Automatic and Executive Language Impairment in Alzheimer's Disease

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To my parents who gracefully support me through the dance of life

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Abstract

The increase in the number of people living with Alzheimer's disease (AD) and the lack of treatment available for them advocate the need to develop diagnostic tools for early and accurate diagnosis. Clinical testing offers high diagnostic accuracy during the advanced stages of the disease, but its utility decreases in detecting subtle cognitive changes during the early stage of the disease. Tests that require the use of linguistic abilities have been proven to be reliable and replicable tools in detecting dementia risk. One of the prominent early changes that can be tested through language is semantic memory (SM). The first part of the study focused on the neuropsychological debate of category specific impairment in early AD by the assessment of living and non-living categories using the category fluency test (CFT) and the second part of the study aimed to modify clinically standardised tests and devise a new one to improve the assessment of the different components of SM, executive functioning (semantic control) and automatic functioning (semantic representation). The modified tests included the CFT, which had greater demand on executive functioning than the standardised test, and confrontation naming test (CNT) which assessed both the executive and automatic functioning. Key findings suggest that semantic memory is degraded earlier on in the disease progression with a greater impairment for living categories. This impairment is highly influenced by word attributes with words higher in frequency being better preserved. Additionally, a progressive degradation of semantic knowledge is observed from the early to the late stages of AD but the pattern of living and non-living dissociation remains qualitatively similar. Results from this thesis support the view that semantic memory

tests are good measures to differentiate between healthy and early AD, as semantic knowledge remains stable in healthy ageing, up until age 70. Performance between different ages in the healthy group does not differ from one group to another except for adults older than 70 years. A major finding was that the executive component of SM is earlier impaired than the automatic functioning which could possibly be that impairment threshold is reached when both the temporal and frontal areas experience neurodegeneration. Compared to the standardised test, the novel ones are more sensitive in detecting people at risk of developing the disease. These results contribute to the understanding of the memory impairment present in early AD and sets the foundation for future research regarding clinical diagnostic tools.

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AD	Alzheimer's disease
AF	Arcuate fusciculus
AoA	Age of acquisition
APOE	Apolipoprotein
APP	Amyloid precursor protein
Aβ	Beta-amyloid
BA	Brodmann area
BNT	Boston naming test
BR	Brain reserve
CAA	Cerebral amyloid angiopathy
CFT	Category fluency test
CH	Cognitively healthy
CNT	Confrontation naming test
CR	Cognitive reserve
CSF	Cerebrospinal fluid
DMN	Default mode network
EM	Episodic memory
EOAD	Early onset Alzheimer's disease
fMRI	Functional magnetic resonance impairment
FOS	Figures of speech
FTD	Frontotemporal dementia
GM	Grey matter
GVD	Granulovacuolar degeneration
HC	Hippocampus

IFG	Inferior frontal gyrus
LS	Literal sentences
LOAD	Late onset Alzheimer's disease
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
NI	Neuroimaging
PA	Physical activity
PET	Positron emission tomography
PFC	Prefrontal cortex
P-tau	Phosphorylated tau
PSEN1	Presenilin 1
PSEN2	Presenilin 2
SCT	Sentence completion test
SGA	Speech graph analysis
SM	Semantic memory
SPECT	Single photon emission computed tomography
STG	Superior temporal gyrus
TPW	Things people wear
ToT	Tip of the tongue
T-tau	Total-tau
VaD	Vascular dementia
VBM	Voxel based morphometry
VLPFC	Ventrolateral prefrontal cortex
WM	White matter

YoE   Years of education

Chapter 1:

Introduction

1.1 When ageing becomes a disability: healthy versus pathological ageing

More work and resources are being invested towards the maintenance of good health and well-being of senior citizens, commonly referred to as 'proactive ageing' (Ilmarinen, 2012). This term is becoming increasingly popular as the global population distribution is shifting towards older ages. Approximately, one-third of Europe's population will be over the age of 60 years, with a rapid increase in the number of people aged 80 years and over in the next 10 years (Health, 2007). The figures of the rest of the world will be similar to the European ones. With age, people become more experienced, better skilled and wiser, and therefore healthy older people can be of great contribution to society, but unfortunately, ageing is also accompanied by changes leading to diseases that impede one's functioning; this is when ageing becomes a social burden.

Alzheimer's disease (AD) is one of the most common age-related diseases affecting close to 44 million people worldwide (Alzheimer 's Disease International, 2015) which makes it the most prevalent form of dementia, accounting for 60-70% of all cases. It is mostly, but not exclusively, known as the disease of old age since more than 95% of the patients are over the age of 65. Recent studies have suggested a decrease in dementia prevalence (Langa, 2015; Matthews et al., 2013; Schrijvers et al., 2012) but the number of people living with AD is still high due to the global increase in the ageing population, and this number is expected to increase exponentially with the growing age of the baby boomers. AD is an irreversible, progressive neurodegenerative disease clinically characterised by a decline in memory and other cognitive functions such as reasoning and language, and a change in behaviour with the common presentation of anxiety, depression and apathy later on as the disease progresses. Being a heterogeneous and insidious disease, AD symptoms are

manifested differently from one individual to another which poses a great challenge to determine the underlying causes and mechanisms.

The main neuropathological characteristics of AD seem to be present in healthy brains and become more abundant with age (Rodrigue et al., 2012; D. A. Snowdon & Nun, 2003; Wharton et al., 2011). AD lesions reduce the likelihood of healthy ageing especially when this is paired with brain infracts (Rodrigue et al., 2012; Smith, Schneider, Wardlaw, & Greenberg, 2012). With AD pathology becoming more common with increasing age it is important to look at the association of healthy ageing and AD and what makes the ageing brain more susceptible to AD pathophysiological changes. Results from a retrospective study based on data from The Nun's Study (Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2007) reported that AD pathologies became more common with decreasing levels of healthy ageing. This does not mean that AD is part of normal ageing as some nuns over the age of 90 years were classified as having excellent ageing and could function well, both cognitively and physically (Tyas et al., 2007). The question remains, whether it is possible to differentiate AD pathology from age-related changes.

Currently, there is a lack of accurate diagnostic instruments, markers and treatment for this debilitating disease which makes it a global concern. AD is now at the forefront of many scientific and medical research studies and the aim is to understand better the cascade of pathology and eventually develop a cure or a disease-modifying drug that will slow down the progression rate of the disease. The remainder of this chapter will highlight the genetic understanding of the disease, the neuropathological changes and symptoms presented by AD patients, it will outline the different stages of the disease and the criteria and guidelines used to diagnose AD, the biological and cognitive AD-related changes, the

current markers used for both research and clinical purposes, and currently available treatment.

1.2 The genetics of Alzheimer's disease

AD is a genetically complex disease with the possibility of having a polygenic architecture. There are two types of AD classified by the age of onset, early onset and late onset AD (LOAD). Different genes are involved in the development of AD and their degree of influence varies with the age of onset. Some studies consider AD as a highly heritable disease with stronger genetic influence in cases with earlier onset, but the role of genetics becomes less important with age and by the age of 85 years environmental factors plays a stronger role than genetics (Pedersen, Gatz, Berg, & Johansson, 2004).

