TESTING THE ADDED VALUE OF DETAILED NEUROPSYCHOLOGICAL ASSESSMENT IN THE DIAGNOSIS AND EVALUATION OF TREATMENT RESPONSE IN DEMENTIA

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***To Luke, with love***

***Without you, life would be very boring.***

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**Abstract**

The incidence of Alzheimer’s Disease (AD), the most common cause of dementia, has been increasing due to the ageing population. Therefore, the need for diagnosis early in the disease course, as well as correct diagnosis is especially important, increasingly so in an age whereby therapeutic interventions are becoming readily available. An important issue is being able to distinguish AD from the effects of normal ageing, and even more so at the Mild Cognitive Impairment (MCI) stage, and also from other causes of dementia.

The main aim of this thesis was to test the value of a comprehensive battery of neuropsychological tests in early and differential diagnosis of the dementias, particularly AD. Data from a range of patient groups were used in these studies to investigate which test, or range of tests, best distinguishes each patient and control group. Performance patterns can then be created and utilised prospectively to predict when an individual is experiencing abnormal decline, and the cause of this decline. In particular, the semantic fluency task was investigated for its differential diagnosis properties. Furthermore, we investigated the optimal time point for prescribing AD patients therapeutic intervention.

In the studies throughout this thesis, it is reported that differential diagnosis can be successfully achieved using a range of neuropsychological tests. Particularly, the semantic fluency task and lexico-semantic analysis is useful at distinguishing normal ageing from that seen in both MCI and AD. Furthermore, delayed memory, episodic memory and visuospatial tests are useful at differentiating FTD with AD patients. Lastly, we argue that optimal time of treatment in AD is in the mild stages of the disease, utilising a new scoring method that gives an individual response evaluation.

Ultimately, successful differential diagnosis of the dementias as well as normal ageing can be achieved clinically by establishing performance profiles on neuropsychological tests.

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# Chapter 1: Alzheimer’s Disease and the dementias

## Dementia

Dementia is a term used to describe abnormal cognitive, structural and chemical changes within the brain, characterised by a reduction in the level of cognitive functioning, and is caused by a range of diseases that occur most often in old age. The most common cause of dementia is Alzheimer’s Disease (AD) ([Knapp, Prince et al. 2007](#_ENREF_246)), which is described as a progressive degenerative neurological disease with characteristic symptoms of memory loss. Other causes of dementia include frontotemporal dementia (FTD), vascular dementia (VaD), and Lewy Body Dementia (LBD), all of which are caused by diverse underlying pathologies and which present themselves behaviourally in different ways. A recent report by the Alzheimer’s Society ([2012](#_ENREF_22)) explored the prevalence of dementia in the UK, and determined that over 800,000 people are living with some form of dementia, showing a notable increase from the 2007 figure of 700,000 individuals ([Knapp, Prince et al. 2007](#_ENREF_246)), while Knapp and colleagues ([2007](#_ENREF_246)) have previously reported that Alzheimer’s Disease, the leading cause of dementia, accounts for 62% of dementia patients, with vascular factors accounting for 17%, and frontotemporal degeneration accounting for 2% of dementia in the population.

### Economic Impact

A recent report by the Health Economics Research Centre at the University of Oxford for Alzheimer’s Research UK (ARUK – formerly Alzheimer’s Research Trust (ART)) has released up-to-date figures in terms of the cost of dementia to the UK, which it then compared to other serious life threatening diseases such as cancer ([Luengo-Fernandez, Leal et al. 2010](#_ENREF_279)). With over 800,000 individuals in the UK living with a form of dementia ([AS 2012](#_ENREF_22)), economically the impact of dementia is huge, and was estimated to cost £23 billion per year ([Luengo-Fernandez, Leal et al. 2010](#_ENREF_279); [AS 2012](#_ENREF_22)), with every single dementia patient costing the UK economy almost £28,000 per year. Comparing this to cancer, a cancer patient costs the UK just £5,999 per year, totalling £12 billion overall. Nevertheless, when it comes to funding for the two diseases, it is noted that cancer receives £590 million towards research per year, with dementia research only receiving £50 million ([Luengo-Fernandez, Leal et al. 2010](#_ENREF_279)). Due to limitations in funding available for research into dementia, as well as having very few specialised memory clinics throughout the UK, and also the lack of willingness and ability of a General Practitioner (GP) to make a diagnosis of dementia, a proportion of individuals living with dementia are not being diagnosed. In fact, it is estimated that only a third of patients who have dementia actually receive a diagnosis ([Knapp, Prince et al. 2007](#_ENREF_246)), with the Alzheimer’s Society suggesting that a proportion of patients are waiting up to 5 years to receive a diagnosis, while over 30% of patients report encountering problems when getting a diagnosis ([AS 2012](#_ENREF_22)). Furthermore, an international comparison report showed how GPs within the UK were more than 50% less likely to prescribe a patient with dementia pharmacological treatment compared to other countries within Europe ([Great Britain. National Audit Office 2007](#_ENREF_182)). The ability of the GP to make a diagnosis has especially come under fire when looking into the misdiagnosis of dementia, and the Alzheimer’s Society’s: ‘Out of the Shadows’ Report ([2008](#_ENREF_21)) gave many examples of why this may be. Reasons why under-diagnosis rates are so high range from the fact that GPs are not specialised in dementia and may be unable to spot early symptoms, to therapeutic nihilism which involves not diagnosing a patient with a particular illness because it is believed nothing can be done about it and that it would be more detrimental than helpful ([Knapp, Prince et al. 2007](#_ENREF_246)). Nevertheless, reports by leading research charities (e.g., ARUK; Alzheimer’s Society) have emphasised the need for early diagnosis. Furthermore, patients themselves have indicated a want for early diagnosis as it can help in many areas of their illness, such as being prepared for what will occur, as well as to find appropriate coping mechanisms for both patient and carer ([Knapp, Prince et al. 2007](#_ENREF_246)).

## Alzheimer’s Disease

### Neuropathological features

Alois Alzheimer, in 1907, was the first to formally describe what we now recognise as AD. He wrote about amyloid deposits and neurofibrillary (NF) changes, such as neurofibrillary tangles (NFTs), as the neuropathological hallmarks of AD ([Alzheimer 1907](#_ENREF_8)), and these features are still recognised today as factors leading to a definite diagnosis of AD ([McKhann, Drachman et al. 1984](#_ENREF_297)). While amyloid deposits are extracellular, i.e., they occur outside of the cell, NF changes are intraneuronal, i.e., they occur inside of the cell ([Braak, Braak et al. 1989](#_ENREF_65)). Braak and Braak ([1997a](#_ENREF_63)) have described the occurrence of two NF symptoms of AD, NFTs and neuritic plaques (NPs), with NFTs believed to accumulate within the brain from the beginning of the disease course and NPs accumulating in the later stages of the disease. Plaques and tangles are said to develop independent of each other in the AD brain, whereas in normal ageing individuals, an interaction between them has been reported ([Price and Morris 1999](#_ENREF_359)).

#### Neurofibrillary changes

Neurofibrillary changes in AD involve the development of tangles (NFTs) and neuropil threads (NTs) with these two NF changes being the first neuropathological changes to occur within the brain ([Braak and Braak 1997a](#_ENREF_63)). NTs are essentially abnormal neurites which contain tau and develop within dendrites ([Braak and Braak 1997a](#_ENREF_63)) as well as axons ([Perry, Kawai et al. 1991](#_ENREF_345)). Neurofibrillary tangles are hyperphosphorylated forms of tau which develop within nerve cells, and congest these cells due to the twisted fragments of protein ([Braak and Del Tredici 2011](#_ENREF_67)). This ultimately contributes to cell deterioration over a period of time, with eventual death of the cells ([Braak and Braak 1997a](#_ENREF_63)). However, these cells have been said to be able to house NF changes for a considerable period of time, years in many cases. Nevertheless, once cell death occurs, they are then transformed into extraneuronal ghost tangles ([Braak and Braak 1997a](#_ENREF_63)).

#### Braak Staging of NFTs

H. Braak, E. Braak and colleagues have studied the neuropathological features of AD extensively, in particular NF changes, and they have described NFTs as having a predictable path of distribution throughout the brain as the disease progresses ([Braak and Braak 1991](#_ENREF_61); [Braak and Braak 1997a](#_ENREF_63); [Braak, Griffing et al. 1999](#_ENREF_58); [Braak and Del Tredici 2006](#_ENREF_66)). Therefore, Braak and colleagues developed a six-stage classification, which describes the distribution and density of NFTs throughout the brain at different stages of the disease process. The projection cells of the transentorhinal region are said to be the first to become involved in the pathological process (stages I and II), ultimately causing the information sent via these projection cells, particularly to the entorhinal region and hippocampus, to become compromised ([Braak and Del Tredici 2006](#_ENREF_66)). The perforant path is among these projection cells that are initially targeted by NFTs, and is a path which originates from the entorhinal cortex (ERC), giving input into the hippocampus ([Gomez-Isla, Price et al. 1996](#_ENREF_178)). Therefore, due to this, the hippocampus becomes increasingly involved as the disease progresses ([Braak and Braak 1990](#_ENREF_59)), and Rossler, Zarski et al ([2002](#_ENREF_387)) described how Braak stages I and II represent the initial disruption of the connection between the ERC and hippocampus. Clinically, impairment at these stages of pathology is not necessarily seen on neuropsychological testing, and far below the necessary requirements to make a diagnosis of AD (e.g., [Grober, Dickson et al. 1999](#_ENREF_184); [Braak and Del Tredici 2006](#_ENREF_66)). In stage III, while the previous involved sites become increasingly compromised, the pathology now spreads to the adjoining fusiform and lingual gyri, while the higher order association areas of the neocortex become involved by stage IV ([Braak and Del Tredici 2006](#_ENREF_66)). Due to the spreading pathology and the damage that has occurred by stages III and IV, neocortical sensory information transmission to the prefrontal neocortex (via the entorhinal region and hippocampal formation) is hindered ([Braak and Del Tredici 2006](#_ENREF_66)). Here, impairment can be seen clinically in some patients, however this is still mild, and some patients are still able to compensate for the pathological burden in these stages due to their own personal cognitive reserve ([Braak and Del Tredici 2006](#_ENREF_66)). The pathology that occurs in stages V and VI means that, clinically, AD can now be defined and diagnosed in an individual. Stage V sees the pathology move into higher order association areas, involving frontal, superolateral and occipital regions, while in stage VI, the primary visual field (the striate area) becomes involved ([Braak and Del Tredici 2006](#_ENREF_66)). Persons in these stages of the disease are, clinically, thought to show severe AD and especially show autonomic function deterioration ([Braak and Del Tredici 2006](#_ENREF_66)). Even in the more severe stages of the disease, certain motor and sensory areas show relative preservation as do the functions they support ([Mesulam 1999](#_ENREF_300)). The preserved sensation and motor brain areas contain relatively few NFTs ([Braak and Braak 1996](#_ENREF_62)), leading researchers to suggest that NFTs have a central role in AD decline – areas of the brain where low accumulation of NFTs are apparent show relatively limited impairment of functions associated with these brain structures; severely impaired cognitive functions are supported by areas of the brain where high accumulation of NFTs occur. It is not until the end phase of the disease when NFT occurrence in the motor region becomes copious that motor skills begin to become largely impaired ([Braak, Griffing et al. 1999](#_ENREF_58); [Mesulam 1999](#_ENREF_300)). Ferreri and colleagues ([2003](#_ENREF_154)) further suggested that, while neuronal loss is occurring within the motor regions of the brain, reorganisation of neuronal circuits could be helping preserve motor skills until the end stages of the disease.

A loss of over 50% of CA1 neurons of the hippocampus has been reported between Braak stages I and V ([Rossler, Zarski et al. 2002](#_ENREF_387)). More specifically, Rossler and colleagues ([2002](#_ENREF_387)) reported that, between stages I and III, CA1 neurons remain relatively constant, while it is at stage IV that loss seems to occur ([Rossler, Zarski et al. 2002](#_ENREF_387)). Other research has supported this sector-specific loss of neurons in CA1 (eg, [West, Coleman et al. 1994](#_ENREF_460); [Bobinski, Wegiel et al. 1997](#_ENREF_50)), nevertheless, no such significant difference in number of neurons has necessarily been seen in sub regions CA2, CA3 or CA4 between Braak stages I and V ([Rossler, Zarski et al. 2002](#_ENREF_387)). Another brain region that does show neuronal loss between stages I and V is the subiculum, whereby Rossler and colleagues ([2002](#_ENREF_387)) found a 22% decrease in neurons here between the earlier and later Braak stages. Research has also shown that duration of the disease, after controlling for age and gender, is correlated with CA1 volume as well as the volumes of the subiculum and ERC ([Bobinski, de Leon et al. 1998](#_ENREF_49)). Furthermore, volume of these brain regions also correlated with severity of the disease (as assessed by the Functional Assessment Staging (FAST) ([Reisberg 1988)](#_ENREF_374)), while sub regions CA2, CA3 and CA4 have not been found to correlate with severity ([Bobinski, de Leon et al. 1998](#_ENREF_49)). Research indicating that neuronal loss in the volume of the CA1 sub region of the hippocampus is correlated with severity and duration of the disease is in agreement with neuropathological studies of AD staging ([Braak and Braak 1991](#_ENREF_61)) which suggest this same region is an early site for NFT formation. Therefore, Bobinski and colleagues ([1998](#_ENREF_49)) have concluded that volume loss in this specific sub region is most likely indicative of a clinical period, while Arriagada, Growden et al ([1992](#_ENREF_19)) further suggested that this CA1 sub region, along with the subiculum, amygdala and ERC are all areas that are particularly affected at an early stage of dementia.

NFTs have been associated with the level of cognitive impairment in AD patients even when assessing moderate/mild patients (Mini Mental Status Examination (MMSE) >10) (eg, [Arriagada, Growdon et al. 1992](#_ENREF_19); [Hof, Bierer et al. 1992](#_ENREF_207); [Bierer, Hof et al. 1995](#_ENREF_42); [Dournaud, Delaere et al. 1995](#_ENREF_131); [Tiraboschi, Hansen et al. 2004](#_ENREF_433)). Using the Blessed Information Memory and Concentration (BIMC) test ([Blessed, Tomlinson et al. 1968](#_ENREF_48)) to assess mental status, and two memory tests (Selective Reminding Test (SRT) and Free and Cued Selective Reminding Test (FCSRT)), Grober and colleagues ([1999](#_ENREF_184)) found that a lower score on all of these tests was related to higher Braak stages. More specifically, whilst mental status has been reported to decline once Braak stage IV is reached, but remain constant during stages 0 to III, memory performance has said to be affected at an earlier neuropathological time, with a detectable difference in memory score between those individuals displaying Braak stage II and those displaying Braak stage III ([Grober, Dickson et al. 1999](#_ENREF_184)). This supports the Braak & Braak ([1991](#_ENREF_61)) staging of NFT distribution as they claim that the earliest stages are clinically silent. Memory impairment has also been shown to predict subsequent dementia status, 5 years before diagnosis ([Grober, Lipton et al. 2000](#_ENREF_185); [Hall, Lipton et al. 2000](#_ENREF_191)), while memory decline, as well as informant reporting of memory decline, appears predictive of MCI status ([Petersen, Smith et al. 1999](#_ENREF_353)).

#### NF changes and normal ageing

As well as being neuropathological features of AD, NFTs and amyloid deposits have also been reported in non-demented individuals (eg, [Tomlinson, Blessed et al. 1968](#_ENREF_436); [Braak and Braak 1990](#_ENREF_59); [Price, Davis et al. 1991](#_ENREF_358); [Arriagada, Growdon et al. 1992](#_ENREF_19); [Bouras, Hof et al. 1993](#_ENREF_55); [Bouras, Hof et al. 1994](#_ENREF_54)), and in fact Gosche, Mortimer et al ([2002](#_ENREF_180)) reported that >40% of their participants who were not demented did meet neuropathological criteria for AD. Furthermore, the neuropathological hallmarks of AD have been reported in individuals as young as 30 years old ([Braak and Braak 1997b](#_ENREF_64)). The NF changes seen in Braak stages I and II have been reported to show an increase with age, before reaching a peak and then showing a gradual decrease ([Braak and Braak 1997b](#_ENREF_64)). More specifically, NFTs have been reported as most dramatically inhabiting layer II of the ERC ([Bouras, Hof et al. 1993](#_ENREF_55)). For example, Bouras and colleagues ([1993](#_ENREF_55); [1994](#_ENREF_54)) reported that, in non-demented individuals (average age 75 years) with no cognitive impairment (average MMSE 26.7), the ERC of all individuals contained NFTs, while only some individuals were devoid of NFTs in sub region CA1 of the hippocampus, with the least amount of NFTs being located in the superior frontal cortex. Furthermore, in all cases, the ERC always contained more NFTs than any other region ([Bouras, Hof et al. 1993](#_ENREF_55)). Nevertheless, while some studies report that the loss of neurons in the CA1 sub region is disease specific, rather than age-specific (eg, [West, Coleman et al. 1994](#_ENREF_460); [Harding, Halliday et al. 1998](#_ENREF_198); [Rossler, Zarski et al. 2002](#_ENREF_387)), others have reported an age-related decline in CA1 neuronal count ([Simic, Kostovic et al. 1997](#_ENREF_404)) and suggested this indicator, while showing sensitivity, lacks specificity ([Bobinski, de Leon et al. 1998](#_ENREF_49)). Differences between neuropathological features apparent in normal ageing and AD patients is seen in the density of NF changes within the neocortex, whereby this region is relatively spared in normal ageing, while it is considerably affected in AD ([Price, Davis et al. 1991](#_ENREF_358)). As the neuropathological features of AD are commonly found in individuals who do not present with cognitive dysfunction, even in individuals younger than 65 years (i.e., 49-59 years) ([Bouras, Hof et al. 1993](#_ENREF_55)) and even in very young individuals (i.e., <30years) ([Braak and Del Tredici 2006](#_ENREF_66)), Bouras et al ([1993](#_ENREF_55)) concluded that, as even moderate to severe NFT density can be found in cognitively intact individuals, then this involvement can still be congruent with a status of normal cognition ([Bouras, Hof et al. 1993](#_ENREF_55)). This argument is supportive of the Braak staging of NFT development ([Braak and Braak 1991](#_ENREF_61)) which states that NFT development in regions implicated in the early Braak stages does not disrupt cognitive abilities, at least as far as can be identified using clinical measures.

#### Specific cells vulnerable to tangles

NFTs seem to develop only within certain types of cells, with large, pyramidal neurons being the most vulnerable, and smaller, pyramidal neurons being less vulnerable ([Lewis, Campbell et al. 1987](#_ENREF_266); [Arendt, Bruckner et al. 1998](#_ENREF_14)). The vulnerability of specific neurons, especially in the hippocampal formation, to develop NF changes leads these areas to disconnect from neocortical association areas, ultimately resulting in a loss of cognitive function ([eg, Lewis, Campbell et al. 1987](#_ENREF_266)). Furthermore, Braak & colleagues ([eg, Braak and Del Tredici 2006](#_ENREF_66)) describe projection neurons that have long, thin axons as other features of particularly vulnerable cells within the brain. Conversely, it is reported that those with short axons are able to resist the pathology ([Braak and Del Tredici 2006](#_ENREF_66)). In addition, it has also been reported that the neuronal cells most vulnerable to developing NF changes are either unmyelinated or thinly myelinated ([Braak and Del Tredici 2006](#_ENREF_66)) and studies have reported the pattern of NF distribution within the brain follows the inverse pattern of myelination development (eg, [Braak and Braak 1996](#_ENREF_62); [Braak and Del Tredici 2006](#_ENREF_66)). It has been reported that, even in the presence of degeneration of myelin, there is still an absence of degeneration of the axon ([Terry, Weiss et al. 1964](#_ENREF_430)). Along with the idea proposed by Braak and colleagues ([Braak and Braak 1996](#_ENREF_62); [Braak and Del Tredici 2006](#_ENREF_66)) that NFT development follows the inverse pattern of myelination, Arendt and colleagues ([1998](#_ENREF_14)) have proposed that NFT distribution also follows the pattern of plasticity, i.e., the areas that are most vulnerable to NFT distribution are also the areas that show most dendritic plasticity. Areas of the brain most vulnerable to NFT distribution has been reported in many studies as CA1 of the hippocampus ([eg, Arendt, Bruckner et al. 1998](#_ENREF_14)), while the areas least affected have been reported as primary visual and motor regions ([eg, Arendt, Bruckner et al. 1998](#_ENREF_14)). Investigating the changes in length of dendrites, illustrating the brain’s capacity to remodel itself, Arendt and colleagues ([1998](#_ENREF_14)) reported that limbic areas show most dendritic growth indicating ample plasticity of these neurons, while the primary visual and motor regions, which are the regions least vulnerable to NFT distribution, show the least dendritic growth, i.e., a lack of plasticity. Investigating this idea further, Arendt and colleagues ([1998](#_ENREF_14)) reported that dendrites of normal healthy controls aged 51-70 years old showed an increase in length compared to adult controls aged 30-50 years of age, while those adults over 71-95 years had the least amount of dendritic growth. Nevertheless, in AD patients, the amount of dendritic growth depended on the presence (or absence) of an Apolipoprotein E epsilon 4 (ApoE ε4) allele, with those positive for ApoE ε4 allele (ε4+) showing regressive changes compared to a group of controls (51-70 years old), while those negative for the ApoE e4 allele (ε4-) showed no differences in dendritic growth with those adult controls aged 30-50 years ([Arendt, Bruckner et al. 1998](#_ENREF_14)).

#### Other diseases involving tau

Other disease processes also involve the accumulation of tau. While some tau based pathological processes develop similarly to that in AD, such as in Down Syndrome, others develop divergently, such as in supranuclear palsy ([Braak and Braak 1997a](#_ENREF_63)). Due to the fact that younger individuals have been seen to present with NF changes within the brain, Braak & Del Tredici ([2006](#_ENREF_66)) suggested that the onset of this pathological process is not dependent on old age - for example, one study showed about 20% of individuals aged 25-30 years of age had NF pathology comparable to Braak stage I ([Braak and Braak 1996](#_ENREF_62)).

### Amyloid deposits

The other neuropathological feature of AD is amyloid deposits. AD has been described as the commonest form of amyloidosis ([Ghiso and Frangione 2002](#_ENREF_176)), which is the collective name for diseases that involve insoluble fibrillar proteins being deposited within the brain. Amyloid protein deposits are found in NPs, and Braak and Braak ([1989](#_ENREF_65)) proposed that three types of plaques are found within the brain which suggest different stages of the accumulation process: ‘primitive neuritic plaques’ which are said to be devoid of an amyloid core; ‘mature neuritic plaques’ which contain an amyloid core as well as an abundance of neurites; and ‘burned out neuritic plaques’ which consists only of an amyloid core, leading researchers to propose they are the leftover remainder of a mature neuritic plaque. Ghiso & Frangione ([2002](#_ENREF_176)) have described how, when amyloid deposits are found in areas of the cortex, including the limbic system, dementia is likely to occur, while amyloid deposits found in the cerebral vessel walls are associated with stroke. Some research has shown that, not only are carriers of the ApoE e4 allele at higher risk of developing AD ([Corder, Saunders et al. 1993](#_ENREF_97)), but are also at higher risk of developing this disease earlier in life (i.e., earlier age of onset), as well as having larger numbers of NPs ([Mayeux, Stern et al. 1993](#_ENREF_292)).

#### Braak staging of amyloid plaques

A specific pattern of plaque distribution throughout the brain has been reported by many different researchers (eg, [Rogers and Morrison 1985](#_ENREF_384); [Braak and Braak 1991](#_ENREF_61)). Braak & Braak ([1991](#_ENREF_61)) developed a staging system (A, B, C) for classifying plaque distributions within the brains of AD patients. In stage A, the plaques are characterised as ill-defined, and are located in the lingual and fusiform gyri ([Braak and Braak 1997a](#_ENREF_63)). Following this, the plaques become better defined and increase in number in these areas ([Braak and Braak 1997a](#_ENREF_63)). In stage B, the basal neocortex is further involved, with involvement of the allocortex also ([Braak and Braak 1997a](#_ENREF_63)). In stage C, plaques are found throughout the neocortex, including the primary areas ([Braak and Braak 1997a](#_ENREF_63)). However, even at stage C, it is noted that some areas of the brain are still free of amyloid plaques ([Hyman, Marzloff et al. 1993](#_ENREF_213)). In severe to very severe patients, it has been reported that areas including the anterior cingulate and superior frontal regions contain at least 40% more plaque count than do sensory areas including the visual cortex and auditory region of the temporal lobe ([Rogers and Morrison 1985](#_ENREF_384); [Braak and Braak 1991](#_ENREF_61)). Similarly as with NFTs, amyloid plaques within an AD patient’s brain are said to begin in poorly myelinated areas ([Braak and Braak 1997b](#_ENREF_64)). Braak & Braak ([1997b](#_ENREF_64)) have described how amyloid plaques begin in temporal regions such as the perirhinal cortex, as these areas are poorly myelinated. As the disease advances, amyloid plaques are found in more richly myelinated regions.

While some research has described a close proximity between choline acetyltransferase fibres and NPs within the brain ([e.g., Armstrong, Bruce et al. 1986](#_ENREF_17)), others have reported plaque density is lowest in layers I and II, which corresponds to areas where cholinergic projections are densest ([eg, Rogers and Morrison 1985](#_ENREF_384)). To support this latter argument, research has pointed out that the nucleus basalis of Meynert (NBM), which is a major source of cholinergic innervation ([Whitehouse, Price et al. 1982](#_ENREF_463); [Mesulam, Mufson et al. 1983](#_ENREF_301)), has a low plaque count.

#### Amyloid and normal ageing

Deposits of amyloid are also said to occur in the brains of normal ageing individuals. Although this is not inevitable ([Tomlinson, Blessed et al. 1968](#_ENREF_436); [Braak and Braak 1997a](#_ENREF_63)), the number of individuals devoid of amyloid deposits decreases with increasing age ([Braak and Braak 1997b](#_ENREF_64)). The accumulation of amyloid deposits has been reported to occur in the later stages of AD, even in the oldest old age range ([Leuba, Saini et al. 2001](#_ENREF_263)).

#### Other diseases and amyloid

Many researchers have indicated how the two main pathological hallmarks of AD – NFTs and amyloid deposits – can both co-occur, as in AD, or occur independently of each other (eg, [Price and Morris 1999](#_ENREF_359); [Ghiso and Frangione 2002](#_ENREF_176)). For example, the brains of individuals with Down Syndrome show both of these AD pathological hallmarks ([eg, Ghiso and Frangione 2002](#_ENREF_176)). Furthermore, whilst NFTs, as seen in AD, are also found in familial British dementia (FBD) and familial Danish dementia (FDD), the amyloid proteins associated with these other two dementias are not related to the ones seen in AD ([Ghiso and Frangione 2002](#_ENREF_176)). Whilst NPs have also been found in the brain of normal ageing individuals, their brains have been found to contain fewer NPs than in AD ([Tomlinson, Blessed et al. 1968](#_ENREF_436); [Hyman, Marzloff et al. 1993](#_ENREF_213)), while the brain of patients with Down Syndrome appear to show more NPs than AD patients ([Hyman, Marzloff et al. 1993](#_ENREF_213)).

#### Identifying the neuropathological features of AD in vivo

Until recently, a definite diagnosis of AD could only be given at post mortem when the neuropathological features would either confirm or deny a clinical diagnosis of AD. However, a novel technique is being used which utilises Pittsburgh Compound B (PiB) alongside positron emission tomography (PET) imaging. Klunk and colleagues (eg, [Klunk, Engler et al. 2004](#_ENREF_244); [Engler, Forsberg et al. 2006](#_ENREF_140)) are the researchers associated with this new technique that works on the idea that uptake of PiB illustrates amyloid accumulation within the brain. This technique has been described as a possible way to detect amyloidosis ([Klunk, Engler et al. 2004](#_ENREF_244)), of which AD is the commonest form ([Ghiso and Frangione 2002](#_ENREF_176)). Ultimately, this may mean that a clearer diagnosis of AD can occur before death, which has implications for improving misdiagnosis rates as well as implications for treatment ([Forsberg, Almkvist et al. 2010](#_ENREF_160)). More specifically, Klunk et al ([2004](#_ENREF_244)) have suggested that PiB, which has been shown to cross the blood brain barrier (BBB) very well (e.g., [Mathis, Bacskai et al. 2002](#_ENREF_288); [Wang, Klunk et al. 2002](#_ENREF_454); [Mathis, Wang et al. 2003](#_ENREF_289); [Klunk, Engler et al. 2004](#_ENREF_244)), has potential to help in therapeutic trials, especially the ones trying to clear the brain of amyloid. Interestingly, this technique has shown to have low variability when AD patients have been tested 20 days after a baseline using PiB ([eg, Engler, Forsberg et al. 2006](#_ENREF_140)). Nevertheless, whilst great advancements have been made in this field, a criticism that can be levied against the PiB technique is that this technique has poor specificity with many cognitively healthy people who may be PiB positive and many AD who can be PiB negative.

Evidence shows that, in areas of the brain where amyloid deposits are lacking, such as the cerebellum, AD patients and controls show similar accumulation of PiB, whereas in areas known to contain large amounts of amyloid deposits, such as the frontal cortices and the striatum, AD patients show a much higher uptake of PiB than controls ([Klunk, Engler et al. 2004](#_ENREF_244)). Therefore, this led researchers to conclude that PiB uptake is related to the accumulation of amyloid deposits within the brain ([Klunk, Engler et al. 2004](#_ENREF_243)). Large variability is seen in the deposition of amyloid plaques in the brain ([Braak and Braak 1991](#_ENREF_61)) while the largest difference in PiB retention between AD and normal ageing individuals was the frontal cortex, whereby AD patients showed a 90% increase in PiB uptake compared to controls ([Klunk, Engler et al. 2004](#_ENREF_244)). High levels of PiB retention have also been found in patients with a diagnosis of MCI ([eg, Lopresti, Klunk et al. 2005](#_ENREF_277)).

A negative correlation has been found between PiB retention and regional cerebral metabolic rate for glucose consumption (rCMRglc), which indicates neural function, both at baseline ([Klunk, Engler et al. 2004](#_ENREF_244)) and at follow-up ([Engler, Forsberg et al. 2006](#_ENREF_140)), suggestive of a relationship between the deposition of amyloid within the brain and neural functioning ([Klunk, Mathis et al. 2006](#_ENREF_245)). In the original study by Klunk and colleagues ([2004](#_ENREF_244)), they remarked on three clinically diagnosed AD patients who showed more similar PiB uptake and rCMRglc profiles as the controls, as well as one control who showed a PiB uptake similar to the profile of the AD patients. Therefore, they suggested that the diagnosed AD patients could be individuals who will not be confirmed as having AD at post-mortem, while the control may be either a pre-symptomatic case or conversely, this case could again highlight the fact that amyloid deposits are common in the normal ageing process ([Klunk, Engler et al. 2004](#_ENREF_243)), especially in the very old population.

In a follow-up study (1.5-2.5 years later) of the original PiB study ([Klunk, Engler et al. 2004](#_ENREF_244)) investigating these same patients and controls, Engler and colleagues ([2006](#_ENREF_140)) reported that significant PiB retention differences were noted between the AD group and control group in all of the cortices within the brain. Furthermore, while no significant retention differences were found between baseline and follow-up scans of the AD patients, when splitting this patient group into those who showed clinical progression from baseline to follow-up (based on ≥ 3 MMSE point decrease) and those who remained stable (≤ 2 MMSE point decrease), it was found that the progressive group showed larger PiB retention scores at both time points compared to the stable AD group, while this reached significance at baseline in the posterior cingulate area ([Engler, Forsberg et al. 2006](#_ENREF_140)). Nevertheless, in terms of rCMRglc values, both AD groups showed decreases ([Engler, Forsberg et al. 2006](#_ENREF_140)), indicating that the AD stable group showed no increase of amyloid deposition between baseline and follow-up, but an increase in neural degeneration. Engler and colleagues ([2006](#_ENREF_140)) have suggested this may indicate an equilibrium being reached by the amyloid deposition, which is in agreement with other studies ([e.g., Christie, Bacskai et al. 2001](#_ENREF_88)).

Cognitive performance (measured by the MMSE) has been negatively correlated with baseline PiB retention in the frontal, parietal and occipital cortex while rCMRglc values have been negatively correlated with MMSE scores in parietal and temporal cortices at baseline, with the addition of the frontal and cerebellar cortex at follow-up ([Engler, Forsberg et al. 2006](#_ENREF_140)). A significant correlation has also been found between Rey Auditory Verbal Learning Test (AVLT) scores and PiB retention, as well as the AVLT scores and rCMRglc values ([Engler, Forsberg et al. 2006](#_ENREF_140)).

It has been reported that the uptake value of PiB is not correlated to ApoE status, age, gender, duration of illness or amount of time on cholinesterase inhibitors (ChEIs), which is the pharmacological treatment option for patients with AD ([Klunk, Engler et al. 2004](#_ENREF_244)). However, other studies have suggested the possibility of ChEI treatment having an effect on amyloid deposition ([Ballard, Greig et al. 2005](#_ENREF_33); [Francis, Nordberg et al. 2005](#_ENREF_164); [Inestrosa, Alvarez et al. 2005](#_ENREF_215)).

### Neurofibrillary changes and amyloid deposition

In contrast to the finding that NFTs have been associated with the level of cognitive impairment in AD patients, even when using moderate/mild patients (MMSE>10) (eg, [Arriagada, Growdon et al. 1992](#_ENREF_19); [Hof, Bierer et al. 1992](#_ENREF_207); [Bierer, Hof et al. 1995](#_ENREF_42); [Dournaud, Delaere et al. 1995](#_ENREF_131); [Tiraboschi, Hansen et al. 2004](#_ENREF_433)), NPs have not been found to reliably correlate with dementia severity (eg, [Arriagada, Growdon et al. 1992](#_ENREF_19); [Bierer, Hof et al. 1995](#_ENREF_42); [Tiraboschi, Hansen et al. 2004](#_ENREF_433)), even though this is not a consistent finding across all studies (eg, [Blessed, Tomlinson et al. 1968](#_ENREF_48); [Cummings, Pike et al. 1996](#_ENREF_102)). Furthermore, NP amount does not appear to correlate with duration of illness in either AD or Down Syndrome patients ([Hyman, Marzloff et al. 1993](#_ENREF_213)). Combining the Braak stages of neurofibrillary changes and amyloid deposits, 16 combinations of these stages can occur ([Braak and Braak 1997b](#_ENREF_64)). Braak and Braak ([1997b](#_ENREF_64)) have suggested that some combinations occur more often than others, whereby they describe the absence of both AD neuropathological features in younger age groups, which decreases with age, with the combination of amyloid stage C and NFT stage V and VI increasing with age. Unlike the clinical expression of ‘regression’, i.e., when a patient regresses back to an earlier/less progressed level of impairment, this is said not to occur with the neuropathology data, whereby an individual who has begun to accumulate NFTs or amyloid deposits in the brain will not regress to a state devoid of them, or show less of pathological features ([Braak and Braak 1997b](#_ENREF_64)).

Whilst some researchers have shown findings in support of plaques being a cause of the decline in AD patients ([Rogers and Morrison 1985](#_ENREF_384)), others have disagreed ([Lee, Casadesus et al. 2004](#_ENREF_261)). A major source of contention with amyloid plaques and AD is that, unlike NFTs, no strong relationship has been found between the distribution of plaques in the brain and the cognitive dysfunction seen in the course of the disease ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). In fact, as well as their distribution not being able to differentiate stages of the disease, position of plaque deposits within the brain also vary considerably between individuals ([Mesulam 1999](#_ENREF_302)). Therefore, whilst the neuropathological features show convincing evidence, much more research is needed in this area to understand more about the relationship between NFTs, NPs and AD dysfunction. Studies have reported that, whilst NFTs are one of the hallmark neuropathological symptoms of AD, they are also seen in normal ageing, more so than are NPs ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). For example, one study reported that NFTs were displayed in 87% of normal ageing individuals, while only 37% displayed NPs, whereas all AD patients displayed NPs ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). The distribution of NPs and NFTs in normal ageing individuals has been reported to be dichotomous, whereby NPs are confined to the neocortex and NFTs to the allocortex ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). Furthermore, The Neuropathology Group for the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) ([Esiri, Matthews et al. 2001](#_ENREF_143)) have shown that relying on neuropathology alone for dementia diagnoses can be subject to problems. In their study, when researching neuropathology at autopsy in relation to clinical status of dementia, they reported that, in their sample of ‘no dementia’ individuals, over 30% had NPs of a moderate or severe level, enough to warrant a diagnosis of AD. Conversely, again, in over 30% of individuals, this time in the ‘dementia’ sample, either no or low NP amounts were found, which would result in these dementia sufferers being classified as not having AD. Therefore, this evidences how, whilst neuropathological features of AD can be useful in aiding diagnoses, they should not be used exclusively and complimenting them with neuroimaging and neuropsychological assessment could lower misdiagnosis rates. Ultimately, a gold standard diagnosis of AD will most likely combine converging evidence from the different investigations performed.

### Current Scientific Opinion

The Braak staging of NFTs in the brains of AD patients is largely accepted throughout the literature. Nevertheless, there are some criticisms of this work – for example, the accumulation of NFTs can only be said to *contribute to* the cognitive decline of these patients, rather than being a direct cause of the decline ([Nelson, Braak et al. 2009](#_ENREF_327)). Furthermore, several studies have reported on patients with a clinical diagnosis of AD, but who show little or no NFT deposition ([Esiri, Matthews et al. 2001](#_ENREF_143)). This would appear to suggest that NFT accumulation is not a necessary event to induce cognitive decline. Furthermore, McKee and colleagues ([2006](#_ENREF_296)) have stated that NFT accumulation is not stage dependent. Another criticism to the Braak staging is that researchers note NFT accumulation does not occur in a stepwise or stage-wise manner, but rather continuously ([Alafuzoff, Arzberger et al. 2008](#_ENREF_3)). It is important, therefore, to remember this when making neuropathological diagnoses on individual patients, and one way in which researchers have tried to overcome this problem is by using several pathologists to assess individual patients Braak stage ([e.g., Alafuzoff, Arzberger et al. 2008](#_ENREF_3)). Nevertheless, even using this approach, Alafzuoff and colleagues ([2008](#_ENREF_3)) reported less agreement over the earlier stages (i.e., milder patients) than with the later stages (i.e., severe patients).

In addition to these criticisms, comorbidities between AD and other diseases or conditions also make the relationship between NFTs and the severity of cognitive decline weaker. For example, cardiovascular disease (CVD) also increases with age, as does AD. Therefore, as the co-occurrence of CVD and AD is common in the ageing population, untangling the true cause of the cognitive decline can be difficult. Furthermore, studies have reported that cognitive decline in patients with AD and CVD is worse even with less pathology, than patients without CVD. Fernando and Ince ([2004](#_ENREF_153)) also reported that ‘pure’ AD was uncommon, and they found only 21% of cases in their MRC CFAS (Neuropathology Group) study had AD without any vascular burden.

Researchers supportive of the Amyloid Cascade Hypothesis – which describes the amyloid-β depositions within the brain as triggering the tau formation – also shed doubt on the true link between NFTs and cognitive decline ([e.g., Hardy and Allsop 1991](#_ENREF_199)). For example, some studies have found tangle-free patients diagnosed with AD. Nevertheless, on the contrary, tangle-only patients have also been reported in the literature. Also, in non-demented individuals under the age of 30 years (4-29 years), Braak & Del Tredici ([2011](#_ENREF_68)) reported that, while the majority of cases (38/42) were found to display abnormally phosphorylated tau protein, only 1 individual (with diagnosed Down’s Syndrome) showed amyloid-β protein or neuritic plaques, suggesting that abnormal tau development precedes the development of amyloid-β or neuritic plaques. This evidence, therefore, also goes against the amyloid cascade hypothesis.

In a recent report by Jack and colleagues ([2010](#_ENREF_218)) these authors have proposed a theoretical model of specific events that lead to clinical AD. Beginning with the deposition of amyloid, and followed by neuronal injury as well as tau phosphorylation and structural changes, the final stage is the emergence of clinical symptoms. Therefore, whilst others have not necessarily found a link between amyloid deposition and severity of decline in AD, this new model at least indicates the importance of amyloid in cognitive dysfunction as the initial stage to begin the events that ultimately lead to AD.

### Imaging

One argument put forward for the use of structural imaging as a biomarker for AD is the fact that the atrophy that patients with AD experience is said to begin years before any clinical changes begin to appear ([e.g., Jack, Knopman et al. 2010](#_ENREF_218)). Being able to predict those individuals who will convert to AD in the future, would allow researchers to study patients in an earlier ‘preclinical’ stage of AD, whereby atrophy and clinical symptoms will be less developed.

#### Medial Temporal Lobe

##### Hippocampus

Volumetric differences of MTL structures between AD patients and controls have been found ([e.g., Jack, Petersen et al. 1997](#_ENREF_221)). For example, it has been reported that AD patients show greater decline in hippocampal volume as well as lower baseline hippocampal volumes ([Jack, Petersen et al. 2000](#_ENREF_219)). Increasing hippocampal volume loss has been found with increasing severity (based on Clinical Dementia Rating (CDR) scores), and Jack and colleagues ([1997](#_ENREF_221)) suggested that this indicates the sensitivity of hippocampal volumetric measurements as markers of the progressive impairment in memory shown within increasing CDR scores. Furthermore, these researchers reported that, with a specificity of 80%, AD patients (CDR scores 1 and 2) were successfully differentiated from controls with 83.7% and 86.7% sensitivity, respectively. Measuring the volume of the hippocampus also discriminates those AD patients in the mildest stages (CDR = 0.5) and normal controls with 77.8% sensitivity ([Jack, Petersen et al. 1997](#_ENREF_221)). Additionally, this group also reported that while the total hippocampal volume decline could differentiate differing severity levels within the same disease, comparing the hippocampal head volume of AD and normal controls showed the best discriminatory power (e.g., [Chang, Parisi et al. 1992](#_ENREF_82); [Jack, Petersen et al. 1997](#_ENREF_221)). This finding could have come from the fact that, whilst normal ageing individuals displayed a greater hippocampal volume loss in the head portion (compared to the tail and body), this difference was not seen in the AD patients, who showed no greater differential loss in any portion of the hippocampus ([Jack, Petersen et al. 1998](#_ENREF_220)). This research is further supported by reports indicating the greatest loss of hippocampal volume seen with age is located within the head portion of this structure (27.43mmᶟ loss) ([e.g., Jack, Petersen et al. 1997](#_ENREF_221)) (body: 8.84mmᶟ; tail: 9.68mmᶟ).

Nevertheless, whilst hippocampal volume has been extensively studied and shown to predict group membership between AD patients (of differing severities) and normal ageing controls, this particular measure is not specific to AD as hippocampal volume loss is also reported in other disorders such as Post-traumatic Stress Disorder (PTSD) ([Villarreal, Hamilton et al. 2002](#_ENREF_450)), schizophrenia ([Wright, Rabe-Hesketh et al. 2000](#_ENREF_470)) and depression ([Sheline, Gado et al. 2003](#_ENREF_402)), and whilst it can discriminate AD and normal controls, hippocampal volume decline is part of the normal ageing process (e.g., [Jack, Petersen et al. 1997](#_ENREF_221); [Raz, Gunning et al. 1997](#_ENREF_370); [Jack, Petersen et al. 1998](#_ENREF_220)) which shows a linear pattern of decline ([e.g., Jack, Petersen et al. 1997](#_ENREF_221)). For example, Jack and colleagues ([1998](#_ENREF_220)) reported a difference in volume of the hippocampus in AD patients and normal ageing individuals, whereby controls showed an annual decrease in hippocampal volume of -1.55% (75mmᶟ) while the AD patients showed -3.98% (150mmᶟ). Research has also shown that effects of age can be seen in volume loss in several areas of the brain further to the hippocampus, including the prefrontal lobes (e.g., [Raz, Gunning et al. 1997](#_ENREF_370); [Tisserand, Van Boxtel et al. 2001](#_ENREF_434)) and the thalamus ([e.g., Van der Werf, Tisserand et al. 2001](#_ENREF_439)). Furthermore, research has proposed that whilst decreases in the volume of the prefrontal cortex (PFC) volume are seen as an effect of the ageing process, decreases in the medial temporal volume is an effect of the pathological process ([Raz, Williamson et al. 2000](#_ENREF_372)). However, this is not consistent across studies, and Tisserand et al ([2004](#_ENREF_433)) reported similar cognitive and age related effects on the PFC and MTL regions.

##### Entorhinal Cortex

Desikan, Cabral et al ([2009](#_ENREF_119)) has suggested that the integrity of the ERC is a more sensitive measure of conversion from MCI to AD than the integrity of the hippocampus ([Dickerson, Goncharova et al. 2001](#_ENREF_122)). In combination, having more atrophy (less volume) in the ERC and inferior parietal lobule at baseline increases the risk of conversion for MCI individuals compared to those with higher volumes of these two areas.

##### Combination of MTL structures

Other studies have reported that it is the combination of several MTL structures volumes, rather than a single one, that can best discriminate controls and AD patients (e.g., [Killiany, Moss et al. 1993](#_ENREF_239); [Lehericy, Baulac et al. 1994](#_ENREF_262); [Laakso, Soininen et al. 1995](#_ENREF_254)). Volumetric differences of MTL structures other than the hippocampus have been found between AD patients and controls ([Jack, Petersen et al. 1997](#_ENREF_221)). For example, annual volumetric declines in the parahippocampal gyrus at 46.65mmᶟ in normal ageing, and 20.75mmᶟ in the amygdala have been reported, with the decline in these areas in AD patients being greater ([Jack, Petersen et al. 1997](#_ENREF_221)). In addition, Jack and colleagues ([1998](#_ENREF_220)) have also investigated the annual change of the temporal horn in normal ageing compared with AD patients. They reported that normal ageing individuals show an annual enlargement of the temporal horn of 6.15% (167mmᶟ) compared with an enlargement in AD patients of 14.16% (660mmᶟ). Atrophy of the amygdala has also been suggested to play an important role in the cognitive deficits seen in AD ([Horinek, Petrovicky et al. 2006](#_ENREF_209)), and therefore measures of atrophy of this structure could also act as a marker for differentiating normal from pathological ageing seen in AD and predicting conversion in MCI ([Liu, Paajanen et al. 2010](#_ENREF_274)). Research has also shown interactions between the amygdala and the hippocampal system ([Phelps 2004](#_ENREF_356)) and an functional magnetic resonance imaging (fMRI) study has shown that compensation for decline related to atrophy of the hippocampus ([Richardson, Strange et al. 2004](#_ENREF_378)) is supported by the amygdala.

#### Imaging Models

Davatzikos, Bhatt et al ([2011](#_ENREF_109)) have used a novel way of recognising AD structural abnormalities that occur early on in the disease. Their method, called ‘Spatial Pattern of Abnormalities for Recognition of Early AD (SPARE-AD)’, works on a system whereby patterns are formed of both patients with AD and controls using brain scans to distinguish the two groups. An individual given a positive SPARE-AD score would evidence a pattern more similar to that from the AD scans. Similarly to Davatzikos and colleagues ([2011](#_ENREF_109)), Vemuri, Wiste et al ([2009](#_ENREF_443)) used a measure that gives a score reflecting AD-like atrophy. Each participant is given a Structural Abnormality Index (STAND) score which reflects how much AD-associated atrophy an individual shows which can then be used to differentiate clinical groups from each other. Vemuri et al ([2009](#_ENREF_443)) concluded that their algorithm to detect AD-atrophy is correlated to a larger extent to the cognitive performance compared to cerebral spinal fluid (CSF) biomarkers used in this study, such as tau. The reason put forward by the authors for this better correlation between STAND scores and clinical performance, compared with CSF biomarkers and clinical performance, is due to the event that each are a marker of. That is the increase of total-tau within the CSF of a neurodegenerative brain is said to be a marker of NFT pathology, while the atrophy shown in the STAND scores is said to represent the loss of neurons and synapses. Therefore, because clinical performance decreases with the inability to compensate for the loss of neurons and synapses, then this would indicate why it is that atrophy (reflected in the STAND score) is better correlated with clinical performance.

