Multimodal studies of brain structure and function in neurodegenerative dementia

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Abstract

Alzheimer's disease (AD) is associated with a prodromal stage of cognitive decline, manifest clinically as mild cognitive impairment (MCI) that progresses ultimately to a stage of dementia. There is an urgent need to recognise AD at its earliest clinical stages, which entails distinguishing AD from other conditions, particularly other neurodegenerative diseases, but at a time when clinical symptoms are non-specific. Investigations such as neuropsychological testing and neuroimaging, using MRI and PET to determine changes in brain structure and metabolism respectively, provide additional useful diagnostic information, the changes associated with these tests now incorporated into diagnostic criteria.

These studies aimed to investigate AD and Frontotemporal dementia (FTD) using these investigative tools, with a particular focus on AD in keeping with its central importance as the commonest cause of dementia. Early AD was the focus of the first study. Given the involvement of the hippocampus from the initial stages of AD, and of the role of the hippocampus in spatial memory, the study hypothesis was that a hippocampus-sensitive test of spatial memory would discriminate prodromal AD and mild AD dementia with high sensitivity and specificity. The 4 Mountains Test of spatial memory (4MT) was chosen in view of its potential usability across different cultural settings.

The second study focused on dementia due to AD and FTD. Given the diagnostic importance of MRI and PET changes, this study aimed to measure the concordance of atrophy and hypometabolism in six syndromic variants of AD and FTD. The primary hypothesis was that concordance would differ across different AD and FTD syndromes, with a secondary hypothesis that determination of the topographical extent of atrophy and hypometabolism would differ according to the method used to determine imaging changes.

Declaration

I declare that the research contained in the thesis, unless formally indicated, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate material already submitted for a degree.

Statement of Contribution

I was responsible for the recruitment of all patients involved in these studies and performed the related behavioural testing in the majority of cases. Dr Ruth Wood, NIHR Academic Clinical Fellow in Neurology, tested any additional patients while Laura Bottomley, CISC data administrator, tested any additional controls. I trained both individuals and also supervised their initial assessments of study participants.

Regarding the neuroimaging, Dr Ludovico Minati (University of Trento) wrote the MRI protocols and Dr John Dickson (University College Hospital London NHS Trust) wrote the PET protocol. Valeria Contarino (Instituto Neurologico Carlo Besta) performed the quantitative MRI processing, and Dr Pasquale Della Rosa (University “Vita-Salute” San Raffaele) performed the SPM-based PET processing.

I undertook all the statistical analyses carried out on the MRI, PET and psychometric data and led on the writing of papers describing the outputs of these studies.

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Preface

Dementia is a major source of personal, societal and fiscal hardship, predicted to spiral further in an ageing society. The diagnosis and management of diseases leading to dementia have been prioritized in an attempt to offset the related socio-economic crisis. Increasing attention is being focused on the earliest clinical stages of these diseases in the hope that this will facilitate drug discovery and improve the delivery of currently available treatments. The research performed as part of this thesis investigates patients in the earliest stages of dementia applying complementary assessments of brain structure and brain function. The work focuses particularly on AD and FTD, two of the most common causes of early-onset dementia in the world, using a multimodal approach that complements the recently updated diagnostic criteria for these disorders.

Acknowledgements

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4MT	Four mountains test of spatial memory
AD	Alzheimer's disease
CDR	Clinical dementia rating scale
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
MMSE	Mini-mental state examination
PM	Place memory subtest of the 4MT
PP	Place perception subtest of the 4MT

1. Introduction

"…the dotage of old persons is often times something more than a mere decay of memory. For they mistake things present for others, and their discourse is often foreign to the objects that are present to them. However the imperfection of their memory in respect of impressions but just made, or at short intervals of past time, is one principal source of their mistakes. One may suppose here that the parts of the brain in which the miniature vibrations belonging to ideas have taken place, are decayed in a peculiar manner…"
(David Hartley, 1834)

1.1 An overview of dementia

The International Statistical Classification of Diseases and Related Health Problems (ICD) defines dementia as "a syndrome due to disease of the brain, usually of a chronic or progressive nature in which there is disturbance of multiple higher cortical functions including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment" (ICD, 10th Revision, 1992).

By comparison, the clinical criteria used in dementia diagnosis are essentially two-tiered. First, they define dementia as a cognitive and behavioural disorder and second, they stipulate that personal, occupational or social independence must be lost as a result thereof (McKhann *et al*., 2011; Zaudig, 1992). The criteria require the presence of subjective and objective cognitive changes, the former based on either direct or collateral history taking, with the latter requiring objective deficits in more than one cognitive domain.

In most instances, the diseases causing dementia (Figure 1) result in a progressive intellectual decline, and dementia severity is reflected by the level of caregiver support needed to complete activities of daily living (ADLs) (Morris, 1993). At current estimates, there are over 850,000 individuals with

dementia in the UK whose estimated annual cost to society exceeds £26 billion (Dementia UK update, 2014; www.alzheimers.org.uk). Approximately £10.3 billion of this reflects social care spending alone. Communities and families provide an estimated £11 billion further in unpaid care while the estimated loss of income to the exchequer, arising from the adoption of full-time caregiver roles, exceeds £ 690 million (Dementia UK report, 2007; www.alzheimers.org.uk).

Alzheimer's disease (AD) is the most prevalent cause of dementia in the world, affecting an estimated 500 000 individuals in the UK alone (Dementia UK report, 2007; www.alzheimers.org.uk). The prevalence of AD increases exponentially with advancing age, doubling every five years after the age of 65 (McDowell, 2001). Coupled with improved societal longevity, the predicted social impact of AD prompted the World Health Organization (WHO) to recognize it as a public health priority (WHO report 2010). The currently licensed treatments for AD do not alter either disease progression or rates of institutionalization and are most effective in enhancing cognition during a stage of mild dementia (Bond *et al*., 2012). As such, should disease-modifying therapies become available, it will be essential to differentiate between AD and non-AD pathology, with minimal diagnostic delay (Brookmeyer *et al*., 2007). The crisis surrounding dementia recognition and treatment has prompted concerted political and scientific efforts to improve on the status quo (https://www.gov.uk/government/publications/g8-dementia-summit-agreements/g8-dementia-summit-communique; https://www.gov.uk/government/policies/dementia).

Neurodegenerative diseases, like AD, are characterised by the progressive loss of functionally related neurons (Przedborski *et al*., 2003). Age and a positive family history are the two leading risk factors for neurodegenerative disease (Macario & de Macario, 2002; Jellinger, 2010). In sporadic and hereditary cases of dementia, the pathological changes observed in surviving neurons have helped provide valuable insights into disease pathogenesis (for

a review, see (Bossy-Wetzel *et al*., 2004). Endogenous peptides accumulate then precipitate to form inclusion bodies, during which other features of impaired cellular and synaptic function become apparent (Ballatore *et al*., 2007). Although the mechanisms that promote inclusion body formation in sporadic and inherited dementias may differ, the inclusions are initially focally distributed within the brain, becoming more widespread over time, appearing to propagate between neurons (Przedborski *et al*., 2003). The earliest pathological changes are asymptomatic although the inclusions are regarded as harbingers of neuronal loss and, later, cognitive decline (H. Braak & E. Braak, 1991). Inclusion body immunocytochemistry has allowed the neurodegenerative dementias to be grouped into Alzheimer-type and non Alzheimer-type pathologies *(*Kovacs *et al.*, 2010) with further sub-classification based on the topography of neuronal loss (Galvin *et al*., 2001; Cairns *et al.*, 2007). Importantly, the different brain regions differ in their susceptibility to Alzheimer and non-Alzheimer pathologies, with the loss of intact function within these areas giving rise to characteristic symptoms; the associations between substrate, pathology and symptoms have been useful in realising diagnostic criteria for the different neurodegenerative dementias. For instance, AD is typically associated with early medial temporal lobe (MTL) neurodegeneration, manifest as progressive memory impairment (Braak and Braak, 1991). In everyday practice, gradual memory decline is synonymous with AD, stipulated within earlier diagnostic criteria as a typical feature of disease (McKhann *et al*., 1984). However, revisions to these criteria have become necessary to incorporate non-amnestic AD presentations (McKhann *et al*., 2011).

Another aspect of neurodegeneration that is clinically relevant is the relationship between age of symptom onset and causal pathology. Early onset dementia (EOD) refers to the appearance of symptoms before the age of 65 years (Rossor *et al*., 2010). Vascular dementia (VaD) is the second most common cause of late-onset dementia (LOD) after AD (Lobo *et al*., 2007) and some vascular risk factors, such as obesity and diabetes, are also independent risk factors for late-onset AD (Breteler, 2000). With advancing

age, there is also an increased prevalence of pathologically mixed dementia (Ebly *et al.*, 1994; Barker *et al*., 2002). Indeed, the UK MRC-funded Cognitive and Function Aging Study (CFAS; 2001) found that most older people with dementia had evidence of mixed VaD/AD pathology (Neuropathology Group, Medical Research Council Cognitive Function and Aging Study, 2001). AD is also the UK's leading cause of EOD although other neurodegenerative diseases also occur more commonly within this demographic (Figures 1,2). EOD is also more likely to arise from non-neurodegenerative diseases, such as infection and metabolic disorders (Harvey *et al.*, 2003). In these cases, progression from mild to severe dementia usually occurs more rapidly than with AD, and early recognition and treatment of the non-neurodegenerative conditions may lead to clinical improvement (Paterson *et al*., 2012). In addition to the causal pathology itself, rates of cognitive decline in dementia are also influenced by epigenetic factors, gender and level of education (Bowler *et al*., 1998).

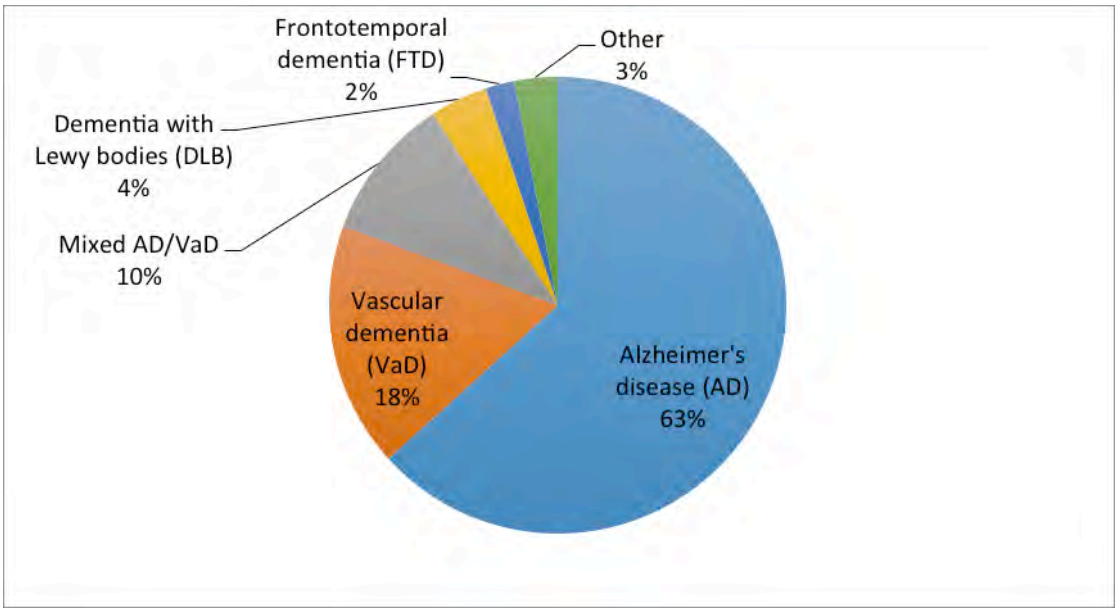

Figure 1. Epidemiology of Dementia in the UK (*adapted from www.alzheimers.org.uk/infographic*)

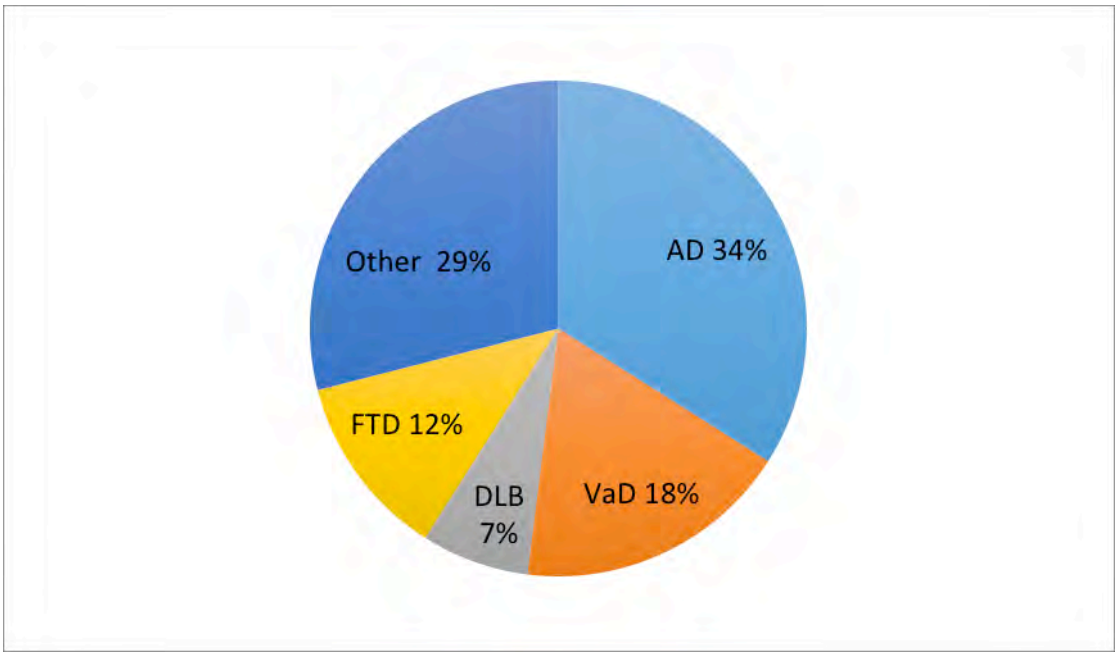

Figure 2. Epidemiology of young-onset dementia *(data from a community study by Harvey et al. 2003)*

At present, treatments for neurodegenerative dementia are symptomatic, having little impact on overall rates of institutionalization. Disease-modifying therapies (DMTs) may soon become available that address this treatment gap although in one scenario their use may be restricted to individuals with mild dementia, and if there is high certainty regarding the underlying pathological diagnosis (Yiannopoulou & Papageorgiou, 2013). Recent revisions to the diagnostic criteria, for AD and non-AD dementias, represent an effort to further improve diagnostic confidence (Gorno-Tempini *et al*., 2011; Rascovsky *et al.*, 2011; McKhann *et al*., 2011). For AD, this includes the incorporation of biomarkers, including radiological and CSF indices of AD neuropathology, within the diagnostic criteria. These indices are also potentially useful for monitoring drug efficacy (Jack *et al.*, 2010).

(The National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention").

1.2 Pre-dementia

Longitudinal studies involving patients with familial AD, inherited in an autosomal dominant fashion, identify a pre-dementia phase of disease comprising of a clinically indolent “presymptomatic” stage and a clinically mild “prodromal” stage (Bateman *et al.*, 2012). During the prodromal stage, subjective and objective cognitive changes become apparent that heralds future deterioration and this is evident with AD and non-AD dementia syndromes (Geschwind *et al.*, 2001; Bateman *et al.*, 2012; Mesulam *et al.*, 2012).

This model of prodromal dementia is not necessarily generalizable to sporadic disease. Individuals with a significant burden of pathology at post-mortem may have appeared cognitively “normal” during life (Neuropathology Group, Medical Research Council Cognitive Function and Aging Study, 2001). Also, even when cognitive changes are apparent, this can remain stable, having little impact on independent function (Kral, 1962). Mild Cognitive Impairment (MCI) was a term that was first introduced to describe individuals with either ‘very mild’ or ‘mild’ cognitive changes on the global deterioration scale (Reisberg *et al.*, 1982). By virtue of retained independent function, these individuals could not be diagnosed with dementia (Flicker *et al.*, 1991). Subsequently, other criteria were issued to study the cognitive changes arising from disease (Zaudig *et al.*, 1992; Christensen *et al.,* 1995; Graham *et al., 1997)* and normal ageing (Levy 1994) although no criteria were operationalized to differentiate between putative pre-dementia and aging.

In 1997, MCI was re-proposed as a transitional stage between normal ageing and dementia characterized by subjective and objective memory impairment and preserved psychosocial function, in which other aspects of cognition were relatively normal (Petersen *et al.*, 1997; Petersen *et al.*, 1999; Petersen 2001). Later, this view of MCI would be expanded, reflecting the clinical

heterogeneity observed in everyday clinical practice, leading to the stratification of MCI into single and multi-domain variants that could be sub-typed further based on the presence, or absence, of amnestic symptoms (Petersen, 2004). Subsequent studies have highlighted that MCI detection itself rests on the psychometric standards used to define 'objective impairment' (Jak *et al.*, 2009; Schinka *et al.*, 2010). The term subjective cognitive impairment (SCI) was later introduced to characterize non-demented individuals presenting with cognitive symptoms but otherwise 'normal' cognitive testing (Jessen *et al.*, 2010). The annual conversion rate of MCI to dementia varies widely, from 10-15% in specialist settings (Petersen & Morris, 2005) to 2-5% in primary care (Mitchell & Feshki, 2009). Longitudinal studies and meta-analyses suggest that the vast majority of patients with MCI remain stable while others spontaneously improve (Ganguli *et al.*, 2004; Mitchell & Feshki, 2009). Amnestic MCI (aMCI), regarded by Petersen as a forbearer of dementia, is clinically heterogeneous, and conversion to dementia is described with AD and non-AD pathology, including vascular disease, 'mixed disease' and other neurodegenerative diseases (Ganguli *et al.*, 2004; Jicha *et al.*, 2006). In an attempt to overcome this heterogeneity within MCI, studies have increasingly focused on AD biomarkers to identify AD pre-dementia (Yu *et al.*, 2012). Even this approach may have limitations as SCI has now also been associated with increased risk for future AD (Mitchell, 2008). Also, psychiatric presentations of pre-dementia, while increasingly recognized, are not catered for within the current MCI construct (Ismail *et al.*, 2016).

Recent consensus criteria for MCI have de-emphasized the importance of amnestic symptoms, simply requiring subjective and objective cognitive changes in the absence of dementia (Albert *et al.*, 2011). A notable inclusion in these criteria is biomarker assessments that permit the stratification of MCI into low- and high-risk for underlying AD. In contrast, the research criteria for prodromal AD, issued by Dubois *et al*. (2010), require specific deficits in declarative memory (impairments in free recall and cued recall), and positive AD biomarkers for diagnosis.

1.3. The clinical assessment of cognitive impairment

Several factors need consideration in the evaluation of a patient with a cognitive disorder. The nature of the symptoms, their impact on independent functioning and the findings of the physical examination require interpretation to determine if the presenting symptoms represent neurodegenerative dementia, neurodegenerative pre-dementia or another disease process (Sorbi *et al.*, 2012). European guidelines recommend that B12 status, thyroid function, serum Folate, full blood count, renal function and liver function tests should be performed in all patients presenting with symptoms of altered cognition; syphilis and HIV testing should be considered in high-risk cases (Sorbi *et al*., 2012). The clinician must also take into account collateral information, provided by a reliable informant, as a loss of insight is common in patients with established dementia (Sorbi *et al*., 2012).

A thorough systemic examination is mandatory in patients with EOD or in cases with rapid progression (arbitrarily defined as progression from symptom-onset to severe dementia within two years), as treatable causes are more likely in this setting (Rossor *et al.*, 2010). The physical examination is often normal in AD although Parkinsonism and spasticity may be observed in very rare instances, either as an early feature in patients with familial AD or as a very late feature in patients with sporadic AD (Rossor *et al.*, 2010).

All patients should undergo a cognitive assessment (Sorbi *et al*., 2012). This varies in its scope according to clinical needs, but a routine bedside assessment should include at minimum a screen of attention, executive function, orientation in place and time, episodic memory language and higher visual processing. This usually entails the use of short cognitive screening tests. The Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) is the most widely used screening test for dementia and is used

also for monitoring disease progression in AD dementia. The major limitations of the MMSE are that it does not adequately assess executive function and is not sensitive for the detection of non-AD dementia. It is also inadequate for the detection of MCI (Arevalo-Rodriguez *et al.*, 2015). Other tests like the Addenbrooke's cognitive examination – Revised (ACE-R) provide additional information about language, verbal fluency and visuoperceptual function that may be useful in diagnosing dementia and in discriminating between AD and non-AD dementias (Mioshi *et al.*, 2006). The Montreal Cognitive Assessment (MoCA) is one of the few bedside tests validated against a formal psychometric battery for the diagnosis of pre-dementia (Nasreddine *et al.*, 2005). The MoCA incorporates several screening tests of executive function and is more sensitive than the MMSE for the detection of early AD, vascular dementia (VaD) and Parkinson's disease (PD) (Nasreddine *et al.*, 2005; Gill *et al.*, 2008).

In contrast to screening tests, formal neuropsychometric testing usually includes a global cognitive measure, such as IQ, and involves a more in-depth assessment of the cognitive domains. It is recommended in patients during the early stages of disease when it is most likely to be useful in localizing the affected brain regions (Knopman *et al.*, 2001).

1.4 Neuropsychometric assessment

A typical test battery for dementia encompasses assessments of attention, psychomotor speed, logical reasoning, constructional praxis, executive functioning, language, memory (verbal and non-verbal) and higher visual function (Cipolotti & Warrington, 1995). It is important to consider the socioeconomic status, age and sex of the patient in interpreting the results of a psychometric battery as well as any other factors that might influence performance such as speech and language deficits (including developmental problems such as dyslexia), primary visual impairment or cultural differences (Doraiswamy & Kaiser, 2000).

Pre-morbid intellectual level

The detection of cognitive impairment needs to be considered against an individual's anticipated level of performance. This may take into account their level of education and vocation including professional achievements. In the case of AD, one may assess a domain that is relatively spared, such as word knowledge, that is reliant on long-term memory representations (Nelson & Willison, 1991). This involves the reading aloud of 'irregular words' where the pronunciation is not bound by lexical rules e.g. chaos, paradigm. The National Adult Reading Test (NART; Nelson and Willison, 1991) and the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) are typically used for this purpose.

Attention and working memory

The ability to focus attention and to make a mental note of information while working on a problem is assessed for two reasons. If it is markedly impaired, this will influence the choice of subsequent tests. Also, inattention and impaired verbal working memory are suggestive of frontal/sub-frontal dysfunction, as observed in neurodegenerative diseases and psychiatric disorders such as depression and anxiety. The forward digit span test is frequently used for this purpose and is performed by reading out strings of random digits at one digit per second then asking the patient to repeat it, as presented, after that (Blackburn and Benton, 1957).

Processing Speed

This provides a measure of thinking speed and usually requires a motor response to a visual stimulus. A widely used test is the Trails-making Test A in which numbers are randomly placed on an A4 sheet of paper requiring the subject to join them in ascending order (Reitan, 1958). There are normative data corrected for age and sex that allow the subject's performance to be assessed. The Symbol-Coding subtest of the WAIS-III is also in common use (Joy *et al.*, 2004). Time-constrained tasks, using common sequences in routine and non-routine format, also provide a measure of processing speed (e.g. reciting the months of the year in order and reverse order). Reduced

speed of processing can be seen in the initial stages of diseases affecting the frontal cortical and sub-cortical structures (Cummings, 1986).

Reasoning ability

Impaired abstract reasoning is common to most neurodegenerative diseases but is a prominent and early feature of diseases involving the frontal lobes. This can be assessed by asking the subject to provide similarities between related word-pairs (e.g. apple and orange, poem and statue), as in the Similarities and Picture Completion subtests from the WAIS (Wechsler 1981). Literal “concrete” responses to the provided stimuli are an early feature of frontal lobe disease.

Language

A typical battery usually only assesses confrontational naming (McKenna & Warrington, 1980). This measures the ability to identify line drawings of objects graded by the frequency of exposure to these objects in everyday life. This allows an assessment of semantic access. Dysnomia is a prominent sign in diseases affecting the left temporal lobe. However, impairments in phonological and semantic processing are characteristic of different diseases. Syntactic language and phrase length is assessed during free, conversational speech. For semantic language, the Pyramids and Palm Trees test assesses the ability to match semantically related pictograms thereby minimizing conversational speech as part of the paradigm (Howard & Patterson, 1992). Comprehensive aphasia batteries are available and usually incorporate tests of speech production, comprehension, repetition, reading and writing (Shewan & Kertesz, 1980).

Construction

Visuoconstructional ability involves a direct copy of a complex geometric shape. The Rey Complex Figure Test (Meyers & Meyers, 1995) allows an assessment of constructional praxis and the approach adopted in how the figure is copied offers insights into executive function. Disease in posterior brain regions impairs the perception of the image resulting in a distorted

reproduction. This is seldom the case with diseases affecting anterior brain regions although sequencing of the task may be less than optimal. Other tests in common use include the Block design subtest of the WAIS (Wechsler, 1981). .

Executive Function

This can be tested through concept formation using the Brixton test (Burgess & Shallice, 1997). Here the patient must anticipate an outcome based on rules that change during the test. Poor performance on this test indicates mental rigidity. The Victoria Stroop test is a test of response inhibition (Demakis, 2004). The test subject is presented with successive cards containing 24 coloured dots, then 24 words and finally 24 incongruent colour names (e.g. the word 'red' printed in blue ink). When presented with the incongruent color name list, the subject must indicate the colour of ink rather than the word itself. The inability to overcome the natural tendency to read the printed word indicates poor executive functioning. During testing, the examiner measures the time taken and error rate for each test condition. Another test that is widely applied involves word generation. Letter fluency requires as many words as possible beginning with a specified letter within a one-minute period. Trials are undertaken for three letters (usually F, A and S) and the composite score provides a measure of self-monitoring and rule observance (Benton & Hamsher, 1976). Category fluency requires as many words as possible relating to a specific semantic category (e.g. animals) and in normal circumstances more words are generated than for letter fluency over the same test duration. In mild AD, this gradient is reversed (Hodges *et al.*, 1999), and category fluency is impaired while letter fluency may be normal.

Episodic Memory

Tests of learning and information recall are used to assess episodic memory. Learning is usually assessed after repeated exposure to information. Testing of information retention requires delayed recall of this information after a 20-30 minute delay during which time the participant is engaged in other

cognitive tasks. This may entail free recall, cued recall, or recognition of the information when presented along with a selection of related foils. Retrieval problems are characterized by poor recall, but near-normal recognition performance, and is attributed to frontal lobe impairment (Cipolotti and Warrington, 1995). Retrieval errors are a feature of depression, frontal lobe disease and frontal-subcortical disease. Encoding/consolidation problems are characterized by poor recall and poor recognition, thought to be medial temporal in origin, indicating the poor formation of a memory trace. This is the quintessential feature of AD that is also apparent in the prodromal stages of disease (Dubois *et al.*, 2010).

Testing can involve verbal (usually word lists, word pairings or short story) and non-verbal material (usually drawn diagrams, faces and/or object locations). Free recall of a short story (e.g. WMS-III Logical Memory) is often tested (Wechsler, 1997), although performance on this test does not necessarily distinguish between an encoding or retrieval problem (Butters *et al.*, 1995). Free recall of a word list, repeated over several trials, combined with delayed free recall and recognition memory testing allows the assessment of encoding and retrieval. The Rey Auditory-Verbal Learning Test (RAVLT) is widely used and comprises fifteen words (List A) that are presented in five successive trials (Rey, 1941; Schmidt, 1996). After each trial, the subject must recite as many words from this list as possible. After thirty minutes, a second list of fifteen words (List B) is presented to the test subject, followed immediately by a recall trial for that list. Following this, there is a delayed, free recall trial (List A) followed by a recognition memory trial (List A). In the recognition memory phase of testing, the subject receives a printed sheet containing the target words and some foils. Recognition memory is assessed either by hit rate (the absolute number of words correctly identified) or by recognition performance (the proportion of target words correctly identified relative to foils incorrectly identified) (Geffen *et al*., 1994). The RAVLT is a sensitive indicator for early AD, but the list length can result in floor effects that limits it usefulness in monitoring disease progression (Crane *et al.*, 2012). The Bushke's Free and Cued selective

reminding test (FCSRT) (Grober *et al.*, 2000; Grober *et al.*, 2008) differs from the RAVLT by excluding previously recalled words from subsequent list-learning trials. Auditory cueing follows the delayed recall component of the test, providing a measure of recognition memory. The FCSRT has been shown to be sensitive for the early stages of AD, including prodromal AD (Grober *et al.*, 2010).

In the non-verbal domain, delayed reproduction of a previously copied design can be used to assess non-verbal memory. The Rey complex figure one example of such a paradigm that requires intact constructional ability to be applied (Meyers & Meyers, 1995). In all these tests, both verbal and non-verbal, patients with AD tend to have difficulty with both free recall and cued recall/recognition recall while patients with frontal cortical and subcortical disease and depression tend to have less difficulty in recognition testing (Strauss *et al.*, 2006).

Spatial Memory

Spatial memory refers to the ability of an organism to store and retrieve spatial information. However, distinctions exist between spatial working memory (SWM), which relates to the ability to process spatial information, over seconds and spatial reference memory, which refers to the longer term ability to process spatial information related to a previously encountered environment (Olton, 1979). These aspects are covered in greater depth in a later chapter. Impairments in spatial navigation and memory are hallmark features of AD (Monacelli *et al*., 2003).

1.5 Alzheimer's disease

1.5.1 Overview

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is typically manifest in the eighth decade of life, presenting initially with an

insidious memory disturbance that heralds progressive cognitive and functional decline culminating in dementia. The neuropathological cascade that underpins AD neurodegeneration is now understood to begin decades before the emergence of cognitive decline, such that the phase of the disease characterised by the development of dementia represents the final phase of AD.

1.5.2 Pathophysiology

On macroscopic examination, AD brains are associated with brain atrophy, manifest as widening of cerebral sulci and ventricular dilatation. Atrophy is most marked in the medial temporal lobe (MTL) with initial changes in the entorhinal cortex and subsequently the hippocampus (Braak and Braak, 1991). Microscopically, extracellular amyloid plaques (APs) and intracellular neurofibrillary tangles (NFTs), first identified by Alois Alzheimer in 1907, are the hallmark histopathological features of disease (Strassnig and Ganguli, 2005). While the exact mechanisms that link amyloid and tau remain to be elucidated, there is substantial evidence supporting their involvement in the widespread synaptic loss and cerebral hypometabolism that precedes overt neuronal losses in AD (Quefurth and Laferla, 2010).

Amyloid

Amyloid plaques in AD exists in two forms; diffuse plaques (DPs) that largely only contain aggregated extracellular beta-amyloid peptide (Aβ) and neuritic plaques (NPs) that are more compact containing a core of Aβ aggregated with Apolipoprotein E (ApoE), complement and degenerating neuronal and glial processes (Akiyama, 2000). Aβ is produced under physiological conditions by the sequential cleavage of Amyloid Precursor Protein (APP), a glycoprotein usually located on cell, endoplasmic reticulum and mitochondrial membranes (Lin & Beal 2006). In AD the homeostatic control of Aβ production and removal is impaired resulting in the accumulation of Aβ 1-42, a particularly oligomeric isomer of Aβ leading in turn to the generation of

neurotoxic dimers and other oligomers (McLean *et al*., 1999, Lesne *et al,* 2013). Soluble Aβ oligomers are detectable within the pyramidal neurons of the entorhinal cortex (EC) and the CA1 hippocampal subfield from the earliest stages of AD associated with endosomal enlargement, impaired mitochondrial function and decreased synaptic and dendritic spine density (Cataldo *et al.,* 2000; Aoki *et al*., 2008). Experimental work involving the Tg2576 transgenic mouse model of AD has also shown that brain levels of a particular Aβ dodecamer (Aβ*56) is correlated with spatial memory impairment while human study suggests that Aβ*56 is over-expressed in ageing and correlates with the presence of soluble Tau pathology, the absence of post-synaptic proteins and cognitive impairment (Lesne *et al*., 2013). The extracellular deposition of Aβ is first detectable in the dorsolateral neocortex (posterior then anterior) then EC and CA1 before involving the remaining MTL and basal forebrain (Thal *et al.*, 2010). The polymerisation of Aβ 1-42 ultimately results in the formation of protofibrils and insoluble fibrils that aggregate as NPs. While neocortical NP pathology does not correlate with cognitive impairment, study of the Tg2576 mice indicates that hippocampal plaque burden in ageing is correlated with impaired place cell firing and spatial memory deficits (Cacucci *et al*., 2008). In humans, CA1 and the molecular layer of the dentate gyrus (DG) appear particularly vulnerable to early NP aggregation associated with altered synaptic density within the perforant path (PP) (Hyman *et al*., 1984), possibly reflecting the sensitivity of CA1 to microglial mediated neuroinflammation in response to NP pathology (Akiyama, 2000).

Tau

In AD dysregulation of phosphokinase activity results in hyperphosphorylation of microtubule associated Tau (Alonso *et al*, 2006). This is turn becomes fibrillar forming pretangles, paired helical filaments and NFTs that accumulate within the perikarya and dendrites of the EC (Hyman *et al*., 1984; Braak and Braak, 1991). Experimental work has shown that these conformational changes may facilitate the ‘prion-like’ spread of NFTs between neurons (Liu *et al*., 2012), which may account for the sequential

spread of NFT pathology in AD. In Braak stages 1 & 2, pathology is restricted to EC appearing to spread in a laminar network that follows the PP to involve CA1, spreading to the remaining hippocampal subregions and MTL (stage 3 & 4) and then the neocortex (posterior then anterior, stage 5 & 6) (Braak and Braak, 1991). Tau hyperphosphorylation impairs axonal trafficking that, together with co-localised oligomeric Aβ , functionally disconnects the PP (Hyman *et al*., 1984). In addition the distribution and density of NFTs are closely linked to eventual neuronal loss and levels of cognitive impairment such that Braak staging is tightly correlated with clinical dementia severity (Gomez Isla *et al*., 1997).