LOAD is the more common form of AD present in approximately 95% of the cases, yet the genetic contribution is not well understood. The most established gene associated with LOAD is the Apolipoprotein (*APOE*) gene on chromosome 19 (Bertram, 2011; Yildiz et al., 2015). There are 3 alleles of *APOE*; the ε4 allele is the gene copy mostly associated with an earlier age of onset (Corder et al., 1993) and having at least one copy of this gene increases the risk of getting the disease (Corder et al., 1993; Qiu, Kivipelto, Aguero-Torres, Winblad, & Fratiglioni, 2004). In saying that, having a copy of the ε4 gene does not confirm AD. The most common allele is ε3 which is thought to have no influence or even lessens the risk of developing AD (Aboud, Mrak, Boop, & Griffin, 2012), while the ε2 allele is a rare form of the allele and might provide protection against AD (Qiu et al., 2004; Talbot et al., 1994). Currently, *APOE* testing is used for research purposes only, as it is not accurate enough to be used in clinics for LOAD since having a copy of the gene increases the risk but does not

confirm the development of the disease. Genome wide association studies have recently

identified 20 new genetic loci associated to LOAD. These genes are involved in cholesterol

metabolism, immune response and endocytosis (refer to review by Giri, Zhang, and Lu,

2016).

Early onset AD (EOAD) occurs before the age of sixty-five and can be of two types;

sporadic and familial. The latter is usually caused by a gene mutation on either of the

chromosomes 21, 14 or 1 (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al.,

1995). The single gene mutation on chromosome 21 results in the formation of abnormal

amyloid precursor protein (APP), which in turn generates harmful forms of amyloid plaques

(H. Zheng & Koo, 2011), a neuropathological hallmark of the disease. The mutation on

chromosome 14 causes abnormal presenilin 1 (PSEN1) and chromosome 1 mutation causes

the formation of abnormal presinilin 2 (PSEN2). Like mutations of APP, mutations of PSEN1

and PSEN2 genes also cause abnormal amounts of harmful beta-amyloid (Aβ) fragments

which accumulate in the cerebral cortex due to the lack of ability of the gene to completely

digest Aβ peptide (De Strooper, 2007). APP, PSEN1 and PSEN2 are the main genetic

mutations associated with EOAD and it is thought that unlike LOAD, genetic testing for the

prediction of developing the former type is appropriate.

1.3 Changes due to Alzheimer's disease pathology

AD pathology can be divided into three main categories as the symptoms vary from

physiological changes to cognitive decline to changes in personality and behaviour. The

progress in AD research has revealed a considerable amount of new information about the

disease but the pathological mechanisms involved are more complex than the advancement

made. Currently, the greatest challenge is to elucidate the sequence of neuropathological changes and what triggers the conversion from a healthy to a pathological brain. Understanding these mechanisms and how these differentiate from those in healthy ageing will aid in developing a more accurate diagnostic procedure and a potential disease-modifying treatment.

1.3.1 Microscopic changes: Beta-amyloid

AD pathology includes microscopic alterations and macroscopic abnormalities. One of the hallmark characteristics of AD pathology is the presence of the transmembrane protein APP. Amyloid plaques are deposits of extracellular accumulation of $A\beta$ peptide (1-42) formed at the cortical level after the cleavage of APP by β and $\gamma-$secretases. These deposits of $A\beta$ in the grey matter (GM) of the brain were first described by Blocq P. (1982), but the association between the plaques and AD was first reported by Alois Alzheimer in his case study of Auguste D. (Alzheimer, 1906). Being one of the main characteristics of AD, there has been great interest in establishing its role in AD neuropathology and elucidating the mechanisms by which $A\beta$ is aggregated.

Two forms of plaques are found in the brain, the dense-core plaques and the diffuse plaques. The former type consists of fibrillar, predominantly proteinaceous deposits of $A\beta$ and exhibits all classical properties of amyloid with a highly aggregated β-sheet structure (Rak, Del Bigio, Mai, Westaway, & Gough, 2007). The dense-core plaques are usually the amyloid type found in brains with AD pathology, especially those with neuritic dystrophies. Diffuse plaques are amorphous deposits and more commonly found in brains of cognitively intact older adults. The distinction between the occurrences of the different forms in brains is not a clear cut one and requires further investigation.

There are two staging systems proposed for the topographic pattern of amyloid plaques in AD. The first one was proposed by Braak & Braak (1991) and it consists of 3 stages. Amyloid deposits start accumulating mainly in the basal portions of the frontal, temporal and occipital lobe. It then spreads to the isocortical association areas while the hippocampal formation is only mildly involved and the primary sensory, motor and visual cortices are devoid of amyloid. In the third stage, deposition of amyloid in the primary isocortical areas and in some cases the appearance of amyloid deposits in the molecular layer of the cerebellum and subcortical nuclei of striatum, thalamus, hypothalamus, subthalamic nucleus, and red nucleus. The more recent staging system was proposed by Thal et al., (2002) and consists of five stages which can be summarized in three: the isocortical, allocortical/limbic and the subcortical.

The amyloid cascade hypothesis (J. Hardy & Allsop, 1991; J. A. Hardy & Higgins, 1992) propose that the deposition of Aβ in the brain parenchyma is a central event in AD and it initiates a sequence of events that lead to the disease. Hence, clinical trials have focused on the removal of Aβ but these trials have been unsuccessful (Cummings, Morstorf, & Zhong, 2014). Therefore, it is reasonable to question if Aβ-directed therapeutics are actually the right treatment for this disease.

Amyloid plaques are observed during the early stages of the disease (Ingelsson et al., 2004; Jack et al., 2010) yet there are mixed views about Aβ deposits being the trigger for subsequent AD pathology (Jack et al., 2013; Karran, Mercken, & De Strooper, 2011). Clinicopathological studies show poor correlation between the density of Aβ plaques and AD severity (Bouras, Hof, Giannakopoulos, Michel, & Morrison, 1994) and only a weak association of amyloid deposition in the entorhinal cortex with cognitive performance is

reported (Giannakopoulos et al., 2003). It is also suggested that Aβ in its soluble oligomeric form can facilitate synaptic plasticity and exhibit neuroprotective, antioxidant and trophic properties (Giuffrida et al., 2009; Lublin & Gandy, 2010; Parihar & Brewer, 2010).

1.3.1.1 Neurofibrillary Tangles

The other main microscopic characteristics of AD are neurofibrillary tangles (NFT), insoluble fibres found intracellularly, described by Alois Alzheimer as 'intraneuronal filamentous inclusions within the perikaryal region of pyramidal neurons' (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011, p.4) The tangles consist mainly of aggregates of tau protein. Tau forms part of a microtubule which aids in the transportation of important substances such as nutrients from one cell to another. The function of normal tau is to stabilise microtubules and promote their assembly (Mephon-Gaspard et al., 2016). In AD, the hyperphosphorylated tau protein is abnormal which results in twisted strands called tangles that disrupt the original transport system of nutrients and other substances.

