in cognitive decline in some of the neuropsychological tests in APP MCs compared to PSEN 1 carriers. This is consistent with previous findings of different rates and patterns of structural decline between the two genetic subgroups (Scahill et al., 2013) (see section 1.6.1). It would be important for future studies to investigate potential differences in the trajectories of cognitive decline between these different genetic cohorts further. A number of longitudinal studies in SAD have also found that some cognitive tests or composite scores showed a slow decline initially followed by an acceleration (Amieva *et al*., 2008; Grober *et al*.,

2008; Wilson *et al*., 2012). However, the recent longitudinal DIAN study found that the most appropriate pattern of change in the composite cognitive score across baseline EAO was linear with a change point (McDade et al., 2018). Other studies have also found no evidence in favour of allowing for two change points instead of one (Wilson et al., 2011) and no evidence of acceleration of decline (Johnson *et al*., 2009; Riley *et al*., 2011). The small sample size as well as the relatively simple change trajectories could have contributed to the wide confidence intervals in some cognitive tests. Since we included participants with varying length of follow-up, bias could have been introduced if the trajectory of change in scores differed in those who dropped out from the study. Lastly, in order to follow individuals over a 20-year period, we were restricted to the battery of neuropsychology tests chosen at the outset. In general, they were designed to diagnose dementia and may therefore not be sufficiently sensitive to detect very early changes over repeated testing (Swainson et al., 2001). Practice effects in the case of RMT for words and GNT could have led to a later estimate for the change point. We also lacked measures of executive function - which may be affected early in AD (Baddeley et al., 2001; Chen et al., 2001; Harrington et al., 2013; Perry et al., 2000)- that are sensitive to longitudinal changes. Overall, however, the battery used was comprehensive and included standard tests which are in wide clinical use.

In summary, my results provide an insight into the natural history of cognitive decline in FAD from a presymptomatic stage to dementia. Longitudinal and cross-sectional analyses offer complementary perspectives on the timing of cognitive decline and patterns of impairment at significant stages of the illness. My results also provide empirical evidence for the current biomarker model of AD and lend support to the concept of FAD as a model for SAD. Future studies should use more sensitive and comprehensive cognitive tests in a multi-modal setting in order to understand the trajectories of cognitive changes in a wider biomarker context. This approach will help to elucidate the link between the pathophysiological processes of AD and the clinical syndrome and inform future design of trials aimed at secondary prevention.

Chapter 3 LESSONS FROM A NOVEL *MAPT* MUTATION CASE

3.1 Introduction

As discussed earlier in the thesis (see section 1.4), the most common clinical presentation of AD is an amnestic syndrome. Typical symptoms are progressive decline in episodic memory, repetitiveness and topographical disorientation. However, occasionally, non-AD causes of dementia can also present with prominent memory difficulties. Here I report an individual who presented with a remarkably long history of amnesia with early semantic loss followed later by behavioural changes. The case illustrates the importance of considering non-AD causes of dementia in the differential diagnosis of progressive amnesia. I discuss the clinical and neuropsychological features and investigation findings that help with the diagnostic process. I also discuss the insight the case offers in terms of the role of the MTL in memory functions.

3.2 Case description

CW is a right-handed lady who was born at term and reached normal developmental milestones. She completed a university degree and worked at a relatively senior level in the public sector. With hindsight, her now former partner recalls a subtle decline in her memory from her late thirties. In her mid-40s her performance at work deteriorated. Around the same time, she became

irritable and argumentative leading to strained relationships with her partner and children.

She was first seen in the cognitive disorders clinic at the age of 49 years old, with a principal complaint of poor memory. She was forgetting appointments and had started to keep a diary. She had been subjected to three separate capability assessments at work. She also developed low mood, what her former partner felt was an exaggeration of pre-morbid pessimism and diminished interest and drive. General and neurological examinations were normal at this point.

As detailed in Table 3.1, CW's first neuropsychological assessment showed a mild reduction in general intellectual function (FSIQ108 compared with NART estimated FSIQ 118) (Wechsler, 1981) (Nelson, 1982) with impaired performance on both verbal and visual versions of the recognition memory test (RMT both $<5^{th}$%ile) (Warrington, 1984). Confrontation naming was poor [Graded Naming Test (GNT): 5^{th}%ile; Oldfield Naming Test: 25-50^{th}%ile] (McKenna & Warrington, 1983) (Oldfield & Wingfield, 1965) which, together with slightly reduced category fluency (animal names: 25^{th} %ile) (Spreen & Strauss, 1998), in retrospect, hinted at early semantic impairment, especially in comparison with preserved phonemic fluency ('s': $>90^{th}$ %ile) (Spreen & Strauss, 1998). The latter indicated grossly preserved executive function at this

stage as did sound cognitive estimates (50^{th} %ile) (Shallice & Evans, 1978). Visual processing was intact (VOSP incomplete letters: $>5^{th}$ %ile) (Warrington & James, 1991). Despite reduced scores on confrontational naming, her spontaneous speech was fluent, and she had preserved vocabulary score on the WAIS-R. In addition, notwithstanding poor memory scores, her ability to provide details regarding her present circumstances appeared intact. These observations were initially taken to be evidence that there were inconsistencies between her presentations and objective neuropsychology tests results. In addition, she showed no implicit learning on the Gollin figures test (Gollin, 1960). These factors, in the context of her relatively young age and reported changes in mood, led to a working diagnosis of depression and possible additional functional overlay as possible causes for her cognitive problems. However, her MRI brain scan (Figure 3.1) showed small MTLs for age.

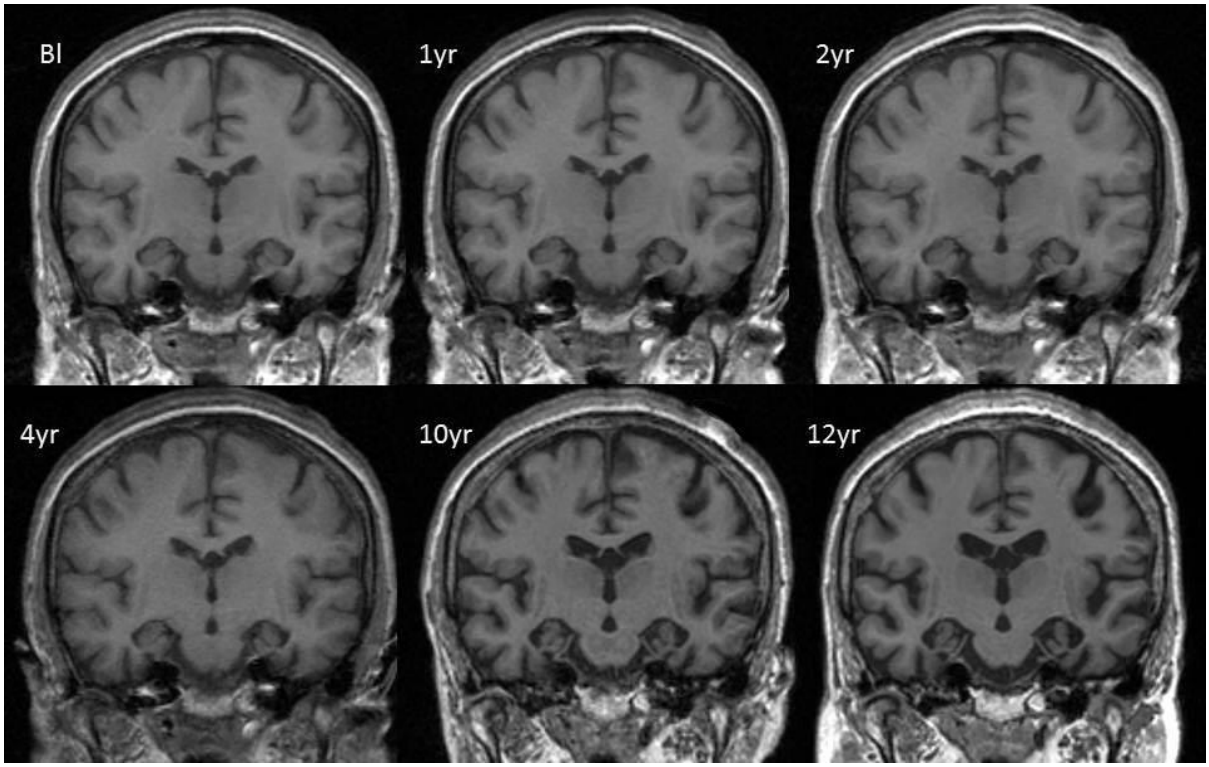
Table 3.1 Select neuropsychology results at baseline, 8 year and 13 year follow up visits

Session	Full scale IQ	Recognition memory test (words)	Recognition memory test (faces)	WMS delayed story recall	Rey complex figure recall
Baseline	108	36(<5%)	35 (<5%)	-	-
8 yr	102	32 (<5%)	20 (<5%)	0 (<1%)	0 (<1%)
13 yr	86	27 (<5%)	25 (<5%)	0 (<1%)	0 (<1%)

Session	Graded Naming Test	Famous Faces	Category fluency	Letter fluency	Synonym matching	
					Concrete	Abstract
Baseline	5 (5%)	-	17 (25%)	21 (>90%)	-	-
8 yr	2 (<1%)	2	9 (<10%)	17 (50-70%)	-	-
13 yr	0 (<1%)	0	4 (<1%)	15 (44%)	16 (<1%)	18 (10%)

Session	Trail Making Test B	Stroop Inhibition	Cognitive Estimate
Baseline	-	-	3 (50%)
8 yr	140’’ (10-25%)	20-24%	-
13 yr	146’’ (10-25%)	25-50%	15 (<1%)

Fig.3.1 Mid-temporal axial volumetric T1-weighted MR images acquired at initial presentation (Bl) and subsequent repeat visits 1, 2, 4, 10 and 12 years after the initial visit. All repeat images have undergone 9 degrees of freedom registration to spatially align them to the baseline (Bl).



Disease progression

The clinical impression that depression was a significant contributor to her cognitive complaints was revised two years later when, at the age of 51 years old, CW's memory had deteriorated significantly, and she had had to give up work. She would now frequently forget the previous day's events and had difficulty finding familiar places while driving. Treatment with Citalopram for low mood and anxiety had had no impact on her cognitive function. At this

point, a more detailed family history-which had previously been censored-emerged. CW's father had developed apathy at the age of 39 years old followed by progressive memory decline. He died at the age of 55 years old. Two of his three siblings were similarly affected.

Further investigations were performed at this point. Cerebrospinal fluid was normal for cell counts, protein and glucose. Oligoclonal bands were negative in the CSF and serum. Testing for CSF Tau and $A\beta_{42}$ levels was not yet available. EEG demonstrated normal alpha rhythm with no epileptic activity. Repeat MRI brain appeared to show stable intracranial appearances but was now reported to be consistent with AD (Figure 3.1). A diagnosis of possible AD was made based on the significant episodic and topographical memory difficulties and radiological appearance of the medial temporal lobes. On account of the strong family history, she was screened for mutations in the *PSEN 1*, *PSEN* 2 and *APP* genes which were all negative.

Continuing cognitive deterioration followed in the succeeding years such that by 57 years of age, eight years after the initial presentation to clinical service, CW required a support worker to assist with daily tasks. In addition to poor memory, occasional word finding difficulties, the onset of a sweet tooth and some weight gains were reported. She tended to oversleep, even during the day. She was no longer oriented in time. There was further decline in naming (GNT:

2/30, <1st %ile; Oldfield naming test: 16/30, 10-25%ile) and semantic fluency (animal names: <10%ile) with a milder deterioration in phonemic fluency (50-70%ile). There was mild executive impairment (Trail Making Part B: 10-25th %ile; Stroop Inhibition: 20-24th %ile) (see Table 3.1). At this time point, the cognitive profile, comprising profound episodic and most likely semantic memory loss together with milder executive problems was still thought to be consistent with a diagnosis of early onset AD. However, there was now the suggestion of disinhibition as evidenced by her responses in the letter fluency task in the form of sex-related words.

Clear behavioural symptoms emerged when CW was 61 years old. She had become disinhibited and frequently gave strangers her phone number and address. She was increasingly apathetic and would lie in bed all day unless prompted and needed encouragement even to attend social functions that she continued to enjoy. She had also become less empathic. Her intake of sweet food had increased, and she had developed musicophilia. The latter took the form of listening to certain types of music continually. She was started on Donepezil to no great effect.

At this point, to facilitate the diagnostic process, her baseline MRI and 4- and 10-year repeat scans were spatially aligned using 12 degrees of freedom (d.o.f.) registration. This procedure allows regions of cortical change between time-

points to be quantified using the boundary shift integral (BSI) and aids in visual assessment of volume loss (Nick C Fox & Freeborough, 1997; Leung, Clarkson, et al., 2010). Review of these registered images indicated a progression in the anterior-posterior gradient of volume loss across the MTLs with disproportionate loss anteriorly. This raised the possible diagnosis of familial FTD due to a tau mutation. She underwent another lumbar puncture, and the CSF analysis revealed a tau level of 429 pg/ml (suggestive of neurodegeneration) (local reference range: abnormal >400 pg/ml) and an $A\beta_{42}$ level of 723 pg/ml (non- AD like) (local reference range: AD profile if < 300 pg/ml). Screening for *MAPT* mutations revealed a novel mutation in exon 12 with a single heterozygous nucleotide change c.1052A>G.

Presently, 13 years after her initial presentation, CW is profoundly amnesic. She is very repetitive and her conversation is impoverished in content. She gives the same highly stereotyped and very restricted account of her childhood to everyone she meets.

The latest neuropsychology assessment at the age of 62 years showed general cognitive decline (WASI-II FSIQ 86) (Wechsler, 2011) (see Table 3.1). Working memory as measured by digit span remained within normal limits (scaled score 10) (Wechsler, 1987). Recognition memory was at chance. She has no recall of a short story in immediate or delayed recall conditions. Naming

scores were progressively lower across all tests (GNT now 0/30, Boston Naming Test 18/30) (Kaplan, Goodglass, & Weintraub, 1983), with worsening semantic fluency (animal names: 4, vegetable names: 0) also a feature. Phonemic fluency was further reduced but executive function *per se* remained otherwise relatively stable. On formal examination, recall of both personal semantic and autobiographic incidents was impaired (Kopelman, Wilson, & Baddeley, 1989), the latter more dramatically so (Table 3.2). Notably posterior function remained relatively intact (VOSP object decision: >5% cut off; complex figure copy: 25-50%). The profile thus remained one of profound episodic and semantic memory loss with less marked executive dysfunction but now in the context of striking behavioural change.