Neurotransmitter Alterations

Acetylcholine

The neocortex and amygdala principally derives its cholinergic input from the basal nucleus of Meynert (bNM) in turn regulated by afferents that relay via EC and hippocampus (Mesulam, 2004). During Braak stage 3 & 4, NFTs and NPs co-localise in the bNM, medial septal nucleus (MSNu) and the diagonal band (DB), the latter two nuclei representing major sources of hippocampal acetylcholine. In AD the resulting neocortical and allocortical cholinergic deficiency contributes to impairments of complex attention, learning and memory (Auerbach and Segal, 1994).

N-Methyl-D-Aspartate (NMDA)

Glutamate-mediated phasic excitation of NMDA receptors (NMDARs) in the EC and hippocampus is required for place cell functioning, LTP and synaptic neuroplasticity. In AD the tonic overactivation of NMDAR, thought to result from oligmeric Aβ -induced oxidative stress leads to neurotoxic intracellular calcium accumulation predisposing to cell death (Choi and Rothman, 1990).

Understanding of these neurotransmitter alterations has led to the use of cholinesterase inhibitors and NMDAR antagonists to slow down cognitive decline in AD with modest benefit for the former in early dementia and the

latter in advanced dementia.

1.5.3 Genetics of AD

After advancing age, family history is the second largest risk factor for AD. While the vast majority of AD is late onset (LOAD), appearing sporadic, more than 50% of the susceptibility for AD is linked to non-Mendelian polymorphisms that interact with age, sex and vascular risk (Barber, 2012). The $\varepsilon 4$ allele of the *Apolipoprotein E* gene (*APOE,* 19q) is the single most significant risk factor for late onset AD (Kim *et al*., 2009). $\varepsilon 4$ homozygotes are 12 times more likely to develop AD compared to non-carriers, also at risk for an earlier onset of dementia compared to $\varepsilon 4$ heterozygotes (in whom the risk of AD is increased three fold). In contrast, the $\varepsilon 2$ allele appears to be protective against AD. Genetic factors also influence phenotypic aspects of disease, in the case of *APOE* $\varepsilon 4$ more often associated with hippocampal atrophy and early memory impairment

Although the effect of other polymorphisms, as identified by genome wide association studies, are modest at best these do provide some insights into pathogenesis (Schellenberg and Montine, 2012). Common homeostatic pathways thus far implicated include altered lipid metabolism (e.g. polymorphisms in *APOE, CLU, PICALM*) and cell membrane homeostasis (e.g. *SORL1, BIN1)* both implicated in Aβ neurovascular clearance while others (e.g. *CR1, CD33, TREM2*) indicate altered intrathecal immune activation. This complex genetic heterogeneity may explain the higher than expected incidence of AD in patients with vascular risk factors (insulin resistance, diabetes, hyperhomocysteinaemia, smoking and sedentary lifestyle).

Only 1% of AD is due to fully penetrant autosomal dominant inheritance (Tanzi and Bertram, 2001). Mutations in the *Presenilin 1 (PSEN1; located on chromosome 14), Presenilin 2 (PSEN2; chromosome 1)* and *Alzheimer Precursor Protein (APP; chromosome 21)* all result in gene products that are involved in APP processing. The overproduction of Aβ both as a result of these mutations and the triplication of the *APP* gene in Down's syndrome are central to the formulation of the 'amyloid hypothesis' of AD (Hardy and Higgins, 1992) that proposes a causal link between Aβ accumulation and AD pathogenesis. While these mutations tend to be associated with an earlier onset of dementia, the description of an autosomal dominant *APP* mutation associated with decreased Aβ 1-42 production and a reduced risk for both AD *and* age-related memory impairment further suggests that soluble amyloid species are relevant to the development of cognitive impairment (Jonsson *et al*., 2012).

1.5.4 Clinical Presentation

Recently updated clinical and research criteria redefine AD as a disorder with prodromal cognitive and behavioural changes occurring in advance of the progressive cognitive and functional impairment that occurs during the stage of dementia (McKhann *et al*., 2011; Sperling *et al*., 2011).

Dementia due to AD

The cardinal symptom of AD is impairment of episodic memory. The symptoms of "getting lost" and becoming disorientated in time and place are other characteristic features of early AD. Patients may not be aware of the extent of their symptoms due to impaired insight.

The clinical criteria for AD dementia (McKhann *et al*., 2011) stipulate the need for the progressive impairment of at least two cognitive domains severe enough to cause a loss in social or occupational functioning. These other

cognitive impairments include: aphasia (disturbance of speech and language), apraxia (defective voluntary movements due to disrupted cortical sensorimotor integration), agnosia (impaired object recognition) and impaired executive function (impaired problem-solving, abstract reasoning and organisational abilities). Clinical AD dementia may be sub-divided into mild, moderate and severe stages based on the degree of cognitive and functional impairment (Morris, 1993). While the majority of AD presents with a typical profile of early memory loss and disorientation, there are three recognised atypical variants associated with focal cortical symptoms that precede memory impairment:

a. Language presentation (Logopaenic Progressive Aphasia): prominent deficits in word finding accompanied by clinical evidence of impaired auditory working memory.
b. The visuospatial presentation (Posterior Cortical Atrophy): prominent visual impairment not related to impaired visual acuity accompanied by dyspraxia or spatial unawareness.
c. The executive presentation (frontal variant of AD): prominent deficits related to reasoning, abstract thinking and problem solving.

Mild Cognitive Impairment due to AD

Please refer to section 1.2 for an earlier account of MCI. In brief, MCI due to AD is now defined not only in terms of the clinical presentation but also in terms of biomarker evidence indicative of underlying AD neuropathology (Sperling *et al.,* 2011). These include markers of Aβ 1-42 (low CSF Aβ 1-42 OR neuroimaging), markers of tau (increased CSF Tau and/or CSF phosphorylated Tau OR neuroimaging) or imaging evidence of AD in the form of hippocampal atrophy or cerebral hypometabolism.

Presymptomatic AD

Presymptomatic AD refers to the clinically silent stage of the disease that predates the onset of MCI. A worldwide study of presymptomatic familial AD

cases (the DIAN study) has shown that biomarker evidence of AD and neuroimaging changes predate the onset of cognitive impairment by up to 20 years (Bateman *et al*., 2010).

1.5.5 Cognitive Changes in AD

1.5.5.1 Memory impairment

Episodic memory: Impairment of episodic memory in AD is exemplified by the inability to learn and remember new information and to recall recent events. This is often characterised by poor recollection for recent events, repetitive questioning and the inability to keep track of appointments and medications accompanied by an increasing dependence on memory supplements such as diaries (Stern *et al.*, 1994). In comparison, the patient's knowledge of distant events is striking, perceived by family as "normal long-term memory" (Piolino *et al.*, 2003). Clinically, testing of delayed recall serves as a useful measure of episodic memory. Patients with AD perform poorly on these tests and show little response to cueing or recognition paradigms.

Topographical memory: Another early symptom of AD is "getting lost", initially in unfamiliar places, also in familiar environments. The hippocampus, particularly the right hippocampus, and the retrosplenial cortex form part of a navigational network that subserves topographical memory and patients with AD perform poorly on virtual reality navigation tasks (Pengas *et al*., 2010) and on tasks of topographical working memory involving the recall of a visual scenes (Bird *et al*., 2009).

Autobiographical memory: In AD, there is loss of recent autobiographical memory with relative preservation of memory for remote events. However, even within remote memory, it is the content of memory that is preferentially spared with greater impairment noted in the ability to recall the context of an event (Piolino *et al.*, 2003). These deficits are thought to be due to hippocampal impairment preventing the consolidation of recent

autobiographical experiences but may also indicate that the hippocampus is required for the recall of context related to distant events.

Semantic memory: The impairment of semantic memory in mild AD is manifest as an inability to generate a word list bound by semantic rules (e.g. names of animals) as opposed to lexical rules (e.g. words starting with a predefined letter of the alphabet). In addition, patients may demonstrate impairments in confrontational naming accompanied by category-specific word errors. In later AD, there is loss of general semantic memory such that they develop deficits in generating verbal definitions, naming high-frequency items (e.g. wristwatch) and have impaired comprehension due to loss of word meaning (Becker & Overman, 2002).

Procedural memory: procedural memory is typically spared until the advanced stages of disease reflecting the relative preservation of neostriatal and cerebellar function (Stern *et al.*, 1994). Even at a moderate-severe stage of dementia, patients are able to learn a new motor skill although the co-existence of apraxia and agnosia in very advanced disease may prevent a patient from being able to complete even overfamiliar tasks such as shaving or making a cup of tea.

1.5.5.2 Non-memory cognitive impairment in AD

Speech and Language: Word-finding difficulties occur early in AD accompanied by word pauses and compensatory circumlocution. Naming is initially preserved but the inability to name parts of an object is characteristic of early AD (Chenery *et al*., 1996). With disease progression, speech becomes increasingly devoid of grammar and syntax and may become paraphasic accompanied by impaired comprehension. In severe AD, speech may become reiterative, perseverative or unintelligible due to phonologic deficits. Ultimately, patients may become completely mute (Emery, 2000).

Apraxia: Apraxia is usually observed at a mild-moderate stage of AD becoming more severe as disease progresses. ‘Body part as object’ errors are particularly common on pantomiming of transitive movements i.e. when

asked to pantomime the use of an imaginary tool, the patient simulates the task using the body part instead of miming the use of the tool (Edwards *et al.*, 1991). Constructional apraxia is also a characteristic feature and may impair the ability of the patient to copy a complex geometric shape. Ideational apraxia (the knowledge of the action rather than the use of a tool) is also seen in AD and usually reflects further breakdown of semantic function.

Higher Visual Function: Visual agnosia in AD, representing a disorder of higher visual processing, is manifest as impairment of objection recognition. This may be apperceptive in nature or associative, in which the deficit is due not to impaired object perception but impairment in associating semantic information with the perceived object (Hodges *et al.*, 1991). Specific forms of agnosia include prosopagnosia, the inability to recognise familiar faces associated with damage to the right temporal lobe, and landmark agnosia, the inability to recognise landmarks (such as buildings, monuments, intersections etc.), leading to topographical disorientation.

Executive Function: Dysexecutive syndrome is characterised by impaired problem solving, abstract reasoning and task-switching and is a consistently early feature of AD and is detectable even in the prodromal phase of illness (Stokholm *et al.*, 2006). During the mild stages of dementia, further deficits in sustained and divided attention become apparent.

Neuropsychiatric symptoms: Up to 80% of patients with AD develop neuropsychiatric symptoms, and in many instances this may precede the recognition of dementia (Jost & Grossberg, 1996). Depression and anxiety are earlier features with agitation, delusions and paranoia being more common in moderate disease. The latter stages of dementia may be associated with increasing restlessness and wandering.

1.5.6 Clinical Assessment of AD

The physical examination in early AD is often normal. Some patients with familial AD may have abnormal physical signs such as myoclonus or spasticity (Rossor *et al.*, 2010). In severe AD, patients may develop

extrapyramidal signs and other examination abnormalities. Further assessment involves the application of cognitive screening tools, as outlined in earlier, and the gathering of collateral information from a reliable informant (Sorbi *et al.*, 2012).

1.5.7 Neuroimaging changes in AD

The changes in brain structure and brain function that occur in AD can be detected using a variety of neuroimaging modalities.

1.5.7.1 Structural Imaging:

Structural imaging, using either Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI), is used to determine the presence of regional and generalised brain atrophy in AD. In clinical practice MRI scans are assessed qualitatively using visual inspection but MRI measures of MTL atrophy may also be evaluated using semi-quantitative techniques, with the five-point Visual Rating Scale of MTL atrophy 85% sensitive and 88% specific in distinguishing AD from controls (Scheltens *et al.*, 2002).

In research settings, automated methods for analysing atrophy offers the advantage of both cross-sectional and longitudinal study with the patient acting as their own control, allowing for the detection of progressive atrophy within an individual (Freeborough & Fox, 1997). Currently employed automated methods include voxel-based morphometry (Diaz-de-Grenu *et al.*, 2014) and Freesurfer (Desikan *et al.*, 2006), used also to measure cortical thickness. In AD, longitudinal study has shown a progression of atrophy that bears similarity with the pathological spread of NFTs in the Braak staging system. Atrophy is detected first in the EC followed by the hippocampus, amygdala and parahippocampus (Chan *et al.*, 2001) spreading to the posterior cingulate gyrus (PCG) and polymodal association areas sparing the occipital cortex until late in disease (Scahill *et al.*, 2002). Progressive EC

volume loss does not appear to be a feature of normal aging and EC atrophy is both sensitive and specific for AD (Du *et al.*, 2001). However, the anatomical delineation of the EC using MRI is labour intensive as a result of the heterogeneous EC morphology in humans and poor inter-rater reliability limits the usage of EC measurements in practice (Xu *et al.*, 2000). In contrast, hippocampal anatomy is easier to segment with corresponding higher measurement reproducibility indices (figure 3). Longitudinal studies have found that hippocampal atrophy rates in AD to be much higher than age-matched controls (Fox *et al.,* 1996; Jack *et al.,* 1997). The rate of hippocampal atrophy is highest earliest in disease (Chan *et al.*, 2003) while cortical atrophy rates accelerate later in disease but in advance of cognitive changes (Scahill *et al.*, 2002). In addition, longitudinal MRI measures can predict the conversion of MCI to AD and is useful in identifying asymptomatic elders at risk for dementia (Jack *et al.*, 1997). Hippocampal atrophy is accepted as a biomarker of neurodegeneration in AD (Albert *et al.*, 2011; McKhann *et al.*, 2011) .

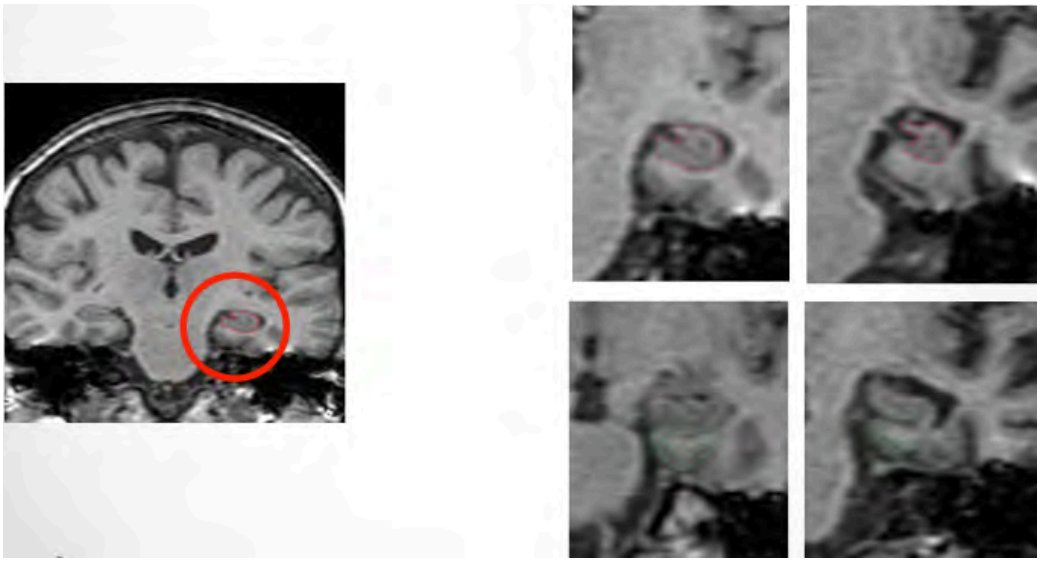

Figure 3. Coronal section at the level of the hippocampus and entorhinal cortex. The image on the left shows a normal hippocampus as seen on T1W MRI. The images on the inside right show a normal hippocampus and EC (upper and lower images respectively) compared to atrophic changes seen in AD (outside right)

1.5.7.2 Functional imaging

FDG-Positron Emission Topography

F-deoxy-fluoro-glucose-Positron Emission Topography (FDG-PET) measures cerebral metabolism by determining the uptake of a radioactive isotope linked to glucose. Decreased FDG uptake (hypometabolism) within the parieto-temporal association cortices and posterior cingulate gyrus is characteristic of early AD while prefrontal hypometabolism is a feature of advanced AD (Mosconi, 2005), The specificity and sensitivity of FDG-PET ranges between 71-74% and 84-95% respectively. Longitudinal study has demonstrated the predictive value of FDP-PET for determining the progression of MCI to AD and in differentiating between AD and other neurodegenerative diseases causing dementia.

Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) determines cerebral perfusion by measuring the decay of a radioactive isotope. In AD, there is a pattern of decreased perfusion in the parieto-temporal cortex, the hippocampus, the cingulate gyrus and the thalamus with a sensitivity of 86% and a specificity of 80% when comparing AD to controls. Despite being more widely available and cheaper than PET, SPECT is limited by poor spatial resolution and lower accuracy in differentiating between dementias (Mosconi, 2005).

Functional MRI

In functional MRI (fMRI), measurement of blood oxygen level-dependent (BOLD) MR signal is used as an indirect measure of neuronal activity (Logothetis *et al.*, 2001). While fMRI has great potential for elucidating changes in brain function in AD, and other disease, it remains a research tool that is not validated for routine clinical practice.

Task-free, or resting state, fMRI permits assessment of brain functional connectivity in the absence of any engagement in specific cognitive tasks to

cause brain activation. This approach has identified several large-scale functional brain networks and within these there is particular interest in the Default Mode Network (DMN), representing a functionally connected network that includes the MTL, the precuneus, PCG, lateral parietal, lateral temporal and medial prefrontal regions (Buckner *et al.*, 2005). Task-free fMRI studies in AD have identified deceased functional connectivity within the posterior DMN (Greicius *et al.*, 2004) in comparison to the increased connectivity that has been observed within the anterior DMN in patients with presymptomatic and prodromal AD (Sheline & Raichle, 2013).

Task-specific fMRI measures patterns of activation while the subject performs a task in the scanner. Studies using memory paradigms have shown that hippocampal and MTL temporal activation decreases with advancing AD, with the accompanying increase in prefrontal activity possibly representative of a compensatory mechanism (Celone *et al.*, 2006). Longitudinal studies have also revealed that early hippocampal hyper-activation is a predictor of cognitive decline in patients with MCI and early AD (O'Brien *et al.*, 2010).

1.5.7.3 Histological Imaging

Ligand PET imaging with “Pittsburgh Compound B” (^{11}C-PiB) allows the in-vivo visualization of extracellular amyloid pathology (Klunk *et al.*, 2004). In early AD, amyloid deposition is noted in the fronto-parietal-temporal association cortices, overlapping both with the regions that subsequently become hypometabolic on FDG-PET, and with the distribution of extracellular amyloid as noted in pathological studies. Studies in earlier stages of AD have shown that amyloid deposition is present during pre-dementia stages of AD (Bateman *et al.*, 2012). Longitudinal studies have shown that positive PiB-PET scanning is predictive of conversion from MCI to AD and can also predict future onset of dementia in cognitively normal individuals (Villemagne *et al.*, 2013). The diagnostic sensitivity of PiB-PET remains uncertain since it may also detect amyloid in-vivo in patients with Dementia with Lewy Bodies, Amyloid angiopathy (without cortical Alzheimer pathology) and senile plaques seen in normal ageing. Widespread use of PiB is limited by its short-

half life of only 20 minutes and as such a number of 18F-based ligands are being explored in view of their longer half-life. Studies to date have shown a good correlation between PiB and ^{18}F distribution in vivo (Johnson *et al.*, 2013). The US Alzheimer's Association has issued guidelines that recommend amyloid imaging in one of three circumstances: persistent MCI when AD still remains a possible diagnosis, atypical AD syndrome, young onset dementia (Johnson *et al.*, 2013).

1.6 Frontotemporal dementia

1.6.1 Overview

Frontotemporal dementia (FTD) is a progressive disorder, typically manifest in the fifth and sixth decades of life, presenting initially with an insidious disturbance in social compartment and/or language (Neary *et al.*, 1998; Johnson *et al.*, 2005). Frontotemporal lobar degeneration (FTLD) refers the non-AD pathology findings associated with clinically diagnosed FTD (Cairns *et al.*, 2007).

FTD is a common cause of EOD within the UK (Harvey *et al.*, 2003), some studies have suggested that FTD is as common as AD as a cause of EOD (Ratnavalli *et al.*, 2002) whereas other studies suggest that FTD is 3-4 times less common than EOAD (Harvey *et al.*, 2003). A positive family history is the biggest risk factor for FTD (Obi *et al.*, 2008). Clinically, FTD is an overarching term that encompasses three widely recognised syndromic variants, namely behavioural variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/aggrammatic variant non-fluent aphasia (nfvPPA) (Neary *et al.*, 2005). A fourth clinical variant is described, the right temporal variant of FTD for which no consensus criteria have been formalised (Edwards-Lee *et al*,, 1997; Chan *et al.*, 2009). Approximately 15% of patients with FTD develop

motor neuron disease (FTD-MND) and there is also considerable overlap with certain extrapyramidal clinical syndromes such as corticobasal syndrome (CBS) (Lomen-Hoerth *et al*., 2002; Forman *et al*, 2006*).*

1.6.2 Pathophysiology

On macroscopic examination, FTD brains are associated with focal atrophy involving the frontal and temporal lobes extending caudally to the insula. The anterior hippocampus, amygdala, basal ganglia and thalamus are variably involved with relative sparing of the posterior parietal regions (Cairns *et al.*, 2007; Seelaar *et al.*, 2011). Microscopically, neuronal loss and gliosis are identified in the affected brain regions. Based on inclusion body immunocytochemistry, FTLD is broadly divided into tau-positive (FTLD-tau) and tau-negative (FTLD-U) subgroups. FTLD-tau is divided further into three-repeat tauopathies (3R-tau), four-repeat tauopathies (4R-tau) and mixed tauopathies (3R/4R-tau) based on the prevailing tau isomer.

FTLD-tau accounts for approximately half of all cases of bvFTD, and 20% of these cases have specific 3R-tau inclusions called Pick bodies, associated with severe frontal cortical neuronal losses and gliosis. Dementia is a relatively advanced feature of 4R-tau that more commonly manifests with Parkinsonism and subcortical cognitive slowly (Forman et al., 2006).

FTLD-U refers to FTLD associated with ubiquitin-positive inclusions, that is subdivided further based on the presence or absence of TAR DNA-binding protein 43 (FTLD-U TDP 43 positive and negative respectively) (Cairns et al., 2007). The majority of TDP 43 negative cases are accounted for by the Fused in Sarcoma (FUS) proteinaceous inclusions (Mackenzie et al., 2010). A tiny proportion of FTLD-U is negative for TDP 43 and FUS, referred to as FTLD-UPS (Seelaar et al., 2011). FTLD-U TDP 43 negative patients are particularly susceptible to FTD-MND (Goldman et al., 2005) while FTLD-U

TDP 43 positive patients account for the majority of svPPA (Hodges & Patterson, 2007).

1.6.3 Genetics of FTD

Approximately 40% of patients with FTD have a positive family history (Rosso *et al.*, 2003). 10-30% of cases of FTD are due to autosomal dominant mutations in one of five genes (Obi *et al.*, 2008): *Microtubule associated protein tau* (*MAPT,* chromosome 17), *Progranulin* (*GRN,* chromosome 17), *charged multivesicular body protein 2B (CHMP2B,* chromosome 3), *valosin containing protein (VCP*, Chromosome 9) and *chromosome 9 open reading frame 72 (C9orf72,* Chromosome 9). Overall *MAPT, GRN and C9ORF72* mutations account for at least 17% of all FTD cases (Majounie *et al.*, 2012). In contrast to bvFTD and SD, most nfvPPA cases appear to be sporadic rather than familial (Harris *et al.*, 2013).

There are several associations between molecular genetics and presenting clinical syndrome. For instance, svPPA is frequently associated with FTLD-U TDP 43 while altered social comportment is frequently associated with FTLD-Tau (Rademakers *et al*., 2012). Clinical reliance on existing diagnostic criteria for FTD may delay the recognition of rtv-FTD, that is associated with intermediate language and behavioural symptoms often misattributed to another cause (Perry *et* al., 2001; Gainotti, 2007).

1.6.4 Clinical presentation of FTD

Behavioral variant frontotemporal dementia (bvFTD)

BvFTD accounts for approximately 70% of all FTD cases (Snowden *et al.*, 2007). It usually presents with an insidious change in personality and behavioural symptoms with relative preservation of higher visual function (Johnson *et al.*, 2005). Common deficits include apathy, disinhibition, changes in food preferences, obsessive-compulsive behaviours, hoarding

and mental rigidity. The clinical criteria for bvFTD require evidence of progressive deterioration in frontal lobe function (Rascovsky et al., 2011). To achieve a diagnosis of ‘possible’ bvFTD, three or more of the following clinical features must be present: disinhibition, apathy, loss of empathy, perseverative behavior, hyperorality, and dysexecutive syndrome. Diagnostic certainty can be upgraded to ‘probable’ bvFTD only if there is evidence of significant functional decline with supporting neuroimaging changes in the form of frontotemporal atrophy or hypometabolism.

Diagnostic delays in bvFTD can arise for several reasons. First, standard neuropsychological testing and MRI can be normal in early bvFTD (Koedam *et al.*, 2010). Second, patients may not be sufficiently symptomatic to be labeled with ‘possible bvFTD’ (Mioshi *et al.*, 2010). Third, symptoms due to FTLD may be misattributed to another cause, as is the case with some mutations, particularly those involving *C9ORF72,* that often presents with delusions and psychosis (Shinagawa *et al.*, 2014). Fourth, slowly progressive deterioration in some *MAPT* and *C9ORF72* mutations may initially be regarded as non-progressive (Khan *et al.*, 2012).

Nonfluent/agrammatic variant primary progressive aphasia

These patients present with prominent, progressive language decline and as such are broadly considered under a broader category of primary progressive aphasia (PPA) (Mesulam, 2001).

Non-fluent/agrammatic variant primary progressive aphasia (nfvPPA) refers to a clinical syndrome in which there is an early disturbance in motor speech output and/or a loss of speech syntax (Gorno-Tempini *et al.*, 2011). This accounts for 15-25% of patients with FTD (Johnson *et al.*, 2005). The mean age of onset is 63 years and typically, there is a slowly progressive clinical syndrome involving language only for up to a decade (Mesulam,

2003). The diagnostic criteria for nfvPPA incorporate previously published criteria for PPA. For PPA, criteria require that the most prominent clinical feature is difficulty with language and that these impairments are the principal cause for impairment in ADLs with aphasia being apparent at symptom onset (Mesulam, 2001). For nfvPAA, there must be additional evidence of either agrammatism or apraxia of speech with at least two of the following features: impaired comprehension of syntactically complex sentences, spared single-word comprehension and spared object knowledge (Gorno-Tempini *et al*., 2011). An image-supported diagnosis requires either prominent left fronto-insular atrophy on structural MRI or prominent left posterior fronto-insular hypometabolism on PET. In the earliest stages of disease, symptoms may be attributed to a non-organic disorder incurring diagnostic delays (Mesulam, 2001).

Semantic variant Primary Progressive aphasia

Semantic variant PPA (svPPA) is a disorder of impaired semantic memory that manifests as anomia, impaired single-word comprehension and semantic paraphasia (semantically related word substitutions such as using ‘table’ for ‘chair’). It is associated with fluent speech but with progression, speech output becomes devoid of nouns and individuals develop a tendency to use ‘stock’ or filler-words (e.g. ‘thing’, ‘it’), also making category-specific naming errors for familiar, everyday items (‘animal’ for ‘dog’) (Gorno-Tempini *et al.*, 2004).

This syndrome is associated with damage to the left anterior temporal lobe (Rosen *et al*., 2002) predominantly associated with TDP-43 pathology (Hodges and Patterson, 2007). There are multimodal dissociations between objects and their sensory representations and object recognition is not possible using non-visual strategies (Snowden *et al*., 1996). Disease extension to the right temporal lobe results in prosopagnosia (Evans *et al*., 1995). The diagnostic criteria for svPPA (Gorno-Tempini *et al*., 2011)

stipulate that patients must first meet the criteria for PPA. In addition, there must be evidence of impaired confrontational naming and impaired single-word comprehension, accompanied by at least two of the following: impaired object knowledge, surface dyslexia or dysgraphia and unimpaired single-word repetition. An image-supported diagnosis requires evidence of left sided anterior temporal lobe atrophy or hypometabolism.

Right temporal variant of FTD

The right temporal variant of FTD (rtvFTD) is usually a post-MRI diagnosis, when scans are undertaken for either progressive behavioural changes or progressive prosopagnosia (Edwards-Lee *et al*., 1997; Seeley *et al*., 2005; Chan *et al*., 2009). The prosopagnosia seen in these cases is no different from the impairments observed at a later stage in svPPA in which there is a marked impairment in the recognition of impersonal faces (Joubert *et al*., 2006). In addition, rtvFTD cases display impairments related to the semantics of emotional meaning and are impaired in their ability to discriminate facial expressions such as happiness or sadness (Henry *et al*., 2014). At present, there are no published consensus criteria for rtvFTD. Emotional detachment and empathy loss often precedes prosopagnosia, frequently accompanied by irritability, expansive behavior and psychomotor agitation (Edwards-Lee *et al*., 1997, Chan *et al*., 2009). As disease progresses, symptoms develop of svPPA reflecting disease spread to the contralateral temporal lobe and a proportion of patients present with concurrent impairments in semantic word meaning (Thompson *et al*., 2003). Hypervigilence for non-facial visual cues (art, puzzles etc.) may lead to compulsive or ritualistic behaviour related to these items (Edwards-Lee *et al*., 1997). Memory-based symptoms are another frequently encountered complaint in rtvFTD, representing a core feature of this syndrome that is usually not apparent with the other syndromic variants of FTD (Chan *et al*., 2009).

1.6.5 Cognitive changes in FTD

Social cognition

This refers to the ability to encode, store, retrieve and process information pertaining to other people and social situations (Adolphs, 1999). This is a core deficit in bvFTD that manifests with social disinhibition and a lack of sympathy and/or empathy, which is underpinned by neurodegenerative damage to the orbitofrontal cortex (Neary *et al*., 1988). This may be assessed using theory of mind testing, which depends on an individual's ability to consider the beliefs, intentions and desires of other individuals and to understand that these may differ from their own. The Faux Pas test and the Reading of the Mind in the Eyes are two batteries that have been applied successfully in research studies of bvFTD (Adenzato et al., 2010). In the former the participant must determine if a faux pas has been committed based on their interpretation of graphically-represented social interactions while the latter requires a participant to speculate on the mental states (e.g. happy, sad, anxious, etc.) based on pictorial stimuli containing pairs of eyes.

Mood and motor behavior

bvFTD: Apathy, defined as a reduction of self-generated voluntary and purposeful behavior, may be seen in any of the syndromic variants of FTD but may be particularly severe in early bvFTD (Levy and Dubois, 2006). 'Utilization behaviour' is another feature of bvFTD manifest by the tendency of the affected individual to interact with physical objects in an environment that is contextually inappropriate e.g. picking up and writing with the examiner's pen during consultation. The performance of motor tasks may also be impaired by motor perseveration or by difficulties with sequencing the components of a task.

nfvPPA: Depression is an early feature (Medina & Weintraub, 2007) with

apathy or irritability emerging later in disease, although often not as marked as observed with bvFTD (Banks and Weintraub, 2008). An exception is observed with nfvPPA arising from Pick body pathology, in which severe behavioural changes can be observed within three years of symptom onset (Kertsz & Munoz, 1996).

svPPA: Individuals become more self-centred and mentally rigid as disease progresses leading to the adoption of a fixed daily routine (Snowden *et al*., 1996). Often there is preoccupation or obsession with activities involving visuospatial skills such as jigsaw puzzles (Green and Patterson, 2009). Likewise, individuals become fixated with certain foods that manifests as a food fad, often for sweet snacks. In contrast to purposeless perseverative behaviour observed in bvFTD, patients with svPPA initially perform well in the activities that preoccupy them and perform better than expected in risk-taking tasks such as gambling (Julien *et al.*, 2010).

Executive function

Impaired executive functioning, attributed to disease affecting the dorsolateral prefrontal cortices, is manifest by perseverative behavior and impairments in planning, abstract reasoning ability, task-switching, vigilance and divided attention. It is commonly observed in bvFTD and with advancing disease severity these deficits can impair performance on almost any cognitive task (Neary *et al*, 1988).

Language

bvFTD: conversational speech may be reduced and verbal responses may be brief or concrete in nature. Verbal stereotypies may also feature and patients may repeat stock words or phrases. However, speech is usually fluent and, in the absence of concurrent MND, there is no difficulty with articulation. Later, speech may become aprosodic or echolalic. Written

communication may be similarly brief and perseverative. Comprehension for simple commands is unimpaired but comprehension of complex sentences and multi-staged commands may be impaired. The ability to read aloud is relatively preserved although inattention and impaired abstract thinking may impair the ability to comprehend narrative prose. During word-generation testing, letter fluency is more impaired than category fluency (Hodges *et al*., 1999).

nfvPPA: The core speech deficits have been described earlier. Confrontational naming is impaired in these patients but compared to svPPA, the semantic information related to the items is largely intact. During word-generation testing, letter fluency is more impaired than category fluency (Hodges & Patterson, 1996).

svPPA: The core speech deficits have been described earlier. Confrontational naming is impaired but is more severe for low frequency items. During reading, surface dyslexia is apparent (Hodges *et al.*, 1999). During word-generation testing, category fluency is more impaired than letter fluency (Hodges *et al*., 1999).