#### Methodological issues in imaging

Volumetric data have been useful in looking at normal and abnormal ageing; however they are not without limitations. Tisserand et al ([2004](#_ENREF_433)) described some disadvantages of volumetric techniques, including that as they are labour intensive, they are unappealing for studies with large sets of participants, and that generally only a single region of interest is investigated. Limitations of volumetric magnetic resonance imaging (MRI) techniques used in studies include the fact that the boundaries between structures varies between studies ([Jack, Petersen et al. 1997](#_ENREF_221)). Voxel Based Morphometry (VBM), which is a relatively novel way of analysing brain imaged data, can be utilised on large sample sizes and is still a fast technique due to its automated nature. Furthermore, the whole brain is analysed which removes the need for a priori hypothesis on which specific brain regions one should target. Nevertheless, whilst criticism has been levied against this technique due to the anatomical variability in individuals’ brains, the automated approach of VBM makes it sensitive enough to detect this variability ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)).

#### Imaging and neuropathology

Using participants from The Nun Study ([Snowdon, Kemper et al. 1996](#_ENREF_410); [Snowdon, Greiner et al. 1997](#_ENREF_409)), Gosche and colleagues ([2002](#_ENREF_180)) identified 4 groups based on: a) whether or not the participant met neuropathological criteria for AD, and b) whether or not the participant was demented. Therefore, it was reported that the group of demented participants who also met AD neuropathological criteria had smaller hippocampal volume than either of the other groups, while the non-demented participants who did not meet AD neuropathological criteria had the largest hippocampal volume. Furthermore, compared to the non-demented participants, the demented participants (irrespective of meeting AD neuropathological criteria) had lower MMSE scores at final evaluation. Group membership, between those demented and non-demented, and those meeting neuropathological criteria for AD, was successfully predicted by hippocampal volume and therefore it was suggested that this measure is successful at identifying individuals who are positive for AD neuropathological criteria (but not demented) ([Gosche, Mortimer et al. 2002](#_ENREF_180)).

## Clinical Profile

### National Institute of Neurological Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria

The NINCDS-ADRDA ([McKhann, Drachman et al. 1984](#_ENREF_297)) have set out the criteria for diagnosing probable Alzheimer’s Disease (AD) which includes:

1) Dementia – established by clinical examination and documented/confirmed by neuropsychological testing;

2) Deficits in two or more areas of cognition;

3) No disturbance of consciousness;

4) Onset most often after 65 years of age (between ages 40-90 years);

5) Absence of systemic disorders or other brain diseases.

Support for this diagnosis can be through the progressive deterioration of specific cognitive functions such as language, impairment in activities of daily living (ADLs), as well as a family history of similar disorders.

Exclusion criteria described by the NINCDS-ADRDA criteria include sudden onset, visual field deficits or seizures early in the course of the illness.

### Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria

Another set of criteria for the diagnosis of AD has also been set out in the DSM, with the most recent version being DSM-IV ([2000](#_ENREF_11)). This criterion includes:

1) Development of multiple cognitive deficits manifested by:

- Memory impairment

- One or more other cognitive disturbance of: aphasia; apraxia; agnosia; executive function impairment.

2) Significant impairment in social/occupational functioning caused by the above cognitive deficits;

3) Gradual onset and continuing cognitive decline;

The DSM-IV also includes exclusion criteria which may have caused the cognitive deficits, including:

- Other nervous system disorders;

- Systemic conditions;

- Substance induced conditions.

### Dubois and colleagues (2007), International Working Group

More recently, Dubois and colleagues ([2007](#_ENREF_134)) have proposed new research criteria for diagnosing AD. The authors emphasise the need to revise previous diagnostic criteria (i.e., NINCDS-ADRDA; DSM-IV) due to the advancements in more novel technologies that is said to improve diagnostic certainty, for example, the use of MRI and CSF biomarkers. This research criteria set out core diagnostic features, as well as supportive features and exclusion criteria in order to diagnose an individual as having probable AD:

Core diagnostic criteria:

A) Significant episodic memory impairment that occurs early and: i) >6 months of gradual change in memory function reported by patient/informant; ii) objective evidence of this memory impairment; iii) associated with or without other cognitive changes.

Supportive features (one or more needed):

B) MTL atrophy;

C) Abnormal CSF biomarker;

D) Specific pattern evidenced using functional imaging with PET;

E) Proven genetic mutation within immediate family.

## Cognitive Profile

Alzheimer’s Disease, the most common form of dementia, is a neurodegenerative disease whereby a person’s cognitive abilities decline progressively, generally indicated by initial memory impairments, followed by many other cognitive impairments, as well as losing the ability to complete ADLs which include handling finances appropriately and taking care of personal hygiene ([Bucks, Ashworth et al. 1996](#_ENREF_73)).

### Memory

#### Episodic Memory

Tulving ([1972](#_ENREF_438)) defined episodic memory:

“Episodic memory receives and stores information about temporally dated episodes or events, and temporal-spatial relations among these events”, (pg. 385-386).

Several researchers have noted that, whilst memory is one of the earliest cognitive functions to become impaired in AD patients, more specifically these patients show very poor encoding of new material in the very earliest stages of the disease (e.g., [Moss, Albert et al. 1986](#_ENREF_320); [Welsh, Butters et al. 1992](#_ENREF_459)) which can be captured using neuropsychological measures of episodic memory ([Small, Fratiglioni et al. 2000](#_ENREF_406)).

An abundance of previous research has focused on episodic memory ability and AD (e.g., [Baudic, Barba et al. 2006](#_ENREF_39); [Dannhauser, Shergill et al. 2008](#_ENREF_106)) and many studies have reported a decline in this type of memory in individuals ageing normally as well as a decline due to AD ([e.g., Ciaramelli, Lauro-Grotto et al. 2006](#_ENREF_90)). Therefore, detecting a deficit in this type of memory does not necessarily distinguish pathological ageing (at least in the early stages) from normal ageing, and the presence of an impairment does not necessarily mean an individual will go on to develop AD ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)). Therefore, the diagnostic potential of other types of memory as well as other cognitive abilities has been investigated.

#### Semantic Memory

Tulving ([1972](#_ENREF_438)) defined semantic memory:

“Semantic memory is the memory necessary for the use of language. It is a mental thesaurus, organised knowledge a person possesses…”, (pg. 386).

The assessment of semantic memory appears to provide one avenue to substantially increase diagnostic confidence. One reason for choosing to examine semantic memory is that, unlike the impairments that have been reported in episodic memory in normal ageing individuals, deficits are not evidenced to occur due to age in semantic memory ([Craik 1994](#_ENREF_100)). Research has also shown that semantic memory impairments are abundant in patients with AD and that increased severity of the disease results in greater decline in semantic memory ([Westmacott, Black et al. 2004](#_ENREF_462)). Nyberg, Backman et al ([1996](#_ENREF_334)) reported that, after controlling for other demographic information (e.g., education), age explained variance seen in performance of normal individuals (age range 35-80) on tests of episodic memory, but not on tests of semantic memory. Therefore, this is in-line with the account that episodic memory shows a decline with increasing age, which would also account for the younger participant’s performing better on these episodic memory tests than the older participants, while semantic memory does not ([Nyberg, Backman et al. 1996](#_ENREF_334)). There are other tests that have been useful in detecting dementia, with the Grober-Buschke test (1987) being popular among clinicians. This tests is based on cued recall (as opposed to free recall), and uses semantic cues to test an individual’s learning. In their original paper, E. Grober and H. Buschke (1987) found this test successful at differentiating dementia patients from normal healthy controls.

##### Semantic fluency task

To test the integrity of semantic memory, fluency tasks have been employed and impairments on these appear very useful indicators of AD. The most widely used is the category fluency task and involves individuals orally generating as many responses as possible to specific categories (for example, ‘Animals’) within a 60 second time limit. Due to their ability to successfully discriminate normal from pathological ageing, many have suggested that these fluency tasks could be utilised as one-minute mental status examinations ([Cummings 2004](#_ENREF_103); [Duff-Canning, Leach et al. 2004](#_ENREF_135)). Research has shown that, along with producing fewer words on the semantic category fluency task, AD patients also perseverate more and include more intrusions and wrong category examples within their answers, when compared with healthy older adult controls ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)). Forbes-McKay and colleagues ([2005](#_ENREF_159)) have also measured the lexical characteristics of the words produced on this task including Age of Acquisition (AoA), which is a measure of when the word was first learned in life; and Frequency, which is a measure of how often a word is used. The study revealed that AD patients produce earlier acquired, as well as more frequent and more typical words on the category fluency tasks when compared to normal ageing controls ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)).

##### Phonemic fluency task

Frontal components are also involved in tests of verbal fluency when participants must employ processes of executive control which help them not repeat words they have previously produced. The letter fluency task, in which participants must produce words beginning with a particular letter (for example, ‘P’), appears to rely (almost solely) on frontal processes. Many studies have reported worse impairment on the semantic vs. the phonemic fluency task in AD (e.g., [Pasquier, Lebert et al. 1995](#_ENREF_340); [Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Capitani, Rosci et al. 2009](#_ENREF_78)). This repeated observation lends support to the neuropathological research that has shown that areas of the brain which support semantic memory, in particular the perirhinal cortex and entorhinal cortex, are the first sites where AD pathology manifests ([Braak and Braak 1991](#_ENREF_61)). While the disproportionate semantic fluency impairment in AD is said to reflect preferential distribution of neuropathology in patients, and while they are also impaired on the letter fluency task compared to normal controls, this impairment is greater in semantic fluency tasks because of the neuropathological burden of the disease jeopardising their semantic store, and therefore leading to an inability to produce many category fluency exemplars.

### Executive Functions

Further to memory, executive functioning has been studied quite extensively in regards to the normal and abnormal ageing processes ([Baddeley, Logie et al. 1986](#_ENREF_27); [Sahakian, Downes et al. 1990](#_ENREF_392)). Additionally, Lafleche & Albert ([1995](#_ENREF_255)) reported that certain types of skills used during executive functioning tasks are differentially impaired in AD rather than the whole process being equally affected. For example, these authors suggested that executive skills such as set shifting and self-monitoring are more impaired in AD patients than abstract thinking and concept formation ([Lafleche and Albert 1995](#_ENREF_255)). Nevertheless, Albert and colleagues ([2001](#_ENREF_4)) concluded that memory impairment most likely precedes executive function impairment in AD, implying that the development of an executive function impairment in an individual who already exhibits a problem in memory is likely to be an indication of pathological processes and of AD.

### Visuospatial/orientation

Driving becomes an issue in AD patients from the early stages when their spatial orientation ability, including judging distance and speed, becomes impaired ([Frittelli, Borghetti et al. 2009](#_ENREF_169)).

### Psychiatric Symptoms

Non-cognitive symptoms may also be present including social withdrawal and mild depression ([Jost and Grossberg 1996](#_ENREF_228)). Psychiatric symptoms are reported to appear in the moderate stage of AD, with hallucinations as well as misidentifications and delusions being common ([Forstl, Besthorn et al. 1993](#_ENREF_161)). In fact, in the earliest patient investigated by Alois Alzheimer, Auguste D, psychiatric symptoms were very prominent ([Alzheimer 1907](#_ENREF_8)).

## Prognosis

Once a patient has been diagnosed with AD, it has been reported that life expectancy is reduced by one third and it is common for patients suffering with AD to die from pneumonia, as well as other related causes ([Molsa, Marttila et al. 1986](#_ENREF_314); [Beard, Kokmen et al. 1996](#_ENREF_41)).

## Risk Factors

Whilst no definitive cause of AD has been found, several factors have been proposed as increasing the likelihood of being diagnosed with AD. For example, head trauma and a family history of AD are reported as risk factors for developing AD, while having a family history of Down Syndrome has also been suggested as a risk factor ([Jost and Grossberg 1995](#_ENREF_227)). Demographic factors, such as age and educational level, are also said to play a role in the development of the disease ([Mendez and Cummings 2003](#_ENREF_299)). While there is strong evidence that having the ApoE 4 allele makes an individual more likely (than an individual without it) to develop AD ([Anstey and Christensen 2000](#_ENREF_10)), there is tentative evidence that smoking is a risk factor for AD ([Mendez and Cummings 2003](#_ENREF_299)).

### Demographics

#### Age

Age is the biggest risk factor for dementia ([Stephan and Brayne 2008](#_ENREF_416)) and, as individuals age, their risk of developing AD increases ([Fratiglioni, Grut et al. 1991](#_ENREF_167)). Therefore, early and correct diagnosis of this neurodegenerative disease is especially important as we are now experiencing an ageing population ([Cracknell 2010](#_ENREF_99)). Due to better health care, living conditions and nutrition, the life expectancy is increasing. For example, whereas in 1901, the average life expectancy was 45 years (males) and 49 years (females), in 1999 this had increased to 75 years (males) and 80 years (females) (House of Commons paper). It is also estimated that by 2012, the average life expectancy will have increased to 78 years (males) and 83 years (females) ([Hicks and Allen 1999](#_ENREF_202)). Therefore, this would go towards explaining why the number of people developing AD is also increasing - as people are living longer, they are also developing diseases associated with increasing age.

#### Education

Stern ([2002](#_ENREF_418)) proposed that education can be a protective factor against neurodegenerative disease. The argument is that, when neuropathological features begin developing in an individual’s brain, and therefore, cells begin to lose function, a person who has greater cognitive reserve (through factors such as educational attainment or intellect level) has the capacity to compensate for this pathology through reorganisation of brain structure allowing for ‘normal’ cognitive functioning to continue. Nevertheless, whilst reserve factors can protect against neurodegenerative diseases, at a certain point the building pathology within the brain becomes too overwhelming and clinical symptoms begin to manifest in the individual.

#### Gender

In AD, women are said to be more likely than men to develop AD ([Barker, Luis et al. 2002](#_ENREF_35)), although this is a controversial topic. However, this is not the pattern found in other types of dementia. For example, in FTD, men are reported to be more likely to develop this particular type of dementia than women ([Ratnavalli, Brayne et al. 2002](#_ENREF_367)).

#### Genetics

It has been established that AD patients who carry the ApoE 4 allele, not only have a higher risk of cognitive decline as well as developing dementia compared to individuals without this particular allele ([e.g., Anstey and Christensen 2000](#_ENREF_10)), but also present with the cognitive decline several years earlier than those without the ApoE 4 allele ([Goldstein, Ashley et al. 2001](#_ENREF_177); [Dal Forno, Carson et al. 2002](#_ENREF_104); [Mendez and Cummings 2003](#_ENREF_299)). In addition, men with the ApoE ε4 allele have been found to survive a shorter period of time when diagnosed with AD than women ([Dal Forno, Carson et al. 2002](#_ENREF_104)).

### Vascular Risk Factors

The rate of cognitive decline in AD patients without cardiovascular disease (CVD) is said to be influenced by vascular risk factors such as diabetes and cholesterol level, with a faster decline being seen in patients with these risk factors ([Helzner, Luchsinger et al. 2009](#_ENREF_201)), while cognitive decline is slower when these vascular risk factors are treated ([Deschaintre, Richard et al. 2009](#_ENREF_118)).

# Chapter Two: Differential Diagnosis

## Differential Diagnosis: Normal ageing, MCI and AD

An important aim in Alzheimer’s Disease research is to be able to identify individuals at risk of developing this disease at an earlier time point than when AD symptoms become clinically manifest, especially as therapeutic interventions are becoming more readily available and disease-modifying therapies are being researched. Emery ([2011](#_ENREF_138)) argued that intervention is occurring too late in AD, and should in fact occur in pre-AD states, as initiating intervention (pharmacological or non-pharmacological) when conversion to AD is already evident, is less beneficial for the patients.

### Normal ageing

#### Cognitive Profile

A decline in some aspects of cognitive ability does occur with age, and it is important to distinguish between decline that is associated with normal ageing, and that which occurs during the pathological process as seen in Alzheimer’s Disease. Memory is the most studied cognitive domain within AD research as this cognitive function is one of the first to show decline. Nevertheless, impairments in some aspects of memory, whilst not to the extent that they are seen in clinical AD patients, are still quite common in the normal ageing population ([for a review see, Light 1991](#_ENREF_270)), and do not necessarily indicate that an individual will progress to manifest AD (e.g., [Rubin, Morris et al. 1989](#_ENREF_389); [Daly, Zaitchik et al. 2000](#_ENREF_105)). Therefore, accurate and early diagnosis is essential and Seltzer ([2006](#_ENREF_399)) recognises that missed or delayed diagnosis of patients is making this hard to achieve. To understand the changes that occur in AD it is important to study normal ageing individuals and the changes that occur here ([Fox and Schott 2004](#_ENREF_163)), to be able to pinpoint what is part of normal ageing and what is part of the pathological process caused by AD. For example, research has reported that atrophy is seen commonly in the ageing brain, and is simply part of the normal ageing process ([e.g., deLeon, George et al. 1997](#_ENREF_115)). Jack and colleagues ([Jack, Petersen et al. 1998](#_ENREF_220); [Jack, Petersen et al. 2000](#_ENREF_219)) reported that the annual atrophy rate of the hippocampus in normal ageing is 1.6-1.7% (compared to 3.5-4% in AD), while Du and colleagues ([2004](#_ENREF_132)) reported that the annual rate of atrophy in the entorhinal cortex is 1.4% (compared to 6.8% in AD). Nevertheless, a different view held by Morris and Price ([2001](#_ENREF_317)) is that cognitive decline during ageing, even very minimal that may be reported as ‘normal’ by other researchers, is actually abnormal ageing and is an indicator of a disease process.

#### Imaging Profile

Autopsy studies indicate that a slow decline in brain weight occurs in normal ageing individuals ([Ball 1977](#_ENREF_30)) until about the 6th or 7th decade of life, at which time this decline accelerates with global atrophy rates in normal ageing individuals reported as 0.4% (+/-0.7%) annually ([Fox, Scahill et al. 1999](#_ENREF_162)). Furthermore, with the development of new techniques, such as voxel based morphometry, studies have concluded that brain areas are differentially affected by the ageing process ([Coffey, Wilkinson et al. 1992](#_ENREF_93); [Raz, Gunning et al. 1997](#_ENREF_370)), with the medial temporal lobe structures, such as the hippocampus and entorhinal cortex, being relatively spared of grey matter (GM) loss in the normal ageing process ([Raz, Gunning et al. 1997](#_ENREF_370); [Good, Johnsrude et al. 2001](#_ENREF_179); [Raz, Rodrigue et al. 2004](#_ENREF_371); [Rodrigue and Raz 2004](#_ENREF_383)), while the greatest loss is found in the prefrontal cortex ([Coffey, Wilkinson et al. 1992](#_ENREF_93); [Raz, Gunning et al. 1997](#_ENREF_370)), with others extending this and reporting greater GM loss in the frontal and parietal cortices compared with that of the temporal and occipital cortices ([Resnick, Pham et al. 2003](#_ENREF_375)). This is a strikingly different pattern than that shown in AD, whereby it is the hippocampus and entorhinal cortex that are the earliest and most affected brain areas ([e.g., Braak and Braak 1991](#_ENREF_61)). Furthermore, research has now investigated changes within the brains of patients diagnosed with MCI, and some studies report that the entorhinal cortex volume can predict conversion to AD in these patients ([Killiany, Gomez-Isla et al. 2000](#_ENREF_238); [Dickerson, Goncharova et al. 2001](#_ENREF_122)).

#### Neuropathology and normal ageing

NFTs and plaques are found in normal ageing individuals ([Tomlinson, Blessed et al. 1968](#_ENREF_436); [Tiraboschi, Hansen et al. 2004](#_ENREF_433)), even in individuals as young as 30 years old ([Braak and Braak 1997b](#_ENREF_64)), and have been shown to occur independently of each other in the normal ageing brain ([Price and Morris 1999](#_ENREF_359)). While research has indicated that tangles are found in a large majority of normal ageing, non-demented individuals ([Price and Morris 1999](#_ENREF_359)), plaques are less numerous, and one study showed that plaques were devoid in some non-demented individuals up to the age of 88 years ([Price and Morris 1999](#_ENREF_359)). In addition, another study reported that 87% of normal ageing individuals, evidenced NFTs in the allocortex, while only 37% displayed neocortical NPs ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). In contrast, all AD patients displayed NPs ([Tiraboschi, Hansen et al. 2004](#_ENREF_433)). Moreover, Gosche et al ([2002](#_ENREF_180)) also reported that >40% of their participants who were not demented did show neuropathological criteria for AD. The vulnerability of specific neurons, especially in the hippocampal formation, to develop NF changes leads these areas to disconnect from neocortical association areas, ultimately resulting in a loss of cognitive function in AD patients (e.g., [Rogers and Morrison 1985](#_ENREF_384); [Lewis, Campbell et al. 1987](#_ENREF_266); [Hof, Bierer et al. 1992](#_ENREF_207)). Nevertheless, these NF changes are also common in normal ageing individuals (e.g., [Braak and Braak 1990](#_ENREF_59); [Arriagada, Growdon et al. 1992](#_ENREF_19); [Arriagada, Marzloff et al. 1992](#_ENREF_20); [Hof, Bierer et al. 1992](#_ENREF_207)); differences between these and AD patients are seen in the density of NF changes within the neocortex, whereby this region is relatively spared in normal ageing, while it is considerably affected in AD (e.g., [Arriagada, Growdon et al. 1992](#_ENREF_19); [Arriagada, Marzloff et al. 1992](#_ENREF_20); [Hof, Bierer et al. 1992](#_ENREF_207)). Further to this, these authors also noted that, whilst normal ageing individuals do show involvement of the hippocampus, the pathological indicator could be the involvement of the neocortex, due to this sparing of it in normal ageing, but becomes affected in the AD process ([Hof, Bierer et al. 1992](#_ENREF_207); [Bouras, Hof et al. 1993](#_ENREF_55); [Bouras, Hof et al. 1994](#_ENREF_54)). While loss of neurons in the hippocampal formation is found in AD patients as well as non-demented patients, this indicator, while showing sensitivity, appears to lack specificity ([Bobinski, de Leon et al. 1998](#_ENREF_49)). Nevertheless, researchers have suggested that investigating the CA1 sub region of the hippocampus may be a more specific indicator of the disease process as loss of neurons here has been found in AD patients but not necessarily in normal ageing individuals ([West, Coleman et al. 1994](#_ENREF_460)), suggesting that a loss of neurons in this region is a specific disease indicator and not a consequence of normal ageing.

### Mild Cognitive Impairment

#### Clinical Profile

One way in which earlier diagnosis of AD may occur is through testing patients with Mild Cognitive Impairment (MCI). Peterson and colleagues (e.g., [Petersen, Smith et al. 1999](#_ENREF_353); [Petersen, Doody et al. 2001](#_ENREF_350)) provided criteria for diagnosing an individual with MCI:

i) subjective memory impairment corroborated by an informant;

ii) objective memory impairment for age;

iii) generally intact cognitive abilities;

iv) intact activities of daily living;

v) not demented.

These researchers pointed out how individuals, especially those who are destined to develop AD, go through subtle changes of cognitive decline at first, suggestive of this MCI stage. As these changes are subtle, yet still detectable when compared against normal ageing individuals, they suggest that being able to spot these MCI individuals would be useful from a therapeutic perspective as interventions could be made available to these patients when they are still at a reasonably earlier impairment level than those who have been diagnosed as having AD. MCI defines a stage of impairment between normal ageing and AD. However, this is not simply a continuum – normal ageing individuals will not necessarily become MCI individuals (in fact only about 1-2% of the general population over the age of 65 years convert from normal ageing to AD per year) ([Petersen and Morris 2003](#_ENREF_352)); and not all individuals who develop MCI carry on to convert to AD (about 15-20% do per year) ([Petersen 2004](#_ENREF_349)). Peterson & Morris ([2003](#_ENREF_352)) have suggested these three states overlap, and so people at these overlaps are especially hard to diagnose as the distinction between either normal ageing and MCI, or between MCI and AD is relatively subtle.

Redefinitions of MCI have occurred in which subgroups have been defined ([Petersen 2004](#_ENREF_349)):

▪ MCI patients with deficits occurring in memory functions alone;

▪ MCI patients with impairments in multiple cognitive domains; and

▪ MCI patients with impairment in a single domain, but which is not memory.

Researchers have described the range of disorders that are known to have a strong relationship with MCI ([Visser 2006](#_ENREF_451)), such as vascular disorders, and Stephan and colleagues ([2009](#_ENREF_415)) have described a group of patients who show cognitive deficits that are associated with vascular disease, however that does not constitute a diagnosis of dementia.

#### Cognitive Profile

As MCI patients do show abnormal ageing and some do progress to a diagnosis of AD, it is suggested that some impairments seen in AD patients (such as in semantic memory) should also be seen in MCI patients and that performance on these tasks should be more similar to AD patients than the normal ageing controls ([Joubert, Brambati et al. 2010](#_ENREF_229)). However, as MCI patients do not have impairments that are as severely affected by impairments as AD patients, on other measures, MCI patients have also shown to perform more similarly to controls ([Adlam, Bozeat et al. 2006](#_ENREF_1)). Therefore, it is important to distinguish which tests MCI patients will be impaired on and which ones they will show normal performance on.

#### Imaging MCI

The hippocampus has been extensively studied in relation to its integrity and functioning in AD. As researchers have suggested that an increased proportion of individuals with a diagnosis of MCI can go on to convert to AD (compared to normal healthy individuals) ([Petersen 2004](#_ENREF_349)), many have now started investigating whether any changes within the hippocampal structure are already detectable at this early stage of decline (MCI). Many different measures involving the hippocampus and surrounding areas have been identified as being useful at distinguishing normal ageing from pathological ageing seen in AD, and also distinguishing MCI-converters to AD (MCI-c) and MCI-non-converters to AD (MCI-nc). Firstly, the grey matter density of the hippocampus has been reported to differentiate normal controls and AD patients, with AD patients showing a decrease in density (e.g., [Risacher, Saykin et al. 2009](#_ENREF_380); [Risacher, Shen et al. 2010](#_ENREF_381)). Furthermore, Risacher et al ([2010](#_ENREF_381)) also showed a significant difference in GM density of the hippocampus between those MCI patients who later converted to AD (MCI-c) and those who did not (MCI-nc), with MCI-c evidencing greater cognitive decline in hippocampal volume than MCI-nc. Interestingly, no significant differences on these particular measures were found between MCI-c and AD patients.

Davatzikos and colleagues ([2011](#_ENREF_109)) employing their method of recognising AD pathology that occurs early on in the disease process, known as SPARE-AD, demonstrated that this method is useful in terms of predicting conversion, showing that it could predict not only conversion from MCI-c to AD ([Misra, Fan et al. 2009](#_ENREF_307)), but also normal healthy individuals who will go on to be diagnosed with MCI ([Davatzikos, Xu et al. 2009](#_ENREF_110)). Using the SPARE-AD method, Davatzikos et al ([2011](#_ENREF_109)) further investigated structural differences between normal healthy controls, MCI-c, MCI-nc and AD patients. These authors reported that all patient groups had positive SPARE-AD scores that were almost indistinguishable from each other. Therefore, the researchers in this study suggested that this showed how patients with MCI – even those who will not go on to develop AD – show severe structural atrophy compared with normal aging individuals even at this early level of cognitive impairment.

#### Neuropathology and MCI

Memory is one of the first cognitive functions to decline in AD patients ([Mesulam 1999](#_ENREF_300)). Furthermore, this memory impairment, whilst not being severe enough to affect activities of daily living, is also seen in patients in the MCI stage. It has been suggested that this preclinical stage of AD can be represented by the first two Braak stages, known as the transentorhinal stages, whereby loss of function is minimal and is confined to memory function, with NFTs being confined to the transentorhinal area of the brain ([Braak, Griffing et al. 1999](#_ENREF_58)).

## Differential Diagnosis: Other types of Dementia

Successful differential diagnosis of the dementias is particularly important, especially in an age where therapeutic interventions are becoming more readily available. Being able to correctly identify the cause of the dementia, will allow for the correct treatment interventions to be made available to patients that will benefit most from them, and will avoid any negative effects brought on by giving inappropriate treatment to patients. For example, whilst Cholinesterase Inhibitors (ChEIs) appear effective in the treatment of patients with AD by slowing down the cognitive decline seen in these patients ([Birks 2006](#_ENREF_43)), this pharmacological option is not suitable for FTD patients as a cholinergic deficit is not reported in these patients ([Procter, Qurne et al. 1999](#_ENREF_360)). Instead, although treatment with ChEIs is unsuccessful in alleviating symptoms in these patients ([Kaye 1998](#_ENREF_235)), however, pharmacological treatment that modulates behavioural symptoms, such as serotonin therapeutic inhibitors (SRI), are more successful in FTD patients ([Kaye 1998](#_ENREF_235)). Similarly, whilst antipsychotics alleviate behavioural symptoms experienced by FTD patients ([Kaye 1998](#_ENREF_235)), they may produce adverse effects if given to patients with AD as some research suggests giving antipsychotics to AD patients can increase the cognitive decline they experience ([Mendez and Cummings 2003](#_ENREF_299)), and increase mortality ([Ballard, Creese et al. 2011](#_ENREF_31)).

Nevertheless, while differential diagnosis is essential it is not simple, especially as the distinction between the different types of dementia is blurred by many factors. For example, Alzheimer Society figures show that a diagnosis of mixed dementia, i.e., a patient that exhibits dementia due to both vascular factors and Alzheimer’s Disease, is given in 10% of dementia cases ([Knapp, Prince et al. 2007](#_ENREF_246)). Therefore, neuropsychological assessment has been used to provide insight into how patients with different types of dementia perform on a wide range of cognitive tests.

### Frontotemporal Dementia

#### Clinical Profile

The clinical criteria for Frontotemporal Dementia have been described by Brun and colleagues ([1994](#_ENREF_71)) for the Lund and Manchester Groups. The core diagnostic components of the behavioural disorder are:

- Insidious onset and slow progression;

- Early loss of personal awareness;

- Early loss of social awareness;

- Early signs of disinhibition;

- Mental rigidity and inflexibility;

- Hyperorality;

- Stereotyped and perseverative behaviours;

- Utilisation behaviour;

- Distractibility, impulsivity, impersistence.

- Early loss of insight.

Further components of the Lund-Manchester criteria include:

- Affective symptoms (e.g., depression, anxiety);

- Speech and language disturbances (e.g., reduction of speech);

- Physical signs (e.g., early primitive reflexes).

Supportive diagnostic criteria also include:

- Onset before 65 years of age;

- Positive family history of similar disorder;

- Motor Neurons Disease (MND).

The Lund-Manchester criteria also suggest exclusion criteria, including abrupt onset and head trauma related to onset, as well as ways of investigating the disorder, including neuropsychological assessment, brain imaging and EEG.

FTD is known as a behavioural disorder and is characterised by changes in personality and behaviour that can be very disturbing for spouses and family members to understand and cope with. As FTD patients have poor insight as well as poor introspection skills, they do not necessarily realise their behaviour is inappropriate. Utilisation behaviour is also described in patients with FTD as well as impulsivity and disinhibition. Therefore, a clinical interview is especially important in diagnosing FTD as these behavioural abnormalities can be evidenced in the patient, either by simply observing the patient or by questioning their accompanying carer. Furthermore, this behaviour change is said to precede any cognitive impairment ([Pasquier, Lebert et al. 1995](#_ENREF_340)). Due to the presence of behavioural disturbances before any cognitive decline is seen on neuropsychological assessments ([Pasquier, Lebert et al. 1995](#_ENREF_340)), these patients can be often misdiagnosed as having a psychiatric disorder ([Walker, Meares et al. 2005](#_ENREF_453)). Gregory and Hodges ([1996](#_ENREF_183)) reported that over half of FTD patients in their sample were initially referred to a psychiatrist, while about 1/3rd were initially given a psychiatric diagnosis. Furthermore, due to the cognitive decline not necessarily occurring in very early stages of FTD, researchers have reported some FTD patients perform at a similar level to healthy controls ([e.g., Walker, Meares et al. 2005](#_ENREF_453)), which could further lead the examiner to a diagnosis of a psychiatric illness as opposed to FTD.

Studies have recently discovered another group of patients who show the same clinical profile of FTD patients, yet lack the atrophy or progression of these symptoms as you would expect to find in FTD (e.g., [Kipps, Hodges et al. 2009](#_ENREF_240); [Kipps, Hodges et al. 2010](#_ENREF_241)).

The prognosis of FTD has been reported to be 6 years (+/-1.1 years), however, differences exist between subtypes of FTD, as well as with the dual diagnosis of FTD and MND which carries a worse prognosis ([Hodges, Davies et al. 2003](#_ENREF_204)).

#### Risk Factors

##### Family history and Mutations

Studies have found a large per cent of patients with FTD have a family history of the disease. For example, Stevens, van Duijin et al ([1998](#_ENREF_420)) reported that individuals with a first degree relative with dementia had a 3.5% increased risk of developing FTD compared with control participants. Furthermore, these authors also indicated that, not only are individuals at an increased risk of developing FTD if they have a first-degree relative with the disease, but also that they are more likely to develop the disease at an earlier time point than FTD in the general population – up to 11 years earlier.

There are two main mutations that cause FTD. The most common is the 43 kDa TAR DNA-binding protein (TDR-43) inclusions. Other FTD patients (about 40%) exhibit microtubule-binding protein tau inclusions. Another mutation has also recently been discovered in which patients exhibit the RNA-binding fused in sucoma (FUS) mutation ([Neumann, Rademakers et al. 2009](#_ENREF_328)), however this is rarer than the other mutations ([Neumann, Rademakers et al. 2009](#_ENREF_328); [Verbeeck, Deng et al. 2012](#_ENREF_449)).

##### Age and Gender

Generally, patients diagnosed with FTD are younger than those diagnosed with AD ([Boccardi, Laakso et al. 2003](#_ENREF_52)). Ratnavalli et al ([2002](#_ENREF_367)) reported that, even in early onset cases of both FTD and AD (i.e., <65 years old), the FTD group had a significantly lower age at symptom onset (52.8 vs. 57.7 years, respectively) as well as at time of diagnosis (56.1 vs. 60.7 years, respectively). Furthermore, whilst women are more likely to develop AD, men are more likely to develop FTD ([Ratnavalli, Brayne et al. 2002](#_ENREF_367); [Boccardi, Laakso et al. 2003](#_ENREF_52)).

#### Cognitive Profile

##### Episodic Memory

Episodic memory deficits, whilst a defining characteristic of AD patients, has been used as an exclusion criteria in FTD patients ([Brun, Englund et al. 1994](#_ENREF_71)). Therefore, for many years, this feature of both patient groups became a way of differentiating AD from FTD. However, historically, episodic memory deficits have been found in FTD patients. For example, in the very first cases described by Arnold Pick, over half of the patients were reported to have episodic memory impairments, with one patient showing very severe impairment ([Pick 1892](#_ENREF_357)). Furthermore, other studies ([Papma, Seelaar et al. 2012](#_ENREF_339)) also reported episodic memory impairments in FTD patients. Moreover, even in the early stages of the disease, studies have found that episodic memory deficits do occur, with pathologically confirmed cases ([Hodges, Davies et al. 2004](#_ENREF_205)). One reason for these differing results could be due to the extensive language deficits and behavioural changes seen in FTD patients covering up episodic memory deficits. Hornberger & Piguet ([2012](#_ENREF_210)) also suggest that, when the FTD clinical criteria were devised and episodic memory became an exclusion criterion, the prominence of AD could have influenced this decision – i.e., those researchers creating the FTD criteria were trying to distinguish it from AD.

##### Neuropsychological findings

FTD patients are said to show a lesser cognitive decline during the early stages, due to the behavioural changes being the first symptoms, compared to AD where the first symptoms are cognitive decline, especially in memory ([Braak and Braak 1991](#_ENREF_61); [Hutchinson and Mathias 2007](#_ENREF_212)). Memory impairment is suggested to be secondary to behaviour changes in FTD patients ([e.g., Pasquier, Lebert et al. 1995](#_ENREF_340)). Furthermore, visuospatial ability is also said to be relatively spared in FTD, especially in the early stages ([e.g., Hutchinson and Mathias 2007](#_ENREF_212)) which is not the case in AD whereby this skill is increasingly lost and is even seen at an earlier level of decline in individuals diagnosed with MCI. Nevertheless, other studies have suggested AD patients do have significantly better executive functioning skills than FTD patients (e.g., [Pachana, Boone et al. 1996](#_ENREF_337); [Walker, Meares et al. 2005](#_ENREF_453)) even though they are still impaired relative to normal ageing individuals. Therefore, this suggests that while these two causes of dementia both show executive functioning deficits, the FTD groups’ impairment is significantly worse. Furthermore, Woodward et al ([2010](#_ENREF_469)) also reported that FTD patients have a faster rate of decline on executive function ability than do AD patients. Contrastingly, Hutchinson & Mathias ([2007](#_ENREF_212)) found that tests of executive function did not seem able to discriminate between these two dementia types, although the authors note that other tasks that involve some level of executive control, for example, the letter fluency task, did show differential diagnosis abilities. Other neuropsychological findings between these two dementia groups include differences in nonverbal memory ([e.g., Pachana, Boone et al. 1996](#_ENREF_337)), verbal abilities and language, constructional ability ([Hutchinson and Mathias 2007](#_ENREF_212)). Whilst not reaching significance, Walker and colleagues ([2005](#_ENREF_453)) noted trends towards FTD patients performing better on attentional tasks and psychomotor speed when compared with a group of AD patients. Some studies have also noted similar performances on tasks assessing constructional abilities ([e.g., Walker, Meares et al. 2005](#_ENREF_453)). Furthermore, measures of concept formation and reasoning could not differentiate the groups ([Hutchinson and Mathias 2007](#_ENREF_212)). From their meta-analytic review, Hutchinson & Mathias ([2007](#_ENREF_212)) concluded that the best cognitive functions that give the best discriminability between AD and FTD are memory, whereby FTD perform better, and verbal ability and language, whereby AD patients perform better.

### Vascular Dementia

#### Clinical Profile

The second most common cause of dementia is Vascular Dementia and can be caused by cerebrovascular disease or hypoperfusive lesions ([Roman and Benavente 2004](#_ENREF_386)). Clinical criteria has been proposed by Roman and colleagues ([1993](#_ENREF_385)) for the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), at the International Workshop (NINDS-AIREN International Workshop), which involves patients displaying all of the following:

1) Dementia – defined by cognitive decline from a previously higher level of functioning.

2) Cerebrovascular Disease (CVD) – defined by the presence of focal signs on neurologic examination.

3) A relationship between 1) and 2) – inferred by the presence of one or more of the following:

a) onset of dementia within 3 months;

b) abrupt deterioration in cognitive functions; or,

c) stepwise progression of cognitive deficits.

Clinical features consistent with the diagnosis of probable VaD include: gait disturbance; unprovoked falls; urinary frequency; urgency; pseudobulbar palsy; personality and mood changes.

Roman & Benavente ([2004](#_ENREF_386)) highlighted the issue that, unlike in other forms of dementia such as AD, there is no neuropathological gold standard for diagnosis of VaD. They also report that diagnosis is particularly difficult in VaD as ascertaining whether the cerebrovascular lesion is ‘causal, contributory, or coincidental’ is extremely hard to determine ([Roman and Benavente 2004](#_ENREF_386)). Furthermore, the co-occurrence of VaD and AD is common ([Snowdon, Greiner et al. 1997](#_ENREF_409); [Zekry, Hauw et al. 2002](#_ENREF_472)), and research has demonstrated that AD patients exhibit cerebrovascular lesions at autopsy in 72% of cases (i.e., less than 30% were ‘pure’ AD) ([Goulding, Signorini et al. 1999](#_ENREF_181)). Other studies have supported this view finding that cerebrovascular lesion severity and Braak staging of AD neuropathology show an inverse relationship ([Goulding, Signorini et al. 1999](#_ENREF_181)).

#### Cognitive Profile

VaD patients are more likely to present with a patchy, step-wise progression of decline ([e.g., Nagata, Saito et al. 2007](#_ENREF_325)) which can distinguish this from the pattern of decline seen in AD patients who show a more linear decline of cognitive functions. Furthermore, VaD patients have slower reactions times ([Almkvist 1994](#_ENREF_6)), poorer performance on tests assessing frontal mechanisms ([Kertesz and Clydesdale 1994](#_ENREF_237)), and better visual and recent memory ([Ballard, Patel et al. 1996](#_ENREF_32)) compared with AD patients.

### Imaging AD, FTD and VaD

Imaging has been used to compliment neuropsychological test data and to support differential diagnosis. As structures in the MTL are the first areas where AD pathology develops, a lot of research has focussed on imaging these structures to investigate their contribution to differential diagnosis. Similar to AD, FTD patients show atrophy in hippocampus and MTL regions even in the early stages of the disease, both at autopsy ([Broe, Hodges et al. 2003](#_ENREF_69); [Kril and Halliday 2004](#_ENREF_251)) and on neuroimaging ([Seeley 2008](#_ENREF_397); [Seeley, Crawford et al. 2008](#_ENREF_398)). Comparing the atrophy patterns of the hippocampus and ERC in AD and FTD patients, Laakso et al ([2000](#_ENREF_253)) reported that FTD patients show specific atrophy within the anterior hippocampus while AD patients show more widespread atrophy of the hippocampus, while the ERC showed similar patterns of atrophy between these two groups ([Frisoni, Laakso et al. 1999](#_ENREF_168)). Furthermore, Laakso and colleagues ([2000](#_ENREF_253)) also noted that the FTD group showed atrophy of the hippocampus in the anterior region, with no significant differences between the control group and FTD group on the volume of the posterior region of the hippocampus. This lends further supporting evidence to reports that atrophy in FTD is confined to the anterior region of the hippocampus. Conversely, in AD, this atrophy is more diffuse throughout the hippocampus when compared with control subjects ([Jack, Petersen et al. 1998](#_ENREF_220)). Therefore, while there is some overlap in atrophy patterns between AD and FTD patients in terms of the ERC, there is also room for differential diagnosis when looking at the differences between atrophy patterns of the hippocampus. Laakso et al ([2000](#_ENREF_253)) suggests that the sparing of the posterior part of the hippocampus in FTD patients is in line with neuropsychological findings as Moser et al ([1993](#_ENREF_319)) have shown that this region supports functions including visuospatial memory – a function that is relatively well preserved in FTD patients ([Hutchinson and Mathias 2007](#_ENREF_212)). Furthermore, whilst the Braak and Braak ([1991](#_ENREF_61)) staging of AD indicates the hippocampus and entorhinal areas of the MTL as the first sites where AD pathology develops, Tartaglia et al ([2011](#_ENREF_427)) have reported various sites within the frontal lobe as the first sites where FTD pathology develops, which research has shown can differentiate FTD patients from controls ([Fukui and Kertesz 2000](#_ENREF_170)).

Boccardi and colleagues ([2003](#_ENREF_52)) argued that using a specific atrophy pattern, rather than singling out individual regions of the brain, is more informative both in diagnosis and in differential diagnosis. This idea has been used in several other patient groups such as Dementia with Lewy Body (DLB), AD, VaD ([Barber, Ballard et al. 2000](#_ENREF_34)), supranuclear palsy and Parkinson’s Disease (PD) ([Cordato, Halliday et al. 2000](#_ENREF_96)). In their study, the researchers found that the FTD patients showed severe atrophy in both frontal and temporal regions, with milder atrophy in the hippocampus, while AD patients showed a similar level of moderate atrophy in the temporal and hippocampal regions, with mild involvement of frontal regions ([Boccardi, Laakso et al. 2003](#_ENREF_52)). Furthermore, while the language impairment would indicate a left-dominant involvement, behavioural changes implicate the right side. Nevertheless, FTD patients show asymmetric atrophy patterns (left>right), while AD patients’ atrophy was more similar in both hemispheres ([Boccardi, Laakso et al. 2003](#_ENREF_52)). This asymmetrical atrophy pattern in FTD patients has been noted in several studies (e.g., [Miller and Gearhart 1999](#_ENREF_304); [Boccardi, Laakso et al. 2003](#_ENREF_52)) including on single-photon emission computed tomography (SPECT) imaging ([Miller and Gearhart 1999](#_ENREF_304)).

Ultimately, differential diagnosis of the cause of the dementia is essential for many different reasons. To effectively treat and help manage the patient’s symptoms is a main priority, in which case accurately diagnosing someone with a particular form of dementia can lead to an appropriate treatment option being available for the individual. Successful differential diagnosis can avoid exposing patients to potentially dangerous medications ([Tartaglia, Rosen et al. 2011](#_ENREF_427)) and leads to better patient management.

## Treatment in AD

### Pharmacological Treatment

At present, there is no known cure for Alzheimer’s Disease. However, successful research has led to the development of pharmacological treatment that has been shown to slow down this progressive disease through acting on the deficits that are seen early in the disease process within the cholinergic system. Treatment options have been devised from observations of AD destroying the cholinergic neurotransmission system in the central nervous system.

#### The Cholinergic Hypothesis

The Cholinergic Hypothesis was first proposed in the 1970s after extensive biochemical studies showed that the amount of acetylcholine (ACh) within the brain is decreased in patients with AD ([Siegfried 1993](#_ENREF_403); [Francis, Palmer et al. 1999](#_ENREF_165)). Since then, research has shown that the death of cholinergic neurons within the brains of patients with AD correlates with the cognitive symptoms that are apparent in this disease ([eg, Siegfried 1993](#_ENREF_403)). The nucleus basalis of Meynert (nbM) in the basal forebrain has been extensively studied as it is a major source of cholinergic innervation in the brain ([eg, Whitehouse, Price et al. 1982](#_ENREF_463)) and shows a greater than 75% depletion of neurons in patients with AD ([Whitehouse, Price et al. 1982](#_ENREF_463)). Some studies have shown how the thickness of the substantia innominata, which is thought to be a marker of damage of the cholinergic neurons within the nbM, decreases with age ([eg, Hanyu, Asano et al. 2002](#_ENREF_195)). However, AD pathology shows even further significant atrophy of the substantia innominata compared to normal ageing individuals ([Hanyu, Asano et al. 2002](#_ENREF_195); [Hanyu, Tanaka et al. 2002](#_ENREF_196)), a finding which has also been documented in other dementia syndromes including FTD, VaD and PD ([Hanyu, Asano et al. 2002](#_ENREF_195)). Furthermore, Muth and colleagues ([2010](#_ENREF_323)) also reported that cell damage within the substantia innominata was already present in MCI patients, with these patients showing 24% less cell volume than normal controls in this region. Furthermore, they reported a correlation between substantia innominata volume in AD and cognitive performance on the word list recall task (Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) subtest). The cholinergic deficit that is seen in AD, whilst not being the sole neurotransmitter (NT) system deficit within the brains of these patients, is the most consistent ([Perry, Perry et al. 1978](#_ENREF_344)). In the brain, acetyl-CoA and choline are synthesised by choline acetyltransferase (ChAT), producing ACh. ACh is released by the pre-synaptic terminal into the synaptic cleft, whereby from here, some of the ACh crosses to the post-synaptic receptor and some is broken down by the enzyme acetylcholinesterase (AChE) into its constituent parts – acetate and choline. This breaking down of ACh terminates its post-synaptic potential because of the lack of response by the post-synaptic receptor to acetate or choline. In normal ageing, ACh has been shown to be depleted within the brain, however, within AD, this depletion of ACh reaches abnormal levels and research has suggested that this reduction correlates with AD severity ([eg, Lanctot, Herrmann et al. 2003](#_ENREF_256)). Further evidence that the cognitive decline seen in AD is, at least in part, related to this cholinergic deficit comes from studies which indicate that this reduction of cholinergic neurons is seen in brain areas that are the earliest affected by AD pathology, including the hippocampus and temporal cortex ([Siegfried 1993](#_ENREF_403)), and that suggest cognitive functions, including attention and tests of language, have a cholinergic basis ([Callaway, Halliday et al. 1992](#_ENREF_76)).