Table 3.2 Autobiographical memory interview aged 61 years (12 year follow up visit)

Total Score Summary	Personal Semantic	Autobiographical Incidents
Section A Childhood	5.5/21	0/9
Section B Early adult life	10/21	2/9
Section C Recent Life	4.5/21	0/9
Total	20/63 (32%)	2/27 (7%)
Cut-off	$\leq$ 47	$\leq$ 12

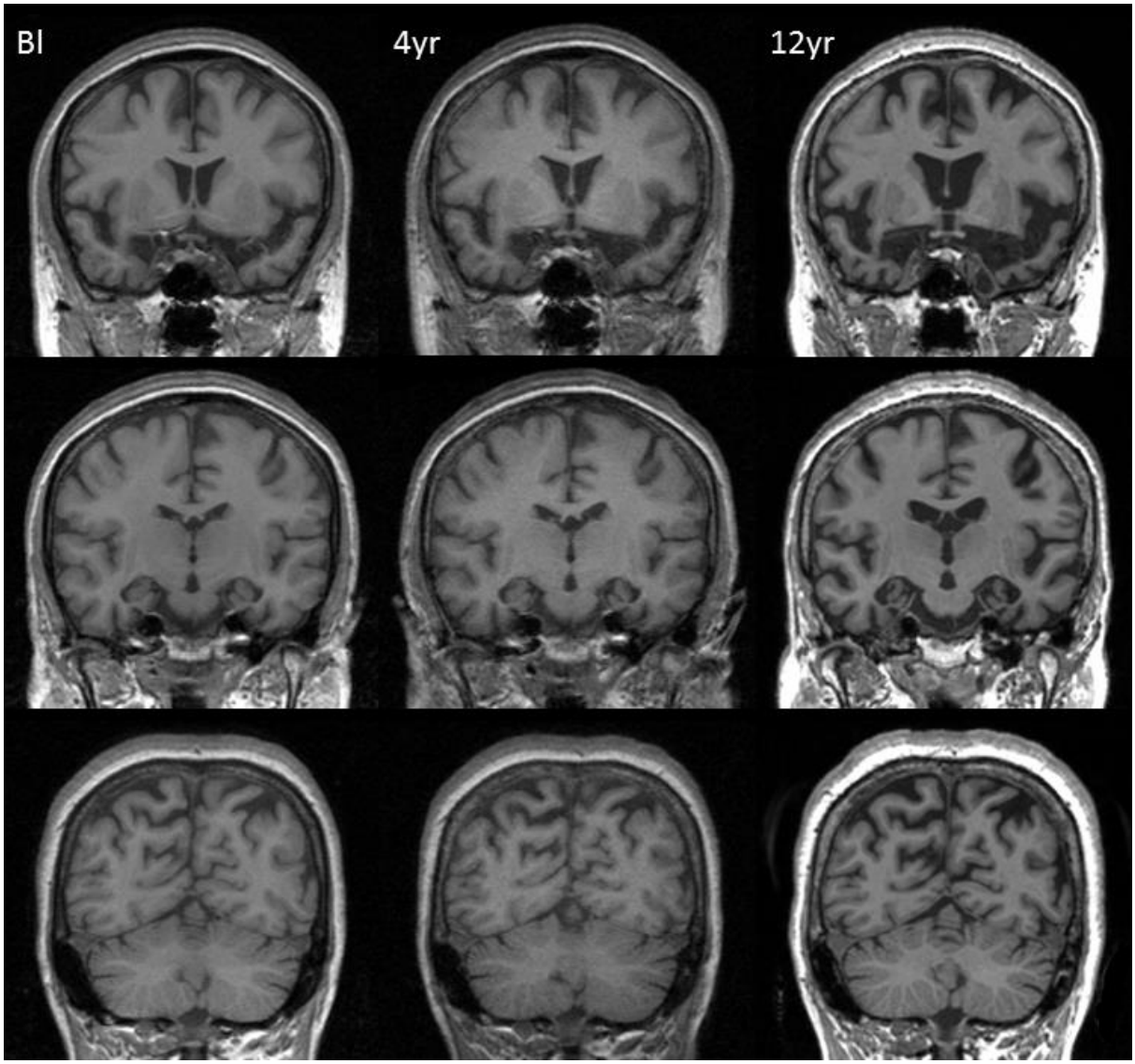
Neurologically she now has evidence of mild asymmetric parkinsonism and pyramidal signs. There is a mild resting tremor in her left hand associated with bradykinesia. She has pathologically brisk reflexes in her right arm and leg, Hoffman's sign in her right hand and an extensor right planter. Orofacial and limb praxis are normal.

3.3 Neuroimaging

As I discussed in the Introduction chapter, atrophy patterns on MRI scans can be helpful in clinical practice in terms of specifying the underlying molecular pathology of neurodegenerative disorders. The present case proved challenging to diagnose. The correct diagnosis was made many years after the initial presentation, after a fuller clinical picture had emerged, and with the benefit of serial structural imaging over a significant time period and the aid of CSF biomarkers. Abnormalities were clearly seen in the early scans, yet visual assessment alone was not sufficient in making an accurate clinical diagnosis based on the initial images. I was therefore interested in exploring the pattern of longitudinal atrophy over the long follow-up period and whether lessons can be learned for future cases. I therefore proceeded to conduct further imaging analysis with the help of colleagues (see Acknowledgement).

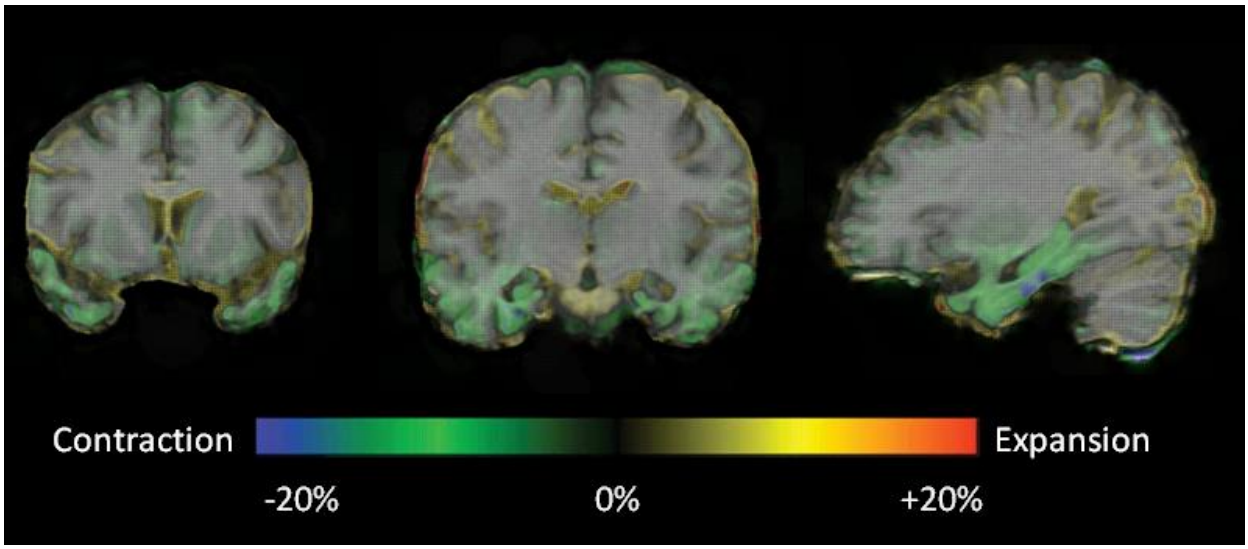
As noted earlier, the first MRI brain scan at presentation (aged 49) was thought to show bilateral medial temporal atrophy. More recent blinded radiological review of these images also reported frontal and parietal lobe atrophy (Fig. 3.2). Subsequent longitudinal MRI scans demonstrated progressive global cerebral atrophy with particularly striking changes in the anterior, inferior and medial aspects of the temporal lobes (Fig. 3.1 and 3.2).

Fig. 3.2 Spatially aligned coronal MR images from baseline (Bl), 4 year and 12 year follow-up visits demonstrating progressive atrophy affecting frontal, temporal and parietal lobes.



The pattern of these early temporal lobe changes is more clearly demonstrated by whole brain fluid registration (Fig.3.3). This method involves nonlinear warping of each scan to match the baseline scan, generating a deformation field that allows visualisation of voxel-level expansion and contraction (Freeborough & Fox, 1998). These images show clear evidence of progressive atrophy in the temporal lobes, frontal gyri and the insular cortices early in the disease process, before it was detectable during routine radiological assessment.

Fig 3.3 Representative coronal and sagittal MRI slices with voxel deformation mapping overlay, over an interval of 4 years post-presentation at clinic. These demonstrate relatively focal bilateral contraction (green/blue = volume loss) in the temporal lobes, particularly involving the temporal pole, parahippocampal and fusiform gyri, with an anterior-posterior gradient.



Given the novel mutation and the atypical clinical presentation, we compared CW's scans with those of nine *MAPT* cases in the research database at the Dementia Research Centre (UCL) and 13 healthy controls matched for age and gender. All images underwent non-uniformity correction, manual whole-brain delineation and affine 12 d.o.f. registration to quantify longitudinal whole brain change. Hippocampal volumes were derived using a template based method for automated segmentations (Jorge Cardoso et al., 2013) and used to investigate

longitudinal hippocampal volume change for CW and the nine *MAPT* mutation cases. We generated a head size measure by estimating total intracranial volumes (TIV) from the summation of the volumes of grey matter, white matter and cerebral spinal fluid using the segmentation toolbox in Statistical Parametric Mapping version 8 (Leung, Barnes, et al., 2010).

CW's early global longitudinal profile appeared very stable with volumetric analysis revealing whole-brain volumes that ranged from 1017 mm^3 (75.9% of TIV) at baseline to 1004 mm^3 (75.0% of TIV) at 4-year follow-up (Figure 3.4). Between these two time points, her average annual loss of 0.28% of baseline whole brain volume was comparable to the controls (mean=0.27%, SD=0.32) T (12)= 0.05, p=0.96 (Crawford & Howell, 1998) and was also consistent with previously published rates for healthy controls (mean 0.32%, 95 % C.I 0.1-0.54%) (Scahill et al., 2003). Compared to the other *MAPT* mutation cases, her whole brain atrophy rate at this early stage was towards the lower end of the range but was not significantly different (mean=1.44%, SD=0.76, range= 0.20 to 2.53%) T (8) =-1.45, p=0.19. When compared to three of the *MAPT* cases of similar disease duration, CW's whole brain atrophy rate was again in the lower range. Her annualised hippocampal rate of change over the same time period (3.35%) was significantly higher than the controls (mean=0.30%, SD=1.30) T (12)=2.26, p=0.04 and was towards the higher end of the range compared to the other nine *MAPT* mutation cases but again not significantly different

(mean=2.16%, SD=2.25, range= -1.66 to 5.40%) T (8) = 0.50, p=0.63 (Figure 3.5). Her hippocampal atrophy rate, however, was similar to those of the three *MAPT* cases of comparable disease duration. Therefore, CW's hippocampal and whole brain atrophy rates were not atypical compared to other *MAPT* mutation cases.

Fig. 3.4 Longitudinal whole brain volumes (as percentage of total intracranial volume) for ● *MAPT* mutation cases and ▲ CW against disease duration

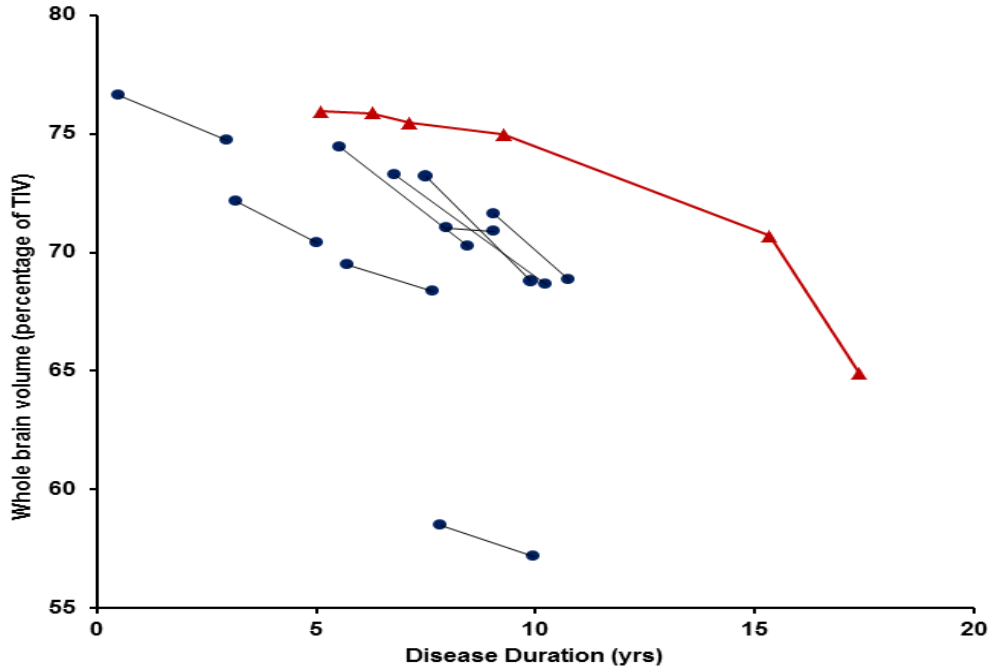
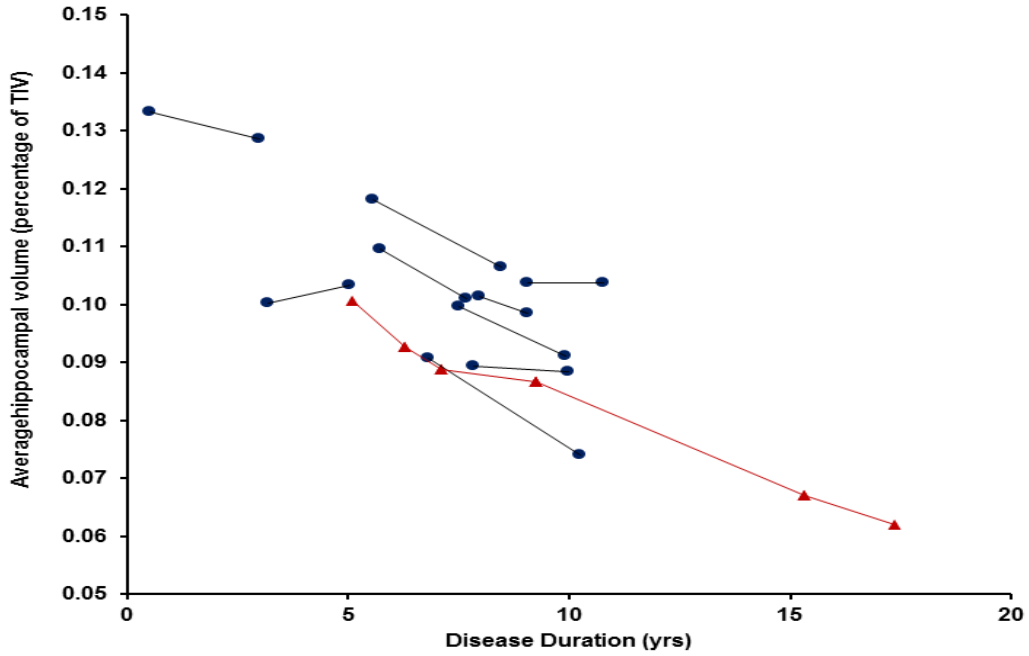


Fig 3.5 Longitudinal average hippocampal volumes (as percentage of total intracranial volume) for ● *MAPT* mutation cases and ▲ CW against disease duration



3.4 Discussion

Here we report a novel *MAPT* mutation case in exon 12 with a predominantly amnestic presentation and which was initially mis-diagnosed as AD. The mutation causes a glutamine to arginine substitution at codon 351 (Q351R) in the fourth microtubule repeat domain with a Polyphen2 score of 0.891, i.e. possibly damaging (Adzhubei et al., 2010). The substitution is likely to lead to reduced capacity of tau protein to bind to microtubules and, or increased fibrillogenicity (Hong et al., 1998) (Spillantini, Van Swieten, & Goedert, 2000).