The NFT spatiotemporal pattern is more predictable than that of Aβ. It starts in the allocortex of medial temporal lobe (entorhinal cortex and hippocampus) and spreads to the associative isocortex. Braak and Braak (1991) described this pattern of progression in six stages that can be summarised in three: the entorhinal stage, the limbic stage and the isocortical stage. The link between NFT and severity of AD is also stronger than that observed with Aβ plaques (Nelson et al., 2007). NFT count in the hippocampus, entorhinal cortex and middle frontal gyrus are predictive of cognitive status (Giannakopoulos et al., 2003). Despite that AD pathology starts in the medial temporal structures the optimal correlation between the count of tangles and premortem cognitive status is observed in the cerebral isocortex (Nelson et al., 2007). The strong association between total tangle counts

with cognitive status and the lack of correlation with Aβ plaques implies that cognitive functioning starts declining when both lesions reach the isocortex.

1.3.1.2 Other neuropathology

Cerebral amyloid angiopathy (CAA), the build-up of β-amyloid peptide deposition on the walls of arteries and sometimes veins of the central nervous system, is another contributing factor to AD. Like the above mentioned pathologies, CAA is also present in brains of healthy elderly people. The prevalence of CAA increases with increasing age (Love, Nicoll, Hughes, & Wilcock, 2003; Vinters & Gilbert, 1983), but higher percentages are seen in brains of people with AD (Esiri & Wilcock, 1986). Although there is no association between APOE ε4, the heritable gene that increases the risk of developing AD, and the presence of CAA (Love et al., 2003) there is a strong association between neuritic AD pathology and CAA severity (Attems, Quass, Jellinger, & Lintner, 2007). Most AD-related changes in the brain start at the medial temporal lobe and progressively spread throughout the brain (H. Braak & Braak, 1991), but CAA is mostly severe in the occipital lobe followed by the frontal region and the hippocampus.

Granulovacuolar degeneration (GVD) is the vacuolar cytoplasmic lesions classically observed mainly in the medial temporal lobe (Ball, 1978). It affects neurons in a hierarchical sequence that can be divided into 5 distinct stages (Thal et al., 2011). Like the other positive lesions mentioned above, GVD-affected neurons are present both in AD as well as in healthy brain although GVD is more common in AD brains (Ball & Lo, 1977). GVD starts in the hippocampal areas, in the CA1 and CA2 subiculum regions, it then spreads to the entorhinal cortex and CA4 with the possibility of CA3 and the basal nucleus being slightly affected. In the third stage affected neurons are present in the temporal neocortex and GVD then

spreads to the subnuclei of the amygdala and hypothalamus until it reaches the nuclei of the brain stem and thalamus, and the neocortex of the frontal and parietal areas with sparing of visual cortex (Thal et al., 2011). The topographical distribution of GVD correlates well with the other neuropathies of AD, namely NFT and Aβ plaques. Additionally, a strong correlation is observed with severity of the disease (Thal et al., 2011). The anatomical distribution pattern corresponds to neural areas that are mostly related to chronic stress response (Thal et al., 2011).

Hirano bodies are intracellular aggregates of filamentous-actin in neurons. Total count in pyramidal layer of the hippocampus of AD patients and healthy people suggests that Hirano bodies are common in the hippocampus at all ages, but are more frequent in people over the age of sixty years. Furthermore, a study found that people with AD had even higher amount of Hirano bodies than their healthy age-matched controls (Gibson & Tomlinson, 1977). It is only now that research is exploring their physiological factors and their interaction with tau and APP fragments. Results from both mouse and cell culture models suggest that the formation of Hirano bodies might be a neuroprotective reaction rather than another pathological process contributing to the disease pathology (Furgerson, Fechheimer, & Furukawa, 2012; Spears et al., 2014).

1.3.2 Macroscopic changes

Neuroimaging data have unravelled a lot of information about the microstructural composition and functional changes as a result of neuronal loss and synaptic dysfunction present in AD. Structural magnetic resonance imaging (MRI) studies provide a characteristic pattern of brain atrophy in brains with AD that deviates from that present in healthy ageing. Cerebral atrophy is a prominent feature in AD and although this is also present in healthy

ageing, brain shrinkage is greater in the former. A difference in the rate of atrophy is observed from the beginning of the disease (Leung et al., 2013), but it accelerates further as the disease progresses to more severe stages. Total brain atrophy is more than double in brains with AD when compared to healthy individuals (Leung et al., 2013).

1.3.2.1 Cortical thinning and ventricular enlargement

Cortical thickness provides a full picture of structural abnormalities. Cortical thinning occurs as early as the presymptomatic stage and it increases in association cortices once dementia starts, with a 10-20% thinner cortex in early AD (Dickerson et al., 2009). Reduction in cortical thickness has a phase and a region specific pattern (Im et al., 2008) which mirrors neuropathological findings (Singh et al., 2006). Thickness of the cortex decreases progressively from healthy ageing to the stage of mild cognitive impairment (MCI) to dementia. The greatest difference between the three stages is observed in the medial and lateral left temporal lobe regions which are close to the entorhinal cortex and the thinning rate accelerates from the MCI to the AD dementia phase (Singh et al., 2006).

Thinning is observed in frontal, temporal, and medial occipital regions, and in the posterior cingulate and precuneus areas (Dickerson et al., 2009; Im et al., 2008). These are areas vulnerable to AD pathology. Primary motor and sensory cortices and occipital cortex are spared (Singh et al., 2006). Cortical thickness strongly correlates with cognitive decline and mirrors well global cognitive function, as measured by the mini mental state examination (MMSE). The worse the cognitive performance, the more thinning is observed, especially in the inferior frontal area, and inferior and medial temporal regions (Dickerson et al., 2009). Cortical thinning is also associated with hippocampal atrophy in AD (Kim et al.,

2012). Same as with cognitive decline, the largest difference is observed between MCI and AD rather than MCI and healthy participants (Singh et al., 2006).

Enlargement of the ventricles due to brain parenchymal shrinkage is associated with AD. This change is also present in healthy ageing and although the changes happen at a slower rate, which can be distinguished from that present in AD, precaution needs to be taken when looking at the lateral ventricles (Apostolova et al., 2012). During the early stages of the disease, enlargement of the lateral ventricles is more pronounced in the posterior aspect of the lateral ventricle and then spreads to the frontal horns with disease progression (Apostolova et al., 2012).

1.3.2.2 Atrophy in medial temporal structures

Medial temporal structures are of major interest in early AD as these are the regions where core pathological changes are observed. Furthermore, earlier on in the course of the disease morphometric changes are most prominent in the entorhinal cortex, hippocampus and amygdala (Lampert et al., 2014) and hence the importance given to the study of medial temporal structures. The entorhinal cortex and hippocampus are structures vulnerable to early AD pathology and volume reductions in both structures may be considered as an early sign of AD pathology (Du et al., 2001; Velayudhan et al., 2013).