#### Cholinesterase Inhibitors

Therefore, based on this hypothesis, new pharmacological treatment options were developed and cholinesterase inhibitors (ChEIs) licensed for use. Tacrine, a first generation ChEI licensed in 1993 ([Bartus 2000](#_ENREF_38)), but which was never licensed in England, showed some promising results in terms of improving cognition ([for a review see, Crismon 1994](#_ENREF_101)). However, the use of this drug for AD treatment has now fully ceased as it has been associated with excessive levels of hepatotoxicity as well as showing a risk for interacting with other medications ([Birks, Evans et al. 2009](#_ENREF_44)). Physostigmine, another first generation ChEI, showed mild improvement in cognitive functioning in normal healthy individuals and AD patients, however due to the effects of this ChEI on cognition being only mild, as well as these effects lasting a very short period of time (a few seconds to minutes), there was little overall clinically meaningful effect ([Siegfried 1993](#_ENREF_403)). Initial promising results were also captured using Eptastigmine ([Imbimbo, Martelli et al. 1999](#_ENREF_214)), however trials were stopped using this drug due to the severe hematologic side effects experienced by a few patients. In England, Donepezil was the first ChEI to be licensed ([Courtney, Farrell et al. 2004](#_ENREF_98)) which, along with Rivastigmine and Galantamine, makes up the second-generation ChEIs. Donepezil is an uncompetitive AChE inhibitor that has the longest half-life of all the second generation ChEIs. Rivastigmine is a dual ChEI, which inhibits both AChE and butyrylcholinesterase (BuChE), as research suggests that BuChE also acts on ACh ([Lane, Potkin et al. 2006](#_ENREF_258)). Galantamine also has a dual mechanism and inhibits AChE as well as modulating nicotinic receptors. Another pharmacological treatment for AD patients is Memantine. This is not in the class of ChEIs, but instead is an N-methyl d-aspartate (NMDA) antagonist.

#### Response

##### Assessment Criteria

One problem researchers have come across is exactly how to determine when a patient has benefitted sufficiently from ChEI treatment over placebo or no treatment. Several organisations have selected criteria for classifying AD improvement as clinically significant, which all differ. For example, whilst the US Food and Drug Administration suggest a 4-point increase or more on the Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-Cog) is sufficient for a patient to be classed as improving, the European Medicines Evaluation Agency suggests a 4-point increase or more on the ADAS-Cog in addition to a stable profile of ADL and clinician evaluation based on the Clinical Interview Based Impression of Change (CIBIC) is necessary. In the UK, whilst the National Institute for Health and Clinical Excellence (NICE) is the organisation that has implemented guidelines for the use of ChEIs in AD, they do not give specific criteria on how to measure response. Further to the aforementioned published response criteria, researchers also tend to use their own devised criteria. In addition, some researchers have put forward the argument that, as AD is a progressive disease, a mild decrement in scores could still be seen to be a response ([Saumier, Murtha et al. 2007](#_ENREF_394)). A large amount of research has looked at response to ChEI treatment to ultimately try to predict response prospectively.

##### Semantic Fluency and Response

Hanyu et al ([2002](#_ENREF_196)) suggest the idea that, as Lewy-Body dementia patients have better response to ChEI treatment than AD patients ([Liberini, Valerio et al. 1996](#_ENREF_269)), it could be that individual response depends on the amount of cholinergic depletion, as LBD patients have more cholinergic neuronal loss in the nbM. Therefore, taken with Hanyu et al’s ([2002](#_ENREF_196)) own results, it could be suggested that better responders to ChEI treatment may be patients with more atrophy and more cholinergic depletion. Venneri, McGeown et al ([2009](#_ENREF_446)) showed support in-line with this as the researchers here evidenced that patients classified as responders to treatment, showed worse semantic fluency performance at baseline.

##### Cognitive Assessment and Response

Whilst no differences were seen in baseline assessments, after 6 months of Donepezil treatment, Saumier et al ([2007](#_ENREF_394)) noted differences between those who responded to the ChEI treatment compared to those who did not respond on tests including the Boston Naming Test (BNT), Clock Drawing test and tracking task, which assess visuo-spatial motor abilities and lexical-semantic functioning. In all significant results, the responders outperformed the non-responders. Nevertheless, Saumier et al ([2007](#_ENREF_394)) concluded that, whilst taken together these tests assessing visuo-spatial motor and lexical-semantic functioning seem able to predict response to donepezil treatment after 6 months, when used individually to assess response this was not the case. Other studies have also shown worse performance by non-responders on baseline measures of concept formation and reasoning ([Venneri, Shanks et al. 2002](#_ENREF_448)). Therefore, it seems that several measures should be used in conjunction with each other to more accurately predict response to ChEI treatment in AD.

# Chapter 3: Aims and Objectives

Dementia leaves a devastating path of destruction and, as the causes of it are varied, the need to detect these causes at a stage whereby intervention (both pharmacological and non-pharmacological) is most likely to succeed, is essential. Being able to differentiate between the causes of dementia and target each individually is needed if we are to achieve accurate diagnoses as well as diagnoses that are made as early in the disease process as possible. One way in which this is achievable is through the use of neuropsychological assessment, which, in the absence of reliable biomarkers of neurodegenerative diseases such as AD, remains the cornerstone in clinical diagnosis. Furthermore, being able to use tests that are readily available and easily interpretable is essential as it is necessary to identify patients in primary care settings, to ensure timely specialist intervention for those who are at risk and avoid unnecessary investigations to those whose decline is not suggestive of an underlining neuropathological process.

## Aims and objectives

As highlighted above, the need for early and differential diagnosis is an important issue in dementia research, but one which has been difficult to resolve to a sufficient success rate. However, the use of a focussed neuropsychological test battery can help to clear this picture. More specifically, the use of semantic tasks, especially semantic fluency tasks, in the differentiation of normal ageing from AD looks like a promising area to investigate. Furthermore, the ability of these tasks to identify individuals in a less severe clinical state than when a diagnosis of AD is made at present, but who do not appear to be ageing ‘normally’, as is seen in the MCI stage, will be of significant clinical importance and a significant goal to achieve. Therefore, to address this point, study 1 and 2 have been carried out and reported in chapters 4 and 5. In detail, study 1 (chapter 4) addressed the issue of differentiating normal and pathological decline through the use of a standardised neuropsychological battery of tests that included the semantic fluency task. We further analysed this task by exploring the words produced based on lexical-semantic attributes such as Age of Acquisition (AoA).

Study 2 (chapter 5) addressed the issue of differential diagnosis amongst different causes of dementia (AD, FTD and VaD), including the preclinical MCI stage. Again, a standardised neuropsychological test battery was used to investigate performance differences between these patient groups. The semantic (category) and phonemic (letter) fluency tasks were further analysed as in study 1 to investigate their utility in differential diagnosis. To be able to accurately distinguish between the different causes of dementia is essential as it would lead to fewer inaccurate diagnoses being made as well as allow for the correct interventions to be tailored to the individual diseases.

Study 2.1 and study 2.2 (chapters 6 and 7, respectively) further investigated differential diagnosis of AD patients, FTD patients and normal healthy controls. Here, a specific visuospatial task (Rey’s Complex Figure) and episodic memory task (Prose Memory) were the focus of investigation. In detail, study 2.1 investigated the utility of the Rey Complex Figure task in differentiating AD from FTD by analysing the organisation of the drawing, instead of the usual method of scoring the construction of the drawing. Based on previous literature, that FTD patients have intact visuospatial skills, the study results, using the Rey Complex Figure task as a test of organisation and planning abilities, would go towards increasing the effectiveness of differential diagnosis between these two forms of dementia.

Study 2.2 investigated the use of a prose memory task assessing short and long-term verbal episodic memory. Here, the story detail recall as well as recall of story themes was analysed to investigate how the different patient groups organise a story, and whether this is helpful in recalling of individual details of the story. Furthermore, we wanted to investigate, using this method, whether the episodic memory impairments seen in FTD patients in previous literature were true memory impairments, indicating hippocampal involvement in this disease, or whether they were determined by poor thematic organisation caused by the frontal dysfunction characteristics of this disease.

Study 3 (chapter 8) addressed the issue of conversion in MCI patients. As not all MCI patients go on to convert to AD, it is a useful task to investigate the neuropsychological differences between converters and non-converters which will help identify those MCI patients at increased risk of developing AD. To address this issue, we investigated the use of neuropsychological tests in identifying patterns of performance indicative of a worsening disease state, which could identify those patients who are most likely to convert to clinical AD (MCI-c) from those who are more likely to remain stable (MCI-nc).

Following this, predicting who will respond to the pharmacological treatment available will allow for these interventions to target those patients who will benefit the most from intervention, and at a stage early enough to have some clinical impact. Ultimately, after successful and early diagnosis has been completed, another issue to tackle is selecting patients who will benefit most from pharmacological treatment (ChEIs), and determining the time point at which intervention is most effective. Therefore, study 4 (chapter 9) addressed this issue, and here we compared the baseline MMSE performance of both mild and moderate AD patients before initiation of ChEI treatment, with MMSE scores at two follow up time periods, one in the short term, and one in the longer term. We analysed the response to ChEI treatment in both AD groups, and investigated whether response to ChEIs differed over the time periods, as well as whether there was any difference in response to treatment in mild compared with moderate AD patients.

# Chapter 4: Distinguishing normal and pathological ageing effects

## Introduction

### Cognitive Changes in Normal Ageing

A decline in some aspects of cognitive ability does occur with age, and it is important to distinguish between decline that is associated with normal ageing, and that which occurs during a pathological process as seen for example in Alzheimer’s Disease.

#### Neuropsychological assessment: general cognitive functioning

Neuropsychological assessment is used by professionals as a means to give a probable diagnosis, or to certify a diagnosis. Neuropsychological assessment can be useful in differentiating diagnosis when used in conjunction with neuroimaging or where neuroimaging is inconclusive. With dementia, such neuropsychological assessments include the Mini Mental State Examination (MMSE). Tests such as this can indicate the presence of cognitive impairment. Whilst Cummings ([2004](#_ENREF_103)) described the MMSE as being very resilient, it does not come without its faults, one being the fact that it is insensitive to changes in patients in the earliest stages of dementia, as well as in individuals who are high-functioning ([Cummings 2004](#_ENREF_103)) or people from different cultural backgrounds who may also score poorly despite no cognitive impairments ([Tombaugh and Mcintyre 1992](#_ENREF_435)). Tombaugh & McIntyre ([1992](#_ENREF_435)) also suggested that the items in it are not all judged to be of equal sensitivity to cognitive impairments. Therefore, while it can highlight in which particular cognitive domain a patient has a deficit, it is less suitable as a diagnostic tool.

#### Episodic Memory

Several researchers have noted that memory is one of the earliest cognitive functions to become impaired in AD patients. Specifically, these patients show very poor encoding of new material in the very earliest stages of the disease ([Moss, Albert et al. 1986](#_ENREF_320); [Welsh, Butters et al. 1992](#_ENREF_459)), which is evidenced in neuropsychological measures of episodic memory. An abundance of previous research has focused on episodic memory ability and AD (e.g., [Baudic, Barba et al. 2006](#_ENREF_39); [Dannhauser, Shergill et al. 2008](#_ENREF_106)). Many studies however, have reported a decline in episodic memory in individuals ageing normally as well as in those experiencing a decline due to AD ([e.g., Ciaramelli, Lauro-Grotto et al. 2006](#_ENREF_90)). Therefore, detecting a deficit in this type of memory does not necessarily distinguish pathological ageing (at least in the early stages) from normal ageing, and the presence of an impairment does not necessarily mean an individual will go on to develop AD ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)).

#### Executive Functions

Due to these problems in distinguishing normal from pathological ageing, the diagnostic potential of other cognitive abilities have been investigated. Further to memory, executive functioning has also been studied quite extensively in regards to the normal and abnormal ageing processes ([Baddeley, Logie et al. 1986](#_ENREF_27); [Sahakian, Downes et al. 1990](#_ENREF_392); [Lafleche and Albert 1995](#_ENREF_255)). Frontal involvement is also required during tests of verbal fluency when participants must employ processes of executive control which help them not repeat words they have previously produced ([Baldo, Schwartz et al. 2006](#_ENREF_29)). The letter fluency task, in which participants must produce words beginning with a particular letter (for example, ‘P’), is said to rely (almost solely) on frontal processes. Many studies have shown a worse impairment level in AD patients on the semantic vs. the phonemic fluency task (e.g., [Pasquier, Lebert et al. 1995](#_ENREF_340); [Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Capitani, Rosci et al. 2009](#_ENREF_78)), which would support the neuropathological research that shows areas of the brain which support semantic memory, in particular the perirhinal cortex and entorhinal cortex, are the first sites where AD pathology develops ([Braak and Braak 1991](#_ENREF_61)). The disproportionate semantic fluency impairment in AD is said to reflect greater effects of AD pathology on brain areas involved in semantic functions, and though AD patients are also impaired on the letter fluency task compared to normal controls, impairments in semantic fluency tasks is greater than in letter fluency because of a greater burden of the disease on the semantic store, affecting therefore patients ability to access/retrieve many category exemplars. Albert and colleagues ([2001](#_ENREF_4)) concluded that memory impairment most likely precedes executive function impairment in AD, implying that the development of an executive function impairment in an individual who already exhibits a problem in memory is likely to be an indication of pathological processes and AD.

#### Semantic Memory

The assessment of semantic memory appears to provide one avenue to substantially increase diagnostic confidence. One reason for choosing to examine semantic memory is that, unlike the impairments that have been reported in episodic memory in normal ageing individuals, deficits are not evidenced to occur due to age in semantic memory ([Craik 1994](#_ENREF_100)). Research has also shown that semantic memory impairments are abundant in patients with AD and that increased severity of disease results in greater decline in semantic memory ([Westmacott, Black et al. 2004](#_ENREF_462)).

##### Semantic Fluency task

To test the integrity of semantic memory, fluency tasks have been used and these appear to be very useful indicators of AD ([Monsch, Bondi et al. 1992](#_ENREF_315)). The most widely used is the category fluency task and involves individuals orally generating as many responses as possible to specific categories (for example, ‘Animals’) within a 60 seconds time limit. Their ability to successfully discriminate normal from pathological ageing has been noted by many authors ([Cummings 2004](#_ENREF_103); [Duff-Canning, Leach et al. 2004](#_ENREF_135)). Along with producing fewer words on the semantic category fluency task, AD patients also perseverate more and include more intrusions and wrong category examples within their answers, when compared with healthy older adult controls ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)).

##### Lexical Characteristics analysis

Forbes-McKay and colleagues ([2005](#_ENREF_159)) also measured the lexical characteristics of the words produced in the category fluency task and compared them between groups. These lexical attributes included Age of Acquisition (AoA), which is a measure that estimates when a word is first learned in life. The study revealed that AD patients produce earlier acquired, as well as more frequent and more typical words on this task when compared with normal ageing controls ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)). One explanation of why AD patients produce earlier acquired words might be that words acquired early in life are more richly connected and embedded and so, while AD pathology disrupts later acquired words making these less likely to be generated in a 60 second semantic fluency task, the earlier acquired words, due to this better connection and support, can still be accessed by AD patients ([Steyvers and Tenenbaum 2005](#_ENREF_421)) even by severely impaired patients. Using the VBM technique, Venneri and colleagues ([2008](#_ENREF_445)) reported that lexical word attributes (AoA and typicality) were associated with grey matter volumes in the parahippocampal gyrus and temporal gyri. This association is a particularly important result as it suggests that these lexical attributes, AoA and typicality, are associated with areas of the brain that are compromised early in AD and also in MCI patients. Therefore, analysing the semantic fluency task using these specific lexical attributes should allow for a significant distinction of normal and pathological ageing.

Forbes-McKay et al ([2005](#_ENREF_159)) also looked into the idea that controls could produce later acquired words simply because they named more words in the 60 second trials. If that were the case, the difference could simply be an artefact due to the reduction in number of items produced rather than a difference in the types of items produced and would therefore have poor diagnostic value. To address this possible criticism it would be sufficient to look at just the first few words produced within the categories of ‘animals’ and ‘fruits’, to verify whether the difference persisted. Therefore, the researchers took the first 5 words from each category from the patient and control groups to test this and compared lexical semantic parameters for only this reduced number of items. The authors found that AoA, frequency and typicality still significantly differed between groups. Forbes-McKay et al’s ([2005](#_ENREF_159)) results showed how, whilst AoA values had good discriminatory power between patients and controls, it was lacking this power when attempting to discriminate disease severity – i.e., minimal, mild and moderate. Therefore, this can be interpreted as being due to the semantic store being jeopardised very early on in the course of AD and so this impairment (naming earlier acquired over late acquired words) is seen throughout the course of AD and begins at a very early stage.

A further way in which the fluency performance of participants can be scored is through the techniques of clustering and switching ([Troyer 2000](#_ENREF_437)). Clustering is described as an ability to generate words that belong to the same subcategory, while switching is described as the ability to switch between these subcategories. Research suggests that, compared with normal ageing controls, AD patients not only produce less clusters, but also make more switches between subcategories ([Fagundo, Lopez et al. 2008](#_ENREF_144)). Since many studies have shown how semantic memory impairments are good indicators of the presence of AD, research has now moved on to look into identifying when this decline actually occurs ([Nutter-Upham, Saykin et al. 2008](#_ENREF_333)). Furthermore, through testing patients in longitudinal designs, researchers have also suggested that cognitive decline, in particular in semantic fluency, is detectable in patients as early as 14 years before diagnosis ([Amieva, Le Goff et al. 2008](#_ENREF_9)).

### Mild Cognitive Impairment

Petersen and colleagues have investigated the concept of MCI for many years (e.g., [2001](#_ENREF_348); [2003](#_ENREF_352); [2004](#_ENREF_349)), highlighting how individuals, especially those who are destined to develop AD, go through subtle changes in cognitive functions at first. The individuals who have these cognitive problems, but do not meet the clinical criteria for AD, are said to be in this MCI stage ([Petersen 2004](#_ENREF_349)). As these changes are subtle, yet still detectable when compared against normal ageing individuals, identifying individuals in the MCI stage who will progress to AD would be useful from a therapeutic perspective as interventions could be made available to these patients when they are still in this early stage of impairment ([Grundman, Petersen et al. 2004](#_ENREF_189)). In terms of cognitive abilities, MCI represents a level of cognitive dysfunction between normal ageing and AD; however, this is not simply a continuum. Problematically, the distinction between either normal ageing and MCI, or between MCI and AD can be relatively subtle and distinguishing one from the other can be difficult ([Petersen and Morris 2003](#_ENREF_352)). Manly and colleagues ([2005](#_ENREF_282)) highlighted issues with the Petersen et al ([Petersen, Doody et al. 2001](#_ENREF_348)) criteria, indicating that, whilst they did set out criteria on which particular impairments are most likely to be seen, they did not specify which tests should be used to diagnose this condition. In a review of the literature, Arnaiz & Almkvist ([2003](#_ENREF_18)) reported that different measures that are used to test similar cognitive domains are not homogenous across studies. For example, several studies have found the best predictor of conversion to AD to be a delayed recall task assessing verbal episodic memory ([Welsh, Butters et al. 1992](#_ENREF_459); [Masur, Sliwinski et al. 1994](#_ENREF_287)), while Jacobs and colleagues ([1995](#_ENREF_223)) found an immediate recall task, which was also assessing verbal episodic memory, was the best predictor of conversion, along with a picture naming test and a test of semantic association. Therefore, finding ways to successfully read standard assessment is needed to improve clinical diagnosis.

## Aims and Objectives

The aim of the present study was to investigate which neuropsychological tests best differentiate normal from pathological ageing (in the form of MCI and AD) to improve clinical diagnosis. By identifying specific tests that have good discriminatory power, these could then be used in clinical settings to identify those older adults who are most likely to go on to age pathologically and receive a diagnosis of MCI or AD. The lexical parameters of the words produced on the verbal fluency tasks were also analysed (e.g., AoA), to further investigate the differences between normal and pathological ageing.

### Hypothesis

From previous research, it can be predicted that, due to the distribution of pathology in many of the individuals with MCI and those with early AD, tests assessing semantic memory (e.g. the category fluency task) will show similar performances by the MCI patients and AD patients compared with the older adult controls. By further analysing the category fluency task in terms of lexical characteristics of the words produced, we should be able to distinguish normal ageing from pathological ageing. As normal ageing effects have not been previously recorded in other studies on semantic memory tasks, it is believed that none will appear here, suggesting that the young and older adult controls should perform similarly on tasks assessing this ability; however, as the literature suggests ageing effects are seen on tests of episodic memory, we expect to replicate this finding. Furthermore, it has been suggested that the letter fluency task does produce normal ageing effects, and these may also be seen in the present study. On other tasks within the neuropsychological test battery that assess function not reported to be impaired as early as the MCI stage, it is predicted that the MCI patients recruited for this study will show performances more like those of the older adult controls than those of the AD group.

## Method

### Research Participants

Data from patients who had attended the Clinical Neuroscience Centre (CNC) (University of Hull) were included in the study. All these patients had psychiatric, neurological and extensive neuropsychological examinations. The NINCDA-ADRDA clinical criteria were used to diagnose all patients with probable Alzheimer’s Disease ([McKhann, Drachman et al. 1984](#_ENREF_297)). Twenty four probable AD patients were included in this study with their age ranging between 52 and 91 years (mean age 71.21; SD 10.81). They had an education level ranging from 9 to 20 years of formal education (mean education 11.79; SD 3.26), and their Mini Mental State Examination ([Folstein, Folstein et al. 1975](#_ENREF_158)) scores were between 12 and 27 (mean MMSE score 19.38; SD 4.27). This group of probable AD patients is referred here as ‘probAD’.

A smaller group of 4 patients with possible AD (following the McKhann et al, 1984 criteria) were also included. The possible AD patients were aged between 59 and 76 years old (mean age 68.25; SD 6.99). This group of patients had an education level ranging from 9 to 16 years (mean education 12.00; SD 3.16), and with MMSE scores ranging from 15 to 25 points (mean MMSE score 19.25; SD 5.06). This group of possible AD patients is referred here as ‘possAD’.

The group of individuals with a diagnosis of Mild Cognitive Impairment consisted of 17 patients who met the Petersen et al ([2001](#_ENREF_351)) criteria. The MCI patients were aged between 55 and 84 years (mean age 71.47; SD 9.49) and had levels of formal education ranging from 9 to 19 years (mean education 10.88; SD 2.52). The MCI patients scores on the MMSE ranged between 24 and 29 (mean MMSE 25.94; SD 1.48).

Two groups of patients with vascular problems also participated in this study. The first group was similar to the patients described in Stephan, Matthews et al’s ([2009](#_ENREF_415)) study, and were classified as having mild cognitive impairment with underlying vascular problems (referred here as ‘vascMCI’). Our vascMCI group consisted of 9 patients, and were aged between 59 and 82 years old (mean age 72.67; SD 7.38). The group had an education level ranging from 9 to 16 years of formal education (mean education 12.00; SD 2.45), with MMSE scores between 24 and 29 points (mean MMSE score 25.56; SD 1.74). The second group were classified as vascular dementia patients, referred here as ‘vascDEM’ ([Roman, Tatemichi et al. 1993](#_ENREF_385)). There were 5 vascDEM patients who were aged between 59 and 83 years (mean age 73.00; SD 9.80). This group had an education level ranging from 9 to 11 years of formal education (mean education 10.40; SD 0.89) and MMSE scores between 15 and 28 (mean MMSE score 20.20; SD 5.54).

Thirty healthy older adult controls were matched for age and education to the patients; and a group of young controls were recruited so their scores could be compared with those of the older adult controls to examine the effect of normal ageing. All controls underwent the same neuropsychological testing as the patients.

The older adult controls were aged between 48 years and 87 years (mean age 69.90; SD 10.24). Their education range was from 7 to 16 years of formal education (mean education 11.60; SD 2.06). Their MMSE scores were between 26 and 30 (mean MMSE score 28.70; SD 1.09).

The young controls were aged between 18 years and 20 years (mean age 18.63; SD 0.67). Their education level ranged from 11 to 16 years of formal education (mean education 13.50; SD 1.28) and they achieved MMSE scores between 26 and 30 (mean MMSE score 28.70; SD 1.06).

The smaller groups (i.e., possAD, vascMCI and vascDEM) will not be included in the statistical comparisons but the results will be shown in the graphs for illustrative purposes.

As these patients came from a clinical population, group sizes were based on suitable patients coming through the clinic. Furthermore, as a large number of tests were carried out on a modest number of patients, which can result in increasing the risk of false positives, GPower analyses were conducted. Post-hoc GPower ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a medium effect size (0.25), α = 0.05, total sample size (n=101) and number of groups (4), revealed an achieved power of 0.5. These have been carried out throughout the studies in this thesis. Ethical approval was granted for this study by the Hull and East Riding Local Research Ethics Committee.

### Task and Procedure

#### Neuropsychological battery

All patients and controls underwent extensive neuropsychological assessment which included the following tests:

##### Mini Mental State Examination (MMSE)

*MMSE* ([Folstein, Folstein et al. 1975](#_ENREF_158)) is a global screening measure, scored out of 30, and tests many different cognitive functions such as spatial and functional orientation, attention and language.

##### Verbal Paired Associates

Verbal Paired Associates ([Wechsler 1987](#_ENREF_458)), testing verbal episodic memory, involves the researcher reading out eight pairs of words to the participant, four of which are semantically related (e.g., BABY-CRIES) and four of which are not semantically related (e.g., CABBAGE-PEN). The researcher then produces one word of a word pair (e.g., BABY), and asks the participant to generate orally which word went with it (i.e., CRIES). This is done for all eight pairs and the whole task is repeated three times. The range of scores that can be attained on this test is between 0 and 24.

##### Pyramid and Palm Trees

*The* Pyramid and Palm Trees Task ([Howard and Patterson 1992](#_ENREF_211)), testing semantic memory, involves showing the participant drawings arranged on a sheet of paper (one target picture at the top, with two choice pictures at the bottom), and the participant must choose of the two bottom pictures, which one is most related to the top target picture. Correct choices are scored. The range of scores that can be attained on this test is between 0 and 52.

##### Rey’s Complex Figure

Rey’s Complex Figure Test ([Rey 1941](#_ENREF_376)), testing visuospatial memory and constructional skills, has two components to it - a Copy component and a Delay component. Firstly, on the Copy component, a drawing is placed in front of the participant and they are asked to simply copy the drawing onto a piece of paper. The range of scores that can be attained on this part of the test is between 0 and 36. Once completed, the researcher uses another non visuospatial task (for example, a fluency task) to distract the participant for 10 minutes. After this time has elapsed, the participant is asked to recreate the picture they drew earlier without being able to see the original picture. The range of scores that can be attained on this part of the test is between 0 and 36. A marking sheet is provided to accurately score both drawings.

##### *Digit Span*

Both Forward and Backward Digit Span tasks ([Wechsler 1987](#_ENREF_458)) test short term and working memory, and involve the participant repeating an increasing sequence of numbers which the researcher reads out, either in the same order (forward) or in reverse order (backward) as they hear it. Both tasks are scored by how many successful trials they complete. The range of scores that can be attained on the forward span is between 0 and 9, while on the backward span it is between 0 and 8.

##### *Stroop Task*

The Stroop task ([Stroop 1935](#_ENREF_422)), in a shortened and modified version ([Venneri, Molinari et al. 1993](#_ENREF_447)), is used to test attention. On this task the participant must read out loud a list of black words written on a white sheet of paper that say different colour names (e.g., RED, BLUE, GREEN). They are timed and errors are noted. Next, they must read out loud the colour names of a list of dots. Finally, they see a list of different colour words and must read out loud the colour of ink that they are printed in. The word and ink colour are always incongruent (e.g., RED). Each time, they must read out loud the colour of the ink, ignoring what the word says. The average time of trial 1 and 2 is taken from the time of trial 3 giving the Time Interference score. The same is done for the number of errors, which gives the Error Interference score.

##### *Digit Cancellation*

Digit Cancellation ([Spinnler and Tognoni 1987](#_ENREF_412)), testing attentional abilities, involves the participant deleting target numbers from a random assortment of digits. Three sets of digits are used requiring cancellation of 1, 2 or 3 different numbers. Correct deletions within 45 seconds are recorded for each set, as well as omissions (missing a target number) and false alarms (deleting a number that is different from the target).

##### *Raven’s Coloured Progressive Matrices*

The Raven’s Coloured Progressive Matrices test ([Raven, Raven et al. 1998](#_ENREF_369)) was used to test non-verbal concept formation and abstract reasoning. This test involves asking the participant to look at an abstract picture with a piece of it missing, and from a choice of six pieces, to correctly identify the missing piece. The pictures become more difficult as the task goes on, and is scored by the number of correct missing pieces identified within a 10 minute period. The range of scores that can be attained on this test is between 0 and 36.

##### *Token Task*

The Token Task ([De Renzi and Faglioni 1978](#_ENREF_113)) involves giving the participants a range of increasingly difficult and lengthier commands, which they must carry out using an array of coloured tokens set out in front of them (e.g., ‘touch the black circle with the red square’). It is scored on every command carried out correctly. The range of scores that can be attained on this test is between 0 and 36.

##### *Wechsler Adult Intelligence Scale (WAIS) - Similarities*

The WAIS-similarities subtest ([Wechsler 1955](#_ENREF_457)) was used to test verbal concept formation and abstract reasoning. This involved verbally giving the participant pairs of words that are related, and asking the participant to explain what the relationship is between them (for example, spoon and fork – answer: they are both pieces of cutlery). The relationships between pairs of words become more abstract as the task goes on. Correctly identified relationships are scored. The range of scores that can be attained on this test is between 0 and 33.

##### *Confrontation Naming*

A short Confrontation Naming task (unpublished) was used to test naming ability. This test includes line drawings taken from the Snodgrass and Venderwart set ([Snodgrass and Vanderwart 1980](#_ENREF_408)). Here, the participant is shown successive pictures of line drawings and asked to name each one. This task is scored for each correct answer given. The range of scores that can be attained on this test is between 0 and 20.

##### *Visuoconstructive Apraxia*

The Visuoconstructive Apraxia test ([Spinnler and Tognoni 1987](#_ENREF_412)) simply involves the participant copying basic geometric line drawings, and is scored by correct replication of the drawings. The range of scores that can be attained on this test is between 0 and 14.

Of particular interest in the present study were the verbal fluency tasks.

##### Category fluency task

During the category fluency task, in trials that lasted 60 seconds each, participants were asked to generate orally as many words from the categories of ‘cities’, ‘animals’ and ‘fruits’ as they could. Each category was performed in separate trials. This task was scored by the amount of correct words generated in each trial. Perseverations were noted (i.e., the same word said twice or more within the same trial).

##### Word Attributes

###### Age of Acquisition

AoA values were obtained for each acceptable word a participant produced in the categories of fruits and animals of the category fluency task only. AoA values were obtained from ratings acquired by an earlier study ([Biundo 2010: PhD dissertation, Hull, UK](#_ENREF_46)). In the study by Biundo, 150 healthy adult participants were recruited and split into age categories depending on their age: 18-20 years; 21-30 years; 31-40 years; 41-50 years; 51-60 years; 61-70 years; >70 years. Participants rated 366 animal exemplars by estimating the age at which they learned each word, and rated 110 fruit exemplars by also estimating at what age they learned each word. They were permitted to use any number which represented the age in years at which they learned each particular word. From this, AoA values were obtained by calculating the harmonic mean of each separate word in each fluency category (‘animals’ and ‘fruits’) for each age category. These values were then used in the present study.

###### Familiarity

Word familiarity values were used to ascertain which group produced the most/least familiar exemplars of each particular category. Familiarity values were, again, acquired for each exemplar by Biundo ([2010](#_ENREF_46)), in a similar way to the AoA ratings. However, here, the participants rated, on a scale of 1 *least familiar* to 7 *most familiar*, how familiar they personally believed each particular animal and fruit was to them. Again, harmonic mean values were calculated and these were used in the present study.

###### Typicality

Typicality refers to how representative a particular word is of the category trial it is produced in. Typicality values were also acquired by Biundo ([2010](#_ENREF_46)), in a similar way to the AoA and Familiarity ratings. The difference here was that the participants rated, on a scale of 1 *least typical* to 7 *most typical*, how typical each particular animal and fruit was of that category. Again, harmonic mean values were calculated and these were used in the present study.

##### Letter fluency task

The letter fluency task is similar to the category fluency except that, instead of generating words for specific categories, the participants were asked to generate orally words beginning with specific letters – in this case, letters P, L and F. Again, the letters were performed in separate trials that lasted 60 seconds each. Proper nouns were not counted. Perseverations were again noted.

The number of correct words produced was used to score this task. We also analysed each individual word and classified it as a noun, verb, adjective and adverb based on the English Oxford Dictionary definition. The number of each word type was then scored for each individual patient and used in the analysis of this task.

## Results

### Demographics

The patient groups (MCI, probAD) did not differ in age or education level from the older adult controls or from each other. As expected, the young control group had a significantly lower age than all other groups (Table 4.1). On years of formal education, the young controls differed significantly from the older adult controls at p<.05 level and MCI group at p<.004. No other significant differences were found between any groups on education. Table 4.1 shows the mean of demographic values for each group.

Table 4.1: Mean age (SD) and education (SD) of participants.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Age | 18.63 (0.63) | 69.90 (10.24) | 71.47 (9.49) | 71.21(10.81) |
| Education | 13.50 (1.28) | 11.60 (2.06) | 10.88 (2.52) | 11.79 (3.26) |
| *N* | 30 | 30 | 17 | 24 |

### Neuropsychological tests

Analyses on individual test scores on the neuropsychological test battery completed by patients in the MCI and probAD groups, and both young and older adult controls were done using one-way ANOVAs, Scheffe post-hoc tests and discriminant analyses.

##### MMSE

A significant difference was found between groups on scores on the MMSE, [F(3,97) = 92.489, p<.0001]. The post-hoc test showed no significant differences between young and older adult control groups on MMSE scores. However, when compared with both patient groups (MCI and probAD), the older adult controls performed significantly better (p<.0002 and p<.0001, respectively). Between the patient groups, the MCI patients outperformed the probAD patients at p<.0001 (Table 4.2).

Table 4.2: Average MMSE scores (SD).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| MMSE | 28.70 (1.06) | 28.70 (1.09) | 25.94 (1.48) | 19.38 (4.27) |

#### Tests of new learning

##### Verbal Paired Associates

A significant difference was found between groups on the Verbal Paired Associates task, [F(3,95) = 71.941, p<.0001]. The young controls performed significantly better on this task than the older adult control group (p<.0001). The older adult controls also, while not performing as well as the young controls, still achieved higher scores than both patient groups (p<.0001). A significant difference was also found between patient groups on this task, with the MCI patients producing more correct word pairs (p<.05). Figure 4.1 shows the mean scores of all groups on this task.

Figure 4.1: Correct mean pairs (and SD) produced in the Verbal Paired Associates Task.

##### Rey’s Complex Figure

###### Copy component

A significant difference was found between groups on the Copy component of the Rey’s Complex Figure task, [F(3, 86) = 28.140, p<.0001]. No differences on the post-hoc test was found between the two control groups on this part of the task (mean of young = 34.82; older = 33.09) (p = .649, ns). The older adult controls and the MCI group also performed similarly to each other (p = .280, ns), as well as both significantly outperforming the probAD patients at p<.0001 (see Figure 4.2).

###### Delay Component

A significant difference was found between groups on the Delay component of the Rey’s Complex Figure task, [F(3,86) = 67.730, p<.0001]. The Delay component of this task yields different results from the Copy component. Scores after a 10 minute delay were significantly different between the young and older adult control groups (mean 21.88 and 13.91, respectively), with the young controls performing better (p<.0001). The older adult controls differed significantly on this component when compared with the MCI and probAD groups at p<.0001 level.

Between patient groups, while before the MCI group performed more similarly to the older adult controls on the copy component, on this delayed part of the task, however, the MCI group showed a performance more similar to the probAD group, with only a slight significant differences being found between these two groups (p<.05) (see Figure 4.2).

Figure 4.2: Average scores on the Copy and Delay components of the Rey’s Complex Figure Test.

#### Tests of Short term and Working memory

##### Digit Span Forward

A significant difference was found between groups on the Digit Span Forward task, [F(3,95) = 3.287, p<.05], however, no differences occurred on the post-hoc analysis between any groups, either control or patient (Table 4.3).

##### Digit Span Backward

A significant difference was found between groups on the Digit Span Backward task, [F(3,94) = 8.895, p<.0001]. The only difference found here on the post-hoc test was between the older adult controls and probAD group (p<.05). No other differences were found on this task (Table 4.3).

Table 4.3: Average scores (SD) for all tests of short term and working memory

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Forward | 6.83 (1.05) | 6.34 (1.32) | 6.29 (1.36) | 5.74 (1.36) |
| Backward | 5.40 (1.07) | 4.76 (1.38) | 4.53 (1.07) | 3.73 (1.04) |

#### Tests of Understanding and Reasoning

##### Raven’s Matrices

A significant difference was found between groups on the Raven’s Coloured Progressive Matrices task, [F(3,93) = 33.418, p<.0001]. The young controls performed similarly to the older adult control group on this task, with no significant differences being found between these two groups (p = .237, ns). The older adult controls also did not differ on performance from the MCI group (p = .743, ns), whereas they did outperform the probAD patient group (p<.0001). Between patient groups, the MCI patients and probAD patients differed significantly, with the MCI group performing significantly better than the probAD group (p<.0001) (Table 4.4).

##### WAIS similarities

A significant difference was found between groups on the WAIS Similarities, [F(3,87) = 2.752, p<.05]. However, on the post-hoc tests, no differences were found between any groups, controls or patients, on their performance of this task (Table 4.4).

Table 4.4: Average scores (SD) for all tests of understanding and reasoning.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Raven's Matrices | 33.30 (1.76) | 30.50 (4.56) | 28.24 (4.55) | 19.36 (8.36) |
| WAIS Similarities | 20.93 (4.60) | 19.18 (8.00) | 19.81 (5.25) | 15.63 (6.53) |

#### Attentional Tests

##### Stroop Task

A significant difference was found between groups on the Error Interference of the Stroop task, [F(3,87) = 10.497, p<.0001]. No significant differences were found on the post-hoc analysis between control groups (p = .939, ns) on this aspect of the Stroop task. Again, both the older adult control group and MCI patient group performed significantly better than the probAD patients (p<.0001 and p<.008, respectively), with the older adult controls and MCI patients making fewer errors than the probAD group. Similarly, a significant difference was also found between groups on the Time Interference of the Stroop task [F(3,88) = 14.484, p<.0001]. Between control groups, while no significant difference was found on the time aspect of this task (p = .406, ns), the young controls, however, did, on average, take less time to perform the Stroop task than the older adult controls. Both older adult controls and MCI patients significantly completed this task faster than the probAD patients at p<.0001 and p<.05 levels, respectively (Table 4.5).

##### Digit Cancellation

A significant difference was found between groups on the Digit Cancellation task, [F(3,94) = 24.955, p<.0001]. Similarly to other tasks within the battery, no difference was found between either control groups, while both older adult controls and MCI patients significantly outperformed the probAD group at p<.0001 (Table 4.5).

Table 4.5: Average scores (SD) for all tests of attention.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Stroop: Error | 0.15 (0.48) | 1.09 (5.00) | 2.41 (5.98) | 9.50 (10.13) |
| Stroop: Time (s) | 11.27 (6.08) | 21.60 (13.01) | 31.03 (13.70) | 56.51 (49.08) |
| Digit Cancellation | 55.97 (3.66) | 50.17 (11.32) | 50.88 (6.71) | 33.82 (13.05) |

#### Visuoconstructive Apraxia

##### Visuoconstructive Apraxia

A significant difference was found between groups on the Visuoconstructive Apraxia task, [F(3,93) = 19.178, p<.0001]. The only significant differences found on this task on the post-hoc analyses were between both the older adult control group and MCI group when compared with the probAD group (p<.0001). No other differences were found (Table 4.6).

Table 4.6: Average scores (SD) for all tests of visuocontructive apraxia.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Visuoconstructive Apraxia | 13.83 (0.46) | 13.37 (0.69) | 12.82 (1.13) | 10.04 (3.72) |

#### Language, Semantic Memory and Processing

##### Confrontation Naming

A significant difference was found between groups on the Confrontation Naming task, [F(3,93) = 13.457, p<.0001]. No effect of normal ageing appeared on performance of this task due to the older adult controls (mean age 69.90) performing significantly better than the young controls (mean age 18.63) at p<.001 level. However, a pathological ageing effect could be seen as the older adult controls also outperformed the probAD group (p<.0001). (Table 4.7).

##### Pyramid and Palm Trees

A significant difference was found between groups on the Pyramid and Palm Trees task, [F(3,91) = 4.569, p<.005]. The only difference found on the post-hoc test was between the older adult control group and the probAD group, p<.007, in which the older adult controls produced the most correct choices (Table 4.7).

##### Token Task

A significant difference was found between groups on the Token Task, [F(3,86) = 11.424, p<.0001]. No significant differences were seen on this task between control groups, while the older adult controls did outperform the probAD group (p<.0001), but not the MCI group (p = .924, ns). Between patient groups, the MCI patients performed better than the probAD group at p<.005 (Table 4.7).

Table 4.7: Average scores (SD) for all tests of language, semantic memory and processing.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Young Controls | Older Controls | MCI | probable AD |
| Confrontation Naming | 18.47 (1.14) | 19.77 (0.43) | 18.75 (1.30) | 17.62 (1.88) |
| Pyramid and Palm Trees | 48.50 (4.69) | 51.03 (1.13) | 50.00 (2.14) | 45.80 (9.16) |
| Token Task | 34.17 (1.44) | 33.95 (1.51) | 33.14 (3.02) | 28.44 (3.72) |

#### Verbal Fluency tasks

##### Category Fluency

A significant effect was found on the category fluency task between the groups on number of words produced on trials: ‘cities’, [F(3,97) = 25.650, p<.0001]; ‘animals’, [F(3,97) = 34.167, p<.0001]; ‘fruits’, [F(3,97) = 22.543, p<.0001]; and also when these three trials were scored as a whole (CAF), [F(3,97) = 40.304, p<.0001].

When including all scores from three trials (‘cities’, ‘animals’ and ‘fruits’) and totalling them together, no ageing effect was seen as no significant difference was found between the young and older adult controls (p = .564, ns). When looking at the three category trials separately, the ‘cities’ category was the only trial to produce a significant difference between young and older adult controls. No normal age related decline was seen here, as it was the older adult controls who produced significantly more words on this trial when compared to the young controls’ performance (p<.05) (see Figure 4.3). No other significant differences were found between control groups on the number of words produced.

When compared with the patient groups, the older adult controls outperformed both MCI patients and probAD patients on the categories of ‘cities’, ‘animals’ and ‘fruits’ trials separately as well as when all trials were scored together, all at p<.001 level (see Figure 4.3).

Between patient groups, when looking at the trials separately, the ‘cities’ category produced a significant difference between MCI and probAD patients, with the MCI patient group producing more exemplars in this category than the probAD group, p<.05 (see Figure 4.3). When category trial scores (‘cities’, ‘animals’, and ‘fruits’) were analysed as one, the MCI group did outperform the probAD group, p<.05 (see Figure 4.4).

Figure 4.3: Average number of words produced on each trial on the category fluency task.

Figure 4.4: Average number of words produced when trial scores on the category fluency task were combined.

##### Analysis of lexical characteristics of words.

When looking at lexical characteristics, the categories that were analysed were ‘animals’, ‘fruits’ as well as ‘animals and fruits’ together, completed by averaging both categories in combination. All ANOVAs completed for AoA values detected significant differences: ‘animals’, [F(3,97) = 5.363, p<.002]; ‘fruits’, [F(3,97) = 25.152, p<.0001]; ‘animals and fruits’, [F(3,97) = 19.194, p<.0001]. All ANOVAs completed for Familiarity values yielded significant differences: ‘animals’, [F(3,97) = 6.282, p<.001]; ‘fruits’, [F(3,97) = 6.215, p<.001]; ‘animals and fruits’, [F(3,97) = 8.245, p<.0001]. All ANOVAs completed for Typicality values also yielded significant results: ‘animals’, [F(3,97) = 2.789, p = .05]; the ‘fruits’, [F(3,97) = 7.415, p<.0001]; ‘animals and fruits’, [F(3,97) = 6.360, p<.001].

Some differences were found between the lexical attribute values derived from the words that were produced by control groups. When compared with the young controls, the older adult controls produced words that were higher in AoA value (i.e., acquired later in life) on the categories of ‘animals’ (p<.05),‘fruits’ and when both category trials were totalled together (‘animals and fruits’) at p<.0001 (see Figure 4.5). The older adult controls also produced less familiar words than the young controls on all categories, at p<.001 on the ‘animals’ category and ‘animals and fruits’ scores, as well as at p<.05 on the ‘fruits’ category. No differences between these two control groups were found on the lexical characteristic of typicality.

The older adult controls produced significantly higher AoA words only in the ‘fruits’ trial and ‘animals and fruits’ combined score when compared with the MCI patients (p<.001). A similar performance was seen when compared with the probAD group as older adult controls also produced words with higher AoA values on the ‘animals’ category (p<.007), as well as on the ‘fruits’ and ‘animals and fruits’ totalled score , (p<.0001) (see Figure 4.5). In terms of familiarity, older adult controls produced words that were less familiar at p<.004 level on the ‘fruits’ category, and p<.007 on the ‘animals and fruits’ totalled together when compared with the probAD group (see Figure 4.6). Less typical words were also produced by the older adult controls only when compared with the probAD patients, on the ‘fruits’ category (p<.05) and on the combined ‘animals and fruits’ score (p<.006) (see Figure 4.7).

No significant differences between the two MCI and probAD patient groups were found on any of the lexical characteristic measures on this task.

Figure 4.5: Average Age of Acquisition of words produced.

Figure 4.6: Average Familiarity of words produced.

Figure 4.7: Average Typicality of words produced.

As in Forbes McKay et al ([2005](#_ENREF_159)), we also analysed the lexical attribute data using only the first 5 words from the categories of ‘Animals’, ‘Fruits’, and the combined ‘Animals and Fruits’ score. The ANOVAs completed for AoA values detected significant differences on the ‘fruits’, [F(3,68) = 4.036, p<0.05] and ‘animals and fruits’, [F(3,68) = 6.046, p<0.004] scores, but not on the ‘animals’ category, [F(3,68) = .174, p=.841]. None of the ANOVAs completed for Familiarity values were significant. Again, for Typicality values, the ANOVAs conducted on the ‘Fruits’ score, [F(3,68) = 16.464, p<0.0001], and ‘Animals and Fruits’ score, [F(3,68) = 4.859, p<0.01], were significant, but not for ‘Animals’.

The older adult controls produced significantly higher AoA words in the ‘fruits’ trial and on ‘animals and fruits’ combined score when compared with the MCI patients (p<0.05) as well as on the ‘animals and fruits’ totalled score when compared with the probAD patients (p<0.006). In terms of familiarity, no significant differences were seen between the older adult control group and both patient groups. Less typical words were also produced by the older adult controls when compared to the MCI patients, on the ‘fruits’ category (p<0.0001) only.

Furthermore, the MCI patients also produced less typical words than the probAD group on the ‘Fruits’ (p<0.0001) and ‘Animals and Fruits’ combined score (p<0.05). No other significant differences were seen between these patient groups.

##### Discriminant Analysis

A discriminant analysis was conducted on the category fluency task on the ‘animals and fruits’ combined score of three groups – older adult controls, MCI patients and probAD patients. The measures that were used included number of words produced as well as AoA values, Familiarity values and also Typicality values. The discriminant analysis revealed two discriminant functions. The first explained 97.5% of the variance (canonical R² = 0.69), whereas the second explained 2.5% of the variance (canonical R² = 0.05). In combination, these discriminant functions significantly differentiated the groups, Λ = .297, X² (8) = 80.733, p<.0001. Removing the first function indicated that the second function could not significantly differentiate the groups alone, Λ = .947, X² (3) = 3.646, p = .302, ns. The correlations between measures and the discriminant functions revealed that the number of words and Typicality values loaded very highly onto function 1 (r = .77 and r = -.27, respectively). Familiarity and AoA values loaded very highly onto function 2 (r = .57 and r = .49, respectively). The classification results table showed that using the ‘Animals and Fruits’ combined score of the category fluency task, and by measuring number of words produced, AoA, Familiarity and Typicality values, 81.7% of the participants could be correctly classified. Individually, 93.3% of the older adult controls could be correctly classified by the discriminant analysis using these variables, while 64.8% of the MCI patients and 79.2% of the probAD patients could also be correctly classified. Whilst this is a robust finding, it should also be noted that these figures may represent an overestimation of the discriminatory model as the model was based only on one sample, and not confirmed using a separate sample. Furthermore, no other discriminatory procedure was carried out to validate this model.