The key clinical features of *MAPT* mutations are behavioural changes, semantic impairment, episodic memory decline and parkinsonism (Rohrer & Warren, 2011). Although behavioural changes are the prototypical presenting symptoms (Rohrer, Lashley, et al., 2011), any of the other non-behavioural features may lead (Doran et al., 2007; Ishizuka, Nakamura, Ichiba, & Sano, 2011; Larner, 2008; Rohrer, Paviour, et al., 2011). When episodic memory impairment is prominent, it is not uncommon for the case to be mis-diagnosed as AD (Doran et al., 2007; Larner, 2008; Mirra et al., 1999; Tolboom et al., 2010). As highlighted in a recent review (Hornberger & Piguet, 2012), the magnitude of anterograde memory deficits in FTD can be very similar to that in AD. It is therefore important to screen for *MAPT* mutations where there is an autosomal dominant history of an amnestic syndrome and where mutations for FAD have proven negative (Larner, 2008).

There was a significant delay in making the correct diagnosis in this case. During the early years, it was thought that there was a significant functional component to CW's presentation. Her very poor performance on tests of memory was felt to be inconsistent with her reasonable account of day-to-day events. Likewise, her impaired confrontation naming was erroneously thought to be inconsistent with her fluent, articulate speech. However, naming deficits are very rarely a cognitive correlate of depression (Emery & Breslau, 1989). In retrospect, her reduced confrontation naming –present even at the initial

assessment- should have raised the possibility of subtle semantic impairment. In fact, fluent spontaneous speech is entirely consistent with early semantic loss (Rohrer et al., 2008). A detailed examination of her semantic memory might have pointed towards a non-AD diagnosis then. Semantic impairment is a frequent finding in *MAPT* mutations (Rohrer & Warren, 2011; Seelaar et al., 2008). Although it usually presents later in the disease course (Woollacott & Rohrer, 2016), it has been reported to occur early or even in the preclinical phase of the illness (Garrard & Carroll, 2005; Ishizuka et al., 2011) . Other evidence of semantic degradation in CW, including reduced semantic fluency and poor synonym matching scores, emerged over time (Table 3.1). However, a major limitation of the study is that due to the initial misdiagnosis, CW was not given comprehensive tests probing her semantic memory such as single word comprehension, object recognition, reading and writing (for evidence of surface dyslexia and surface dysgraphia). Interestingly, apart from the observation of poverty of speech content later in the disease, no major concern with her language function was raised at any time by her family.

Similarly, CW's poor performance on the retention trials of the Gollin figure test was seen as supportive evidence of a functional component as it was assumed that even amnestic patients would usually show some implicit learning (Warrington & Weiskrantz, 1968). The most likely explanation is that her profoundly impaired episodic memory system, together with weakened support

from the visual semantic system resulted in an inability to achieve such implicit learning.

The early neuropsychiatric symptoms such as depression and apathy were erroneously thought as a likely cause of her subjective memory complaint rather than being part of the symptomatology. In fact, pathology in her right temporal pole may have contributed to her depressive symptoms (Chan et al., 2009) and lack of motivation (Kumfor & Piguet, 2012). Later in her disease course, more profound behavioural changes emerged including disinhibition, obsession with certain types of music and a preference for sweet food. Progressive involvement of bilateral temporal lobe structures as all as frontal cortex could all have contributed to the progression in her behavioural symptoms (Kamminga et al., 2015). It is a limitation of the study that she was not formally tested on emotion processing or social cognition.

Both MRI and CSF examinations played a role in making the eventual diagnosis. Progressive MTL atrophy along an anterior-posterior gradient provided a useful diagnostic pointer (Chan et al., 2001). Arguably MR techniques such as fluid registration allow more focal measurements and regional visualization so could potentially detect these changes before routine radiological review. At the time of initial investigations and CSF examination, tau and $A\beta_{42}$ protein assays were not available. When re-investigation - 10 years

later - was prompted by the atypical clinical course, these assays had been established and lent support to a non-AD pathology.

For the last few years, CW has given a very circumscribed and highly stereotyped account of her autobiographical history. Her extremely limited repertoire of autobiographical accounts is unlike that typically seen in patients with either AD or semantic dementia (Leyhe, Müller, Milian, Eschweiler, & Saur, 2009) (Graham & Hodges, 1997) and is likely to be the result of an interaction of her impaired episodic and semantic memory systems with additional contribution from impaired strategic retrieval mechanisms (Matuszewski et al., 2006). Autobiographical memory has both an episodic component and a personal semantic memory component (Tulving, 1993). The impairment CW shows in both components of autobiographical memory is consistent with the neuroimaging findings of severe temporal lobe atrophy involving the anterior and medial aspects but also, to a lesser extent, the lateral temporal cortex. In terms of a temporal gradient, patients with early AD typically remember remote personal facts and incidents better than recent ones (maintenance of the reminiscence bump and absence of the "recency" effect) (R. G. Morris & Mograbi, 2012). The opposite pattern is seen in early SD (Graham & Hodges, 1997) (Hou, Miller, & Kramer, 2005) (Irish et al., 2011) although as disease progresses, memory for all time periods is degraded (Matuszewski et al., 2009). Interestingly CW appeared to have slightly better recall of the

autobiographical memory for early adulthood compared with childhood and recent life, namely a relatively preserved reminiscence bump, but with no other temporal gradient in either direction. The autobiographical memory interview (Kopelman et al., 1989) used in our study has a free recall and a general probing condition. A more detailed procedure such as one that employs specific probes could potentially yield more informative findings (Irish et al., 2011).

CW's serial volumetric MR images over a 12-year period and fluid registration of her MRI brain scans demonstrate a relatively symmetrical pattern of atrophy affecting the frontal, temporal and to a lesser extent, parietal lobes with particular emphasis on the anterior, medial and inferior aspects of the temporal lobes (Figures 3.1-3.3). This concurs with previous MRI findings of bilateral anteromedial temporal lobe involvement in *MAPT* mutation (Whitwell, Jack, Boeve, Senjem, Baker, Rademakers, et al., 2009) (Rohrer et al., 2010) (Rohrer, Lashley, et al., 2011) (Whitwell et al., 2012). As noted earlier, compared with other *MAPT* cases, during the early years, CW's whole brain atrophy rate was towards the lower end of the range whilst her hippocampal atrophy rate was towards the higher end. This could suggest that the overall rate of clinical progression may be better correlated with the extent to which pathology spreads outside the initial focus. A caveat of making such comparisons with other *MAPT* mutation cases is that we were limited by the number of cases in the local FTD cohort with comparable disease duration.

Despite the initial atypical presentation of the case, subsequent development of semantic deficits and behavioural changes as well as the MRI atrophy patterns are consistent with existing literature on *MAPT* mutations. This supports the hypothesis that in *MAPT* mutations, although the initial target of the disease may be stochastic, the subsequent propagation is likely to conform to a specific, intrinsic brain network according to the underlying molecular pathology (Warren, Rohrer, & Hardy, 2012).

This case also illustrates a number of clinical and neuropsychological issues: the significance of anomia in the context of atypical amnesia in pointing towards a non-AD diagnosis; the value of searching for a *MAPT* mutation in cases of early onset dementia characterized by amnesia and relevant family history with negative familial AD mutations; the complexity in differentiating organic and functional amnesia and the unique effect on autobiographical memory as a result of an interaction between damaged episodic and semantic memory systems.

Chapter 4 VISUAL SHORT-TERM MEMORY BINDING IN FAMILIAL ALZHEIMER'S DISEASE

4.1 Introduction

In the longitudinal neuropsychological study presented in Chapter 2, I found that an associative learning task (CPAL) was sensitive in detecting cognitive decline in FAD mutation carriers. This is consistent with the established view that the hippocampus-one of the earliest structures affected in AD- plays a key role in relational memory (Eichenbaum, 2006; Mayes et al., 2007; Konkel et al., 2008). More recent findings from lesion and functional imaging studies also suggest that the hippocampus plays a role in relational binding in short-term memory (STM) (Hannula et al., 2006, 2015; Olson et al., 2006; Watson et al., 2013; Libby et al., 2014).

Short-term memory is one component of working memory, the cognitive system that underlies our ability to temporarily maintain as well as manipulate information when it is no longer accessible in the environment (Baddeley & Hitch, 1974; Baddeley, 2010; D'Esposito & Postle, 2015; Postle, 2006). The ability to hold onto information over short periods of time has a pivotal role in almost every cognitive task. In clinical practice, it is not unusual for individuals

with mild AD to report difficulty in recalling either auditory or visual information after even a very brief delay, implying impaired STM.

While long-term, episodic memory dysfunction has been widely documented and studied in AD (Greene et al., 1996; Hodges, 2000), much less is known about STM deficits in this condition. In an early study examining visuospatial memory and learning in AD, Sahakian et al. found that whilst individuals with AD performed normally in the simultaneous condition of a match-to-sample test, their performance rapidly declined as a function of delay. This suggests that although they were able to perceive and attend to complex visual stimuli, they had difficulty in retaining the stimuli in STM (Sahakian et al., 1988) (also see section 1.8.2.2.1). Others have reported a general deficit in the central executive component of working memory (Baddeley at al., 1986, 1991) or a reduction in working memory capacity, highlighting a difficulty in storage (Stopford et al., 2012) linked to atrophy in temporo-parietal regions (Snowden et al., 2007; Stopford et al., 2012). More recently, work by Parra and colleagues has provided evidence that the ability to bind object features together in working memory might be critically affected. In their pioneering studies, Parra *et al.* reported that binding in visual short term memory (VSTM) of simple object features such as colour and shape or colour and colour is selectively disrupted in AD (Parra et al., 2009, 2010, 2011).

However, as discussed in section 1.8.2.2.2, colour-shape or colour-colour bindings tasks are often considered to probe *conjunctive binding*: the ability to form a single representation of an item with multiple elements, with accurate retrieval depending crucially upon the ability to access the unitary, integrated representation (see Moses & Ryan, 2006). By contrast, retrieval of multi-feature items that can be performed by remembering individual parts separately (e.g. identity and location) is considered to depend upon *relational binding* (Hannula et al., 2015). Several studies have shown that conjunctive binding can be preserved in patients with hippocampal lesions (e.g., Baddeley, Allen, & Vargha-Khadem; Mayes et al., 2007; Parra et al., 2015). These considerations therefore raise the possibility that the deficits in VSTM conjunctive binding reported in Alzheimer's cases (Parra et al., 2009, 2010, 2011) might not depend upon hippocampal loss.

Furthermore, just because an individual fails to recall an item correctly does not necessarily mean that it was completely erased from memory. However, change detection paradigms such as those used by Parra *et al*. (Parra et al., 2009, 2010, 2011) depend upon a binary response: either something is remembered correctly or it is not. They do not provide more fine-grained information on the reason underlying an incorrect response.

In this study, I used a delayed reproduction paradigm developed by Pertzov *et al.* It tests the participants' object-location relational memory over a delay of seconds (i.e. using working memory). Instead of asking participants to report whether they detect a change between the sample and test arrays, they are asked to localize precisely on a touch screen the remembered location of items they had seen only seconds previously (Bays, Catalao, & Husain, 2009; Gorgoraptis, Catalao, Bays, & Husain, 2011; Wilken & Ma, 2004). The "What was where?" paradigm therefore not only provides a continuous measure of localization error in memory, but also an index of *relational binding* by determining the frequency with which an object is misplaced to the location of one of the other items held in memory.

Pertzov *et al.* previously found that individuals with focal MTL damage due to voltage-gated potassium channel antibody (VGKC-ab) mediated limbic encephalitis had a specific impairment in binding object identity to location but had no difficulty remembering the identities and locations on their own (Pertzov et al., 2013). Thus when participants mislocalized objects, their reports were often clustered around the locations of other objects in the array rather than occurring randomly (Pertzov et al. 2012, 2013).

Here I tested whether relational memory binding in VSTM is impaired in a group of 20 individuals who were carriers of pathological mutations for FAD using the 'What was where?' task (Pertzov et al., 2013). Subsidiary analyses are

performed in 12 asymptomatic and 8 symptomatic cases respectively in order to determine whether deficits can be detected in the asymptomatic group. To examine the relationship between performance on this task and the hippocampus, I also related misbinding rate to hippocampal volume.

Based on previous work in individuals with MTL damage due to VGKC-ab encephalitis, I hypothesized that similar binding deficits might be demonstrated in individuals with FAD and that such findings could also extend to presymptomatic mutation carriers as the hippocampus is one of the earliest structures involved in AD pathology. I further hypothesized that there could be a significant association between hippocampal volume and performance on the binding task such that lower hippocampal volume would predict greater deficits on the binding task.

4.2 Methods

4.2.1 Participants

Participants were recruited from an on-going longitudinal FAD study at the Dementia Research Centre, University College London (UCL), which receives referrals from across the UK. Individuals at risk of FAD were recruited into the

study if there was an autosomal dominant family history of AD and a known pathological mutation in either presenilin 1 (*PSEN1)* or amyloid precursor protein (*APP*) genes in at least one affected family member. Based on the results of genetic tests and clinical assessments (see below), individuals were classified as symptomatic FAD individuals, asymptomatic FAD gene carriers or non-carriers.