Memory

bvFTD: individuals perform poorly on free recall tasks and cued recall tasks involving word lists (Hornberger *et al*., 2010). In rare instances, *GRN* and *MAPT* mutations may present with an amnestic syndrome resembling AD. In contrast to AD, spatiotemporal and topographical orientation is rarely impaired in bvFTD (Yew *et al*., 2012).

nfvPPA: individuals perform similar to controls on free and cued recall tasks. In advancing disease, the inability to repeat words can confound standard list-learning paradigms (Gorno-Tempini *et al*., 2004).

svPPA: individuals perform similar to controls on free and cued recall tasks. In contrast to AD, there is impairment in remote autobiographical and semantic memory (Graham & Hodges, 1997),

1.6.6 Clinical Assessment of FTD

The physical examination may reveal frontal ‘release’ signs, representing the re-emergence of neonatal or primitive reflexes, that may become associated with urinary incontinence (Gregory *et al*., 1997). In FTD with Parkinsonism or FTD-MND one may find additional clinical features suggestive of these processes (Rossor *et al.*, 2010). As outlined earlier, some patients may have features suggestive of psychosis such as hallucinations and paranoid delusions (Woolley *et al*., 2011).

The MoCA is used for the bedside screening of executive function while the ACE-R is useful in differentiating FTD from sporadic AD (Nasreddine *et al*., 2005; Mioshi *et al.,* 2006). The Frontal Behavioural Inventory requires collateral information from an informant but is usual for identifying impaired social cognition, particularly in early bvFTD when performance on screening tests of executive function and language may still be intact (Kertesz *et al*., 1997).

Profound apathy or disinhibition may be clinically apparent, the latter usually manifest by inappropriate social commentary or sexual innuendo. Stereotypic or ritualistic behavior may be observed in the form of pacing and the repetition of stock words or phrases. Patients with Pick body pathology can present with features of Kluver-Bucy syndrome (hyperorality, constant manual exploration and utilization behavior sometimes accompanied by autosexual behavior) (Pilleri, 1966). A systemic examination may sometimes reveal evidence of Paget’s disease or myopathy in patients with *VCP* mutations (Rossor *et al*., 2010).

1.6.7 Neuroimaging changes in FTD

Structural Imaging

***bvFTD*:** MRI may appear normal in early disease and the determination of subtle atrophy is highly rater-dependent (Chow *et al*., 2011). As disease progresses, MRI reveals focal atrophy in the medial frontal and/or anterior temporal regions (Kipps *et al*., 2007). In research settings, quantitative analyses have revealed early gray matter loss in the ventromedial frontal region, posterior orbitofrontal cortex, insula and left anterior cingulate cortex extending to the dorsolateral prefrontal cortex and medial premotor regions (Frisoni *et al*., 1996; Galton *et al,* 2001; Rosen *et al.*, 2002). Longitudinal MRI studies have shown that rates of atrophy are most severe in the frontal lobes (Krueger *et al.*, 2010), particularly marked in the medial frontal cortices (Brambati *et al*., 2007). MRI studies have also been used to investigate social cognition changes in bvFTD identifying correlations between disinhibition and anterior cingulate atrophy and between apathy and medial frontal atrophy (Rosen *et al*., 2005). Other MRI studies have focused on atrophy profiles based on neuropathology. Pick bodies are associated with a greater degree of frontal atrophy than either *MAPT* mutations or TDP-43 pathology (Whitwell *et al*., 2005, Whitwell *et al*., 2010). *MAPT* mutations cause more severe temporal lobe atrophy than either Pick's disease or TDP-43 pathology, these mutations also associated with brainstem atrophy (Whitwell *et al*., 2010). Parietal atrophy occurs with *MAPT* and TDP-43 pathology but tends to be more severe with the latter, and asymmetric in FTLD due to *GRN* mutations (Whitwell *et al.*, 2011; Rohrer & Warren, 2011).

nfvPPA: Qualitative MRI is often interpreted as being normal in early disease; some studies also observing bilateral perisylvian atrophy in this condition (Westbury & Bub, 1997; Mesulam *et al*., 2008). Group studies, using voxel-based morphometry, identify atrophy involving the anterior perisylvian region, specifically the left inferior frontal lobe and insula, extending to the premotor cortex during early disease (Caselli and Jack 1992l; Nestor *et al*., 2003). With disease progression, atrophy is observed

in the thalamus and caudate nucleus. Pick bodies are associated with medial and lateral temporal atrophy whereas *GRN* mutations are associated with prominent lateral temporal and inferior parietal atrophy (Rohrer *et al*., 2010).

svPPA: Qualitative MRI reveals asymmetric, left > right, focal atrophy of the anterior and inferior temporal lobe. Quantitative analyses reveal atrophy involving the left temporal pole, anterior EC, anterior hippocampus and anterior fusiform gyrus extending to the inferior temporal region (Mummery *et al*., 2000, Chan *et al*., 2001). Longitudinally, there is progressive atrophy of the left and right temporal lobe although right-sided atrophy remains comparatively less extensive. Over time, atrophy 'spreads' to involve the left superior temporal region and left frontal lobe also involving the left insula and left ACG (Rohrer *et al*., 2009). In patients with TDP-43 pathology, atrophy involves the temporo-parietal regions compared to cases with Tau pathology, which involves the orbitofrontal and temporal cortices (Rohrer *et al*., 2010).

rtv-FTD: There have been no large studies that have investigated the longitudinal MRI changes in rtvFTD. In one study that investigated the behavioural and MRI changes in three patients, atrophy was observed in the right anterior and inferior temporal lobe (Joubert *et al*., 2006). In the study by Chan *et al*. (2009), imaging analysis, restricted to temporal lobe structures, identified asymmetric atrophy lateralized respectively to the right and left amygdala, hippocampus and temporal lobe in rtv-FTD and svPPA. In comparison, the study by Josephs *et al*. (2009) observed prominent right fusiform atrophy in individuals with progressive prosopagnosia, in association with TDP-43 pathology. In contrast, inferior-medial frontal atrophy and marked neuropsychiatric symptoms were indicators of tau-pathology (Josephs *et al*., 2009). .

Functional imaging

FDG-PET

bvFTD: FDG-PET studies reveal prominent hypometabolism in the frontal, anterior temporal and anterior cingulate cortices (Ishii *et al*., 1998, Diehl *et* al., 2004). At a single-subject level, ventromedial frontal hypometabolism is the most consistent feature of bvFTD (Salmon *et al*., 2003). When frontal sub-regions are not considered separately, anterior cingulate hypometabolism serves as a specific marker of bvFTD (Womack *et al.,* 2011). In presymptomatic FTD due to GRN mutations, the anterior cingulate and ventromedial frontal regions are amongst the earliest regions to become hypometabolic, along with the insula, precentral and middle frontal gyrus (Jacova, *et al*., 2013).

nfvPPA: Several studies identify left lateralized hypometabolsim in nfvPPA (Tyrell *et al.,* 1990; Nestor *et al.,* 2003) involving the left inferior frontal gyrus, frontal operculum, insula, premotor cortex and supplementary motor area (Grossman *et al.,* 1996; Nestor *et al.,* 2003).

svPPA: PET studies demonstrate asymmetric, left > right, hypometabolism in the left anterior temporal lobe (Nestor *et al.,* 2006; Rabinovici *et al.,* 2008) while temporoparietal and anterior cingulate hypometabolism have also been variably reported by other studies (Mosconi *et al.,* 2008; Womack *et al.,* 2011).

rtvFTD: Dedicated PET studies of rtvFD are limited. A case series observed asymmetric, right > left, hypometabolism in the temporal pole and fusiform patients with TDP-43 pathology (Coon *et al.,* 2012). The general lack of PET studies may reflect the relative rarity of this condition or the tendency for these patients to be diagnosed with either bvFTD or sv-PPA (Thompson *et al.,* 2003; Coon *et al.,* 2012).

1.7 The role of the hippocampus in memory

The dissociated impairments in episodic and semantic memory observed in case H.M. suggested the existence of a distributed declarative memory system within the brain that required intact medial temporal lobe (MTL) function for the acquisition of episodic verbal and non-verbal memory (Scoville and Milner 1957). According to the standard model of consolidation, the MTL is required for the long-term neocortical representation of personal experiences but not for the retrieval of these representations; accordingly, MTL injury would result in anterograde amnesia and temporally graded retrograde amnesia, reflecting the failure to consolidate recent experiences (Squire 1992, Bayley and Squire, 2005). It is widely accepted that the hippocampus is critical for the acquisition of declarative memory (Eichenbaum *et al.,* 2007; Squire *et al.,* 2007). However, several human and animal studies have given rise to other models of memory that challenge the standard model of consolidation and the role of the hippocampus in memory retrieval (Cipolotti and Bird, 2006; Wixted and Squire, 2011). Nonetheless, these converge in suggesting that the hippocampus is involved in either the indexing or retrieval of a memory trace, or the components thereof (for a review see Bird and Burgess, 2008).

Recognition memory is a form of declarative memory, referring to the ability to identify previously encountered stimuli (Tulving, 1985). Recognition memory encompasses two processes: recollection and familiarity. Conceptually, familiarity is a ‘sense of knowing’, the ability to recognize a stimulus but not the context in which it occurred, whereas recollection refers to the ability to retrieve an experience or stimulus, and the context in which it occurred (Tulving, 1985). Some anatomical studies support a double dissociation between recollection and familiarity given that hippocampal lesions are associated with impaired recollection but intact familiarity, whereas perirhinal lesion are associated with impaired familiarity but preserved recollection (Brown and Aggleton, 2001; Aggleton *et al.,* 2005; Bowles *et al.,* 2007). However, other studies have observed deficits in

recollection and familiarity in individuals with focal hippocampal damage that contradict the double dissociation model of recognition memory (for a review see Cipolotti & Bird, 2006). These apposing outcomes may be due to several factors, including the age of the hippocampal injury and any involvement that extends beyond the hippocampal formation (Vargha-Kadem *et al.,* 1997).

Insights into hippocampal function from AD and FTD

At first glance, the patterns of memory loss observed in svPPA and AD lend support to the standard model of consolidation. In AD, the ability to retrieve recent events is impaired compared to the ability to retrieve remote events, conforming to Ribot's Law, reflecting prominent hippocampal neurodegeneration (Sagar *et al.,* 1988; Irish *et al.,* 2011). In comparison, remote rather than recent memories are impaired in svPPA, regarded as an indicator of prominent extra-hippocampal, neocortical neurodegeneration (Hodges & Patterson, 2007).

However, other studies of AD and FTD indicate that the lateralization of episodic and semantic memory is more complex than the standard model posits. Detailed assessments of seemingly intact remote memory in early AD reveal that the ability to recall to the contexts of events is impaired (Kopelman, 1989; Piolino *et al.,* 2003; Irish *et al.,* 2011), a feature that is also observed in non-neurodegenerative, focal hippocampal damage (Cipolotti *et al.,* 2001). Piolino *et al*. (2003) provide further evidence that the retrieval of the spatial context of memory is critically dependent on intact hippocampal function. In comparison, the temporal context of memory and temporal-ordered learning are supported by prefrontal and hippocampal regions, that may account for the impairments in list recall that are observed in AD and bvFTD (Hornberger *et al*., 2010; also see Hannula and Greene, 2012).

In terms of recognition memory, AD is associated with impairments in recollection and familiarity, although the former is more pronounced (Smith

and Knight, 2002). During testing, patients with AD and focal hippocampal damage tend to select foil items more often than anticipated by chance alone. Given that foil items are either semantically- or phonetically similar to target items, this observation suggests that familiarity is relative spared compared to recollection in patients with prominent hippocampal damage. In comparison, healthy controls tend to make fewer but appropriate choices compared to patients with AD and focal hippocampal damage (Bird and Burgess, 2008).

Spatial memory

The role of the hippocampus in spatial memory is discussed later. In brief, there is ample evidence that highlights the critical importance of the hippocampus in the processing of spatial information (Burgess *et al*., 2002). This is of particular relevance to the recognition of AD, and in discriminating AD from FTD.

Conclusion

The hippocampus is critically involved in declarative memory. In particular, the spatial context of episodic memory and recognition memory appear highly dependent on intact hippocampal function.

1.8 Hippocampal atrophy in neurodegenerative dementia

Structural neuroimaging in dementia traditionally fulfilled two roles. First, it provided the means to detect neurodegenerative brain changes otherwise only previously apparent at post mortem. Second, it allowed the detection of occult lesions that may be contributing to cognitive decline (Scheltens *et al.,* 2002). Compared to CT, T1-weighted MRI acquisition offer superior spatial resolution allowing for a more detailed inspection of smaller structures within the brain facilitating the detection and quantification of hippocampal atrophy (Jack *et al.,* 1997).

Hippocampal atrophy in AD

Qualitative, or visually rated, MRI and CT scanning of patients with established AD reveal generalised cerebral atrophy with prominent involvement of the MTL. The known early involvement of the MTL in AD led to the development of an MRI-based visual rating scale to assess MTL atrophy, incorporating the choroidal fissure, the width of the temporal horn ad the height of the hippocampus. This method was 85% sensitive and 88% specific in differentiating AD from controls (Scheltens *et al.,* 1992). Subsequent study demonstrated that atrophy of the medial parietal region was useful for discriminating between AD and FTD (van de Pol *et al.,* 2006). In research settings, atrophy may be assessed quantitatively using either manual tracing, semi-automated or automated techniques. A unifying feature of automated methods is that scan data require normalisation to correct for the anatomic variations in skull size and shape and this is achieved by registering the scan data to a standardised digital atlas. The boundaries of the hippocampus and the tissue contrast permitted by the surrounding CSF make it ideally suited for large-scale visual and automated study (Scheltens *et al.,* 1992). Hippocampal volume, obtained by manual tracing, is concordant with post-mortem hippocampal measurements and in AD, it serves as a reliable index of neuropathology such that hippocampal volume is inversely related to hyperphosphorylated Tau pathology (Bobinski *et al.,* 1999; Jack *et al.,* 2002).

Voxel-based morphometry is a semi-automated procedure that permits group-wise comparisons of whole brain and regional atrophy between AD and other groups of interest. In contrast, fluid registration is an automated procedure that allows a single subject's initial scan to be registered as a control scan by which subsequent changes can then be tracked (Freeborough and Fox, 1997). More recently Freesurfer and FSL have emerged and both contain semi-automated algorithms to measure hippocampal volume while Freesurfer also allows the user to measure hippocampal cortical thickness. Hippocampal atrophy of a magnitude of 30% is detectable at the onset of dementia (van der Flier *et al.,* 2005) and volume reductions of up to 15% may be observed in prodromal AD (Shi *et al.,* 2009). The rate of hippocampal atrophy is three times higher in AD compared to controls and accelerated hippocampal atrophy is also observed during the predementia stages of disease (Barnes *et al.,* 2009). Longitudinal measures of hippocampal atrophy not only predict conversion of MCI to AD but also may be useful in identifying asymptomatic elders at risk for AD (Jack *et al.,* 1997). Progressive hippocampal atrophy has also been shown to occur upstream to NFT dissemination to the neocortex and is therefore apparent prior to clinical worsening of dementia (Whitwell *et al.,* 2008). Studies involving asymptomatic individuals with an autosomal dominant genetic risk for AD has yielded mixed results in terms of rates of hippocampal atrophy (Fox *et al.,* 1997; Apostolova *et al.,* 2011) possibly reflecting the clinical heterogeneity of EOAD. In comparison, the ApoE4 allelic frequency strongly correlates with an accelerated rate of hippocampal atrophy, also detectable during the predementia stages of disease (Shuff *et al.,* 2009).

Hippocampal atrophy in non-AD dementia

Hippocampal atrophy also occurs in other neurodegenerative diseases such as FTD, dementia with Lewy bodies and hippocampal sclerosis. Visual assessments of the topography and symmetry of atrophy is useful in recognising FTD syndromic variants which are associated with asymmetric atrophy of the anterior MTL including the anterior hippocampus, extending to

the temporal pole and temporal neocortex (Galton *et al.,* 2001; Chan *et al.,* 2001).

Hippocampal sclerosis (HS), Neurofibrillary tangle predominant dementia (NFTD) and argyrophillic grain disease (AGD) are neurodegenerative diseases associated with indolent, slowly progressive amnestic syndromes and hippocampal atrophy (Yamada, 2002; Ferrer *et al.,* 2008; Nelson *et al.,* 2011). AGD is usually associated with an onset of symptoms after the age of 80 years that is associated with atrophy restricted to the hippocampus and amygdala (Braak & Braak, 1989). By comparison, hippocampal sclerosis is associated with prominent hippocampal neuronal losses and gliosis (Nelson *et al.,* 2011). NFTD is also associated with symptom-onset after 80 years of age, associated with mild, symmetric atrophy involving the MTL, that does not spread to frontal or parietal regions (Yamada, 2002).

2. Survey of previous work

2.1 Multimodal neuroimaging of Alzheimer's disease

Hypometabolism and atrophy, as assessed by FDG-PET and MRI respectively, are key determinants of diagnostic certainty in patients with suspected neurodegenerative dementia (Gorno-Tempini *et al.,* 2011; Rascovsky *et al.,* 2011; McKhann *et al.,* 2011). In routine practice, recommendations are that FDG-PET is a second-line diagnostic test, for use in cases with unremarkable MRI changes (Weiner & Khachaturian, 2005).

In research settings, existing PET and MRI studies have allowed the chronology of biomarker changes to be modelled in AD and this will be of particular relevance to any future preventative and treatment strategies that may become available in this area (Jack *et al.,* 2010). It is worth noting that in AD, hypometabolism exceeds atrophy during the predementia stage of disease (Morbelli *et al.,* 2010). Generally, studies have not focused on the concordance between hypometabolism and atrophy in the different dementias. Given the spatial and temporal resolution strengths of MRI and FDG-PET respectively, the determination of any regional concordance, or discordance, between atrophy and hypometabolism may have relevance for diagnosis and prognosis. In addition, these differences may highlight important features that aid our understanding of these diseases. For instance, Pitel et al. (2009) applied parametric structural MRI and FDG-PET analyses to nine patients with Korsakoff's syndrome, a dementia syndrome linked to thiamine deficiency characterized by psychosis and confabulation. The study identified several differences in gray and white matter density, and hypometabolism in patients compared to controls. Within the Korsakoff group, middle cingulate hypometabolism in excess of atrophy was evident in all subjects whereas there was marked within-group heterogeneity in terms of other PET and MRI changes.

The Dominantly Inherited Alzheimer's Network (DIAN) study applies combined FDG-PET, amyloid-PET and structural MRI studies to individuals with presymptomatic autosomal dominant AD (Bateman *et al.,* 2010). The onset age of dementia in familial AD is highly conserved between parent and offspring; DIAN focuses on AD biomarker changes based on an individual's expected age of dementia onset. Recent re-analysis of study data reveals heterogeneity in terms of hypometabolism-atrophy concordance. For all regions except the hippocampus, hypometabolism was evident approximately five years before changes in cortical thickness and hypometabolic changes arose sequentially that involved the precuneus, posterior cingulate cortex and lateral parietal region (Benzinger *et al.,* 2013). In comparison, changes in hippocampal cortical thickness occurred ten years before any corresponding hypometabolism. Within the limitations of the study assumptions (assuming similar biomarker trajectories in all individuals based on a theoretical age of onset), it suggests that there is heterogeneity in terms of the topography of PET and MRI changes during the course of the disease. Further, higher degrees of atrophy-hypometabolism concordance in AD may therefore serve as an indicator of longstanding or advancing disease.

Other cross-sectional studies have also highlighted marked inter-regional differences between atrophy and hypometabolism in AD, observing more extensive neocortical hypometabolism than atrophy and more extensive hippocampal atrophy compared to hypometabolism (Villain *et al.,* 2008; Chetelat *et al.,* 2008; La Joie *et al.,* 2012). In an earlier study, Ishii *et al*. (2005) demonstrated group level differences in the topography of hypometabolism and atrophy in patients with mild AD (MMSE > 23; mean age 66.8) identifying posterior cingulate hypometabolism in the absence of significant parietal atrophy. In contrast, medial temporal hypometabolism was detectable only when applying corrections for partial volume effects and even then, this did not reach statistical significance.

It should be noted that most previous studies have all involved sequential PET and MRI acquisition on separate scanners with subsequent data analysis either performed in parallel or requiring an additional PET/MR coregistration step (Catana *et al.,* 2008). The introduction of integrated PET/MR scanners permits simultaneous acquisition and co-registration of this data (Judenhofer *et al.,* 2008), also lending itself to incorporation within machine-learning paradigms (Dukart *et al.,* 2011). In addition to providing structural information about the brain, advances in MRI have allowed for the detection of microstructural neurodegenerative changes in multimodal studies of AD. The potential application of these techniques, should they become validated for single subject study, is briefly outlined below.

Functional MRI is described in an earlier chapter. Drzezga *et* al. (2011) compared 'amyloid positive' MCI, 'amyloid positive' elderly controls and 'amyloid negative' elderly controls using resting state fMRI, FDG-PET, and structural MRI. In MCI, there were significant disruptions of whole-brain connectivity that overlapped considerably with hypometabolic changes in the posterior cingulate cortex and precuneus (dice coefficient of similarity = 42%). Similar but milder reductions occurred in 'amyloid positive' controls but not the 'amyloid negative' group. This relationship between FDG-PET and functional MRI did not appear to be related to any structural changes in the retrosplenial cortex and did not correlate directly with hippocampal volume.

Diffusion tensor imaging (DTI) is based on the physical properties of moving water protons. In white matter this motion is slower compared to free-flowing CSF and occurs more readily along highly myelinated neurons. MRI quantifies this motion as the apparent diffusion coefficient (ADC) and the direction of motion is quantified using the fractional anisotropy index (FA). With Wallerian degeneration, ADC is increased and FA decreased. Cingulum anisotropy serves as the DTI hallmark of AD (Clerx *et al.,* 2012). Villain *et al*. (2010) studied longitudinal changes in structural MRI and FDG-PET in prodromal AD and surmised that hippocampal atrophy preceded cingulum and uncinate fasciculus atrophy that in turn determined the severity of posterior cingulate hypometabolism. In related work, the authors found that cingulum bundle atrophy preceded changes in cingulum FA also reporting

that cingulum atrophy and cingulum FA were correlated to posterior cingulate hypometabolism (Bozoki *et al.,* 2012). Taken together, this suggests cingulum atrophy results in the disconnection of the hippocampus and retrosplenial cortex, the latter giving rise to cortical hypometabolism and altered functional connectivity.

Other advanced MRI techniques such as magnetization transfer imaging and arterial spin labelling, that provide indirect measures of cell membrane integrity and regional perfusion respectively, have also been studied in AD. The strength of multimodality lies in its ability to aid clinical diagnosis on one hand and to advance research relating to pathogenesis on the other. However, unless microstructural MRI analyses become validated for single-subject use, clinical practice will continue to focus on structural MRI and FDG-PET scanning (Caroli and Frisoni, 2009).

2.2 Multimodal neuroimaging of FTD

In comparison to AD, multimodal studies involving FTD are confounded by clinical, genetic and neuropathological heterogeneity. This is particularly important given that FTLD-tau and FTLD-U (and its subtypes) are associated with differing patterns of atrophy and hypometabolism (Pereira *et al.,* 2009). Existing studies have focused therefore on the syndromic variants described by the relevant diagnostic criteria (Rascovsky *et al.,* 2010, Gorno-Tempini *et al.,* 2010).

BvFTD is traditionally associated with asymmetric frontal atrophy but this is not uniformly apparent during early disease (Koedam *et al.,* 2010). A high degree of concordance has been observed between structural and functional changes over the right frontal hemisphere whereas atrophy was the predominant abnormality in the left frontal hemisphere (with the exception of the anterior cingulate cortex, in which hypometabolism was observed without associated atrophy) (Tosun *et al.,* 2013). Shimzu *et al*. (2010) also observed frontal atrophy in excess of functional brain changes in early bvFTD, with the

strongest concordance between structure and function occurring in the right prefrontal cortex and medial frontal lobes. Together, these studies may reflect the non-neuronal, astrocytic, losses described in the earliest stages of bvFTD (Broe *et al.,* 2004) although this requires validation by dedicated MRI-histopathology study.

In addition, the study by Kanda *et al*. (2008) suggests that neurons in the medial frontal lobes and anterior cingulate are selectively vulnerable to FTLD. In that study, combined PET and MRI were applied to patients with early AD and bvFTD, revealing atrophy-hypometabolism colocalisation in medial frontal regions in bvFTD whereas atrophy was more pronounced than hypometabolism in anterior temporal and dorsolateral frontal regions. Teichman *et al*. (2013) applied quantitative SPECT and structural MRI to patients with logopaenic progressive aphasia (lgvPPA), stratified by AD biomarker status. Compared to controls, both groups demonstrated significant hypoperfusion in the left temporoparietal junction. Hypoperfusion was also apparent at the single subject level whereas temporoparietal atrophy was not. Additional hypoperfusion was apparent in the precuneus in patients with lgvPPA-AD, and in the left superior frontal gyrus in patients with lgvPPA-FTLD. Subsequent studies, using FDG-PET and MRI, identified similar changes but confirmed that temporoparietal functional changes were more marked with AD compared to FTLD (Whitwell *et al.,* 2015).

In nfvPPA, Nestor *et al*. (2003) observed discordant FDG-PET and MRI changes in the left perisylvian region, where mild perisylvian atrophy was associated with extensive hypometabolism that extended to the inferior frontal operculum and insula. In a subsequent study utilising structural MRI and DTI, atrophy involved the inferior frontal and fusiform gyrus extending to the anterior cingulate and premotor area, associated with increased ADC in the inferior frontal region (left>right) and reduced FA in the left cingulum (Botha *et al.,* 2015).

In contrast to bvFTD and PPA, there is a high degree of overlap between atrophy and hypometabolism in svPPA particularly within the anterior temporal region (Desgranges *et al.,* 2007; Acosta-Carbronero *et al.,* 2011).

2.3 Quantitative neuroimaging analysis

MRI and FDG-PET represent the techniques of choice for identifying respective structural and functional brain changes that arise due to neurodegenerative pathophysiology (Weiner and Khachaturian 2005). Although not specified by the criteria, MRI is preferred to PET reflecting its widespread availability and sensitivity for non-neurodegenerative processes (Scheltens *et al.,* 2002, Weiner and Khachaturian, 2005).

In clinical settings, PET and MRI data is interpreted qualitatively (Weiner and Khachaturian, 2005), using region-of-interest based visual rating scales that have been cross-validated against parametric neuroimaging analyses (Scheltens *et al.,* 1992; Galton *et al.,* 2001; Kipps *et al.,* 2007; Mosconi *et al.,* 2008). In contrast, research settings deploy quantitative paradigms that determine group-level differences between health and disease states. This approach is also used to infer brain-behavior correlations and, via longitudinal study, for the 'mapping' of disease-specific neuroimaging changes (Jack *et al.,* 2010).

The inability to generalize parametric neuroimaging analyses to the clinical environment, in part, reflects the technological demands and expertise required of these methods, and in the case of MRI, the limitations imposed by parametric statistical methods and their scalability for single-subject study (Caroli and Frisoni, 2009).

2.3.1 Quantitative structural neuroimaging

Manual volumetry is undertaken on T1-weighted 3D MRI acquisitions. It is operator dependent, requiring the alignment of acquired MR images to a standard orientation specific for the region of interest (ROI) being studied and the ROI is then manually traced on contiguous slices in a single plane (for a review see Geuze *et al.,* 2005). Highly experienced operators produce reliable measures of volume but the labour intensity of this process lacks applicability outside of research settings (for a review see Brewer, 2009). However, it is still regarded as the gold standard for volumetric measurement by which computational techniques are validated (Hsu *et al.,* 2003).

By comparison, computational anatomy algorithms may be automated or semi-automated and are less laborious than manual tracing (Ashburner, Csernansky *et al*., 2003). These algorithms may be applied in cross-sectional studies to assess the 'signature' of a disease and in longitudinal studies to track disease progression either within an individual (Freeborough & Fox, 1997) or disease groups (Chetelat *et al.,* 2005). Semi-automated techniques require the manual delineation of some anatomical landmarks while fully-automated methods utilize geometric template-matching paradigms to extract whole brain volumetric measures (Mazziota *et al.,* 2002). Semi- and fully-automated methods generally entail the same processing steps i.e. brain extraction, tissue segmentation, spatial normalization and statistical analysis. Following brain extraction, images are registered to a reference stereotactic template allowing them to be spatially normalized. In its most basic form, the computational software produces segmentations for grey matter and white matter based on differences in their signal intensity.

Voxel-based morphometry (VBM, Ashburner and Friston, 2000) is a fully automated technique that permits voxel-wise statistical group comparisons over the whole brain. Acquired scans are spatially transformed in a common reference space to remove confounding variations in brain size and brain

shape (for a review of VBM methodology see Ashburner and Friston, 2000). Thereafter, these normalized scans are segmented into grey and white matter and the gray matter is smoothed to allow between-group voxel-level comparisons. This approach, based on group-level statistics, limits the standard VBM procedure from being applied to the single subject and VBM should also be avoided in small group studies or if there is significant biological heterogeneity within any of the groups being studied (Brookstein, 2001). Another consideration with VBM, and indeed with any of the quantitative paradigms, relates to the group-comparisons themselves. In dementia research, VBM has played a key role in establishing the neuroimaging signatures of AD and FTD (for a review see Whitwell and Jack, 2005).

Cortical thickness mapping is highly relevant to neurodegeneration and provides an index of cortical neuronal loss (Jones *et al.,* 2000, Thompson *et al.,* 2000). The manual tracing of cortical gray matter maps, whilst possible, is labour-intensive and impractical for large-scale studies. In research settings, cortical thickness is assessed using fully-automated procedures that are either voxel-based or vertex-based. Surface-based, also referred to as vertex-level, techniques involve the construction of grey and white matter surface models based on the topographic characteristics of a bespoke spherical coordinate system (Fischl & Dale, 2000). FreeSurfer (www://surfer.nmr.mgh.harvard.edu) is a freely available imaging analysis suite based on this principle that computes cortical thickness at any point in the following way: for each point on the grey matter/pial surface, the shortest distance to the gray/white matter surface is found. To date, several studies have highlighted the potential of cortical thickness to detect AD-specific brain changes (Thompson *et al.,* 2000; Lerch *et al.,* 2005), identifying atrophy within the medial temporo-parietal region although Freesurfer is more sensitive than VBM for detecting any medial parietal changes (Diaz-de-Grenu *et al.,* 2014). However, FreeSurfer-based vector support algorithms perform poorly in detecting prodromal AD (less than chance alone). This observation could be due to limitations of study design, particularly study

duration as conversion to AD could yet occur outside of the study window (Cuingnet *et al.,* 2011).

Hippocampal volumetry is of particular relevance to any discussion relating to MR quantification. Manual tracing has been applied in cross-sectional and longitudinal studies of AD and is regarded as the gold standard for *in-vivo* hippocampal quantification (Jack *et al.,* 1992; Fox *et al.,* 1996, Chan *et al.,* 2001). A number of manual hippocampal segmentation protocols are described and there is an ongoing effort to achieve a standardized procedure (Frisoni & Jack, 2011). Longitudinal studies permit the assessment of single-subject hippocampal atrophy rates (expressed as percentage volume change per year), requiring serial MRI scans with every subject acting as his or her own control (for a review see Barnes *et al*., 2008). Of these, the boundary shift integral demonstrates good correlation with manual morphometry but uses bespoke software, that is not freely available, to determine the measurements of shifts at the boundary of the hippocampus (Barnes *et al.,* 2004).

While early cross-sectional studies focused on group differences between AD and controls, recent methodological advances have focused on the incorporation of large databases of MRI data to examine changes in anatomy that could be applied at the single-subject or between-group level (for a review see Morey *et al*., 2009). FreeSurfer, described above, achieves cortical and sub-cortical gray matter segmentations at the single subject level using a paradigm that models the spatial relationships of voxels by virtue of their signal intensity (Fischl *et al.,* 2002). In contrast, FSL/FIRST (FMRIB Integrated Registration and Segmentation Tool, Oxford University, Oxford) performs subcortical gray matter segmentation using Bayesian shape and appearance models constructed from a library of manually segmented images (Patenaude *et al.,* 2011). Both FreeSurfer and FSL/FIRST are in the public domain, applied extensively to various degenerative and periodic disorders affecting the human brain. One issue that does arise with these

tools relates to software updates and the absolute measurements obtained by their iterative versions may vary although any corresponding group-level differences are statistically similar.

Several studies have compared these methodologies, using manual delineation as gold standard, with contrasting results. Morey *et al*. (2009) reported that FreeSurfer exhibited greater volume overlap and higher correlation to manual hippocampal morphometry in healthy controls compared to FSL. However Nestor *et al.* (2013) compared five popular automated software packages to the harmonized hippocampal tracing methods described by Frisoni and Jack (2011) in patients with AD. This study concluded that the estimation of caudal hippocampal volume was heavily dependent on the anatomical borders being used by the different packages such that FreeSurfer was particularly susceptible to under-evaluating caudal hippocampal volume. Although FSL/FIRST was not included in this study, Lim and colleagues (2012) observed that FSL/FIRST achieved good classification of the entire hippocampal length, also reporting a correlation between total hippocampal volume and episodic memory in untreated early AD. By comparison, studies involving other automated procedures find a correlation between episodic memory and the anterior hippocampus only, which may reflect the inability of these techniques to classify the posterior hippocampus adequately (Nestor *et al.,* 2013). Mulder *et al*. (2014) compared FreeSurfer and FIRST/FSL in a longitudinal study that also used a bespoke manual method, reporting higher rates of segmentation automation with FreeSurfer but comparable rates of hippocampal volume change with all three techniques. The matter of which automated procedure is most sensitive to hippocampal volume changes remains a matter of ongoing debate.