##### Letter Fluency

A significant effect was found on the letter fluency task between the groups on number of words produced on all trials analysed separately and also when combined: ‘P’, [F(3,96) = 10.213, p<.0001]; ‘L’, [F(3,96) = 10.407, p<.0001]; ‘F’, [F(3,96) = 6.530, p<.0001]; ‘P+L+F’, [F(3,96) = 10.696, p<.0001].

On this fluency task, no differences on any of the measures used to analyse the task were found between the young controls and the older adult controls.

When compared with the MCI patients, the older adult controls produced more words on this fluency task when all letter trials were totalled together (‘P+L+F’) at p<.01 (see Figure 4.9). When the letter scores were reported in separate trials, the older adult controls produced more words than the MCI patients but only on the letter ‘L’ trial (p<.01) (see Figure 4.8). When compared with the probAD patients, the older adult controls performed better (p<.001) on all measures (i.e., ‘P’, ‘L’ and ‘F’ separately, and ‘P+L+F’ together).

No differences were seen between patient groups on number of words produced on this task.

Fig: 4.8: Average Number of Words produced on separate trials in the letter fluency task.

Fig 4.9: Average Number of Words produced on combined trials in the letter fluency task.

The words produced on the letter fluency task were analysed further for type of word produced – i.e., noun, verb, adjective and adverb. ANOVA results showed significant differences between groups on number of nouns produced: ‘P’, [F(3,96) = 9.091, p<.0001]; ‘L’, [F(3,96) = 9.649, p<.0001]; ‘F’, [F(3,96) = 6.137, p<.0001]; and ‘P+L+F’, [F(3,96) = 10.461, p<.0001]. Also, significant differences occurred between groups on number of verbs produced: ‘P’, [F(3,96) = 14.700, p<.0001]; ‘L’, [F(3,96) = 7.506, p<.0001]; ‘F’, [F(3,96) = 7.159, p<.0001] and ‘P+L+F’, [F(3,96) = 13.154, p<.0001]. Significant differences between groups on number of adjectives produced were found on: ‘P’, [F(3,96) = 4.175, p<.008]; ‘L’, [F(3,96) = 3.555, p<.05]; and ‘P+L+F’, [F(3,96) = 4.335, p<.007]; however, not on: ‘F’, [F(3,96) = 2.688, p = .051, ns]. Finally, significant differences between groups on number of adverbs produced were seen on: ‘P’, [F(3,96) = 2.833, p<.05]; ‘L’, [F(3,96) = 5.701, p<.001]; and ‘P+L+F’, [F(3,96) = 4.742, p<.004]; but not on: ‘F’, [F(3,96) = 0.187, p = .905, ns].

No differences between young controls and older adult controls were found on the type of words produced.

The older adult controls produced more nouns on the ‘L’ and ‘P+L+F’ (p<.05) analyses compared with the MCI patients (see Figures 4.10 and 4.11), and more verbs on the ‘L’ (p<.01) and ‘P+L+F’ (p<.05) analyses (see Figures 4.12 and 4.13). No other differences were found between these two groups on the type of words produced.

Compared with the probAD patients, the older adult controls produced more nouns (see Figure 4.10 and 4.11) and verbs (see Figures 4.12 and 4.13) on all trials when analysed separately and also when totalled together, at p<.001 level. On the amount of adjectives produced, the older adult controls produced significantly more than the probAD group on letter trials ‘P’ and ‘P+L+F’ (p<.05) (see Figures 4.14 and 4.15); and more adverbs than the probAD group on letter trials ‘P’, ‘L’ and ‘P+L+F’ (p<.05) (see Figures 4.16 and 4.17). No other differences between the older adult controls and probAD group were found.

No differences between patient groups were seen on the type of words produced.

Figure 4.10: Average number of Nouns produced.

Figure 4.11: Average number of Nouns produced on combined letter fluency trials.

Figure 4.12: Average number of Verbs produced on the letter fluency task.

Figure 4.13: Average number of Verbs produced in the letter fluency task on combined trial scores.

Figure 4.14: Average number of Adjectives produced on the letter fluency task.

Figure 4.15: Average number of Adjectives produced on the letter fluency task on combined trial scores.

Figure 4.16: Average number of Adverbs produced on the letter fluency task.

Figure 4.17: Average number of Adverbs produced on the letter fluency task on combined trial scores.

##### Clustering and Switching.

Cluster size was analysed using the method described in Troyer (2000). Briefly, a cluster was defined as words generated in succession beginning with the same first two letters. For example, ‘play’ and ‘plough’ would make a cluster, whereas ‘play’ and ‘power’ would not. The cluster size was calculated starting with the second word until the end of that cluster. For example, ‘play’ and ‘plough’ would score a cluster size of 1, whereas ‘play’, ‘plough’ and ‘plight’ would score a cluster size of 2.

No significant between group differences were found on any of the letter trials. Post-hoc analyses did not reveal any significant differences between any of the groups, both controls and patients.

The number of switches made by the participants were also calculated ([Troyer 2000](#_ENREF_437)). Briefly, switching occurs when a participant changes between clusters, including single unclustered words.

Switching analyses showed significant differences between groups on the ‘P’ trial, [F(3,96) = 7.652, p<.0001]; ‘L’ trial, [F(3,96) = 9.630, p<.0001]; and ‘F’ trial, [F(3,96) = 4.700, p<.004]. No significant differences were found between control groups on any trial on number of switches made. Compared with the MCI patients, the older adult controls only differed on the ‘L’ trial, making more switches (p<.006). Compared to the probAD group, older adult controls made significantly more switches on the ‘P’ and ‘L’ trials (p<.0001) and on the ‘F’ trial (p<.004). Within patient groups, no significant differences were found on number of switches made.

##### Discriminant Analysis

A discriminant analysis was conducted on the letter fluency task with all of the trial scores when combined (i.e., ‘P+L+F’). The measures used were number of words produced as well as type of words produced (i.e., nouns, verbs, adjectives and adverbs) from the groups of ‘Older Adult controls’, ‘MCI patients’, and ‘probAD patients’. The discriminant analysis revealed 2 discriminant functions. The first explained 92.1 % of the variance (canonical R² = 0.35), whereas the second explained 7.9% (canonical R² = 0.04). In combination, these discriminant functions significantly differentiated the groups, Λ = .626, X² (10) = 30.439, p<.001. Removing the first function indicated that the remaining second function could not differentiate the groups alone, Λ = .957, X² (4) = 2.881, p = .578, ns. The correlations between measures and discriminant functions revealed that the number of words, nouns, verbs, adjectives and adverbs all loaded highly onto function 1 (r = .83; r = .83; r = .91; r = .51; r = .54, respectively). The classification results table showed that using all trials of the letter fluency task combined into one score, and by measuring number of words, nouns, verbs, adjectives and adverbs produced, 62.9 % of the participants could be correctly classified. Individually, 73.7% of the older adult controls were correctly classified by the discriminant analysis using these variables, while 29.4% of the MCI patients and 73.9% of the probAD patients were also correctly classified. As mentioned previously, this finding may overestimate the model’s discriminatory power as no other sample or procedure was carried out using the model to test its validity.

## **Discussion**

Overall, general cognition was impaired in the patient groups, with AD patients being the most severe, while the MCI patients performed between that of the AD patients and older adult controls. Tests of new learning showed normal ageing effects – namely on the verbal paired associates and delay component of Rey’s Complex Figure, whereby the young controls outperformed the older adult controls. While the AD patients performed worse on most tests within the battery when compared with the older adult controls; the MCI patients showed a worse performance on tests of language, semantic memory and processing, as well as tests of new learning, when compared with the older adult controls. Among the patient groups, the MCI group, who are at a less severe stage than the AD patients, outperformed the AD group on tasks of new learning, attention, understanding and reasoning, as well as number of words on some of the categories of the fluency tasks.

The results from this study identified specific tests which are sensitive enough to differentiate normal from abnormal ageing. The neuropsychological test battery has shown that significant differences occurred between the older adult control group and the MCI patients on verbal and visuospatial long term memory tasks, i.e., the Verbal Paired Associates Task and the Delay component of the Rey’s Complex Figure Task. Nevertheless, these tests are not necessarily specific to the effects of pathological ageing as the older adult controls also differed significantly from the young controls. Therefore, these tasks assessing verbal and visuospatial long term memory appear to be sensitive to age related effects on memory abilities, and therefore do not seem suitable to differentiate between normal and abnormal ageing effects.

Differences also occurred between older adult controls and MCI patients on tests of naming ability (on the Confrontation Naming task) and also on the global screening measure (MMSE) with the MCI patients performing worse; their scores however, were higher than those of the probAD group. This finding suggests that these tasks are sensitive enough to distinguish between normal and pathological ageing, as well as between severities of pathological ageing. Ultimately, the differences seen on tasks within the neuropsychological test battery used in the present study allow us to see the typical performance of normal and pathological ageing groups. Taken as a complete battery (instead of individual tests), differences between age related effects and abnormal age related effects allow for more accurate differentiation of these three states (normal ageing, MCI, AD), which others have suggested is hard to achieve due to the subtle differences that can be displayed ([Petersen, Doody et al. 2001](#_ENREF_351)).

Tasks within the neuropsychological battery used to assess semantic memory and knowledge have also shown that they can contribute to the differentiation between the participant groups. For example, the Pyramid and Palm Trees test can distinguish, as shown in Table 4.7, between older adult controls and probAD patients, while the semantic category fluency task shows the greatest discriminant potential and can distinguish older adult controls from MCI and probAD patients, in addition to differentiating milder pathological impairment (MCI patients) from more severe pathological impairment (probAD patients). Of interest, the older adult controls’ performance on the Pyramid and Palm Trees test was better than that of the young controls (although not significantly), indicating that no ageing effect is detectable on this particular task assessing semantic memory. However, reasons why this may have occurred include the fact that the pyramid and palm trees task is very old and the pictured stimuli are very basic line drawings. It could have been that, because of the age of the young group, they could not recognise the picture they were looking at, or possibly even did not know what the item was after being told the name of it by the examiner as it is not commonly used anymore (for example, the bellow). Klein & Buchanan ([2009](#_ENREF_242)) discuss similar limitations about this particular test in a sample of 17-37 year olds (mean age = 19.8 years). They suggested that younger participants may not know the function of some items used in this test ([Klein and Buchanan 2009](#_ENREF_242)). For instance, using the example of thimble (target item) with choices of thread bobbin or needle, Klein & Buchanan ([2009](#_ENREF_242)) argue that such items may not be popular with the younger participants and the hobby of sewing not undertaken (as much) anymore, meaning that if the participants do not know what function the thimble does, they cannot accurately identify the correct choice.

From the results produced in this study, the strengths and contributions of the category fluency task can be seen. Firstly, when looking into normal ageing, the current study has shown that no normal ageing decline occurs on this task, in fact, as seen on the ‘cities’ category trial and also on the lexical attribute analysis, the older adult controls outperformed the young controls, producing more ‘cities’ examples, as well as ‘animals’ and ‘fruits’ words that were higher in AoA value and less familiar, while performing at a similar level on all other measures assessing performance on this task. Therefore, the results here support earlier research suggesting that semantic memory is intact in normal ageing individuals ([Craik 1994](#_ENREF_100)) and an impairment in this type of memory can be considered abnormal, further supported by the result that the older adult controls produced more words than the MCI group as well as words that were higher in AoA value, less familiar and less typical. No differences were seen between the MCI patients and the probAD patients on any of the measures used to analyse their performance on this task. This shows pathological ageing in AD can be distinguished relatively easily and successfully from normal ageing, even when it is in the very early, mild stages (as with MCI patients). This is especially important as it has been suggested that being able to successfully discriminate at the very early stages of abnormal ageing is extremely difficult ([Petersen, Doody et al. 2001](#_ENREF_351)). Prior to this research, others have gone as far as to say that this semantic fluency task could be a 1-minute mental status examination ([Cummings 2004](#_ENREF_103)). The need for earlier, quicker and more accurate measures to assess an individual who could be in the stage of MCI or who could be developing AD is urgently needed, and it seems the category fluency task can do this job with great success. Not only does each trial take only 60 seconds to complete, but there are many useful ways to analyse the words produced which all lead to a distinction between normal and pathological ageing. Therefore, this approach to testing can be easily implemented in primary care to identify quickly, easily and effectively individuals who might need more extensive neuropsychological testing, or who may simply need additional observation and follow up in a clinically relevant period (e.g., 6-12 months) from those who do not need any further investigations.

Braak and Braak ([1991](#_ENREF_61)) suggested that neuropathological changes in AD begin in the medial temporal regions (such as the hippocampus complex, especially the perirhinal cortex). This region has been said to affect the storage of semantic representations resulting in lexical effects, such as AoA, ultimately influencing residual language retrieval ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Venneri, McGeown et al. 2008](#_ENREF_445)). Whilst these lexical effects’ origins are relatively unknown ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)), Venneri et al ([2008](#_ENREF_445)) reported that they were significantly correlated with the integrity of regions of the medial temporal lobes, including the perirhinal cortex, in the early stages of AD. Therefore, this suggests that the early degeneration of these structures that are most vulnerable to AD may make a contribution to the lexical effects seen within this current study.

Frontal structures have also been suggested to play a role during tests of verbal fluency such as the category task. When participants are naming animals, they must also rely on processes of executive control which help them not repeat words they have previously produced ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)). Research has suggested that the frontal processes have an impact on this task ([Szmalec, Vandierendonck et al. 2005](#_ENREF_423)); however, it is probably over estimated as to how much influence these processes have over the participant’s performance. Research that can support a minimum amount of influence of frontal processes on semantic fluency tasks are studies on the phonemic (letter) fluency task ([Pestell, Venneri et al. 2000](#_ENREF_347)). Evidence from phonemic fluency tasks have reported that this particular task is one of executive control and other frontal processes, and results show AD patients are less impaired in phonemic fluency compared to performance in semantic fluency ([Pestell, Venneri et al. 2000](#_ENREF_347)). Therefore, if deficits in semantic fluency were due to a breakdown of frontal processes, then a similarly poor performance should be also be observed on the letter fluency task in AD participants as this letter task relies (almost solely) on frontal processes. Earlier research has repeatedly demonstrated that this is not the case in AD, and the available evidence suggests that in AD performance on the semantic fluency task is influenced greatly by an impaired semantic store (or impairment to retrieval from this store) rather than impaired frontal processes ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)).

The letter fluency task results do not evidence an age related decline as young controls and older adult controls performed similarly on all measures of this task, with no significant differences being found between them. Performance by the older adult controls on this task differed from the patients’, with this control group producing more words compared to the probAD patients on all trials, as well as on the ‘L’ trial and ‘PLF’ combined total score when compared with the MCI patients. Furthermore, when analysing the type of words produced, again, the older adult controls produced more nouns and verbs than the probAD group. Similar to the number of words results, the older adult controls produced more nouns and verbs on some trials (nouns: ‘L’ and ‘P+L+F’; verbs: ‘L’ and ‘P+L+F’) than the MCI patients, but not on all. No differences between patient groups, however, were found on the letter fluency analyses. The ability to produce verbs is more impaired in pathological ageing of the Alzheimer-type ([Matzig, Druks et al. 2009](#_ENREF_291)), and patients would be expected to differ most on the production of this type of word than other type, such as nouns, adjectives or adverbs. Many researchers have suggested that verbs are not only harder to process than nouns, but they are also learned later in life than nouns ([Matzig, Druks et al. 2009](#_ENREF_291)). This would suggest a sort of AoA effect on the letter fluency, similar to that seen on the category fluency task. Just like with the categories of ‘animals’ and ‘fruits’, whereby the normal ageing individuals (i.e., older adult control group) produced words that were, on average, later acquired in life than those produced by the pathological ageing groups of MCI patients and probAD patients, this process can also be seen in the words produced by the different groups in the letter fluency task. The pathological ageing groups (MCI and probAD), on this task, produced less verbs than the older adult controls, indicating that these are less intact in the patient’s memory than nouns, just as the later acquired category fluency examples are less intact and so less likely to be produced by the pathological ageing patients.

The discriminant function analysis, using the total number of words as well as the lexical-semantic attributes, was able to discriminate between the control and patient groups with 81.7% accuracy. This adds support to the notion that the semantic fluency task is a useful measure to differentiate normal from pathological ageing seen in AD, and also in the less severe stage of MCI. 93.3% (28 out of 30) older adult controls, 64.8% of the MCI patients (11 out of 17), and 79.2% of the AD patients (19 out of 24) were successfully discriminated using these variables. The extra analysis of the word attributes contributes to the ability of the semantic fluency task to distinguish with such accuracy. Compared to this fluency task, the total number of words and word classification analysis of the letter fluency task was not as successful, with only 62.9% of the groups being successfully differentiated – including 73.7% of the older adult controls (22 out of 30), 29.4% of the MCI patients (5 out of 17), and 73.9% of the AD patients (17 out of 23). The low discriminant value in terms of the MCI group – whereby 6 were misclassified as controls, and 6 misclassified as AD patients – makes this task less appealing to use in differential diagnosis. One reason why the semantic fluency task could more successfully discriminate between normal and pathological ageing than the letter fluency task could be due to the stage at which the supportive brain regions become compromised by the disease. Research has shown that areas of the brain that support semantic memory, such as the hippocampus and the perirhinal cortex, are areas which are affected by the neuropathological process of AD very early in the disease course ([Braak and Braak 1991](#_ENREF_61)) as well as in MCI patients. However, in normal ageing individuals, semantic memory is relatively intact ([Craik 1994](#_ENREF_100)) – a finding which is supported by this current study. Nevertheless, areas supportive of phonemic tasks, such as frontal regions, are implicated by the disease at a later stage. Also, some research suggests that frontal brain regions are compromised even in normal ageing ([Raz, Gunning et al. 1997](#_ENREF_370)), which may account for why less disparity was seen between the controls scores and the patients’ scores on the letter fluency task.

In conclusion, what we report in this study is that the semantic fluency task is a very useful and accurate discriminator of normal and pathological ageing, as seen in MCI and AD patients. When further analyses of the lexical attributes of the words produced in this task are also carried out, its discriminatory power increases. Furthermore, when assessing normal ageing impairments, we found that, whilst older adult controls are equally or better than young controls on tests of semantic and phonemic fluency, normal ageing effects do appear on tests of new learning – such as the verbal paired associates task and the delay component of Rey’s Complex Figure. Taken together, this research suggests a simple assessment method that can be easily implemented by clinicians working in primary care settings and in specialist settings to achieve a more accurate assessment and diagnosis of individual patients. Many studies have looked at dementia progression and shown that the disease actually occurs many years before conspicuous behavioural symptoms appear, and before anyone is alerted to any problems. One advantage of neuropsychological assessment is that it allows for follow-ups of the patient’s abilities in these tests over a period of time. This helps in identifying those that have started to age pathologically and also in looking at conversion from MCI to AD, which is an important topic to consider and one that will be investigated following on from this one, as being able to predict MCI converters from non-converters would have positive implications for therapeutic interventions.

# Chapter 5: Differential diagnosis of the dementias

## Introduction

### Differential diagnosis difficulties: general

Dementia might be caused by different forms of neurodegenerative disease but also be the consequence of vascular brain disease or secondary to metabolic, endocrinous or infectious diseases. Whilst Alzheimer’s Disease is reported to be cause of dementia in the majority of cases (62%), there also are many other different causes ([Knapp, Prince et al. 2007](#_ENREF_246)). Therefore, an emphasis needs to be placed on differential diagnosis, which will ultimately lead to earlier and accurate diagnosis of the specific dementia, as well as hopefully a decrease in the cost of dementia to the economy.

### Differential diagnosis difficulties: AD and VaD

Vascular Dementia and Alzheimer’s Disease both show high prevalence rates in the ageing population ([Barker, Luis et al. 2002](#_ENREF_35)). White matter abnormalities are present within both patient groups which can blur the distinction and make differential diagnosis difficult ([Nagata, Saito et al. 2007](#_ENREF_325)). Tatemichi and colleagues ([1992](#_ENREF_428)), looking at patients in hospital after an acute ischemic stroke, found that 26% of patients developed vascular dementia after this event. Furthermore, Kalaria & Ballard ([1999](#_ENREF_230)) found that CV lesions were present in at least 10% of AD cases in their study. Therefore, neuropsychological assessment is useful to support neuroimaging in the differential diagnosis process.

Kaye ([1998](#_ENREF_235)) reported that the diagnosis of VaD is among the most difficult of all the dementias, particularly due to the fact that Cardiovascular Disease (CVD) becomes increasingly common in the ageing population, as does dementia, and in fact CVD has been suggested to be as common in the elderly as AD is ([Lindeboom and Weinstein 2004](#_ENREF_272)). Whilst AD is generally considered to be the most common cause of dementia, several studies have indicated this may actually be VaD ([e.g., Skoog, Nilsson et al. 1993](#_ENREF_405)). However, the main cause of dementia does differ throughout the world, and also does change over time. For example, VaD was named the most common cause of dementia among Japanese people until more recently when AD became the most common ([Dodge, Buracchio et al. 2012](#_ENREF_125)).

Unlike AD, CVD is not necessarily progressive, and research has suggested that subcortical ischemia might in part explain normal age related decline ([Gunning-Dixon and Raz 2000](#_ENREF_190)). White matter lesions are said to produce a cognitive profile that indicates a slowing of performance, with only mild cognitive changes, particularly in executive functioning and memory ([Lindeboom and Weinstein 2004](#_ENREF_272)).

Vascular pathology appeared to increase the prevalence of dementia in ageing individuals (aged 76-100 years) who met neuropathological criteria for AD ([Snowdon, Greiner et al. 1997](#_ENREF_409)). More specifically, when these vascular lesions occurred in areas including the basal ganglia, thalamus as well as in deep white matter (WM), less AD neuropathology was needed to result in the diagnosis of AD, in comparison with patients without vascular lesions ([Snowdon, Greiner et al. 1997](#_ENREF_409)). Therefore, it seems that the combination of amyloid-β and vascular pathology affects cognitive functioning to a larger extent than the two separately ([van Norden, van Dijk et al. 2012](#_ENREF_441)), with dementia setting in at a lower threshold when there is an interaction between the two ([Snowdon, Greiner et al. 1997](#_ENREF_409); [van Norden, van Dijk et al. 2012](#_ENREF_441)). Resulting vascular factors, such as ischemia, seem to interact with amyloid-β ([van Norden, van Dijk et al. 2012](#_ENREF_441)), for example, studies have shown that vascular risk factors can result in an increase of the amyloid precursor protein (APP) ([Li, Zhang et al. 2009](#_ENREF_268)), NPs and NFTs ([Honig, Kukull et al. 2005](#_ENREF_208); [Beach, Wilson et al. 2007](#_ENREF_40)) as well as decrease the clearance of amyloid-β from the CSF ([Cirrito, Yamada et al. 2005](#_ENREF_92)). Neuroimaging data also suggests there is an interaction between AD associated atrophy and vascular pathology. For example, patients with vascular risk factors, such as diabetes ([den Heijer, Vermeer et al. 2003](#_ENREF_117)) and high blood pressure ([den Heijer, Launer et al. 2005](#_ENREF_116)), have more MTL atrophy (as shown on MRI) than those without these vascular risk factors.

#### VaD – criteria for diagnosis

The clinical criteria for diagnosing VaD in an individual has been proposed by Roman and colleagues ([1993](#_ENREF_385)) for the NINDS-AIREN International Workshop (given in detail in Chapter 2, Section 2.2.2.1).

Not only can diagnosis be hard between different dementias, but some research by Nagata et al ([2007](#_ENREF_325)) also pointed out that, based only on the International Classification of Diseases version 2010 (ICD-10) criteria ([WHO 2010](#_ENREF_466)), an individual patient presenting with vascular causes of dementia could be categorised as several different types of vascular dementia (for example, ‘acute-onset VaD’ as well as ‘cortical VaD’). Therefore, it is difficult to be consistent across studies when diagnosing the cause of the dementia as there are many different criteria to use for diagnosis and even problems within diagnostic criteria can occur.

#### Similarities and differences in cognitive profile: AD vs. VaD

Cognitive deterioration rates differ among the different causes of dementia ([e.g., Oh, Lee et al. 2011](#_ENREF_335)). AD patients show a more rapid rate of decline than patients diagnosed with VaD ([Aguero-Torres, Fratiglioni et al. 1998](#_ENREF_2); [Oh, Lee et al. 2011](#_ENREF_335)) and with PD ([Oh, Lee et al. 2011](#_ENREF_335)). Furthermore, the decline seen in AD patients appears to be linear ([Rebok, Brandt et al. 1990](#_ENREF_373)), with the early and late stages showing a slower rate of decline compared with the middle stage which shows a relatively fast rate of decline ([Brooks, Kraemer et al. 1993](#_ENREF_70)). In VaD, a stepwise progression with abrupt onset of cognitive impairment is instead characteristic (e.g., [Roman, Tatemichi et al. 1993](#_ENREF_385); [Kaye 1998](#_ENREF_235)), with these patients also showing a plateau period where cognitive functioning appears stable ([Kaye 1998](#_ENREF_235)). Nevertheless, this is not a consistent finding, for example, one study showed that, among AD, PD and VaD patients, the largest decline in MMSE score between a 6 month and 24 month follow-up was seen in the AD group ([Oh, Lee et al. 2011](#_ENREF_335)). While this was significantly different for the AD and PD group, it was not for the AD and VaD group, which is in agreement with Ballard and colleagues ([1996](#_ENREF_32)) who did not find differences in the rate of decline in AD and VaD patient groups over a 1 year follow-up period.

Similarities between the neuropsychological test performance by AD and VaD patients has been noted in some studies (e.g., [Almkvist 1994](#_ENREF_6); [Almkvist, Fratiglioni et al. 1999](#_ENREF_7); [Fahlander, Wahlin et al. 2002](#_ENREF_145)) while others have emphasised performance differences (e.g., [Kertesz and Clydesdale 1994](#_ENREF_237); [Doody, Massman et al. 1998](#_ENREF_129)). VaD patients have been shown to recognise famous faces better than patients with AD, while the recognition of novel faces did not show differences between the two groups ([Ricker, Keenan et al. 1994](#_ENREF_379)). It has also been reported that better performance by AD patients is seen on visuoperceptual tasks (e.g., clock reading) compared to performance by VaD patients, while visuoconstructual tasks (e.g., Block Design) could not distinguish the two patient groups ([Almkvist 1994](#_ENREF_6); [Ricker, Keenan et al. 1994](#_ENREF_379); [Hill, Backman et al. 1995](#_ENREF_203); [Fahlander, Wahlin et al. 2002](#_ENREF_145)). Patients with VaD, AD and also control participants perform better on Block Design when time constraints are not placed on the task ([Fahlander, Wahlin et al. 2002](#_ENREF_145)). Clock reading abilities are superior than clock setting abilities in AD patients, as well as in normal ageing controls, but this was not significant in the VaD group ([Fahlander, Wahlin et al. 2002](#_ENREF_145)).

The cognitive profiles of AD and VaD patients appear similar when controlling for disease duration, with differences still presenting in slower reaction times and worse performance on letter fluency and tasks that involve planning in VaD patients ([Almkvist 1994](#_ENREF_6)). Furthermore, Kertesz & Clydesdale ([1994](#_ENREF_237)) suggested that VaD patients perform worse on tests assessing frontal functions, while AD patients show worse performance on memory tests. Whilst VaD patients are reported to show better performance on tests of recent memory and visual memory than the AD patients at baseline assessment, this difference disappears at 1-year follow-up ([Ballard, Patel et al. 1996](#_ENREF_32)). As the amount of decline over a 1-year period between AD and VaD patients is broadly similar, the indication is that the advantage that VaD patients exhibit in some memory tasks disappears at follow-up.

### Differential diagnosis difficulties: AD and FTD

FTD is commonly misdiagnosed as AD ([Varma, Snowden et al. 1999](#_ENREF_442); [Halliday, Ng et al. 2002](#_ENREF_192)) as well as underdiagnosed ([Litvan, Agid et al. 1997](#_ENREF_273)). Varma and colleagues ([1999](#_ENREF_442)) noted how, whilst the NINCDS-ADRDA ([McKhann, Drachman et al. 1984](#_ENREF_297)) criteria for diagnosing AD have high sensitivity, with the criteria correctly classifying 93% of AD patients, they have poor specificity, with over 75% of FTD patients being classified as having AD in their study.

#### FTD – criteria for diagnosis

The clinical criteria for Frontotemporal Dementia have been described by Brun and colleagues ([1994](#_ENREF_71)) for the Lund and Manchester Groups (given in detail in Chapter 2, Section 2.2.1.1).

#### Similarities and differences in cognitive profile: AD vs. FTD

Whilst the pattern of cognitive decline in AD is linear, in FTD (behavioural variant) a more stepwise pattern is evident, whereby a loss of cognitive decline is dramatically seen, followed by a stable period with little change ([Kril, Macdonald et al. 2005](#_ENREF_252)). The pattern of atrophy is also different in these two types of dementia. For example, Chan and colleagues ([2001](#_ENREF_81)) reported that, while FTD (frontal/behavioural variant) patients showed a 3.7% decrease in annual brain volume loss, the temporal/language variant of FTD showed a 2.5% decrease, with the AD patients showing a similar rate of atrophy progression of about 2.4%. Furthermore, while the atrophy pattern is similar within anterior and posterior areas in AD, in FTD, researchers found that the anterior regions were dramatically more atrophic than posterior regions in FTD ([Chan, Fox et al. 2001](#_ENREF_81)). Imaging studies have shown atrophy of the frontal and anterior temporal lobes ([Hartikainen, Rasanen et al. 2012](#_ENREF_200)) in FTD, while SPECT studies have shown decreased blood flow in the frontal lobes ([Miller, Cummings et al. 1991](#_ENREF_303)), which is ultimately different from the pattern seen in AD and VaD.

A pathological difference that is useful in differentiating AD and FTD, at least at autopsy, is the fact that amyloid does not accumulate in the brains of FTD patients, strikingly dissimilar to AD patients, whereby amyloid is a pathological hallmark of the disease ([e.g., Braak and Braak 1991](#_ENREF_61)).

Harciarek & Jodizo ([2005](#_ENREF_197)) in their review of the literature reported that, although often used in clinical settings, the clock drawing test is relatively unsuccessful in distinguishing between AD and FTD patients. The interpretation for this is that, whilst the clock drawing task is a task of visuospatial and visuoconstructional ability, which is relatively preserved in FTD but impaired even in early AD, this task also taps into executive functioning which is a frontal function, and therefore is impaired in FTD patients ([Mendez and Cummings 2003](#_ENREF_299)). Therefore, the impairment in this task can be seen in both patient groups due to its nature to tap several different cognitive domains which are all differentially affected in both AD and FTD patients.

AD patients generally show memory impairments as an early symptom of the disease, while FTD patients are more likely to show early executive functioning deficits ([Mendez, Cherrier et al. 1996](#_ENREF_298); [Lindau, Almkvist et al. 2000](#_ENREF_271)). Research has shown that, whilst both patient groups show impairment on both of these cognitive functions relative to controls, FTD patients show a greater impairment on executive function tests (e.g., Stroop task) than memory tests (e.g., Rey’s Complex Figure, delay component), whilst AD patients show the reverse pattern. However, this is not a consistent finding with other researchers finding no difference between the two groups on executive functioning ability ([Grossman 2002](#_ENREF_187)). It has been proposed that FTD patients are able to use compensatory mechanisms, such as cueing or priming, on neuropsychological tests of memory ([Mendez and Cummings 2003](#_ENREF_299)), which suggests how FTD patients outperform AD patients on tests of memory ([Rascovsky, Salmon et al. 2002](#_ENREF_365)) and appear to show less forgetting ([Mendez and Cummings 2003](#_ENREF_299)). Performance on tests of word-list learning and delayed verbal recall is also significantly worse in AD patients than FTD patients ([Diehl and Kurz 2002](#_ENREF_124)). Furthermore, better performance on naming of actions than of naming of objects ([Williamson, Adair et al. 1998](#_ENREF_468)), while FTD patients appear to show a particular impairment in action naming which can be the product of dysexecutive problems ([Cappa, Binetti et al. 1998](#_ENREF_79)).

As well as neuropsychological test performance differences, studies have also looked at the differences in driving styles between patients diagnosed with AD or FTD. While AD patients drive with poor orientation, FTD patients are more likely to indulge in risky or unsafe behaviour and violate more traffic laws ([de Simone, Kaplan et al. 2007](#_ENREF_114)) as well as being unable to understand that their driving is potentially dangerous ([Ernst, Krapp et al. 2010](#_ENREF_142)).

Emotional disturbances are also seen in AD and FTD patients, with AD patients reporting more depression – one review indicated up to 50% of patients had depression ([Modrego 2010](#_ENREF_312)) – than patients with FTD ([Levy, Miller et al. 1996](#_ENREF_265)). Nevertheless, the depression seen in AD is suggested to be mostly mild ([Mendez and Cummings 2003](#_ENREF_299)). Furthermore, other emotional disturbances are seen in the FTD patients, particularly anger and irritability ([Mendez and Cummings 2003](#_ENREF_299)) as well as compulsive and perseverative behaviour ([Miller, Ikonte et al. 1997](#_ENREF_305)) and social withdrawal ([Miller, Cummings et al. 1991](#_ENREF_303)). Bozeat and colleagues ([2000](#_ENREF_56)) reported large behavioural and social alterations are noted in FTD patients, while these are not usually seen in the early stages of AD. Furthermore, Mychack and colleagues ([2001](#_ENREF_324)) suggested that the behavioural and personality changes seen in FTD can go towards distinguishing not only FTD and AD, but also between largely right and left sided degeneration whereby those with right-sided degeneration develop the behavioural disturbances more readily. Neuropsychological assessment has also added to this research and the ability to name emotional states was more impaired in FTD patients relative to AD patients, with the states such as sadness, anger and disgust being correctly identified less often by FTD patients ([Lavenu, Pasquier et al. 1999](#_ENREF_259)).

#### Fluency tasks

Many studies have looked at differentiating the various types of dementia by using the semantic and phonemic fluency tasks among their range of battery tests. These specific fluency tasks have been widely used especially in AD research and many studies have shown a worse impairment level of AD patients on the semantic vs. the phonemic fluency task (e.g., [Pasquier, Lebert et al. 1995](#_ENREF_340); [Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Capitani, Rosci et al. 2009](#_ENREF_78)). Neuropsychological and neuropathological research are supportive of each other as the areas of the brain which support semantic memory, in particular the perirhinal cortex and ERC are also the first sites to be affected by AD pathology ([Braak and Braak 1991](#_ENREF_61)). Therefore, researchers can capitalise on these finding to distinguish AD from other types of dementia where the pathology does not begin in these MTL regions. In addition, the pattern of performance within groups on the fluency tasks has also been researched. Some studies have reported that FTD patients perform better on the semantic fluency than letter fluency task ([e.g., Hodges, Patterson et al. 1999](#_ENREF_206)), as is the pattern also seen in normal ageing (e.g., [Pasquier, Lebert et al. 1995](#_ENREF_340); [Hodges, Patterson et al. 1999](#_ENREF_206)). Nevertheless, other researchers have reported similar performance on both fluency tasks in patients with FTD ([e.g., Rascovsky, Salmon et al. 2007](#_ENREF_364)). This pattern is due to the frontal lobe atrophy that affects the retrieval of exemplars within each trial in the fluency tasks, while the disproportionate semantic fluency impairment in AD is due to the pathological effect of the disease on the anatomical substrates associated with the semantic store. Patients with AD are also impaired on the letter fluency task when compared with normal controls, nevertheless, in relative terms, the reduction in verbal fluency is greater in semantic fluency tasks because of their greater disease burden in the temporal lobe disrupting this semantic store, ultimately resulting in the inability to retrieve appropriate exemplars for each category. Rascovsky and colleagues ([2007](#_ENREF_364)) pointed out that both FTD and AD result in atrophy of the frontal lobes, providing support to a worsened performance on both fluency tasks in comparison with controls. FTD patients are also shown to make more perseverative errors in semantic and letter fluency tasks than AD groups which Rascovsky et al ([2007](#_ENREF_364)) suggested was due to FTD pathology causing more severe atrophy in frontal brain structures and compromising abilities generally associated with these frontal lobe structures. The authors also noted that the FTD group produced more intrusions on the letter vs. the category task, with the AD patients producing the opposite pattern. This greater intrusion error in the FTD group on the letter fluency task could be due to the fact that the letter fluency task is said to be less structured than the category fluency task, and therefore, it could possibly be easier in the letter fluency task to forget what words you have already generated.

Some neuropsychological research has shown no differences in performance of AD and VaD patients on either fluency tasks ([Fahlander, Wahlin et al. 2002](#_ENREF_145)); however, others have reported more words being generated on the letter fluency task by VaD patients ([Duff-Canning, Leach et al. 2004](#_ENREF_135)). In a study that looked at AD, VaD and FTD performance, no differences in number of words produced were reported on either of the fluency tasks between any of these groups ([Grossman, D'Esposito et al. 1996](#_ENREF_188)). Pasquier et al ([1995](#_ENREF_340)) also concluded that, whilst these fluency tasks do seem useful and can discriminate between normal ageing (healthy controls) and abnormal ageing (dementia), they are less useful when trying to distinguish between different types of dementia. Nevertheless, one criticism of Pasquier and colleagues’ ([1995](#_ENREF_340)) procedure was that they only carried out one trial in each of the fluency tasks, i.e., they only tested patients on the ‘animals’ category, and only on the ‘P’ letter. More reliable results, however, can be obtained by combining several categories or several letters rather than simply using one ([Monsch, Bondi et al. 1992](#_ENREF_315)).

## Aims and Objectives

The aim of the present study is to show how different dementia syndromes can be distinguished from each other using neuropsychological tests. AD, FTD, VaD and MCI patients will be tested on a range of neuropsychological tests. These profiles can then be utilised to perform differential diagnosis. Furthermore, we will analyse the category fluency task using lexical parameters obtained from measures of verbal fluency, which might ultimately lead to being able to predict group membership (e.g., [Duff-Canning 2004](#_ENREF_136); [Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Marczinski and Kertesz 2006](#_ENREF_285)). As 15-20% of MCI patients convert to AD per year ([e.g., Petersen, Doody et al. 2001](#_ENREF_348)), a group of MCI patients was also included. It would be useful to look at any differences that may occur between the dementias and MCI, especially as it has been shown that MCI patients have an increased risk of developing dementia than a normal healthy control sample.

## Method

### Research Participants

Data from patients who had attended the Clinical Neuroscience Centre (CNC) (University of Hull) as well as the Memory and Dementia Clinic at the Royal Hallamshire Hospital (RHH) in Sheffield (University of Sheffield) were included in the study. Over 80% of study patients had been seen by an old age psychiatrist who then referred them to the CNC for neuropsychological assessment and had, therefore, had a thorough psychiatric examination. All the remaining study patients who had been referred to the RHH neuropsychology ‘memory and dementia clinic’ had been seen by a neurologist and had received screening for psychiatric illnesses, either before referral or at the time of their neuropsychological assessment. Some of the AD and MCI patients included in this study do overlap with the previous study. The NINCDA-ADRDA clinical criteria was used to diagnose all patients with probable Alzheimer’s Disease ([McKhann, Drachman et al. 1984](#_ENREF_297)). Twenty five probable AD patients were included and were aged between 52 and 91 years (mean age 70.12; SD 10.86). They had an education level ranging from 9 to 20 years of formal education (mean education 11.96; SD 3.30), and their Mini Mental Status Examination scores were between 12 and 27 (mean MMSE score 19.48; SD 4.21).

A group of 25 patients with a diagnosis of Mild Cognitive Impairment were also included. All patients diagnosed with MCI met the Petersen et al ([2001](#_ENREF_348)) criteria. The MCI patients were aged between 42 and 84 years (mean age 69.12; SD 11.44) and had levels of formal education ranging from 9 to 19 years (mean education 11.36; SD 2.55). Their scores on the MMSE ranged between 24 and 29 (mean MMSE 26.56; SD 1.69).

The group with a diagnosis of Vascular Dementia included 24 patients. All VaD patients were diagnosed using the NINDS-AIREN criteria ([Roman, Tatemichi et al. 1993](#_ENREF_385)). They were aged between 57 and 83 years (mean age 72.29; SD 7.79) and had levels of formal education ranging from 9 to 21 years (mean education 12.21; SD 3.12). The VaD patients scores on the MMSE ranged between 11 and 29 (mean MMSE 22.67; SD 4.57).

In the Frontotemporal Dementia group there were 16 patients. All were diagnosed using the Lund-Manchester criteria ([Brun, Englund et al. 1994](#_ENREF_71)). The FTD patients were aged between 42 and 79 years (mean age 63.88; SD 9.98) and had levels of formal education ranging from 7 to 16 years (mean education 11.06; SD 2.32). Their scores on the MMSE ranged between 14 and 29 (mean MMSE 22.80; SD 5.23).

Post-hoc G\*Power ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a medium effect size (0.25), α = 0.05, total sample size (n=90) and number of groups (4), revealed an achieved power of 0.47.

This study received ethical approval by the Hull & East Riding Local Research Ethics Committee. All demographic data can be seen in Table 5.1.

### Task and Procedure

#### Neuropsychological battery

All patients underwent extensive neuropsychological assessment. Tasks included global screening measures such as the MMSE, as well as tests assessing many cognitive abilities including language, memory and visuospatial ability. Please refer to Chapter 4, Section 4.4.2 for a description of each test. Additionally a prose memory task was also used. The procedure for this is explained below:

##### Prose Memory

The Prose Memory task ([Wechsler 1945](#_ENREF_456)) assesses verbal episodic memory in the short and long term. Firstly, the researcher reads out a short story and asks the participant to listen carefully. After the story is read, the participant must recall the story with as many details as possible, in no particular order – this is the immediate component. Once completed, the researcher then reads out the same story again to the participant using other tasks, not involving verbal episodic memory, to distract the participant for 10 minutes. After this time has elapsed, the participant is asked to recall as many details from the story without hearing it again – this is the delayed component. A marking sheet is provided to accurately score the story details recalled from the story for both time points (score range 0-25).

Of particular interest in the present study were the verbal fluency tasks.

##### Category fluency task

During the category fluency task, in trials that lasted 60 seconds each, participants were asked to generate orally as many words from the categories of ‘cities’, ‘animals’ and ‘fruits’ as they could. Each category was performed in separate trials. This task was scored by the amount of correct words generated in each trial. Perseverations were noted (i.e., the same word said twice or more within the same trial). Productions on this task for the trials of fruits and animals will also be scored in terms of the lexical-semantic attributes of each word.

##### Word Attributes

###### Age of Acquisition (AoA)

AoA values were obtained for each acceptable word a participant produced in fruits and animals trials of the category fluency task. AoA values were obtained from ratings acquired by an earlier study ([Biundo 2010](#_ENREF_46)). For details please refer to Chapter 4, Section 4.4.2.1.1.4.1.

###### Familiarity

Word familiarity values were used to ascertain which group produced the most/least familiar exemplars of each particular category. Familiarity values were, again, acquired for each exemplar by Biundo ([2010](#_ENREF_46)). For details please refer to Chapter 4, Section 4.4.2.1.1.4.2.

###### Typicality

Typicality refers to how representative a particular word is of the category trial it is produced in. Typicality values were also acquired by Biundo ([2010](#_ENREF_46)). For details please refer to Chapter 4, Section 4.4.2.1.1.4.3.

##### Letter fluency task

The letter fluency task requires participants to generate orally words beginning with specific letters – in this case, letters P, L and F. Again, word generation for each letter was performed in separate trials that lasted 60 seconds each. The task was scored by the amount of correct words generated in each trial. Proper nouns were not counted. Perseverations were again noted. We also analysed each individual word and classified it as a noun, verb, adjective and adverb based on the English Oxford Dictionary definition. The number of each word type was then scored for each individual and used in the analysis of this task.

## Results

### Demographics

There was no significant difference in age [F (3,86) = 2.374, p<.076] or education [F(3,86) = 0.687, p<.563] among the groups. Table 5.1 shows the mean of each group on demographic variables. Table 5.1: Number of participants, their mean age and education (SD).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| N | 25 | 25 | 24 | 16 |
| Age | 69.12 (11.44) | 70.72 (10.86) | 72.29 (7.79) | 63.88 (9.98) |
| Education | 11.36 (2.55) | 11.96 (3.30) | 12.21 (3.12) | 11.06 (2.32) |

### Neuropsychological tests

Analyses on individual test scores from the neuropsychological test battery completed by patients were done using one-way ANOVAs and Scheffe post-hoc tests.

##### MMSE

A significant difference was found between groups on performance on the MMSE, [F(3,85) = 13.117, p<.0001]. The trend of the data shows MCI>FTD>VaD>AD. Post-hoc tests highlighted significant differences between MCI and all three patient groups - at p<.0001 compared with the AD group, and at p<.05 compared with the FTD and VaD patient groups - with the MCI patients showing better performance. No other significant differences were seen between patient groups (Table 5.2).

Table 5.2: Average MMSE scores (SD).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| MMSE | 26.56 (1.69) | 19.48 (4.21) | 22.67 (4.57) | 22.80 (5.23) |

#### Tests of New Learning

##### Verbal Paired Associates

A significant difference was found between groups on the Verbal Paired Associates task, [F(3,81) = 7.086, p<.0001]. The trend of the data shows MCI>VaD>FTD>AD. The MCI patients performed significantly better on this task, producing more correct word pairs, than the AD group (p<.0001). No other significant differences were seen between the groups (Table 5.3).

##### Rey’s Complex Figure

###### Copy component

A significant difference was not found between groups on the Copy component of the Rey’s Complex Figure task, [F(3, 75) = 2.663, p=.054], although the p value was close to significance level. The trend of the data shows MCI>FTD>VaD>AD. There was no significant difference between the performance of any group(Table 5.3).

###### Delay Component

A significant difference was found between groups on the Delay component of the Rey’s Complex Figure task, [F(3,75) = 5.439, p<.002]. The Delay component of this task yielded different results from the Copy component. The trend of the data shows FTD>MCI>VaD>AD. Scores after a 10 minute delay showed that the FTD group performed significantly better than the AD group, with the FTD group remembering more of the picture they had previously drawn than the AD patients (p<.008). Furthermore, there were significant differences between the MCI and AD group (p<.015) and VaD and AD group (p<.05) (Table 5.3).

Table 5.3: Average scores (SD) for all tests of new learning.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Verbal Paired Associates | 8.88 (2.44) | 4.58 (2.80) | 6.82 (3.84) | 6.73 (3.94) |
| Rey's Figure: Copy | 29.64 (5.08) | 22.11 (9.64) | 26.00 (10.25) | 27.71 (10.40) |
| Rey's Figure: Delay | 7.36 (4.15) | 2.08 (2.96) | 6.77 (4.99) | 8.57 (8.17) |

#### Prose Memory

##### Immediate Recall

No significant difference was found between groups on the Immediate Recall on the Prose Memory Task, [F(3,68) = 1.352, p=.265]. The trend of the data shows VaD >MCI> FTD >AD. There was no significant difference between any of the groups on their Immediate Recall scores (Table 5.4).

##### Delayed Recall

A significant difference was found between groups on the Delayed Recall on the Prose Memory task, [F(3,68) = 3.992, p<.01]. The trend in the data shows FTD>VaD>MCI>AD. Even though there was no significant differences found between any groups on the Immediate Recall scores, the difference between the FTD group and AD group was significant (p<.05), with the FTD group having better Recall scores than the AD patients (Table 5.4).

Table 5.4: Average scores (SD) for all tests of logical memory.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Memory: Immediate | 6.04 (3.90) | 4.47 (3.57) | 7.24 (4.72) | 6.00 (3.80) |
| Memory: Delay | 7.00 (4.77) | 2.18 (3.63) | 7.53 (7.84) | 7.93 (5.11) |

#### Tests of Short term and Working memory

##### Digit Span

No significant difference was found between groups on the Digit Span Forward task, [F(3,81) = 1.503, p=.220] or on the Digit Span Backward task, [F(3,79) = 1.301, p=.280]. The trend of the Forward Digit Span data shows MCI>AD>VaD>FTD; the trend of the Backward Digit Span data shows MCI>FTD>AD>VaD (Table 5.5).