Symptomatic individuals were those who had a positive genetic test and cognitive symptoms consistent with AD. Asymptomatic gene carriers were at-risk individuals who had a positive genetic test but did not have symptoms and who scored zero on the CDR (see below). Non-carriers were at-risk individuals who tested negative for pathological mutations. The controls for the study consisted of both non-carriers and healthy individuals recruited for the study. As the symptomatic and asymptomatic gene carrier groups differed significantly in terms of age, two different but overlapping sets of controls were selected from the entire control group (n=62) to be age-matched for each gene carrier group (see Appendix A1 for further details). Baseline characteristics of the groups are presented in Tables 4.1.

All participants had normal or corrected-to-normal visual acuity and colour vision by self-report or according to their informants. We used “years from parental age of onset” as an indicator of how far the asymptomatic gene carriers

were likely to be from manifesting symptoms (Bateman et al., 2012). This was calculated by subtracting the individuals' age at the time of the assessment from that at which their parents first developed symptoms of FAD (see Table 4.1). One symptomatic FAD individual was on acetylcholinesterase inhibitor treatment at the time of assessment. To ensure that level of performance was sufficiently above chance, we set a minimum threshold of 70% average accuracy in identification performance as an inclusion criterion (see section 4.2.4 for further details). On this basis, six symptomatic FAD participants who took part were excluded. The study was approved by the local ethics committees (University College London and University College Hospital London) and all subjects gave written informed consent.

4.2.2. Protocol

The study protocol included a clinical assessment, a neuropsychological assessment, the 'What was where?' VSTM experiment and a 3T structural MRI scan. Detailed interviews were conducted with individuals at risk of FAD and their close informants by a neurologist (YL, NF) to probe the presence of cognitive or behavioural symptoms attributable to AD. AD was diagnosed using the most up-to-date research criteria at the time of assessment (Dubois et al., 2010, 2007). Folstein's mini-mental state examination (MMSE) (Folstein, 1975), the CDR (J. C. Morris, 1993) and Hospital Anxiety and Depression scale (HADS) (Zigmond and Snaith, 1983) were administered to all participants.

Genetic results were available for all at-risk individuals, either on a clinical or research basis. Research genetic results were only fed back to the statistician involved in the study and were not disclosed to the participants or to other researchers.

4.2.3. Neuropsychological assessment and statistical analysis

The neuropsychological test battery included measures of current intelligence and estimate of premorbid intelligence (the National Adult Reading Test) (NART) (H. Nelson, 1991). The following tests for memory function were included: RMT for words and faces (Warrington, 1984), story recall from the logical memory subset of WMS-R (WMS-logical memory) (Wechsler, 1987), Rey complex figure (measured as the ratio of score for the immediate delay condition over score for the copy condition) (Osterreith, 1944), digit span (Wechsler, 1987) and spatial span (Kessels et al., 2000). Also included in the neuropsychology battery were verbal fluency (sum total of words generated in one minute beginning with letters F, A and S respectively) (Spreen & Strauss, 1998), Stroop (difference in time taken to complete the conflict and word conditions) (Stroop, 1935), Trail Making Test (difference in time taken to complete TMB and TMA) (Reitan, 1958), category fluency (sum total of animal and vegetable names generated in one minute respectively) (Spreen & Strauss, 1998), Graded Naming Test (McKenna & Warrington, 1983); Graded Difficulty

Arithmetic Test (Jackson & Warrington, 1986); object decision test from the Visual Object and Space Perception battery (VOSP) (E. K. Warrington & James, 1991a) and digit symbol test (Wechsler, 1981).

Linear regression was used to compare neuropsychological test scores between the entire FAD group and controls, the symptomatic group and age-matched controls and between the asymptomatic group and their controls. Where test scores were not normally distributed, the data was transformed where suitable approximations to the normal distribution could be achieved. Where parametric assumptions were not met even after transformation, analysis proceeded with the untransformed score and bias-corrected accelerated bootstrap confidence intervals for the differences between groups were provided based on 2000 replications. All comparisons were adjusted for the effects of NART and sex.

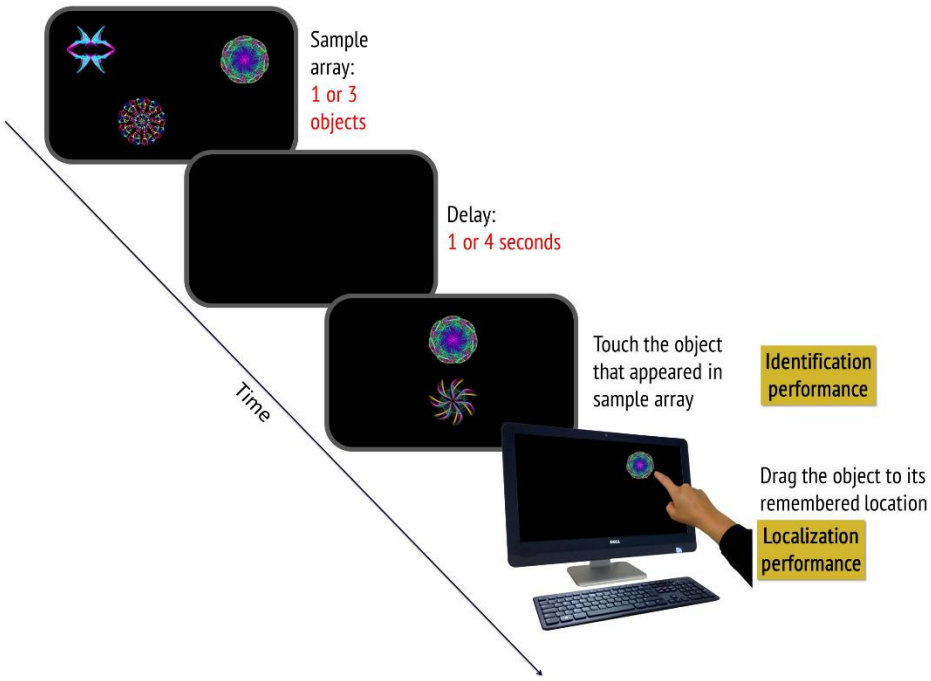
4.2.4. Visual short-term memory experiment

The stimuli and procedure used have been described in detail in previous publications (Pertzov et al., 2012, 2013, 2015). A schematic of the task is shown in Fig. 4.1. Participants sat approximately 42 cm in front of an interactive touch-sensitive screen (Dell Inspiron One 2320) with a 1920 x 1080 pixel matrix corresponding to approximately 62 x 35° of visual angle. In each trial, participants viewed 1 or 3 fractal objects, each randomly located on the

screen. They were asked to remember both the objects and their locations. A blank screen was then displayed for 1 or 4 s duration, followed by a test array in which two fractals appeared along the vertical meridian. One of these was in the memory array, namely the target fractal whereas the other one was a foil or distractor. The foil was not an unfamiliar object but was part of the general pool of fractal images presented across the experiment.

Participants were required to touch the fractal which they remembered to have been in the memory array and drag it on the touch screen to its remembered location. This provides us with a continuous, analogue measure of localization error. Each participant performed a practice block of 10 trials followed by two test blocks. Each test block consisted of ten trials with one fractal and 40 trials with three fractals. In each test block, the number of trials with one or three fractals and 1s or 4s delay between memory and test arrays were balanced.

Figure 4.1 Schematic of 'What was where?' task



One or three fractals were shown prior to a variable delay of either 1 or 4s, after which one of the objects was displayed together with a foil (distractor which had not appeared in the memory array). Participants were required to touch the item they recalled (**identification performance**) and drag it to its remembered location (**localization performance**).

Fractal stimuli were drawn from a library of 60 pictures of fractals (see Appendix Fig 1; http://sprott.physics.wisc.edu/fractals.htm). Each fractal was presented between 2 and 3 times in different trials within the block. The

locations of the fractals were determined by a Matlab script (MathWorks, Inc) in a pseudorandom manner, with several restrictions.

Importantly, fractals were never located within 9° of each other in order to prevent spatial uncertainty as a result of crowding and to create a clear zone around the original locations of the items which is critical for the analysis of localization errors. Moreover, they were positioned with a minimum of 3.9° from the edges of the screen and 6.5° degrees from the centre of screen.

Memory for **object identity** was measured as the proportion of trials where the correct object was chosen in the test array. **Gross localization error** was computed as the distance (expressed as visual angle) between the centre of the target object after it had been dragged to its remembered location and at its true (original) location in the memory array. It was only measured on trials where an object was correctly identified.

Previous studies have indicated that when participants mislocalize objects, some of their reports can be clustered around the locations of other objects in the memory array, rather than occurring randomly (Pertzov et al., 2012, 2013). These are called **swap errors** because the location of the target fractal was swapped with that of another fractal in the original memory array. The number

of swap errors was indexed by the percentage of correctly identified objects placed within 4.5° eccentricity of other fractals in the original array. A threshold of 4.5° was used because objects were never presented less than 9° from each other in the memory array. Using a cut-off of 4.5° means that the reported location of an object could never be attributed to more than one object.

It might be argued that objects localized further away from their original location simply by chance might lead to more apparent swap errors. To ensure that swap errors did not simply result from increased gross localization errors, we also used a measure of **swap errors corrected for chance** (see Appendix A2 for calculation as originally described (Pertzov et al., 2013)).

In order to investigate the effect swap errors have on the overall gross localization error and to determine whether swap errors can explain all of the memory deficits in remembering the location of the target fractal, I also computed the distance between the remembered location of the target fractal and the nearest fractal in the original memory array, *regardless* of whether it was the target. This **nearest neighbour control** analysis provides a simple index of the **localization precision** regardless of object identity. It effectively provides a measure of localization error subtracting out the effects of swap errors (see Pertzov et al., 2013). Comparison of gross localization error with the

error computed by the nearest neighbour control analysis therefore provides an important measure of the impact of swap errors on overall recall localization.

4.2.5 Statistical analysis for VSTM outcomes

Analysis of identification performance used a logistic regression model for the odds of choosing the correct object in the test array. Analysis of localization performance used a linear regression model for natural logarithm of gross localization error and localization precision (using "nearest neighbour control" analysis). Analysis of swap errors used a linear regression for square root of proportion of swaps and square root of proportion of swaps controlled for chance. A square root transformation was necessary because of the skew in the proportion of swap errors. The same transformation was used for both swap analyses to allow comparison of performance with and without control for chance.

For each outcome, performance was compared between the entire FAD group and all controls, asymptomatic individuals and aged-matched controls and symptomatic individuals and age-matched controls. For each outcome, I first tested for main effects of group, delay and block. For object identity and gross mislocalization error, I also tested for main effect of item number. Further analysis then explored two-way interactions between group and each condition,

namely delay, block and number of items (in the case of object identity and gross mislocalization error). This allowed me to examine whether any between-group differences in performance depended on the task condition. Where a significant two-way interaction was found or where there was an *a priori* hypothesis, I also examined three-way interactions between group, delay and block or item number. Results of interactions are only presented if they were statistically significant or relevant to the overall interpretation of the experiment. All analyses of the outcomes of VSTM experiments were adjusted for the effects of NART and sex. The analyses corrected for NART- a marker of education - but not IQ as NART has previously been shown to be relatively resistant to the effect of AD (Law & O'Carroll, 1998) whereas, importantly, IQ is not (Fox et al., 1998; Godbolt et al., 2005; Godbolt et al., 2004). If I were to correct for IQ, any effect related to AD itself could be falsely diminished. Furthermore, for both the FAD mutation carriers as a whole and for controls, there is a statistically significant association between total IQ and NART (see section 4.3.2). Robust standard errors were used to allow for repeated measures within the same individual.

4.2.6 Brain image acquisition and statistical analysis of relationships between VSTM outcomes and hippocampal volumes

T1-weighted volumetric MR brain images were acquired on a 3T Siemens TIM Trio scanner using a magnetization prepared rapid gradient echo (MPRAGE) protocol acquired in sagittal orientation (TR=220ms, TE=2.9ms, TI=900ms, Flip angle=9^{o}, FOV=282x282x228mm, voxel size=1.1x1.1x1.1mm). Hippocampal volumes were estimated using a template-based method for automated segmentations (Jorge Cardoso et al., 2013) and manually edited where required. For each participant, total hippocampal volume (sum of left and right hippocampus) was calculated. We generated a head size measure by estimating total intracranial volumes (TIV) from the summation of the volumes of grey matter, white matter and cerebral spinal fluid using the segmentation toolbox in Statistical Parametric Mapping version 8 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007; Leung, Barnes, et al., 2010).

Linear regression was used to compare hippocampal volume between groups, adjusting for age, sex and TIV. To examine the association between hippocampal volume and the outcomes of the VSTM task (overall memory for object identity and localization and overall swap error rates), we used the same modelling approach as described for analysis of VSTM outcomes (see section 4.2.5). The analyses compared the association between hippocampal volume and VSTM outcomes between the entire FAD group and controls, by including main effects for group, hippocampal volume (entered as a continuous predictor), and interaction between hippocampal volume and group. To ensure that any

association found in FAD participants was not simply driven by differences in hippocampal volume between asymptomatic and symptomatic gene carriers, analyses were then repeated with inclusion of separate terms for these two groups and their interactions with hippocampal volume. All analyses were adjusted for age, sex and TIV.

4.3 Results

4.3.1 Baseline characteristics of participants

The FAD cohort as a whole had on average fewer years of formal education and lower MMSE, depression (measured by HADS) and NART scores. Asymptomatic FAD gene carriers had similar baseline characteristic as age-matched controls except for slightly lower depression score and fewer years of formal education. As expected, symptomatic gene carriers had lower MMSE and NART scores than age-matched controls (Table 4.1).

Table 4.1 Characteristics of FAD gene carriers and age-matched controls.

Mean values are given with SDs.