2.3.2 Quantitative functional neuroimaging

In line with the diagnostic criteria for AD and FTD and the experimental work carried out in this thesis, this discussion will be restricted to the quantitative analysis of FDG-PET. The uptake of FDG provides an indirect measure of cerebral cortical metabolic rate, regarded as an index of synaptic function

and synaptic density (Attwell and Iadecola, 2002). While functional MRI and quantitative SPECT both provide indirect measures of brain function, in the form of functional connectivity and perfusion respectively, a comprehensive review of these subjects is beyond the scope of the work carried out in this thesis.

ROI-based PET analysis involves the visual rating of single subject FDG-uptake based on *a priori* diagnostic bias. Traditionally, this used a limited number of transaxial images and required a qualitative assessment of FDG-uptake. With advances in PET and CT, PET data was co-registered onto multi-slice transaxial CT (and, later, MRI) that improved the spatial localization of PET uptake. This allowed the quantification of mean FDG-uptake within an ROI (standardized uptake value, SUV) and the normalization of cortical SUVs relative to the pons or cerebellum (standardized uptake value ratio, SUVR), based on the assumption that the pons and cerebellum are relatively 'spared' in neurodegenerative dementia. Visual rating of SUV and SUVR is associated with a sensitivity of 76-93% and a specificity of 72-93% for the differentiation of AD from controls (Patwardhan *et al.,* 2004); the ROIs used for the determination of AD include the lateral temporoparietal and posterior cingulate cortices (Foster *et al.,* 1984). However, these ratings are highly operator dependent and the research studies that involve highly experienced PET raters may not be adaptable to a real world setting (Perani *et al.,* 2014).

Voxel-based FDG-PET analyses involve the evaluation of FDG uptake at the whole brain level and involve similar processing steps as VBM but with the additional incorporation of metabolic counts during spatial normalization (Ashburner & Friston, 1999; Herholz *et al.,* 2004). Statistical comparisons are then performed (single subject versus controls or groupwise pairings) and the levels of statistical significance are then projected onto an anatomical brain template (parametric maps).

NEUROSTAT is an automated software analysis package that projects maximal PET counts (in the case of FDG-PET, FDG-uptake) into a uniform stereotactic space such this data is then represented on a standard brain model as a 3D surface projection map (Minoshima *et al.,* 1995). This process involves the interpolation of the acquired PET data to establish a uniform image matrix (and voxel size) that is then scaled linearly to correct for variations in brain size. This allows for comparable data sets, based on a Talairach anatomical template, to be analyzed on a pixel-by-pixel basis; the automated procedure also includes the application of non-linear warping correction to account for any regional anatomical differences between the reconstructed and atlas brain (Minoshima *et* al., 1995; Foster *et al.,* 2007). Surface projections are represented by the highest pixel value found within a six pixel longitudinal vector running perpendicular to the medial and lateral surface of each cerebral hemisphere; in the current version of NEUROSTAT the output maps may be represented in terms of SUV or SUVR, the later representing an automated normalization to the highest 300 pixels within a reference region, traditionally the pons (Minoshima *et al.,* 1995). A complementary set of surface projections are obtained by comparing the uncorrected peak counts to those of an age-stratified, control database representing these comparisons as colour-coded z-scores (usually ranging from 0 to 5) but without any thresholding for multiple comparisons. This method has been shown to be more reliable than the visual inspection of transaxial images (depicting FDG uptake only) for the identification of PET abnormalities (Foster *et al*., 2007). Studies have also highlighted that NEUROSTAT is better than clinical assessment alone in differentiating AD from other dementias, including FTD and DLB (Minoshima *et al.,* 2001, Foster *et al.,* 2009). An inherent limitation of this technique is that it is not optimized for the detection of hypometabolism involving the hippocampus and the sub-cortical gray matter structures such as the thalamus.

In comparison to NEUROSTAT, the PMOD Alzheimer's discrimination automatic tool uses voxel-wise comparisons to compute age corrected t-scores for brain regions known to be affected in early AD, referred to as the

AD t-sum (Herholz 2002). This method deploys a bespoke AD mask to evaluate FDG uptake in only selected brain areas and permits single-subject comparisons to a control database. It has a reported specificity of 93% and sensitivity of 84-93%, the sensitivity being inversely related to the severity of clinical symptoms (Herholz *et al.,* 2002). However, by virtue of design, this tool is not validated for differentiating between AD and non-AD dementias.

In contrast to the visual and quantitative methods described above, SPM allows for the whole brain analysis of PET data (Signorini *et al.,* 1999). Application of this approach has revealed disease-specific topographic patterns of hypometabolism that is able to discriminate between AD and the non-AD dementia also allowing for statistical thresholding to be applied to minimize the false positive rates that may arise otherwise (Signorini *et al.,* 1999; Perani *et al.,* 2014). The SPM-based techniques involve similar processing steps that involve the registration, normalization and smoothing of PET data using a template image. Voxel-wise two sample t-tests are then performed comparing single subject data against a control database and the resulting t-map is then projected onto an anatomical template (Perani *et al.,* 2014). The principal differences that exist between the different SPM based PET analysis methodologies reside in their smoothing protocol, the brain template used for standardization, the size of the control database and the statistical thresholds applied to the resulting t-map (Signorini *et al.,* 1999; Perani *et al.,* 2014). The smoothing protocol is particularly important and directly impacts on the ability of these methods to detect hypometabolism within the hippocampus (Mosconi *et al.,* 2005). In a recent study, Perani and colleagues (Perani *et al.,* 2014) developed an optimized, brain template for spatial normalization. In brief, this template was derived from single-subject FDG-PET scans of healthy controls and patients with probable neurodegenerative dementia (Della Rosa *et al.,* 2014). This was done to overcome any potential bias that may have had arisen in the creation of the existing SPM PET template (the existing template was derived using oxygen rather than glucose as the radioactive ligand, acquired from patients who were otherwise healthy). The control database is large (comprising 112

normal controls; age range = 50-80) and a strict level of statistical significance is applied to the resulting t-map ($p < 0.05$; FWE-corrected) and only clusters > 100 voxels are considered significant for reporting. This method was associated with a sensitivity and specificity of 96% and 84% respectively with an AUC of 0.67 (compared to 0.5 for standard FDG images) and was better than clinical assessment alone in achieving a correct diagnosis (associated with a sensitivity and specificity of clinical assessment 91% and 40% respectively). This difference in specificity bears further consideration and supports previous study conclusions that a 'negative' PET scan, assessed quantitatively, has a high negative predictive value for a neurodegenerative cognitive disorder (Jagust *et al.,* 2007). Another crucial observation, also identified in earlier studies using NEUROSTAT and other SPM based methods, was that medial cortical hypometabolism was more frequently observed with quantitative PET maps (Herholz *et al.,* 2002; Caroli *et al.,* 2012). Considering that these regions are critically important in recognizing AD and FTD and in differentiating these disorders from each other, this suggests that visual inspection of standard PET maps, as applied in everyday practice, may have a high sensitivity but poor specificity (Caroli *et al.,* 2012).

Conclusion

There is a vast literature that supports the use of quantitative MRI and FDG-PET analysis for the earlier identification of disease biomarkers. MRI visual scales require significant neuronal loss for diagnostic patterns to emerge while non-parametric PET data are sensitive but not specific. Frisoni and colleagues (2013) have highlighted the importance of a standard operating procedure for these modalities, concluding that the method of neuroimaging analysis influences diagnostic accuracy more than the choice of modality itself.

2.4. Spatial memory impairment in Alzheimer's disease

2.4.1 The clinical relevance

Getting lost is a well-recognized symptom of early AD (Reisberg 1983; Henderson *et al.,* 1989; Cherrier *et al.,* 2001, Monacelli *et al.,* 2003; Pai & Jacobs 2004; Guariglia & Nitrini 2009). Topographical disorientation (TD), which refers to the inability to orientate oneself to one's surroundings, has been observed in 25% of patients at symptom-onset, doubling in frequency within three years, most often causing patients to first loose their way in familiar surroundings (Pai & Jacobs 2004; Tu & Pai 2006). In AD, progressive TD is associated with a seven-fold increased risk of institutionalization (McShane *et al.,* 1988). TD is under-reported as a first-person symptom in AD and, in early disease, it may not be apparent due to self-imposed restrictions on travel and routes of travel (Burns 1999). Several studies have investigated AD-related changes in spatial memory (defined as the ability to encode, store and retrieve information pertaining to the location and orientation of objects within an environment) and spatial navigation (defined as the ability to determine and maintain a route from one place to another). In particular, there is particular interest in being able to detect AD-specific changes in spatial memory during AD pre-dementia.

2.4.2 A brief overview of spatial memory

The hippocampus has been implicated in spatial memory ever since the discovery of place cells in single cell recordings of the rodent hippocampus, with the firing rates of hippocampal neurons found to be correlated with the location of a freely-moving rodent within a maze (O'Keefe and Dostrovsky 1971). The firing rates of these cells are location-specific, irrespective of head direction or direction of travel, and utilize the location of distal environmental cues to drive place cell firing when an animal is re-introduced to a previously-encountered environment. In being independent of the animal's head-centred (i.e. egocentric) location and movement, these firing

patterns encode spatial representations that are allocentric in nature. Similar hippocampal properties are described in other mammals, including primates (Hori *et al.,* 2003) and humans, as determined by depth electrode recording from the hippocampus of patients awaiting temporal lobectomy for intractable temporal lobe epilepsy (Ekstrom et al., 2003). In contrast, egocentric or 'self-centred' location appears dependent on the posterior parietal cortex (PPC) and inferior parietal lobule. Primate studies have identified neurons in this region that integrate retinal position with eye and head position, in theory forming the basis for the orientation of a spatial scene relative to the midline of the animal (Andersen et al., 1985; Zipser and Andersen, 1988).

Spatial information is mentally represented using egocentric and allocentric frames of reference. To recap, egocentric orientation uses one's body as a central reference point so that place and object locations are represented using conventional directions such as forward and backward or left and right. This is critically reliant on the dorsal and ventral visual streams to represent the different components of a spatial scene (Ungerleider and Mishkin, 1982). By comparison, allocentric orientation or processing is 'world-centred', making use of distal cues, to represent object locations relative to the environment as a whole (O'Keefe and Nadel, 1978; Maguire et al., 1998). During spatial navigation, these systems work in parallel and allocentric representations are particularly important in novel and visually complex environments (Burgess, 2006). Spatial navigation is also influenced by path integration (the ability to estimate distance travelled and direction of travel relative to the starting point), landmark recognition, temporal order memory (the order in which landmarks were encountered during a route), spatial memory, and optic flow (the apparent motion of environmental features caused by the movement of the observer) (Lithfous et al., 2013).

A distinction must be drawn between spatial working memory, i.e. the storage of spatial information for short periods of time, and spatial reference memory which is involved in the processing of spatial information upon

repeat exposure to an environment (Olton 1979). As the latter is contextual, it is regarded as a subtype of episodic memory (O'Keefe and Nadel, 1978), requiring the formation of mental representations of space (so called 'cognitive maps') that may be stored and retrieved for purposes such as topographical orientation or spatial navigation (O'Keefe and Nadel, 1978).

Topographic disorientation (TD) may therefore encompass a range of deficits including egocentric disorientation (the inability to orientate environmental objects with respect to self), heading disorientation (the inability to orientate the direction of travel with respect to external stimuli), landmark agnosia (the inability to recognize and use important environmental features for orientation) and anterograde disorientation (the inability to create a new representation of an environment) (Aguirre and D'Esposito 1999).

Brain lesion and electrophysiological studies suggest that spatial attention is lateralized to the right cerebral cortex; lesions involving the right posterior parietal cortex (PPC) result in egocentric spatial neglect i.e. a right-sided lesion results in neglect of objects to the left of the individual ((Heilman *et al.,* 1985; Kleinman *et al.,* 2007). In comparison, lesions involving the right angular and inferior temporal gyri result in allocentric spatial neglect i.e. neglect of the left half of an element regardless of its position in the environment (Chechlacz *et al.,* 2010). Elements of both forms of spatial neglect are observed with lesions that involve the temporoparietal junction and frontal lobe although the latter do not persist beyond the subacute period of stroke recovery (Chechlacz *et al.,* 2010).

Functional neuroimaging studies have also identified a network of brain regions involved in spatial navigation. An fMRI study identified PHG activation during free exploration of an unfamiliar environment during which participants were instructed to construct a mental map of that environment, suggesting that the PHG is involved in allocentric memory by encoding the location and relative positions of landmarks (Aguirre *et al.,* 1996). In contrast,

the inferior parietal cortex is implicated in egocentric processing; the computation of left/right turns relative to landmarks and the determination of landmark location relative to self is associated with activation of these regions (Maguire *et al.,* 1988; Wolbers *et al.,* 2004). Within familiar environments, response learning is associated with the activation of the caudate nucleus (Iaria *et al.,* 2003) while survey knowledge and navigation tasks requiring an allocentric strategy are associated with activation of the hippocampus (Maguire *et al.,* 1998; Hartley *et al.,* 2003; Iaria *et al.,* 2003). In familiar environments, successful allocentric navigation is correlated with posterior hippocampal activation (Hartley *et al.,* 2003) while anterior hippocampal activation is observed during the initial exploration of a new arena (Wolbers and Buchel 2005). Several models have been proposed to explain how egocentric and allocentric processing may interact; lesion and functional neuroimaging studies suggest that the retrosplenial cortex is critical for this interaction (Maguire 2001; Burgess *et al.,* 2001; Byrne *et al.,* 2007). The retrosplenial cortex is also implicated in landmark recognition and scene encoding. However, unlike the PHG, repeat exposure to 'same' viewpoint spatial scenes does not result in suppression of activation on fMRI; this suggests that the PHG may be involved in scene perception while the retrosplenial cortex is involved in scene recognition (Epstein and Higgins, 2007). Temporal order memory paradigms are associated with activation of the medial frontal gyrus (Wolbers *et al.,* 2004).

Structural MRI studies have identified correlations between structure and specific aspects of spatial memory. Response learning ability has been correlated to caudate nucleus volume (Iaria *et al.,* 2003) while allocentric spatial navigation ability has been correlated with hippocampal volume (Bohbot *et al.,* 2007). In comparison, temporal order memory correlates with dorsolateral prefrontal cortical thickness (delpolyi *et al.,* 2007). Maguire et al. found that posterior hippocampal volume was significantly increased in London taxi drivers, who must legally acquire multiple mental maps of the city that also facilitate flexible navigation strategies, compared to age-matched controls (Maguire *et al.,* 2000) and London bus-drivers, who travel

by fixed routes (Maguire *et al.,* 2006). In these studies, the volume of the right posterior hippocampus and the right mid-posterior hippocampus respectively correlated with the number of years of taxi driving experience; in contrast, the anterior hippocampal volume of taxi-drivers was relatively decreased compared to controls and bus-drivers. These studies suggest that the posterior hippocampus is critical for either the storage, recall and/or processing of learned spatial information.

2.4.3 AD neuropathology involves the spatial memory network

The network of regions involved in spatial memory, outlined above, overlap with those brain regions pathologically affected in the earliest stages of AD (see Chapter on AD). Furthermore, TD in AD is strongly correlated with NFT density in the CA1 hippocampal subfield, the precuneus and the ventral portion of the posterior cingulate gyrus, controlling for dementia severity and duration of disease (Giannokopoulos *et al.,* 2000). However, AD pathology also affects cortical regions involved in motion processing and several early studies established an association between AD-related visuoperceptive deficits and navigational impairment (Cogan 1985; Becker *et al.,* 1988; Tetewsky and Duffy 1999).

Studies that have focused on spatial memory impairment in AD have employed either a spatial navigation paradigm or focused on traditional psychometric assessment. Most spatial navigation tasks are analogues of the Morris Water Maze (MWM, Morris 1984), an experimental paradigm used in rodents that assesses the ability of the animal to reach a hidden location using an allocentric strategy. Performances in real-world settings correlate strongly with virtual reality settings and computerized tasks can also be used to evaluate spatial impairments in AD (Cushman *et al.,* 2008). These tasks are of particular interest to early drug discovery programs that assess the ability of an agent to either prevent or improve spatial memory impairment, the earliest manifestation of disease in rodent models of AD (Karran *et al.,*

2011).

2.4.4 Spatial Navigation studies in AD and MCI

Route-learning is impaired from the earliest stages of dementia and is detectable even in familiar surroundings (Cherrier *et al.,* 2001; Monacelli *et al.,* 2003). Patients are impaired in their ability to freely recall and recognize landmarks, and in temporally ordering landmarks encountered (Cherrier *et al.,* 2001; Monacelli *et al.,* 2003; delpolyi *et al.,* 2007). To date, the majority of studies involving spatial navigation have focused primarily either on visuoperceptive processing or other specific factors contributing to TD. Impairments in optic flow in AD are evident during real world route-learning paradigms (e.g. walking in a hospital lobby) (Tetwesky and Duffy 1999). However, impairments in optic flow do not account for overall spatial navigation performance in AD, nor does there appear to be any correlation between any impairment in spatial and verbal memory in AD (Henderson *et al.,* 1989; Cushman and Duffy, 2007).

By comparison, studies involving the blue velvet arena (BVA), an analogue of the MWM, have shown a discrete allocentric spatial deficit in mild AD (Kalova *et al.,* 2005) while other studies highlight additional egocentric deficits in this cohort (Hort *et al.,* 2007; Laczó *et al.,* 2009). Allocentric orientation correlates with right hippocampal volume (Nedelska *et al.,* 2012) and is particularly impaired in LOAD. Morganti *et al*. (2013) found that EOAD patients were more impaired in tasks requiring allocentric-egocentric interaction (such as using a map to navigate in a virtual or real world environment) that may reflect the greater involvement of the retrosplenial cortex in these patients.

In studies involving real-world navigation, successful route-learning and landmark location in patients with AD and MCI were correlated with right posterior hippocampal and right inferior parietal cortical volume (delpolyi *et*

al., 2007). A similar paradigm involving a familiar virtual environment found that right precuneus volume strongly correlated with egocentric strategies in navigation (Weniger *et al.,* 2011). Pengas *et al*. (2012) also observed heading disorientation in AD, but not MCI, which correlated with retrosplenial and hippocampal volume. Taken together, these studies suggest that the hippocampus is involved in allocentric orientation and that the interaction between egocentric and allocentric strategies represent the interaction between the posterior hippocampus and precuneus respectively.

The memory of non-spatial objects encountered during navigation is also impaired in AD (Buck *et al*., 1997; Kessels *et al.,* 2010) compared to controls. However, evidence suggests that an impairment in attention or optic flow may not fully account for this finding given that the recognition of 'nuisance' objects located at navigation decision points were significantly better compared to 'nuisance objects' located elsewhere (Kessels *et al.,* 2011). Importantly, while impaired navigation and TD have been robust findings in studies involving AD and MCI, these were not correlated with impairment in other domains of cognitive testing, including verbal memory, nonverbal memory, language and executive function (Monacelli *et al.,* 2003; delpolyi *et al.,* 2007).

Overall, these studies suggest that at the stage of dementia, patients with AD are likely to have several deficits that contribute to impaired spatial navigation. Further support for this comes from a study of MCI that investigated the effect of cholinesterase inhibitors on the navigation network. Treatment modulated an increase in activation of several brain regions including the hippocampus, PHG, inferior parietal cortex and PCG (Grön *et al.,* 2006), suggesting that reference spatial memory formation and retrieval is likely to compromised for several reasons as disease progresses.

2.4.5 Neuropsychometric assessment of spatial memory

The psychometric tools used to assess spatial memory do not include active spatial exploration but rather require spatial processing for the completion of the task. Given the face validity of spatial navigation paradigms (delpolyi *et al.,* 2007; Cushman *et al.,* 2008), one would expect these assessments to incorporate the basic levels of spatial representation proposed by Siegel and White (1975) i.e. landmark recognition, route-planning or scene survey. This is particularly important given the lack of correlation between traditional non-verbal and verbal memory testing with navigation ability in patients with AD and MCI (Monacelli *et al.,* 2003; delpolyi *et al.,* 2007). In particular, constructional tasks such as the Rey-figure and Block design rely heavily on visual attention, planning and praxis as well as visual perception suggesting that these are not suitable for the dedicated assessment of spatial memory, particularly spatial working memory (for a review see Iachini *et al.,* 2009). In other instances, tests provide a reliable indication of visual perception only as is the case with clock drawing or judgment of line orientation that are not able to detect deficits in optic flow or scene survey that may be apparent on a spatial representation or navigation paradigm.

The Money Road Map Test (MRMT) is a test specifically designed to assess for TD; in this test the examiner traces a dotted pathway asking the subject to report the direction (right or left) taken at each turn requiring the subject to make egocentric mental rotations (Money, 1976). Patients with AD and MCI are impaired on the MRMT despite otherwise normal right-left discrimination (Rainville *et al.,* 2002). In MCI patients, MRMT performance correlates to impairments in optic flow and abnormal performance are also observed in patients with right parietal lobe damage suggesting that test performance is highly dependent on perceptual processes (Mapstone *et al.,* 2003). The topographical recognition memory test is a 30-item test of long term recognition memory in which the stimuli, pictures of outdoor scenes containing either an object or a person, are presented sequentially thereafter employing a delayed recall paradigm that uses a three-alternative forced-

choice format where the target is represented along with two foils containing different views of the same location (Warrington, 1996). This test is useful in discriminating MCI and AD from controls but it may lack specificity given that impaired performance is also in observed in patients with FTD, possibly due to impaired executive function (Bird *et al.,* 2009). The Corsi block-span test is a test of working spatial memory that consists of nine identical blocks that are regularly arranged on a board that requires participants to copy novel sequences of increasing length as tapped by the examiner (Kessels *et al*., 2000). Studies involving this paradigm have reported conflicting results for mild AD dementia with normal performance reported in some studies (Guariglia *et al.,* 2007) and impaired performance reported in others (Baudic *et al.,* 2006). The Walking Corsi Test, an adaptation of Corsi block-span, requires a test subject to copy routes taken between black squares positioned on the ground. A preliminary study involving mild AD and healthy controls found significant group differences in walking-span performance whereas no differences were observed on tapped block-span performance, suggesting that an impairment in egocentric working memory, but not visuospatial working memory, in the cohort studied (Bianchini *et al.,* 2014).

2.3.6 The four mountains test of spatial memory

The four mountains test of spatial memory (4MT) is a short test of allocentric spatial memory that assesses the ability of the participant to recall the spatial configuration of a series of computer-generated landscapes from a shifted viewpoint, specifically designed to reflect the role of the hippocampus in spatial cognition (Hartley *et al.,* 2007). Each item in the 4MT is composed of five images of computer-generated landscapes (as shown in Figure 4). Participants view a sample image and are then required choose from four alternatives a target image which shows the same place from a different viewpoint. The remaining three images are foils depicting landscapes whose topography is systematically related to the target landscape.

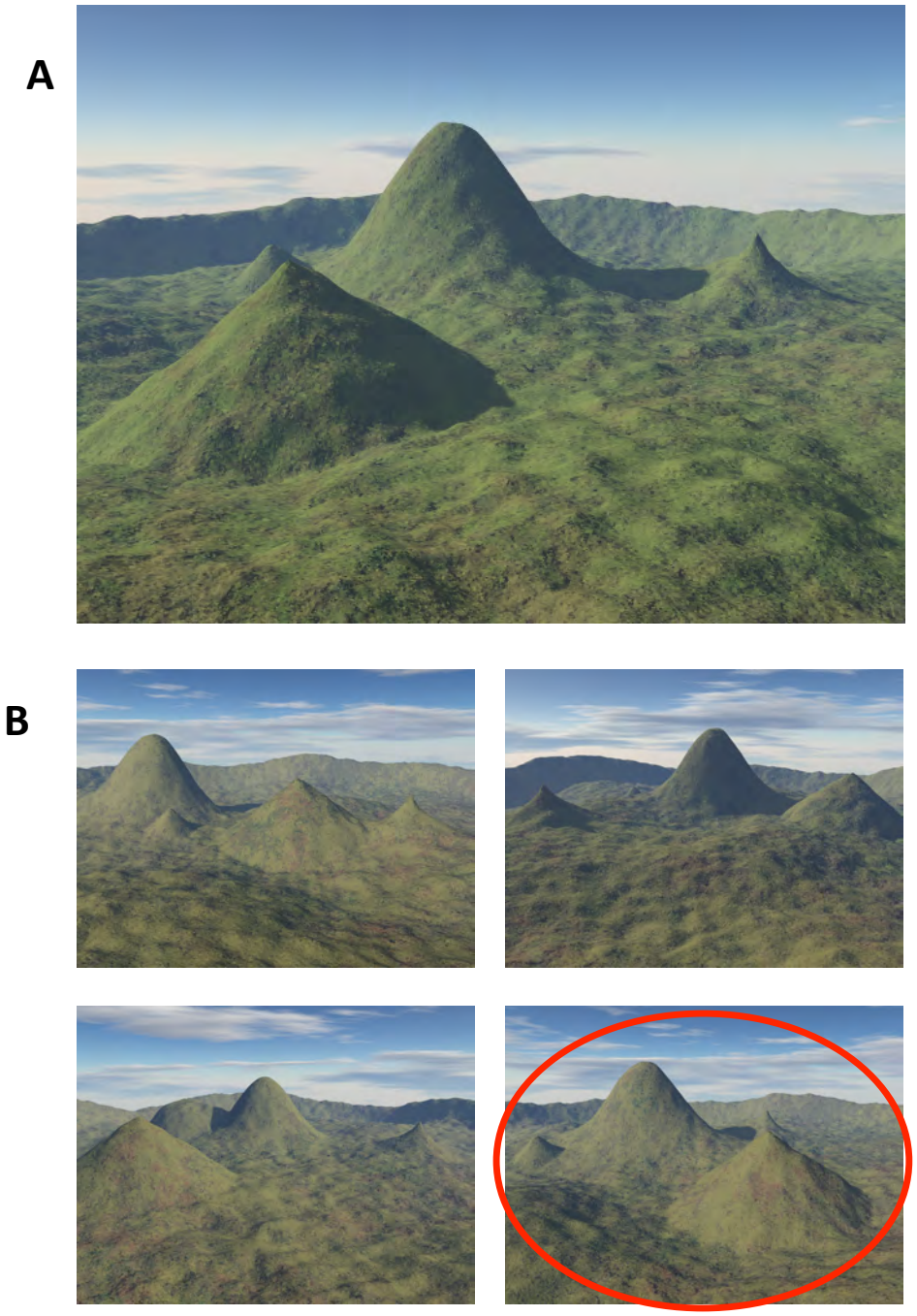

Figure 4. Four Mountains test. Subjects have to identify which of the images (B) shows the same 4 mountain spatial configuration as seen in (A); the correct response is circled. Between-image differences in nonspatial features (e.g. cloud cover, vegetation colour) exclude usage of any strategy other than that involving allocentric spatial memory.

Landscapes are generated by creating heightfields that specify the elevations of each location in a 2D array using custom MATLAB code (www.uk.mathworks.com). Each landscape is made up of similar topographical features: the ground plane with small scale undulations, a semicircular mountain range (defining the horizon in each image), and four prominent mountains of varying shape and size (Figure 4; an example of the contour map used to generate these stimuli is shown Figure 5).

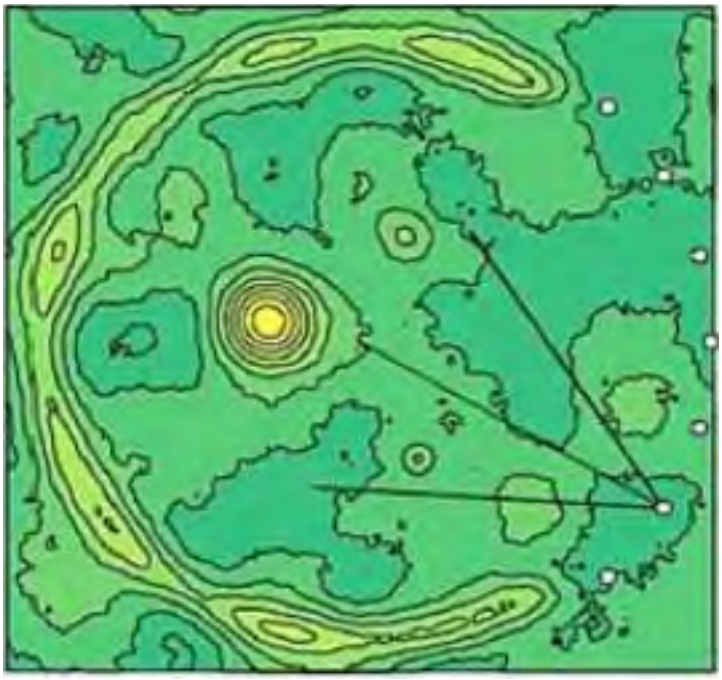

Figure 5. The 4MT stimuli are based on computer-generated heightfields as illustrated in the contour map above. Images are rendered using a virtual camera place at one of the indicated seven locations.

Stimuli are selected from a large number of landscapes, created such that each has an unambiguously distinct global topography within which individual local features are shared between items and between target and foil landscapes. This step ensures that non-spatial local visual strategies, such as remembering a single distinctive landmark, are ineffective in identifying global topography. Landscapes used to generate foil images are created by varying the size, shape, and location of mountains in the sample / target

landscape. This step is to provide a set of foils sharing (to a similar degree across items) local topographical features such that non-spatial strategies cannot be used to select the target image. For each target / sample landscape created, the foils include: one spatial foil, in which the locations of the hills are varied, while preserving their order around the center of the array (quadrant); one configural foil, in which the locations of two or more distinctive hills are exchanged (altering their order around the center of the array but preserving approximate locations); one elemental foil, in which the distinctive size or shape of one or two of the mountain features is changed, while preserving the order and location of the other hills. Images of the topography are rendered to create realistic lighting, atmospheric effects and textures associated with outdoor scenes. For each image, the virtual camera is placed at one of the seven locations (Figure 5), equidistant from the center of the array. Sample and target images are rendered using the same topography but different camera locations. The aim of the viewpoint change is to encourage allocentric spatial strategies (exploiting spatial representations which are known to exist within the hippocampal formation) and to discourage strategies based on egocentric or visual representations. To further discourage visual or egocentric strategies, lighting (azimuth and direction), landscape texture and weather conditions are varied between sample and test / foil images. Each item thus comprises a sample image with one set of non-spatial features, a target image depicting the same landscape from a different viewpoint and different non-spatial features and three foil images with distinct topography but sharing nonspatial features with the target.

The 4MT comprises Place Perception (PP) and Place Memory (PM) subtests. For the perceptual task, the target image and the one-of-four array are presented simultaneously, whereas for the memory task the one-of-four array is presented after a two second delay. For PP and PM testing, a thirty second forced-choice design is applied. In total 15 PP and 15 PM stimuli are presented. In the PP task, a maximum of 30s is allowed to register a response. In the PM task, a 4MT landscape is shown for 8s, followed by a 2s

interval during which the landscape is removed and replaced by a blank screen. Then, the one-of-four array is presented leaving the participant approximately 20s to register a response. If no response is registered timeously, then the participant must provide a forced-choice response.

Subsequent studies in patients with focal hippocampal damage demonstrated impairments in allocentric short-term memory (PM) and, to a lesser extent, allocentric perception (PP) but not in the perception or short-term recall of nonspatial features (Hartley 2007). In additional work, this group also demonstrated that PM was significantly impaired in AD and amnestic MCI compared to controls and FTD ($p < 0.001$ and $p = 0.004$ respectively) also observing no difference in PM between amnestic MCI and AD or controls and FTD (Bird 2009). There were no differences between these groups in terms of nonspatial memory or PP.

Pengas and colleagues (Pengas *et al.,* 2010) subsequently applied the PM and PP subtests of the 4MT when investigating the diagnostic ability of spatial memory testing to discriminate between HC, amnestic MCI, AD and SD. The findings were similar to Bird *et al.* (2009) given that PM performance was impaired in AD and MCI compared to HC and SD. Furthermore, there was no difference in PM between controls and SD, or between AD and MCI. The authors also reported a positive correlation between PM performance and real-world topographical orientation. In contrast to Bird *et al.* (2009), Pengas *et al.* (2010) studied dementia patients with a lower mean baseline MMSE, also observing impaired PP performance in AD compared to HC and SD. A limitation of the studies undertaken to date is that these have not assessed any potential differences in PM and PP performance in MCI cohorts stratified by AD biomarker status. In addition, none of these studies examined the correlation between PM performance and brain structure. Hartley and Harlow (2012) subsequently reported positive correlation between PM and hippocampal volume in healthy young adults using an extended 30-item version of the PM subtest (Hartley and Harlow 2012).

3. EXPERIMENTS

3.1.1 The four mountains test of spatial memory: sensitivity for early Alzheimer's disease

3.1.1.1 Abstract

The hippocampus is one of the earliest brain regions to exhibit neurodegeneration in Alzheimer's disease (AD) and as such tests of hippocampal function have the potential to detect Alzheimer's disease (AD) in its earliest stages. Based on the theory that the hippocampus is critically involved in allocentric spatial memory, this study applied a short test of spatial memory, the 4 Mountains Test (4MT) to determine whether test performance can differentiate between MCI patients with and without CSF biomarker evidence of underlying AD.