Table 5.5: Average scores (SD) for all tests of short term and working memory

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Digit Span Forward | 6.16 (1.34) | 5.79 (1.35) | 5.61 (1.41) | 5.23 (1.24) |
| Digit Span Backward | 4.36 (1.08) | 3.87 (1.22) | 3.78 (1.04) | 3.92 (1.08) |

#### Tests of Understanding and Reasoning

##### Raven’s Progressive Matrices

A significant difference was found between groups on the Raven’s Coloured Progressive Matrices task, [F(3,81) = 6.416, p<.001]. The trend of the data shows MCI>FTD>VaD>AD. Post-hoc tests revealed that the MCI group outperformed the AD group (p<.001). No other significant differences were found (Table 5.6).

##### WAIS similarities

A significant difference was found between groups on the WAIS Similarities, [F(3,74) = 4.832, p<.004]. The trend of the data shows MCI>VaD>AD>FTD. Post-hoc tests showed that the MCI patients performed significantly better on this task than the FTD patients (p<.008). No other significant between group differences were observed (Table 5.6).

Table 5.6: Average scores (SD) for all tests of understanding and reasoning.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Raven's Progressive Matrices | 28.52 (4.17) | 19.36 (8.36) | 23.65 (7.35) | 24.00 (8.77) |
| WAIS Similarities | 20.29 (5.76) | 15.60 (6.35) | 16.18 (6.49) | 12.42 (6.35) |

#### Attentional Tests

##### Stroop Task

No significant difference was found between groups on the Error Interference of the Stroop task, [F(3,70) = 2.593, p=.059]. The trend of the data shows AD>VaD>FTD>MCI, with the AD group producing the most amount of errors on the Stroop task and the MCI patients producing the smallest amount of errors. However, no differences were found on the post-hoc analysis between any groups on the error score. Similarly, no significant difference was also found between groups on the Time Interference of the Stroop task, [F(3,71) = 1.994, p=.123]. The trend of the data shows AD>VaD>FTD>MCI. The analysis showed that the AD group produced the greatest amount of errors, and also took the longest amount of time to complete the task. Again, no post-hoc tests between group differences were found on the time interference score of this task (Table 5.7).

##### Digit Cancellation

A significant difference was found between groups on the Digit Cancellation task, [F(3,81) = 4.664, p<.005]. The trend of the data was MCI>FTD>VaD>AD. The post-hoc tests showed that the MCI patients outperformed the AD group on this task (p<.007). No other differences between groups were found (Table 5.7). Furthermore, significantly more omissions were produced by both the AD group (p<.0001) and VaD group (p<.05), when compared with the MCI group. Whilst not reaching significance level, the AD group also produced more omissions than the FTD group (p=.069).

Table 5.7: Average scores (SD) for all tests of attention.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Stroop: Error | 2.38 (5.38) | 8.94 (10.08) | 4.62 (5.72) | 4.54 (9.33) |
| Stroop: Time | 32.21 (16.03) | 53.65 (49.14) | 46.31 (30.13) | 33.86 (21.50) |
| Digit Cancellation | 47.40 (11.66) | 34.13 (12.84) | 37.55 (12.34) | 39.93 (15.09) |

#### Visuoconstructive Apraxia

##### Visuoconstructive Apraxia

A significant difference was found between groups on the Visuoconstructive Apraxia task, [F(3,82) = 3.987, p<.05]. The trend of the data shows MCI>FTD>VaD>AD. The only significant difference found by the post-hoc analyses was between the MCI group and the AD group (p<.01) (Table 5.8).

Table 5.8: Average scores (SD) for all tests of visuoconstructive apraxia.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MCI | AD | VaD | FTD |
| Visuoconstructive Apraxia | 13.00 (1.04) | 10.21 (3.73) | 11.64 (2.72) | 11.87 (3.36) |

#### Language, Semantic Memory and Processing

##### Confrontation Naming

A significant difference was found between groups on the Confrontation Naming task, [F(3,79) =3.768, p<.01]. The trend of the data shows MCI>VaD>AD>FTD. The post-hoc revealed that the MCI named correctly more pictures than the FTD group (p<.05). No other differences were found on this task (Table 5.9).

##### Pyramid and Palm Trees

No significant difference was found between groups on the Pyramid and Palm Trees task, [F(3,76) = 1.219, p=.309]. The trend of the data shows MCI>VaD>AD>FTD (Table 5.9).

##### Token Task

A significant difference was found between groups on the Token Task, [F(3,72) = 3.338, p<.05]. The trend of the data shows MCI>VaD>FTD>AD (Table 5.9).

Table 5.9: Average scores (SD) for all tests of language, semantic memory and processing.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | MCI | | AD | VaD | FTD |
| Confrontation Naming | 19.04 (1.16) | | 17.68 (1.86) | 18.13 (2.32) | 16.43 (4.11) |
| Pyramid and Palm Trees | 49.30 (2.90) | | 45.90 (8.94) | 47.19 (7.18) | 45.40 (8.60) |
| Token Task | | 33.52 (2.50) | 28.84 (7.10) | 30.14 (3.92) | 29.27 (7.13) |

#### Verbal Fluency tasks

##### Category Fluency

A significant difference was found on the category fluency task between the groups on number of words produced on the ‘Cities’ trial separately, [F(3,84) = 4.646, p<.005]; ‘Animals’ trial separately, [F(3,84) = 3.323, p<.05]; and also when the three trials (‘Cities’, ‘Animals’, ‘Fruits’) were scored as one, [F(3,84) = 3.415, p<.021]; but not on the ‘Fruits’ trial [F(3,84) = 2.503, p=.065].

The ‘cities’ category was the only category to produce a significant difference between the groups with the MCI patients producing significantly more words on this trial than the AD patients (p<.007) (see Figure 5.1). When all three categories were analysed together, the MCI group again showed an overall total word score significantly larger than the AD group (p<.05) (Figure 5.2). No other significant differences were found between any of the groups on the number of words produced.

Figure 5.1: Overall number of words produced on each trial of the category fluency task by the different four groups.

Figure 5.2: Average number of words produced on the category fluency task by the different four groups.

##### Analysis of lexical characteristics of words.

When looking at lexical characteristics, the categories that were analysed were ‘animals’, ‘fruits’ as well as ‘animals and fruits’ together completed by averaging both categories in combination. ANOVAs completed for AoA values on the ‘Fruits’ separate trial and the combined scores produced significant results: ‘fruits’, [F(3,84) = 2.893, p<.05]; ‘animals and fruits’, [F(3,84) = 3.616, p<.05]; but not for the ‘animals’ category, [F(3,84) = 1.282, p=.286]. None of the ANOVAs completed for Familiarity values produced significant results: ‘animals’, [F(3,84) = 2.191, p=.095]; ‘fruits’, [F(3,84) = 2.333, p<.080]; ‘animals and fruits’, [F(3,84) = 2.384, p=.075]. For Typicality values only the ‘animals’ category produced significant results, [F(3,84) = 2.755, p<.05]; ‘animals and fruits’, [F(3,84) = 0.942, p=.424]; ‘fruits’, [F(3,84) = 1.928, p<.131].

The only significant difference found on post-hoc tests between the lexical attribute values derived from the words produced was between the VaD and FTD groups. Compared with the FTD patients, the VaD patients produced words that were higher in AoA value (i.e., acquired later in life) on the ‘fruits’ category and the combined categories score (p<.05). Figures 5.2 to 5.8 show the lexical attribute analysis performance.

When analysing the first 5 words produced by each group on both the ‘Animals’, ‘Fruits’ and combined scores in terms of lexical characteristics, no significant differences were found between any group.

Figure 5.3: Average Age of Acquisition score, ‘Animals’ and ‘Fruits’ trials scored separately.

Figure 5.4: Average Age of Acquisition score, ‘Animals and Fruits’ combined score.

Figure 5.5: Average Familiarity score, ‘Animals’ and ‘Fruits’ trials scored separately.

Figure 5.6: Average Familiarity score, ‘Animals and Fruits’ combined score.

Figure 5.7: Average Typicality score, ‘Animals’ and ‘Fruits’ trials scored separately.

Figure 5.8: Average Typicality, ‘Animals and Fruits’ combined score.

##### Letter Fluency

A significant difference was found on the letter fluency task between the groups on number of words produced on all letter trials separately, and also when they were scored as one: ‘P’, [F(3,82) = 4.791, p<.004]; ‘L’, [F(3,82) = 3.175, p<.05]; ‘F’, [F(3,82) = 5.384, p<.002]; ‘PLF’, [F(3,82) = 5.093, p<.003].

On the letter fluency task, the MCI group produced more words beginning with the letter ‘P’ than the AD group (p<.05) and the FTD group (p<.01); more words beginning with the letter ‘L’ than the FTD group (p<.05); and more words beginning with the letter ‘F’ than the AD group (p<.05) and FTD group (p<.005). When all letter trials were combined and analysed together, there was a significant difference on this combined score between the MCI group and the AD group (p<.05) and FTD group (p<.006), with the MCI group producing more words overall on this task (see Figure 5.9 and 5.10).

Figure 5.9: Average performance on number of words produced on the separate trials of the letter fluency task.

Figure 5.10: Average performance on number of words produced over all trials on the letter fluency task.

Additional analyses were carried out to investigate the type of word – i.e., noun, verb, adjective and adverb. ANOVA results showed significant differences between groups on number of nouns, verbs and adjectives produced in the ‘P’ and ‘F’ individual letter trials and the combined total score: Nouns - ‘P’, [F(3,82) = 4.761, p<.004]; ‘F’, [F(3,82) = 5.208, p<.002]; and ‘P+L+F’, [F(3,82) = 3.886, p<.05]; Verbs - ‘P’, [F(3,82) = 4.445, p<.006]; ‘F’, [F(3,83) = 3.493, p<.05] and ‘P+L+F’, [F(3,82) = 4.377, p<.007].; Adjectives - ‘P’ [F(3,82) = 3.377, p<.05]; ‘F’ [F(3,82) = 3.182, p<.05]; and ‘P+L+F’ [F(3,82) = 4.260, p<.008]. Finally, significant differences between groups on number of adverbs produced were seen on: ‘P’, [F(3,82) = 3.648, p<.05]; ‘L’, [F(3,82) = 2.722, p<.05]; and ‘P+L+F’, [F(3,82) = 4.014, p<.01].

The MCI patients produced more nouns on the ‘P’, ‘F’ (p<.006) and ‘PLF’ (p<.05) analyses than the FTD patients, more verbs on the ‘P’ (p<.05) analyses than the AD patients, and on the ‘PLF’ when compared with the AD group (p<.05) and FTD group (p<.05). The MCI group also produced more adjectives on the ‘P’ trial compared to the AD group (p<.05), and on the ‘PLF’ total score when compared with the FTD group (p<.05). Finally, the MCI group produced more adverbs on the ‘P’ trial than the AD group (p<.05), as well as more on the overall ‘PLF’ score when compared with the AD group (p<.05). No other differences were found between the patient groups on the type of words produced.

Figure 5.11: Overall performance on number of words produced in the category and letter fluency tasks.

Comparing the performance of each group on both of the fluency tasks, we can see that every group produced more words on the category task compared with the letter task (Figure 5.11). We can also notice that the FTD group produced the smallest amount of words on both tasks. Interestingly, the FTD group also showed the largest difference of performance between the two tasks.

## Discussion

The current study investigated the use of neuropsychological assessment to highlight useful tests that can be used when trying to make a differential diagnosis in patients with cognitive decline. There were many tests within the battery that could differentiate MCI and AD, including the Verbal Paired Associates, Raven’s Progressive Matrices, Digit Cancellation task and Visuoconstructive Apraxia. The pattern of performance on these tests (MCI>AD) was expected as MCI patients are at an earlier stage of impairment than AD patients. It is especially important to distinguish these two as they do show performance patterns similar to each other (even if the MCI group outperform the AD group on some measures) as MCI is said to exist on a spectrum between normal ageing and AD and can be difficult to distinguish from AD ([e.g., Petersen, Doody et al. 2001](#_ENREF_348)) especially from the mild stage of AD. In addition to this, some tests within the battery also showed positive signs that differential diagnosis within the dementia types is possible. In particular, the Delay Component on both Rey’s Complex Figure and Prose Memory were especially able to distinguish significantly between AD and FTD, with FTD patients performing better on these tasks. Therefore, this shows that tests assessing visuospatial and verbal long-term memory abilities can be utilised to distinguish between these two types of dementia. This finding is further supported by the fact that the FTD group, whilst not significantly, did even outperform the MCI group on these two delay components, patients who are milder in their cognitive impairments than patients diagnosed with clinical dementia. Therefore, as previously been found in the literature ([e.g., Hodges, Patterson et al. 1999](#_ENREF_206)), FTD patients’ visuospatial and verbal long-term memory ability are relatively spared, especially in the earliest stages.

Our neuropsychological findings are also supported by those of volumetric brain imaging research (e.g., [Frisoni, Laakso et al. 1999](#_ENREF_168); [Laakso, Hallikainen et al. 2000](#_ENREF_253)). When comparing the atrophy that is seen in the ERC in AD and FTD, similar patterns of atrophy between the two groups have been found for this structure ([Frisoni, Laakso et al. 1999](#_ENREF_168); [Laakso, Hallikainen et al. 2000](#_ENREF_253)). Nevertheless, Laakso et al ([2000](#_ENREF_253)), whilst reporting this overlap of the ERC atrophy, also showed that the hippocampus displays variable patterns of atrophy between the two groups, with FTD patients showing specific atrophy within the anterior hippocampus while AD patients show more widespread atrophy of the whole hippocampus. Further to this, Laakso and colleagues ([2000](#_ENREF_253)) also reported no significant differences between the control group and the FTD group on the volume of the posterior region of the hippocampus, further suggesting that atrophy in FTD is confined to only the anterior region of the hippocampus. Conversely, in AD, this atrophy is more diffuse throughout the hippocampus when compared with control subjects. Therefore, there is some overlap in atrophy between the AD and FTD patients in terms of the ERC, however, there is also room for differential diagnosis when looking at the differences in atrophy of the hippocampus. Braak and Braak ([1991](#_ENREF_60)) describe the degeneration of the MTL structures including the hippocampus seen in AD patients, showing that these regions are the most atrophied as well as the earliest to be affected by disease pathology. Laakso et al’s ([2000](#_ENREF_253)) findings are in line with our current neuropsychological results as this posterior region of the hippocampus has been shown to support functions including visuospatial memory ([Moser, Moser et al. 1993](#_ENREF_319)) – which is shown to be preserved in FTD, but not in AD. Therefore, the need for neuropsychological assessment to be used in conjunction with brain imaging techniques is vitally important as the two methods used jointly may contribute to clinical differential diagnosis.

The trend on the category fluency task, when looking at number of words produced, shows how, on all categories and on combined scores, the MCI group and VaD group produced the most exemplars. Nevertheless, differences between the groups were not significant with the exception of the amount of words generated in the ‘Cities’ trial and on the combined categories score (MCI>AD). Previous research has indicated differences between AD and FTD patients on the number of words produced on the semantic fluency task, with FTD patients producing more words ([e.g., Hodges, Patterson et al. 1999](#_ENREF_206)). An explanation given for this suggests that normal semantic fluency performance relies on intact MTL structures, however, there is severe MTL damage seen in AD, leading these patients to have impaired performance on this task. However, the FTD group in our current study performed at a more similar level to the AD patients, which is contradictory to this previous literature. One reason for this could be that within our FTD group we did not differentiate frontal from temporal (semantic dementia (SD)) types. Therefore, the temporal patients’ performance could be lowering the average performance of the whole FTD group on the category fluency task to a level that that is more similar to the AD patients’ performance. To prevent this similar issue, Rascovsky and colleagues ([2007](#_ENREF_364)) used a semantic index (SI) to classify FTD and AD autopsy-confirmed patients into their correct group, and found that, using the SI measure, 12 out of the 16 FTD patients were correctly classified. Of the four that were wrongly classified as AD rather than FTD, three were originally clinically diagnosed as having semantic dementia, which may indicate why their SI scores were lower than the other FTD patients, and why they were therefore classified as AD. However, when Rascovsky et al ([2007](#_ENREF_364)) excluded these three SD patients, they found that the SI was even better at discriminating FTD from AD patients, with now 84.6% (compared with 75.0% previously) of the FTD patients being correctly classified. Therefore, by removing these three cases of clinically diagnosed SD they found that the FTD group did significantly differ on overall fluency performances when they ran the analyses again, with FTD patients now producing significantly more category exemplars than letter exemplars. Comparing the groups together with the excluded SD patients, Rascovsky et al ([2007](#_ENREF_364)) also found a significant difference with the AD patients producing more words on the letter fluency task than the FTD group.

Marczinski & Kertesz ([2006](#_ENREF_285)) have highlighted how rich the data retrieved from a simple fluency task can be. However, whilst the researchers in that study only looked at frequency as a lexical characteristic, in this current study we analysed for age of acquisition, familiarity and typicality. It has been suggested that patients with different types of dementia show dissimilar performance on fluency measures because of the different areas of the brain being affected by the diseases. Braak and Braak ([1991](#_ENREF_61)) suggested that neuropathological changes in the medial temporal regions (such as the hippocampus complex, especially the perirhinal cortex) preceded neocortical damage in AD. This region has been said to affect the storage of semantic representations resulting in lexical effects, such as AoA, ultimately influencing residual language retrieval ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159); [Venneri, McGeown et al. 2008](#_ENREF_445)). Whilst these lexical effects’ origins are relatively unknown ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)), Venneri et al ([2008](#_ENREF_445)) reported that they were significantly correlated with the integrity of regions of the medial temporal lobes, including the perirhinal cortex, in the early stages of AD. Therefore, this suggests that the early degeneration of these structures that are most vulnerable to AD pathology may make a contribution to the appearance of lexical effects ([Venneri, McGeown et al. 2008](#_ENREF_445)). On the extra, in-depth lexical characteristic analysis we conducted in this current study, it was found that significant differences occurred between the VaD and FTD groups. We found that VaD patients produced later acquired words than the FTD group (fruits score and the combined score). However, from research done by Rascovsky and colleagues ([2007](#_ENREF_364)), we could again interpret the results as being driven by the heterogeneity of profiles in the FTD sample which also included cases of SD. These particular patients, as they have very specific semantic impairments which have been evidenced on the category fluency task previously ([e.g., Marczinski, Davidson et al. 2004](#_ENREF_284)), could be bringing the average scores of the FTD group down, which is further evidenced by this lexical analysis.

We also analysed the letter fluency task, with significant differences on the number of words produced becoming evident between the MCI and FTD group (MCI>FTD). This result, when combined with the results of the battery, which saw the FTD patients perform better on tasks of visuospatial and verbal long-term memory abilities, can be used in conjunction to differentiate further these two patient groups. Therefore, this shows that the FTD patients produced the smallest amount of exemplars on each letter trial and is consistent with the literature as other studies have shown that FTD patients perform worse on the letter fluency task than AD patients ([e.g., Rascovsky, Salmon et al. 2007](#_ENREF_364)).

In conclusion, it can be seen from this study, as well as previous literature, that there is room for differential diagnosis using standard neuropsychological assessment. Whilst similarities between the groups are seen, there are subtle differences that can be measured and act as criteria for differential diagnosis when trying to determine whether an individual patient has a particular dementia type. Furthermore, and equally important, is the use of neuroimaging to detect any structural changes that occur in the brains of patients with dementia, as well as utilising the clinical interview to flag up any behavioural changes that may be distinctive of each dementia type. Using all of these techniques in conjunction will ultimately lead to a successful differentiation of the wide ranging causes of dementia.

# Chapter 6: Organisation and Planning Impairments in Frontotemporal Dementia

## Introduction

Rey’s Complex Figure task ([Rey 1941](#_ENREF_376)) has been used for many years to assess visuospatial ability and involves the copy of a geometric shape. A delay component, assessing long-term memory, is usually performed after a 10 minute delay period of completing other tasks, in which the geometric shape is recreated from memory. To avoid distorting the encoding and memory for the figure, these other ‘distractor’ tasks are usually language orientated and not visual in nature. Both copy and delay components yield a score out of 36, based on a scoring system devised by Osterrieth, and assesses the position accuracy of 18 segments and the completeness of each segment. Rey’s Complex Figure task is a popular method used by clinicians and researchers to assess visuospatial ability in different patient groups. For example, visuospatial ability has been shown to be impaired in some patient groups, such as in AD ([Hodges, Patterson et al. 1999](#_ENREF_206)) as well as in Parkinson patients ([Levin, Llabre et al. 1991](#_ENREF_264)), while in other groups, such as FTD patients, this ability is generally intact ([Hutchinson and Mathias 2007](#_ENREF_212)), and studies have shown that FTD patients perform visuospatial tasks in line with controls’ performance ([Hodges, Patterson et al. 1999](#_ENREF_206)).

Studies have reported that visuospatial ability is supported by the posterior region of the hippocampus ([Moser, Moser et al. 1993](#_ENREF_319)). Relating this to dementia patients’ performance, this makes sense as, mentioned previously, AD patients show impaired performance on tasks assessing visuospatial ability even in the earliest stages of the disease, and research has shown that the hippocampus of patients with AD is the first site of atrophy and neuropathology ([Braak and Braak 1991](#_ENREF_61)). In contrast, while research has shown some atrophy of the hippocampus in FTD patients ([Seeley 2008](#_ENREF_397)), this has mainly been confined to the anterior region, while the posterior region is left intact, and does not differ in volume to this same region in healthy controls ([Laakso, Hallikainen et al. 2000](#_ENREF_253)). Again, this is in line with neuropsychological findings as FTD patients show normal performance on visuospatial tasks ([Hutchinson and Mathias 2007](#_ENREF_212)).

Nevertheless, Rey’s Complex Figure has also been shown to assess more than simply visuospatial memory, including visual perception, constructional praxis, planning, organisation and memory ([Lezak, Howieson et al. 2004](#_ENREF_267)). Whilst research has shown that patients with FTD do not differ from controls on the copying of a geometric shape ([Hodges, Patterson et al. 1999](#_ENREF_206)), their ability to organise the drawing has been somewhat overlooked. Due to the frontal dysfunction in these patients, it could be predicted that FTD patients would score lower on organisation and strategic planning of a geometric figure as these functions are supported by the frontal lobes ([Scarmeas and Honig 2004](#_ENREF_395)), which are the first site of atrophy in these patients ([Tartaglia, Rosen et al. 2011](#_ENREF_427)).

Rey’s Complex Figure task has been successful in differentiating many diverse patient groups. However, since Osterrieth ([1944](#_ENREF_336)) proposed the original scoring system, limitations have arisen with this, for example, its inability to assess the organisation of the drawing. Therefore, several other scoring systems have been proposed (e.g., [Loring, Lee et al. 1988](#_ENREF_278); [Stern, Singer et al. 1994](#_ENREF_417); [Canham, Smith et al. 2000](#_ENREF_77)) which enhance this original method and assess the organisational approach and planning abilities of the individuals being tested. For example, comparing a traditional scoring system against one which measures spatial-relational errors developed by Loring and colleagues ([1988](#_ENREF_278)), Frank & Landeira-Fernandez ([2008](#_ENREF_166)) reported that the traditional system, while it could differentiate between temporal lobe epilepsy patients (both left and right) and controls based on performance on the delayed recall component (30 minute delay), it could not differentiate between patient groups – i.e., between right and left temporal epilepsy patients. Other studies have also reported similar findings to this ([Kneebone, Lee et al. 2007](#_ENREF_247); [McConley, Martin et al. 2008](#_ENREF_293)). However, based on the Loring et al ([1988](#_ENREF_278)) criteria, right temporal lobe epilepsy patients produced more errors that were spatial in content (66%), than left temporal lobe epileptic patients (38%) ([Frank and Landeira-Fernandez 2008](#_ENREF_166)) indicating an improvement in discriminatory ability over the traditional system.

Nevertheless, these additional scoring systems are not perfect either, and limitations levied against them include an increase in the time taken to score the drawing, as well as poor inter-rater reliability ([Canham, Smith et al. 2000](#_ENREF_77)). Also, the strategy in which the drawings are assessed involve the tester copying the patients drawing as they draw it and number the lines in sequence as they are drawn. For use in clinical and research settings, this approach is not necessarily suitable or easily employable. Therefore, due to these problems, Canham and colleagues ([2000](#_ENREF_77)) proposed creating an automated programme that, based on Gestalt psychology, would objectively assess accuracy of task performance based on distortion of the drawing. A strength of this method is that it would not require a clinician to score the task themselves and so would exclude inter-rater variability as well as be time effective. Nevertheless, limitations of this design include that patient drawings are extremely variable and can be hard to interpret and whether this automated programme could be put into clinical practice is debatable.

Hamby and colleagues ([1993](#_ENREF_194)) proposed an alternative scoring method that assessed both the organisation of the drawing as well as the nature of errors produced using a 5-point Likert scale. To use this approach the tester simply had to change the colour of the patient’s pen throughout their drawing of the figure. This proposed method investigated which elements of the drawing were copied first and the types of errors that patients made. The actual scoring of this method is shown in the ‘Methods’ section (Section 6.4.2). In their original paper, Hamby and colleagues ([1993](#_ENREF_194)) reported that this method could differentiate symptomatic (AIDS) and asymptomatic (HIV) patients. Whilst the raw score did not differ between the two patient groups, i.e., using Osterrieth’s original scoring method, the symptomatic patients did evidence significantly poorer organisational and planning ability. Due to the more simplistic nature of analysis (coloured pens) compared with the previous methods, this approach is easier to implement in both clinical and research settings.

## Aims and objectives

Due to the ease of use as well as effectiveness of assessing organisational impairments, we proposed to use this Hamby et al ([1993](#_ENREF_194)) scoring method to investigate whether the additional analysis of organisational ability of this method was sensitive enough to detect strategic planning impairments in FTD patients when compared with a group of healthy controls.

### Hypothesis

We hypothesise that, while FTD patients will produce copy drawings comparable with controls, their construction of the drawing will show poor organisation and planning, and a significant difference between the groups will be shown.

## Method

### Research Participants

Data from patients who had attended the Clinical Neuroscience Centre (CNC) (University of Hull) as well as the Memory and Dementia Clinic at the Royal Hallamshire Hospital in Sheffield (University of Sheffield) were included in the study. Over 80% of study patients had been seen by an old age psychiatrist who then referred them to the CNC for neuropsychological assessment and had, therefore, had a thorough psychiatric examination. All the remaining study patients who had been referred to the RHH neuropsychology ‘memory and dementia clinic’ had been seen by a neurologist and had received screening for psychiatric illnesses, either before referral or at the time of their neuropsychological assessment.

Data from 14 patients diagnosed with Frontotemporal Dementia were included. All FTD patients were diagnosed using the Lund-Manchester criteria ([Brun, Englund et al. 1994](#_ENREF_71)). The FTD patients were aged between 42 and 79 years (mean age 62.93; SD 9.56) and had levels of formal education ranging from 7 to 16 years (mean education 11.07; SD 2.40). Their scores on the MMSE ranged between 14 and 29 (mean MMSE 23.29; SD 5.06).

The NINCDA-ADRDA clinical criteria were used to diagnose all patients with probable Alzheimer’s Disease ([McKhann, Drachman et al. 1984](#_ENREF_297)). Fourteen probable AD patients were included and were aged between 52 and 83 years (mean age 67.64; SD 10.47). They had an education level ranging from 9 to 20 years of formal education (mean education 12.29; SD 3.15), and their MMSE scores were between 15 and 27 (mean MMSE score 21.29; SD 2.84).

Fourteen healthy older adult controls were matched for age and education to the patients. All controls underwent the same neuropsychological testing as the patients. They were aged between 44 years and 78 years (mean age 63.20; SD 9.69) with an education range was from 9 to 16 years of formal education (mean education 11.60; SD 2.29). Their MMSE scores were between 26 and 30 (mean MMSE score 28.60; SD 1.40).

Post-hoc GPower ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a one-tailed t-test, effect size (0.5) and α = 0.05 revealed an achieved power of 0.36.

This study received ethical approval by the Hull & East Riding Local Research Ethics Committee. All demographic data can be seen in Table 6.1.

### Task and Procedure

FTD patients, AD patients and healthy controls performed Rey’s Complex Figure task as part of completing a larger battery of neuropsychological tests. The procedure for Rey’s Complex Figure Test ([Rey 1941](#_ENREF_376)), testing their visuospatial memory, has two components to it - a Copy component and a Delay component. Firstly, on the Copy component, a drawing is placed in front of the participant and they are asked to simply copy the drawing onto a piece of paper. Once completed, the researcher uses another task (for example, a fluency task) to distract the participant for 10 minutes. After this time has elapsed, the participant is asked to recreate the picture they had drawn earlier without being able to see the original picture. A marking sheet is provided to accurately score both drawings using the original Osterrieth scoring method.



Fig 6.1: Rey’s Complex Figure drawing.

Whilst the patients and controls completed both components of the drawing, the researcher would systematically change the colour of the pen that the individual was using. This was to ensure analysis using Hamby et al’s ([1993](#_ENREF_194)) method could occur. The copy component was analysed using this method, which is shown below and taken from Lezak ([2004](#_ENREF_267)):

5. No mistakes; overall organisation is “excellent”

4. Detail mistakes and/or completion of upper left cross before major structures; organisation is “good”

3. One configural or diagonal (e.g., lines don’t cross in middle rectangle) mistake with or without detail mistakes; organisation is “fair”

2. Two configural or diagonal mistakes with “poor” organisation

1. Three or more configural or diagonal mistakes; one configural or diagonal element missing, much segmentation, and “poor” organisation

Fig 6.2: Hamby et al ([1993](#_ENREF_194)) scoring instructions ([reproduced from Lezak, Howieson et al. 2004](#_ENREF_267)).

## Results

### Demographics

There was no significant difference in age [F(2,39)=.968, p=.389] or education [F(2,39)=.916, p=.408] between the groups. Whilst the two patient groups did not differ on MMSE scores, the control group did outperform both the FTD group (p<.002) and the AD group (p<.0001). Table 6.1 shows the demographic variables of each group.

Table 6.1: Number of participants, their mean age, education and MMSE score (SD).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Controls | FTD | AD |
| N | 14 | 14 | 14 |
| Age | 63.20 (9.69) | 62.93 (9.56) | 67.64 (10.47) |
| Education | 11.60 (2.29) | 11.07 (2.40) | 12.29 (3.15) |
| MMSE | 28.60 (1.40) | 23.29 (5.06)\* | 21.29 (2.84)\*\* |

\*Controls > FTD, p<0.002; \*\*Controls > AD, p<0.0001.

### Rey’s Complex Figure

A typical neuropsychological profile of the controls, FTD patients and AD patients was seen on the complete battery of tests (not shown here). No significant differences were seen on the total Osterrieth score of the copy component of Rey’s Complex Figure between the controls and FTD groups (t(26)=2.062, ns) or FTD and AD groups (t(26)=1.013, ns). However, on the delay component, the controls significantly outperformed the FTD patients (t(26)=2.157, p<0.05), while the FTD patients outperformed the AD group (t(26)=2.875, p<0.01) (Table 6.2).

Table 6.2: Raw scores (mean and SD) on the Copy and Delay component of Rey’s Complex Figure.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Controls | FTD | AD |
| Copy | 33.47 (2.77) | 27.71 (10.40) | 23.50 (8.29) |
| Delay | 14.03 (4.29) | 8.57 (8.17)\* | 2.32 (3.27)\*\* |

\*Controls > FTD, p<0.05; \*\*FTD > AD, p<0.05

Closer evaluation of the Copy drawings analysed using the Hamby et al ([1993](#_ENREF_194)) method showed that the FTD patients’ drawings were less structured and less well organised than the controls’ drawings (t(26)=2.283, p<0.05). No significant differences were found between the FTD and AD patient scores on the Hamby measure (Table 6.3). Examples of the drawings produced by each group are shown in Figures 6.3 (controls), 6.4 (FTD patients) and 6.5 (AD patients).

Table 6.3: Average (and SD) organisation and planning score using the Hamby method.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Controls | FTD | AD |
| Hamby | 4.13 (0.64) | 3.13 (1.68)\* | 2.07 (1.44) |

\*Controls > FTD, p<0.05

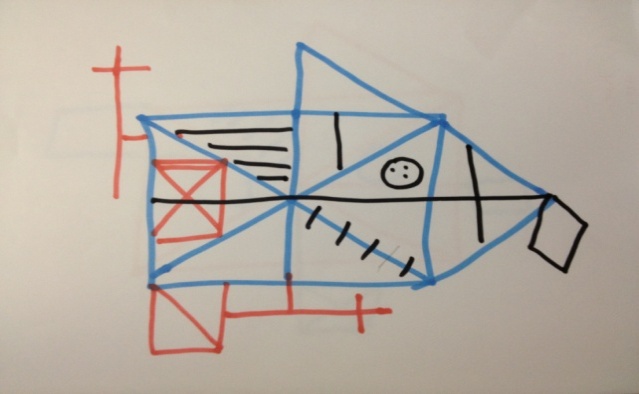
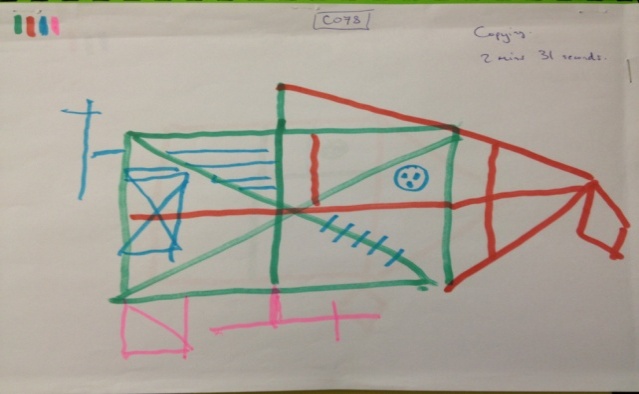
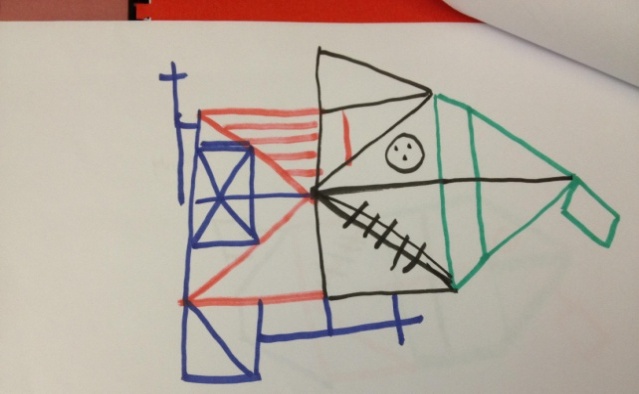
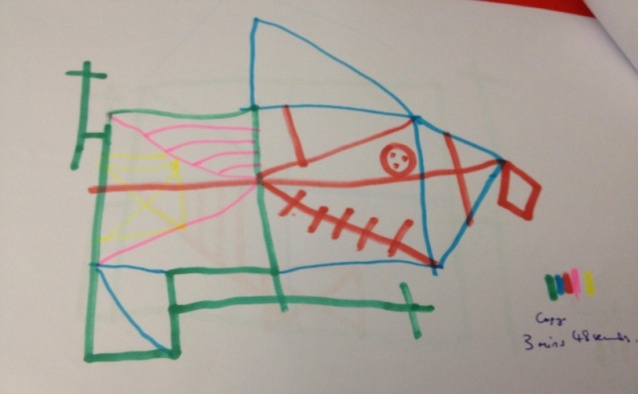
A regression analysis was conducted for the control group and FTD group, using the Delay score as the dependent variable and Hamby score as the predictor variable. From this we see that the Hamby score was positively correlated with the Delay component score (r=.635, p<0.0001), indicating that, the higher the Delay score, the better the drawing was organised (Hamby). The model summary shows that the Hamby score accounts for 40.3% of the variance in the Delay component scores [F(1,26)=17.581, P<0.0001], with the predictor variable significantly adding to the model (p<0.0001). We conducted the same regression analysis with the FTD and AD patient group scores. Here, we found that, again, there was a significant correlation between Delay scores and Hamby scores (r=.581, p<.0.001). The model summary shows that the Hamby score accounts for 33.7% of the variance in the Delay score [F(1,26)=13.243, p<0.001], with the Hamby score significantly adding to the model (p<0.001).

Figure 6.3: Examples of Copy drawings by controls

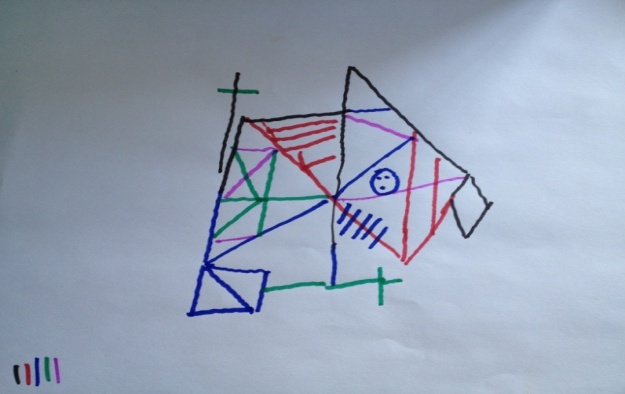
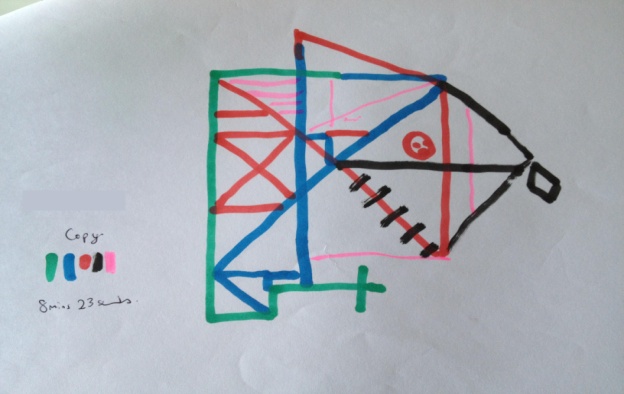


Figure 6.5: Examples of Copy drawings by AD patients

Figure 6.4: Examples of Copy drawings by FTD patients

As there was no significant difference between the Hamby scores of the FTD and AD groups, we investigate whether this could be due to the worsening visuospatial ability of the AD group, i.e., was the copy of the original drawing so poor that it was affecting organisation and planning (Hamby)? Therefore, we conducted another regression analysis, this time using the Hamby score as the dependent variable and the Copy score as the predictor variable for both patient groups. From this, we found that there was a significant correlation between these two variables (r=.806, p<0.0001). Furthermore, the model summary shows that the Copy component score accounted for 64.9% of the variance in the Hamby score [F(1,26)=48.150, p<0.0001], with the predictor variable significantly adding to the model (p<0.0001).

## Discussion

Visuospatial skills are preserved in FTD patients, and we reported that the raw score of the copy component of Rey’s Complex Figure could not differentiate between FTD patients and normal healthy controls. However, organisational and strategic planning skills appear to be more affected by the disease as we found that, when using the Hamby et al ([1993](#_ENREF_194)) method to investigate organisation and strategic planning errors on this task, the FTD patients performed significantly worse than the normal controls.

Support for these results comes from imaging work which has reported that visuospatial learning is supported by the posterior region of the hippocampus ([Moser, Moser et al. 1993](#_ENREF_319)). This region is relatively spared in FTD patients, even though the anterior portion is atrophied ([Laakso, Hallikainen et al. 2000](#_ENREF_253)). Contrastingly, organisation and planning abilities are supported by the frontal lobes ([Hodges, Patterson et al. 1999](#_ENREF_206)), which are affected in the earliest stages of FTD ([Tartaglia, Rosen et al. 2011](#_ENREF_427)). Therefore, taken together, this research would explain why FTD patients can copy a geometric shape with relative precision, but show impairments on their ability to organise an effective strategy for this. This ineffective organisation of the original copy drawing most likely leads to poor encoding of the figure resulting in worse scores on the delay component. We found this hypothesis to be supported in our study, as the FTD patients’ delay performance was significantly poorer than the controls, supported by the regression analysis which showed that the Hamby score predicted over 40% of the performance on the delay component. An improvement in organising the original copy could therefore, improve the delayed recreation of this same drawing – as seen in the performance of the controls.

Other tasks assessing visuospatial and visuoconstructive ability, such as the Clock Drawing task, have found similar results to the ones of the current study. Harciarek & Jodizo ([2005](#_ENREF_197)) conducted a review of the literature and reported that the clock drawing task could not differentiate AD and FTD patients. Nevertheless, the authors argued that, while these skills are relatively preserved in FTD and impaired in AD, in fact the clock drawing task also taps into frontal related cognitive abilities such as executive function. Therefore, as the frontal lobes, and ultimately the functions they support, are the first sites affected in FTD, the impairment in FTD patients on the clock drawing task can be attributed to a breakdown in executive processes, while the impairment seen in AD can be attributed to a breakdown in visuospatial and visuoperceptual processes.

Various researchers have worked on additional scoring methods of Rey’s Complex Figure to investigate organisation and planning ability in different patient groups (e.g., [Loring, Lee et al. 1988](#_ENREF_278); [Stern, Singer et al. 1994](#_ENREF_417); [Canham, Smith et al. 2000](#_ENREF_77)). The method by Hamby and colleagues ([1993](#_ENREF_194)) is a particularly useful method as it also assesses the nature of errors as well as the strategy used by the individual to create the figure. Furthermore, it is a simple method to employ within both a clinical and research setting and has already proved its effectiveness and additional ability over the original Osterrieth method. Therefore, the method proposed by Hamby and colleagues ([1993](#_ENREF_194)) to further analyse Rey’s Complex Figure is a useful tool and is sensitive enough to detect these organisation and planning impairments in FTD patients. This method could be used as an additional element in the process of detecting these impairments and using this information to differentiate successfully FTD from normal ageing, even in the early stages of the disease whereby cognitive impairment is limited.

# Chapter 7: The Nature of Episodic Memory in Frontotemporal Dementia

## Introduction

Many FTD patients are entering the clinic with memory complaints, either reported by themselves or by their caregivers ([Hornberger and Piguet 2012](#_ENREF_210)). Nevertheless, if a patient shows primary memory complaints, then the diagnosis is more likely AD than FTD, however, specificity for this is low ([Varma, Snowden et al. 1999](#_ENREF_442); [Rascovsky, Salmon et al. 2007](#_ENREF_364); [Rascovsky, Hodges et al. 2011](#_ENREF_363)). While research has previously suggested FTD patients do not show episodic memory impairment, and in fact impairment in this type of memory has been used as an exclusion factor in the clinical criteria for FTD ([Brun, Englund et al. 1994](#_ENREF_71)), more recent studies have challenged this stance and have reported that episodic memory impairment is seen in these patients. For example, in the very first cases described by Arnold Pick ([1892](#_ENREF_357)), over half of the patients were reported to have episodic memory impairments, with one patient being severe in this symptom. Furthermore, other more recent studies have also reported episodic memory impairments in FTD patients ([Papma, Seelaar et al. 2012](#_ENREF_339)).

The anterior hippocampus has been related to episodic memory performance ([Yakushev, Muller et al. 2010](#_ENREF_471)) and memory encoding ([Chua, Schacter et al. 2007](#_ENREF_89)), rather than the hippocampus as a whole. A reason put forward for this difference in function of the hippocampus head and tail (i.e., anterior and posterior regions) is due to the fact that input from neocortical areas reaches the hippocampus at the anterior region, and does so through the entorhinal cortex ([Van Hoesen, Augustinack et al. 2000](#_ENREF_440)). This pathway is known as the perforant pathway ([Van Hoesen, Augustinack et al. 2000](#_ENREF_440)) and is not known to be damaged in normal ageing individuals ([Yakushev, Muller et al. 2010](#_ENREF_471)). However, a disrupted perforant pathway has been shown to produce memory impairment, such as in MCI and AD patients. For example, one study found an association between delayed verbal recall performance and the volume of this pathway ([Kalus, Slotboom et al. 2006](#_ENREF_231)).

While hippocampal volume reduction is apparent in both AD and MCI patients ([Convit, DeLeon et al. 1997](#_ENREF_95); [Risacher, Shen et al. 2010](#_ENREF_381)), as well as the amount of reduction being able to predict conversion from MCI to AD ([Risacher, Shen et al. 2010](#_ENREF_381)), others have concluded that atrophy of the hippocampus (i.e., volume reduction) is not the best indicator of hippocampal dysfunction ([Yakushev, Muller et al. 2010](#_ENREF_471)). This could be due to the fact that hippocampal volume reduction (which is an indicator of neuronal loss) is already in progress by the time cognitive symptoms become apparent and the patient is given a diagnosis. Furthermore, it is indicated that there is less hippocampal volume loss when dementia has become apparent and therefore, the measures of hippocampal volume may not in fact reflect an on-going functional deterioration of the hippocampus.

The use of diffusivity and episodic memory performance is less controversial and research has found that this measure shows a positive correlation between mean diffusivity (MD) and episodic memory ([Yakushev, Muller et al. 2010](#_ENREF_471)). Diffusion tensor imaging (DTI) methods of predicting cognitive performance from diffusivity levels have been proposed as more sensitive than volumetric methods ([Muller, Greverus et al. 2005](#_ENREF_321); [Yakushev, Muller et al. 2010](#_ENREF_471)). MD is raised in hippocampal regions of AD and MCI patients ([Kantarci, Jack et al. 2001](#_ENREF_232); [Fellgiebel, Wille et al. 2004](#_ENREF_152)) as DTI measures the motion of water molecules, and as blockages allowing the free movement of water occur in these patients, i.e., through neuronal loss, this is identified by DTI and reported as an elevated MD level. Conversion from MCI to AD can also be predicted using this method, as has been shown in several studies, and again is reported to be a more sensitive method than volumetric methods ([Kantarci, Petersen et al. 2005](#_ENREF_233); [Fellgiebel, Dellani et al. 2006](#_ENREF_151)). Yakushev and colleagues ([2010](#_ENREF_471)) have reported a positive correlation between (left) hippocampal head diffusivity and verbal episodic memory performance on a delayed verbal recall test even when controlling for global cognitive impairment (CERAD test). The diffusivity measure was also the only significant predictor of performance on this episodic memory test on a regression analysis. This result was also found in very mild AD patients with CDR scores of 0.5 ([Yakushev, Muller et al. 2010](#_ENREF_471)). Nevertheless, researchers using different methodology have reported diverging results. For example, using volumetric measures, a lack of association between hippocampal sub regions and episodic memory has been reported ([Mizuno, Wakai et al. 2000](#_ENREF_311)). Furthermore, individual hippocampal volume is variable in nature and therefore can devalue the diagnostic utility of it as an indicator of the disease process.

Atrophy of the frontal lobe has been reported to cause problems in memory due to its function in executive components such as inhibition and response monitoring, planning and organisation. To support this, Kramer et al ([2005](#_ENREF_250)) reported that delayed recall (memory accuracy) is related to hippocampal volume, while semantic clustering and response bias (strategic processing) is related to frontal volume, indicating a dissociation between these two brain regions in relation to episodic memory performance. Correlations have also been reported in between autobiographical memory and executive dysfunction which is commonly seen in FTD patients ([e.g., Irish, Hornberger et al. 2011](#_ENREF_216)), and is supported by imaging evidence ([Seeley, Crawford et al. 2008](#_ENREF_398)). Further work supports this finding that, instead of being a true memory impairment, the deficit seen in FTD patients is actually due to the frontal dysfunction that these patients exhibit ([Collette, Van der Linden et al. 2010](#_ENREF_94)). Furthermore, this prefrontal retrieval failure is also said to account for false recognition rates seen in FTD ([de Boysson, Belleville et al. 2011](#_ENREF_112)) as well as confabulations reported to occur in these patients ([Nedjam, Devouche et al. 2004](#_ENREF_326)).

## Aims and objectives

The current study aimed to clarify the nature of episodic memory impairment in FTD patients. Using a group of patients diagnosed with FTD, we compared performance on an episodic memory task involving the recall of a short story. This was then be analysed in terms of amount of details recalled as well as amount of themes recalled.