Group	Age (yrs)	Males	Education (yrs)	MMSE (/30)	Anxiety HAD scale (/21)	Depression HAD scale (/21)	NART (/50)
All Controls (N=62)	40.1 (7.9)	31	15.5 (2.7)	29.5 (0.8)	5.9 (3.8)	3.13 (2.88)	32.3 (9.1)
All FAD (N=20)	41.3 (8.7)	10	13.6 (2.6)	28.0 (2.8)	5.5 (4.2)	1.68 (2.24)	26.7 (10.6)
P value	0.61	1	0.01	0.01	0.68	0.03	0.04

Group	Age (yrs)	Males (%)	Education (yrs)	MMSE (/30)	Anxiety HAD scale (/21)	Depression HAD scale (/21)	NART (/50)	Years to parental age of symptom onset
Controls (N=50)	36.9 (4.1)	50%	15.7 (2.6)	29.5 (0.9)	6.1(3.8)	3.1 (2.8)	31 (9.0)	NA
Asymptomatic carriers (N=12)	37.2 (4.4)	25%	13.4 (2.4)	29.4 (0.9)	5 (4.2)	1.3 (2.2)	28.3 (9.3)	8.5 (3.8)
***p* value**	0.85	0.75	0.01	0.74	0.43	0.02	0.37	NA

Group	Age (yrs)	Males (%)	Education (yrs)	MMSE (/30)	Anxiety HAD scale (/21)	Depression HAD scale (/21)	NART (/50)
Controls (N=28)	46.8 (6.9)	46%	14.3 (2.6)	29.7 (0.5)	4.9 (3.5)	2.6 (2.7)	31.9 (10.3)
Symptomatic carriers (N=8)	47.4 (10.2)	63%	13.9 (3.1)	25.8 (3.4)	6.3 (4.4)	2.4 (2.3)	24.3 (12.6)
***p* value**	0.89	0.69	0.74	<0.001	0.47	0.84	<0.001

4.3.2. Neuropsychological assessment

On average, **FAD participants** were significantly worse than controls at current IQ, RMT Words, WMS-logical memory immediate and delayed conditions, Rey complex figure, spatial span forward maximum, Stroop, Trail making, Graded Difficulty Arithmetic test and Digit symbol test. **Asymptomatic** gene carriers were not, on average, significantly different to their controls in any of the measures including conventional indices of working memory (e.g., digit and spatial spans), other than WASI IQ score (controls=116.9, asymptomatic=103.6, $p<0.001$) (see Table 4.2). On the other hand, **symptomatic** FAD individuals were, on average, significantly worse than their controls on IQ, RMT for words, WMS-logical memory immediate and delayed conditions, Rey complex figure, digit span backward maximum, spatial span forward maximum, Stroop test, Trail making, GDA and the digit symbol test (see Table 4.2).

Table 4.2 Neuropsychology results of FAD gene carriers and age-matched controls. Mean values are given with SDs.

Test	All controls (N=62)	All FAD (N=20)	P value or C.I. estimates by boot strapping
IQ (WASI)	117.4 (11.8)	97.9 (18.0)	<0.001
RMT Words /50	48.4 (2.1)	43.4 (7.4)	-7.7 to -1.88
RMT Faces /50	42.2 (4.8)	42.1 (3.7)	0.58
WMS-LM immediate /25	16.4 (4.02)	11.9 (4.73)	0.001
WMS-LM delayed* /25	15.0 (3.83)	10.3 (5.28)	0.001
Rey* (delay: copy)	0.69 (0.12)	0.52 (0.24)	0.002
Digit span forward max /8	7.20 (1.1)	6.5 (1.4)	-0.95 to 0.19
Digit span backward max/7	5.26 (1.15)	4.95 (1.39)	0.81
Spatial span forward max /9	5.81 (0.97)	4.95 (1.27)	-1.49 to -0.34
Spatial span backward max /9	5.42 (1.0)	5.16 (1.17)	0.49
Letter fluency (FAS)	46.5 (10.4)	40.3 (9.1)	0.13
Stroop	27.7 (10.7)	42.5 (29.3)	7.60 to 14.0
Trail making	31.3 (19.4)	56.3 (54.8)	5.05 to 47.2
Category fluency	40.0 (8.13)	35.5 (10.6)	0.20
GNT /30	21.4 (4.78)	19.1 (5.58)	0.81
GDA /24	0.69 (0.12)	0.52 (0.24)	0.002
VOSP (object decision) /20	17.9 (1.76)	18.2 (1.46)	0.28
Digit symbol	62.2 (11.1)	50.6 (18.3)	0.003

Legend:

RMT: recognition memory test

WMS-LM: Wechsler Memory Scale-logical memory

GNT: Graded naming test

GDA: Graded difficulty arithmetic test

VOSP: Visual Object and Spatial Perception

*Scores from WMS-LM delayed and Rey complex figure underwent square transformation

Test	**Controls (*N*=50)**	**Asymptomatic carriers (*N*=12)**	***p* value or C.I. estimates by boot strapping**
IQ (WASI)	116.9 (11.9)	103.6 (13.2)	<0.001
RMT Words /50	48.4 (2.2)	47 (2.6)	-3.1 to 0.2
RMT Faces /50	41.6 (4.9)	43.3 (3.4)	0.21
WMS-LM immediate /25	16.4 (4.2)	14.3 (3.8)	0.10
WMS-LM delayed /25	14.9 (3.9)	13.5 (3.3)	0.25
Rey (delay: copy)	0.69 (0.1)	0.61 (0.2)	0.11
Digit span forward max /8	7.2 (1.1)	6.9 (1.0)	-0.34 to 0.09
Digit span backward max /7	5.31 (1.2))	5.42 (1.0)	0.36
Spatial span forward max /9	5.9 (1.0)	5.3 (1.2)	-1.5 to 0.04
Spatial span backward max /9	5.5 (1.0)	5.4 (1.2)	0.96
Letter fluency (FAS)	46.7 (11.0)	43.8 (5.8)	0.57
Stroop	28.1 (10.4)	32.8 (10.2)	0.22
Trail making	30.7 (20.5)	34.4 (14.8)	-8.6 to 13.2
Category fluency	39.4 (8.3)	38.4 (11.7)	0.94
GNT /30	20.7 (4.7)	19.6 (4.5)	0.85
GDA /24	16.2 (5.3)	15.6 (4.3)	0.9
VOSP (object decision) /20	17.7 (1.7)	18.4 (1.3)	0.13
Digit symbol	39.4 (8.3)	38.4 (11.7)	0.18

Test	**Controls (*N*=28)**	**Symptomatic carriers (*N*=8)**	***p* value or C.I. estimates by boot strapping**
IQ (WASI)	116.7 (11.1)	89.4 (21.6)	<0.001
RMT Words /50	48 (1.9)	38 (8.5)	-10.4 to -7.1
RMT Faces /50	42.6 (4.2)	40.3 (3.7)	0.40
WMS-LM immediate /25	15.1 (3.8)	8.4 (3.7)	0.01
WMS-LM delayed /25	14.5 (3.5)	5.5 (3.6)	<0.001
Rey (delay: copy)	0.67 (0.14)	0.36 (0.22)	<0.001
Digit span forward max /8	7.0 (1.1)	5.9 (1.6)	0.15
Digit span backward max/7	5.1 (1.2)	4.3 (1.6)	0.005
Spatial span forward max*/9	5.5 (0.7)	4.3 (1.1)	0.003
Spatial span backward max /9	5.1 (0.8)	4.7 (1.1)	0.19
Letter fluency (FAS)	46.4 (11.2)	35.1 (11.1)	0.051
Stroop	28.7 (11.6)	56.9 (43.3)	0.02
Trail making	35.2 (23.6)	89.1 (75.8)	13.9 to 95.2
Category fluency	39.3 (8.3)	31 (7.3)	0.053
GNT /30	22.4 (4.7)	18.4 (7.2)	0.35
GDA /24	16.4 (4.5)	9.5 (5.9)	0.003
VOSP (object decision) /20	18.1 (2.0)	17.8 (1.7)	0.86
Digit symbol	56.6 (8.9)	38.6 (14.5)	0.001

Legend:

RMT: recognition memory test

WMS-LM: Wechsler Memory Scale-logical memory

GNT: Graded naming test

GDA: Graded difficulty arithmetic test

VOSP: Visual Object and Spatial Perception

∗ Scores from spatial span forward maximum underwent cube transformation

Relationship between NART and IQ (WASI)

There is a statistically significant association between total IQ and NART in both the FAD cohort (0.49 point increase in NART score for every point increase in total IQ, $p<0.001$) and in controls (0.54 point increase in NART for every point increase in total IQ, $p<0.001$). However, there is no significant interaction in the relationship between NART and IQ between the two groups (0.05 point difference in NART for every 1 point difference in IQ, $p=0.6$)).

4.3.3. Visual short-term memory experiment

4.3.3.1. All FAD cases

Consistent with findings of previous studies (Pertzov et al., 2013; Pertzov et al., 2012), performance was significantly influenced by memory load (1 or 3 objects), delay (1 or 4 s) and block (first vs second block of trials) for both object identification and gross mislocalization error such that all participants (FAD cases and controls) were worse in higher memory load and longer delays and improved in the second block.

The FAD group performed significantly worse than controls in memory for object identity (FAD=86.7% vs. controls=91.7%, $p=0.009$, $z=-2.61$) as well as in gross localization memory performance, measured as raw error from the

original location of the probed item in the memory array (FAD=7.89^{o} vs. controls=5.64^{o}, p=0.001, t=3.39).

For localization, there was a significant interaction between group and block, as well as a significant triple interaction between group, block and item number [F(3,81) =4.79, p=0.004]. Further analysis revealed that FAD participants were significantly impaired in both the 1- and 3-item conditions in the first block (Fig. 4.2), but in the second block this was the case for only the 3-item condition (*Block 1 for 1 item:* FAD=3.44^{o} vs controls=2.42^{o}, p=0.009, t=2.67; *Block 1 for 3 items:* FAD=10.2^{o} vs controls=7.28^{o}, p<0.001, t=3.99; *Block 2 for 1 item:* FAD= 2.43^{o} vs controls=2.33^{o}, p=0.41, t=0.83; *Block 2 for 3 items:* FAD=7.59^{o} vs controls=5.63^{o}, p=0.009, t=2.69).

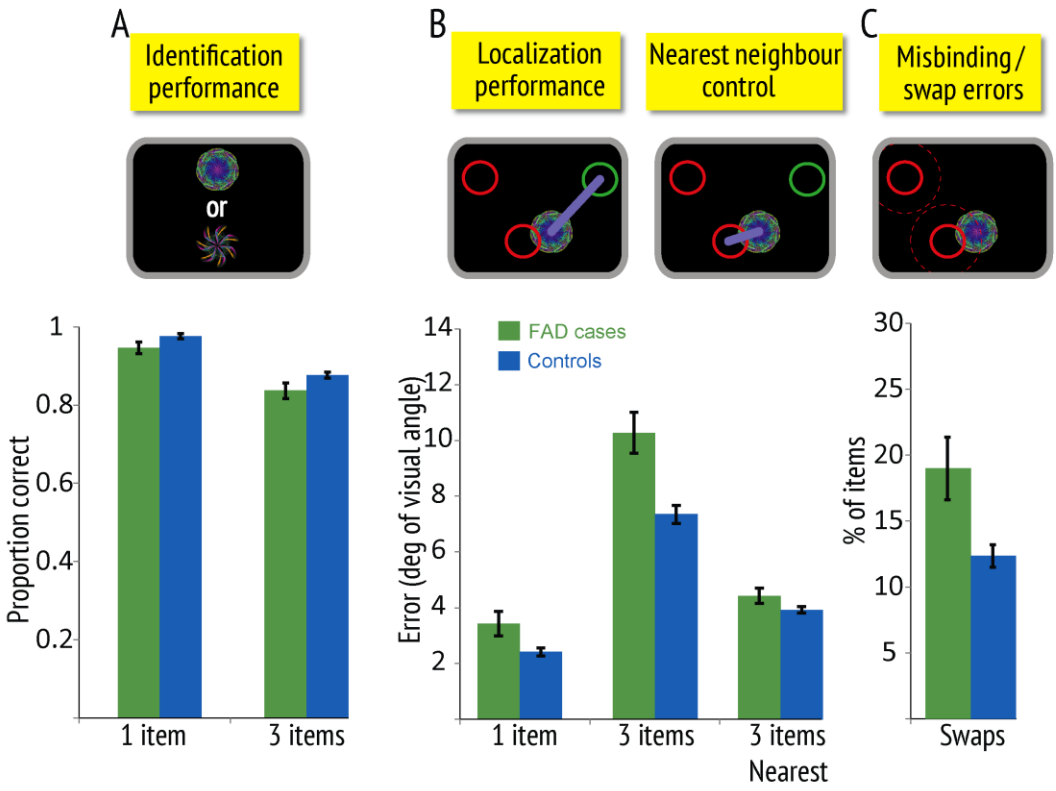


Figure 4.2 Memory performance of all FAD cases versus controls in first block.

(A) Identification performance for one or 3 items in the memory array. **(B) Localization performance** (gross localization error) – measured as error from the true location of the item in the memory array. The "nearest neighbour" control error was calculated as the minimal distance between a reported location and any one of the previously presented fractals for three-item trials. Top inset images illustrate how outcomes are measured. Circles represent the original location of the target fractal (green) and two other, non-probed fractals (red); purple lines illustrate how localization errors are measured for gross localization and nearest neighbour

distances. **(C) Swap or misbinding errors** are proportion of times target objects were localized close to the remembered locations of *non-probed fractals* in the original display (red circles). The inset image above shows how a target fractal might be misplaced to the location of a non-probed item, thereby generating a swap error. Error bars represent standard errors of the mean.

When they correctly identified the objects, FAD individuals were significantly more likely to make swap errors than controls (FAD=16.5% vs controls=10.6%, p=0.006, t=2.84). Thus, they mislocalized the probed item to the position of another object in the original memory array more often than healthy controls. Even after controlling for swap errors due to chance (see Methods 4.2.4), the group difference remained significant (FAD=11.2% vs controls=7.12%, p=0.006, t=2.83). A main effect of block was found, reflecting lower number of swaps in the second block in both groups.

In the first block alone, the FAD group made significantly more swap errors than controls (FAD=18.9% vs controls=12.3%, p=0.005, t=2.85). As it has previously been shown that healthy participants make significantly more swap errors when delay length is extended (Pertzov et al., 2012), I also examined the effect of delay on swap errors (see section 4.2.5) and found a borderline significant group and delay interaction (p=0.08, t=-1.79). Further analysis

revealed that the FAD group was significantly worse than controls in the longer delay condition (FAD=18.6% vs controls=10.7%, p=0.002, t=3.25) but not over shorter delays (FAD=14.4% vs controls=10.6%, p=0.13, t=1.54).