Healthy controls (HC, n=20) and patients with MCI (n=21) and mild AD dementia (n=11) were studied. Nineteen MCI patients were stratified into CSF biomarker-positive (MCI+, n=10) and biomarker-negative (MCI-, n=9) subgroups. Behavioural data were correlated with hippocampal volumes and cortical thickness measures of the precuneus and posterior cingulate gyrus, representing other brain regions affected early in AD.

Performance on 4MT place memory (PM) testing was impaired in MCI and mild AD. However, test performance also differentiated between MCI+ and MCI- subgroups ($p = 0.001$). A 4MT score of <8/15 was associated with 100% sensitivity and 90% specificity for detection of early AD (MCI+ and mild AD dementia). PM performance correlated with hippocampal volume and precuneus cortical thickness.

In conclusion, performance on a hippocampus-sensitive test of spatial memory differentiates MCI due to AD with high diagnostic sensitivity and specificity. The scalability and potential usability of the test in community

memory clinics, support future application of the 4MT in the diagnosis of pre-dementia AD.

3.1.1.2 METHODS AND MATERIALS

Subjects

Patients with MCI (n=21) and mild AD dementia (n=11) were recruited from the Cognitive Disorders Clinic, Hurstwood Park Neurological Centre, Hayward Heath, West Sussex. MCI and AD were diagnosed respectively according to Petersen (Petersen, 2004) and McKhann criteria(McKhann *et al.*, 2011). For patients with AD dementia, mild dementia was determined by Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) scores > 22 and a Clinical Dementia Rating (CDR) (Morris, 1993) of one. All MCI patients had MMSE scores equal to or above 26 with CDR ≤ 0.5.

As part of their diagnostic workup 19 MCI patients testing for CSF AD biomarkers using the CSF collection protocol and ELISA assay kits (Innotest, Innogenetics, Ghent, Belgium), as outlined in the CSF substudy of the Alzheimer's Disease Neuroimaging Initiative (Shaw *et al.*, 2009). Patients were divided into MCI biomarker-positive (MCI+), indicative of prodromal AD consistent with the diagnostic criteria outlined by Dubois et al., (2010) and Albert et al., (2011), and MCI biomarker-negative (MCI-) groups on the basis of abnormal CSF β-amyloid$_{1-42}$ and tau levels according to updated normal ranges for these indices (Mulder *et al.*, 2010). These were as follows: CSF β-amyloid$_{1-42}$>550 pg/mL, CSF tau <375 pg/mL, tau:amyloid ratio <0.8. MCI+ patients were classified accordingly on the basis of CSF β-amyloid$_{1-42}$< 550 pg/mL *and* CSF tau > 375 pg/mL, with tau:amyloid ratio > 0.8. For the MCI-group, all but three patients had CSF amyloid and tau levels in the normal range, with correspondingly normal CSF tau:amyloid ratios; the remaining three patients had high tau levels but had normal range amyloid levels (>900 pg/mL in all cases) and, in addition, had a history of stable cognitive function

over a minimum 24 month follow-up period. All patients underwent clinical and laboratory assessments (including blood tests for thyroid function, vitamin B12 status) to exclude potentially treatable causes of cognitive decline. All subjects observed to have a significant vascular lesion load on initial brain scanning were excluded from the study.

Age-matched healthy control (HC; n=20) subjects without a history of cognitive impairment, were also recruited. Approval was obtained from the UK Research Ethics Committee South East Coast - Brighton and Sussex (references 10/H1107/23 and 13/LO/0277) and the study was performed in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Demographics

There were no significant differences between HC, MCI and AD groups in terms of age, gender and years of education (Table 1). No significant demographic differences were noted on comparison of the MCI+ and MCI- subgroups, who were also matched for disease duration (Table 2).

Study population				
	HC n = 20	MCI n = 21	AD n = 11	*p*
Gender, M:F	7:13	15:6	5:6	0.06
Age, years	62.6 (6.1)	68.1 (8.9)	66.2 (8.9)	0.10
Education, years	12.1 (1.7)	11.7 (1.9)	12.4 (2.2)	0.6

Table 1. Demographics. HC = healthy controls, MCI = mild cognitive impairment, AD = Alzheimer's disease dementia

MCI sub-groups			
	MCI-	MCI+	*p*
Gender, M:F	7:2	8:2	0.7
Age, years	65 (9.5)	68.1 (6.2)	0.4
Education, years	11.6 (1.9)	12.1 (2.1)	0.6
Disease Duration, years	3.8 (0.4)	3.7 (0.8)	0.8

Table 2. Demographics of MCI patients grouped according to CSF AD biomarker status

Behavioural studies

General neuropsychological assessment

Subjects underwent a battery of neuropsychological tests. The following domains were tested, with the tests used in parentheses: 1) Episodic memory [Rey Auditory Verbal Learning Test, RAVLT (Rey, 1941; Van der Elst *et al.*, 2005)], 2) Attention and Executive function [Trail Making Test A and B (Reitan, 1958)], 3) Executive function [Lexical and semantic fluency (Lezak, 1995)], 4) Working memory [Digit span (Blackburn and Benton, 1957)], 5) Higher visual processing [Object decision (James and Warrington, 1991)], 6) Premorbid IQ [National Adult Reading Test (NART) estimated IQ (Nelson and Willison 1991)]. Inkeeping with local practice, participants unable to complete the Trail making B test were allocated a score of 300 seconds, with all psychometric data presented as raw scores.

The test battery outlined above was not undertaken in three HC subjects, who opted out of these tests, and two MCI patients (one with no CSF biomarker data, one CSF biomarker negative) who declined these aspects of

testing due to anxiety (in comparison, all subjects completed the 4MT). The NART was not administered to one MCI patient older than 85 years of age who did not undergo CSF studies (Nelson & Willison 1991).

The 4 Mountains Test

In order to maintain consistency with the terminology used in previous work involving application of the 4MT (Hartley *et al.*, 2007; Bird *et al.*, 2009; Pengas *et al.*, 2010), the allocentric spatial perception and memory subtests of the 4MT are referred to as the place perception (PP) and place memory (PM) tests, and abbreviated accordingly in the tables and figures. In total 6 or 15 PP and 15 PM scenes were presented to each participant (see below), with testing preceded by the presentation of three training slides to aid familiarisation with the task. In brief, the task involves presentation of computer-generated landscapes containing four mountains with a semi-circular mountain range in the background. Participants are shown a sample landscape along with a panel of four landscapes, consisting of the original landscape seen from a shifted viewpoint alongside three foils. For the perceptual task this panel is presented at the same time as the target image, whereas for the memory task the panel is presented after a 2 s delay. The three foils for each test item were generated from the target image as follows. For the “spatial” foil the position of one mountain is shifted but the order of the four mountains around the centre of the image is preserved. For the “ordinal” foil exchanging the location of two or more of the mountains alters the ordering of the mountains about the origin. In the “elemental” foil the shape and/or size of one mountain is changed, whereas spatial layout is preserved. The design and usage of these foils helped to ensure that generation of an allocentric representation of the presented image would be required to distinguish the target image from the foils while maintaining local visual similarities between target and foils.

In the PP task a maximum of 30 s is given for a forced choice match-to-sample. In the PM task a 4MT landscape is shown for 10 s, followed by a 2 s interval during which the landscape is removed, with subsequent

presentation of the original landscape seen from another viewpoint and three foils (Figure 4), with a maximum of 30s given for the forced choice delayed match-to-sample.

Non-spatial features (e.g. lighting level, extent of vegetation cover) varied between presentation and testing in order to ensure that correct matching to sample could not be made on the basis of non-spatial aspects of the task.

All landscapes are shown in printed form on A4 sized pages within a ring-bound booklet such that, for the PP task, the target image is shown on one page and the four match-to-sample choices simultaneously on a separate page. For the PM task, after presentation of the target image, participants are shown a blank white page for 2s before being presented with the four match-to-sample choices on a subsequent page. Total test duration was approximately 20 minutes.

In the Bird *et al.* (2009) and Pengas *et al.* (2010) studies 15 PP and 15 PM scenes were presented, reflecting the fact that a common aim of both studies related to the comparison of spatial perception and spatial memory performance. In contrast Hartley and Harlow (2012) omitted the PP subtest altogether, in light of that study's aim of determining an association between 4MT PM performance and hippocampal volume.

In the present study, the original protocol involving 15 PP scenes was initially adhered to, but following completion of the pilot phase of the project, in 16 participants from the UK cohort (5 controls, 10 MCI, 1 AD), the PP phase was shortened to 6 scenes to limit session duration. This did not affect the PM scores (for the MCI patients who received 15 or 6 PP scenes: 7.3±3.6 vs. 7.8±1.9, p=0.7).

Volumetric MRI studies

Subjects underwent MRI on a 1.5T scanner (Avanto, Siemens AG, Erlangen DE) at the Clinical Imaging Sciences Centre, Brighton and Sussex Medical School. Two AD patients were unable to tolerate MRI scanning. T1-weighted

3D volumetric MRI data were acquired by means of a magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence, having 1x1x1mm^3 voxel size, TI=600ms, TE=4 ms, TR=1160ms. Due to logistical reasons, 4 patients from MCI+ group could not have a scan; structural correlations are therefore reported for the remaining 17 cases.

Cortical thickness was measuring using the FreeSurfer workflow (Massachusetts General Hospital, Harvard University, Boston MA, USA), which, as detailed elsewhere (Fischl, 2012), involves iterative reconstruction of the white-gray matter interface and pial surface, and subsequent labelling with non-linear morphing to a probabilistic brain atlas. The Desikan probabilistic brain atlas was used (Desikan *et al.*, 2006), with the posterior cingulate gyrus and precuneus chosen a priori as regions of interest (ROIs) for quantitative analysis. All segmentations were manually cleaned up and refined by a specialized operator blinded to disease status.

Hippocampal volumes were measured using the FSL/FIRST tool (FMRIB, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK) (Patenaude et al., 2011). This additional segmentation was undertaken in view of the current lack of consensus regarding the different semi-automated tools used to analyse hippocampal volume (Morey et al., 2009; Sánchez-Benavides et al., 2010; Mulder et al, 2014); on our images, preliminary expert evaluation revealed that FreeSurfer tended to include parts of other medial temporal structures such as the parahippocampal gyrus and amygdala.

These ROIs were specifically chosen to encompass regions that are affected early in AD and represent components of the brain network considered to underpin memory functions (Greicius *et al.*, 2003; Buckner *et al.*, 2008).

Statistical analysis

For HC, MCI and AD group data, ANOVA was used to determine between-group differences for the demographic and neuropsychometric data. Post-hoc pair-wise comparisons were undertaken using the conservative Scheffé

test, which controls for family wise error rate across all planned contrasts. Two-tailed t-tests were used for comparison of MCI+ and MCI- subgroups; the alpha threshold was Bonferroni adjusted for multiple comparisons (twelve comparisons inclusive of general and 4MT psychometric measures; alpha = 0.004). To allow comparison between patients who received 15 and 6 PP scenes, the PP scores were rescaled in the range 0-6.

Place memory scores were correlated with total (i.e. combined left and right) hippocampal volumes. Additional correlations were undertaken with total cortical thickness of the precuneus and posterior cingulate gyrus, in view of previous studies that have suggested a role for these brain regions in spatial memory (Pengas *et al.*, 2012). Age was inserted as covariate for both analyses, having excluded effects of sex. Total intracranial volume from Freesurfer segmentation was included as an additional covariate in hippocampal volume-place memory correlation analyses. All correlations were undertaken using patient data only; controls were conservatively excluded, to avoid biasing the correlations due to the strong group differences. A univariate general linear model was used to assess mean differences between HC, MCI and AD quantitative MRI group data and between MCI +ve and MCI -ve subgroup data, age inserted as a covariate for comparisons involving the PCG and precuneus, age and TIV inserted as covariates for hippocampal comparisons; Bonferroni adjusted for multiple comparisons (alpha = 0.02). Post-hoc pairwise comparisons were not undertaken for volumetric MRI data.

Areas under the Receiver Operating Characteristics (ROC) curves were calculated, relating to the ability of 4MT test scores to differentiate early AD (AD and MCI +) from HC and MCI - patients.

3.1.1.3 RESULTS

Behavioural studies

General neuropsychometric assessment

Compared with control subjects, MCI patients were impaired on tests of delayed recall and executive function whereas AD patients were impaired in all tested cognitive domains (Tables 1-4).

	HC	MCI	AD	F (df)	P
NART IQ	119.0 (5.5)	112.3 (10.3)	112.4 (13.4)	2.52 (2,43)	0.09
MMSE	-	27.5 (1.0)	24.4 (1.4)	t = 7.5 (30)	< 0.001
VOSP-OD	16.8 (2.0)	16.6 (2.0)	15.9 (2.0)	0.76 (2,44)	0.48
RAVLT-DR	10.9 (3.1)	2.7 (2.1)	2.2 (1.1)	71.43 (2,44)	< 0.001
RAVLT-RP	0.9 (0.06)	0.6 (0.2)	0.6 (0.09)	44.71 (2,44)	< 0.001
Lexical Fluency	49.4 (13.2)	39.4 (9.9)	32.9 (6.5)	8.56 (2,44)	< 0.001
Semantic Fluency	38.7 (6.8)	28.0 (5.4)	19.0 (5.6)	37.44 (2,44)	< 0.001
Trails A	32.4 (11.0)	41.6 (13.4)	88.5 (33.4)	30.93 (2,44)	< 0.001
Trails B	68.9 (30.7)	108.8 (39.6)	224.9 (98.6)	26.28 (2,44)	< 0.001
Digit Span	6.8 (1.0)	6.6 (1.1)	6.1 (0.9)	1.40 (2,44)	0.26

*MMSE not performed in HC. VOSP-OD = Visual object and space perception battery. RAVLT-DR = Rey auditory verbal learning test delayed recall (List A). RAVLT-RP = Rey auditory verbal learning test recognition performance (List A)

Table 3. Neuropsychometric data for the study population

	HC vs. MCI	HC vs. AD	MCI vs. AD
NART IQ	0.14	0.23	1.00
VOSP-OD	0.96	0.50	0.63
RAVLT-DR	< 0.001	< 0.001	0.85
RAVLT-RP	< 0.001	< 0.001	0.66
Lexical Fluency	0.03	0.001	0.29
Semantic Fluency	< 0.001	< 0.001	0.001
Trails A	0.37	< 0.001	< 0.001
Trails B	0.12	< 0.001	< 0.001
Digit Span	0.87	0.26	0.48

Table 4. Pairwise post-hoc comparisons, Scheffe corrected, for neuropsychometric data obtained in the study population.

A direct comparison of the test results obtained in the MCI- and MCI+ patients revealed no significant differences in any component of the general neuropsychological assessment once corrections for multiple comparisons were applied (Table 5).

	MCI-	MCI+	t(df)	Uncorrected p
NART	116.3 (8.0)	109.1 (11.1)	1.53 (16)	0.2
MMSE	27.6 (0.7)	27.4 (1.3)	0.32 (17)	0.8
VOSP	17 (1.7)	16.4 (2.3)	0.62 (16)	0.5
RAVLT-DR	2.8 (2.7)	2.7 (1.8)	0.05 (16)	1.0
RAVLT-RP	0.6 (0.2)	0.6 (0.2)	-0.14 (16)	0.9
Lexical Fluency	42.9 (9.2)	36.9 (10.6)	1.26 (16)	0.2
Semantic Fluency	28.6 (3.9)	27.9 (6.7)	0.27 (16)	0.8
Trails A	37.3 (8.3)	43.8 (16.2)	-1.03 (16)	0.3
Trails B	82.6 (24.6)	125.0 (39.0)	-2.67 (16)	0.02
Digit Span	6.9 (1.5)	6.3 (0.8)	1.06 (16)	0.3

All uncorrected p-values greater than the Bonferroni-adjusted threshold (alpha = 0.004)

Table 5. Neuropsychometric results for MCI patients, grouped according to CSF AD biomarker status.

4 Mountains Test

Place perception

ANOVA revealed group differences in test performance ($p < 0.001$; table 6). Pairwise comparisons, corrected for multiple comparisons, revealed that the difference in scores was significant between HC and AD groups ($p < 0.001$) and between MCI and AD groups ($p = 0.001$). Further analyses revealed a significant difference between the MCI biomarker negative and AD groups only ($p < 0.001$; table 7). No significant differences were observed between the MCI subgroups or between MCI subgroups and HC.

Place memory

ANOVA revealed group differences in test performance ($p < 0.001$; table 6). Pairwise comparisons, corrected for multiple comparisons, revealed that the difference in scores was significant between HC and MCI groups ($p < 0.001$), between HC and AD groups ($p < 0.001$) and between MCI and AD groups ($p = 0.004$). Further analyses revealed significant differences in PM scores for the following pairwise group comparisons: HC vs. MCI+ ($p < 0.001$; table 7), HC vs. AD ($p < 0.001$), MCI- vs. MCI+ ($p = 0.002$), MCI- vs. AD ($p < 0.001$). By comparison no significance difference in PM test scores was observed for the comparison between HC and MCI- ($p = 0.3$) or between MCI+ and AD ($p = 0.6$). Figure 6 shows the individual PM scores for the participant groups.

	HC	MCI	AD	ANOVA	HC vs. MCI	HC vs. AD	MCI vs. AD
PP	4.9 (0.9)	4.3 (1.2)	2.8 (0.8)	F(2,49) = 16.0 p < 0.001	p = 0.1	p < 0.001	p = 0.001
PM	11.1 (2.1)	7.6 (2.7)	4.6 (1.3)	F(2,49) = 32.0 p< 0.001	p< 0.001	p < 0.001	p = 0.004

Table 6. 4MT place perception (PP; scored out of 6) and place memory (PM; scored out of 15) scores for participants, grouped according to clinical status. HC = healthy controls; MCI = mild cognitive impairment; AD = Alzheimer's disease.

	HC	MCI-	MCI+	AD	ANOVA
PP	4.9 (0.9)	4.9 (1.2)	3.9 (0.9)	2.8 (0.8)	F(3,46) = 13.8 p < 0.001
PM	11.1 (2.1)	9.6 (1.6)	5.8 (2.3)	4.6 (1.3)	F(3,46) = 34.3 p < 0.001

	HC vs. MCI-	HC vs. MCI+	HC vs. AD	MCI- vs. MCI+	MCI- vs. AD	MCI+ vs. AD
PP	p = 1.0	p = 0.06	p < 0.001	p = 0.2	p < 0.001	p = 0.09
PM	p = 0.3	p < 0.001	p < 0.001	p = 0.002	p < 0.001	p = 0.6

Table 7. 4MT place perception (PP; scored out of 6) and place memory (PM; scored out of 15) scores for MCI patients, grouped according to CSF AD biomarker status.

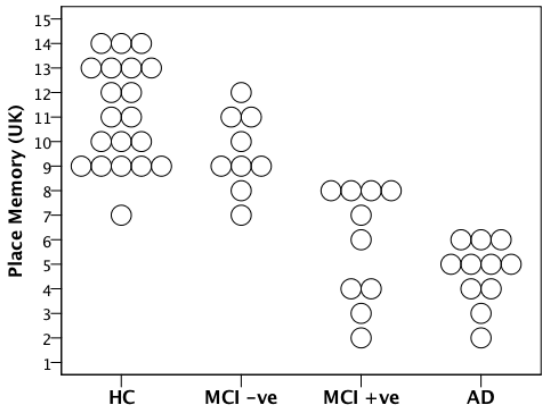

Figure 6. Scatterplot depicting 4MT place memory test scores in the study population.

Receiver operating characteristic (ROC) curves

The discriminative ability of 4MT place memory testing is illustrated by use of Receiver Operating Characteristics (ROC) curves (Figure 3). PM performance is associated with an area under the curve of 0.98 (differentiating MCI+ and AD patients from controls and MCI- patients). PM score of 8 or less was associated with 100% sensitivity and specificity of 90%.

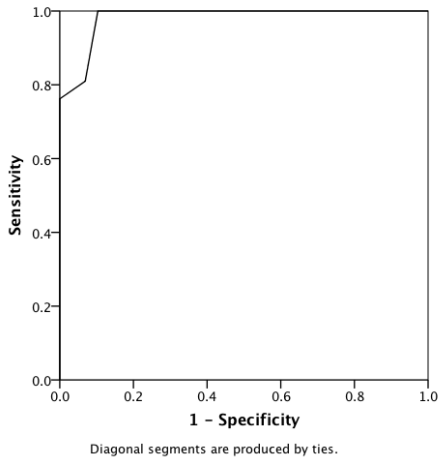

Figure 7. ROC curve: Discrimination of patients with evidence of AD (MCI+ plus AD dementia) from controls and MCI- patients. Area under ROC curve 0.98.

Group anatomical differences

Significant differences in hippocampal volume, precuneus cortical thickness and posterior cingulate cortical thickness were observed between patients (MCI and AD) and controls in both study populations (Table 8). However, after correction for multiple comparisons, only hippocampal volume and precuneus cortical thickness differences remained significant.

When the quantitative MRI data for MCI+ and MCI- patient groups are directly compared, there were no significant differences in hippocampal volumes (p=0.48) or the cortical thickness of brain regions of interest (Table 9).

Study population					
ROI	HC	MCI	AD	F(df)	p
Hc	7.5 (0.8)	6.3 (1.1)	5.5 (0.8)	16.60 (4,43)	< 0.001
Precuneus	4.6 (0.3)	4.3 (0.3)	3.9 (0.4)	10.35 (3,44)	< 0.001
PCG	5.0 (0.3)	4.7 (0.3)	4.7 (0.4)	3.21 (3,44)	0.03

Table 8. Comparison of ROI measurement for study population. Precuneus and PCG comparisons include age as a covariate. Hippocampal comparisons include age and total intracranial volume as covariates (general linear model, SPSS). Bonferroni correction for multiple comparisons applied, null hypothesis rejected for uncorrected p values < 0.02

	MCI-	MCI+	F(df)	p
Hc	6.7 (1.1)	6.0 (0.9)	0.88 (3,11)	0.48
Precuneus	4.4 (0.2)	4.1 (0.4)	1.48 (2,12)	0.27
PCG	4.7 (0.3)	4.7 (0.4)	0.34 (2,12)	0.72

Table 9. Comparison of ROI measurement for MCI patients grouped by CSF AD biomarker status. Precuneus and PCH comparisons include age as a covariate. Hippocampal comparisons include age and total intracranial volume as covariates (general linear model, SPSS). Bonferroni correction for multiple comparisons applied, null hypothesis rejected for uncorrected p values < 0.02

Correlations between spatial memory performance and quantitative MRI

Partial correlations undertaken for the patient population (MCI and AD), corrected for age and total intracranial volume (hippocampal volume only), revealed, after averaging between left and right hemisphere, significant associations between 4MT PM score, hippocampal volume (r=0.42, p= 0.03)

and cortical thickness of the precuneus (r=0.55, p = 0.003) but not the posterior cingulate gyrus (r=0.19, p = 0.4). Scatterplot representations of the correlations between behavioural data and measures of hippocampal volume and cortical thickness of the precuneus and posterior cingulate gyrus are provided in Figure 8-10. .

Considering each hemisphere in isolation, no statistically significant effects were obtained.

Vertex level comparisons revealed an association between PM and cortical thickness of the precuneus, lateral parietal and supramarginal regions (Figure 11; Monte Carlo simulation, threshold = 0.5, fwhm = 10, p < 0.001).

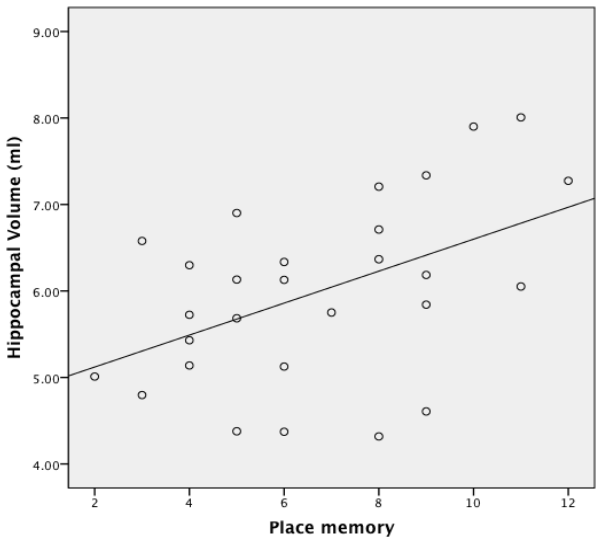

Figure 8. Scatterplot between 4MT place memory score and hippocampal volume

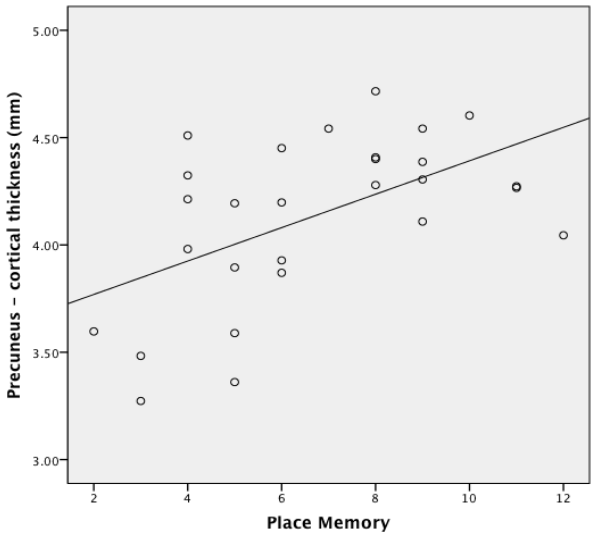

Figure 9. Scatterplot between 4MT place memory score and cortical thickness of the precuneus

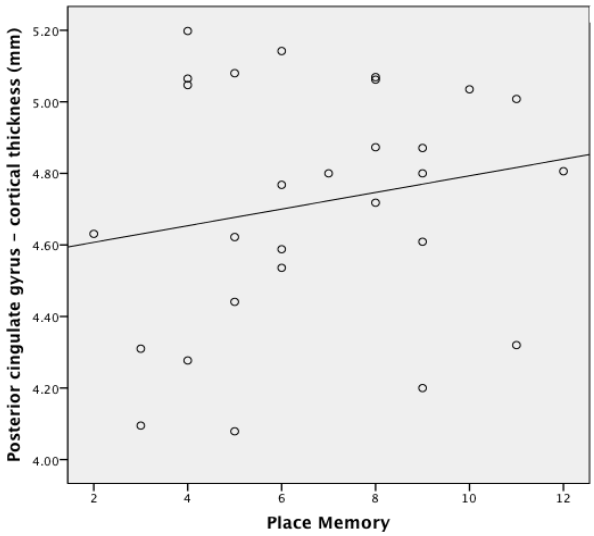

Figure 10. Scatterplot between 4MT place memory score and cortical thickness of the posterior cingulate gyrus.

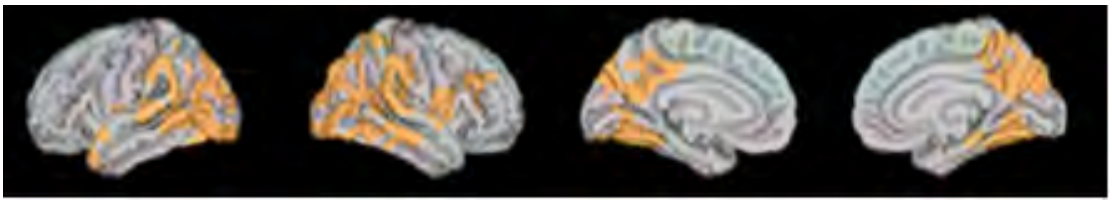

Figure 11. Vertex level correlation between place memory and cortical thickness (Monte Carlo simulation, threshold = 0.5, fwhm = 10, $p < 0.001$)

3.1.1.5 Discussion

Spatial memory performance, as tested using the 4 Mountains Test (4MT), is impaired in patients presenting with mild cognitive impairment (MCI) as a manifestation of prodromal AD. In keeping with previously published results (Bird *et al.*, 2009; Pengas *et al.*, 2010), performance on the 4MT place memory testing (PM) was significantly impaired in patients with MCI and AD compared to age- and gender-matched control subjects without a history of cognitive impairment. When the MCI patients were grouped according to CSF AD biomarker status, 4MT PM scores differed significantly between MCI patients with positive CSF AD biomarkers from MCI patients with negative CSF AD biomarkers. The MCI subgroups did not differ in terms of demographics, symptom duration, premorbid IQ and performance on general neuropsychometric testing. In particular there were no differences in the scores obtained on the Rey Auditory Verbal Learning Test and the Trail Making Test part B, both tests that have been shown to have high diagnostic sensitivity for early AD and as such are widely used in clinical and research practice (Chapman *et al.*, 2011; Ewers *et al.*, 2012; Gainotti *et al.*, 2014).

The PM scores in MCI and AD were significantly lower than corresponding control scores while there were no significant differences between MCI and AD, in keeping with previous study results in the UK (Bird et al.; 2010) and Italy (Moodley et al.; 2015). A notable aspect of previous 4MT studies was their focus on amnestic MCI, as defined by extensive neuropsychometric

assessment, involving patients from tertiary-quaternary cognitive disorder clinics (Bird et al., 2009; Pengas et al.; 2010). The level of PM impairment in these studies is similar to that observed in our MCI+ patients, who were defined using screening assessment tools (ACE-R, MMSE and CDR) and CSF profile only. The potential utility of the 4MT as a future clinical diagnostic tool for early AD is underlined by examination of test sensitivity and specificity, as illustrated by calculation of the area under the ROC curve (AUC). The AUC was 0.98 for patients, a score of 8 or below yielding 100% sensitivity and 90% specificity for early AD (i.e. MCI+ and mild AD dementia). Further PM scores of 9 or over were only observed in MCI- patients and controls, yielding a negative predictive value of 100%. These results, taken together with pre-existing studies of 4MT in 'high-risk' MCI populations, suggests an advantage of the 4MT over other neuropsychological tests in that it is independent of language and cultural setting.

Previous work (Hartley *et al.*, 2007) has shown that the sensitivity of the 4MT to hippocampal damage relates to the insertion of the 2s delay within the match-to-sample PM test, and as such there is relative preservation of place perception in the context of hippocampal damage. This observation is translated to the study of early AD, with Bird *et al.*, (2009) showing that PM, but not PP, scores differentiate AD from syndromic variants of FTD. Given these earlier findings, the decision was made *a priori* to include a shorter PP test battery within the test protocol for the current study with a view to reducing total test time, which is of relevance in the context of the potential future application of the 4MT as a test for use in clinical practice. Performance on the abbreviated 6-item PP test did not discriminate between controls and MCI patients, or between MCI+ and MCI- subgroups. PP performance was impaired in patients with AD dementia, consistent with the spread of pathology into cortical regions in more advanced disease.

Quantitative MRI analyses revealed that hippocampal volume, and the cortical thickness of the precuneus and posterior cingulate gyrus were

reduced in patients with MCI, and that this atrophy was more severe and extensive in patients with AD dementia. These observations are in keeping with a number of previous MRI studies conducted in MCI and AD (Du et al., 2001, Hämäläinen et al, 2007). However, and in contrast to the place memory test performances, no differences in these ROI structural measurements were observed between MCI+ and MCI- subgroups.

PM scores correlated with total hippocampal volume and with the cortical thickness of the precuneus but not with cortical thickness of the posterior cingulate gyrus. The correlation with hippocampal volume is in keeping with the central study hypothesis with regard to impairment of hippocampal function in early AD, and as such it is proposed that this relationship is causal, and not merely associative, in nature.

The correlation between PM and cortical thickness of the precuneus can be interpreted in two main ways. The first of these is that this correlation is indicative of a noncausal association, relating to the early involvement of the precuneus in AD (Braak and Braak, 1991; Mirra *et al.*, 1991; Thal *et al.*, 2002). However, such an explanation would not easily explain the absence of a significant correlation with the cortical thickness of the posterior cingulate gyrus, which like the precuneus is affected early in AD. The second interpretation is that the precuneus is directly implicated in allocentric spatial memory. Evidence from non-human primates (Selemon & Goldman-Rakic, 1988) and from human studies (reviewed by Cavanna and Trimble, 2006) suggests that the precuneus is involved in spatially-related behaviours. Within these behaviours functional imaging studies have shown activation of the precuneus during mental rotation tasks (Butler *et al.*, 2006; Semrud-Clikeman *et al.*, 2012). While there is a component of mental rotation within the 4MT task it is important to note that these study results demonstrate that it is the test of allocentric place memory, rather than allocentric place perception, that differentiates patients with early AD. However, even when taking into account the initial 4MT study findings that focal hippocampal

damage is associated with impairment of spatial memory but preserved spatial perception (Hartley *et al.*, 2007) the possibility remains that allocentric spatial memory is subserved by the precuneus as part of a functional network including the hippocampus. Task-free fMRI studies show that the hippocampus and precuneus represent highly interconnected hubs within a "default mode network" underpinning spatial and episodic memory(Greicius *et al.*, 2004; Vincent *et al.*, 2006) and the vulnerability of this network to early AD *(*Rombouts *et al.*, 2005) is of note in the context of this current study.

Several aspects of this study warrant further discussion in light of the potential future application of the 4MT as a clinical diagnostic tool. First of all, this study did not aim to assess the effect of gender on 4MT place memory performance. While previous work has suggested the presence of sexual dimorphism in spatial cognition (Maguire et al., 1999) no significant difference in 4MT performance between men and women was observed in the recent study by Hartley et al. (2012). However unpublished results from a large study undertaken in healthy individuals suggest a small but significant gender effect with lower scores obtained from women on a 30-item test, with mean scores of 20 and 18.6 for men and women respectively (T. Hartley, C. Bird, H. Spiers, personal communication). The issue of gender effect on 4MT performance needs further clarification and this issue is being explored within current studies involving much larger numbers of young and older cognitively normal subjects. Another issue relates to the selection of controls in studies of this kind. Other 4MT studies have observed lower PM scores in control subjects, nonetheless reporting high levels of diagnostic accuracy for MCI and AD (Pengas et al., 2010). As is the norm for dementia research studies of this kind, the primary criterion for recruitment of control subjects was an absence of reported cognitive symptoms. Testing for AD biomarkers, in the form of amyloid-PET scanning or CSF examination, was not undertaken in any control subjects. Given that the incidence of AD rises with age, and that a high prevalence of AD neuropathology is observed in otherwise 'cognitively normal' elders, it is possible that individuals with presymptomatic AD may have been included as controls in other studies.