The rate of hippocampal atrophy is considered to be a good discriminator between healthy people and early AD (Henneman et al., 2009). This is in parallel with histological studies that report a decline in neuronal density in the hippocampus in AD brains most particularly obvious in the CA1 and CA3 hippocampal areas (Padurariu, Ciobica, Mavroudis, Fotiou, & Baloyannis, 2012), as well as a reduction in the total number of synaptic connections which correlate highly with cognitive performance, including memory function,

one of the earliest function to show impairment in AD (Scheff, Price, Schmitt, & Mufson, 2006). But the specificity of hippocampal atrophy is questioned as there is no difference in the rate of hippocampal atrophy in presymptomatic individuals with a profile indicative of AD and healthy individuals (Sabuncu et al., 2011).

Clinical studies suggest that atrophy of the entorhinal cortex is a better measure than hippocampal atrophy to predict people who are at risk of developing the disease, furthermore, structural changes in the entorhinal cortex precede those observed in the hippocampus (Dickerson et al., 2001; Du et al., 2001; Stoub et al., 2005). Greater entorhinal cortex shrinkage is not only a good predictor of cognitive abilities in patients with AD but can also be a good predictor of worse memory performance in cognitively healthy people (Rodrigue & Raz, 2004; Velayudhan et al., 2013). A longitudinal study that explored the relationship of total brain volume, hippocampus volume and thickness of the entorhinal cortex with cognitive performance to identify the optimal measure of cognitive decline found that individuals with more shrinkage of the entorhinal cortex performed less well on the neuropsychological tasks, had higher disease severity and predicted well subsequent cognitive decline (Velayudhan et al., 2013). The entorhinal cortex together with the hippocampus are important structures to consider for early diagnosis and interventions.

1.3.2.3 Functional changes

The functional organisation of a brain with AD pathology is altered from that of a healthy one where segregated complex areas are interconnected by a dense network of axonal pathways (Hagmann et al., 2008). AD is increasingly being considered as a disconnection syndrome (Delbeuck, Van der Linden, & Collette, 2003) with supportive evidence from neuroimaging and neuropsychological studies. Abnormalities in the

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organisation of the brain network and in the connections between segregated areas are present in both late as well as in early AD (Chen et al., 2015; Medina et al., 2006; Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011). Changes in functional connectivity include longer path lengths (Pereira et al., 2016) mostly in the right hemisphere and in the intrahemispheric connections between regions (Suckling et al., 2015). Longer and indirect connections hinder the process of rapid transmission of information between neighbouring neural areas and hence communication is less efficient resulting in poorer cognitive performance (Shu et al., 2012). Other changes observed in AD are fewer connections between neighbouring neural areas and the break-down of whole brain networks into larger isolated components (Pereira et al., 2016). These changes result in a less efficient communication system between immediate neural areas and a lack of integration of information. Connectivity dysfunction is also associated with global cognitive impairment (Liu et al., 2014; P. Wang et al., 2015). Extensive research has been done regarding functional abnormalities in the default mode network (DMN), a set of interacting neural areas activated during free, undirected mental states where a decrease in connectivity is mainly reported. Connectivity reductions are observed in the medial temporal subsystem of the DMN, including the right hippocampus, the precuneus and the right thalamus (Montembeault, Rouleau, Provost, Brambati, & Alzheimer's Disease Neuroimaging, 2016; Y. Wang et al., 2013). A decrease in strength of functional connections between posterior DMN components (Liu et al., 2014) is also reported in AD. Alterations in the DMN connectivity pattern are associated with clinical measurements of memory and clinical dementia severity (Y. Wang et al., 2013).

Cortical hypometabolism is another feature present in AD which precedes the onset of cognitive decline. It also correlates with clinical dementia severity and post-mortem pathology severity of AD (Mosconi et al., 2009). It is unclear if the change in glucose metabolism is a contributing factor to the disease or a consequence of the neurodegenerative process that requires less glucose (Cunnane et al., 2011). The APOE ε4 gene is associated with lower cerebral metabolic rate for glucose (Reiman et al., 2005) in all the brain areas that exhibit hypometabolism in AD; these are the precuneus, posterior cingulate, parietotemporal and frontal cortex (Bailly et al., 2015; Harwood et al., 2005; Mosconi et al., 2006). Having more than one copy of the ε4 allele, further decreases the metabolic rate of glucose (Reiman et al., 2005). During the early stages of the disease, the predementia phase, hypometabolism is present in the HC and, as the disease progresses to full-blown dementia, abnormal metabolic rates for glucose become present in the cortical regions.

1.3.3 Clinical symptoms

Due to the widespread atrophy and neuropathological changes described above, it is expected that AD patients experience a range of cognitive decline. Cognitive functioning becomes progressively worse as the pathology extends to various neocortical regions (E. Braak et al., 1999; Jack et al., 2010) but the progression rate of the symptoms varies from one person to another. AD pathology is initially mostly evident in the limbic area responsible for memory function and indeed memory loss is a prominent feature of clinical AD. Increasing forgetfulness or mild confusion are major complaints and also one of the main criteria for early diagnosis (Petersen et al., 2001).

Episodic memory (EM), the collection of context-rich personal experiences with a specific time and place connected to the event, declines very early and is considered to be a major clinical characteristic of AD with impairments present six years before clinical diagnosis (Backman, Small, & Fratiglioni, 2001). But recently, a paradigm shift has been suggested (Venneri, Mitolo, & De Marco, 2016) and EM impairment as a first symptom in preclinical AD has been debated. As previously described (section 1.3.2.2) abnormalities are observed in the parahippocampal gyrus before the hippocampus (Didic et al., 2011) and this structure is responsible for semantic memory (SM), the part of long term memory that stores context-free information about objects and concepts encountered in daily living. SM provides names and meanings for everything encountered in life and it is required for daily conversations. A mild impairment in SM will have less of a negative impact on patients compared to the frustration of the inability to recall specific life events provided by EM impairment. Hence, SM difficulties go unnoticed by patients and carers during the early stages of the disease. Moreover, a decline in EM is also present in healthy ageing making EM less sensitive in discriminating between the two types of ageing (Kinugawa et al., 2013). Meanwhile age has no effect on SM and this remains stable later on in life (McGeown, Shanks, Forbes-McKay, & Venneri, 2009).

Poorer performance in patients, including asymptomatic individuals at risk of developing the disease, is detected on clinical language tasks that require SM functioning such as naming objects, generating items from a given category and generating similarities between two concepts (Arango-Lasprilla, Cuetos, Valencia, Uribe, & Lopera, 2007; Wakefield, McGeown, Shanks, & Venneri, 2014). A decline in language abilities is indeed one of the early impairments present in AD. Both analyses of natural speech as well as lab

research suggest that language impairment is present decades before clinical diagnosis (Berisha, Wang, LaCross, & Liss, 2015; Cuetos, Arango-Lasprilla, Uribe, Valencia, & Lopera, 2007; Garrard, Maloney, Hodges, & Patterson, 2005; Riley, Snowdon, Desrosiers, & Markesbery, 2005). SM and language impairment will be discussed in further detail in chapter 2.