## Method

### Research Participants

Data from patients who had attended the Clinical Neuroscience Centre (CNC) (University of Hull) as well as the Memory and Dementia Clinic at the Royal Hallamshire Hospital in Sheffield (University of Sheffield) were included in the study. Over 80% of study patients had been seen by an old age psychiatrist who then referred them to the CNC for neuropsychological assessment and had, therefore, had a thorough psychiatric examination. All the remaining study patients who had been referred to the RHH neuropsychology ‘memory and dementia clinic’ had been seen by a neurologist and had received screening for psychiatric illnesses, either before referral or at the time of their neuropsychological assessment.Some of the patients included in this study do overlap with previous studies within this thesis.

Data from 14 patients diagnosed with Frontotemporal Dementia were included. All FTD patients were diagnosed using the Lund-Manchester criteria ([Brun, Englund et al. 1994](#_ENREF_71)). The FTD patients were aged between 42 and 79 years (mean age 61.86; SD 8.93) and had levels of formal education ranging from 7 to 16 years (mean education 11.21; SD 2.42). Their scores on the MMSE ranged between 14 and 29 (mean MMSE 23.29; SD 5.06).

The NINCDA-ADRDA clinical criteria were used to diagnose all patients with probable Alzheimer’s Disease ([McKhann, Drachman et al. 1984](#_ENREF_297)). Fourteen probable AD patients were included and were aged between 52 and 83 years (mean age 67.07; SD 10.84). They had an education level ranging from 9 to 20 years of formal education (mean education 12.21; SD 3.19), and their Mini Mental Status Examination (MMSE) ([Folstein, Folstein et al. 1975](#_ENREF_158)) scores were between 12 and 27 (mean MMSE score 21.07; SD 3.41).

Fourteen healthy older adult controls were matched for age and education to the patients. All controls underwent the same neuropsychological testing as the patients. They were aged between 32 years and 81 years (mean age 59.00; SD 15.92). Their education range was from 11 to 17 years of formal education (mean education 14.21; SD 2.46). Their MMSE scores were between 28 and 30 (mean MMSE score 29.36; SD 0.63).

Post-hoc GPower ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a medium effect size (0.25), α = 0.05, total sample size (n=42) and number of groups (3), revealed an achieved power of 0.26.

Ethical approval was granted for this study. All demographic data can be seen in Table 7.1.

### Task and Procedure

All groups (Controls, FTD patients, AD patients) completed a Prose Memory task ([Wechsler 1945](#_ENREF_456)) as part of completing a larger battery of neuropsychological tasks. The procedure for this task, testing their episodic memory, has two components to it – an immediate recall and a delayed recall. Firstly, the researcher reads out a short story and asks the participant to listen carefully. After the story is read, the participant must recall the story with as many details as possible, in no particular order – this is the immediate component. Once completed, the researcher then reads out the same story again to the participant using other tasks, not involving verbal episodic memory, to distract the participant for 10 minutes. After this time has elapsed, the participant is asked to recall as many details from the story without hearing it again – this is the delayed component. A marking sheet is provided to accurately score both the story details and thematic elements recalled from the story, for both time points.

## Results

Analyses were carried out using ANCOVAs (controlling for education), Bonferroni post-hoc tests and regression.

### Demographics

There was no significant difference of age between any of the groups [F(2,39) = 1.561, p=.223], however there was on years of education [F(2,39) = 4.438, p<0.05]. While there was no significant difference between the AD group and controls on the years of education (p=.163) or between the AD and FTD group (p=.625), the FTD group did have significantly lower years of education than the controls (p<0.05). Therefore, subsequent analyses were run including education as a covariate.

The MMSE score did show a between groups significant difference, [F(2,38) = 16.093, p<0.0001], with both patient groups scoring significantly lower on this task than the controls (p<0.002). There was no significant difference between patient groups on this task (p=.257). Table 7.1 shows the mean of each group on demographic variables.

Table 7.1: Number of participants, their mean (SD) age, education and MMSE score (SE).

|  |  |  |  |
| --- | --- | --- | --- |
|  | AD | FTD | Controls |
| N | 14 | 14 | 14 |
| Age | 67.07 (10.84) | 61.86 (8.93) | 59.00 (15.92) |
| Education | 12.21 (3.19) | 11.21 (2.42) | 14.21 (2.46) |
| MMSE | 21.13 (0.95) | 23.53 (0.99) | 29.05 (1.01) |

### Prose Memory

ANCOVA analyses showed that there was a significant difference between groups on all measures (Immediate and Delay) assessing the prose memory performance:

Immediate Story Unit total, [F(2,38) = 29.788, p<0.0001].

Immediate Thematic Unit total, [F(2,38) = 17.980, p<0.0001].

Delayed Story Unit total, [F(2,38) = 38.374, p<0.0001].

Delayed Thematic Unit total, [F(2,38) = 22.369, p<0.0001].

Bonferroni post-hoc analyses indicated several significant differences between the groups. On the Immediate Story Unit total, significant differences between AD patients and controls (p<0.0001) and FTD patients and controls (p<0.0001) were found; however, no differences between patient groups were found (p=.906). This same pattern was also found on the Immediate Thematic Unit total: AD vs. Controls (p<0.0001); FTD vs. Controls (p<0.0001); AD vs. FTD (p=1.000). However, a different pattern was seen on the Delayed recall of both the Story and Thematic Units. On the Delayed Story Unit total, there were significant differences between all groups: AD vs. Controls (p<0.0001); FTD vs. Controls (p<0.0001); and AD vs. FTD (p<0.007). On the Delayed Thematic Unit total, again this same pattern was seen: AD vs. Controls (p<0.0001); FTD vs. Controls (p<0.0001); and AD vs. FTD (p<0.05). In both delayed scores (Story unit and Thematic Unit), the FTD patients outperformed the AD patients, while the controls outperformed both patient groups. These results are shown in Graph 7.1 and 7.2.

Graph 7.1: Average Story Units recalled at both Immediate and Delayed recall.

Graph 7. 2: Average Thematic Units recalled at both Immediate and Delayed recall.

We analysed the data using a multivariate ANCOVA, with time (Immediate and Delayed) and Memory Type (Story Unit and Thematic Unit) as the within-subject variables, and the Group (AD, FTD, Controls) as the between-subject variables. On the multivariate tests, there was a significant effect of memory type (p<0.003), time (p<0.0001), as well as significant interactions: time X group (p<0.0001), memory type X group (p<0.0001) but not time X memory type (p=.060). There was also a significant three-way interaction between time X memory type X group (p<0.0001). Graphs 7.3 and 7.4 show the significant interactions of time X group and memory type X group.

Graph 7.3: Time X Group interaction showing average units recalled at Immediate and Delayed recall.

Graph 7.4: Memory type X Group interaction showing average units recalled of the Story units and Thematic units.

We conducted a discriminate analysis with Groups (Controls, AD, FTD) as the dependent variable, and Immediate Story and Thematic Unit totals and Delayed Story and Thematic Unit totals as the discriminant variables. The discriminant analysis revealed 2 discriminant functions. The first explained 94.4% of the variance (canonical R² = 0.79), whereas the second explained 5.6% (canonical R² = 0.18). In combination, these discriminant functions significantly differentiated the groups, Λ = .171, X² (8) = 66.322, p<0.0001. Removing the first function indicated that the remaining second function could not differentiate the groups alone, Λ = .817, X² (3) = 7.586, p = .055, ns. The correlations between measures and discriminant functions revealed that all loaded highly onto function 1 (r = .89; r = .74; r = .66; r = .58, respectively). The classification results table showed that using Immediate Story and Thematic Unit totals and Delayed Story and Thematic Unit totals, 81.0 % of the participants were correctly classified. Individually, 85.7% of the AD patients were correctly classified by the discriminant analysis using these variables, while 64.3% of the FTD patients and 92.9% of the control participants were also correctly classified. Whilst this is a robust finding, no other procedure to test this discriminatory model was carried out. Therefore, these figures may represent an overestimation of the model.

A regression analysis was also conducted. Here, we wanted to see whether the Immediate Story Unit total score (predictor variable) could predict the performance seen on the Delayed Thematic Unit total score (dependent variable). There was a significant correlation between these two variables (r=.805, p<0.0001). The regression analysis showed that the Immediate Story Unit total could predict 64.8% of the variance in the Delayed Thematic Unit total, which was significant [F(1,40)=73.617, p<0.0001]. Furthermore, the Immediate Story Unit score significantly added to the model (p<0.0001).

Finally, we normalised the data for the patient groups (AD and FTD) performance on Immediate and Delayed Story and Thematic Unit totals. To do this we created z-scores using the controls mean performance on each of these measures as the reference mean. Using a t-test on these z-scores, we found that there was a significant difference between the AD and FTD patients performance on the Delayed Story Unit total (t(26)=3.091, p<0.005) and Delayed Thematic Unit total (t(26)=2.546, p<0.05), with the FTD groups outperforming the AD patients. No significant differences were seen in the Immediate recall on either the Story Unit z-scores (p=.460) or Thematic Unit z-scores (p=.755) between the two patient groups. The z-scores (and SDs) can be seen in Graphs 7.5 and 7.6.

Graph 7.5: Z scores for Story Units recalled at both Immediate and Delayed recall

Graph 7.6: Z scores for Thematic Units recalled at both Immediate and Delayed recall

Using this normalised data, we also ran a regression analysis to investigate whether the Immediate Thematic Unit score could predict the Delayed Story unit score, i.e., could the amount of themes that a patient recalled immediately predict how many story details they recalled after a 10 minute delay? Therefore using Delayed Story unit score as the dependent variable, and the Immediate Thematic Unit score as the predictor variable, we found that these two variables were positively correlated (r=.628, p<0.0001) which shows that, as the Immediate Thematic Unit score increased the Delayed Story unit score increased. The model summary shows that the predictor variable accounted for 39.5% of the variance in the dependent variable [F(1,26)=16.954, p<0.0001], with the Immediate Thematic Unit score significantly adding to the model (p<0.0001).

Following this, we conducted this same regression analysis using only the FTD patient z score data to answer this same question: can the amount of themes that a patient recalled immediately predict how many story details they recalled after a 10 minute delay? Again, using the Delayed Story unit score as the dependent variables, and the Immediate Thematic Unit score as the predictor variable, we found that these two variables were positively correlated (r=.755, p<0.001) which shows that, as the Immediate Thematic Unit score increased the Delayed Story unit score increased. Now, the model summary shows that the predictor variable accounted for 57.0% of the variance in the dependent variable [F(1,12)=15.879, p<0.002], with the Immediate Thematic Unit score significantly adding to the model (p<0.002).

## Discussion

The current study investigated the nature of episodic memory impairments in FTD patients. We found that, when compared with patients with AD, the FTD group did show an impairment in this type of memory, however one that was less severe in nature. Furthermore, we found that the frontal dysfunction that occurs with FTD pathology may be exacerbating this impairment as the FTD patients’ recall of the themes of a story was still significantly lower than that of a control group.

Episodic memory is impaired in AD patients and a large amount of literature has focussed on this as a defining feature of the disease. Nevertheless, studies have shown that, whilst specificity for this feature is high, sensitivity is low ([e.g., Varma, Snowden et al. 1999](#_ENREF_442)). Varma and colleagues ([1999](#_ENREF_442)), for example, reported that 75% of FTD patients were misdiagnosed as having AD using the NINCDS-ADRDA criteria. Episodic memory research in FTD patients, however, has been limited and also contradictory. For example, the Lund-Manchester ([Brun, Englund et al. 1994](#_ENREF_71)) clinical criteria uses impairment in episodic memory as an exclusion criteria in FTD patients, however, many researchers report that FTD patients do show impairment in this type of memory ([e.g., Pennington, Hodges et al. 2011](#_ENREF_342)). Furthermore, others still suggest that the episodic memory impairment seen in FTD patients is caused by the frontal dysfunction, i.e., that executive components supported by the frontal lobes, such as response monitoring as well as organisation and inhibition, can influence normal episodic memory performance ([Collette, Van der Linden et al. 2010](#_ENREF_94)). Our results suggest that there is episodic memory impairment in FTD patients as they were impaired on both immediate and delayed recall of a story compared with controls. However, this impairment is less severe than that seen in AD patients.

Similar to AD, FTD patients show atrophy in the hippocampus as well as other MTL regions even in the early stages of the disease, both at autopsy ([Broe, Hodges et al. 2003](#_ENREF_69); [Kril and Halliday 2004](#_ENREF_251)) and on neuroimaging ([Seeley 2008](#_ENREF_397); [Seeley, Crawford et al. 2008](#_ENREF_398); [Whitwell, Shiung et al. 2008](#_ENREF_465)). Furthermore, Laakso and colleagues ([2000](#_ENREF_253)) reported that these patient groups show similar levels of atrophy, nevertheless, the specific region of this is different – with AD patients showing whole hippocampal atrophy, and FTD patients showing anterior>posterior atrophy. Studies have reported that memory encoding as well as episodic memory performance is supported by the anterior hippocampus due to its input through the perforant pathway ([Chua, Schacter et al. 2007](#_ENREF_89); [Yakushev, Muller et al. 2010](#_ENREF_471)). Therefore, taken together, it can be argued that, as FTD patients show atrophy in the anterior region of the hippocampus, then a true episodic memory impairment may be occurring in these patients.

Once our results indicated that FTD patients do show a memory impairment, we also wanted to clarify whether this might be considered a true episodic memory deficit, or whether it might be considered secondary to dysfunction related to frontal damage. We were able to investigate this by analysing the thematic recall of a story in a control group and in patient groups (FTD, AD). The frontal lobe is responsible for executive functions such as response organisation and planning and during a story recall task, like the one used in the present study, it would contribute to the organisation of the story to allow the patient to repeat the story back, as well as remember unifying themes which may increase total amount recalled. In this current study, we found that the FTD patients recalled more thematic units than the AD patients, both at immediate and delayed recall, suggesting that the FTD patients’ episodic memory impairment is not caused by their inability to organise and recall the main elements of the story. If it were the case that frontal dysfunction was driving the memory impairment, then patients with FTD should have shown poorer recall of the underlying themes of the story. Therefore, based solely on these results, we could conclude that FTD patients do present with a true episodic memory impairment. Nevertheless, we wanted to further investigate this idea and so we normalised the data using the control performance as the reference mean, and here we found more evidence to implicate frontal dysfunction in this impairment. Now, the FTD group showed a z score that was below that of the control group in terms of thematic elements, but above in terms of story details. This gives evidence to the argument that episodic memory impairment in FTD patients is, at least in part, caused by the frontal dysfunction which is impairing these patients ability to unify the story through themes, leading to lower story details being retrieved and recalled. This is then further supported by the regression analysis conducted in which we asked whether the delayed story recall was predicted by how many thematic units were recalled immediately. The FTD patients’ performance on detail recall was significantly predicted by their ability at immediate recall to unify the themes of the story, again indicating that the episodic memory impairment is driven at least in part by a frontal organisational problem. Baddeley and colleagues ([2000](#_ENREF_26); [2002](#_ENREF_28)), in reference to their working memory model, proposed that episodes of data are held within memory in an ‘episodic buffer’, which is a fourth component of their model. The authors proposed that this episodic buffer holds a limited amount of data, which is chunked, and which integrates several modes of data from the other components of the model. Furthermore, the episodic buffer is controlled by the central executive and retrieves this data consciously. More specifically, within a working memory framework, failure at the episodic buffer level may result in lack of integration of the story details into themes. Applying this framework to the current study, since appropriate working of the episodic buffer would require the support of functions associated with frontal lobe structures it might be suggested, therefore, that FTD patients are less able to hold the prose memory story data in the episodic buffer because of frontal dysfunction. While chunks of the story could be stored and recalled to a level of performance on the story detail recall which matched that of the control group, their ability to integrate these story details into themes, which more heavily relies on the integrity of frontal abilities, is clearly impaired.

# Chapter 8: Predictors of Conversion in Mild Cognitive Impairment

## Introduction

One well researched group of individuals that show a higher risk of developing AD compared to normal ageing individuals are patients with Mild Cognitive Impairment ([Petersen, Smith et al. 1999](#_ENREF_353); [Petersen, Stevens et al. 2001](#_ENREF_354); [Petersen 2004](#_ENREF_349)). The criteria that Petersen and colleagues ([2001](#_ENREF_348); [2004](#_ENREF_349)) set out for diagnosing a patient with MCI require:

i) subjective memory complaint, corroborated by an informant;

ii) objective memory impairment for age exhibited on neuropsychological assessment;

iii) preserved general cognition;

iv) mostly intact activities of daily living (ADL);

v) no presence of dementia as defined by the NINCDA-ADRDA clinical criteria ([McKhann, Drachman et al. 1984](#_ENREF_297)).

Previous research has shown that patients diagnosed as having MCI have a 10-15% increased risk of developing AD per year ([e.g., Petersen and Morris 2003](#_ENREF_352)), compared to 1-2% risk found in the general population. Being able to identify these MCI individuals is useful from a therapeutic perspective as interventions could be made available to these patients when they are still at a reasonably earlier impairment level than those who have been already diagnosed as having clinical AD ([Grundman, Petersen et al. 2004](#_ENREF_189)). Research has found positive results when cholinesterase inhibitor treatment, which is the only approved pharmacological treatment for AD patients, is administered to patients with an MCI diagnosis (eg, [Petersen, Thomas et al. 2005](#_ENREF_355); [Doody, Ferris et al. 2009](#_ENREF_127)). For example, Petersen and colleagues ([2005](#_ENREF_355)) found that there was a significantly less likelihood of progressing to AD within the first 12 months when treated with a ChEI compared to being treated with placebo or Vitamin C, along with a slower rate of cognitive decline also seen with the ChEI treatment. However, the literature on the MCI concept is abundant and whether an individual is displaying cognitive decline as described by the MCI criteria is not a clear cut case for many individuals. Reasons for this include that the cognitive profile of each MCI patient can differ in regards to the specific cognitive domain(s) which show impairment, and an MCI diagnosis does not necessarily result in developing AD at a later time point.

### MCI Single Domain and Multiple Domain

Researchers have made a case for distinguishing between subtypes of MCI based on their individual neuropsychological profile. A lot of research has focussed on memory and MCI, as memory is one of the earliest cognitive functions to deteriorate in AD, and the criteria for MCI proposed by Petersen ([2004](#_ENREF_349)) suggests memory is impaired while all other cognitive functions are generally left intact. However, research has identified further subtypes of MCI patients. The subtypes identified include: i) single amnestic MCI (a-MCI), i.e., only memory is impaired ([as described by Petersen 2004](#_ENREF_349)); ii) multiple domain amnestic MCI (md a-MCI), i.e., memory is impaired along with one or more cognitive domains; iii) single non-amnestic MCI (na-MCI), i.e., one cognitive domain is impaired, which is not memory; iv) multiple domain non-amnestic MCI (md na-MCI), i.e., two or more cognitive domains are impaired but memory is not one of them. Using these subtypes, some research has argued that MCI patients with a single memory impairment (a-MCI) have a greater risk of converting to AD than MCI patients with impairment in domains other than memory ([eg, Fischer, Jungwirth et al. 2007](#_ENREF_155)), while others have not supported this (eg, [Rozzini, Chilovi et al. 2007](#_ENREF_388); [Mitchell, Arnold et al. 2009](#_ENREF_310); [Nordlund, Rolstad et al. 2010](#_ENREF_332)). Ravaglia and colleagues ([2008](#_ENREF_368)) reported that, while MCI patients with memory impairment (irrespective of number of other cognitive domain impairments) had a 5-fold greater risk for dementia than normal individuals, MCI patients with no memory impairment (irrespective of number of other cognitive domains impaired) showed no association with dementia risk. However, a limitation of this is that it could simply be that the a-MCI patients had additional impairments in other domains also, as the number of cognitive domains impaired was not controlled, while the non-amnestic group could have had fewer cognitive domains impaired. Therefore, this would account for the fact that more a-MCI patients converted to AD than did na-MCI patients in this study. Others investigating this issue have suggested that those patients who exhibit deficits in several cognitive domains (md MCI) show an increased likelihood of progression to AD than those with a single impaired cognitive domain (sd MCI) (eg, [Tabert, Manly et al. 2006](#_ENREF_425); [Ravaglia, Forti et al. 2008](#_ENREF_368); [Mitchell, Arnold et al. 2009](#_ENREF_310); [Aretouli, Okonkwo et al. 2011](#_ENREF_16)). Furthermore, others have suggested that it is the combination of deficits in multiple domains (and not whether memory is one of the domains affected) that increases the risk of conversion (eg, [Rasquin, Lodder et al. 2005](#_ENREF_366); [Alexopoulos, Grimmer et al. 2006](#_ENREF_5); [Baars, van Boxtel et al. 2009](#_ENREF_25)). Mitchell et al ([2009](#_ENREF_310)) and others (e.g., [Visser 2006](#_ENREF_451); [Nordlund, Rolstad et al. 2010](#_ENREF_332)) have raised the argument that, if it is true that patients with impairments outside of memory are more likely to convert to AD, and are also more likely to convert in a shorter time period, then instead of distinguishing MCI patients on what deficits they show (e.g., amnestic-MCI, md-MCI) they should be distinguished on their level of impairment (e.g., mild, moderate). Visser ([2006](#_ENREF_451)) also puts forward the argument that placing patients on an MCI spectrum would be more beneficial in a clinical setting rather than simply labelling them as ‘MCI’ patients. In these cases therefore, multi-domain MCI could be seen as moderate MCI, as they show impairments outside of memory and involve several cognitive domains. These patients, therefore, could even be at a pre-dementia stage by this point due to their MMSE scores and preserved ADLs (eg, [Alexopoulos, Grimmer et al. 2006](#_ENREF_5); [Mitchell, Arnold et al. 2009](#_ENREF_310)). Furthermore, those with single domain MCI are most likely to be at an earlier stage of impairment and may subsequently convert at a later stage than the multi-domain patients ([Nordlund, Rolstad et al. 2010](#_ENREF_332)). In support of this idea, Nordlund et al ([2010](#_ENREF_332)) reported that only patients in an md-MCI subgroup (irrespective of whether they have a memory impairment or not) converted to AD within a 2 year follow-up period. Therefore, the argument for mild vs. moderate MCI would suggest that Nordlund et al’s ([2010](#_ENREF_332)) sd-MCI patients were at an earlier stage of MCI, and so may convert after this 2 year period, while at least 25% of their md-MCI patients were in late stage MCI, and would explain why they converted in a shorter period of time within this 2 year follow-up period.

### MCI Subtypes

While the Petersen et al ([2004](#_ENREF_349)) criteria for MCI indicates that memory impairment is necessary for a diagnosis, research has now described how some patients demonstrate single impairment in cognitive domains other than memory. Comparing the incidence rates of the subtypes of MCI, Manly and colleagues ([2008](#_ENREF_283)) reported that those MCI patients with an isolated impairment in executive functioning had the lowest incidence rate (0.7 relative risk) while a-MCI and MCI patients with an isolated impairment in language had the highest (3.2 and 2.0 relative risk, respectively). Furthermore, while patients diagnosed at baseline as either a-MCI, MCI-language or md-MCI were more likely to develop AD at follow-up compared to normal ageing individuals at baseline, there was no increased risk of developing AD in those patients diagnosed with MCI-executive or MCI-visuospatial, in which the authors suggested that these two subtypes of MCI are the least likely to have AD pathology underlying their diagnosis ([Manly, Tang et al. 2008](#_ENREF_283)). In their community based study investigating demographic influence on the different subtypes of MCI, Manly and colleagues ([2005](#_ENREF_282)) found that individuals with less than 9 years of education were more likely to show impairments in language, visuospatial ability, and to show multiple deficits on a range of neuropsychological tests (not including memory). In contrast to this, individuals with more than 9 years of education were more likely to have isolated memory or executive functioning impairments. Furthermore, this study also showed differences between men and women, whereby women were more likely to have more functional complaints as well as isolated memory impairment, while men were more likely to show isolated language impairments ([Manly, Bell-McGinty et al. 2005](#_ENREF_282)). In the race analyses, whilst Hispanics and African Americans were more likely to show visuospatial deficits, white people were more likely to show isolated memory impairment than these two groups ([Manly, Bell-McGinty et al. 2005](#_ENREF_282)). However, no differences were found between the different races of people on functional complaints or memory complaints ([Manly, Bell-McGinty et al. 2005](#_ENREF_282)).

### Conversion

#### Cognitive Impairment

While MCI does represent an increased risk of developing AD at a later time point, it is recognised that not all patients diagnosed with MCI will convert within their lifetime. Therefore, many studies have investigated conversion rates to AD (as well as other forms of dementia) and investigated ways to be able to differentiate these two groups (i.e., converters and non-converters). Differences between MCI patients classified as converters (MCI-c) and those as non-converters (MCI-nc) have been reported on cognitive assessment, with converters showing poorer performance on the category fluency task, clock drawing task, delayed recall portion of the logical memory task ([Aretouli, Okonkwo et al. 2011](#_ENREF_16)), Trail Making Test part B (TMT-B), Wechsler Memory Scale (WMS) immediate figure recall ([Albert, Moss et al. 2001](#_ENREF_4)), delayed recall of the selective reminding test ([Pagani, Dessi et al. 2010](#_ENREF_338)), Wechsler Adult Intelligence Scale – Revised (WAIS-R) digit symbol test, and Selective Reminding Test (SRT) immediate recall ([Devanand, Liu et al. 2008](#_ENREF_120)), as well as on global cognitive screening measures such as the MMSE ([Devanand, Liu et al. 2008](#_ENREF_120); [Nordlund, Rolstad et al. 2010](#_ENREF_332)). Investigating differences between patients with MCI ([based on the Petersen 2004 criteria](#_ENREF_349)) and those with very mild MCI (vMCI) (based on CDR score ≤ 0.5), Dickerson et al ([2007](#_ENREF_123)) found that, whilst both these groups were more likely to decline (62% and 49% respectively, vs. 28% in healthy controls) and convert to AD (41% and 20% respectively, vs. 0% in healthy controls) than a control group, the Petersen MCI group converted to AD at a higher rate than the vMCI group. Several researchers have reported that deficits in executive function are useful predictors of conversion ([Tabert, Manly et al. 2006](#_ENREF_425); [Aretouli, Okonkwo et al. 2011](#_ENREF_16)). Aretouli et al ([2011](#_ENREF_16)) showed that higher scores on these tests of executive functioning indicated a lower likelihood of conversion to AD within a 2 year time period. Nevertheless, the authors of this study identified that the specific executive tasks that were found to be different between the two groups here relied also on semantic memory. Therefore, as semantic memory is one of the earliest impairments noted in AD, this could suggest why, in MCI patients, tasks with a semantic memory element are the most sensitive at differentiating those that will later convert to AD and those that will not. Furthermore, this argument is strengthened by the fact that the category fluency task (another measure of semantic memory) could also differentiate the MCI-converters from MCI-non-converters in this study ([Aretouli, Okonkwo et al. 2011](#_ENREF_16)).

#### Functional Impairment

Further to cognitive impairment, mild functional ability impairment at baseline has been associated with an increased risk of conversion to AD (e.g., [Daly, Zaitchik et al. 2000](#_ENREF_105); [Peres, Chrysostome et al. 2006](#_ENREF_343); [Rozzini, Chilovi et al. 2007](#_ENREF_388); [Farias, Mungas et al. 2009](#_ENREF_146)), as well as a faster rate of decline ([Purser, Fillenbaum et al. 2006](#_ENREF_361)). Studies have shown that an AD patient’s instrumental ADLs (IADLs) begin to decline within the early stage of the disease, with more basic functions (ADLs) declining later within the disease course ([Gauthier and Gauthier 1990](#_ENREF_173); [Gauthier, Gelinas et al. 1997](#_ENREF_174)). The ability to be aware of one’s impairment in AD has also been shown to be poor as the disease progresses. Fewer studies have looked at this issue in MCI, but results indicate that, while self-reported deficits are generally higher in MCI patients than in normal controls ([Tabert, Albert et al. 2002](#_ENREF_424)), when comparing MCI-c and MCI-nc, although the two MCI patient groups report a similar amount of functional deficits, MCI-c have more informant-reported functional deficits than MCI-nc ([Tabert, Albert et al. 2002](#_ENREF_424)). Furthermore, converters appear to report less functional deficits than are reported by their informants, while the pattern is reversed in non-converters ([Tabert, Albert et al. 2002](#_ENREF_424)), and research has suggested that informant reports of cognitive impairment are a more successful predictor of conversion from MCI to AD, than self-reported deficits ([Tierney, Black et al. 2001](#_ENREF_431); [Tabert, Albert et al. 2002](#_ENREF_424)). Further to this, these authors reported that the disparity between the self-reported and informant-reported deficits could predict time to AD conversion, with greater informant-reported deficits being an indicator of a lack of awareness in the patient and a reason to investigate further. Therefore, Tabert et al ([2002](#_ENREF_424)) suggested that this has important clinical implications and proposed the notion of including informant reported functional scales to aid in diagnosis, while others have also suggested they are sensitive and could be useful in the early detection of dementia (e.g., [Mcglone, Gupta et al. 1990](#_ENREF_295); [Koss, Patterson et al. 1993](#_ENREF_248); [Jorm 1997](#_ENREF_226); [Carr, Gray et al. 2000](#_ENREF_80); [Morris, Storandt et al. 2001](#_ENREF_318); [Tierney, Black et al. 2001](#_ENREF_431); [Baars, van Boxtel et al. 2009](#_ENREF_25)).

The different subtypes of MCI are also said to show dissimilar levels of functional ability at baseline. For example, Teng and colleagues ([2010](#_ENREF_429)) reported that those with a-MCI had more functional impairment than na-MCI patients; however, within these subgroups, it did not make a difference whether the impairment was in a single domain or whether it was in multiple domains. Therefore, while the authors concluded that functional impairment, as assessed by IADL scales, is related to the subtype of MCI but not to the number of cognitive domains impaired ([Teng, Becker et al. 2010](#_ENREF_429)), others have found a difference between those with sd-MCI and those with md-MCI (e.g., [Burton, Strauss et al. 2009](#_ENREF_74); [Aretouli and Brandt 2010](#_ENREF_15)). For example, Burton et al ([2009](#_ENREF_74)) reported more self-reported and informant-reported functional deficits in md-MCI compared to sd-MCI patients. Nevertheless, it has been suggested that this difference in informer vs. self-reported functional deficits could be due to the different measures used with patients and accompanying partners, as the patient is asked to describe complaints that they experience at the time that they answer the questions, whereas the accompanying carer questions asks about the progression of any cognitive complaints within the past year ([Baars, van Boxtel et al. 2009](#_ENREF_25)). However, ultimately, Baars and colleagues ([2009](#_ENREF_25)) concluded that those patients who do not complain are more likely to develop dementia in a shorter time period due to problems with insight into their condition.

When investigating subjective memory complaints, which are commonly reported in normal ageing individuals ([e.g., Manly, Bell-McGinty et al. 2005](#_ENREF_282)) even without objective memory impairments, patients with a-MCI (81.3%), na-MCI (81.7%) and cognitively normal individuals (80.0%) report a similar amount of (mild) memory complaints ([e.g., Fischer, Jungwirth et al. 2007](#_ENREF_155)). The Petersen ([2004](#_ENREF_349)) diagnostic criteria of MCI includes subjective memory complaints, however when researchers operationalise these criteria, some have found that excluding the subjective complaints increases predictive value of progression to dementia ([Baars, van Boxtel et al. 2009](#_ENREF_25)). And in fact, while Manly and colleagues ([2008](#_ENREF_283)) did find memory complaints as a predictor of progression in their sample, they conclude that the significance level was low, and that neuropsychological test data were more accurate at this prediction and therefore more importance should be placed on this than on memory complaints.

### Stable vs. late converters

When investigating the issue of MCI and conversion to AD, most studies have been conducted on two groups of MCI patients: those who convert to AD (MCI-converters) and those who remain at a stable MCI state (MCI-non converters). However, Pagani and colleagues ([2010](#_ENREF_338)) argued that this stable group actually comprises two different sets of patients: those that are actually stable (MCI non-decliners) and those who continue declining yet don’t reach criteria for dementia (MCI-decliners) ([Pagani, Dessi et al. 2010](#_ENREF_338)). Furthermore, they suggest these two groups of ‘stable’ patients may actually represent the MCI condition at different stages on the continuum, with MCI-decliners being at a later, more developed stage of MCI, and MCI non-decliners being at an earlier, less developed stage ([Pagani, Dessi et al. 2010](#_ENREF_338)). Chincarini and colleagues ([2011](#_ENREF_87)) went on to suggest that these ‘late’ converters to AD could muddy the distinction between actual MCI-nc and MCI-c and behavioural and brain metabolic differences between these MCI groups have been reported ([Pagani, Dessi et al. 2010](#_ENREF_338)). Therefore, knowing the difference between those true stable patients vs. those declining patients is useful clinical information which could be used to inform families/carers, but also to prevent patients receiving potentially dangerous pharmacological treatment if they do not need it ([Pagani, Dessi et al. 2010](#_ENREF_338)).

### CSF Biomarkers

Prediction of conversion to AD has been studied using CSF biomarkers. Schott and colleagues ([2010](#_ENREF_396)), using cut-off scores that had been previously defined, showed how a significant proportion of cognitively normal individuals possess features of AD pathology. Comparing a group of low level Aβ1-42 normal controls (<192pg/ml) and high level amyloid-β1-42 normal controls (>192pg/ml), they showed that a higher percentage of low level controls were within the AD range for phosphorylated tau (p-tau) (53% vs. 25%), tau/amyloid-β1-42 ratio (75% vs. 12%), and p-tau/amyloid-β1-42 ratio (85% vs. 25%) compared with the high level controls. Furthermore, whilst no significant cognitive differences were found at baseline between the low amyloidβ1-42 group and high group (except on the TMT-B test), the fact that the low group were more likely to possess AD features, led the researchers to suggest that this could indicate these individuals were already on the road towards developing AD ([Schott, Bartlett et al. 2010](#_ENREF_396)). Kennedy and colleagues ([2011](#_ENREF_236)) also reported similar findings in a-MCI patients. Furthermore, Nordlund et al ([2010](#_ENREF_332)) reported that, in combination with an md a-MCI diagnosis, the strongest predictors of conversion to AD were total-tau (t-tau) and amyloid-β levels. More specifically, they reported that those with high t-tau and low amyloid-β values were the most likely to convert, with 52% of the high t-tau and low amyloid-β individuals converting to AD within 2 years ([Nordlund, Rolstad et al. 2010](#_ENREF_332)). However, despite positive research into the use of biomarkers in predicting conversion in MCI patients, Devanand et al ([2008](#_ENREF_120)) argues that patients generally show a lack of acceptability for the lumbar puncture which limits the use of these CSF markers.

### Conversion and Imaging

With the advancements in imaging techniques, these have now been used to investigate atrophy patterns in the different subtypes of MCI as well as investigating variables to predict conversion. Research has indicated that the atrophy seen in the hippocampus of AD patients is not uniform, with CA1 subfield being the earliest affected (e.g., [Braak and Braak 1991](#_ENREF_61); [Rossler, Zarski et al. 2002](#_ENREF_387); [West, Kawas et al. 2004](#_ENREF_461)), and CA2-4 subfields being implicated later in the disease process ([e.g., Bobinski, Wegiel et al. 1995](#_ENREF_51)). Furthermore, atrophy of the hippocampus has also been reported in patients with MCI (e.g., [deLeon, George et al. 1997](#_ENREF_115); [Jack, Shiung et al. 2004](#_ENREF_222); [Apostolova, Dutton et al. 2006](#_ENREF_12)). Whitwell and colleagues ([2007](#_ENREF_464)) concluded that a-MCI patients who later convert to AD show a progressive pattern of atrophy, beginning in temporal regions, including the anterior hippocampus and entorhinal area at least 3 years prior to AD diagnosis, then progressing to a more severe state of GM loss in this medial temporal region, with involvement extending to the parietal lobe at 1 year prior to AD diagnosis, with an extension into the frontal lobes at the time of AD diagnosis. Using a Cox proportional hazard model, Apostolova, Thompson et al ([2010](#_ENREF_13)) reported that atrophy of the right CA1 subfield predicted conversion to AD, but not the left CA1 subfield. Therefore, due to the progressive nature of atrophy seen in the hippocampus throughout the AD process, Whitwell and colleagues ([2007](#_ENREF_464)) argued that this goes against the research that suggests the atrophy in the hippocampus reaches a plateau ([e.g., Chetelat, Desgranges et al. 2002](#_ENREF_85)). Differences between stable MCI patients and those who convert to AD have been found in relation to atrophy, in that MCI converters show more atrophy in areas of the hippocampus (i.e., CA1 and subiculum) ([Apostolova, Dutton et al. 2006](#_ENREF_12)). Furthermore, Hamalainen and colleagues ([2007](#_ENREF_193)) reported that, while the delayed wordlist recall performance of a group of stable MCI patients showed a positive correlation with hippocampal GM density, converters MCI patients’ Trail Making Test (part A) score was negatively correlated with GM density values in the right precuneus.

Chincarini, Bosco et al ([2011](#_ENREF_87)) described several areas of the brain that could be used to distinguish AD from normal controls, using volumes of Interest (VOIs), including areas of the MTL such as the hippocampus, entorhinal cortex, middle and inferior temporal gyrus, as well as the amygdala. However, trying to discriminate MCI-c from MCI-nc proved to be a more difficult task. Chen and colleagues ([2011](#_ENREF_83)), using a hypometabolic index, found that this index score correlated with cognitive scores on a range of neuropsychological measures (including ADAS-Cog, CDR, MMSE, AVLT, BNT, Category Fluency, TMT) as well as correlating with baseline volume of the hippocampus and also CSF measures of tau and amyloid-β – in each case, higher index scores (i.e., higher disease severity) correlated with lower neuropsychological scores, hippocampus volume and (higher) CSF tau/amyloid-β levels. While normal controls had the lowest index, and the AD group had the highest index, all differences were significant except for the difference between the AD and MCI-c indexes ([Chen, Ayutyanont et al. 2011](#_ENREF_83)). Furthermore, Chetelat and colleagues ([2005](#_ENREF_86)) reported MTL regions, especially the entorhinal cortex, show the fastest rates of atrophy, with more involvement of the prefrontal cortex in MCI-nc. Apostolova et al ([2010](#_ENREF_13)) argued for the use of 3D maps when assessing hippocampal atrophy, such as the radial distance technique, as they state that these can show hippocampus atrophy in a-MCI patients even when, visually, there is no atrophy that can be detected (i.e., Medial Temporal Atrophy (MTA) score 1, visual rating). Furthermore, the 3D maps have also been used in normal participants, and it has been reported that they are useful in detecting changes up to 3 years prior to a diagnosis of MCI, and up to 7 years prior to a diagnosis of AD ([Apostolova, Thompson et al. 2010](#_ENREF_13)).

Imaging studies of a-MCI patients have failed to find atrophy in the frontal lobes (e.g., [Chetelat, Desgranges et al. 2002](#_ENREF_85); [Pennanen, Testa et al. 2005](#_ENREF_341); [Whitwell, Przybelski et al. 2007](#_ENREF_464)), even up to 1-year prior to AD diagnosis ([Whitwell, Przybelski et al. 2007](#_ENREF_464)). Whitwell et al ([2007](#_ENREF_464)) also failed to find differences in GM volume between a-MCI and controls in the posterior cingulate, or between AD patients and controls in this same brain area, which is similar to findings in some reports ([e.g., Pennanen, Testa et al. 2005](#_ENREF_341)) but contradictory to those of other reports where differences have been found (e.g., [Minoshima, Giordani et al. 1997](#_ENREF_306); [Baron, Chetelat et al. 2001](#_ENREF_36); [Chetelat, Desgranges et al. 2002](#_ENREF_85); [Matsuda, Kitayama et al. 2002](#_ENREF_290)).

### Reversion

As well as conversion to AD, MCI patients have also been shown to revert back to a ‘normal’ status, and rates for reversion differ between studies (e.g., [Ritchie, Artero et al. 2001](#_ENREF_382); [Fisk, Merry et al. 2003](#_ENREF_156); [Ganguli, Dodge et al. 2004](#_ENREF_172)). Reversion can occur for many different reasons, and Manly et al ([2008](#_ENREF_283)) found that the most frequent cause of reversion in their sample was not meeting the cognitive criteria any longer. Other reasons include no longer meeting the functional criteria, as well as issues with the original diagnosis. Fischer et al ([2007](#_ENREF_155)) reported that, of all MCI patients at baseline, 21.5% reverted to normal cognitive health at 30 month follow-up, with 16.2% being a-MCI subtype, and 27.0% being na-MCI subtype. Furthermore, it has been reported that sd-MCI patients (38.0%) are more likely to revert than md-MCI patients (19.3%) ([Manly, Tang et al. 2008](#_ENREF_283); [Aretouli, Okonkwo et al. 2011](#_ENREF_16)). However, differences between md a-MCI and md na-MCI is less consistent, with some suggesting no differences between these two subgroups in reversion rates ([e.g., Manly, Tang et al. 2008](#_ENREF_283)), while others suggest sd a-MCI patients are the most likely to revert back to normal cognition ([Nordlund, Rolstad et al. 2010](#_ENREF_332)). Furthermore, some MCI patients also show a stable cognitive profile once diagnosed with MCI and remain like this throughout the rest of their life. Research has shown how a proportion of MCI patients remain stable even after a 10-year follow-up period ([Ganguli, Dodge et al. 2004](#_ENREF_172); [Fisk and Rockwood 2005](#_ENREF_157); [Visser, Kester et al. 2006](#_ENREF_452); [Mitchell and Shiri-Feshki 2009](#_ENREF_309)).

### Other risk factors

One risk factor of developing AD is being diagnosed as having MCI. However, another risk factor for AD is having at least one ApoE ε4 allele ([e.g., Anstey and Christensen 2000](#_ENREF_10)). Some studies found that individuals with a-MCI (50%) are more likely to have an ε4 allele than normal ageing individuals (28%) ([Manly, Bell-McGinty et al. 2005](#_ENREF_282)), while others have reported no differences in ApoE ε4 allele distribution between MCI converters and non-converters ([e.g., Tabert, Manly et al. 2006](#_ENREF_425)). Furthermore, not all studies have reported significant differences between ε4 carriers and non-carriers in regards to predicting conversion (e.g., [Albert, Moss et al. 2001](#_ENREF_4); [Devanand, Liu et al. 2008](#_ENREF_120)). Biundo and colleagues ([2011](#_ENREF_47)) investigated the combination of these two risk factors on conversion rates to AD, as well as the residual lexical-semantic abilities of these patients. It was reported that MCI ε4 carriers showed a higher rate of conversion than MCI non ε4 carriers ([Biundo, Gardini et al. 2011](#_ENREF_47)). Furthermore, these two patient groups also differed on their semantic abilities, with MCI ε4 carriers producing words that were earlier acquired on a test of semantic fluency compared with MCI non ε4 carriers ([Biundo, Gardini et al. 2011](#_ENREF_47)). Therefore, it can be concluded that MCI patients can be discriminated from normal controls using a simple semantic memory task, and even further so when a lexical characteristic analysis is carried out, suggesting that lexical-semantic impairments are important and should be investigated even at an early stage of cognitive decline as they can produce evidence of decline that is not part of the normal ageing process ([Biundo, Gardini et al. 2011](#_ENREF_47)). Furthermore, in another study of MCI ApoE ε4 carriers and non-carriers, Venneri and colleagues ([2011](#_ENREF_444)) reported a ‘genotype by lexical-semantic ability interaction’ which occurred principally in regions of the left mediotemporal and anterior temporal pole.

Recruitment source (clinic vs. community) has been shown to be associated with risk of conversion to dementia ([e.g., Farias, Mungas et al. 2009](#_ENREF_146)), with studies reporting that higher conversion rates are found in clinical studies compared with studies using community samples. For example, Farias et al ([2009](#_ENREF_146)) found a 13% compared with a 3% annual conversion rates to dementia in clinical vs. community based samples. Nevertheless, the authors state that, whilst no cognitive differences were seen between the two groups, they did differ in terms of functional impairment (community<clinic), hippocampus volumes (clinic<community) and total brain matter volume (clinic<community), suggestive of a more advanced disease state in the clinical sample, which could go towards this higher conversion rate in this particular group ([Farias, Mungas et al. 2009](#_ENREF_146)). Furthermore, differences were also found in age, education and sex, with the clinic sample being older, more educated and having more males, as well as race, with the community sample more likely being of an ethnic minority background ([Farias, Mungas et al. 2009](#_ENREF_146)). Farias et al ([2009](#_ENREF_146)) also reported that functional impairment at baseline was associated with conversion rate, as well as episodic memory ability and white matter hypertensity (WMH) volume. Further to this, conversion rates have been reported to be lower in studies with a longer follow-up duration ([Mitchell and Shiri-Feshki 2008](#_ENREF_308)).

Studies have reported lower scores on tests of olfaction in MCI patients when compared with controls ([e.g., Devanand, Michaels-Marston et al. 2000](#_ENREF_121)), as well as in AD when compared with controls (e.g., [Doty, Reyes et al. 1987](#_ENREF_130); [Murphy, Gilmore et al. 1990](#_ENREF_322); [Morgan, Nordin et al. 1995](#_ENREF_316); [Nordin and Murphy 1996](#_ENREF_331)). Furthermore, Devanand et al ([2000](#_ENREF_121)) found that the best predictor of conversion to AD was a low olfaction score as well as a low score of subjective reports of olfaction problems, even in high MMSE scoring patients (≥ 27/30). The combination of low olfaction scores as well as a lack of awareness of the olfaction problem also predicted time to conversion in this study.

### Summary of previous findings

Stephan and colleagues (2013) published a systematic review of random controlled trials (RCT) using Petersen et al’s (1999) criteria and investigated the use of the 5 key points described by Petersen and colleagues to diagnose an individual as having a-MCI (see 8.1). Stephan et al (2013) reported many problems and limitations with the way different authors operationalize these criteria, including the fact that some authors do not specify for each criteria point exactly how the patients have fulfilled them. The main concern with the operationalisation of these criteria is that different authors use a number of variable tests and methods to diagnose patients individually. For example, Stephan and colleagues (2013) reported that the MMSE is utilised in many studies, but the cut-off by which patients are diagnosed varies between ≥23-26. Furthermore, whether cut offs below 1SD, 1.5SD or 2SD are used also varies between studies. Ultimately, the need for a standard set of criteria to be utilised for diagnosing a-MCI will be useful to allow the inclusion of similar patients into RCTs and to standardise the way in which the diagnosis is reached. In addition there is also a need for standardising the way in which patients who receive a diagnosis of MCI are categorised in subtypes (as described in 8.1.2) including the category of MCI which most likely is not due to AD.

## Aims and objectives

The aim of the present study was to investigate whether we could retrospectively look back over the neuropsychological test performance of a group of MCI patients and identify specific tests that would be able to discriminate MCI patients who convert to a diagnosis of AD from MCI patients who remain stable at this diagnosis.

## Method

### Research Participants

Data were collected from patients who had attended the Outpatient Cognitive Disorder Unit, Parma (Italy). All of the patients had psychiatric, neurological and extensive neuropsychological examinations. Data from 27 patients with a diagnosis of Mild Cognitive Impairment were included in this study. The MCI patients varied among the subtypes, with a large majority of patients showing memory only impairments (a-MCI) or memory and executive function impairments (md a-MCI). The MCI patients were aged between 52 and 86 years (mean age 72.07; SD 8.53) and had levels of formal education ranging from 3 to 17 years (mean education 7.15; SD 3.69). Their scores on the MMSE at baseline ranged between 24 and 29 (mean MMSE 26.22; SD 1.63). All demographic data can be seen in Table 8.1.

Patients were followed up in the clinic routinely. The follow-up time period differed between patients and the average follow-up time was 12 months (range: 7-19 months).

Post-hoc G\*Power ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a one-tailed t-test, effect size (0.5) and α = 0.05 revealed an achieved power of 0.34.

This study received ethical approval by the Local Research Ethics Committee.