A third aspect relates to the choice of 4MT for testing spatial memory. In the detailed study conducted by Pengas et al. (2010) AD patients were found to be impaired on a variety of spatial memory tests and of these, the Virtual Route Learning Test (VRLT) was found to be slightly superior to the 4MT in terms of diagnostic accuracy (differentiation of AD from semantic dementia AUC 0.93 for VRLT vs. AUC 0.85 for 4MT). However, operational issues favoured the choice of the 4MT over the VRLT in this study. In the Pengas et al. (2010) study 2/32 (6%) of MCI patients were unable to complete the VRLT due to nausea from perceived motion, whereas all MCI (and all AD) patients tolerated the 4MT. Furthermore the need to employ a computer-based platform for the VRLT, allied with the requirement for extensive (and thus time-consuming) pre-testing task familiarisation, limits the potential future usage of the VRLT outside academic centres. By comparison the 4MT may be applied in paper as well as electronic forms and this, along with a short test duration, would favour future usage of the 4MT over the VRLT as a diagnostic tool in routine clinical practice. These study findings therefore have impact for both academic and clinical practice. The diagnostic benefits of a theory-driven test of hippocampal function are demonstrated; no less importantly, the use of a test that fulfils both diagnostic requirements with regard to sensitivity and specificity and operational requirements with regard to scalability and usability is of particular relevance given the high prevalence of memory impairment in the ageing population and the fact that the majority of patients with MCI are evaluated in community memory clinics rather than academic centres.

Conclusion

Performance on the “4 Mountains Test” of spatial memory differentiates mild cognitive impairment due to Alzheimer’s disease with high diagnostic sensitivity and specificity. High diagnostic accuracy of was observed in separate study populations recruited from two different countries. The correlation of test performance with atrophy of the hippocampus and

precuneus is consistent with the role of these brain regions in spatial cognition and with their early involvement in the AD pathological process.

These findings demonstrate the potential of spatial memory testing for detecting early AD and of the 4MT as a cross-cultural diagnostic tool suitable for widespread use across different clinical settings.

3.1.2 The four mountains test of spatial memory: specificity for early Alzheimer's disease

3.1.2.1 Abstract

This study applied the 4 Mountains Test (4MT) to patients with AD and non-AD cognitive impairment in order to assess it's ability to discriminate between these patient populations.

The study comprised HC (n=39), MCI (n=21), mild AD dementia (n=12) and mild FTD (n=9); MCI was stratified into AD CSF biomarker-positive (MCI+, n=10) and biomarker-negative (MCI-, n=11) subgroups.

Performance on 4MT place memory testing was impaired only in individuals with early AD (i.e. MCI + and mild AD dementia) while performance was comparable between HC, MCI - and FTD. A 4MT score of <8/15 was associated with 82% sensitivity and 90% specificity in distinguishing between early AD and non-AD cognitive impairment (i.e. MCI - and FTD; AUC=0.96), outperforming the MMSE and Rey Auditory Verbal Learning Test in this regard (AUC 0.80 and 0.63 respectively). Also, a strong association between PM and CSF total tau was observed (r=-0.4; p=0.02).

In conclusion, performance on a hippocampus-sensitive test of spatial memory differentiates AD from non-AD with high diagnostic specificity, and correlates with a measure of neurodegeneration, in the form of CSF total tau. The contrast between the specificities of the 4MT and the RAVLT, if replicated in future larger scale studies, may have significant implications for the choice of memory tests used in clinical and research practice to discriminate between AD and non-AD.

3.1.2.2 Introduction

In clinical settings, short cognitive tests such as the MMSE (Folstein *et al.*, 1975) are commonly applied for diagnostic purposes but lack sensitivity and specificity in differentiating between neurodegenerative diseases, particularly in the setting of MCI (O'Bryant *et al.,* 2008). Impaired free and cued recall, tested using either list learning or a short story, have been regarded to be cardinal features of early AD despite similar impairments also being observed in early FTD (Hodges *et al.*, 1999). Behavioural and neuropsychiatric impairment are also unreliable as indicators of early FTD as they may also be observed in AD (Mega *et al.,* 1996).

Spatiotemporal disorientation is another hallmark feature of AD but one that is seldom encountered in FTD (Yew *et al.*, 2012). Pathological studies suggest that the severity of spatiotemporal disorientation is strongly correlated with the density of NFT pathology in the CA1 hippocampal subfield and retrosplenial cortex (Giannakopoulos *et al.*, 2000). Previous cross-sectional studies using the 4MT highlighted significant differences in PM between AD and FTD but not between FTD and controls (Bird et al., 2009; Pengas *et al*., 2010).

The work described in Section 3.1.1. highlights the sensitivity of spatial memory testing for MCI due to AD. In this section the issue of test specificity is investigated. The central study hypothesis was that spatial memory performance (as tested using the 4MT) would be impaired in early AD but not in FTD. A second hypothesis was that PM performance would be positively correlated with CSF total tau, as a molecular marker of neurodegeneration.

3.1.2.3 METHODS AND MATERIALS

Subjects

Patients with MCI, mild AD dementia and mild FTD dementia were recruited from Hurstwood Park Neurological Centre. MCI, AD and FTD were diagnosed respectively according to Petersen (Petersen, 2004), McKhann (McKhann *et al.*, 2011) and Neary criteria (Neary *et al.*, 1998). Patients with dementia were matched for dementia severity using a CDR of one (Morris, 1993) and an MMSE of > 22. All MCI patients had MMSE scores equal to or above 26 (UK) with CDR ≤ 0.5. Patients with syndromic variants of FTD were diagnosed according to standard diagnostic criteria (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011) and, given the number recruited, their data was pooled to permit statistical analysis.

The study group consisted of 39 HC, 11 MCI -, 10 MCI +, 12 AD and 9 FTD (6 bvFTD, 2 svPPA and 1 nfvPPA).

Demographics

There were no significant differences between HC, MCI and AD groups in terms of age and gender. However, ANOVA revealed significant differences in level of education (table 10). Contrast tests identified significant difference only between HC and patients (p=0.002). No further differences were observed with Scheffe corrected post-hoc pairwise comparisons. Contrast tests identified further differences in terms of disease duration between MCI and FTD (p = 0.01 MCI - vs. FTD; p = 0.02 MCI + vs. FTD)

	HC n = 39	MCI - n = 11	MCI + n = 10	AD n = 12	FTD n = 9	*p*
Gender, M:F	18:21	8:3	8:2	6:6	7:2	0.3
Age, years	64.5 (5.6)	66.1 (8.9)	68.1 (6.2)	66.7 (8.7)	66.6 (10.0)	0.7
Education, years	13.3 (1.9)	11.2 (2.0)	12.1 (2.1)	12.5 (2.1)	10.7 (1.7)	0.02**
Disease Duration	N/A	3.6 (0.5)	3.7 (0.8)	4.9 (1.0)	5.4 (1.8)	0.01

Table 10. Demographics. HC = healthy controls, MCI = mild cognitive impairment, AD = Alzheimer's disease dementia, FTD = Frontotemporal dementia

Behavioural studies

General neuropsychological assessment

The following domains were tested, with the tests used in parentheses: 1) Episodic memory [UK: Rey Auditory Verbal Learning Test, RAVLT (Rey 1941, Van der Elst *et al.*, 2005)], 2) Attention and Executive function [Trail Making Test A and B (Reitan, 1958)], 3) Executive function [Lexical and semantic fluency (Lezak, 1995)], 4) Working memory [Digit span (Blackburn and Benton, 1957)], 5) Higher visual processing [Object decision (James & Warrington, 1991)], 6) Premorbid IQ [National Adult Reading Test (NART) estimated IQ (Nelson and Willison 1991)]. The test battery outlined above was not undertaken in three HC subjects (who opted out of these tests) and one MCI patient (with negative CSF biomarkers). The RAVLT was not completed in two patients with FTD due to expressive speech impairment.

The 4 Mountains Test

PP and PM were assessed in all subjects using the same test protocol outlined in Section 3.1.1. with 6 PP and 15 PM test items.

Statistical analysis

For HC, MCI and AD group data, ANOVA was used to determine between-group differences for the demographic and neuropsychometric data. Post-hoc pair-wise comparisons were undertaken using the conservative Scheffé test, which controls for family wise error rate across all planned contrasts.

Areas under the Receiver Operating Characteristics (ROC) curves were calculated, relating to the ability of 4MT test scores to differentiate early AD (AD and MCI +) from non-AD (FTD and MCI -).

3.1.2.4 RESULTS

Behavioural studies

General neuropsychometric assessment

Compared with controls, patients were impaired on all tests except object decision (Table 11).

	HC	MCI -	MCI +	AD	FTD	F (df)	P
NART IQ	121.4 (6.1)	116.7 (7.2)	109.1 (11.1)	110.9 (13.7)	107.3 (7.2)	4.3 (4,72)	< 001
MMSE	-	27.5 (0.7)	27.4 (1.3)	24.3 (1.4)	26.4 (1.8)	20.7 (3,38)	< 001
VOSP-OD	17.2 (2.1)	16.9 (1.5)	16.4 (2.3)	15.6 (2.2)	16.7 (3.1)	1.2 (4,72)	0.3
RAVLT-DR	10.6 (3.2)	2.8 (2.7)	2.7 (1.8)	2.0 (1.2)	4.9 (3.0)	38.4 (4,70)	< 001
RAVLT-RP	0.9 (0.9)	0.6 (0.2)	0.6 (0.2)	0.5 (0.1)	0.6 (0.2)	27.0 (4,70)	< 001
Lexical Fluency	51.9 (12.2)	45.0 (12.7)	36.9 (10.6)	31.4 (8.1)	19.4 (10.6)	19.1 (4,72)	< 001
Semantic Fluency	38.3 (6.0)	29.5 (4.0)	27.9 (6.7)	18.5 (5.6)	20.7 (11.6)	26.8 (4,72)	< 001
Trails A	31.6 (9.5)	35.2 (8.5)	43.8 (16.2)	92.2 (34.3)	46.4 (15.8)	29.1 (4,72)	< 001
Trails B	69.2 (28.5)	78.3 (24.5)	125.0 (38.9)	231.2 (96.5)	134.6 (62.1)	25.3 (4,72)	< 001
Digit Span	6.7 (1.0)	6.8 (1.3)	6.3 (0.8)	6.1 (0.9)	6.5 (1.0)	1.5 (4,72)	0.2
PP	4.9 (0.9)	4.9 (1.1)	3.9 (0.9)	2.8 (0.8)	4.1 (0.9)	13.9 (4,76)	< 001
PM	10.6 (2.1)	9.6 (1.7)	5.8 (2.3)	4.7 (1.2)	8.9 (1.2)	29.1 (4,76)	< 001

Table 11. Neuropsychometric and 4MT results: Specificity of the 4MT for AD

Compared to controls, MCI- and MCI+ were impaired on verbal memory ($p < 0.001$ HC vs. MCI-; $p < 0.001$ HC vs. MCI+) and semantic verbal fluency ($p = 0.02$ HC vs. MCI-; $p = 0.002$ HC vs. MCI+). In contrast, MCI+ patients were also impaired on lexical verbal fluency ($p = 0.01$) whereas MCI- patients performed similar to controls (Table 12). MCI patients were not impaired on the Trail-making A and B test.

In contrast to controls, AD and FTD were impaired on verbal memory ($p < 0.001$ HC vs. AD; $p < 0.001$ HC vs. FTD), semantic and lexical verbal fluency ($p < 0.001$ HC vs. AD; $p < 0.001$ HC vs. FTD) and Trail-making B ($p < 0.001$ HC vs. AD; $p =0.02$ HC vs. FTD). On the Trail-making A, patients with AD were impaired compared to controls ($p < 0.001$) whereas FTD performed similar to controls (Table 12).

Compared to MCI - patients, FTD patients were impaired on lexical verbal fluency ($p < 0.001$), while AD patients were impaired on semantic verbal fluency ($p = 0.01$) and both components of the trail-making test ($p < 0.001$) (Table 12). There were no significant differences in verbal memory between MCI - and the other patient groups and no differences in the standard psychometric profile of MCI- and MCI + patients.

Compared to MCI- and MCI+, AD was significantly impaired on both components of the Trail Making Test ($p < 0.001$).

There were also differences in NART-IQ observed between HC and MCI + ($p = 0.01$), HC and AD ($p = 0.02$) and HC and FTD ($p = 0.002$). Importantly, pairwise comparisons did not reveal any significant differences between patient groups (Table 12).

Pairwise comparisons between HC and Patient groups				
	HC vs. MCI -	HC vs. MCI +	HC vs. AD	HC vs. FTD
NART IQ	0.7	0.01	0.02	0.002
MMSE	-	-	-	-
RAVLT-DR	< 0.001	< 0.001	< 0.001	< 0.001
RAVLT-RP	< 0.001	< 0.001	< 0.001	< 0.001
Lexical Fluency	NS	0.01	< 0.001	< 0.001
Semantic Fluency	0.02	0.002	< 0.001	< 0.001
Trails A	NS	NS	< 0.001	NS
Trails B	NS	0.05	< 0.001	0.02
PP	NS	NS	< 0.001	NS
PM	NS	< 0.001	< 0.001	NS

Pairwise comparisons between patient groups						
	FTD vs. MCI-	FTD vs. MCI +	FTD vs. AD	MCI - vs. MCI +	MCI - vs. AD	MCI + vs. AD
NART IQ	NS	NS	NS	NS	NS	NS
MMSE	NS	NS	< 0.001	NS	< 0.001	< 0.001
RAVLT-DR	NS	NS	NS	NS	NS	NS
RAVLT-RP	NS	NS	NS	NS	NS	NS
Lexical Fluency	< 0.001	0.03	NS	NS	NS	NS
Semantic Fluency	NS	NS	NS	NS	0.01	0.04
Trails A	NS	NS	< 0.001	NS	< 0.001	< 0.001
Trails B	NS	NS	0.002	NS	< 0.001	< 0.001
PP	NS	NS	0.04	NS	< 0.001	NS
PM	NS	0.02	< 0.001	0.001	< 0.001	NS

Table 12. Post-hoc comparisons of neuropsychometric and 4MT testing, Scheffe corrected, between HC and patient groups

4 Mountains Test

Place perception

ANOVA revealed group differences in test performance between HC and patients ($p < 0.001$; table 11). Pairwise comparisons, corrected for multiple comparisons, revealed that the difference in scores was significant between HC and AD ($p < 0.001$; table 12). For patient groups, differences were observed between MCI biomarker negatives and AD ($p < 0.001$; table 12) and between FTD and AD ($p = 0.04$; table 12). No differences were observed between HC and MCI subgroups or between FTD and MCI subgroups.

Place memory

ANOVA revealed group differences in test performance between HC and patient groups ($p < 0.001$; table 11). Pairwise comparisons, corrected for multiple comparisons, revealed that the difference in scores was significant between HC and early AD, comprising MCI biomarker positive and AD ($p < 0.001$). No differences in test performance were noted between HC and non-AD, comprising MCI biomarker negative and FTD. For patient groups, differences were observed between AD and non-AD groups but not within these groups i.e. there was no difference in PM between MCI - and FTD or between MCI + and AD (Table 12, also see Figure 12).

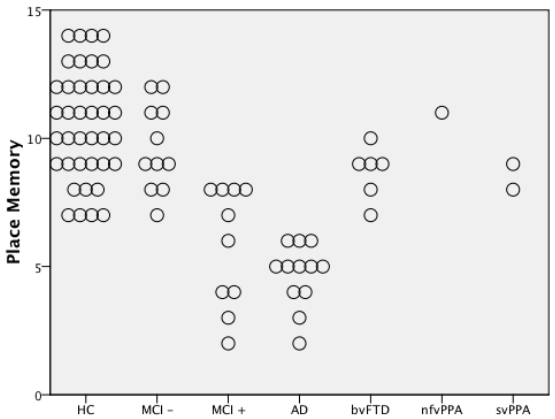

Figure 12. Scatterplot representation of PM scores in the study population

Receiver operating characteristic (ROC) curves

The discriminative ability of 4MT place memory testing is illustrated by use of Receiver Operating Characteristics (ROC) curves (Figure 13). In addition, the discriminative ability of MMSE and RAVLT were assessed for comparison.

For PM, test performance is associated with an area under the curve of 0.96 for differentiating early AD (MCI + and AD) from non-AD (MCI - and FTD). In comparison the AUC for MMSE and RAVLT were 0.80 and 0.63 respectively. A PM score of 8 or less was associated with sensitivity and specificity of 82% and 90% respectively for discriminating AD from non-AD while scores of 7 or below was associated with a sensitivity and specificity of 77% and 100% respectively. For the RAVLT, delayed recall scores of 6 or below were associated with sensitivity and specificity of 100% and 35% respectively whereas scores of 3 or below were associated with a sensitivity of 55% and a specificity of 65%. In comparison, an MMSE of 27 or less was associated with a sensitivity and specificity of 64% and 85% respectively for discriminating AD from non-AD.

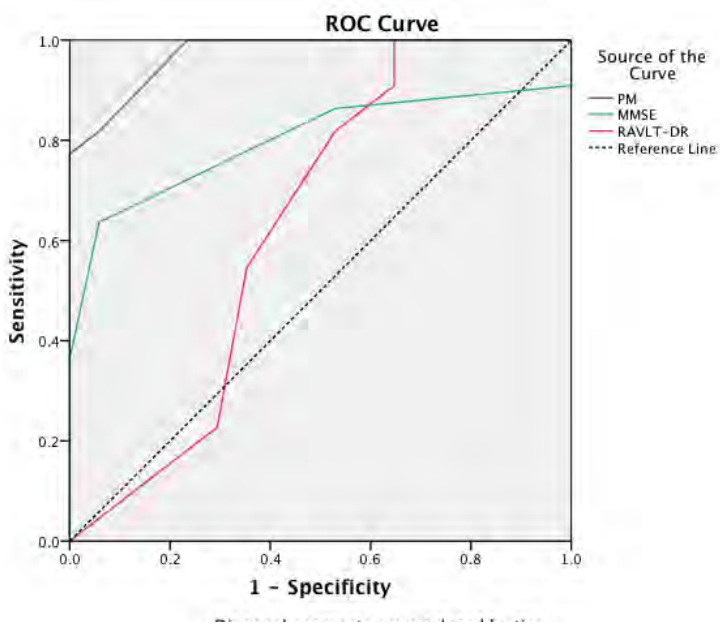

Figure 13. ROC curves for PM, MMSE and RAVLT-DR. Discrimination of patients with evidence of AD (MCI+ plus AD dementia) from non-AD (MCI- and FTD).

Relationship between AD CSF biomarkers and PM performance

Correlations between PM performance and CSF Abeta 1-42 were not undertaken as there was clear separation of data points between early AD (MCI + and mild AD dementia) and non-AD (MCI- and FTD; figure 14). This separation was entirely consistent with the method used to define the MCI sub-groups. In terms of CSF-Tau levels, all MCI+ patients had elevated levels of CSF-Tau whereas MCI- patients were heterogenous, including individuals with increased and normal CSF-Tau but also normal CSF levels of Abeta 1-42 (Albert *et al.,* 2011).

There was a significant association between PM and CSF total tau (r=-0.4, p=0.02; Figure 14). The association strengthened when corrections were applied for age, years of education and disease duration (r=-0.5, p=0.01). Individuals with FTD and raised CSF Tau (>375 pg/ml), but normal CSF Abeta 1-42, achieved higher PM scores than individuals with AD CSF biomarkers (figure 14).

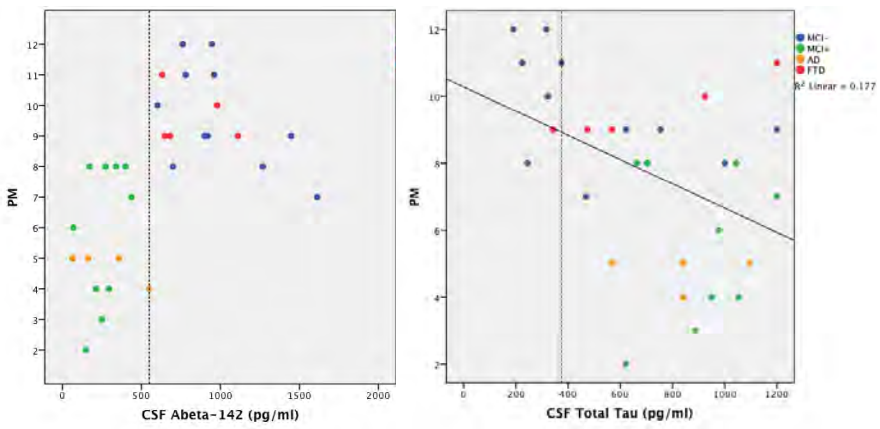

Figure 14. Scatterplots representations of PM scores versus CSF markers of neurodegeneration (CSF Abeta 1-42 and Total Tau; left and right respectively). The vertical dashed lines represent the cut-offs used to recognize underlying AD neuropathology (i.e. CSF Abeta 1-42 < 550 pg/ml and CSF total tau > 375 pg/ml).

3.1.1.5 Discussion

4MT spatial memory testing was applied to patients with AD, FTD and MCI, the latter stratified by their AD CSF biomarker profile. Given the involvement of the hippocampus in early AD, it was predicted that spatial memory performance would discriminate between AD and non-AD patients.

4MT scores were lower in AD patients compared with FTD patients ($p=0.04$) whereas FTD patients did not perform significantly different to control subjects. This is in line with previously published work involving the 4MT (Bird *et al.*, 2009; Pengas *et al.*, 2010). In comparison, verbal memory was impaired in all four patient groups compared to controls ($p < 0.001$) but did not discriminate between the patient groups studied.

This dissociation between verbal and spatial memory in discriminating between these groups is noteworthy for several reasons. While 'severe amnesia' is a listed exclusion criteria for bvFTD (Rascovsky *et al.*, 2011), there is mounting evidence that episodic memory can be impaired in some FTD patients (Hornberger *et al*., 2010). The severity of episodic memory impairment can vary widely in FTD and, without overt behavioural or language symptoms, symptoms may be misattributed to AD pathology (Kramer *et al.,* 2005; Hornberger *et al*.; 2010). Existing work suggests FTD-mediated memory deficits are underpinned by impairments in temporal source memory ('remembering when') rather than spatial source memory ('remembering where') (Ekstrom *et al.,* 2011; Irish *et al.,* 2011; Irish *et al.*, 2012).

In the previous study relating to the sensitivity of the 4MT, I observed smaller hippocampal volumes in MCI- and MCI+ compared to controls. I also outlined that MCI- were unimpaired in PM compared to controls despite MCI- and

MCI+ displaying similar levels of verbal memory impairment and hippocampal atrophy. Further to this, some of the MCI- patients are now noted to have high levels of CSF Total Tau yet these individuals also appear relatively unimpaired on PM. This is consistent with the findings of Jicha *et al*. (2006) who discovered non-Alzheimer, medial temporal Tauopathies in some MCI patients at post-mortem. Taken together, this may suggest that PM performance in neurodegeneration might be dependent on the topography of hippocampal disease involvement. This idea is supported by the earlier work of Bird et al. (2009) who also observed unimpaired PM in FTD and attributed the contrasting impairments in PM observed in AD to greater disease involvement of the posterior hippocampus given that FTD is associated with preponderant anterior hippocampal atrophy. In this study, FTD patients with high CSF total tau (n=4) were relatively unimpaired on PM (all scoring above eight) although the lack of neuroimaging analysis prevents any firm conclusions being reached regarding the pattern of atrophy in these individuals.

An alternate explanation for the relationship between PM and CSF Total Tau may relate to medial parietal involvement by AD pathology. As outlined in section 1.8, the other tauopathies involving the hippocampus spare the medial parietal lobe, another brain region that is also heavily involved in spatial processing (Maguire *et al.,* 1998). Another consideration relates to the density of AD neuropathology within the CA1 hippocampal subfield that correlates to the severity of spatiotemporal disorientation observed in affected individuals (Giannakopoulos *et al.,* 2000). This may be important in considering PM performance in AD given that patients with hypoxic hippocampal injury, a risk factor for CA1 neuronal loss, are also impaired on PM but not PP testing (Hartley *et al.*, 2007).

From a clinical perspective, the correlation between PM and total tau in MCI is also relevant. Low CSF amyloid levels is a poor predictor of future AD in asymptomatic individuals (Stomrud *et al*., 2015) yet paradoxically, is highly

predictive of AD in MCI (Nettiksimmons *et al*., 2014). However, this may reflect that symptomatic deterioration in AD predementia is Tau-mediated and depends on the spread of Tau beyond the medial temporal lobe (Braak and Braak, 1991). Further, in the previous study, we have already observed that PM performance, but not hippocampal volume or verbal memory performance, discriminated between MCI - and MCI + patients lending further support for PM being a sensitive and specific behavioural measure of AD-related hippocampal neurodegeneration.

The prominent lexical fluency impairment (and relative sparing of semantic fluency) observed in FTD is consistent with previous work (Hodges *et al.*, 1999) and discriminates FTD from controls and MCI. In contrast, the results also suggest that Trail making B test is a non-specific indicator of executive dysfunction rather than of any potential diagnostic use for prodromal AD, as suggested by earlier studies that only focused on controls and patients with amnestic symptoms (Chapman *et al.*, 2011; Ewers *et al.*, 2012; Gainotti *et al.*, 2014).

In interpreting the ROC curves, the limitations of the study in terms of sample size must be acknowledged. Also, the decision to combine the MCI- and FTD patients into a single group for this analysis reflects the limitation of cross-sectional study. Within these limitations, the ROC analysis suggests that PM is superior to the MMSE and RAVLT for discriminating between AD and non-AD pathology.

As outlined previously, in studies of this kind the primary criterion for recruitment of control subjects was an absence of reported cognitive symptoms. Testing for AD biomarkers, in the form of amyloid-PET scanning or CSF examination, was not undertaken in control subjects. Sub analysis in our control patients, based on age cut-off, identified significant differences in delayed verbal recall between patients aged 70 and over (n=5) compared to patients below the age of 65 (n=18) and those aged 65-69 (n=16); H = 7.5, df

(2), p = 0.02; no differences were observed on other psychometric measures including PM and PP.

The impairments in PM observed in early AD were not apparent in FTD, despite the detection of Tauopathy in some FTD patients. This is worthy of further study, particularly given that similar levels of verbal memory impairment may be observed in AD and FTD. As PM performance is not reliant on temporally ordered learning, it is less likely to become impaired in FTD. The discordance in PM and delayed recall in FTD patients suggests that these abilities may be subserved by different hippocampal and extra-hippocampal sub-regions.

Conclusion

Topographic working memory was impaired in patients with AD and prodromal AD but not in patients with FTD or non-AD MCI. The small sample size prevents any firm conclusions about diagnostic specificity being drawn. Nonetheless, the study complements existing 4MT studies that strongly suggest that allocentric working memory is impaired in AD but not in non-AD dementias. The ease of test administration and compliance with test taking should encourage greater uptake of the test in research settings to enable powered studies of diagnostic specificity to be undertaken.

3.2 Simultaneous PET-MRI studies in syndromic variants of Alzheimer's disease and frontotemporal dementia

3.2.1 Abstract

Background. Multimodal neuroimaging studies reveal marked inter-regional differences between atrophy and hypometabolism in different dementia syndromes.

Aims. The primary objective was to conduct a proof-of-concept study regarding the concordance of brain atrophy and hypometabolism in syndromic variants of Alzheimer's disease (AD) and frontotemporal dementia (FTD). A second objective was to determine the effect of image analysis methods on identification of atrophy and hypometabolism.

Method. PET and MRI data were acquired simultaneously on 24 subjects with six variants of AD and FTD (n=4 per group). Atrophy was rated visually and quantified using FreeSurfer cortical thickness measures. Hypometabolism was rated visually and quantified using atlas-based NEUROSTAT and a recently validated SPM-based approach. Concordance was measured using weighted Cohen's kappa.

Results. Atrophy-hypometabolism concordance differed markedly between patient groups; kappa scores ranged from 0.13 (nonfluent/agrammatic variant of primary progressive aphasia, nfvPPA) to 0.49 (posterior cortical variant of AD, PCA). Heterogeneity was also observed within groups, with the confidence intervals of kappa scores ranging from 0-0.25 for PCA, to 0.29-0.61 for nfvPPA. More widespread MRI and PET changes were identified using quantification, SPM-based evaluation identifying hypometabolism in 81% additional brain regions compared to NEUROSTAT.

Conclusion. The marked differences in concordance identified in this proof-of-principle study may reflect differences in the molecular pathologies underlying AD and FTD but also operational differences in the methods used

to diagnose these syndromes. The superior ability of quantitative methodologies to detect MRI and PET changes, if confirmed on larger cohorts, may favour their usage over current qualitative visual inspection in future clinical practice.

3.2.2 **Introduction**

In neurodegenerative dementias, MRI and 18-fluorodeoxyglucose PET (18-FDG PET) represent the respective tools of choice for detecting brain atrophy and hypometabolism. These imaging changes serve as surrogate markers of neurodegenerative pathology and their importance for diagnosis in vivo is reflected in the explicit reference to neuroimaging changes in updated diagnostic criteria. For instance, the new criteria for Alzheimer's disease (AD) (McKhann *et al.*, 2011) differ from the previous criteria (McKhann *et al*., 1984) in specifying the presence of hippocampal atrophy on MRI and/or temporo-parietal hypometabolism on FDG-PET. In the case of behavioural variant FTD (bvFTD), imaging changes are central to determination of diagnostic probability, with imaging evidence of frontal lobe damage, in the form of atrophy and/or hypometabolism, required to increase diagnostic confidence from "possible" to "probable" (Rascovsky *et al.*, 2011). Similarly, the new diagnostic criteria for the variants of FTD presenting with different types of aphasia include neuroimaging changes as supportive features (Gorno-Tempini *et al.*, 2011). However a noteworthy difference between the AD and FTD diagnostic criteria is that for the former the neuroimaging changes are included as markers of AD pathophysiology whereas for the latter they are not specific to the underlying molecular pathologies.

In contrast to the abundance of single-modality studies using MRI or PET (Whitwell and Jack, 2007), relatively few multimodal studies have sought to compare patterns of brain atrophy and hypometabolism in different dementias. Those studies published to date have shown marked inter-regional differences in atrophy and hypometabolism, as exemplified by the observation that in AD hypometabolism is more widespread than atrophy (Villain *et al.*, 2008; Chételat *et al*., 2008; La Joie *et al.*, 2012). In FTD the overlap of MRI and PET changes differ between syndromic variants, with the divergent patterns of atrophy and hypometabolism in bvFTD (Koedam *et al.*,

2010; Tosun *et al.*, 2012) contrasting with the high degree of overlap associated with the semantic variant of primary progressive aphasia (formerly known as semantic dementia) (Desgranges *et al.*, 2007; Acosta-Cabronero *et al*., 2011).

To date, multimodal imaging studies have tended to involve either analysis of individual disorders, or comparison across two dementia syndromes. In this study, representing an extended case series, simultaneous acquisition of PET and MRI on an integrated scanner is used to extend the scope of investigation to encompass six dementia syndromes, representing variants of AD and FTD. These disorders are particularly well suited for this study not only because abnormalities on MRI or PET are central to diagnosis, but also in view of the contrast between AD and FTD in terms of the relationship between molecular pathology and clinical phenotype. While in AD the same amyloid/tau proteinopathy can manifest as distinct clinical variants (Galton *et al*., 2000; Lehmann *et al*., 2013), in FTD a given syndromic variant may be associated with diverse underlying molecular pathologies [for example, bvFTD which can occur in the context of tau, TDP-43 or FUS protein deposition (Josephs, 2008)].

The primary study hypothesis was that different syndromic variants of AD and FTD would be associated with different concordance of atrophy and hypometabolism. Above and beyond the evidence that hypometabolism both precedes atrophy in these disorders, as shown in at risk individuals (Bateman *et al*., 2012), and exceeds the latter in terms of topographical extent (Villain *et al*., 2008; Koedam *et al*., 2010; La Joie *et al*., 2012), it is hypothesised that these differing relationship between molecular pathology and phenotype would be reflected in between- and within-syndrome differences in concordance and this was tested across six syndromic variants (two AD and four FTD syndromes).

The second study hypothesis was that determination of the extent of atrophy and hypometabolism would differ according to the use of qualitative or quantitative evaluation methods. Proof of hypothesis would have significant implications for clinical practice given that this typically involves qualitative visual inspection of scans, in contrast to the use of quantitative methodologies in research. This study therefore compared the extent of cerebral atrophy and hypometabolism as determined by qualitative visual analysis with that identified using quantitative methodologies at a single subject level. For MRI, FreeSurfer was used to measure cortical thickness, whereas quantitative PET analyses were undertaken both with the established atlas-based NEUROSTAT method and with a recently validated voxel-based approach for single subject FDG PET analysis based on optimized statistical parametric mapping (Della Rosa *et al.*, 2014; Perani *et al.*, 2014).

Here, we acquired an extended case series of patients' studies with simultaneous PET-MRI to obtain preliminary evidence regarding the above hypotheses.