The assessment of SM and EM skills might be a good tool to predict dementia conversion (Molinuevo et al., 2011), but various studies have explored neuropsychological performance extensively in a large group of patients to establish a clinical profile for AD and its earlier and less severe forms (Molinuevo et al., 2011; Vliet et al., 2003). An accurate profile will contribute to earlier identification of people at risk of developing the clinical stage of the disease and those converting from one stage to another. Even in the mild severity phase of the disease, the neuropsychological profile is different from that observed in healthy ageing (Vliet et al., 2003).

Anterograde amnesia, the inability to learn and remember new information is present as an early symptom (Weintraub, Wicklund, & Salmon, 2012). Patients with AD are impaired in the consolidation and storage of new information (Weintraub et al., 2012). Later on in the disease progression, as the pathology spreads throughout the brain, other cognitive functions become impaired. At some point in the transition from mild to severe dementia, patients perform poorly on tests that involve attention, visuospatial abilities and abstract reasoning especially when a test is multicomponental and involves more than one cognitive function to perform the task (Vliet et al., 2003).

1.3.4 Neuropsychiatric symptoms and personality changes

Research on neuropsychiatric symptoms in AD is limited, but a high percentage of patients develop psychological and personality changes at some stage during the duration of the disease. Fifty percent of patients with mild impairment have a least one neuropsychiatric symptom (Geda et al., 2008) and a higher prevalence of neuropsychiatric problems is reported in the dementia stage with approximately 75% developing 1 or more symptoms (Geda et al., 2008; Lyketsos et al., 2011). The most common symptom, which is also the best distinguishable feature between healthy and pathological ageing, is apathy followed by agitation, anxiety, irritability and depression while psychosis is rarely encountered in early AD (Geda et al., 2008).

1.3.5 Biological vs clinical changes

It was thought that clinical symptoms were manifested according to the severity of the neuropathology, but post-mortem studies have shown an overlap of pathological alterations between healthy brain and demented brain (Thal, Del Tredici, & Braak, 2004; Wharton et al., 2011). A study that has contributed to this discovery is the Nun's study (Snowdon,1986). The Nun's study is a longitudinal research study that collected data on early and middle-life risk factors for AD. Results showed that, even though AD neuropathological features were present in the post-mortem brain, clinical symptoms were not always present, while some nuns with severe brain pathology never experienced any disease related cognitive decline (D. Snowdon, 2007). This resistance to the clinical expression of the AD neuropathology has led to the inclusion of a new stage of AD in the revised criteria for AD termed preclinical AD (figure1.1) (Jack et al., 2011; Sperling et al., 2011).

1.3.5.1 Brain and cognitive reserve

The theoretical concepts of cognitive reserve (CR) and brain reserve (BR) were proposed by Stern (2009) to explain the discrepancy between the pathophysiological changes and clinical manifestation of dementia. Both cognitive and brain reserve suggest that the higher the reserve the more insults the brain can tolerate before it reaches its threshold for the appearance of clinical symptoms. The brain is able to compensate for the presence of pathology by relying and making use of additional brain areas or alternative brain networks to perform a task for which the most appropriate neurobiological substrate might have been impaired by AD pathology. Although these terms are sometimes used interchangeably, CR and BR are different concepts and offer different explanations for the lack of correlation between AD pathologies and clinical symptoms.

BR is explained as a passive effect and refers to the quantitative measures of the brain such as neuronal count, brain size and measures of head circumference (Stern, 2009, 2012). The larger the brain the more AD-related insults it can sustain and therefore delay the emergence of clinical symptoms. Brains with higher reserve have increased numbers of dendrites and synapses, neurotrophic differences and improved neurovasculature and neurometabolic coupling (Whalley, Deary, Appleton, & Starr, 2004). Neuronal density in the brainstem is also related to the clinical onset of AD and the presence of accelerated cognitive decline (Halliday et al., 1992). There are implications that the locus coeruleus might be a structural component of brain reserve and might contribute to brain reserve capacity given the evidence of an association between higher noradrenergic neuronal density in the locus coeruleus and reduced cognitive decline (Wilson, Nag, et al., 2013). All these features provide greater capacity for the brain to compensate for the neural damage

caused by AD and, therefore, brain damage has to reach a higher threshold before any symptoms are clinically manifested.

The CR theory is relevant for research in pathological ageing. CR is described as an active model (Stern, 2009, 2012) and depicts the brain as a flexible and efficient organ that makes use of pre-existing cognitive processes and is also able to establish compensatory mechanisms to cope with neural damage. The main questions are whether clinical AD can be prevented by enhancing CR and whether there are any specific factors and activities that one can engage in to increase CR and therefore brain resilience. There is a relationship between CR level and severity of the disease (Sobral, Pestana, & Paul, 2015), an increase in CR level reduces the risk of clinical onset by 50% and this delay is irrespective of the severity of neural atrophy (Soldan et al., 2015). CR does not modify the pathophysiological damage as such but it modifies the way the disease is clinically manifested, individuals with higher CR function at a higher clinical level than those with lower CR at any given level of neural atrophy (Soldan et al., 2015).

1.3.5.2 Protective lifestyle factors

Several factors may modify the pattern and rate of cognitive decline in AD. The link between social background and the prevalence of dementia dates back to the paper published by Kittner and colleagues in 1986 suggesting that education needs to be controlled for when investigating dementia. It was also noted that certain jobs such as professional musicians and taxi drivers have a positive effect on brain structure and function with differences in grey and white matter and hippocampal volumes (Gaser & Schlaug, 2003; Maguire, Woollett, & Spiers, 2006) that might enhance cognitive reserve. Since then

the link between lifestyle factors and cognitive decline has been a new area of investigation in dementia.

Education together with occupation makes up a large proportion of one's life and if these have an impact on cognitive performance it is important to explore and elucidate any potential mechanisms through which these activities may modify late-life cognitive functioning. The studies on education and AD provide support for the CR hypothesis. Higher education plays a role in delaying the onset of clinical symptoms in AD (Jonaitis et al., 2013). Less Aβ depositions are found in higher educated people (Yasuno et al., 2015) which leads to the question whether education has a protective effect against amyloid deposition and if this is the mechanism by which the onset of clinical AD is delayed. In a longitudinal study that had a 20 year follow up and looked at the pattern and duration of cognitive decline before dementia onset in high and low educated individuals it was found that highly educated people achieved the threshold for dementia criteria after 15 years of preclinical AD while low educated people required only 7 years (Amieva et al., 2014). This study showed that the decline pattern differs between highly educated and low educated people. In high educated people decline involves 2 successive periods of decline; it starts 15 years before the onset of the disease with subtle impairment on some tests that require verbal fluency and psychomotor speed but show no impairment in global cognition, cognitive complaints or daily living problems. About seven years before dementia onset, global abilities start to deteriorate together with the appearance of difficulties dealing with complex daily living tasks, increase in self-perceived difficulties and depressive symptoms. On the other hand, low educated people present a single period of decline lasting approximately 7 years and the clinical course of the disease is characterised by decline

concomitantly affecting specific and more global cognitive function along with alteration in functional abilities (Amieva et al., 2014). Several studies support the view of education acting as an active mechanism of compensation for neural damage due to AD. One additional year of school for a 60-year old with ten years of education compensates for four years of cognitive ageing (Adam, Bonsang, Grotz, & Perelman, 2013).