### Task and Procedure

#### Neuropsychological battery

All patients and controls underwent extensive neuropsychological assessment at baseline. Tasks included global screening measures such as the MMSE, as well as tests assessing many cognitive abilities including language, memory and visuospatial ability. Please refer to Chapter 4, Section 4.4.2 for a description of each test. The ADL/IADL measures were literally translated into Italian from the original measures ([Lawton and Brody 1969](#_ENREF_260)). Additionally the AVLT and BNT tasks were also used. The procedure for each are explained below:

##### Auditory Verbal Learning Task

The Auditory Verbal Learning Task (AVLT) ([Rey 1964](#_ENREF_377)) is a verbal learning and memory test, and involves two lists of 15 words. The participant hears the words in list 1 read out by the examiner, and is then asked to recall as many words as possible from the list and in any order. Five trials of this same procedure is completed, at which time the examiner then reads out list 2 and asks the participant to recall as many words as they can. After this, the participant is asked again to recall as many words as possible from list 1. Finally, after a delay, the participant is asked to recall as many words as they can from list 1.

##### *Boston Naming*

The Boston Naming Task (BNT) ([Kaplan, Goodglass et al. 1983](#_ENREF_234)), assessing naming, involves showing the participant, one by one, black and white drawings of various items (total = 60) which range in familiarity, and asking them to name each drawing. If the participant cannot name a drawing, semantic then phonemic then multiple choice hints are given. The score is the number of correct drawings identified.

##### Category fluency task

For details please refer to Chapter 4, Section 4.4.2.

##### Word Attributes

The normative values used were taken from an earlier study and they are Italian norms (Biundo, 2010: PhD dissertation, Hull, UK).

###### Age of Acquisition.

For details please refer to Chapter 4, Section 4.4.2.1.1.4.1.

###### Familiarity.

For details please refer to Chapter 4, Section 4.4.2.1.1.4.2.

###### Typicality

For details please refer to Chapter 4, Section 4.4.2.1.1.4.3.

### Conversion status

MCI patients were split into ‘converters’ and ‘non-converters’ based on their follow-up MMSE scores, with MCI-converters having MMSE scores ≤ 23 points, and MCI non-converters having MMSE scores ≥ 24 points. There were 11 patients who were classified as ‘converters’ using this criterion and 16 patients classified as ‘non-converters’. The converters were aged between 68 and 86 years (mean age 75.54; SD 5.91), while the non-converters were aged between 52 and 84 years (mean age 69.69; SD 9.39). The converters had levels of formal education ranging from 5 to 17 years (mean education 7.55; SD 4.48), while the non-converters had levels of education between 3 and 13 years (mean education 6.88; SD 3.16). The MCI converters scores on the MMSE at baseline ranged between 24 and 28 (mean MMSE 25.64; SD 1.21), while the MCI non-converters showed scores between 24 and 29 (mean MMSE 26.63; SD 1.78). At follow-up, the MCI converters scores on the MMSE ranged between 18 and 23 (mean 21.64; SD 1.80), while the MCI non-converters scores ranged between 24 and 30 (mean 26.44; SD 1.97). This comparison of demographic data between the two groups can be seen in Table 8.1.

## Results

### Demographics

There was no between groups significant difference on age or education, nor were there any significant difference in average follow-up time. Table 8.1 shows the mean of each group on demographic variables.

Table 8.1: Demographics of the full sample and when split into converters and non-converters.

|  |  |  |  |
| --- | --- | --- | --- |
|  | MCI (full sample) | MCI converters | MCI non-converters |
| *N* | 27 | 11 | 16 |
| Sex (M:F) | 12:15 | 6:5 | 6:10 |
| Age | 72.07 (8.53) | 75.54 (5.91) | 69.69 (9.39) |
| Education | 7.15 (3.69) | 7.55 (4.48) | 6.88 (3.16) |
| Follow-up time (months) | 11.93 (3.00) | 12.73 (3.72) | 11.38 (2.36) |

### Neuropsychological Tests

Analyses on individual test scores from the neuropsychological battery completed by patients at baseline were done using t-tests. Table 8.2 shows the range of baseline neuropsychological tests used and all patients’ performance on these tasks, as well as when split into converters and non-converters.

Table 8.2: Neuropsychological test performance (mean and SD).

|  |  |  |  |
| --- | --- | --- | --- |
| Test | MCI (full sample) | MCI converters | MCI non-converters |
| MMSE baseline | 26.22 (1.63) | 25.63 (1.21) | 26.63 (1.78) |
| MMSE follow-up | 24.48 (3.04) | 21.64 (1.80) | 26.43 (1.97)\* |
| AVLT: Immediate Recall | 27.82 (8.46) | 21.56 (5.64) | 32.15 (7.36)\* |
| AVLT: Delay Recall | 5.36 (2.87) | 3.67 (1.80) | 6.54 (2.93)\* |
| Raven’s Coloured Matrices | 23.54 (4.75) | 22.55 (5.32) | 24.27 (4.33) |
| Rey's Figure: COPY | 24.73 (5.55) | 20.88 (5.07) | 26.93 (4.65)\* |
| Rey's Figure: DELAY | 8.14 (4.91) | 6.06 (4.15) | 9.32 (5.06) |
| Stroop: ERROR | 3.69 (6.75) | 4.55 (7.63) | 3.07 (6.22) |
| Stroop: TIME | 41.31 (27.80) | 51.73 (29.54) | 33.67 (24.67) |
| Digit Cancellation | 46.67 (8.01) | 42.45 (8.74) | 49.56 (6.20)\* |
| Boston Naming | 15.73 (3.48) | 15.50 (5.37) | 15.86 (1.99) |

\* significantly better performance in the MCI-nc group compared to the MCI-c group.

Significant differences can be seen between the converters and non-converters on several tests, including on the AVLT Immediate (t(20) = -3.636, p<0.002) and Delayed recall (t(25) = -2.478, p<0.05), on the Digit Cancellation task (p<0.05) and on the Copy Component of Rey’s Complex Figure (t(20) = -2.846, p<0.01). On all of these, the non-converters performed significantly better than the converters. No differences were found between any of the measures used to analyse the semantic fluency task.

The data were then analysed using a linear regression, with follow-up MMSE scores as the dependent variable, and the neuropsychological test scores as the predictor variables. From this we see that follow-up MMSE scores was positively correlated with Digit Cancellation scores (r=.522, p<0.05), the Delay component of Rey’s Complex Figure (r=.480, p<0.05), and with Raven’s Progressive Coloured Matrices scores (r=.486, p<0.05). All of these positive correlations indicate that, as the follow-up MMSE score increased, the patient score on each task increased. Overall the model was not significant [F(9,4)=.692, p=.704, ns]: the summary shows that the predictor variables account for 60.9% of the variance in the follow-up MMSE scores, however none of the predictor variables significantly added to the model.

## Discussion

This study investigated differences in the neuropsychological performance of MCI patients who had converted to a diagnosis of AD compared with MCI patients who had not converted (i.e., remained stable at a diagnosis of MCI). The current study showed that MCI converters could be differentiated from MCI non-converters specifically with three different tests, namely the AVLT (both immediate and delayed recall), Digit Cancellation, and the copy component of Rey’s Complex Figure. Previous studies have shown that MCI patients do show impairment on the AVLT task compared with normal ageing individuals ([Tierney, Szalai et al. 1996](#_ENREF_432); [Petersen, Smith et al. 1999](#_ENREF_353)), but the current study has furthered this as we have evidenced that performance on this task actually differentiates those MCI-c from MCI-nc. Therefore, this suggests that, as a group, MCI patients show an impairment on this task when compared with normal ageing individuals; however, when we analyse the performance of those MCI-c’s and nc’s, it could be argued that the lower score of the converters decreased the average of the whole group. Therefore, by splitting these patients up, we see that not all MCI patients show this same AVLT impairment indicating that verbal memory impairment in MCI is more severely affected in those who will later convert to AD.

While the MCI groups did significantly differ on the delayed AVLT test (MCI-nc>MCI-c), this was not seen on the delayed component of Rey’s Complex Figure (MCI-nc=MCI-c). This difference in performance on delayed memory measures could be due to several factors, including severity of memory impairment and type of delayed memory. Firstly, in terms of severity of the memory impairment, it is likely that, as MCI patients do show a decline in memory functioning, whilst it is captured in the Rey delay component (i.e., on which groups show a decline), the AVLT delay result indicates that this memory impairment is more severe in those MCI patients who go on to convert to clinical AD. Secondly, in terms of the type of delayed memory measure, it could be argued that the visuospatial delayed memory test (delayed recall of the Rey Figure) is more sensitive to deficits in MCI patients as a whole, while the verbal delayed memory (AVLT) is less sensitive to deficits. Impairments in visuospatial delayed memory, therefore, are more pronounced in those MCI converting to clinical AD than in those MCI patients who remain stable. A previous study has shown that both verbal and visuospatial memory skills are impaired in MCI, but that there might be individual differences in the level of severity of impairment of these types of memories among patients (Alladi et al, 2006).

The current study also reported an impairment in MCI-c’s (compared with MCI-nc’s) in tasks which assess frontal functioning, namely the Digit Cancellation task. As the main complaint with MCI patient is that they show memory impairment, this study further shows that, whilst memory impairment is seen in both groups, those MCI patients who are most likely to convert to a diagnosis of AD also show further impairment that extends beyond memory into frontal domains including attention and executive functioning. Others have also reported an importance of executive functioning impairment as a possible marker of cognitive deterioration or conversion ([Chen, Ratcliff et al. 2000](#_ENREF_84); [Perry, Watson et al. 2000](#_ENREF_346); [e.g., Albert, Moss et al. 2001](#_ENREF_4); [Rozzini, Chilovi et al. 2007](#_ENREF_388)). Previous imaging studies have reported findings in line with our behavioural data and have shown that MCI-c show an increased amount of atrophy, that extends beyond memory areas such as the hippocampus, when compared with stable MCI patients. For example, comparing normal ageing participants, AD patients as well as two groups of MCI patients (converters and non-converters), Davatzikos et al ([2011](#_ENREF_109)) reported that MCI-nc exhibit GM patterns more similarly to normal ageing individuals, whereas the analysis between MCI-c and AD patients did not show any significant differences in terms of GM atrophy. This suggests that significant AD-like atrophy has already occurred by the time an MCI diagnosis is given in patients who are most likely to convert to a diagnosis of AD. In another study, amnestic MCI patients who converted to AD, showed GM loss in primarily medial temporal regions including the anterior portion of the hippocampus (posterior portion was relatively spared), entorhinal cortex and amygdala when compared with normal controls, when imaged 3 years prior to diagnosis of AD ([Whitwell, Przybelski et al. 2007](#_ENREF_464)). The authors commented that, outside of the temporal lobes, when compared with controls, no significant differences in GM were observed. When imaged 1 year prior to AD diagnosis, a-MCI patients still showed this GM loss in the MTL, but also showed further loss in the middle temporal gyrus as well as throughout the whole hippocampus and in the parietal lobe, but sparing of the frontal lobes. When imaged at the time of AD diagnosis, however these patients showed greater involvement of the frontal lobes, as well as substantial MTL involvement, which the authors of this paper suggested fitted with the Braak and Braak staging of AD neuropathology ([Whitwell, Przybelski et al. 2007](#_ENREF_464)).

Davatzikos and colleagues ([2011](#_ENREF_109)) have shown how in a third of MCI-nc, using their SPARE-AD method, the GM pattern is similar to that seen in healthy ageing, suggesting that a subgroup of MCI patients have a normal brain structure. This finding is similar to the argument put forward by another research group, Pagani and colleagues ([2010](#_ENREF_338)), who raised the issue that studies have been conducted on two groups of MCI patients: MCI-converters and MCI-stable. However, the authors in this study argued that the stable group really comprises two different sets of patients, i.e., those that are actually stable (MCI non-decliners) and those who continue declining yet don’t reach criteria for dementia (MCI-decliners) ([Pagani, Dessi et al. 2010](#_ENREF_338)). They also suggest that MCI-non decliners and MCI-decliners may represent the MCI condition at different stages on the continuum, with MCI-decliners being at a late stage of MCI, and MCI-non decliners being at an earlier stage ([Pagani, Dessi et al. 2010](#_ENREF_338)). Brain metabolic patterns have been shown not to differ significantly between MCI-c and MCI-decliners or between MCI-non decliners and controls ([Pagani, Dessi et al. 2010](#_ENREF_338)), however differences were seen between MCI-non decliners and MCI-decliners. For example, fluorodeoxyglucose positron emission tomography (FDG-PET) comparisons between patient groups and controls revealed that the MCI converters showed significant hypometabolic clusters in the bilateral posterior cingulate cortex, the left precuneus and the left fusiform gyrus compared to controls; the MCI-decliners showed a hypometabolic cluster in the left medial temporal lobe; however, no significant differences were reported between controls and the MCI non-decliner group ([Pagani, Dessi et al. 2010](#_ENREF_338)). Comparing between patient groups, no significant differences were found between MCI converters and MCI-decliners, whereas hypometabolic differences were reported in the left parahippocampal gyrus and hippocampus in the MCI decliners compared with MCI non-decliners ([Pagani, Dessi et al. 2010](#_ENREF_338)). Furthermore, the MCI converters also showed hypometabolism in the left middle and superior temporal gyri and in the left inferior parietal lobule compared with MCI non-decliners ([Pagani, Dessi et al. 2010](#_ENREF_338)). Ultimately, this indicates that brain metabolic patterns do not differ significantly between MCI converters and MCI-decliners, as well as between MCI non-decliners and controls ([Pagani, Dessi et al. 2010](#_ENREF_338)); however differences can be seen between MCI non-decliners and MCI-decliners, suggesting that there are distinctive behavioural and imaging patterns between MCI patients referred to as ‘stable’ in previous research which should be taken into account when comparing MCI patients. Pagani et al’s ([2010](#_ENREF_338)) argument for this differentiation suggests that, not only will knowing the difference between those true stable patients vs. those declining patients be useful information to inform families/carers of patients of, but that also knowing this difference could also prevent patients receiving potentially dangerous pharmacological treatment if they do not need it ([Pagani, Dessi et al. 2010](#_ENREF_338)). Therefore, using this argument, it could be that the third of MCI-nc patients in Davatzikos et al’s ([2011](#_ENREF_109)) study who showed normal brain structure were the ones who were most likely to be MCI-non decliners, whilst the other two-thirds of MCI-nc patients could have been MCI-decliners. The data from Davatzikos et al ([2011](#_ENREF_109)) do lend support to this as the authors noted that the baseline SPARE-AD score of the MCI-nc group was mixed, suggesting that the MCI-nc group was heterogeneous and possibly contained MCI-decliners and MCI-non decliners. When further analysing this group of MCI-nc they reported that the MCI-nc with the most negative SPARE-AD scores not only showed the highest baseline MMSE scores, but also showed that a small amount of decline on the MMSE between baseline and follow-up ([Davatzikos, Bhatt et al. 2011](#_ENREF_109)). Misra and colleagues ([2009](#_ENREF_307)) also reported similar results, using a similar method to Davatzikos et al ([2011](#_ENREF_109)), whereby MCI-nc showed a mix of scores relating to AD-like atrophy, indicating a group of patients that, whilst none converted in the time period, may convert at a later time point. Others have also reported differences within the atrophy extent in MCI patients who convert after a longer period of time, than those who convert in a shorter time period (e.g., [Chetelat, Landeau et al. 2005](#_ENREF_86); [Bozzali, Filippi et al. 2006](#_ENREF_57)).

The wide range of follow-up time (7-19 months) is a limitation of this study as some of the patients who were followed up for the shortest time could still have converted subsequently. Pagani et al’s ([2010](#_ENREF_338)) argument also has implications for our current study in that our group of MCI-nc patients could also be split into those who are true non-decliners and those who are decliners. However, due to the number of patients in our MCI-nc group (n=16), splitting them further would leave small numbers in each group, making statistical comparison harder to achieve. Furthermore, this sample only received full neuropsychological testing at baseline (and only MMSE at follow-up) which leaves the comparison of baseline and follow-up performance impossible. However, with follow-up neuropsychological performance and an increase in sample size, this analysis could be undertaken and it would be interesting to see the results.

It would have been useful to have a more extensive assessment of the MCI patients at follow-up. An assessment with the full neuropsychological battery of tests would have allowed a better quantification of their abilities over this time period and to measure any specific decline more accurately. This approach would have been useful in determining whether the patients are true stable MCI or whether they have declined within this time period but simply not enough to fulfil criteria for clinical AD – i.e., MCI-decliners. It may be useful to use parallel forms of tests for this follow-up period, depending on the length of time between testing sessions. Parallel test forms are particularly useful to avoid practice effects on the tests which might compensate for ability loss and which might result in a falsely stable cognitive profile. Nevertheless, whilst parallel forms are useful, a disadvantage is that the two forms of the tests (A and B) have to have high parallel form reliability to ensure comparison across testing sessions, and for many tests there is insufficient evidence about this form of reliability or in some cases this aspect has not been studied.

Our current study indicates that frontal dysfunction is present in MCI patients who are more likely to convert to AD compared with MCI-nc. Other studies have also showed a relationship (positive) between MCI patients executive function ability and the left middle frontal gyrus volume ([Duarte, Hayasaka et al. 2006](#_ENREF_133)). Aretouli et al ([2011](#_ENREF_16)) also showed that three different tests of executive cognition could differentiate MCI-c from MCI-nc, whereby the higher the scores on these tests, the lower the likelihood they would convert to AD within the 2 year time period. Nevertheless, the authors of this study detailed these executive control tests relying also on semantic memory. Therefore, as semantic memory is one of the earliest impairments seen in AD, this could suggest why, in MCI patients, these tasks with this semantic memory element are the most sensitive at differentiating those that will convert to AD and those that will not. The finding from Aretouli et al ([2011](#_ENREF_16)) supports this point as it was the converters who showed lowest scores on these tasks, possibly indicating that those MCI patients who carry on to develop AD also show semantic memory impairments, and therefore this could be a potential measure for differentiating MCI-c from MCI-nc even before the patients convert. Furthermore, this argument is strengthened by the fact that the category fluency task (another measure of semantic memory) could also differentiate the MCI-converters from MCI-non-converters in this study ([Aretouli, Okonkwo et al. 2011](#_ENREF_16)).

In this current study we did not separate the MCI patients into separate subtypes. Primarily, this is because the sample size would not allow for this – splitting 27 patients into the different subtypes (i.e., a-MCI, na-MCI, sd-MCI, md-MCI) and then again into converters and non-converters would not provide the necessary power for reliable statistical inferences. However, some previous literature does tell us that conversion rates between the subtypes do differ. For example, research has suggested that impairment can be seen in one cognitive domain or several, with those who have several deficits in different cognitive domains showing an increased likelihood of progression to AD than those with only one impaired cognitive domain ([e.g., Aretouli, Okonkwo et al. 2011](#_ENREF_16)). Furthermore, others have suggested that it is the combination of deficits in multiple domains (and not whether memory is one of the domains affected) that increases the risk of conversion ([Alexopoulos, Grimmer et al. 2006](#_ENREF_5); [Manly, Tang et al. 2008](#_ENREF_283); [Baars, van Boxtel et al. 2009](#_ENREF_25)).

# Chapter 9: Response to Cholinesterase Treatment in Alzheimer’s Disease

## Introduction

### Pharmacological Treatment of AD

At present, there is no known cure for Alzheimer’s Disease. However, successful research has led to the development of pharmacological symptomatic treatment that has also been shown to slow down this progressive disease through its action on the deficits that are seen early in the disease process within the cholinergic system.

#### The Cholinergic Deficit

The cholinergic deficit that is seen in AD, whilst not being the sole neurotransmitter (NT) system deficit within the brain of these patients, is the most consistent ([Perry, Perry et al. 1978](#_ENREF_344)). For a description of the Cholinergic Hypothesis, please refer to Chapter 2, Section 2.3.1.1.

In normal ageing, ACh has been shown to be depleted within the brain, however, in AD, this depletion of ACh reaches abnormal levels and research has suggested that this reduction correlates with the severity of AD ([Lanctot, Herrmann et al. 2003](#_ENREF_256)). Further evidence that the decline seen in AD is, at least in part, related with cholinergic deficit comes from studies which indicate that this reduction of cholinergic neurons is seen in brain areas that are the earliest affected by the pathology of AD, including the hippocampus and temporal cortex ([Siegfried 1993](#_ENREF_403)), and it is also well known that cognitive functions, including attention ([Callaway, Halliday et al. 1992](#_ENREF_76)) and memory ([Gallagher 1997](#_ENREF_171)), have a cholinergic basis.

#### Cholinesterase Inhibitors

Based on this hypothesis pharmacological treatment options were developed and cholinesterase inhibitors licensed for use – please refer to Chapter 2, Section 2.3.1.2 for an overview. Donepezil, Rivastigmine and Galantamine are the most commonly used ChEIs, and the next section will review the current literature on these inhibitors.

### Research:

#### i) ChEI vs. placebo/untreated

Evidence that ChEIs are beneficial to patients with AD in terms of cognitive and functional improvements has come from studies comparing groups of ChEI-treated patients with either placebo-treated patients, or patients who received no treatment. In a review of the literature, Lanctot et al ([2003](#_ENREF_257)) concluded that ChEI treatment did show superior effects over placebo, and therefore should be used as treatment in patients with AD. Specifically, research has shown that patients score significantly better on the MMSE after ChEI treatment compared to untreated patients ([eg, Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)), as well as compared with placebo treated patients (eg, [Bryson and Benfield 1997](#_ENREF_72); [Erkinjuntti, Kurz et al. 2002](#_ENREF_141); [Venneri, Shanks et al. 2002](#_ENREF_448)). Patients treated with ChEI also show cognitive improvements on the ADAS-Cog (eg, [Bryson and Benfield 1997](#_ENREF_72); [Farlow, Anand et al. 2000](#_ENREF_147); [Seltzer, Zolnouni et al. 2003](#_ENREF_400); [Seltzer, Zolnouni et al. 2004](#_ENREF_401); [Birks and Harvey 2006](#_ENREF_45)), CIBIC ([eg, Bryson and Benfield 1997](#_ENREF_72)) and ADL functioning ([Birks, Evans et al. 2009](#_ENREF_44)). Furthermore, Seltzer and colleagues ([2003](#_ENREF_400)) also documented that over 50% of Donepezil-treated patients, compared with only 29% of placebo-treated patients, improved by at least 1.5 points from baseline on the MMSE, while placebo-treated patients also declined at a more accelerated rate compared with ChEI-treated patients after 1 year ([Doody, Dunn et al. 2001](#_ENREF_126)). This superior effect of ChEI treatment over placebo has also been reported in MCI individuals whereby those treated with Donepezil did not show cognitive decline within the first 18 months of a 3-year study ([Petersen, Thomas et al. 2005](#_ENREF_355)). It has been widely noted in the literature that patients receiving treatment for the full study duration improved further in comparison with patients receiving placebo for a period of time before being moved onto ChEI treatment, evidence that is used to argue for initiation of treatment early in the course of the disease ([Farlow, Anand et al. 2000](#_ENREF_147)). Furthermore, Farlow and colleagues ([2000](#_ENREF_147)) reported that there were significantly more patients responding with ≥ 7 ADAS-Cog points from an original 6-12 mg/day Rivastigmine treatment group compared with a Rivastigmine group who received placebo for 26 weeks previous to the ChEI. Nevertheless, it can still be seen that if treatment cannot be initiated early, whilst maximum benefits may not be attained as in those treated with ChEIs from an earlier stage ([Doody, Geldmacher et al. 2001](#_ENREF_128)), it can still be beneficial to initiate treatment at a later stage as Farlow and colleagues ([2000](#_ENREF_147)) reported that the original placebo group did benefit when they finally received ChEI treatment. Furthermore, it has been argued that a late response, i.e., an initial decline, does not necessarily indicate an absence of treatment success in the longer term as Johannsen, Barcikowska et al ([2003](#_ENREF_224)) reported that following treatment with Donepezil and showing no beneficial effect of the drug, once randomised to either placebo or to continue Donepezil treatment, significant differences on the MMSE and Neuropsychiatric Inventory (NPI) scales in favour of Donepezil treatment was found, as well as less deterioration on the ADAS-Cog and Disability Assessment for Dementia (DAD) scales ([Johannsen, Barcikowska et al. 2003](#_ENREF_224)). This has also been evidenced using ADL scales, for example, the AD2000 Collaborative Group found that, whilst no difference could be seen between Donepezil-treated patients and placebo-treated patients at 12 weeks on the Bristol Activities of Daily Living Scale (BADLS), after this period, the Donepezil group outperformed the placebo group throughout the rest of the study ([Courtney, Farrell et al. 2004](#_ENREF_98)). Furthermore, research has also indicated that ChEI treatment can delay the time admission to a nursing home compared with patients who have not received treatment ([eg, Geldmacher, Provenzano et al. 2003](#_ENREF_175)). However, others reported no difference between ChEI treatment and placebo in terms of institutionalisation over a 3-year period ([Courtney, Farrell et al. 2004](#_ENREF_98)).

Studies have also reported that, in addition to cognitive and functional improvement, patients treated with ChEIs have increased regional cerebral blood flow (rCBF) compared with baseline rCBF ([Staff, Gemmell et al. 2000](#_ENREF_413)), and an increase in cerebral glucose metabolism compared with placebo-treated patients ([Stefanova, Wall et al. 2006](#_ENREF_414)). Increased rCBF has been shown to coincide with improvement on cognitive measures compared with baseline performance ([Venneri, Shanks et al. 2002](#_ENREF_448)). Some research has also investigated CSF levels of AChE (eg, [Davidsson, Blennow et al. 2001](#_ENREF_111); [Darreh-Shori, Almkvist et al. 2002](#_ENREF_108)) and BuChE ([Darreh-Shori, Almkvist et al. 2002](#_ENREF_108)). For example, correlations between the Digit Symbol test scores and TMT-B test scores with CSF AChE have been found after 3 months of treatment ([Darreh-Shori, Almkvist et al. 2002](#_ENREF_108)). Negative correlations have also been reported between performance on executive and attentional tasks and the degree of AChE inhibition ([Bohnen, Kaufer et al. 2005](#_ENREF_53)).

#### ii) ChEI vs. ChEI

When comparing the effectiveness of Donepezil, Rivastigmine and Galantamine, some researchers have shown that patients do exhibit different treatment effects on these (eg, [Lanctot, Herrmann et al. 2003](#_ENREF_257); [Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)). For example, Doody et al ([2001](#_ENREF_126)) showed how a more accelerated decline by placebo-treated patients was seen compared with Donepezil-treated patients after 1 year but not compared with Tacrine-treated patients, who showed a similar rate of decline as the placebo-treated group. Furthermore, despite showing similar performances on baseline assessment of global cognition (MMSE) and functional scores IADL, patients on Rivastigmine showed better stability than Donepezil treated patients after 9 months ([Caffarra, Vezzadini et al. 2007](#_ENREF_75)), though the authors reported that this was only marginal. However, this is not a consistent finding, and others report opposite findings, i.e., patients treated with Donepezil show slightly greater improvement on the MMSE than patients treated with other ChEI drugs (Rivastigmine and Galantamine) ([eg, Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)). A review of studies using Donepezil, Rivastigmine and Galantamine found that, compared with placebo, treatment was effective in 13% more cases with Donepezil, 5% with Galantamine, and 12% more cases with Rivastigmine ([Lanctot, Herrmann et al. 2003](#_ENREF_257)), showing a somewhat differential effect of the ChEIs compared with placebo. It has also been reported that Donepezil shows an advantage over Galantamine in increased cognitive functioning following treatment as assessed by the ADAS-Cog, ADL functioning, MMSE ([Soininen, Martin et al. 2002](#_ENREF_411)) and physician and caregiver satisfaction/ease of use questionnaires ([eg, Jones, Soininen et al. 2004](#_ENREF_225)). One study did in fact report the opposite, that Galantamine-treated patients deteriorated significantly less on the ADAS-Cog compared with the deterioration seen in the Donepezil-treated patient group; however this was the case only in patients with MMSE scores of between 12-18 ([Wilcock, Howe et al. 2003](#_ENREF_467)). In this study by Wilcock and colleagues ([2003](#_ENREF_467)) there was also a difference between the groups in dosage, whereby the Donepezil patients received 10mg/day, and the Galantamine patients received 24mg/day, which could have had an impact on the results. Furthermore, patients given Galantamine treatment have been shown to experience more adverse effects (AEs) with this particular ChEI than patients on Donepezil ([eg, Jones, Soininen et al. 2004](#_ENREF_225)). The differential effectiveness of the ChEIs could be due to the different pharmacodynamic and pharmacokinetic properties of each drug. Nevertheless, some research has reported no difference or only marginal difference between the effectiveness of the different ChEIs ([eg, Caffarra, Vezzadini et al. 2007](#_ENREF_75)).

### Response to ChEIs

One problem researchers have come across is exactly how to determine when a patient has benefitted sufficiently from ChEI treatment over placebo or no treatment. Several organisations (e.g., US Food and Drug Administration) have selected criteria for classifying AD improvement as clinically significant, while researchers also tend to use their own devised criteria. A large amount of research has looked at response to ChEI treatment to ultimately try to predict response prospectively. AD patients treated with Rivastigmine for 3 months and classified as responders (≥ 2 point increase on MMSE scores) showed significantly greater scores on a range of neuropsychological tests compared with their baseline performance and a stabilisation of scores at 6 months of treatment (with a further increase in their sustained attention scores), compared to a group of age, education and severity matched untreated patients who decreased in cognitive ability in these same tests at 3 and 6 months compared with their baseline scores ([Venneri, Shanks et al. 2002](#_ENREF_448)). In this study, performance in Rivastigmine-treated AD patients classified as non-responders showed a decrease in cognitive ability in these same tests at 3 and 6 months of treatment compared with baseline ([Venneri, Shanks et al. 2002](#_ENREF_448)). Furthermore, some researchers, when looking at response to treatment, have found no differences on baseline functional scores (IADL and ADL) between those classified as responders and non-responders ([eg, Caffarra, Vezzadini et al. 2007](#_ENREF_75)). Therefore, not all patients treated with ChEIs will respond, and it is important to identify the patients that are most likely to respond well to this treatment as being able to target successfully patients who will benefit most from ChEI treatment is useful for avoiding prescribing the drug to patients with poor potential for response the drug ([Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)), potentially avoiding treatment options that will be of no benefit cognitively or functionally.

Response to treatment has also been evidenced using imaging tools, specifically with responders showing increased rCBF compared with non-responders ([eg, Venneri, Shanks et al. 2002](#_ENREF_448)). SPECT studies have shown increases in areas including the medial frontal and anterior cingulate regions in treated patients after 6 months of treatment compared with baseline SPECT activity alongside cognitive improvement, which is dissimilar to that seen in patients treated and classified as non-responders, who have shown decreased regional uptake in extensive brain regions ([Venneri, Shanks et al. 2002](#_ENREF_448)). In a study by Hanyu and colleagues ([2002](#_ENREF_196)), these authors found an inverse relationship between response to treatment (5mg of Donepezil for an average of 14.85 weeks) (measured by the MMSE score) and the thickness of the substantia innominata, a finding which had also been previously documented ([Hanyu, Asano et al. 2002](#_ENREF_195)). While the AD patient group as a whole showed more atrophy compared with a control group ([presented in an earlier study: Hanyu, Asano et al. 2002](#_ENREF_195)), when split along response classification, the responders showed more atrophy of the substantia innominata than the non-responders ([Hanyu, Tanaka et al. 2002](#_ENREF_196)). Several research groups also suggested the idea that, as Lewy-Body dementia patients appear to respond better to ChEI treatment than AD patients ([Liberini, Valerio et al. 1996](#_ENREF_269); [Hanyu, Tanaka et al. 2002](#_ENREF_196)), it could be that individual response could depend on the amount of cholinergic depletion, as Lewy-body patients are said to have pronounced cholinergic neuronal loss in the nbM. Therefore, taken with Hanyu et al’s ([2002](#_ENREF_196)) own results, it could be suggested that better responders to ChEI treatment may be patients with more atrophy and more cholinergic depletion.

Whilst no differences were seen in baseline assessments, after 6 months of donepezil treatment, Saumier et al ([2007](#_ENREF_394)) noted differences between those who responded to the ChEI treatment compared with those who did not respond on tests including the BNT, Clock Drawing test and tracking task, which assess visuo-spatial motor abilities and lexical-semantic functioning. In all significant results, the responders outperformed the non-responders. Nevertheless, Saumier and colleagues ([2007](#_ENREF_394)) concluded that, whilst taken together, these tests assessing visuo-spatial motor and lexical-semantic functioning seem able to predict response to donepezil treatment after 6 months, when each test was used individually to assess response this was not seen to be the case. Others have also shown worse performance by non-responders on baseline measures of concept formation and reasoning ([Venneri, Shanks et al. 2002](#_ENREF_448)). Therefore, it seems that several measures should be used to predict response.

Response as assessed by a ≥4 point increase on the ADAS-Cog was seen in 28.3% of the donepezil treated patients, and 11.5% of the Galantamine treated patients in the Jones et al ([2004](#_ENREF_225)) study, showing a significant improvement of Donepezil over Galantamine. Furthermore, response as assessed by a ≥ 7 point increase on the ADAS-Cog was seen in 53.3% of Donepezil-treated patients, and 28.8% of Galantamine-treated patients, showing an even larger improvement of donepezil over Galantamine ([Jones, Soininen et al. 2004](#_ENREF_225)). Wattmo and colleagues ([2011](#_ENREF_455)), looking at age and response to ChEI treatment, reported that individuals aged 85 years old showed a better treatment response compared with 65 year old individuals, but only when their MMSE was below 22 points. Furthermore, this outcome was also true of the ADAS-Cog scores (over all levels of scores) ([Wattmo, Wallin et al. 2011](#_ENREF_455)). Education has been investigated as a predictor of response to treatment, and some researchers have reported higher educational attainment results in a more increased level of cognitive impairment over time ([eg, Wattmo, Wallin et al. 2011](#_ENREF_455)). This result can be explained by the cognitive reserve hypothesis – which states that people with higher levels of education are at a more severe stage of AD neuropathologically, whilst appearing at a similar level of cognitive impairment on neuropsychological tests when compared with an individual with less years of education ([Stern, Albert et al. 1999](#_ENREF_419)).

Nevertheless, after a review of cognitive and behavioural response to ChEIs, Lanctot and colleagues ([2003](#_ENREF_256)) concluded that there was no single convincing predictor coming from these studies. However, it is still understood that prediction of response to treatment is especially important as not all patients with AD show the same degree of response to ChEIs. However, one promising avenue that requires further attention is the semantic fluency task and response. Venneri and colleagues ([2009](#_ENREF_446)) reported that performance on this fluency task was predictive of response – i.e., those who showed an improvement to ChEI treatment (responders) also demonstrated worse baseline performance compared with those who did not respond (non-responders). The interpretation for this is that it could be those with the largest depletion in semantic memory, and therefore those who have greater depletion of the cholinergic system, that treatment is most effective with.

### Rate of progression

Not all patients progress at the same rate of decline with AD and therefore, due to the heterogeneity of progression, research has investigated whether rate of progression can predict response to treatment with ChEIs ([eg, Farlow, Hake et al. 2001](#_ENREF_148)). Some researchers have reported a significant improvement on ADAS-Cog scores to Rivastigmine treatment by patients initially showing a fast rate of progression of the disease (assessed by ≥ 4 point deterioration on the ADAS-Cog during placebo trial) compared with a slower rate of progression (assessed by < 4 point deterioration) ([eg, Farlow, Hake et al. 2001](#_ENREF_148)), suggesting that, not only could response to treatment be predicted by disease progression rate but also that it may be that Rivastigmine is most suitable for AD patients who show a fast disease progression rate. This better performance by the rapidly progressing AD group was maintained over the further 14 week follow-up period in this study. Furthermore, scores on the Progressive Deterioration Scale (PDS) were also significantly better for the rapidly progressing patients compared with the slowly progressing patients ([Farlow, Hake et al. 2001](#_ENREF_148)). Nevertheless, some researchers have reported slower cognitive deterioration progression occurs in those AD patients who show less cognitive deficits at baseline testing ([Wattmo, Wallin et al. 2011](#_ENREF_455)). Furthermore, in a group of amnestic-MCI patients, those treated with Donepezil showed no cognitive decline within the first 18-months of the 3-year study, which the authors concluded was most likely the reason why this Donepezil-treated group also showed a slower rate of progression to AD ([Petersen, Thomas et al. 2005](#_ENREF_355)). Having an ApoE 4 allele can greatly increase your risk of developing AD and in fact, out of all the MCI patients who progressed to AD over a 3-year period in the Petersen et al ([2005](#_ENREF_355)) study, 76% of those patients carried the ApoE 4 allele. However, the researchers found that, in MCI patients with an ApoE 4 allele, being on Donepezil treatment reduced the risk of progressing to AD to a greater extent than patients treated with placebo.

### Severity of the disease

Until 2011, the NICE guidelines stated that ChEI treatment could only be administered in patients with moderate stage AD (MMSE 10-20) ([NICE 2009](#_ENREF_329)). Nevertheless, research has made a growing case for initiating treatment earlier in the disease course, i.e., in mild AD (eg, [Farlow, Anand et al. 2000](#_ENREF_147); [Seltzer, Zolnouni et al. 2004](#_ENREF_401)). Furthermore, Petersen et al ([2005](#_ENREF_355)) also reported that Donepezil treatment in MCI patients reduced the risk of progressing to AD more than patients treated with placebo. Therefore, after evidence that mild stage AD patients do benefit from ChEI treatment, NICE now allows ChEI treatment to be initiated in mild and moderate stages of AD, as well as the introduction of Memantine for moderate AD patients who cannot tolerate ChEIs, or for patients in the severe stage of the disease (MMSE <10) ([NICE 2011](#_ENREF_330)). Milder patients (MMSE>18) have been seen to improve more on MMSE scores after ChEI treatment than more moderate patients (MMSE<18) ([Erkinjuntti, Kurz et al. 2002](#_ENREF_141)). Seltzer and colleagues ([2004](#_ENREF_401)), using only mild AD patients with CDR scores of 0.5 or 1, and MMSE scores ranging between 21 and 26, found that patients treated with donepezil showed improvements over those treated with placebo from 6 weeks of treatment on the MMSE, and from 12 weeks of treatment on the ADAS-Cog, through until the end of the study at 24 weeks ([Seltzer, Zolnouni et al. 2004](#_ENREF_401)). Furthermore, they reported that, compared with 47% of the placebo group, 70% of Donepezil-treated patients did not decline at all, as measured by the ADAS-Cog, throughout the whole 24-week study ([Seltzer, Zolnouni et al. 2004](#_ENREF_401)). In addition, a significant difference was also seen in the MMSE scores, with the placebo-treated patients showing an increased decline as early as 6-weeks of treatment, and continuing throughout the study, as well as on scores of visual and verbal learning tasks (Seltzer et al, 2004). When looking at the differences between mild and moderate AD patients receiving Donepezil treatment, Molinuevo and colleagues ([2011](#_ENREF_313)) reported similar benefits in terms of MMSE score and Memory Alteration Test (M@T) score at 6 months. However, in terms of their IADL and ADL scores, whilst both groups decreased in performance, the mild group decreased less than the moderate group. Furthermore, when looking at baseline MMSE scores, Caffarra and colleagues ([2007](#_ENREF_75)) showed that the ‘non-responder’ group displayed significantly higher baseline MMSE scores than both the ‘good-responders’ (≥2 points) and ‘responders’ (>0-2 points) groups, and whilst not significantly, also higher than the ‘unchanged’ (=0 points) group. Similar to Venneri et al (2009), the explanation for this could be that patients with worse baseline performance gain the most benefit from ChEI treatment. Conversely, Wattmo et al ([2011](#_ENREF_455)) reported different findings, whereby they showed that those patients who showed slower cognitive deterioration after treatment with ChEIs also showed less cognitive deficits at baseline testing. Salloway et al ([2003](#_ENREF_393)) found that MCI patients improved significantly more on tests assessing global cognition (ADAS-Cog) and executive functioning (e.g., Backwards Digit Span and Symbol Digit Modalities test) compared with patients treated with placebo. Nevertheless, another study reported that after 7 days of Galantamine treatment (4mg/day), only performance on verbal episodic memory tests showed improvement compared with baseline, while no differences were seen in attention, executive functioning or short-term/working memory ([Gron, Brandenburg et al. 2006](#_ENREF_186)).

### Short-term vs. long-term benefit

Looking at the difference between global response in the short-term and in the long-term in their review of the literature, Lanctot et al ([2003](#_ENREF_257)) found that ChEI treated patients performed significantly better in both the short-term and long-term compared with placebo. Patients also score significantly better on the MMSE after 6-months of ChEI treatment compared with untreated patients ([eg, Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)), as well as when compared with placebo treated patients (eg, [Bryson and Benfield 1997](#_ENREF_72); [Birks and Harvey 2006](#_ENREF_45)). Some researchers have found that patients who showed response in the short-term (3 months) are also most likely responders in the long term (9 months) ([Raschetti, Maggini et al. 2005](#_ENREF_362)), with short-term response and having no other concomitant diseases being the best predictors of response in the longer term ([Raschetti, Maggini et al. 2005](#_ENREF_362)).

### Adverse Effects (AEs)

Compared with placebo, ChEI treatment has been shown to increase the likelihood of AEs (eg, [Erkinjuntti, Kurz et al. 2002](#_ENREF_141); [Lanctot, Herrmann et al. 2003](#_ENREF_257); [Courtney, Farrell et al. 2004](#_ENREF_98); [Birks and Harvey 2006](#_ENREF_45)). It has been suggested that more patients receiving ChEIs experience AEs and leave clinical trials compared with patients receiving placebo (eg, [Lanctot, Herrmann et al. 2003](#_ENREF_257); [Birks and Harvey 2006](#_ENREF_45)). In a review of the literature, Birks and colleagues ([2009](#_ENREF_44)) found that Rivastigmine-treated patients (6-12mg/day) showed significantly higher cases of AEs, in particular gastroenteritis side effects, compared to placebo. Tacrine, whilst being associated with hepatoxicity, has a greater risk for interaction with a patient’s concomitant medications ([eg, Birks, Evans et al. 2009](#_ENREF_44)). This is obviously disadvantageous for a disease such as AD, whereby the majority of cases involve older adults who are likely to be taking several different medications. Nevertheless, Birks et al ([2009](#_ENREF_44)) have suggested that this specific problem is a lower risk with Rivastigmine. In particular, Birks et al ([2009](#_ENREF_44)) concluded that AEs appear less frequent in those who take Rivastigmine without interruption and frequently, and in those who take a lower dose (≤ 4mg/day).

A similar drop-out level of patients between the different ChEI drugs (Donepezil, Rivastigmine and Galantamine) has been reported in some studies ([Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)), while others have found differences in tolerability levels, and patients taking Donepezil usually report experiencing less AEs than those on Rivastigmine ([eg, Birks and Harvey 2006](#_ENREF_45)), or Galantamine (eg, [Lanctot, Herrmann et al. 2003](#_ENREF_257); [Jones, Soininen et al. 2004](#_ENREF_225); [Raschetti, Maggini et al. 2005](#_ENREF_362)). Furthermore, Jones and colleagues ([2004](#_ENREF_225)) reported more of their Donepezil-treated patients were taking the maximum dose at the end of the study (92.2%) compared with their Galantamine-treated patients (71.4%). Others have also reported good tolerance levels, with between 92-97% of Donepezil-treated patients being on the highest dosage throughout the study ([Doody, Geldmacher et al. 2001](#_ENREF_128)). In terms of drop-out rates, Birks & Harvey ([2006](#_ENREF_45)) reported less drop-outs in the placebo group compared with those patients receiving 10mg of Donepezil, but not compared with those receiving 5mg. Whilst it has been shown to be the case that ChEIs produce more AEs than placebo, good tolerance levels have been reported, and Seltzer et al ([2004](#_ENREF_401)) described only slightly elevated levels (16%) withdrawing due to AEs, compared with 9% of patients on placebo.

### Switching

Patients who may not respond well to a particular type of ChEI have been shown to benefit from switching to a different ChEI. Reasons such as AEs, lack of efficacy or loss of efficacy has been reported for switching ([Emre, Farlow et al. 2003](#_ENREF_139)). However, others have suggested that *lack of efficacy* – which is described as a decrease of cognitive abilities since baseline following ChEI treatment – and not *loss of efficacy* – which is described as showing a decrease of cognitive abilities after a period of improvement or stabilisation following ChEI treatment – is an appropriate reason to switch ChEIs ([Massoud, Desmarais et al. 2011](#_ENREF_286)). Researchers investigating the switching of ChEIs have reported improved cognitive functioning based on MMSE scores after the switch as well as functional improvement assessed by IADL measures ([eg, Auriacombe, Pere et al. 2002](#_ENREF_24)), while others have found improvement in switching from an AChE inhibitor to a dual AChE-BuChE inhibitor (e.g., Donepezil to Rivastigmine) (eg, [Auriacombe, Pere et al. 2002](#_ENREF_24); [Bartorelli, Giraldi et al. 2005](#_ENREF_37)). The rationale behind this comes from the fact that these drugs show different pharmacodynamic and pharmacokinetic properties. Earlier studies have reported using washout periods, i.e., periods of no treatment when in the process of switching from one ChEI to another, as not allowing for this washout was suspected to be damaging for the patient. However, now it is recognised that there is no need for this washout period and switching without it has been shown to be well tolerated (eg, [Maelicke 2001](#_ENREF_281); [Sadowsky, Farlow et al. 2005](#_ENREF_391)). In fact, having a gap between treatment for a long period can be harmful (i.e., in regards to AEs) ([eg, Sadowsky, Farlow et al. 2005](#_ENREF_391)) and also can reduce the cognitive gains the patient has already received from ChEI treatment or even eliminate those gains to below baseline ([Doody, Geldmacher et al. 2001](#_ENREF_128)). For example, Sadowsky and colleagues ([2005](#_ENREF_391)) have reported a good tolerance rate of patients switching from Donepezil to Rivastigmine without a washout period. Furthermore, they suggest that the switch is well tolerated due to the fact that these patients have already adjusted to ACh levels and therefore, a switch that occurs without a washout period will mean the patients do not have to tolerate the ChEI again ([Sadowsky, Farlow et al. 2005](#_ENREF_391)). Emre et al ([2003](#_ENREF_139)) have suggested specifically that a washout period is unnecessary for a loss or lack of efficacy reason, but is necessary for switching due to AEs. However, it has been reported that these AE occurrences on the first ChEI are not predictive of the same occurrences arising with the second ChEI ([Auriacombe, Pere et al. 2002](#_ENREF_24)).Whilst they are all in the drug class of cholinesterase inhibitors, Donepezil, Rivastigmine and Galantamine all have different pharmacokinetic and pharmacodynamic properties which can go towards an explanation for the different cognitive performances seen following treatment as well as the difference after switching from one ChEI to another.

Massoud and colleagues ([2011](#_ENREF_286)) have argued for switching ChEIs when a lack of benefit is evidenced, but not when a loss of efficacy is evidenced. In this loss of efficacy case, the researchers have suggested that including Memantine to the current ChEI, instead of terminating ChEI treatment altogether, is beneficial for the patient, and has shown no interactions with the current ChEI in studies on healthy, young participants ([Lundbeck](#_ENREF_280)). Dantoine et al ([2006](#_ENREF_107)) evaluated the efficacy and safety of patients switching to Rivastigmine after failing to improve on either Donepezil or Galantamine. If the patient still failed to improve sufficiently on Rivastigmine, they also included Memantine in addition to the Rivastigmine. Dantoine et al ([2006](#_ENREF_107)) reported that, in patients who failed to respond to Donepezil or Galantamine treatment, 46.7% of them responded (stable/improvement) to Rivastigmine assessed by their MMSE score. Therefore, this goes as evidence that, if a patient does not respond to one type of ChEI, it is worth switching to a different ChEI to give them another treatment option. Furthermore, looking at the patients who did not respond to the switch to Rivastigmine, 77.9% of these did respond (stable/improvement) on this dual treatment (Rivastigmine plus Memantine) phase as assessed by their MMSE scores, indicating a further switching option if all others have been exhausted. The addition of Memantine to a patient’s ChEI treatment has also been reported to benefit patients more compared with ChEI treated patients who were also given a placebo ([Tariot, Farlow et al. 2004](#_ENREF_426)). There was also a slower cognitive deterioration measured by ADL scales in ChEI-Memantine combination therapy compared with ChEI therapy alone ([Atri, Shaughnessy et al. 2008](#_ENREF_23)). In addition to this, compared with ChEI treatment alone, ChEI-Memantine combination therapy is said to delay time to institutionalisation ([Lopez, Baker et al. 2009](#_ENREF_276)).