In order to establish whether the additional error in mislocalization observed in the FAD group could be entirely attributed to swap errors, the "nearest neighbour control" analysis was carried out (see Methods 5.2.4). When localization error was measured with respect to the nearest neighbour in the memory array, the difference between FAD cases and controls reduced considerably, indicating that misbinding errors made a large contribution to their gross localization error. However, there still remained a significant difference between the groups (overall FAD=4.30^{o} vs controls=3.69^{o}, p=0.012, t=2.58; in first block FAD=4.41^{o} vs controls=3.86^{o}, p=0.049, t=2.00; Fig. 4.2). Therefore, in addition to making significantly more swap errors, there was an extra source of error in the overall FAD group. This source of localization error might be due to noisier encoding, storage, recall or all three of these potential processes. These results show that the FAD group as a whole had deficits in both memory for identity and location. Furthermore, location memory over a few seconds was significantly corrupted by misbinding errors, but these did not account completely for all the gross localization error.

4.3.3.2. Asymptomatic gene carriers

Compared to age-matched controls, across the two blocks, asymptomatic gene carriers did not differ significantly in their ability to remember the identity of the fractals (asymptomatic FAD= 89.9% vs controls= 92.1%, p= 0.29, z= -1.06) or in gross localization error (asymptomatic FAD= 6.47^{o} vs controls= 5.58^{o}, p= 0.12, t= 1.58). Both groups showed learning across blocks and worse performance with longer delay and higher memory load. Importantly, there was a significant group by block interaction in localization performance (p= 0.03, t= -2.27).

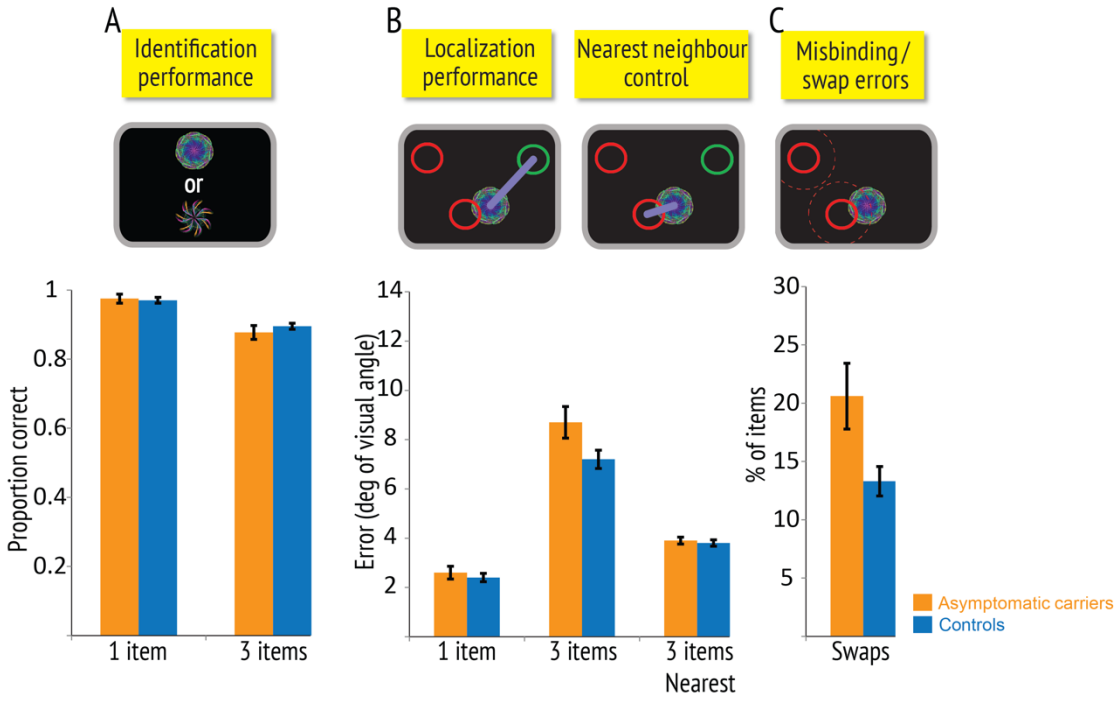


Figure 4.3 Memory performance of asymptomatic carriers versus controls in first block.

(A) Identification performance: proportion of times participants selected the correct fractal on two-alternative forced choice, when there were one or three items in the memory array. **(B) Localization performance** shows gross localization error – simply measured as the error from the true location of the item in the memory array. The "nearest neighbour" control error (localization precision) was calculated as the minimal distance between a reported location and any one of the previously presented fractals for three-item trials. Top inset images illustrate how the outcomes are measured. Circles represent the original location of the target fractal (green) and two other, non-probed fractals (red); purple lines illustrate the localization errors for the two different measures. **(C) Swap or misbinding errors 4s delay**: proportion of times target objects were localized close to the remembered locations of non-probed fractals in the original display (red circles). The inset image above shows how a probed fractal might be misplaced to the location of one of the non-probed items, thereby generating a swap error. Error bars represent standard errors of the mean.

Assessment of the data of each block separately revealed that while asymptomatic gene carriers were significantly worse in localization memory

than controls in the first block (asymptomatic FAD= 7.52^{o} vs controls= 6.25^{o}, p= 0.03, t= 2.19), there was no difference in the second block (asymptomatic FAD= 5.42 ^{o} vs controls= 4.90 ^{o}, p= 0.40, t= 0.84) (Fig. 4.3). Further analysis revealed that asymptomatic gene carriers were significantly worse than controls in only the multiple item conditions in the first block (*3 items:* asymptomatic FAD= 8.74^{o} vs controls= 7.21^{o}, p= 0.02, t= 2.33; *1 item:* asymptomatic FAD= 2.65^{o} vs controls= 2.38^{o}, p= 0.16, t= 1.43; Fig. 4.3).

To evaluate the contribution of misbinding to the impairment in localization memory in this condition, the frequency of swap errors was computed. As delay had an effect on swap errors in the entire FAD group, I also examined the effect of delay and block on swap errors here. There was a borderline significant three-way interaction between group, block and delay [F(3, 61)= 2.54, p= 0.06]. Compared to controls, asymptomatic gene carriers made significantly more swap errors in the 4s delay condition of the first block (Fig. 4.3: asymptomatic FAD= 20.6% vs controls= 13.3%, p= 0.009, t= 2.71). This was evident even after controlling for swap errors due to chance (asymptomatic FAD= 13.6% vs controls= 9.1%, p= 0.03, t= 2.24). Thus, the asymptomatic carriers group was significantly more likely to misbind identity and location of items in the longer delay condition in the first block.

As with the analysis for the FAD group overall, I then used the "nearest neighbour control" analysis to investigate whether all the error in localization performance of asymptomatic gene carriers could be attributed to identity-location misbinding. When this was performed, the difference in localization memory performance between asymptomatic gene carriers and controls in the extended delay condition of the first block was no longer significant (Fig. 4.3: asymptomatic FAD= 3.92^{o} vs controls= 3.83^{o}, p= 0.55, t= 0.38). This finding strongly suggests that the increased gross mislocalization error of asymptomatic FAD cases can be accounted for entirely by their increased tendency to make swap errors, namely, misbinding item identity and location.

In summary, the asymptomatic gene carriers were significantly worse than controls in localisation memory performance in the first block when multiple items were remembered. This deficit can be attributed specifically to increased swap errors when there was longer delay between the memory and test conditions and not impaired precision of localization *per se,* e.g. due to increased noise in memory. Thus recall in these individuals seems to be systematically corrupted by interference from other items in memory. This contrasts with the findings for location memory for all FAD cases which cannot entirely be attributed to misbinding errors alone.

4.3.3.3. Symptomatic FAD cases

Unlike asymptomatic gene carriers, symptomatic FAD cases were overall significantly worse than age-matched controls both in their ability to remember object identity (symptomatic FAD= 81.8% vs controls= 91.3%, $p< 0.001$, $z= -4.71$) and location (symptomatic FAD= 10.0^{o} vs controls= 5.90^{o}, $p< 0.001$, $t= 4.76$). For gross localization, there was a significant interaction between group and block, as well as a significant three-way interaction between group, item and block [$F(2,35)= 6.88$, $p= 0.003$].

Thus symptomatic FAD individuals were significantly worse than controls in *both* 1- and 3-item conditions in the first block (Fig. 5.4: *3 items:* symptomatic FAD= 12.5^{o} vs. controls= 7.72^{o}, p< 0.001, t= 4.18; *1 item:* symptomatic FAD= 4.62^{o} vs. controls= 2.54^{o}, p= 0.01, t= 2.58). This differs from asymptomatic gene carriers who were only impaired on the 3-item condition in the first block. Symptomatic cases, like healthy controls and asymptomatic gene carriers, showed learning. Thus, in the second block the difference between them and controls was apparent only for 3-items trials (*3 items:* symptomatic FAD= 9.97^{o} vs. controls= 5.82^{o}, p< 0.001, t= 5.52; *1 item:* symptomatic FAD= 2.68^{o} vs. controls= 2.30^{o}, P= 0.24, t= 1.20). Again, this differs from asymptomatic gene carriers who were not significantly different from healthy controls in the second block.

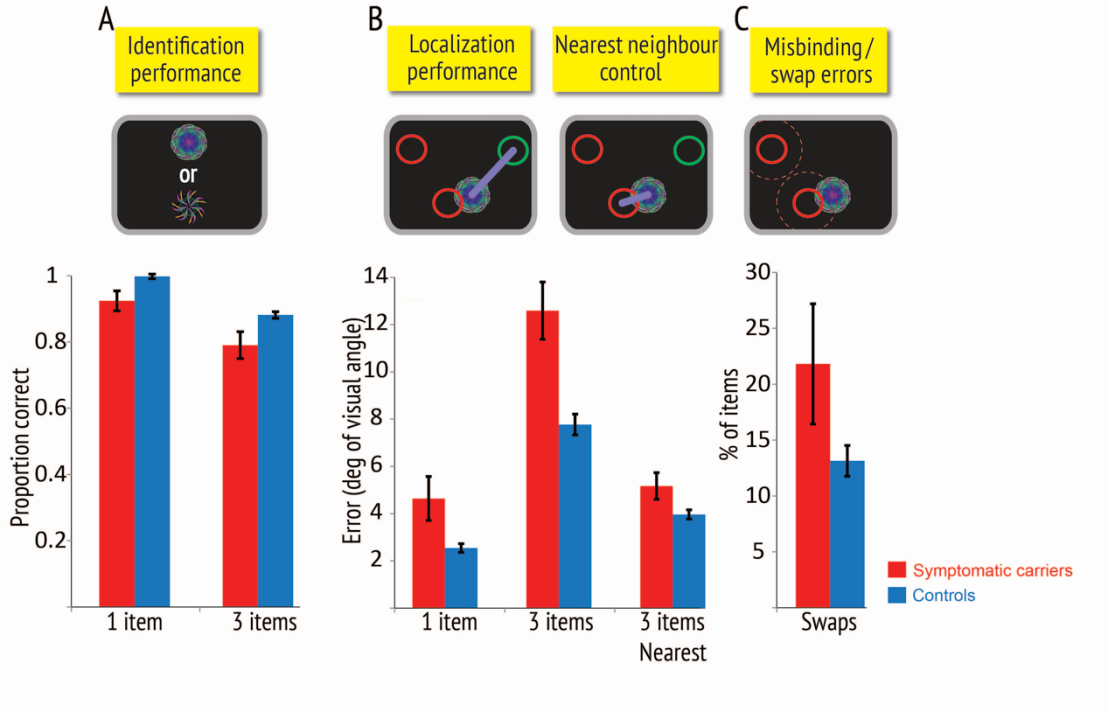


Figure 4.4 Memory performance of symptomatic FAD cases versus controls in first block.

(A) Identification performance for one or three items in the memory array. **(B) Localization performance** (gross localization error) – measured as error from the true location of the item in the memory array. The "nearest neighbour" control error was calculated as the minimal distance between a reported location and any one of the previously presented fractals for three-item trials. Top inset images illustrate how the outcomes are measured. Circles represent the original location of the target fractal (green) and two other, non-probed fractals (red); blue lines illustrate the localization errors for the two different measures. **(C) Swap or misbinding errors** are proportion of times target objects were

localized close to the remembered locations of non-probed fractals in the original display (red circles). The inset image above shows how a target fractal might be misplaced to the location of a non-probed item, thereby generating a swap error. Error bars represent standard errors of the mean.

Next, I assessed the contribution of swap errors to the impairment in the localization memory. Symptomatic FAD cases made significantly more swap errors than controls overall (symptomatic FAD= 21.3% vs controls= 11.6%, $p< 0.001$, $t= 4.12$). Even after controlling for swap errors due to chance, the overall group difference remained significant (symptomatic FAD= 14.3% vs controls= 7.8%, $p= 0.008$, $t= 2.82$). Symptomatic FAD cases also made significantly more errors than controls in the first block (Fig. 4.4: symptomatic FAD= 21.6% vs controls= 13.0%, $p< 0.05$, $t= 2.06$). However, there were no significant two-way interactions between group and delay, or three-way interactions between group, delay and block. In order to ascertain whether misbinding explained all their error on localization memory performance, just as it did for asymptomatic cases, again I used the "nearest neighbour control" analysis to investigate this. Unlike asymptomatic gene carriers, symptomatic FAD cases remained significantly impaired compared to controls on this purer localization precision measure too, both overall and in the first block (Fig. 4.4: *Block 1:* symptomatic FAD= 5.14^{o} vs controls= 3.95^{o}, $p= 0.009$, $t= 2.44$; *Overall:* symptomatic FAD= 4.82^{o} vs

controls= 3.73^{o}, p= 0.005, t= 3.00). Thus, their poor memory for location cannot be attributed solely to increased misbinding of identity to location.

In summary, the symptomatic FAD group was significantly impaired in memory for object identity and gross localization for the 3-item condition. Unlike asymptomatic cases, their increased gross mislocalization was due to both increased swap errors (misbinding) and reduced precision of localization. Degradation of localization precision was also evident in localization errors even when they had to remember one item (i.e. when no misbinding was possible), at least in the first block.

4.3.4. Hippocampal volumes and correlations with VSTM outcomes

54 controls, 12 asymptomatic and six symptomatic gene carriers had usable structural MRI scans. Mean (SD) total (left plus right) raw hippocampal volumes in these groups were 5.8 (0.64), 6.0 (0.69) and 5.2 (0.55) cm^3 respectively.