Occupational activity is associated with cognitive reserve and people who continue working in a nonprofessional activity delay the onset of cognitive decline. The strength of the association between nonprofessional activity and cognitive functioning depends on the type of activity. The strongest association is when the activity involves attending education or training courses (Adam et al., 2013), this can be interpreted that this sort of activity is highly cognitive stimulating. Moderate association is seen with activities such as being a member of a social or sports club and taking part in political/community-related organisations and helping family or friends. No association is reported between stressful situations and social isolation (Adam et al., 2013). This confirms the hypothesis that cognitive decline is experienced when a person retires because he or she will be engaging in less intellectual stimulating activities. Cognitive scores are in fact better in European countries with higher ages of retirement (Adam et al., 2013).

The majority of the studies investigating lifestyle factors have looked at diet and physical exercise (Di Marco et al., 2014) to evaluate their impact on the onset and progression of AD. Major importance is being given to physical activity (PA) as stimulating exercise can counterbalance the cognitive decline presented due to pathology and neural damage in AD (Wilson, Boyle, et al., 2013). It is suggested that cognitively stimulating leisure activities such as dancing, playing an instrument and engaging in board game sessions have

a protective role against dementia (Verghese et al., 2003), especially if the activity is practised frequently and over a long period of time. A positive impact of PA on cognitive functioning is suggested on a molecular and a structural level. PA reduces the effect of age on key biomarkers of AD pathophysiology. Active middle aged individuals at risk of developing the disease show less age-related alterations in $\beta-$amyloid aggregations, cerebral glucose metabolism, hippocampal volume, immediate memory and visuospatial ability (Okonkwo et al., 2014). A randomized control trial with 120 healthy middle-aged and older adults found that PA increases the size of the hippocampus which is accompanied by improved memory function (Erickson et al., 2011), an early impairment in AD. Aerobic exercise is also associated with a reduction in loss of grey and white matter in healthy ageing (Colcombe et al., 2003). Mixed results on PA and dementia have been presented. A study in which walking was used as an intervention found no difference in cognitive performance in people with dementia (Eggermont, Swaab, Hol, & Scherder, 2009).

The way the above mentioned variables interact and affect cognitive performance is still not well understood and it makes sense to assume that cognitive stimulating activity delays the onset of the disease, but it cannot be excluded that cognitive inactivity promotes neuropathological damage. Usually the higher the education, the better the job and socioeconomic status and the more active the lifestyle, all permit a highly enriched environment contributing to a high CR level. This is also observed in animal models where mice living in enriched environments have greater numbers of dendritic density in the hippocampus and increased number of glial cells (Beauquis et al., 2013) which affect cognitive performance.

Understanding CR will contribute to the slowing down of cognitive deterioration and hence, delay the onset of the clinical phase of the disease. Certain lifestyle activities may lessen normal age-related decline in cognitive functioning. The understanding of the influence of lifestyle factors on cognitive performance has implications for clinical tests. It will indicate that tests that require higher education levels and are more challenging and appropriate for today's population need to be developed, and it has implications for interventions to understand what is most effective for slowing down the clinical progression of the disease.

1.4 The AD spectrum

The scientific advancement in medicine and other health related matters have increased knowledge about the relationship between clinical symptoms and pathophysiology in the different stages of AD which in turn has led to the redefinition of some concepts or to the introduction of new ones. This has also led to a revised version of the guidelines and clinical criteria for diagnosing AD which were published in May 2011 (McKhann et al., 2011). Being the first revision since 1984 reflects the complexity and lack of knowledge about the disease. These revised guidelines differentiate between the presence of pathophysiology and the manifestation of clinical symptoms as recent converging studies from clinically healthy individuals and cohorts at genetic risk suggest that the presence of damage and other abnormal neurophysiological changes in AD brains begin between 10-20 years before the presence of any noticeable cognitive decline (Jack et al., 2010). Additionally, the presence of AD neuropathology does not confirm full blown dementia. In response to this temporal lag between the initiation of neuropathological characteristics

and the manifestation of clinical symptoms, the new revised AD guidelines and criteria have introduced a new stage to the AD spectrum in addition to the MCI (predementia, prodromal) and the dementia stage which is referred to as the preclinical (presymptomatic) stage.

1.4.1 The preclinical stage

The preclinical stage, also known as presymptomatic AD phase, is referred to as 'clinically silent' and characterised by the absence of clinical symptoms in the presence of neuropathological changes. Preclinical AD is associated with an increased risk for future cognitive decline (Vos et al., 2013) and it is common in people above the age of 65 and carriers of the APOE ε4 allele, but neither of these factors predict the rate of decline (Juva et al., 2000; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996).

Individuals at the preclinical stage have abnormal levels of Aβ and tau proteins in the cerebrospinal fluid (CSF) as well as changes in ventricular volumes (Bertens, Knol, Scheltens, Visser, & Alzheimer's Disease Neuroimaging, 2014). These seem to be the most sensitive measures and the revised criteria and guidelines for AD propose an agenda to identify markers that may detect any presymptomatic changes that could facilitate early diagnosis. Although clinical impairment is not present at this stage, performance on cognitive tests is poorer when compared with cognitively healthy people (Bertens et al., 2014) and there is still the possibility of detecting such subtle cognitive decline, but this requires further investigation and operationalisation.

Longitudinal studies that have assessed cohorts with clinical tasks over a long period of time (9-16 years) report a change in cognitive function especially in the SM and working memory domain which precedes decline in all other cognitive domains (Wilson et al., 2012).

By the time they are given an established clinical diagnosis, patients would have already experienced many years of accelerated cognitive decline with a marked increase in decline speed 5-6 years before the clinical diagnosis of dementia (Wilson et al., 2012). Nine years before diagnosis, global cognition, as measured by the MMSE score, was already lower in people who progressed to AD compared to those who did not develop the disease (Amieva et al., 2005). The cognitive decline present during this stage is not enough to affect or cause disruption to one's life and deficits are minimal enough to go unnoticed.

This stage has only been introduced for research purposes, to help research establish whether there is a biological change caused by AD which can be detected through blood tests, spinal fluid tests or neuroimaging. Research in this field is still in progress, however. This stage is a long lasting and progressive one and hence it would be the ideal period to identify individuals who will go on to develop full blown dementia as symptomatic treatment and potential therapy that might delay the onset of dementia would be most effective during this stage.

1.4.2 Mild cognitive impairment

MCI proceeds preclinical AD and is the transitional stage between healthy ageing and dementia. With a few exceptions, the disease gets diagnosed at this stage. It is characterised by mild impairment usually most obvious in memory functioning and linguistic abilities. During this stage cognitive decline is more than that expected for the age and education level which usually raises concern for the patient or the care giver. The clinical diagnosis for this stage suggests an impairment in one or more cognitive domain but this does not affect daily living activities and the person is still functioning well. At this stage the patient is usually referred for a comprehensive neuropsychological assessment. If monitored, the

cognitive performance of individuals at risk of developing dementia declines over time and scores are 1-1.5 standard deviations below age adjusted means. Some patients (usually those with mild deficits in multiple domains including memory) are given the diagnosis of 'probable AD'. But this phase remains a grey area. Some people will go on to develop the disease, but some others remain stable or even revert back to healthy cognitive function. The heterogeneous evolution of MCI makes it challenging to predict who will convert to dementia.