3.2.3 **Materials and methods**

Subjects

Ethics approval for this study was obtained from the UK South East Coast Brighton and Sussex National Research Ethics Service (reference number: 12/LO/0356). Twenty four patients with mild-to-moderate dementia (clinical dementia rating of 1-2) (Morris, 1993) were recruited from the Cognitive Disorders Clinic, Hurstwood Park Neurosciences Centre, Haywards Heath, UK. Ten age-matched cognitively normal control subjects were recruited for comparative purposes. All patients underwent routine laboratory investigations and independent clinical assessments by two physicians.

Subjects were divided into six groups (n=4 per group). These were: typical Alzheimer's disease (AD), atypical AD associated with posterior cortical atrophy (PCA), behavioural variant FTD (bvFTD), non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA), semantic variant of primary progressive aphasia (svPPA) and right temporal variant of FTD (rtvFTD). For all except rtvFTD diagnoses were made according to diagnostic guidelines (Gorno-Tempini *et al.*, 2011; McKhann et al., 2011; Rascovsky *et al*., 2011); at present there are no guidelines or criteria for the diagnosis of rtvFTD and patients with this disorder were diagnosed on the basis of focal, predominantly right-sided, temporal lobe atrophy in line with previously published studies (Chan *et al*., 2009; Josephs et al., 2009). Subsequently, an R406W MAPT mutation was identified in one of the rtvFTD patients (Wood *et al*., 2015).

The rtvFTD patients in this study presented with early, prominent neuropsychiatric symptoms and impairments in social cognition, memory, spatial orientation and prosopagnosia resulting in altered social and occupational functioning; the diagnosis of bvFTD in these individuals was precluded by the presence of early spatiotemporal disorientation and memory impairment (Rascovsky *et al*., 2011). Demographic and clinical data are reported in Table 13; full psychometric data are provided in Tables 14 and 15 for 20 of the 24 subjects with dementia for whom they were available. To avoid issues of circularity, it is important to clarify that while imaging data were acquired for clinical diagnostic purposes, diagnoses were made on the basis of changes observed either on MRI or on PET, in other words the concordance of MRI and PET changes was neither investigated nor considered for diagnosis.

	HC	AD	PCA	bvFTD	nfvPPA	svPPA	rtvFTD	p-value
n	10	4	4	4	4	4	4	
Age, mean (SD)	68.0 (3.2)	75.0 (8.8)	63.8 (2.5)	64.8 (7.9)	73.3 (12.7)	69.5 (4.0)	65.8 (6.9)	0.37
Sex, M:F	4:6	4:0	3:1	2:2	3:1	3:1	2:2	0.58
YOE, mean (SD)	11.3 (2.5)	12.3 (2.1)	12 (2.9)	11.25 (2.5)	12.5 (3.2)	13.5 (1.7)	11.8 (2.4)	0.72
CDR (2:1)	N/A	2:2	2:2	2:2	1:3	1:3	1:3	1.00
MMSE, mean (SD)		24.5 (2.4)	23.8 (4.5)	26.5 (1.7)	N/A	N/A	28.0 (1.4)	0.18

Table 13. Demographic data

KEY: M=Male, F=Female, YOE=Years of education, CDR=Clinical dementia rating scale, MMSE=Mini mental state examination. CDR (2:1) refers to the proportion of patients with CDR=2 and CDR=1 respectively in each of the dementia sub-groups. NB. MMSE was not routinely assessed in all patients with nfvPPA and svPPA.

	Typical AD				PCA			
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age, years	79	71	65	85	67	64	63	61
YOE, years	10	12	12	17	15	8	12	12
Duration of disease, years	6	6	4	4	5	6	3	3
Handedness	R	R	L	R	R	R	R	R
CDR	2	1	2	1	2	1	1	2
Predicted IQ	109	110	94	119	113	107	93	104
Mental Processing Speed	NT	^	**	^	ABN	NT	**	ABN
Executive Function								
Trails B	NT	^	***	*	ABN	NT	**	NT
Lexical Fluency	**	^	*	^	*	^	^	***
Semantic Fluency	***	***	**	*	***	^	^	***
Verbal Problem Solving								
Similarities	^	^	***	^	**	^	*	^
Digit Span Forwards	*	*	^	*	*	*	^	^
Digit Span Backwards	^	^	^	^	*	*	^	**
Nonverbal Problem Solving								
Block design	^	^	***	^	***	***	*	***
Figure Copy	***	***	*	^	***	***	**	***
Verbal Memory								
Story Learning DR	***	***	**	***	**	^	^	***
List Learning LDR	NT	***	**	**	**	^	*	NT
List Learning Recognition	NT	**	**	**	**	^	^	NT
Nonverbal Memory								
Figure delayed recall	*	*	***	***	***	**	^	NT
Confrontational Naming	*	*	**	*	***	**	^	**
Visuospatial								
VOSP screening	NT	^	^	NT	^	^	^	^
VOSP object decision	NT	NT	**	NT	***	***	^	***
VOSP cube analysis	NT	^	^	NT	**	***	**	***

Table 14. Psychometric data for AD syndromic variants.

Individual test scores were standardised and expressed as t-scores that were ordered using a four-point system: t-score > 42: ^ (unimpaired); 37-42: * (impairment in the 10-25th centile); 29-36: ** (impairment in the 2nd-9th centile); < 29: *** (impairment below the 2nd centile). ABN: abandoned. NT: Not tested.

	bvFTD				PNFA				ltvFTD				rtvFTD			
	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17	Case 18	Case 19	Case 20	Case 21	Case 22	Case 23	Case 24
Age, years	73	67	54	65	81	62	87	63	72	64	73	69	64	69	57	73
YOE, years	10	10	10	15	15	15	8	12	15	12	15	12	12	10	10	15
Duration of disease, years	4	4	5	3	3	8	8	6	5	6	5	5	6	7	4	4
Handedness	R	R	R	R	R	R	L	R	R	R	R	R	R	R	R	R
CDR	1	2	2	1	2	1	1	1	1	1	1	2	1	1	1	2
Predicted IQ	100	90	100		90		86	92	120		90	83	96	96	95	
Mental Processing Speed	^	^	ABN	NT	*	NT	^	^	^	NT	^	^	^	ABN	^	NT
Executive Function																
Trails B	*	ABN	NT	NT	***	NT	ABN	ABN	**		ABN	**	*	NT	***	NT
Lexical Fluency	*	**	**	NT	**	NT	**	*	*		*	*	^	*	**	NT
Semantic Fluency	^	*	**	NT	*	NT	**	**	***		**	**	*	***	***	NT
Planning	**	**	ABN	NT	NT	NT	*	**	*		NT	***	NT	ABN	***	NT
Response inhibition	**	**	**	NT	NT	NT	**	NT	NT		NT	**	NT	ABN	NT	NT
Verbal Problem Solving				NT		NT										
Similarities	*	^	**	NT	*	NT	*	*	^		***	**	^	*	**	NT
Digit Span Forwards	*	*	**	NT	*	NT	*	**	*		*	*	^	^	^	NT
Digit Span Backwards	*	*	*	NT	^	NT	^	*	^		*	*	^	^	^	NT
Nonverbal Problem Solving				NT		NT										NT
Block design	^	*	ABN	NT	^	NT	^	^	^		^	^	^	*	***	NT
Figure Copy	^	NT	NT	NT	^	NT	^	NT	^		^	^	^	^	ABN	NT
Verbal Memory						NT										
List Learning LDR	^	^	**	NT	**	NT	^	**	*		**	**	***	***	**	NT
List Learning Recognition	^	^	*	NT	**	NT	^	*	*		*	*	**	***	**	NT
Nonverbal Memory						NT										
Figure delayed recall	^	NT	NT	NT	^	NT	^	NT	*		^	^	*	**	NT	NT
Facial Recall	^	NT	NT	NT	NT	NT	NT	NT	*		^	^	***	***	***	NT
Confrontational Naming	**	^	^	NT	**	NT	**	**	***		***	***	***	***	***	NT

Table 15. Psychometric data for FTD syndromic variants.

Individual test scores were standardised and expressed as t-scores that were ordered using a four-point system: t-score > 42: ^ (unimpaired); 37-42: * (impairment in the 10-25th centile); 29-36: ** (impairment in the 2nd-9th centile); < 29: *** (impairment below the 2nd centile). ABN: abandoned. NT: Not tested. No psychometric data was available for cases 12,14,18 and 24.

Simultaneous PET/MRI acquisition

PET and MRI data were acquired simultaneously on an integrated Siemens Biograph mMR PET/MR scanner, consisting of a 3T MRI scanner with integrated PET detector assembly, University College London Hospital, UK. MRI was performed, acquiring both volumetric T1-weighted (1x1x1 mm3 voxel size, 240x256 mm FoV, TI = 900 ms, TE = 2.98 ms) and T2-weighted sequences (slice thickness 4mm, 256x256 mm FoV, TR = 4780ms, TE = 101ms). MR-based attenuation correction was derived from the 2-point DIXON gradient echo sequence (Coombs *et al*., 1997).

18F-FDG PET imaging was obtained in dementia subjects only due to ethical constraints. PET images (1.4 x 1.4 voxel size, 2.03 mm slice thickness) were reconstructed using Ordered Subset Expectation Maximization (OSEM), 21 subsets, 3 iterations 5mm FWHM Gaussian smoothing, matrix 256x256, zoom=2 (Hudson and Larkin, 1994).

MRI Analysis

Qualitative analysis

Two neuroradiologists with experience in dementia imaging were blinded to clinical diagnosis. Visual ratings of brain atrophy were independently generated for the following regions of interest (ROIs): frontal lobe, hippocampus, temporal pole, perisylvian region and parietal lobe. This choice of ROIs was specifically made to reflect the raters' standard clinical diagnostic practice and the fact that visual analogue rating scales already exist for several ROIs (hippocampus, frontal lobe, parietal lobe) (Wahlund *et al*., 1999; Kipps *et al*., 2007; Moller *et al*., 2014). Atrophy ratings, averaged across the two raters, were scored using a four-point scale (0-3, where 3 indicates severe atrophy). Here, the focus was on volume loss and white matter hyperintensities were not considered.

Cortical thickness quantification

Cortical thickness analysis was performed using the FreeSurfer workflow (Massachusetts General Hospital, Harvard University, Boston MA, USA), which involves reconstruction of the white-gray matter interface and pial surface, followed by labelling based on non-linear morphing to a probabilistic brain atlas. The Freesurfer workflow is detailed elsewhere (Fischl, 2012). A specialized operator unaware of disease status performed visual verification and manual clean-up of the segmentations. Starting from Desikan atlas measurements (Desikan *et al.*, 2006), the following ROIs were considered: frontal lobe, lateral temporal lobe, temporal pole (TP), medial parietal lobe / precuneus (Pc), lateral parietal lobe (LP), occipital lobe, anterior cingulate gyrus and posterior cingulate gyrus. For ROIs comprising more than one region (frontal lobe, lateral temporal lobe, lateral parietal lobe and occipital lobe) cortical thickness measurements were aggregated. For comparison with visual ratings, Z-scores for comparison between each patient and controls were remapped on a 0-3 discrete scale (0= $z < 2$; 1 = $2<z<3$; 2 = $3<z<4$; 3 = $z>4$).

Hippocampal volumetry

Hippocampal segmentation was performed using the FSL/FIRST tool (FMRIB, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK) (Patenaude *et al*., 2011), and all segmentations were visually verified. One bvFTD patient (case 13) was excluded due to poor image quality. FSL hippocampal segmentation was chosen over FreeSurfer because preliminary expert evaluation revealed that the latter tended to include parts of other medial temporal structures such as the parahippocampal gyrus and amygdala, and as such was not reliable on our data. The accuracy of FreeSurfer vs. FSL hippocampal segmentation is

matter of ongoing debate (Morey *et al*., 2009; Sánchez-Benavides *et al.,* 2010; Mulder *et al*., 2014).

FDG-PET Analysis

Qualitative analysis

Three nuclear medicine consultants experienced in dementia imaging were blinded to clinical diagnosis. Visual ratings of FDG-PET uptake maps (as produced by the scanner, without additional normalization) as presence of hypometabolism were independently generated for the following ROIs: frontal lobe, lateral temporal lobe, temporal pole (TP), hippocampus (Hc)/ medial temporal lobe (MTL), medial parietal lobe/ precuneus (Pc), lateral parietal lobe (LP), occipital lobe, anterior cingulate gyrus and posterior cingulate gyrus. This set of ROIs was chosen to reflect the raters' standard clinical diagnostic practice. As above, visual ratings were scored using a four-point severity scale (0-3 where 3 represents severe hypometabolism), which was averaged across raters.

NEUROSTAT

Parametric analysis of FDG-uptake yielding z-scores for the comparison between each patient and a controls template was undertaken using the Neurological Statistical Image Analysis package (NEUROSTAT; University of Seattle, WA, USA) (Minoshima *et al*., 1995). In brief, scans were transformed and realigned to the Talairach and Tournoux atlas (1988) and then surface rendered using 3D stereotactic surface projections to demonstrate the topography of hypometabolism. Surface rendered reads were normalized

using a pons reference region, and compared to an age-stratified, normative reference database.

Statistical Parametric Mapping

Parametric analysis of FDG-uptake was also performed using voxel-level statistical parametric mapping (SPM5) by means of two-sample t-tests comparing each case against a control database of normalized and smoothed PET scans, comprising 112 scans (53 men and 59 women; mean age = 64.7 years; SD = 9.3 years) from the European Alzheimer's Disease Consortium and the San Raffaele Scientific Research Institute databases (Della Rosa *et al*., 2014). In brief, each 18F-FDG PET patient scan was warped to the standard MNI space using a new 18F-FDG PET aging and dementia-specific template for spatial normalization and subsequently smoothed with an isotropic 3D Gaussian kernel of 8 mm FWHM. Age was included as a covariate in the two-sample t-test design of SPM5and global normalization of voxel values used proportional scaling to a mean voxel value of 6.5mg/100 mL/min (Signorini *et al.,* 1999).

The comparison between each case and the control database yielded a contrast map testing for areas with relative decreases in metabolism (i.e. hypometabolism) compared to the control population

Significance values from the voxel-wise t-test were corrected for family-wise error over multiple comparisons at voxel level (threshold pFWE<0.05), and a cluster extent threshold of ≥100 voxels was additionally imposed.

Visual assessment of PET NEUROSTAT and SPM maps was undertaken for the following ROIs: frontal lobe, lateral temporal lobe, temporal pole (TP), hippocampus (Hc)/ medial temporal lobe (MTL), medial parietal lobe/ precuneus (Pc), lateral parietal lobe (LP), occipital lobe, anterior cingulate gyrus and posterior cingulate gyrus. Regional reads were binarized (0 = no detectable hypometabolism; 1 = detectable hypometabolism reported by at

least two raters); this choice reflected the manner in which parametric maps of subject-to-group comparisons are reported in clinical practice.

PET-MRI concordance

A linear weighted Cohen's kappa statistic (Cohen, 1960; Warrens, 2008) was used to provide an adaptable metric of the concordance of atrophy and hypometabolism given the requirement to compare diverse PET and MRI datasets. A 4x2 normalised weight matrix was applied in order to relate binarized (0-1) and scaled (0-3) scores consistently. Kappa is used in situations when an association is expected to exist in order to quantify the degree of agreement or concordance beyond that expected by chance. In these disorders atrophy and hypometabolism are known to be highly correlated in general (confirmed for these study data using Fisher's exact test with resultant $p < 0.001$ for all patient groups) and the kappa statistic is used to provide a measure of the strength of this concordance in any particular patient or group.

3.2.4 Results

Inter-rater reliability of atrophy and hypometabolism scores

According to Cohen's kappa (Cohen, 1960), the inter-rater reliability of qualitative atrophy ratings was 0.34 ($p < 0.001$; 95% CI: [0.24, 0.43]). According to Fleiss' kappa (Fleiss, 1971), the inter-rater reliability of qualitative hypometabolism ratings on uptake maps was 0.43 ($p < 0.001$; 95% CI: [0.41, 0.45]). For NEUROSTAT and SPM-based analysis, this increased to 0.53 ($p < 0.001$; 95% CI: [0.49, 0.57]) and 0.90 ($p < 0.001$; 95% CI: [0.86, 0.94]), respectively.

Typical Alzheimer's disease (AD)

MRI

Qualitative assessment revealed in all cases bilateral, and largely symmetrical, mild-moderate atrophy of the medial temporal lobe and temporal pole, with additional mild-moderate frontal atrophy and lateral parietal atrophy also observed (representative case in Figure 15, remaining cases and score plots in Figure 16). Cortical thickness measurements revealed additional lateral temporal atrophy in three cases, and atrophy of the precuneus and posterior cingulate gyrus in two cases.

FDG-PET

Qualitative visual FDG PET uptake reads revealed hypometabolism overall maximal in the lateral temporal and lateral parietal regions. NEUROSTAT and SPM-PET analyses both identified hypometabolism in the lateral parietal and, less markedly, in occipital regions, but additional hypometabolism in the precuneus and posterior cingulate gyrus was more consistently detected with SPM-PET.

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.17 (95% CI: [0.00, 0.42]). Hypometabolism overall was more widely distributed across the brain than atrophy, particularly in posterior cortical regions (Figure 15).

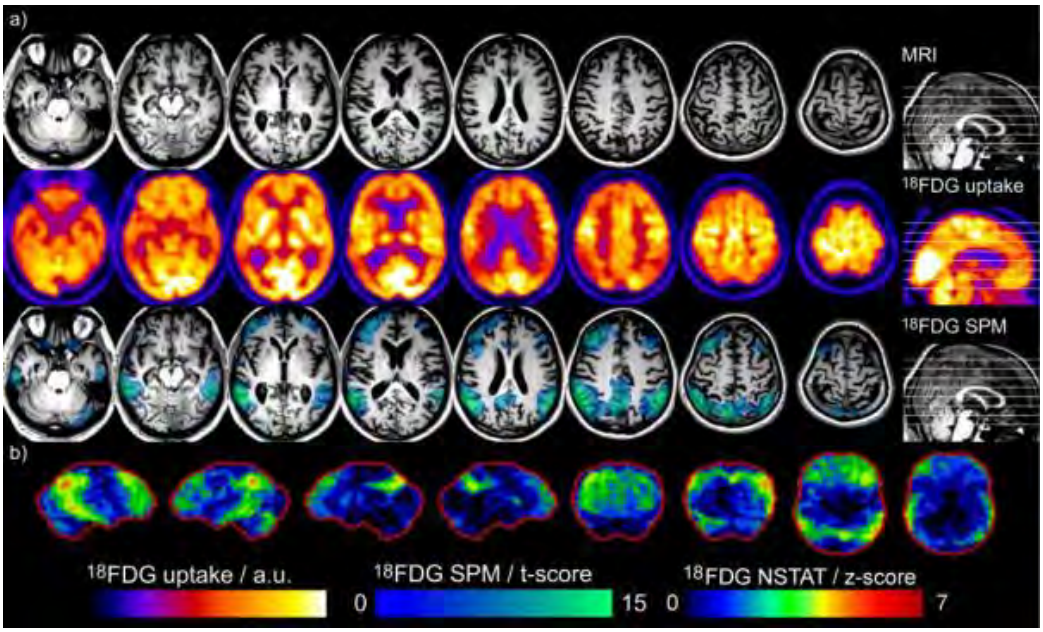

Figure 15. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 71-year old male with probable Alzheimer's disease (case no. 2). Moderate hippocampal atrophy is observed, alongside severe hypometabolism in retrosplenial, lateral parietal and dorsolateral prefrontal cortex. Medial temporal structures have normal metabolism on SPM maps, which, by comparison with uptake maps, emphasize the involvement of extra-temporal regions. NEUROSTAT projections reveal overall similar changes, but with limited anatomical specificity. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

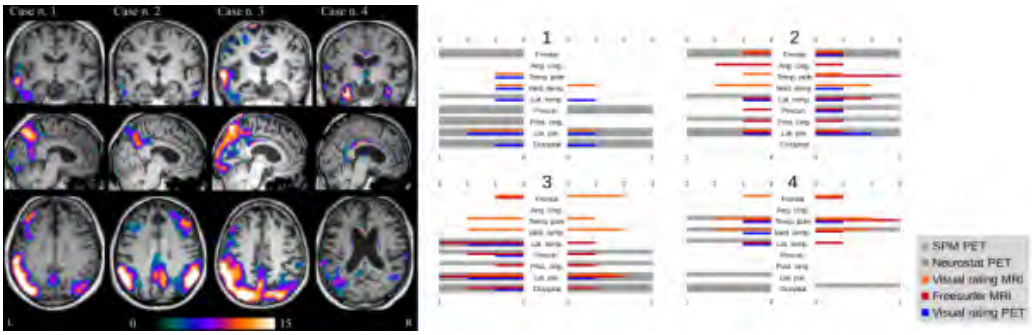

Figure 16. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in Alzheimer's disease. Hippocampal atrophy is associated with posterior cingulate and lateral temporo-parietal hypometabolism. The dorsolateral frontal and medial parietal hypometabolism observed in cases no. 1-3 contrast with the medial temporal hypometabolism observed in case no. 4. Occipital lobe hypometabolism appears decoupled from the severe precuneus hypometabolism found in cases no. 1, 2 and 3. For images and plots, left side corresponds to left hemisphere.

Posterior Cortical Atrophy (PCA)

MRI

Qualitative assessment revealed in all cases bilateral, symmetrical, moderate to severe atrophy of the lateral parietal cortex with additional, but less severe, atrophy of the frontal lobes (representative case in Figure 17, remaining cases and score plots in Figure 18). Cortical thickness measurements identified more extensive atrophy, maximal in parietal and occipital regions, but also involving the right temporal pole and lateral temporal regions bilaterally in three cases.

FDG-PET

In all cases qualitative FDG-PET uptake reads revealed hypometabolism primarily affecting the occipital and lateral parietal regions bilaterally, with less severe hypometabolism additionally noted particularly in the lateral temporal lobe. NEUROSTAT and SPM-PET analyses similarly identified predominant parieto-occipital hypometabolism but additionally detected changes not only in left frontal but also in the precuneus and posterior cingulate regions. A comparison of these two analyses revealed that SPM-PET identified changes in nearly all ROIs where hypometabolism was observed using NEUROSTAT, but detected hypometabolism in the lateral temporal lobe and precuneus more consistently.

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.49 (95% CI: [0.29, 0.61]). Overall, there was good concordance between atrophy and hypometabolism in the frontal as well as posterior cortical regions (Figure 15), however some discordance was evident in the temporal poles and medial temporal lobe, where mild-moderate atrophy was not always accompanied by hypometabolism.

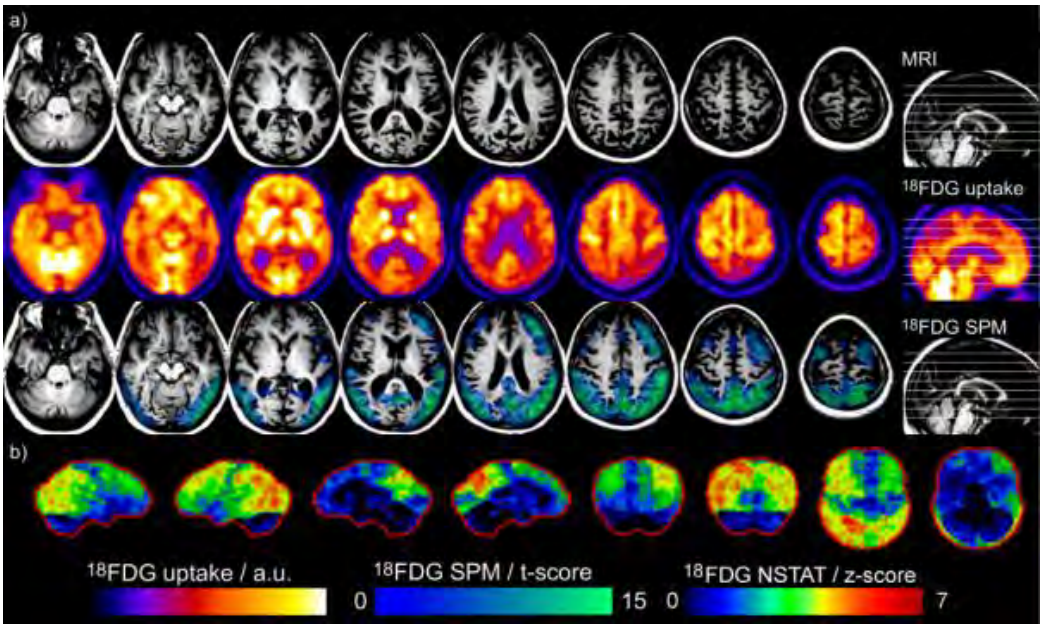

Figure 17. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 61-year-old female with posterior cortical atrophy (case no. 8). Severe parietal atrophy and hypometabolism are concurrently observed. PET uptake maps, SPM maps and NEUROSTAT projections additionally show hypometabolism in medial parietal, posterior cingulate, left dorsolateral prefrontal and superior temporal cortex. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

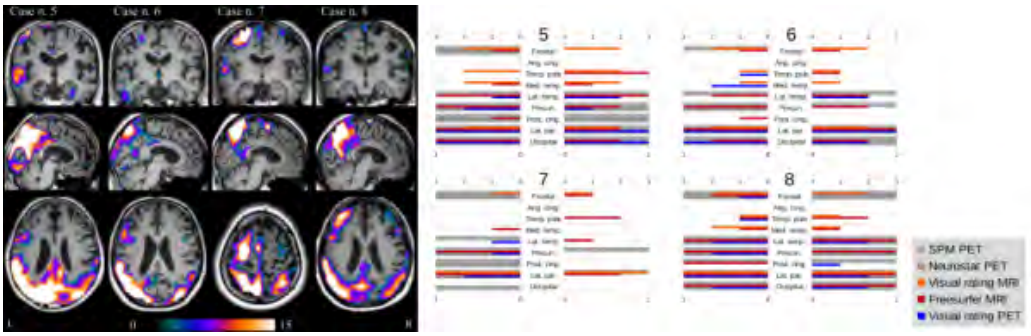

Figure 18. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in posterior cortical atrophy. Co-localised parietal atrophy and hypometabolism are observed, with additional hypometabolism in lateral temporal and dorsolateral frontal regions. Occipital hypometabolism is noted in cases with primary visual failure (cases no. 5, 6 and 8); by comparison, the case with biparietal syndrome (case no. 7) demonstrates particularly marked hypometabolism over both parietal lobes, extending to the left post-central gyrus and supplementary motor area. For images and plots, left side corresponds to left hemisphere.

Behavioural variant FTD

MRI

Qualitative assessment revealed mild-moderate frontal lobe atrophy in all cases and, albeit less strongly and consistently, additional lateral parietal lobe and temporal lobe (temporal pole and medial temporal lobe) atrophy (representative case in Figure 19, remaining cases and score plots in Figure 20). Compared to the qualitative reads, cortical thickness measurements revealed marked inter-individual differences in atrophy pattern; in two cases there was highly restricted or no atrophy measured, whereas in the remaining two cases atrophy was observed in the frontal regions with involvement of medial temporal or parietal regions.

FDG-PET

Qualitative PET uptake readings revealed hypometabolism primarily in the frontal lobes but with differing degrees of severity; no frontal hypometabolism was observed in one case (Case 12) whereas in another case (Case 11) moderate to severe hypometabolism was observed not only in the frontal lobes but also in lateral parietal regions. NEUROSTAT and SPM-PET analyses overall revealed significant changes in the frontal lobes and anterior cingulate gyri in all cases; in particular highlighting anterior cingulate involvement not detected visually in one case (Case 12) and diffuse parietal involvement in another (Case 11).

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.22 (95% CI: [-0.11, 0.47]). For this subgroup, the overlap appeared highly variable across individuals, as exemplified by the high co-localization of hypometabolism and cortical thinning in Case 11 and the observation of significant hypometabolism in multiple regions without corresponding atrophy in Case 12 (Figure 20).

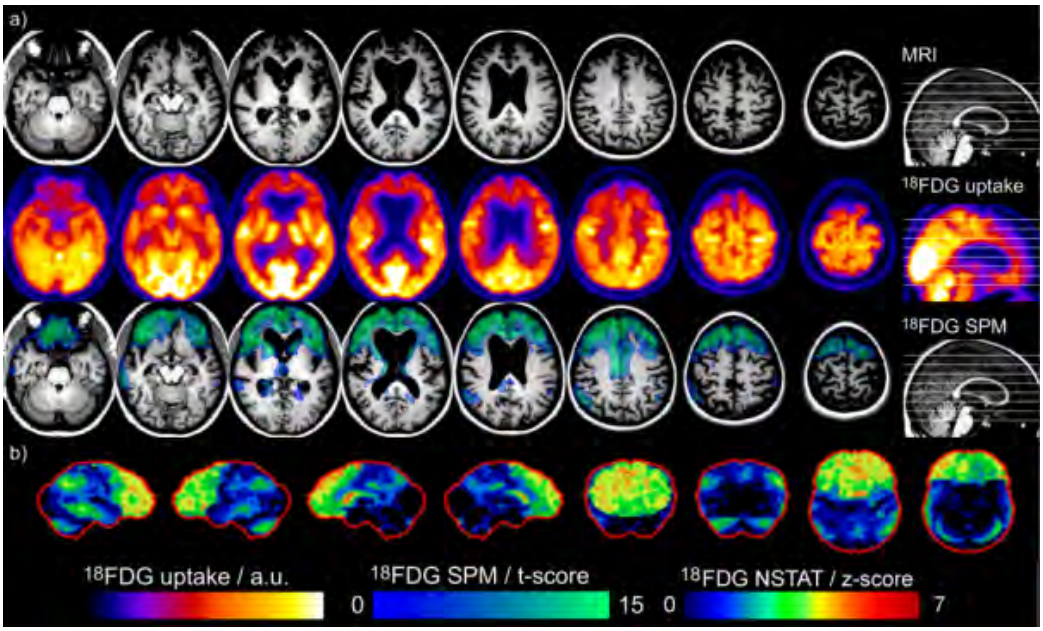

Figure 19. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 67-year-old female with probable behavioural variant fronto-temporal dementia (case no. 10). Medial frontal atrophy is observed with co-localised hypometabolism on PET uptake and SPM maps and NEUROSTAT projections. SPM maps and NEUROSTAT projections additionally demonstrate mild involvement of lateral parietal regions and caudate nuclei. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

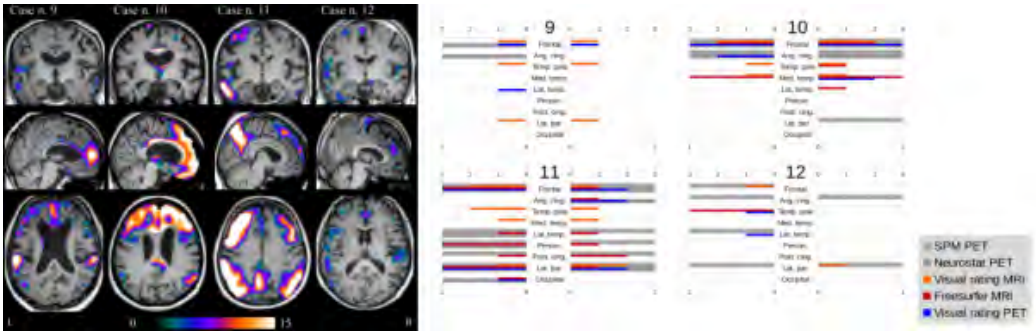

Figure 20. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in behavioural variant fronto-temporal dementia. Frontal atrophy is accompanied by medial frontal and parietal hypometabolism, however the topography of frontal lobe hypometabolism is distinct in each case. The anterior cingulate is involved in cases no.9, 10 and 12, whereas this is less evident in case no. 11, for which severe lateral fronto-parietal hypometabolism is observed, with marked involvement of the precuneus and posterior cingulate gyrus. For images and plots, left side corresponds to left hemisphere.

Nonfluent/agrammatic variant of primary progressive aphasia

MRI

Qualitative assessment revealed in all cases bilateral, mild-moderate atrophy of the frontal and parietal regions, with additional atrophy of the medial temporal pole observed in two cases (representative case in Figure 21, remaining cases and score plots in Figure 22). Cortical thickness measurements revealed marked inter-individual differences, with lateral temporal lobe (bilaterally), left precuneus and left lateral parietal atrophy jointly observed in 2/4 cases and much more limited involvement of these regions in the other cases.

FDG-PET

Qualitative PET reads were characterised by overall predominantly left-sided hypometabolism that was maximal in the perisylvian regions (lateral temporal, lateral parietal and inferior frontal cortex) with additional right parietal and temporal hypometabolism less consistently observed. NEUROSTAT and SPM-PET analyses revealed a similar but more extended pattern of hypometabolism, both in the left hemisphere (e.g., Case 15) and in terms of right hemispheric involvement (e.g., Case 16).

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.13 (95% CI: [0.00, 0.25]). Overall, hypometabolism was more extended than atrophy: notably, in the left frontal lobe and parietal regions hypometabolism was consistently observed without corresponding atrophy (Figure 22).