After adjusting for the effects of age, sex and TIV, the hippocampal volumes of the asymptomatic gene carriers were not significantly different to the control volumes (mean difference 0.26 cm^3, p=0.10). However, symptomatic individuals had significantly smaller hippocampal volumes compared with both

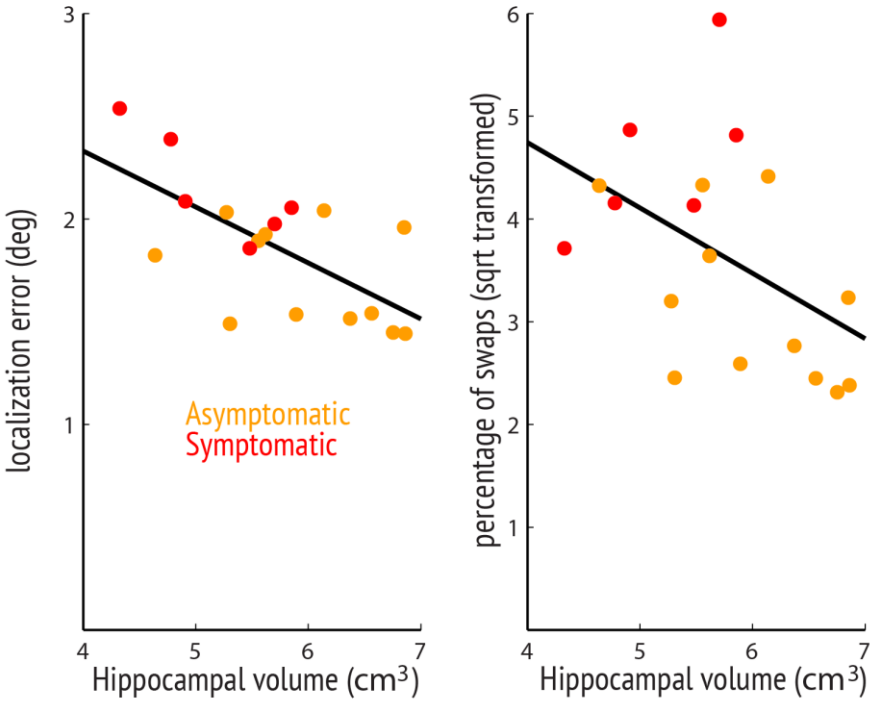
controls (mean difference 0.67 cm^3, p=0.003) and asymptomatic gene carriers (mean difference 0.93 cm^3, p=0.001).

There was no statistically significant association between identification performance and hippocampal volumes in either the entire controls group (odds ratio=0.94, p=0.64) or the entire FAD group (odds ratio=1.35, p=0.15) without any significant interactions between the groups (odds ratio=1.44, p=0.10).

Unlike identification performance, there was a statistically significant association between gross mislocalization error and total hippocampal volume in the entire FAD group (21% reduction in error per cm^3 increase in volume, p=0.02) (Fig. 5.5) but not in controls (2% reduction per cm^3, p=0.79) and the group interaction was marginally significant (mean difference 19% reduction per cm^3, p=0.050). The association in the FAD group appeared to be driven by the symptomatic (41% reduction per cm^3, p<0.001) rather than asymptomatic gene carriers (7% reduction per cm^3, p=0.42) with significant interactions between both symptomatic individuals and controls (mean difference of 42% reduction per cm^3, P<0.001) and between symptomatic and asymptomatic gene carriers (mean difference of 37% reduction per cm^3, p=0.003). However, there were no significant associations between hippocampal volume and pure localization precision (as measured using the "nearest neighbour control" analysis) in either the entire FAD group (7% reduction per cm^3, p=0.35) or

controls (1% reduction per cm^3, p=0.82) with no interaction between the two groups (mean difference of 11% reduction per cm^3, p=0.21). This suggests that hippocampal volume was more likely to be associated with swap errors rather than localization precision *per se*.

Figure 4.5 Relationship between hippocampal volume and memory.



Total hippocampal volumes (adjusted for TIV) were inversely correlated with overall gross mislocalization error and overall swap errors (square root transformed) across FAD individuals.

Lastly, there was a significant association between proportion of overall swap errors and hippocampal volume in the entire FAD group (regression

coefficient=-0.76, $p<0.001$) (Fig. 5.5) but not in controls (regression coefficient=-0.03, $p=0.91$) with significant interaction between the two groups (mean difference in regression coefficient=-0.73, $p=0.008$). The correlation in the FAD cases is significant even when considering only asymptomatic gene carriers (regression coefficient=-0.64, $p=0.045$) but not in the symptomatic cases (regression coefficient=0.71, $p=0.15$). There were significant interactions between the asymptomatic gene carriers and controls (mean difference in regression coefficient=-0.68, $p=0.02$) and between asymptomatic and symptomatic gene carriers (mean difference in regression coefficient=1.35, $p=0.02$).

4.3.5 Relationship between depression (HAD) scores and swap error rate

There was no statistically significant association between HAD depression scores and the average misbinding rate (swap error rate) in either the FAD cohort as a whole (coefficient=-0.01, $p=0.93$) or in controls (coefficient=0.02, $p=0.76$) using regression analysis with no statistically significant interaction between the two groups (coefficient=0.02, $p=0.82$).

4.4 Discussion

In this study, I investigated VSTM in individuals with pathological mutations for FAD using a delayed reproduction paradigm (Pertzov et al., 2012, 2013). Overall, FAD mutation carriers showed significantly worse memory for both object identity and location. Crucially, they more frequently mislocalized the probed item (target fractal) to the location of one of the other, non-probed fractals held in memory array (Fig. 4.2). Such swap or relational binding errors provide direct behavioural evidence of an impaired ability to bind together memory for object identity to its location.

For the entire FAD group, misbinding of object identity and location accounted for much of their mislocalization error, but not for all of it. In the asymptomatic gene carriers, however, this was the only deficit identified when multiple objects were present in the memory array for 4 s, accounting fully for the localization deficit in these individuals (Fig. 4.3). As this was only evident in the longer delay condition, it suggests that the impairment may be related to difficulty in maintenance processes rather than memory encoding or retrieval as impairment in encoding\retrieval should influence performance in the short delay as well. Furthermore, it was observed only in the first block of the experiment. This may reflect the ability of participants to successfully recruit high level strategies leading to significantly improved performance with practice (Pertzov et al., 2014). The learning effect could explain why relational binding performance between asymptomatic mutation carriers and controls was

observed only in the most challenging condition, i.e. longer delay condition in the first block, with any differences disappearing with practice.

These misbinding errors cannot be explained by a failure to remember the identity of the objects as asymptomatic gene carriers exhibited normal performance when required to recognize fractals in the memory array and localization analysis was performed only in trials with accurate identification. Furthermore, the "nearest neighbour control" analysis – which measures the shortest distance from any fractal in the original memory array to the location where the probed item was located by the participant – shows that they also remembered the locations of the fractals well (Fig. 4.3). This points to the conclusion that although the locations of items in the memory array were retained in asymptomatic gene carriers, they were not correctly bound to the identities of the fractals that occupied those locations – a deficit of *relational binding* (Eichenbaum, 2006; Konkel et al., 2008; A. Mayes et al., 2007).

This finding echoes directly the similar result in VGKC-Ab mediated limbic encephalitis using the same paradigm (Pertzov et al., 2013). Because both FAD cases and VGKC-Ab patients have evidence of hippocampal atrophy or lesions respectively (Fox et al., 1996; Khan et al., 2009; Pertzov et al., 2013; Ridha et al., 2006; Schott et al., 2003), the results of my study further contribute to

evidence of a role for the hippocampus in relational binding even over short retention delays.

Symptomatic FAD cases in the current study also showed increased swap errors. In addition, they also had deficits in memory for individual features, namely, object identity and location even for 1 item (Fig. 4.4), where there is no scope for an object-location misbinding error.

For all FAD cases, there was a significant negative correlation between hippocampal volume and swap error rate (Fig. 4.5), but not for object identity or localization *per se*, again consistent with the view of a relationship between hippocampus and relational binding. The lack of a significant correlation between hippocampal volume and swap errors in the symptomatic group may be due to their exaggerated localization error so even when they misremembered the location of a fractal to that of another fractal, their localization was too imprecise for it to count as a swap error.

The results show that in FAD, object-location misbinding errors are observable even when performance on standard neuropsychological tests of working memory and long-term memory did not differ from healthy controls. The findings of my study extend previous reports of impaired *conjunctive binding* in

AD, for colour-shape or colour-colour, before deficits on standard neuropsychological tests are apparent (Parra et al., 2009, 2010, 2011).

While the dichotomy of *conjunctive* and *relational* binding is open to debate, several investigators have swayed strongly towards the conclusion that the hippocampus is crucial for relational binding for long-term storage of items (Cohen & Eichenbaum, 1993; Eichenbaum, 2006; Konkel et al., 2008; Moses & Ryan, 2006), but is less critical for item memory or binding of features within objects (Baddeley et al., 2010; Konkel et al., 2008; Murray & Mishkin, 1998; Staresina & Davachi, 2008). Indeed, several studies have reported that conjunctive binding can be preserved in hippocampal patients (Baddeley et al., 2010; Mayes et al., 2007; Parra et al., 2015) and recent neurophysiological studies provide evidence that the hippocampus or MTL structures may act as a hub for integrating and co-ordinating disparate cortical representations to support relational binding (Cashdollar, Duncan, & Duzel, 2011; Watrous, Tandon, Connor, Pieters, & Ekstrom, 2013).

The findings presented here and previously in VGKC-Ab cases (Pertzov et al., 2013) suggest that the relational binding role of the hippocampus is not confined to long-term memory but also affects short-term retention. This, along with evidence from other studies of MTL lesion cases suggest that the distinction between long- and short-term, conscious and unconscious memory

systems may be less clear than traditionally considered (Cohen and Eichenbaum, 1993; Hannula et al., 2006; Olson et al., 2006; Ranganath & Blumenfeld, 2005).

The current study has several limitations. First, it might be argued that the VSTM deficits in mutation carriers might be confounded by perceptual difficulties. This is more plausible for the symptomatic FAD cases, who showed deficits in memory for object identity, but seems less likely to influence the results from the asymptomatic gene carriers because their identification performance was unimpaired and binding deficits were mainly observed for long delays (perceptual impairment should affect both delays). Second, the sample size was relatively small due to the rarity of FAD and the limited number of symptomatic individuals who were able to perform the task to a reasonable level. As a result, the mutation carriers in the study were pooled from pedigrees with different *PSEN1* and *APP* mutations. Therefore, it is not possible to draw conclusions about individual genotypes or to assess differences between *PSEN1* and *APP* mutations. However, given that our findings were achieved with a heterogeneous genetic cohort, it is likely that the effect is related to hippocampal dysfunction, common to all FAD mutations, rather than some gene-specific property.

In summary, I have shown that failure in object-location binding in VSTM is an early cognitive feature of FAD, observable before impairment in object

identification, localization and standard neuropsychology measures of working memory and long- term memory appear. Consistent with the concept that the hippocampus is fundamentally engaged in relational binding in memory, we found that hippocampal volume significantly predicted the degree of binding errors in mutation carriers. Abnormal object-location binding might therefore be a sensitive cognitive biomarker for early MTL lobe pathology including AD.

Chapter 5 CONCLUSIONS

This thesis provides new insights into the neuropsychological changes that occur in the early stages of FAD. There was an emphasis on investigating intra-individual cognitive trajectories in order to determine the timing of pathological cognitive decline and to characterize qualitative changes such as intra-individual variability over time. This thesis also used a novel computer-based paradigm for investigating object-location binding in visual short-term memory and related the behavioural findings to hippocampal volume. Lastly, the thesis described a case of frontotemporal dementia due to a *MAPT* mutation which presented with marked amnesia and was challenging to diagnose. The case illustrates the neuropsychological and imaging features which can be helpful in differentiating AD from non-AD dementia.

5.1 Chapter 2 Cognitive function in individuals at risk of FAD

This chapter describes a longitudinal study investigating the cognitive features of 19 individuals who were followed from an asymptomatic phase through to Alzheimer's dementia. The key findings are as follows. At a group level, mutation carriers and non-carriers from the same kindreds performed similarly at baseline, suggesting similar cognitive function many years before symptom onset. There was a clear correlation between neuropsychological scores and how close mutation carriers were to symptom onset at baseline, implying a

decline in objective cognitive function during the presymptomatic phase. Tests probing memory and learning function were the first to show a decline with carriers and non-carriers showing divergent rate of change approximately 2 years before the actual onset of symptoms. Decline in most other tests were found to occur around the time of symptom onset. These findings have subsequently been replicated or are supported by studies from the DIAN collaboration and other FAD cohort (Almkvist et al., 2019; McDade et al., 2018; Storandt et al., 2014).

Although its sample size was relatively small, the study benefitted from the use of rigorous selection criteria for inclusion of asymptomatic individuals at baseline, the long follow-up time for converters (mean 10 years; S.D. 5 years) and the certainty of age of symptom onset. This meant that it was possible to investigate the intra-individual trajectories from an asymptomatic baseline through symptom development to the subsequent dementia diagnosis. This contrasts with most longitudinal studies in FAD where the average follow-up period was much more limited (McDade et al., 2018). This dataset therefore offers a unique longitudinal perspective.

The results of my study contribute to our knowledge of the likely timing and sequence of objective cognitive changes in FAD and, along with existing body

of biomarker research, provide empirical evidence which supports the proposed sequence of biomarker dynamics in the current model of AD (Jack et al., 2013).

The longitudinal nature of the study with repeated assessments also revealed some interesting findings which had not been systematically studied in FAD previously. One such result was that the variance in the scores on a number of cognitive tests (assessed annually) showed an increase soon after the onset of symptoms. I was motivated to investigate the possibility of fluctuations in neuropsychological performance based on my clinical observations of fluctuations in subjective memory symptoms as well as in neuropsychological scores in some FAD mutation carriers who have mild symptoms attributable to AD. At this clinical stage, cross-sectional performance in neuropsychology tests may still be in the normal range and the interpretation of the scores may be made more difficult by such fluctuations in performance. Therefore, an understanding that longer-term (e.g. year-to-year) fluctuations in cognitive performance is consistent with early stages of AD and may be a marker of cognitive decline is useful in both research and clinical settings. Increased IIV-I variability may also be a useful marker of cognitive decline in individuals whose baseline or premorbid cognitive performance fall outside the normal range. These findings of increased IIV-I and practice effects also have important bearing on clinical trial designs. To date, most research on IIV-I in aging and dementia has focused on short-term IIV-I. More research is needed to

investigate the presence and extent of long-term IIV-I cross different cognitive tests as individuals transition from normal cognition to MCI and dementia.

The main limitation of the study is the relatively small sample size which limits the type of modelling that is appropriate. Given the known phenotypical and imaging biomarker differences between *APP* and *PSEN1* mutations (Scahill et al., 2013), it would be of interest for future studies to further investigate longitudinal neuropsychological changes in these two sub-groups separately.