1.4.3 Dementia

The dementia stage is the final and most severe phase of the AD spectrum. Clinical diagnosis requires an impairment in two or more cognitive domains that cannot be explained by any other major psychiatric or organic disorder. Although a definite diagnosis is not possible, at this stage clinical diagnosis is quite accurate but it is past the period when current symptomatic treatment would be effective. During this stage impairment becomes too severe and the person can no longer function well and struggles with daily living activities. A change in behaviour is also common. Once dementia starts, the progress from mild to severe AD varies from one person to another but usually the course of the disease lasts about eight to ten years from the onset of clinical symptoms. Symptoms worsen with disease severity across the spectrum.

The difference between clinical and preclinical phases is in the severity of the disease. All stages have tangles, plaques, CAA and GVD but the preclinical stage shows less pathology than the clinical stage (Thal et al., 2013). Tangles, CAA and GVD are also present in cases that have no amyloid plaque pathology, which suggests that three pathological

features precede amyloid plaque pathology and Aβ deposits might contribute to conversion from preclinical AD to clinical AD (Thal et al., 2013).
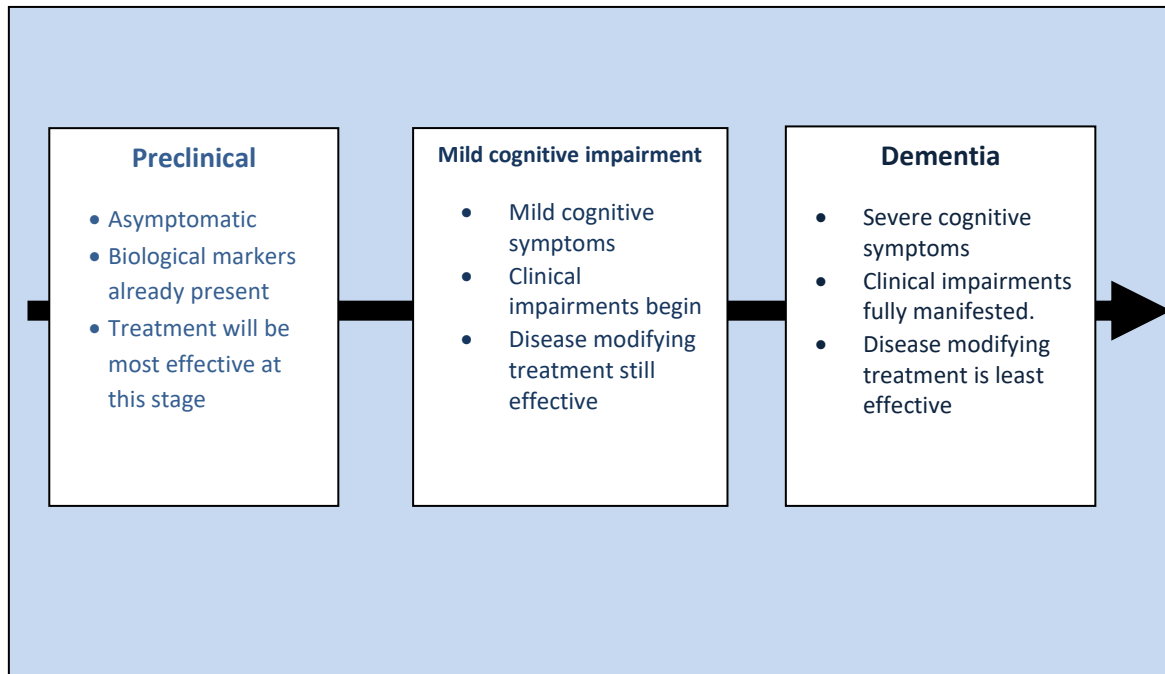
Figure 1.1 The AD spectrum. A summary of the three stages of AD according to the revised criteria for AD by the national Institute of Ageing and the Alzheimer's Association (McKhann et al., 2011)

1.5 AD diagnosis

During the last 30 years, research on AD diagnosis has gained momentum and a lot has been revealed but, due to the complex nature of this disease, the underlying mechanisms and the sequence of symptom onset are still not well understood. This makes criteria for accurate diagnosis difficult to identify, and in turn hinders the development of effective disease modifying treatment. Definite diagnosis requires a post-mortem histopathological analysis for AD features.

Being able to diagnose the disease accurately in the very early stage of progression offers a number of advantages making early diagnosis highly critical. Presently, the only treatment available is symptomatic and is mostly effective before too much irreversible

damage occurs in the neural system. Having an early diagnosis will also allow patients to plan and manage their disease better, including choosing a proxy consent. Most importantly, early diagnosis will additionally aid in recruiting the right people for clinical drug trials and, therefore, facilitate the process of developing a cure or a treatment that will slow down, if not reverse, the progression of the disease.

There is a lot of ongoing research with the aim of establishing a marker that could offer an early accurate diagnosis and shift from a 'probable' diagnosis to a 'definitive' one. An effective marker should be able to fulfil a set of criteria, namely: able to diagnose the disease with at least 80% sensitivity and specificity, able to detect the disease at the preclinical stage, able to discriminate incipient AD from stable MCI, reflect the disease progression, and monitor therapeutic efficacy (Wattamwar & Mathuranath, 2010). There are no diagnostic or progressive markers presently used during clinical examination but different forms of markers have been identified and are currently under study to develop an appropriate one for clinical routine screening. The different forms of marker include those based on the examination of cerebrospinal fluid, of brain scans and on blood tests.

1.5.1 Cerebrospinal fluid markers

A biological marker is a neurochemical signal that can be detected for diagnosis with the possibility of measuring disease progression. Parameters derived from CSF are promising markers due to the direct contact of the fluid with the extracellular space of the central nervous system and its molecular composition that reflects the neurochemical changes in the brain linked to the pathological hallmark of AD (Biagioni & Galvin, 2011). The three main chemical markers in CSF that appear to have a high diagnostic performance in research settings are total-tau (T-tau), phosphorylated-tau (P-tau) protein and $A\beta_{42}$

(Andreasen, Vanmechelen, Vanderstichele, Davidsson, & Blennow, 2003; Fagan et al., 2006; Mattsson & Zetterberg, 2009) with T-tau having the highest sensitivity and specificity Zetterberg, Wahlund, & Blennow, 2003 (Ibach et al., 2006; Zetterberg, Wahlund, & Blennow, 2003). Increased levels of T-tau and P-tau and decreased levels of $A\beta_{42}$ are detected at early and advanced stages of the disease (Jack et al., 2010; Liu et al., 2014; Zetterberg et al., 2003) as well as before the onset of clinical AD (Andreasen et al., 1999).