### Dosage

Many studies have looked at how the dose a patient is receiving affects how well the treatment is tolerated and how beneficial it is. In a review of the literature, Lanctot et al ([2003](#_ENREF_257)) showed that both the low dosage group (i.e., Donepezil 5mg/day; Rivastigmine 3-6mg/day) and high dosage group (Donepezil 10mg/day; Rivastigmine 9-12mg/day) showed an increase of 8% and 11%, respectively, in global response compared with placebo. Many other studies have supported this view ([eg, Doody, Geldmacher et al. 2001](#_ENREF_128)) that ChEI treatment, even at a low dose, is more beneficial than placebo/untreated patients in global cognitive response ([Birks and Harvey 2006](#_ENREF_45)). Furthermore, the changes in CSF-AChE levels was also seen to be dose-dependent in Davidsson et al’s ([2001](#_ENREF_111)) study. These authors reported that the patients receiving 10mg/day of Donepezil showed significantly increased CSF-AChE levels compared with patients receiving 5mg/day, however this difference was not significant in the separate Galantamine dosage groups ([Davidsson, Blennow et al. 2001](#_ENREF_111)). A difference was also seen on the BADLS between patients receiving 10mg/day of Donepezil and patients receiving 5mg/day, whereby the 10mg/day patients had significantly better scores ([Courtney, Farrell et al. 2004](#_ENREF_98)).

### Summary of previous findings

Lanctot et al ([2003](#_ENREF_257)) concluded from their review of the literature that ChEI treatment does show superior effects over placebo, and therefore should be used as treatment in patients with AD. Whilst improvement using ChEIs has been found, many studies have reported this as modest or minimal, and Raschetti et al ([2005](#_ENREF_362)) only reported 15.7% of their patients to be responders (using ≥ 2 MMSE points criteria) after 9 months of treatment, with response at 3 months and not having any other concomitant diseases being the best predictors of this response. While Massoud and colleagues ([2011](#_ENREF_286)) suggested that a treatment length of 6-months is required to establish whether they exhibit a clinically relevant response these authors ultimately concluded that the physician’s personal judgement is most important and superior to these guidelines. Doody et al ([2001](#_ENREF_128)) suggested that patients on the maximum dosage of Donepezil (10mg) and who do not have a disruption of treatment show the best, sustained response. In addition, some researchers have put forward the argument that no response (i.e., stability of cognitive functioning) is still a response. Specifically, as ChEIs are used to treat AD, a progressive degenerative disease, researchers accept that stabilisation, as well as improvement of cognitive functioning, is a reasonable outcome when assessing patients who have been treated with a ChEI ([eg, Massoud, Desmarais et al. 2011](#_ENREF_286)). Nevertheless, ultimately, even if a conclusive predictor was found, Lanctot et al ([2003](#_ENREF_256)) pointed out that this is very unlikely to stop a patient receiving ChEI treatment even if they have been deemed to be doubtful to respond to it. Again, even though predictive tests of response have been suggested, it seems unlikely that, on the bases of these tests, that a patient will be refused ChEI treatment ([Saumier, Murtha et al. 2007](#_ENREF_394)). Nevertheless, identifying patients who will respond to ChEI treatment without response potential the drug ([eg, Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)) could potentially avoid giving people treatment options that will give them no benefit cognitively or functionally, and allow for more suitable options to be tried, whether they are pharmacological or non-pharmacological options.

## Aims and Objectives

The aim of this study was to predict response to ChEI treatment using a range of neuropsychological tests, including the MMSE, and assess patients in the short-term and long-term to evaluate ChEI effectiveness over a longer time period. We also aim to investigate differences between mild and moderate AD patients in terms of their response to ChEI treatment.

## Method

### Participants

Data from patients who had attended the Dementia Unit in the Department of Neuroscience, University of Parma and the Outpatient Cognitive Disorder Unit, Italy were included in this study. All patients had psychiatric, neurological and extensive neuropsychological examinations at baseline. The NINCDA-ADRDA clinical criteria was used to diagnose all patients with probable Alzheimer’s Disease ([McKhann, Drachman et al. 1984](#_ENREF_297)). Fifty-six probable AD patients were included. They were aged between 53 and 88 years (mean age 73.13; SD 6.50), had an education level ranging from 4 to 18 years of formal education (mean education 7.52; SD 3.77), and their Mini Mental Status Examination scores were between 17 and 28 (mean MMSE score 22.46; SD 2.65). All demographic data can be seen in Table 9.1.

Only patients who were initiated on either Donepezil (n=42) or Rivastigmine (n=14) were included in this study. Dosage was titrated up to the maximum tolerable dose for each patient and included 15 patients on a ‘Low’ dosage (i.e., Donepezil = 5mg/day; or Rivastigmine = 3-6mg/day) and 41 patients on a ‘High’ dosage (i.e., Donepezil = 10mg/day; or Rivastigmine = 9-12mg/day).

Post-hoc G\*Power ([Faul, Erdfelder et al. 2007](#_ENREF_150); [Faul, Erdfelder et al. 2009](#_ENREF_149)) analyses, based on a one-tailed t-test, effect size (p = 0.3) and α = 0.05 revealed an achieved power of 0.75.

### Task and Procedure

Baseline assessment - Baseline tasks included global screening measures, such as the MMSE, functional measures of IADL and ADL, as well as tests assessing many different cognitive abilities including naming, memory, attention and visuospatial ability. The range of tasks each patient completed at baseline can be seen in Table 9.2.

Follow-up assessment – At follow-up assessment, the patients completed the MMSE, ADL and IADL scales. The first follow-up was completed for all patients (n=56) at around 5 months after treatment was initiated (mean time of follow-up 4.73 months (SD1.26); range 2-8 months). A second follow-up was also completed for the majority of patients (n=49) at around 12 months after treatment was initiated (mean time of follow-up 11.96 months (SD1.68); range 10-16 months). Further follow-ups are on-going for these patients; however, I will not look any further these two time points for the current study.

Please refer to Chapter 8, Section 8.3.2 for a description of each test used.

##### Category fluency task

For details please refer to Chapter 4, Section 4.4.2.

##### Word Attributes

###### Age of Acquisition.

For details please refer to Chapter 4, Section 4.4.2.1.1.4.1.

###### Familiarity.

For details please refer to Chapter 4, Section 4.4.2.1.1.4.2.

###### Typicality

For details please refer to Chapter 4, Section 4.4.2.1.1.4.3.

Furthermore, we analysed the AoA, Familiarity and Typicality performance for the first 5 ‘Animal’ exemplars and first 5 ‘Fruit’ exemplars.

### Response Criteria

To control for severity level of baseline, MMSE difference scores were created which involved working out the per cent that a patient recovered from baseline after treatment at first follow-up, and at second follow-up. For example, a patient showing an MMSE score of 26 at baseline, who increases to an MMSE score 27 at first follow-up would be showing recovery of 25%. A patient who remains stable at 6 months (i.e., no change from baseline MMSE score) would be showing 0% recovery, while a patient who decreases in MMSE score from baseline would show a negative % of recovery (e.g., baseline MMSE 25, to follow-up MMSE 18, shows -28% recovery). This was then also worked out for second follow-up. This method allows for control of initial severity, and therefore, was employed to evaluate response in this study.

## Results

Analysis of this data was completed using SPSS package 18. The range of analysis used included t-tests, correlations, partial correlations, ANOVA and UNIANOVA.

### Demographics

Table 9.1 shows the demographic data. There were 56 AD patients who took part in this study (28 males; 28 females).

Table 9.1: Demographic data of all AD patients.

|  |  |
| --- | --- |
|  | All patients |
| *N* | 56 |
| Age | 73.13 (6.50) |
| Education | 7.52 (3.77) |
| Sex (M:F) | 28:28 |

Table 9.2 shows the range of neuropsychological tests used at baseline and the performance of the patients on each task.

Table 9.2: Neuropsychological data of all patients in the study (SD).

|  |  |
| --- | --- |
| Test | All Patients |
| MMSE | 22.46 (2.65) |
| Category Fluency | 19.21 (6.74) |
| Letter Fluency | 19.22 (8.94) |
| AVLT: IMMEDIATE | 19.73 (5.81) |
| AVLT: DELAYED | 1.40 (1.59) |
| Raven's Progressive Matrices | 21.12 (5.21) |
| Digit Cancellation | 36.80 (11.27) |
| Rey's Figure: IMMEDIATE | 23.07 (6.32) |
| Rey's Figure: DELAYED | 3.77 (3.83) |
| Stroop: Time | 59.63 (31.83) |
| Stroop: Error | 7.31 (8.16) |
| Boston Naming | 14.21 (3.38) |

Taken as a whole group, the patients at first follow-up showed an average recovery on the MMSE score of 6.93% greater than baseline, while at second follow-up they showed an average recovery of 1.00% greater than baseline (Graph 9.1).

Graph 9.1: Percentage recovered by patients on the MMSE at first and second follow-up by all patients.

### Analysis by per cent recovery

A partial correlation was conducted which controlled for initial severity to investigate correlations between the per cent recovered and baseline neuropsychological test scores. Correlations that were seen in this analysis included the per cent recovered at first follow-up with the score on Rey’s Complex Figure, Delayed recall, r=-.497, p<.026. This shows that, patients who recovered more at first follow-up had better Delayed recall scores on this task at baseline assessment. Furthermore, at second follow-up, the per cent recovered by patients again correlated with Rey’s Complex Figure, Delayed recall, r=.520, p<.019 showing that the patients who recovered more at second follow-up had better Delayed recall scores on this task at baseline assessment. Second follow-up also correlated with the verbal fluency score, r=.527, p<.017, meaning that patients who recovered more at second follow-up produced more words on this task at baseline assessment. Also correlated with second follow-up per cent recovered was the AoA score of the first 5 fruits produced in the category fluency task, r=.310, p<.045, meaning that the patients who showed more recovery at second follow-up also produced later acquired fruit exemplars on this task at baseline assessment.

### Analysis by Response

We then analysed the data and separated patients into responders and non-responders based on the criteria that responders showed an increase from baseline MMSE, while non-responders showed a stable MMSE performance from baseline, or they showed a decrease from baseline MMSE. There were 21 responders at first follow-up, and 35 non-responders; there were 17 responders at second follow-up and 32 non-responders. Graph 9.2 illustrates the per cent recovered by responders and non-responders at first and second follow-up. From this we can see that, the patients classed as non-responders decreased from baseline by -8.26% at first follow-up and -11.84% at second follow-up, while the patients classed as responders improved from baseline by 32.26% at first follow-up and 25.17% at second follow-up.

Graph 9.2: Response based on the per cent recovered after first and second follow-up of treatment.

Furthermore, we split patients into 1 of 4 groups: ‘responder-responder’ (R-R), i.e., those who showed response at first follow-up and at second follow-up; ‘non-responder-non-responder’ (NR-NR), i.e., those who did not respond at first or second follow-up; ‘responder-non-responder’ (R-NR), i.e., those who showed response at first follow-up, but did not at second follow-up; and ‘non-responder-responder’ (NR-R), i.e., those patients who did not show response at first follow-up, but did show response at second follow-up. Excluding those patients who did not have a second follow-up, we found that 28.57% of patients (n=14) were R-R; 53.06% of patients (n=26) were NR-NR; 12.24% of patients (n=6) were R-NR; 6.12% of patients (n=3) were NR-R.

Using an ANOVA, it was shown that there was a significant between group difference for the per cent recovered at second follow-up, [F(3,45)=47.707, p<.0001]. The post-hoc analysis showed that those patients who showed response at both first and second follow-up had a significantly larger per cent recovery (31.74%) than those who were non-responders throughout both time points (-10.26%) (p<.0001), than those who responded at first follow-up, but not at second follow-up (7.43%) (p<.0001), and those who were classified as non-responders at first follow-up, but classified as responders at second follow-up (5.52%) (p<.004). There was a significant difference between the stable non-responders (NR-NR) and the patients classified as responders only at first follow-up (R-NR) (p<.007) whereby those stable non-responders showed significantly less average per cent recovery. Those who responded at second follow-up but did not respond at first follow-up (NR-R) did not significantly differ from those who were stable non-responders (p=.130) or from those who responded at first follow-up, but not at second follow-up (p=.996) (Graph 9.3).

Graph 9.3: Average per cent recovered after treatment at first and second follow-up.

### Analysis by severity

We then analysed the data and separated patients into mild and moderate AD groups based on their baseline MMSE score, with mild patients showing scores of ≥ 24 points while moderate patients showed scores of 17-23 points. Table 9.3 shows the range of neuropsychological tests used at baseline, and the performance of each severity group on the tasks.

Table 9.3: Neuropsychological data of patients (Means and SDs) in the study split into those with Mild AD (≥ 24 MMSE) and those with Moderate AD (17-23 MMSE).

|  |  |  |
| --- | --- | --- |
| Test | Mild | Moderate |
| MMSE | 25.59 (1.28)\* | 21.10 (1.79) |
| Category Fluency | 20.42 (3.75)\* | 15.90 (4.65) |
| Letter Fluency | 23.38 (6.63)\* | 17.54 (9.01) |
| AVLT: IMMEDIATE | 21.31 (6.73) | 19.06 (5.37) |
| AVLT: DELAYED | 2.00 (2.08) | 1.13 (1.28) |
| Raven's Matrices | 22.59 (4.17) | 20.36 (5.58) |
| Digit Cancellation | 42.59 (9.39)\* | 33.91 (11.13) |
| Rey's Figure: IMMEDIATE | 25.53 (6.30)\* | 21.40 (5.88) |
| Rey's Figure: DELAYED | 5.91 (4.73)\* | 2.32 (2.18) |
| Stroop: Time | 56.53 (18.91) | 61.22 (36.94) |
| Stroop: Error | 4.53 (5.73)\* | 8.74 (8.90) |
| Boston Naming | 15.67 (2.53) | 13.38 (3.57) |

The t-test analysis showed that there were many significant differences that could be seen at baseline between the two severity groups: Digit Cancellation task, [t(2.758)=p<0.008]; Immediate component of Rey’s Complex Figure, [t(2.170)=p<0.05]; Delay component of Rey’s Complex Figure, [t(2.926)=p<0.008]; Error Interference of the Stroop task, [t(-2.023)=p<0.05]; and number of words produced in the category fluency task on the ‘Animals’ category, [t(2.425)=p<0.05], on the ‘Fruits’ category, [t(2.530)=p<0.05], as well as on the combined ‘Animals’ and ‘Fruits’ total score, [t(3.066)=p<0.004], whereby, in all cases, the mild patients outperformed the moderate patients. Furthermore the mild patients also produced later acquired examples on the ‘Animals’ category, [t(2.061)=p<0.05], and on the combined ‘Animals’ and ‘Fruits’ total score, [t(2.489)=, p<0.05].

When split into responders (improvement from baseline) and non-responders (stable or decrease from baseline) we saw that, even in patients responding, the mild group achieved a larger per cent recovered at both first (45.00%) and second (48.75%) follow-up compared with the moderate patients classified as responders at first (28.28%) and second (17.92%) follow-up (Graph 9.4).

Graph 9.4: Per cent recovered at first and second follow-up time points in mild and moderate patients classified as responders and non-responders.

Furthermore, we split patients into 1 of 4 groups: ‘responder-responder’ (R-R), ‘non-responder-non-responder’ (NR-NR), ‘responder-non-responder’ (R-NR), and ‘non-responder-responder’ (NR-R). Graph 9.5 shows the average per cent recovered in the four response groups, when split among severity. Whilst no statistical analyses were carried out on this data due to the small numbers in some groups, the trend in the data shows that, mild patients showed a larger per cent recovery (or less decrease) than moderate patients in all response groups.

A univariate ANOVA (UNIANOVA) was carried out on the average per cent recovered. Patients were classified by severity at baseline (mild=MMSE ≥ 24 or moderate=MMSE 17-23) and by response (R-R, NR-NR, R-NR, NR-R). This analysis showed that there was a main effect of severity [F=9.734, p<.003] and of response group [F=88.067, p<.000], as well as a significant interaction between severity and response type [F=6.911, p<.001] on the average per cent recovered. Again, we see that even in patients responding at both time points (R-R), the mild group achieved a larger average per cent recovery (55.55%) than the moderate R-R group (25.24%). This was also seen in the R-NR groups (13.70% mild; 4.30% moderate) and NR-R groups (6.00% mild; 5.28% moderate). The mild group also decreased less than the moderate group in the patients classified as non-responders at both time points (NR-NR) (-8.83% and -11.31%, respectively).

Graph 9.5: Average per cent recovered, comparing the different response groups in mild and moderate patients.

## Discussion

This study investigated the use of cholinesterase inhibitor treatment in mild and moderate AD patients, and response to this pharmacological treatment option. Overall, taken as a whole group, we found that an average of 6.93% was recovered at first follow-up by patients after ChEI treatment compared with the potential to recover on MMSE score at baseline. However, when taking response into account, we now see that those who responded well to treatment (i.e., improvement from baseline) achieved an average improvement of 32% at first follow-up, and 25% at second follow-up. Furthermore, 28% of patients (n=14) responded positively to ChEI treatment at both time points. We also noted in this current study that, even in patients who did not respond in the longer term (i.e., R-NR) or those who show a late response (i.e., NR-R), benefit could still be gained from ChEI treatment, shown by the differentiation of per cent recovered from those who show no response at all (NR-NR). In the severity analysis (mild vs. moderate AD), we provide evidence for initiating treatment early in the disease course as patients who showed a good response rate in the moderate group, still did not reach the level of improvement that the mild patients achieved following ChEI treatment.

Previous studies have similarly made a case for initiating treatment early in the disease course of AD (e.g., [Farlow, Anand et al. 2000](#_ENREF_147); [Seltzer, Zolnouni et al. 2004](#_ENREF_401)), while other studies have shown that MCI patients also respond well to ChEI treatment ([Petersen, Thomas et al. 2005](#_ENREF_355)). Prior to 2011, the UK guidelines for administering ChEI treatment, set by NICE, suggested that only moderate patients (MMSE 10-20) were eligible to receive ChE inhibitors. Nevertheless, it has also been noted in the literature, which came as additional evidence for an early initiation of ChEI treatment, that patients receiving treatment for the full study duration improved further compared with patients receiving placebo for a period of time before being moved onto treatment ([e.g., Farlow, Anand et al. 2000](#_ENREF_147)). Due to the growing literature for early initiation of ChEI treatment, NICE recently changed their guidelines and now recommend this treatment for mild as well as moderate AD patients. In this current study, we showed evidence towards the argument that ChEI treatment should be initiated as early as possible within the disease course as we found that, comparing mild and moderate patients both classified as responders at both follow-up time points (R-R), the mild group recovered a larger average per cent than the moderate group. Therefore, this indicates that, even when the moderate patients improve following ChEI treatment, they do not reach the same benefit that mild patients responding to ChEI treatment do. Similar findings have also been previously documented in the literature, with milder patients improving more on MMSE performance than moderate patients after ChEI treatment ([Erkinjuntti, Kurz et al. 2002](#_ENREF_141)), as has also been found on ADAS-Cog performance ([Seltzer, Zolnouni et al. 2004](#_ENREF_401)), M@T scores ([Molinuevo, Berthier et al. 2011](#_ENREF_313)), and with less decline seen on ADL/IADL scales in mild AD patients ([Molinuevo, Berthier et al. 2011](#_ENREF_313)). Wattmo and colleagues ([2011](#_ENREF_455)) reported a slower cognitive deterioration after ChEI treatment in patients who showed less cognitive deficits at baseline testing, which is in-line with the findings we report in this study as it was shown that the mild AD patients performed better at baseline testing and gained a larger per cent of recovery following treatment.

Some research has reported that patients classified as responders in the short-term (e.g., 3 months) are most likely responders in the long term (e.g., 9 months) and Raschetti et al ([2005](#_ENREF_362)) found that 67% of those patients who showed response in the short-term (3 months) were still responders by the long-term (9 months). In the current study, we found that over 80% of patients were stable in terms of response, whether it was that a patient did or did not respond to ChEI treatment. We found that 28% remained a responder to the treatment after second follow-up, and 53% remained a non-responder to the treatment after second follow-up, when using the criteria of per cent recovered from baseline. Here, we report a lower per cent than that by Raschetti and colleagues ([2005](#_ENREF_362)); however, this could be due to the fact that different methods to measure response were utilised. A variety of methods have been employed to classify patients as responders and non-responders throughout the literature, with many choosing to compare follow-up MMSE scores with baseline scores, with the point increase used to classify response varying widely. For example, some studies have used a 4-point or more increase on the MMSE to classify responders, and a 3 point or more decrease to classify non-responders ([Hanyu, Tanaka et al. 2002](#_ENREF_196)), while others have looked at variable levels of improved response, investigating those with ≥ 4 points and those with ≥ 7 points on the ADAS-Cog ([e.g., Farlow, Anand et al. 2000](#_ENREF_147)). Using their own criteria of responders showing stability or any level of improvement, Raschetti et al ([2005](#_ENREF_362)) found that 50.9% of patients could be classed as responders at 3 months (compared with 17.8% using ≥ 2 MMSE points criteria) and 32.9% at 9 months (compared with 15.7% using ≥ 2 MMSE points criteria). Ultimately, response criteria data proves hard to interpret because there have been a vast range of studies using largely different criteria. As a consequence, it is also hard to compare across studies as some criteria may be more liberal than others, and therefore an increased rate of response may be reported. For example, Raschetti et al ([2005](#_ENREF_362)) reported 67% of those classified as responders at 3 months of treatment were still showing response at 9 months, using the US Drug and Food Administration criteria of ≥ 2 MMSE points, in patients ranging on the MMSE 14-26 points, whilst in this current study, we found that only 28% of patients remained a responder after second follow-up (mean = 4.73 months) when we used the per cent recovered method. Nevertheless, the per cent recovered method has advantages over other response criteria adopted in studies including Rachetti et al’s ([2005](#_ENREF_362)), in that it controls for baseline severity ([Caffarra, Vezzadini et al. 2007](#_ENREF_75)), which most do not. It is important to control for baseline disease severity as we have shown that those with mild AD perform differently to those with moderate AD in terms of the overall potential to gain from ChEI treatment. Whilst this study, and the per cent recovered method, does allow for an improvement in the way that treatment can be evaluated, one limitation is that we have not taken into account improvement/decline on ADL measures. There is an indication that more importantly than showing a difference on cognitive measures, is how much ChEI treatment improves functional abilities of the patients. The effect of treatment on everyday function was, however, beyond the scope of our study which focussed on overcoming the intrinsic psychometric limitations of a widely used screening instrument, the MMSE, which has found large application in the evaluation of response to treatment. Nevertheless, there is evidence of a correlation between cognition and functional abilities in AD ([Sabbagh, Silverberg et al. 2005](#_ENREF_390)), suggesting that a measure of treatment efficacy based on the assessment of cognitive change is also very likely to be reflective of changes in everyday functioning.

A main finding in this study was that baseline scores on the Delayed Component of Rey’s Complex Figure correlated in the short-term (first follow-up) and in the long-term (second follow-up), even after controlling for baseline severity, with the average per cent a patient recovered. This Delayed aspect of the Rey’s Complex Figure task assesses visuospatial long-term memory ability and has been shown to be impaired in patients with AD relative to normal ageing individuals (e.g., Chapter 4, Section 4.5.2.2.2). Therefore, this current study suggests that a patient’s baseline score on this task may predict the per cent a patient is likely to recover after treatment using ChEIs, i.e., their response to treatment. Previous literature has suggested that not only do patients treated with ChEIs and who respond well to the treatment show better neuropsychological test performance but also evidence increased SPECT uptake in medial frontal and anterior cingulate regions than those not treated and those treated but classified as non-responders ([e.g., Venneri, Shanks et al. 2002](#_ENREF_448)). Others have also found differences between those who are classed as responders compared with non-responders on tasks assessing visuospatial motor and lexical-semantic functioning.

It was reported in this study that 6.12% of non-responders showed a late response (NR-R) after treatment at second follow-up (mean = 11.96 months). Other researchers have also suggested that lack of response in the short-term is not a reason to terminate treatment and does not predict a lack of response to ChEI treatment throughout a longer time period ([Johannsen, Barcikowska et al. 2003](#_ENREF_224); [Kozubski, Hasselbalch et al. 2003](#_ENREF_249)). Kozubski et al ([2003](#_ENREF_249)) reported that following treatment with Donepezil and showing no beneficial effect of the drug, once randomised to either placebo or to carry on Donepezil treatment, significant differences favouring those carrying on ChEI treatment were found on the MMSE and NPI scales. Furthermore, after randomisation in this same way, others have also found those carrying on ChEI treatment indicate less decline than those given placebo on the ADAS-Cog and DAD scales ([Johannsen, Barcikowska et al. 2003](#_ENREF_224)). Furthermore, the current study also showed that those who were late responders still showed more improvement than those who were stable non-responders (NR-NR) from baseline. Therefore, this goes as evidence for the argument that stable cognitive functioning or slight improvement can be classified as a response, in a progressive disease such as AD, and can be beneficial in terms of slowing down disease progression. Furthermore, this is also true of ADL scales, for example, the AD2000 Collaborative Group found that, whilst no difference could be seen between Donepezil-treated patients and placebo-treated patients at 12 weeks on the BADLS, after this period, the donepezil group outperformed the placebo group throughout the rest of the study ([Courtney, Farrell et al. 2004](#_ENREF_98)). Nevertheless, the researchers in this AD2000 Collaborative Group questioned whether their significant increase over and above placebo of 0.8 points on the MMSE, and 1 point on the BADLS was a significant enough improvement to warrant it as a clinical response. As ChEIs are used to treat AD, which is a progressive degenerative disease, some researchers accept that stabilisation, as well as improvement, of cognitive functioning is a reasonable outcome when testing patients who have been treated with a ChEI ([e.g., Massoud, Desmarais et al. 2011](#_ENREF_286)).

Whilst we did not compare the individual effectiveness of the different ChEI drugs, some studies have investigated this. For example, one study reported that Galantamine-treated patients deteriorated less on the ADAS-Cog compared with the deterioration seen in a Donepezil-treated patient group, however only in patients with MMSE scores between 12-18 points ([Wilcock, Howe et al. 2003](#_ENREF_467)). This result seems to suggest that Donepezil may be more beneficial for patients in the earlier, milder stages of the disease as the patients here who deteriorated less with Galantamine would be classified as moderate (MMSE 12-18 points). Nevertheless, one important difference to note between the two ChEI treatments in Wilcock and colleagues’ ([2003](#_ENREF_467)) study was that dosage varied, whereby the Donepezil patients received 10mg/day, and the Galantamine patients received 24mg/day, which could have impacted their results in favour of Galantamine. However, other studies have reported similar findings whereby Rivastigmine is purported to be more beneficial for patients in the moderate stages of the disease. Furthermore, Memantine, a NMDA antagonist is licensed for use in England in severe patients (MMSE <10 points). Overall, this data suggests that there may be differential effects of the individual pharmacological treatment options in patients of varying severities. This is an important factor to take into account when investigating response to treatment, and also as a physician choosing which pharmacological treatment to initiate for individual patients.

Massoud and colleagues ([2011](#_ENREF_286)) have suggested that a treatment length of 6 months is required to establish whether a patient exhibits clinically meaningful response. A limitation of the current study comes from the fact that we used a mean first follow-up of 4.73 months (range 2-8 months) which is shorter than that specified by Massoud et al ([2011](#_ENREF_286)). Nevertheless, we also investigated a longer term follow-up of 11.96 months (range 10-16) which satisfies the need for a follow-up time of at least 6 months to establish a clinical response following ChEI treatment. Few studies have looked further than screening measures (e.g., MMSE) to assess response, such as neuropsychological tests assessing memory, language and attention abilities ([Venneri, Shanks et al. 2002](#_ENREF_448)). In this current study, we only had full neuropsychological data for baseline assessment; however, full follow-up assessment would be useful to establish whether differences were seen on any of the other tasks within the battery, as well as on the MMSE within this study.

Accurate and early diagnosis is essential to allow for effective treatment strategies to be put into place as early as possible, and Seltzer ([2006](#_ENREF_399)) recognised that missed or delayed diagnosis of patients is making this hard to achieve. After a review of cognitive and behavioural response to ChEIs, Lanctot and colleagues ([2003](#_ENREF_256)) concluded that there was no single convincing predictor coming from these studies. However, it is still understood that prediction of response to treatment is especially important as not all patients with AD do respond well to ChEIs, and in this current study we found 21 out of 56 patients responded to ChEI treatment at first follow-up; 17 out of 49 responded at second follow-up; and 28% of responders sustained improved response at both time points. Identifying patients who will respond to ChEI treatment is useful for avoiding giving patients with poor or no potential for response the drug ([e.g., Lopez-Pousa, Turon-Estrada et al. 2005](#_ENREF_275)); prediction of responders could potentially avoid giving people treatment that is of no benefit cognitively or functionally. Nevertheless, even if a conclusive predictor is found, Lanctot et al ([2003](#_ENREF_256)) pointed out that this is very unlikely to stop a patient receiving ChEI treatment even if they have been deemed to be doubtful to respond to it. Even though predictive tests of response have been suggested ([e.g., Saumier, Murtha et al. 2007](#_ENREF_394)), it seems unlikely that, on the bases of these tests, a patient will be refused ChEI treatment ([Lanctot, Herrmann et al. 2003](#_ENREF_256); [Saumier, Murtha et al. 2007](#_ENREF_394)). However, being able to predict response may go towards finding other treatments (pharmacological and non-pharmacological) that those patients, classified as non-responders to ChE inhibitors, may be better suited for. Whilst the cholinergic deficit is the only hypothesis turned into symptomatic treatment, ChEIs do not stop the AD process ([Dumas and Newhouse 2011](#_ENREF_137)) and so other treatment options should also be sought until a cure for this disease is found.

# Chapter 10: General Conclusion

### Normal and pathological aging decline

We addressed the issue of early and differential diagnosis in normal and pathological ageing decline (as seen in MCI and AD). Normal healthy individuals do experience a level of decline in some aspects of cognitive functioning as they age. The set of studies presented in this dissertation identified performance profiles on neuropsychological tests that can guide the distinction between normal and abnormal cognitive decline in ageing.

We reported impairment in tasks assessing verbal and visuospatial long-term memory in older adult controls compared with young controls (and a further decline was detectable in the patient groups). On the category fluency task, however, no detrimental effects of normal ageing were detected, and on the lexical measures derived from the words produced, older adults produced later acquired and less familiar words than the young controls. This pattern of semantic intactness in normal ageing has also been evidenced by previous studies. For example, Ciaramelli and colleagues ([2006](#_ENREF_91)) reported that a group of older controls relied more heavily on semantic access (as opposed to episodic memory access) when compared with younger controls, with the opposite pattern being found in young participants, on a test of famous faces. Furthermore, Nyberg et al ([1996](#_ENREF_334)) reported, after controlling for other demographic information (e.g., education), that age explained variance in performance of normal individuals (age range 35-80) on tests of episodic memory, but not on tests of semantic memory. This research suggests that, while the young controls still used episodic memory to complete these tests as a decline was not severe enough to warrant switching to another strategy, the normal ageing decline in episodic memory that has been evidenced throughout the literature did warrant changing strategies to improve performance, which could be seen as a compensatory mechanism used to overcome this episodic memory decline.

The results from the older adult and young controls analyses are especially important as they show a pattern of performance that can be identified to distinguish normal ageing patterns of performance from ones that are suggestive of pathological ageing.

Compared with the patient groups, the older adults produced significantly more words on the category fluency task, as well as words which were significantly later acquired, less familiar and less typical. A similar idea has also been found when using other semantic tasks. For example, Research by Small & Sandhu ([2008](#_ENREF_407)) supports the current results that AD patients name earlier (rather than later) acquired words, as they found that AD patients could more successfully name dated object pictures compared to contemporary object pictures. Furthermore, it has been suggested that not only is AD performance on naming influenced by the period in which they acquired the word (i.e., earlier/later; dated period/contemporary period) but also the frequency of that particular word ([Forbes-McKay, Ellis et al. 2005](#_ENREF_159)). Again, research by Small & Sandhu ([2008](#_ENREF_407)) supports this view as they found that AD patients performed best when the objects were in the ‘Common’ category – i.e., when objects were consistently used throughout several time periods (e.g., a camera, as opposed to a gramophone).

From study 1 it can be concluded that the non-specific decline in verbal and visuospatial long-term memory tasks observable in both the older adult controls and the patient groups suggests that impairment in these cognitive functions does not necessarily signal pathological brain ageing. In contrast, no negative normal ageing effects were seen on either of the verbal fluency tasks with the older adults outperforming the young controls on most lexical measures assessing these tasks. Furthermore, both fluency tasks appeared useful at discriminating normal from pathological brain ageing, not only in established AD, but also at the preclinical MCI stage. Notably, by combining the number of words produced with the lexical characteristics, a more successful and accurate discrimination can be made. In addition, this result is further supported by the fact that the older adult controls, when only analysing the first 5 words produced by each patient and control, still produced later acquired words than both MCI and AD patients indicating that it was not a result of the controls simply producing more words on the semantic fluency task overall. FMRI studies have also confirmed the sensitive nature of semantic impairment, even in pre-clinical individuals ([McGeown, Shanks et al. 2010](#_ENREF_294)). This result is of particular importance, firstly, as it means that a task such as the category fluency task, which is simple and quick to administer, is able to successfully discriminate normal aging decline from that decline seen in neurodegenerative diseases, but also from patients who are experiencing abnormal decline not expected in normal aging, but which does not affect their ADLs. Secondly, it is an important finding as category fluency is a helpful task with potential to act as an indicator of pathological decline, even in a primary care setting. This is due to the simple nature of administration and interpretation. Clinically, performance on this task could be used by a patients primary care physician as an indicator as to whether or not it is necessary to send the patient on for further specialist investigations.

Ultimately, when all results are taken in conjunction from this study, early and differential diagnosis can be more successful, and reduces the demand for specialist interaction with individuals who are not experiencing pathological decline, even when the subtle differences that classify normal ageing, MCI and AD can make the distinction between these three states particularly difficult to distinguish ([Petersen, Doody et al. 2001](#_ENREF_350)).

### Differential diagnosis of pathological ageing

Following the differentiation of normal and pathological decline, it is also useful to investigate whether differential diagnosis between various types of pathological decline is achievable. Therefore, in study 2, we addressed this issue and investigated the neuropsychological profiles of different types of dementia (AD, FTD, VaD) as well as MCI, to identify differences in the neuropsychological profile observed in patients who are experiencing cognitive decline due to a range of neuropathological processes.

In this study, impairment was seen in tasks assessing language, attention and new learning in the AD patients compared with MCI patients. Similar to study 1, the semantic fluency task was not as useful at differentiating these two patient groups (compared to when distinguishing normal and pathological aging), indicating that patients diagnosed with MCI already have evidence of decline in semantic memory and most likely atrophy at this stage, in brain areas that support this function. Support for this comes from previous imaging literature, for example, Whitwell and colleagues ([2007](#_ENREF_464)) showed that, whilst atrophy of the hippocampal complex, in particular the entorhinal areas, is seen in MCI patients, this is to a lesser extent than that seen in AD patients. Furthermore, Braak and Braak ([1991](#_ENREF_61)) reported that stage I and II of NFT distribution as indicative of the MCI stage. Here, NFTs are enclosed to transentorhinal areas, in particular to the hippocampus and entorhinal/perirhinal regions. Therefore, this suggests that, whilst not showing severe clinical symptoms, MCI patients do show decline in semantic memory ability due to the fact that pathology has begun accumulating in areas that support this function. In fact, Venneri et al ([2008](#_ENREF_445)) also reported that the lexical attributes of AoA and typicality are associated with MTL brain regions such as the parahippocampal gyrus. Similar results were also obtained in a study of semantic competency in MCI patients ([Venneri, McGeown et al. 2011](#_ENREF_444)). The findings of this latter study explain why MCI patients are impaired on the semantic fluency task as well as the word attribute analysis, and why they perform at a level more similar to AD patients.

Furthermore, this study also highlighted the use of neuropsychological assessment in differential diagnosis of the dementias. Previous literature has highlighted the difficulty of distinguishing dementia sub groups ([e.g., Varma, Snowden et al. 1999](#_ENREF_442)). Therefore, using thorough neuropsychological assessment, useful performance patterns to distinguish AD, FTD and VaD patients successfully were identified. In particular, the VaD patients showed a less defined performance pattern, but did show performance more similar to the MCI patients (i.e., non-demented patients) than AD and FTD on tasks assessing language, semantic memory and processing. The VaD patients also outperformed the FTD patients on aspects of the category fluency task. A more specific and significant pattern of performance useful for differentiation came from the FTD and AD patients, whereby the FTD patients were superior on both delay components of a visuospatial and episodic memory task. These findings were investigated in more detail in studies 2.1 and 2.2.

The ability to differentiate these dementia types is particularly important, especially when interventions are available, and also when it has been reported that a therapeutic treatment is beneficial for one type of dementia, but the same treatment is detrimental for another ([Mendez and Cummings 2003](#_ENREF_299); [Ballard, Creese et al. 2011](#_ENREF_31)). Therefore, correct diagnosis is essential to avoid potentially harmful treatment options being prescribed to the wrong type of patient.

### Organisational deficits and visuospatial ability

Following on from the results in study 2, we further investigated visuospatial ability in FTD patients. Patients diagnosed with Frontotemporal Dementia have been reported to show relatively intact visuospatial ability when compared with normal controls ([Hodges, Patterson et al. 1999](#_ENREF_206)). Nevertheless, this patient group does have particularly poor performance on organisational tasks as well as a diminished ability to develop and follow a strategy due to these abilities being supported by the frontal lobes, which are the first sites of atrophy in FTD ([Tartaglia, Rosen et al. 2011](#_ENREF_427)). Therefore, in study 2.1 we investigated whether a task requiring the copy of a complex geometrical figure would be suitable to detect organisation and strategic planning impairments in patients with mild FTD.

In detail, the FTD patients’ scores on the visuoconstructive task did not differ from those of the healthy matched controls, which have been shown in other studies on visuospatial tasks ([Hodges, Patterson et al. 1999](#_ENREF_206)). Closer evaluation of their drawings, however, showed that FTD patients produced drawings which were less structured and poorly organised when analysed using the Hamby et al ([1993](#_ENREF_194)) scoring criteria. The findings of this study confirm previous evidence of preserved visuoconstructional skills in FTD. They also indicate that the Rey Complex Figure task, in addition to testing for visuocontructional impairments can be a useful instrument to detect organisational and strategic planning impairments in FTD and might be a useful additional element in the successful differential diagnosis of FTD. This is particularly useful as FTD patients are reported to show less cognitive decline in the early stages of the disease as personality and behavioural changes are more prevalent. Therefore, to be able to identify abnormal decline in FTD is beneficial, and we showed that even the subtle cognitive impairments can be detected with extensive testing with a standardised neuropsychological battery.

### The nature of episodic memory deficits

Episodic memory impairment is an early indicator of Alzheimer’s Disease. Contrastingly, episodic memory is said to be substantially preserved in Frontotemporal dementia especially in the early stages of the disease. Nevertheless, recent studies ([e.g., Ivanoiu, Cooper et al. 2006](#_ENREF_217)) have suggested that the neurodegenerative process in FTD involves hippocampal structures, indicating that impairment in episodic memory, whilst being less severe than that seen in AD, is expected in FTD patients. In study 2.2 we addressed this issue, and investigated whether there is any evidence of episodic memory impairment in FTD patients, and if so, whether this impairment is a true deficit of episodic memory or whether it is due to frontal dysfunction seen in this patient group.

Detailed analysis of the episodic memory task showed abnormal scores in both patient groups, although scores of FTD patients were higher than those of the AD group, both at immediate and delayed recall. FTD patients performed better on thematic element recall than story unit recall, while the AD patients showed the opposite pattern. Nevertheless, compared to the healthy matched control group, both patient groups showed significantly worse performance on both story and thematic elements.

The results indicate that FTD patients do present with an episodic memory deficit, which is less severe than that seen in AD patients; however, in FTD this impairment may at least in part be due to a frontal organisational problem that these patients experience. A regression analysis indicated that their delayed recall of individual story details was largely predicted by their immediate recall of the themes of the story, suggesting that poorer encoding of the overall themes is predictive of how much of the story is recalled.

### Neuropsychological predictors of conversion

The next issue we addressed with study 3 was that of conversion in MCI patients. This seemed the next logical question to investigate after the previous studies as we have identified ways to successfully differentiate normal and pathological aging in different types of dementia. Therefore, to further allow for earlier diagnosis, it would be useful to identify those individuals that, whilst not having a dementia, are experiencing decline that is not considered normal in healthy ageing. As about 15-20% of patients diagnosed with MCI go on to develop AD ([Petersen, Doody et al. 2001](#_ENREF_350)), and since it is challenging to distinguish MCI and AD when it is in the mild stages, in study 3 we analysed the use of neuropsychological tests that could retrospectively predict converters from non-converters.

Baseline tests of memory, visuospatial ability and attention were found to significantly differentiate MCI-converters (MCI-c) from MCI non-converters (MCI-nc). From this, we can argue that patients who do go on to further decline and ultimately convert to a diagnosis of AD show more widespread cognitive impairment than those who will remain stable. This finding is supported by imaging research which has shown more widespread atrophy in converters compared with non-converters ([Whitwell, Przybelski et al. 2007](#_ENREF_464)). Furthermore, these results also suggest that memory impairment is a general feature of this patient group, however, it is more severely affected in those MCI patients who convert to AD, even at a time when their current diagnosis is MCI and when ADLs are still intact. The further attentional and visuospatial deficits seen in MCI-c go on to further support the imaging evidence and show a pattern of performance, even at this early and non-demented stage of impairment, that is similar to AD, albeit less severe.

These results are particularly important when compared with those of study 1 in this thesis in which we compared normal ageing individuals with a group of MCI patients who were not followed-up, indicating that this study 1 MCI group most likely consisted of both converters and non-converters. Here, we found that memory tests, but not attention or visuospatial tests, significantly differentiated these two groups. This suggests that, whilst memory is a feature of MCI patients in both those who are destined to develop AD and those who are not, attentional and visuospatial impairments are a feature of conversion and therefore deficits in these cognitive functions are useful for identifying patients at risk of developing AD in the future. Ultimately, this study shows that neuropsychological tests can distinguish sensitively those MCI destined to develop AD and those stable.

The argument put forward by Pagani et al ([2010](#_ENREF_338)) regarding MCI-decliners and non-decliners is also an important issue, but one which was out of the scope of this study. Nevertheless, it may be useful for future studies to take this into account and investigate whether differences between stable MCI patients who do or do not decline can reliably predict future converters and non-converters.

Even though our results from study 3 did not show significant differences between semantic skills in MCI-converters and non-converters, other researchers have reported such differences particularly in reference to genotype. For example, Biundo and colleagues ([2011](#_ENREF_47)) reported that MCI patients positive for the ApoE ε4 allele had poorer semantic skills and also showed a higher conversion rate to AD compared with MCI patients negative for the ApoE ε4 allele. Furthermore, in another study by this group, MCI ε4 positive patients also evidenced smaller hippocampal and posterior cingulate regions, which correlated with earlier acquired words ([Venneri, McGeown et al. 2011](#_ENREF_444)). A limitation of the current study which likely had an impact on these fluency results is that the sample size was small, but could have been increased if a standard battery had been used with all suitable patients within this clinic. Unfortunately some of the patients had incomplete assessment and could not be included in the study. This discrepancy in assessments of individual patients is due to the fact that these patients are from an International Collaboration project and therefore the assessment of these patients was not under my control. Nevertheless, from previous studies it can be concluded that the use of semantic fluency and the lexical-semantic analysis is especially useful at indicating pathological decline in patients at a less severe state of impairment than clinical AD, as well as predicting conversion to AD.

### Treatment response in Alzheimer’s Disease

The final study in this thesis addressed the issue of response to pharmacological treatment in AD patients. While there is no known cure for Alzheimer’s Disease, successful research has led to the development of pharmacological treatment that can alleviate the symptoms and that might help stabilise progression of the disease. Cholinesterase inhibitors are still the only licensed drugs for the treatment of AD. In detail, with study 4 we investigated response to ChEI treatment over a short and long-term follow-up period. Furthermore, we also investigated the differences in response in mild and moderate AD patients using a novel method that allowed for individual patient response evaluation.

Taken as a whole group, the AD patients showed poor response to ChEI treatment both at first and second follow-up based on the MMSE difference score. Therefore, the sample was divided in responder and non-responder subgroups. Responders showed 32% recovery compared with -8% for non-responders at first follow up, with a similar pattern of findings being observed at second follow-up. Whilst other studies have shown prolonged improvement in AD patients taking ChEIs up to 9 months of treatment ([Caffarra, Vezzadini et al. 2007](#_ENREF_75)), the current study extended this and showed that good responders can sustain this improvement for at least 12 months of treatment. Furthermore, previous imaging studies have also reported that responders show increased activation in task-relevant areas and decreased activation in task-irrelevant areas, while non-responders show increases in task-irrelevant brain areas ([McGeown, Shanks et al. 2010](#_ENREF_294)). Therefore, good response to treatment can have beneficial effects on cognition both at a behavioural and anatomical level. Taking into account disease severity, mild AD patients showed a higher average recovery (55%) compared with moderate patients who showed a more modest increase from baseline (25%). Furthermore, mild patients who did not respond to ChEI treatment, however, also showed a more modest decrement in performance than non-responders who were of moderate severity. This result is in direct contrast to previous NICE ([2009](#_ENREF_329)) guidelines which stated that only patients in the moderate stage of AD (MMSE 10-20) could be treated with ChEI. According to our results, these guidelines would be detrimental to patients who miss out on treatment for being of mild severity even though it could improve disease progression.

Venneri and colleagues ([2009](#_ENREF_446)) reported that the semantic fluency task was a useful predictor of response to treatment. Here, they found that those who had lowest baseline semantic fluency performance showed the most positive response to ChEI treatment at follow-up. The argument for this is that semantic fluency relies on regions of the hippocampus, which receive large cholinergic input ([Francis, Palmer et al. 1999](#_ENREF_165)). Therefore, in patients with poor semantic fluency, and therefore hippocampal dysfunction (also indicating greater cholinergic disruption), the cholinergic level has depleted to a point that would benefit from a boost and is responsive to ChEI treatment. Furthermore, in patients with better semantic fluency at baseline (non-responders), these authors argued that their cholinergic level is above that point which will show large benefits from cholinergic treatment.

The findings of this current study provide evidence suggesting that initiation of treatment in the mild stage of AD appears to result in more substantial improvements in cognitive performance in the course of AD than treatment initiated when patients are already in the moderate stage of the disease. Even in the absence of a detectable response, performance of patients in the mild stage appears to decrease to a lesser extent than that observed in non-responders who are in the moderate stage of the disease, indicating a possible effect on progression of the disease in addition to alleviation of symptoms. This study however was a retrospective analysis of data collected in routine clinical practice in an out-patient clinic for the diagnosis and therapy of cognitive disorders in Italy and part of an International Collaboration study between the UK and Italy. The timing of the neuropsychological examination, initiation of treatment and reassessment were, therefore, not under control by the experimenters, but those dictated by routine clinical practice. The evaluation of treatment in a retrospective study might have limited the actual effect size of ChEI treatment. It is likely that, had a prospective designed being used and had all patients received treatment for the same time period, treatment with ChEIs might have shown even greater benefits to patients with AD than those observed in our retrospective assessment.

### Conclusion

Overall, this thesis investigated the value of a comprehensive battery of neuropsychological tests in early and differential diagnosis of the dementias, particularly AD, as well as treatment response in AD. In the studies throughout this thesis, it is argued that early and differential diagnosis can be successfully achieved by deriving performance profiles from a range of neuropsychological tests. Establishing performance profiles on neuropsychological tests helps clinician and researchers in achieving higher accuracy in the differentiation of normal and abnormal cognitive decline in ageing and also in differentiating amongst the different forms of dementia. This approach has implications for accuracy of diagnoses, but can also be applied to ensure correct and timely interventions (pharmacological and non-pharmacological) to maximise the potential of positive effects for patients.

# Chapter 11: References

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