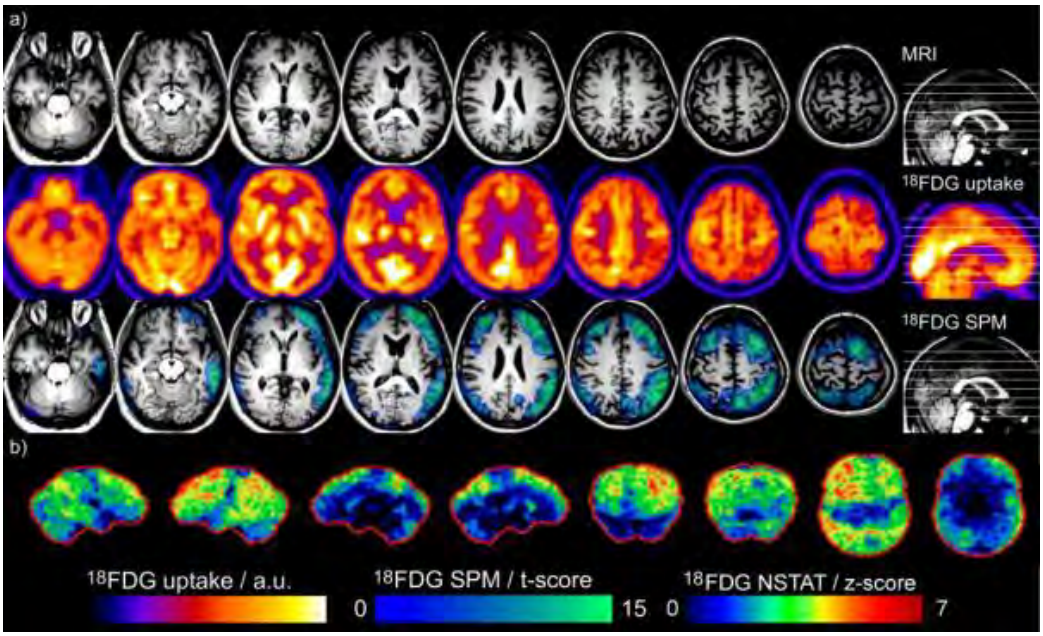

Figure 21. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 63-year-old male with progressive non-fluent aphasia (case no. 16). Mild atrophy of the left Sylvian fissure is observed, while the SPM PET maps reveal hypometabolism in lateral temporo-parietal and frontal regions predominantly on the left. Uptake maps and NEUROSTAT projections show comparable effects. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

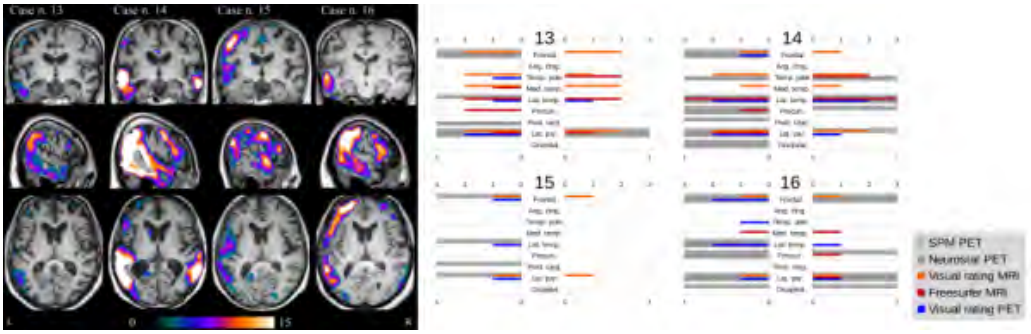

Figure 22. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in progressive non-fluent aphasia. Left perisylvian atrophy of variable severity is accompanied by lateral frontal and lateral temporo-parietal hypometabolism, which were particularly marked in cases 14-16. For images and plots, left side corresponds to left hemisphere.

Semantic variant of primary progressive aphasia

MRI

Qualitative assessment revealed in all cases moderate-severe bilateral medial temporal and temporal pole atrophy with milder degrees of atrophy observed in frontal and parietal regions (representative case in Figure 23, remaining cases and score plots in Figure 24). Cortical thickness measurements identified more extensive atrophy, with asymmetrical, predominantly left sided temporal involvement except in one case that was relatively symmetrical (Case 20), with additional changes involving the medial parietal and the anterior and posterior cingulate regions observed in that case.

FDG-PET

Qualitative FDG-PET uptake evaluation identified diffusely left sided hypometabolism involving the medial temporal, lateral temporal and lateral parietal lobes; the distribution of hypometabolism was less asymmetrical in one case (Case 20). NEUROSTAT and SPM-PET analyses confirmed diffuse hypometabolism in the left hemisphere, particularly revealing additional precuneus and posterior cingulate involvement. Furthermore, SPM-PET also identified contralateral frontal, temporal and parietal changes not visible to qualitative and NEUROSTAT evaluation in three cases.

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.35 (95% CI: [0.19, 0.44]). Overall, there was high concordance between atrophy and hypometabolism in left temporal regions. However, discordance was evident particularly in the left lateral parietal lobe and left anterior cingulate gyrus, where hypometabolism was observed without corresponding atrophy in 3/4 cases (Figure 24).

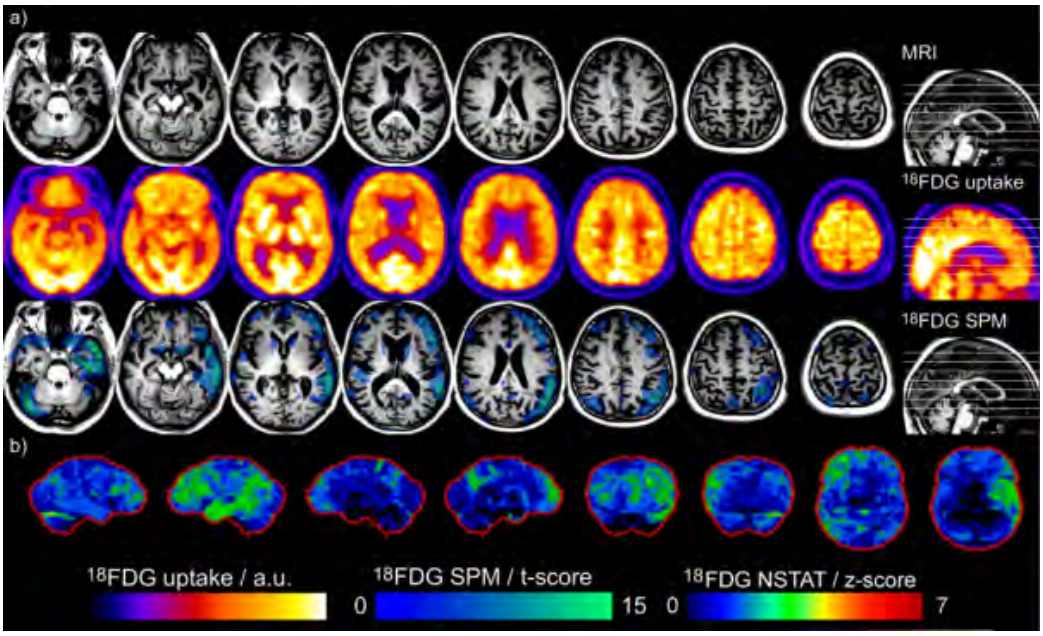

Figure 23. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 72-year-old male with semantic variant of primary progressive aphasia (case no. 17). Bilateral antero-medial temporal lobe and dorsolateral frontal atrophy are observed, predominantly on the left. The corresponding SPM PET maps highlight predominantly left-sided hypometabolism in medial and lateral temporal, inferior parietal and medial frontal regions with additional involvement of the left ventral tegmentum and caudate nuclei. This diffuse pattern of hypometabolism is not observed on uncorrected uptake maps and NEUROSTAT projections, however the changes in the temporal regions are observed. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

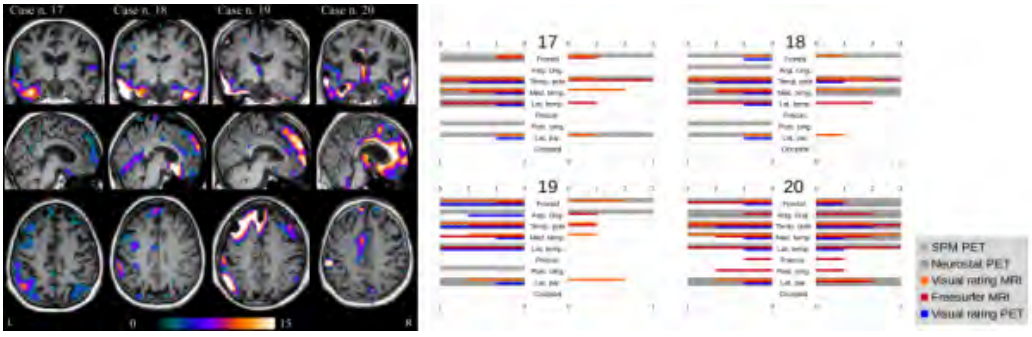

Figure 24. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in semantic variant of primary progressive aphasia. Left temporal atrophy and hypometabolism are consistently co-localized, but individual differences are observed especially with regards to anterior cingulate and medial frontal hypometabolism. Parietal atrophy and hypometabolism are predominantly observed in the left hemisphere. For images and plots, left side corresponds to left hemisphere.

Right temporal variant FTD

MRI

Qualitative assessment revealed in all cases moderate-severe bilateral medial temporal and temporal pole atrophy with milder degrees of atrophy observed in the frontal and parietal regions bilaterally (representative case in Figure 25, remaining cases and score plots in Figure 26). Cortical thickness measurements identified more extensive atrophy, with asymmetrical, predominantly right-sided, temporal pole and lateral temporal lobe atrophy in all cases and asymmetrical, predominantly right-sided, parietal lobe atrophy in 2 cases.

FDG-PET

Qualitative PET assessment identified right-sided temporal pole and lateral temporal hypometabolism with additional involvement of medial temporal lobe, lateral parietal and left temporal pole hypometabolism that was observed in three cases. NEUROSTAT and SPM-PET analyses identified bilateral hypometabolism of the temporal poles and lateral parietal lobes, right frontal lobe and left medial temporal region. When compared with the NEUROSTAT reads, widespread additional hypometabolism was observed with SPM-PET, encompassing the anterior cingulate gyrus bilaterally, and the right medial temporal regions in two cases.

PET-MRI concordance

The measured weighted kappa for cortical thickness and hypometabolism assessed via SPM PET was 0.35 (95% CI: [0.23, 0.45]). As anticipated given the focal nature of the changes, there was concordance between atrophy and hypometabolism bilaterally in the right lateral temporal lobe and temporal pole (Figure 26). Discordance was most evident in the frontal regions and anterior cingulate gyrus where hypometabolism without atrophy was observed.

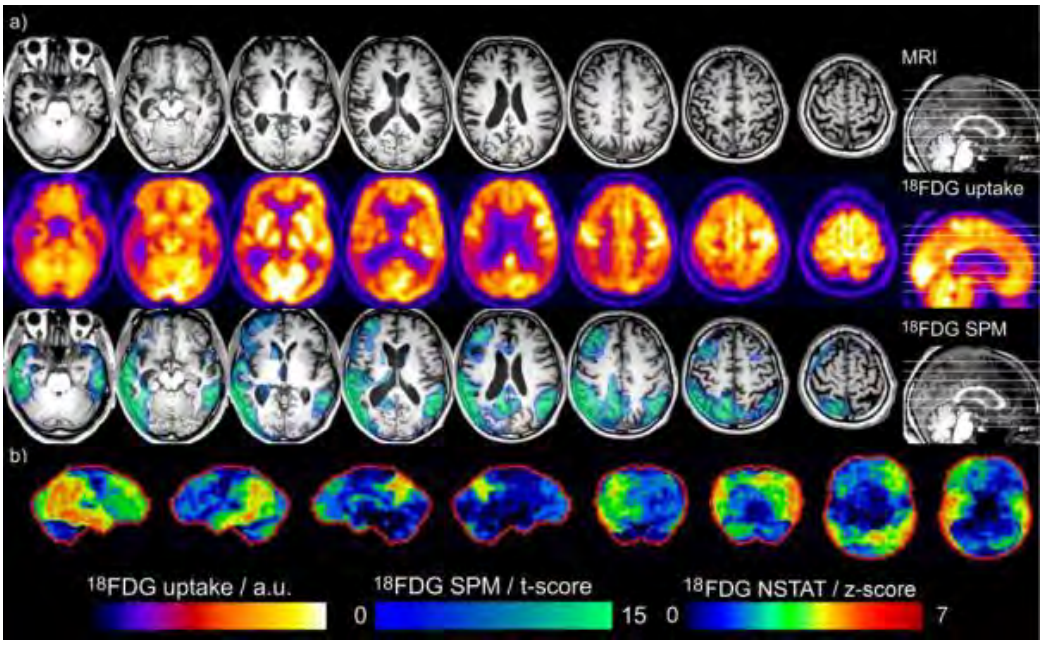

Figure 25. Combined T1-MRI, PET uptake and SPM maps (a) and NEUROSTAT projections (b) from a 57-year-old male with right temporal variant fronto-temporal dementia (case no. 23). Focal right medial temporal atrophy and more weakly dorsolateral prefrontal atrophy are observed. SPM PET maps highlight severe inferior-lateral temporal and parietal hypometabolism, with moderate changes also in right precuneus and cingulate cortex. The corresponding uptake maps and NEUROSTAT projections highlight similar changes but are less definitive in terms of localization of cingulate and frontal changes. Sections in (a) are shown in radiological convention (left side corresponds to right hemisphere), whereas NEUROSTAT projections (b) are shown in neurological convention (left side corresponds to left hemisphere).

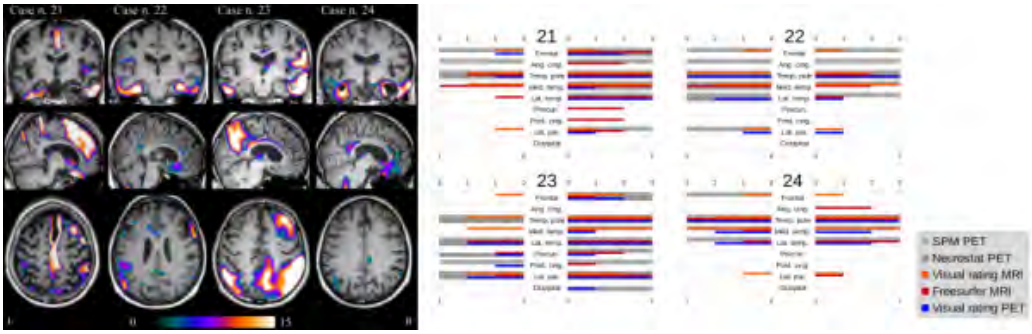

Figure 26. Combined T1-MRI, PET uptake and SPM maps (left) and atrophy and hypometabolism ratings (right) in right temporal variant frontotemporal dementia. There is consistent co-localisation of atrophy and hypometabolism in the antero-medial temporal lobes and limbic cortex, with individual differences observed in terms of frontal lobe hypometabolism. The medial frontal and anterior cingulate hypometabolism observed in cases no. 21, 22 and 24 is contrast with the involvement of the dorsolateral frontal lobe, precuneus and posterior cingulate cortex in case no. 23. For images and plots, left side corresponds to left hemisphere.

3.2.5 Discussion

Even in this small cohort, analysis of simultaneously acquired PET and MRI revealed marked differences in the degree of topographic overlap, or concordance, of atrophy observed on MRI and hypometabolism identified using FDG-PET in patients with syndromic variants of Alzheimer's disease (AD) and frontotemporal dementia (FTD). Concordance between cortical thickness, as measured on MRI using Freesurfer, and hypometabolism as identified using a novel SPM-based technique for quantitative PET analysis (Signorini *et al*., 1999; Della Rosa *et al*., 2014) was measured using a weighted Cohen's kappa statistic, to permit the comparison of graded outputs (Freesurfer) with a binary read (SPM-PET). There was more than a threefold difference in concordance between the various AD and FTD syndromes, with kappa scores ranging from 0.13 in patients with nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) to 0.49 in patients with the posterior cortical variant of AD (PCA). The range of concordance varied also within each group of patients with different syndromes, as shown by comparing the confidence interval of the kappa scores; confidence intervals of 0-0.25 for the group of patients with nfvPPA group, indicative of greater within-group heterogeneity, contrasted with scores of 0.29-0.61 for the PCA patient group. While the limited sample size dictates that these results should only be interpreted as preliminary evidence, these data do suggest that there is significant heterogeneity in hypometabolism-atrophy coupling across the disease subtypes, which is worthy of further investigation using the methodology that we have outlined.

Furthermore, this study at single-subject level has also shown that determination of the extent of atrophy and hypometabolism in these disorders is dependent on the choice of analysis method. For MRI, quantitative measures of cortical thickness typically revealed more widespread cortical change than was detected on qualitative visual inspection, and similarly the two quantitative PET analysis methods (the

atlas-based NEUROSTAT and the novel SPM-based technique) identified more widespread hypometabolism than visual inspection of FDG uptake distributions. A direct comparison of the two quantitative PET methods revealed that both methods detected hypometabolism in 108 regions of interest (ROIs), out of the 432 ROIs evaluated in all patients, but that the SPM-PET alone detected change in a further 88 ROIs, representing an 81% increase. These 88 ROIs were spread across all patients and all disease groups, and in all lobes of the brain, rather than being evident in selected cases or brain regions only, suggesting that the additionally detected hypometabolism is indicative of a generally higher sensitivity of the SPM-PET technique rather than due to specific pathological or anatomical considerations. This in turn may relate to the methodological differences between NEUROSTAT and SPM-PET; while the former is based on projections from an atlas (Talairach and Tournoux 1988), the latter involves elastic normalization to a tailored control template, followed by voxel-level inference, with attendant increase in spatial specificity (Della Rosa *et al*., 2014; Perani *et al*., 2014). Inter-rater reliability was also superior for quantitative PET techniques, with inter-rater reliability indices of 0.53 and 0.9 for NEUROSTAT and SPM-PET respectively comparing with a reliability index of 0.43 for visual PET reads.

Atrophy and hypometabolism reflect different aspects of pathophysiology and analysis of simultaneously acquired PET and MRI data provides an opportunity to compare and contrast patterns of brain involvement at different “severity stages” in the disease process. In keeping with many previous studies, this extended case series has shown that there is divergence in the patterns of atrophy and hypometabolism, with the latter typically exceeding the former in terms of topographical extent. The occurrence in certain brain regions of hypometabolism without corresponding atrophy is consistent with the notion that in these neurodegenerative diseases, impairment of synaptic and neuronal function precedes neuronal loss and may be indicative of a stage of pathology of sufficient severity to be manifest as altered metabolism, as marker of neuronal injury, but insufficiently advanced to result in overt

regional atrophy. In AD, this has been clearly documented (Chetelat *et al*., 2008; Bateman *et al*., 2012) supporting also the proposed order of neuroimaging changes in the AD cascade model (Jack *et al*., 2010; Jack *et al.,* 2013). In addition, it has been shown that a significant fraction of cortical hypometabolism is due to mechanisms other than local atrophy, such as disconnection effects (Villain *et al*., 2008; Perani *et al.,* 2014). Thus, disconnection also plays a part in the observed hypometabolism. While this may serve to explain the differing patterns of atrophy and hypometabolism, it is insufficient to explain the between-group differences in the concordance of these imaging changes. Several alternative explanations therefore need to be considered. First of all, the heterogeneous concordances may represent differences among these syndromic variants in terms of the temporal relationship between the onset of hypometabolism and subsequently of atrophy, and in the extent of functional disconnection associated with each disorder. However, it is probable that at least part of the explanation relates to the way in which these syndromes are diagnosed clinically. Concordance was greatest in patients with PCA (kappa score 0.495) and in patients with right temporal variant FTD (rtvFTD; kappa 0.347), but in both instances the presence of imaging changes is not just diagnostically supportive but the defining characteristic for clinical diagnosis. By contrast, patients with typical AD, in whom the kappa score was 0.167, were diagnosed according to clinical (not research) criteria (McKhann *et al*., 2011), which do not stipulate the requirement for imaging changes. By the same token, there was a near three-fold difference in concordance between the two variants of primary progressive aphasia (PPA), with kappa scores of 0.353 and 0.132 for semantic variant PPA (svPPA) and nonfluent/agrammatic PPA (nfvPPA) respectively. While PPA overall is diagnosed on clinical grounds (Mesulam, 2001), a more recently published classification of PPA variants (Gorno-Tempini *et al.,* 2011) outlines criteria for the diagnosis of “imaging-supported” svPPA and nfvPPA. However the striking disparity in concordance of imaging changes associated with these two PPA subtypes, observable even with n=4 group sizes, indicates that future revisions of PPA diagnostic criteria may need to take into account the heterogeneity of functional and structural imaging changes. It should be underlined that potential issues of circularity

related to the inclusion of imaging features in the diagnostic criteria were mitigated by the fact that concordance of MRI and PET findings was not considered during diagnosis, and by the fact that all raters were blinded to clinical diagnosis. At the same time, the different inter-individual variability observed across the syndromic variants cannot be explained solely by the inclusion of imaging in the diagnostic criteria for some variants and not others.

Within each patient group there was marked inter-individual variability in patterns of atrophy and hypometabolism, and in their concordance, unrelated to differences in demographics, age or disease severity as determined by the Clinical Dementia Rating. The demonstration of such within-group differences, albeit limited in statistical robustness by small sample size, is particularly relevant given the tendency to report multimodal imaging changes in AD or FTD variants at a group level (Lehmann *et al*., 2013). In FTD different molecular pathologies have been found to be associated with different patterns of cerebral hypometabolism and one possible explanation for this within-group heterogeneity may therefore be that of differences in underlying molecular pathology (Josephs *et al*., 2010; Teune *et al*., 2010). However, in the absence of genetic or immunohistochemical confirmation such an explanation is necessarily speculative. In this context, the finding of similar heterogeneity in AD (in patients considered to have the same molecular pathology) and FTD (in patients with potentially diverse pathologies) suggest that additional factors, such as environmental, genetic or epigenetic modifiers, may influence the imaging phenotype (Galton *et al*., 2000; Lehmann *et al*., 2013).

The current study has limitations that need to be acknowledged. First, there were four patients in each disease subgroup, and these small sample sizes precluded generalization through statistically robust group-level conclusions. Instead it is proposed that this study be considered as an extended case

series, the findings from which will inform the hypotheses and design of future large scale multimodal imaging studies, interest in which will be heightened by the more widespread availability of integrated PET-MRI scanners of the kind used in this study. Second, any analyses of PET data in dementia studies need to consider potential confounds relating to concomitant atrophy and to the partial volume effect although with regard to the latter previous PET studies in AD have demonstrated that the observation of reduced FDG uptake in crucial brain regions remained robust independent of any partial volume correction (Samuraki *et al.,* 2007). Comparison of MRI and PET data also needed to take into account the different approaches to scoring change. In accordance with clinical practice qualitative assessments of MRI and PET employed a severity scale ranging from 0 (absent) to 3 (severe); in contrast NEUROSTAT- and SPM-PET outputs are in the form of binary reads (absent or present). For this reason concordance of atrophy and hypometabolism was determined using a weighted Cohen's kappa, which unlike other measures of similarity such as the Jaccard index, can be scaled to deal with comparison between binary and many-valued scores.

Finally, the control groups were different for SPM-PET, NEUROSTAT and FreeSurfer. This is a reflection of the different image analysis methodologies; NEUROSTAT has a standard set of controls which is nearly always utilized with the tool, whereas for SPM-PET patient data were compared against an extensive, locally acquired, template and controls dataset (Della Rosa *et al*., 2014; Perani *et al*., 2014). However an equivalent dataset was not available for MRI and so MRI control data were obtained from a separate control group who were scanned on the study scanner as the study patients.

Conclusion

Two main findings arose from this proof-of-concept study. The concordance of atrophy and hypometabolism appears to differ markedly across syndromic variants of AD and FTD. This heterogeneity may reflect not only differing underlying molecular pathologies but also operational differences in the criteria used to diagnose these syndromes. Although inherently limited by sample size, the tentative demonstration of additional heterogeneity within patient groups has potential implications for the current practice of describing the imaging correlates of AD and FTD at group level.

Quantitative methods identified more widespread atrophy and hypometabolism than qualitative visual ratings and for the PET analyses in single individuals, the most extensive change was detected using a novel SPM-based technique (Perani *et al*., 2014). These observations, in combination with their superior inter-rater reliability, if confirmed in future work on larger populations can have implications for the implementation of quantitative methodologies in clinical practice, and through use of integrated PET/MRI scanners.

4. Discussion

4.1 Conclusion

The unifying theme within the body of work outlined in this thesis is the determination of altered brain function to differentiate neurodegenerative disorders, with a view to improving diagnosis. Hippocampal function, tested behaviourally using the 4 Mountains Test (4MT) of allocentric spatial memory, is evaluated in patients with mild cognitive impairment (MCI) and the ability of this test to discriminate effectively between MCI patients with and without biomarker evidence of underlying AD proves the concept that this theory-driven approach, founded on hippocampal place cell studies, can be applied to the diagnosis of pre-dementia AD. These findings are supplemented by additional preliminary work assessing the specificity of this test for AD. The impact of this work is considerable. As well as bridging the translational divide to cellular neuroscience, the brevity and ease of administration of the 4MT favours its future usage in clinical practice, where there is an urgent unmet need for simple accurate tests of pre-dementia AD, a need not met either by the insensitive MMSE or invasive and expensive biomarker tests (ligand-PET or CSF studies).

This behavioural work is complemented by a study utilising PET scanning to determine differences in the patterns of cerebral hypometabolism in syndromic variants of AD and FTD. The advent of integrated PET-MRI scanners provided the opportunity to compare cerebral signatures of hypometabolism and atrophy, with results showing marked differences in the within- and between-group concordance of these imaging changes, highlighted the potential added diagnostic value of functional imaging above and beyond structural MRI. As a corollary, this study also highlighted the importance of quantitative MRI and PET analysis for the detection of

disease-related changes, and this has major implications given the current clinical practice of qualitative reporting of scan changes.

In conclusion, the findings outlined in this dissertation demonstrate the importance of tests of brain function for the diagnosis of neurodegenerative disease, both in terms of early diagnosis and diagnostic differentiation.

4.2 Future work

Further follow up of our MCI cohort is important to establish the relationship between 4MT performance, CSF biomarker profile and ultimate conversion to AD or non-AD dementia. Given its ease of use, and the findings suggesting that it detects AD hippocampal damage specifically, it would be ideal to include in larger scale longitudinal studies of asymptomatic patients at risk for AD dementia, such as ApoE4 positive individuals or presymptomatic members of families with autosomal dominant AD. It should also be applied in longitudinal studies in MCI, as well as in people with subjective cognitive impairment, to determine the ability to predict AD dementia in these symptomatic ‘at-risk’ groups. Future specificity work should focus on a larger sample of patients with FTD and also incorporate patients with other neurodegenerative syndromes.

Future PET-MRI work should attempt to create normative imaging libraries to facilitate detection of disease effect. Larger scale studies in confirmed genetic variants of FTD would be of great value in determining the association between specific FTD molecular pathologies and regional alterations of brain structure and function, while application to presymptomatic genetic FTD cohort in longitudinal studies will help in the phenotyping of FTD from its earliest stages.

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APPENDIX: Publications

HIPPOCAMPUS 25:939–951 (2015)

Diagnostic Differentiation of Mild Cognitive Impairment Due to Alzheimer's Disease Using a Hippocampus-Dependent Test of Spatial Memory

Kuven Moodley,[1] Ludovico Minati,[1,2] Valeria Contarino,[3] Sara Prioni,[4] Ruth Wood,[1] Rebecca Cooper,[5] Ludovico D'Incerti,[3] Fabrizio Tagliavini,[4] and Dennis Chan[1]*

ABSTRACT: The hippocampus is one of the earliest brain regions affected in Alzheimer's disease (AD) and tests of hippocampal function have the potential to detect AD in its earliest stages. Given that the hippocampus is critically involved in allocentric spatial memory, this study applied a short test of spatial memory, the 4 Mountains Test (4MT), to determine whether test performance can differentiate mild cognitive impairment (MCI) patients with and without CSF biomarker evidence of underlying AD and whether the test can distinguish patients with MCI and mild AD dementia when applied in different cultural settings. Healthy controls (HC), patients with MCI, and mild AD dementia were recruited from study sites in UK and Italy. Study numbers were: HC (UK 20, Italy 10), MCI (UK 21, Italy 14), and AD (UK 11, Italy 9). Nineteen UK MCI patients were grouped into CSF biomarker-positive (MCI+, $n = 10$) and biomarker-negative (MCI–, $n = 9$) subgroups. Behavioral data were correlated with hippocampal volume and cortical thickness of the precuneus and posterior cingulate gyrus. Spatial memory was impaired in both UK and Italy MCI and AD patients. Test performance additionally differentiated between MCI+ and MCI– subgroups ($P = 0.001$). A 4MT score of $\leq$8/15 was associated with 100% sensitivity and 90% specificity for detection of early AD (MCI+ and mild AD dementia) in the UK population, and with 100% sensitivity and 50% specificity for detection of MCI and AD in the Italy sample. 4MT performance correlated with hippocampal volume in the UK population and cortical thickness of the precuneus in both study populations. In conclusion, performance on a hippocampus-sensitive test of spatial memory differentiates MCI due to AD with high diagnostic sensitivity and specificity. The observation that similar diagnostic sensitivity was obtained in two separate study populations, allied to the scalability and usability of the test in community memory clinics, supports future application of the 4MT in the diagnosis of pre-dementia due to AD.

KEY WORDS: Alzheimer's disease; mild cognitive impairment; spatial memory; hippocampus; precuneus

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INTRODUCTION

Alzheimer's disease (AD) is the commonest cause of dementia and its management represents one of the highest priorities for health systems worldwide. It is now recognized that the AD pathological process begins many years before the onset of dementia and this is reflected in the replacement of the 1984 NINDS-ADRDA diagnostic criteria for AD by new criteria that encompass the concept of prodromal AD (Dubois et al., 2010) and that of mild cognitive impairment (MCI) as a pre-dementia stage of AD (Albert et al., 2011). However, MCI due to underlying AD may be clinically indistinguishable from MCI due to other causes, including non-neurodegenerative disorders such as anxiety. Furthermore, memory tests commonly used in clinical psychometric testing, such as the Rey Auditory Verbal Learning Test (RAVLT), the Logical Memory test of the Wechsler Memory Scale, or the various versions of the paired associate learning test (PAL) (Wechsler, 1945) lack diagnostic specificity for AD (Fowler et al., 2002).

Differentiation of MCI due to AD has major prognostic implications. However, while testing for AD biomarkers, in the form of amyloid-PET scanning or CSF studies of amyloid and tau, has discriminatory value their usage in routine clinical diagnostic practice is limited by their invasive nature, high cost, and restricted availability, all of which preclude their application to the wider population of patients with MCI that are diagnostic not in university hospitals but in community clinics.

An alternative strategy for identification of MCI due to AD involves the use of a theory-driven approach based on the knowledge that the hippocampus and related medial temporal lobe structures are affected from the earliest stages of AD. Evidence that the hippocampus is critically involved in spatial memory originates from the initial demonstration of place-

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Simultaneous PET-MRI Studies of the Concordance of Atrophy and Hypometabolism in Syndromic Variants of Alzheimer's Disease and Frontotemporal Dementia: An Extended Case Series

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Abstract.
Background: Simultaneous PET-MRI is used to compare patterns of cerebral hypometabolism and atrophy in six different dementia syndromes.
Objectives: The primary objective was to conduct an initial exploratory study regarding the concordance of atrophy and hypometabolism in syndromic variants of Alzheimer's disease (AD) and frontotemporal dementia (FTD). The secondary objective was to determine the effect of image analysis methods on determination of atrophy and hypometabolism.
Method: PET and MRI data were acquired simultaneously on 24 subjects with six variants of AD and FTD ($n = 4$ per group). Atrophy was rated visually and also quantified with measures of cortical thickness. Hypometabolism was rated visually and also quantified using atlas- and SPM-based approaches. Concordance was measured using weighted Cohen's kappa.
Results: Atrophy-hypometabolism concordance differed markedly between patient groups; kappa scores ranged from 0.13 (nonfluent/agrammatic variant of primary progressive aphasia, nfvPPA) to 0.49 (posterior cortical variant of AD, PCA). Heterogeneity was also observed within groups; the confidence intervals of kappa scores ranging from 0–0.25 for PCA to 0.29–0.61 for nfvPPA. More widespread MRI and PET changes were identified using quantitative methods than on visual rating.

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IMAGE OF THE MONTH

Simultaneous PET/MRI in frontotemporal dementia

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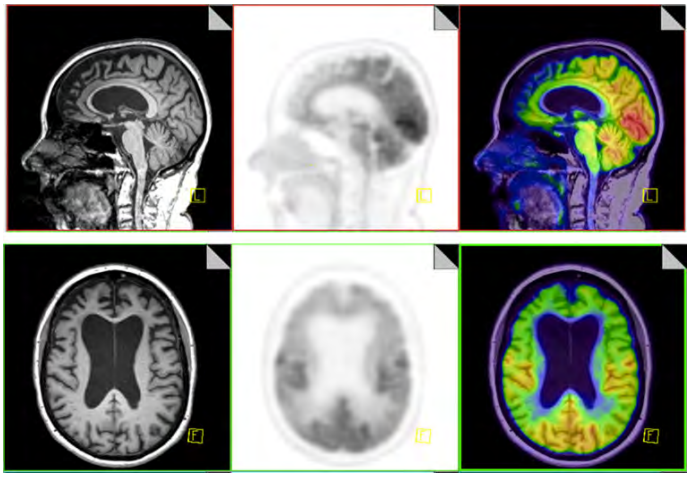
A 64-year-old woman presented with a 3-year history of apathy, emotional blunting and hyperorality. Initial MRI and neuropsychometric data were consistent with a diagnosis of behavioural variant frontotemporal dementia (bv-FTD) [1]. The images presented are sagittal (top) and axial (bottom) views of 3-T MRI and FDG PET scans acquired simultaneously on an integrated PET/MRI scanner. The combined images show colocalized atrophy and hypometabolism in the frontal lobe (top right) as well as parietal hypometabolism without atrophy (bottom right), possibly reflecting disruption of the frontoparietal connections in bv-FTD.



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