5.2 Chapter 3 Lessons from a novel *MAPT* mutation case

In this study, I described a case of FTD which presented with marked amnesia, and which had posed a significant diagnostic challenge. Analysis of the longitudinal clinical, neuropsychological and imaging findings helped to reveal features that could be helpful in differentiating AD from non-AD dementia. Specifically, early impairment in confrontational naming in the context of amnesia should prompt directed investigation of semantic memory function which could help uncover anterior temporal lobe dysfunction, a feature that is in keeping with certain phenotypes of FTD. Second, the use of brain registration techniques such as whole brain fluid registration can provide a sensitive means of delineating regions of atrophy. In this case, it helped to reveal the progressive anterior temporal lobe atrophy that is more typically associated with FTD (Chan

et al., 2001). Third, the case illustrates the usefulness of CSF biomarkers in the differential diagnosis of AD and FTD. Lastly, it highlights the important point that non-AD dementias may present with profound amnesia and that FTD caused by *MAPT* mutations should be considered when there is a positive family history.

5.3 Chapter 4 Visual short-term memory binding in FAD

In this chapter, I investigated VSTM function in a group of FAD mutation carriers. Most standard memory batteries such as Logical Memory (immediate and delayed recall) or Recognition Memory Tests (Warrington, 1984) probe memory functions minutes (or longer) after initial learning. Memory over a period of seconds, i.e. short-term memory function, has been relatively little studied in AD. However, anecdotally, it is not uncommon for affected individuals and family to report difficulties with holding onto information over an extremely short delay. Therefore, investigating short-term memory function in AD is clinically relevant.

I used a recently developed delayed reproduction paradigm (Pertzov et al., 2013) which allows assessment of participants' recognition memory of object identity independent of their recall of object location. By using a continuous scale of report of object location, it was possible to probe the nature and magnitude of

localisation errors. I found that the FAD mutation carriers as a whole showed significantly worse memory for both object identity and location. Importantly, even when they correctly recognized the correct fractal, they more frequently mislocalized it to the location of one of the other, non-probed fractals held in memory array, i.e. made swap errors. In the asymptomatic gene carriers however, this was the only deficit identified when multiple objects were present in the memory array, accounting fully for the localization deficit in these individuals.

This was the first study which provided direct behavioural evidence that individuals with FAD had an impaired ability to bind together memory for object identity to its location in STM. Further, I found that, for all FAD cases, there was a significant negative correlation between hippocampal volume and swap error rate, but not for object identity or localization *per se*. Given the well-established role of the hippocampus in associative memory, my findings, together with previous report of misbinding errors shown by individuals with VGKC-antibody mediated limbic encephalitis using the same paradigm suggest that the MTLs support relational memory over both long-term and short-term. My findings also extend our knowledge of the nature of STM deficits in FAD and SAD (Parra et al., 2009, 2010) as only conjunctive binding deficits had been demonstrated previously.

It is noteworthy that the asymptomatic mutation carrier group as a whole performed similarly to healthy controls on a wide range of standard neuropsychological tests, suggesting relatively intact general cognition. Therefore, the computerized paradigm may have utility as a diagnostic test for diseases which affect the hippocampus or MTLs, including AD (Pavisic, Suarez-Gonzalez, & Pertzov, 2020). VSTM binding in normal older individuals has been investigated using the same paradigm (Pertzov et al., 2014). Normal ageing was not associated with increased swap error rates once errors for object identity were corrected for. It would be important for future studies to investigate the specificity of VSTM misbinding errors by testing individuals with conditions which may present diagnostic challenges such as depression and non-AD dementia, e.g. FTD. It would also be of interest to test individuals at-risk of FAD on this VSTM paradigm in a longitudinal fashion and compare the sensitivity of this task with other cognitive tests in detecting cognitive decline. It is unlikely, however, that any single behavioural test is 100% sensitive and specific for AD. As with all para-clinical tests, results need to be interpreted in the clinical context and in conjunction with other diagnostic tools.

This study is a good example of how development in neuroscience-in this case a new theoretical approach to VSTM and a task that can dissect out sources of error contributing to the imprecision in localization memory- can improve our understanding of the brain mechanisms underlying a behavioural phenomenon

in AD. On the other hand, the unique characteristics of the research participants who are likely to have pathological changes in MTLs even in the asymptomatic stage of the disease provide a rare lesion model to test neuroscientific hypothesis. The result is improved knowledge of brain-behavioural relationships. Pavisic *et al.* recently used eye-tracking devices to record eye movement of FAD mutation carriers whilst performing the same VSTM task. They found that the encoding of object location may be vulnerable in preclinical FAD mutation carriers, potentially accounting for weakened spatial memory (Pavisic et al., 2021). Future research in AD will benefit from continued collaboration and dialogues between clinical and cognitive neuroscience research.

Learning effect was evident in FAD mutation carriers during the asymptomatic and mildly symptomatic clinical stages in both the longitudinal neuropsychology study and in the VSTM binding experiment. This implies a degree of neuroplasticity at this stage of the FAD. Future studies should explore whether interventions aimed at harnessing this effect may provide symptomatic benefits, albeit on a temporary basis.

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7 STATEMENTS OF ATTRIBUTION

Chapter 2: Cognitive function in individuals at risk of FAD

I conceived and designed the study with advice from Professors Nick Fox and Sebastian Crutch. I was involved in the acquisition and analysis of clinical data. Dr Tim Shakespeare, Dr Keir Yong and colleagues in the neuropsychology department at the National Hospital for Neurology and Neurosurgery conducted the neuropsychological assessment of the participants. Dr Sebastian Crutch provided additional help with acquisition and analysis of neuropsychological data. Much of the historical clinical information of the participants were acquired by successive clinical researchers who had worked on the longitudinal familial Alzheimer's study at the Dementia Research Centre, UCL. Dr Tom Yeatman and Professor Nicholas Fox provided additional support in the acquisition of clinical data. Dr Jennifer Nicholas was involved in the design of the study and provided vital statistical support for the study. Professors Elizabeth Warrington and Martin Rossor gave feedback of the script. The MRC Prion Unit conducted much of the genetic analysis.

Chapter 3: Lessons from a novel *MAPT* mutation case

I was involved in the conception and design of the study with advice from Dr Diane Caine, Professors Nick Fox and Jason Warren. I was also involved in the acquisition and analysis of clinical data. Professor Lisa Cipolotti and other colleagues in the neuropsychology department at the National Hospital for Neurology and were involved in assessing the patient. Dr Diana Caine provided interpretation of the neuropsychology data for the manuscript. Dr Jagger gave interpretation of the MRI scans. Dr Elizabeth Gordon performed brain segmentation and much of the brain volume analysis. Kelvin Leung assisted with the fluid registration. Dr Jennifer Nicholas provided statistical support. Dr Susie Henley reviewed the manuscript.

Chapter 4: Visual short-term memory binding in FAD

Professors Masud Husain and Yoni Pertzov developed the experimental paradigm and original design of the study. I was involved in the study design with advice from Professors Yoni Pertzov, Masud Husain, Sebastian Crutch and Nick Fox. I was involved in the acquisition of clinical data of the participants and neuropsychological data of the controls. Drs Tim Shakespeare and Kier Yong performed neuropsychological assessment of FAD mutation carriers and those at risk of FAD. I performed the statistical analysis with advice and

support from Dr Jennifer Nicholas. Dr Susie Henley gave feedback on the manuscript. Brain segmentations were performed mostly by Felix Woodward. The MRC Prion Unit conducted much of the genetic analysis.

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9 PUBLICATIONS ARISING FROM THIS THESIS

Chapter 1 Introduction

Liang, Y., Ryan, N. S., Schott, J. M., & Fox, N. C. (2013). Imaging the onset and progression of Alzheimer's disease: implications for prevention trials. Journal of Alzheimer's disease: JAD, 33 Suppl 1, S305–S312.

Ryan, N. S., Nicholas, J. M., Weston, P., Liang, Y., Lashley, T., Guerreiro, R., Adamson, G., Kenny, J., Beck, J., Chavez-Gutierrez, L., de Strooper, B., Revesz, T., Holton, J., Mead, S., Rossor, M. N., & Fox, N. C. (2016). Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. The Lancet. Neurology, 15(13), 1326–1335.

Cash, D. M., Ridgway, G. R., Liang, Y., Ryan, N. S., Kinnunen, K. M., Yeatman, T., Malone, I. B., Benzinger, T. L., Jack, C. R., Jr, Thompson, P. M., Ghetti, B. F., Saykin, A. J., Masters, C. L., Ringman, J. M., Salloway, S. P., Schofield, P. R., Sperling, R. A., Cairns, N. J., Marcus, D. S., Xiong, C., … Dominantly Inherited Alzheimer Network (DIAN) (2013). The pattern of atrophy in familial Alzheimer disease: volumetric MRI results from the DIAN study. Neurology, 81(16), 1425–1433.

Chapter 3 Lessons from a novel *MAPT* mutation case

Liang, Y., Gordon, E., Rohrer, J., Downey, L., de Silva, R., Jäger, H. R., Nicholas, J., Modat, M., Cardoso, M. J., Mahoney, C., Warren, J., Rossor, M., Fox, N., & Caine, D. (2014). A cognitive chameleon: lessons from a novel MAPT mutation case. Neurocase, 20(6), 684–694.

Chapter 4 Visual short-term memory binding in FAD

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S., Crutch, S., Woodward, F., Leung, K., Fox, N. C., & Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. Cortex; a journal devoted to the study of the nervous system and behaviour, 78, 150–164.

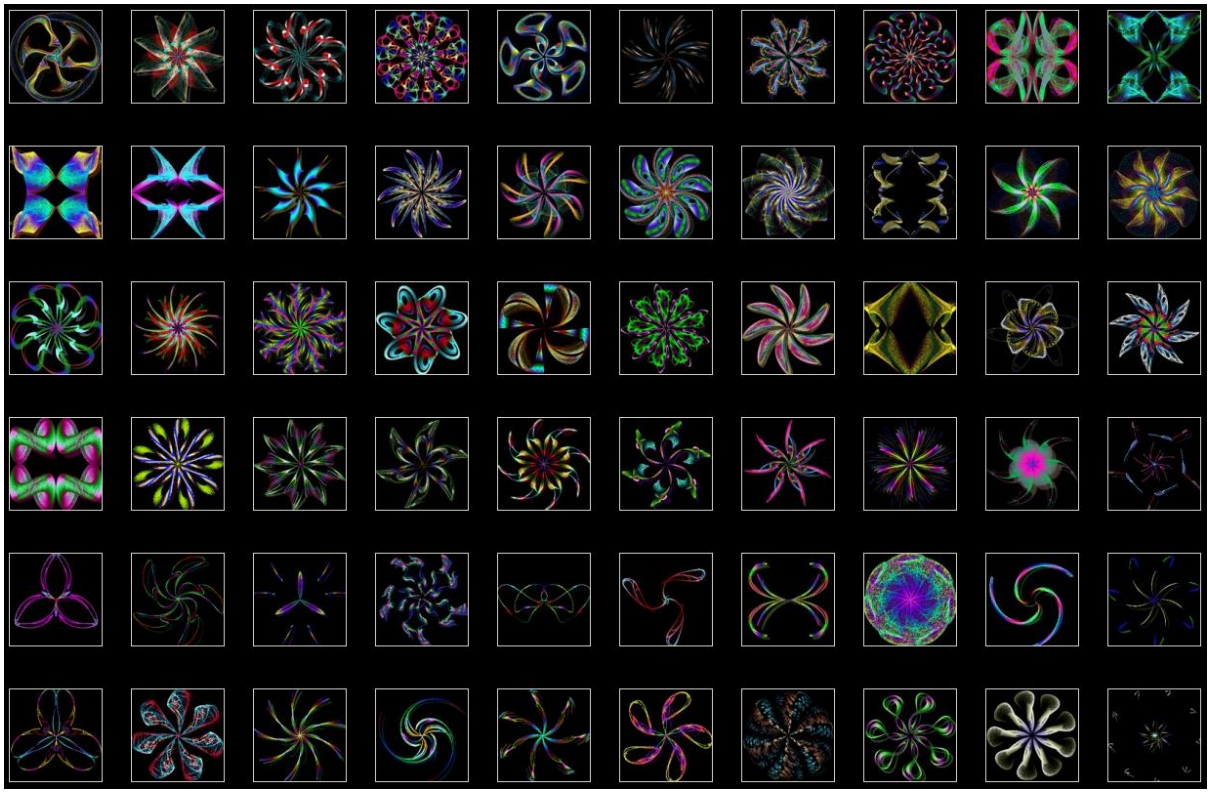
Pertzov, Y., Heider, M., Liang, Y., & Husain, M. (2015). Effects of healthy ageing on precision and binding of object location in visual short term memory. Psychology and aging, 30(1), 26–35.

10 APPENDIX

Appendix A1. Selection of control groups for VSTM binding study

To select subsets of controls who were age-matched to the asymptomatic and symptomatic mutation carriers groups respectively, we used box plots (showing the median, interquartile range and total range for age) to guide us in terms of the appropriate age cut-offs to apply. Guided by the box plots, controls older than 47 years of age were excluded when selecting individuals to be age-matched to the asymptomatic group and controls younger than 39 years of age were excluded when selecting those to be age-matched to the symptomatic group. We then performed t-tests to check that the resultant two subsets of controls were well matched to the two gene carrier groups in terms of the group means and standard deviations. The selection of the controls was solely based on age criteria and no reference to task performance.

Appendix Figure 1. Visual stimuli used in VSTM binding study



60 colored fractals on black background were used. Symmetrical fractals were generated using code provided in Sprott's Fractal Gallery (http://sprott.physics.wisc.edu/fractals.htm). Fractals were resized to have maximum width and height of 120 pixels (~4° of visual angle in experimental set-up).

A2 Calculation of swap error corrected for chance for VSTM study

In order to ensure that the increased number of swap errors did not simply result from increased gross localization errors, i.e. objects localized further away from their original location might generate more (apparent) swap errors simply by chance, we performed the following calculation. For each trial, we calculated the probability of obtaining swap errors by chance by computing all potential locations with the same absolute distance of error from the original target location at all possible angular deviations (using steps of 1^0) with the proviso that a simulated location had to be within the screen dimensions and the invisible margins used for generating the display. The chance probability of obtaining a swap error is therefore the number of simulated locations within our 4.5^0 threshold perimeter around non-targets, divided by all possible valid, simulated locations (Pertzov et al., 2012) (Pertzov et al., 2013). This calculation was performed for every trial using its specific distance of error from the target item. The number of swap errors predicted by chance was subtracted from the measured number of swap errors. This gave a measure of swap errors corrected for chance.