All three measures identify incipient AD in patients with MCI prodromal to AD with good accuracy (70-80% sensitivity) (Andreasen et al., 2003; Malnar et al., 2012) and abnormal levels in two or more CSF biomarkers reliably predict MCI conversion to AD (Parnetti, Lanari, Silvestrelli, Saggese, & Reboldi, 2006; Zetterberg et al., 2003). CSF markers correlate with MRI measurements of brain and ventricular volumes. Lower levels of $A\beta_{42}$ correlate with smaller brain volumes and larger ventricular volumes. This reflects the stage of the disease, having lower CSF levels as the disease progresses. Due to the markers being abnormal before the onset of the disease and its sensitivity to identifying MCI patients that will convert to AD, these markers are considered to be a good supplement to diagnostic procedures in clinical routine. But CSF procedures have several disadvantages: collection of CSF using lumbar puncture is invasive with possible side effects, screening patients and following them up is difficult and therefore the question remains if it is worth using CSF and whether it is practical for a fragile population.

1.5.2 Blood biomarkers

Despite the semi-permeable membrane between the brain and the bloodstream, it is widely accepted that there is communication between the brain and the periphery tissue. There are AD blood associated changes that can be detected. AD has recently been linked to

metabolic dysfunctions, oxidative, inflammatory and biochemical pathways in peripheral tissues such as blood and skin cells. Blood tests are also non-invasive which is better than the previous mentioned methods for use in the older population. This has directed research to explore and develop assays of peripheral AD markers.

Platelets could be a possible source for a peripheral AD marker. The limitation is the challenge to reproduce AD-related plasma protein (Veitinger, Varga, Guterres, & Zellner, 2014). Patients have altered platelet APP (Borroni et al., 2002). Coated-platelets are a subpopulation of platelets that are stimulated by two agonists, collage and thrombin. The coated-platelets are found to be synthesized at a higher level in early AD and decline as the disease progresses (Prodan, Ross, Vincent, & Dale, 2007).

There is also potential for blood expression to be an AD marker. Lunnon et al. (2013), identified and validated an AD diagnostic gene expression marker that could distinguish people with AD from healthy ones. Forty-eight genes have been identified that can distinguish between healthy individuals and those that go on to develop the disease with a 75% accuracy. This was found in a small sample of 75 people and requires further investigation.

1.5.3 Neuroimaging

Different neuroimaging techniques produce different information and depending on this information they can be broadly classified into three categories: structural imaging, functional imaging and molecular imaging. Brain imaging is popular in research as it provides highly useful information with practical clinical implications. Imaging is useful for the differentiation between healthy and early dementia when performance of memory tests is similar to that of healthy ageing and for following up the progression of the disease, for the

elimination of other types of dementia or reversible causes of dementia syndrome and for differential diagnosis (Scheltens, 2009).

Structural imaging is currently used as a supplement to neuropsychological assessment for clinical diagnosis. The most common form of structural imaging is based on MRI technology. MRI uses radiofrequency energy emitted from hydrogen atoms of water molecules to measure and provide a representation of the brain structure (Small, 2002). Previous work using MRI has explored abnormalities/alterations in the medial temporal structures, with most of the focus given to the hippocampus (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). This is due to the fact that these structures are the first to be affected by AD pathology.

Functional and molecular imaging has an important role in the neuroimaging of dementia. Changes in function and molecular composition of brain tissue typically precede atrophy detectable by structural imaging. Functional magnetic resonance imaging (fMRI) is the most common form used to measure neural activity by calculating the changes in cerebral blood volume. Brain areas that receive more blood flow during a cognitive task produce a stronger MRI signal than other areas. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are also common measures and brain perfusion or metabolism abnormalities in AD-related regions are good predictors of conversion from MCI to AD.

Pittsburgh compound B, the first substance to detect amyloid plaques in PET imaging was created in 2001 (Klunk et al., 2001). The first person with Alzheimer's disease was tested a year later (Klunk et al., 2004). This laid down the foundation for the current molecular agents. Since 2012 three molecular tracers have been approved by the U.S. Food

and Drug Administration for *in vivo* amyloid imaging. These are: Florbetapir F_{18} (Amyvid), Flutametamol F_{18} (vizamyl) and Florbetaben F_{18} (Neuraceq). All three tracers bind to and reveal Aβ plaques in the brain during PET imaging. There is great interest in this marker due to its direct measure of the hallmark of AD pathology, but plaques are currently not used to diagnose the disease since their presence is not always suggestive of cognitive decline (Nelson et al., 2012). All this makes amyloid imaging inappropriate for clinical purposes.

1.5.4 Clinical diagnosis

Currently clinical neuropsychological assessment is the optimal method of diagnosis. The procedure involves a clinical examination based on physical and neurological examination to eliminate any other possible disorder, extensive neuropsychological testing, medical records, family history, and neuroimaging scans. Neuropsychological testing makes use of standardised tests to examine various cognitive functions (for list of main tests see Table 1.1). The test battery used in most clinics is the CERAD-Plus battery (produced by the consortium to establish a Registry for Alzheimer's Disease) that tests for various aspect of cognitive functioning.

A relatively new test recommended for the assessment of amnestic MCI (of the hippocampal type) is The Free and Cued Selective Reminding Test (FCSRT). The test consists of three phases that evaluates verbal episodic memory. The first phase is an encoding phase using words from different semantic categories, the second phase consists of free recall and the final phase is a delayed recall one (performed 20 minutes later). This test has shown good sensitivity and specificity for the prediction of AD conversion at 5 years, although the predictive value is low (Auriacombe et al., 2010).

Table 1.1: Example of a battery of tests and cognitive functions assessed that might be included in a standard clinical assessment battery

Name of test	Function assessed
Mini mental state exam	Global cognitive function.
Confrontational naming	Linguistic abilities
Verbal paired associates	New learning
The pyramids and palm trees test	Access to semantic representation.
Rey's complex figure test	Visuospatial abilities, memory, attention, planning, working memory, executive functioning.
Semantic fluency	Semantic memory, executive function & language
Phonemic fluency	Executive functioning
Digit span forward	Short term memory
Digit span backward	Working memory
Raven's progressive matrices	Reasoning, problem solving
Stroop task	Attention
Digit cancellation	Attention
Visuoconstructive apraxia test	Visuospatial
Token test	Comprehension of language
WAIS-similarities	Reasoning
Logical memory	Short/long term memory

Clinical diagnosis has an 80-90% accuracy when patients are examined thoroughly with a multidisciplinary (i.e. clinical, neuropsychological, neuroimaging) approach. Neuropsychological assessment has helped in tracking the disease by identifying and establishing cognitive impairment throughout the progression of the disease with recent research looking at the earliest subtle changes. The problem with clinical testing is that they are not sensitive and specific enough to differentiate between normal age-related changes and the subtle cognitive deficits due to AD in its earliest stage. Further refinement is needed to improve clinical testing and be able to detect the earliest signs possible, preferably during the preclinical phase.

Non-invasive, easy to administer and cost effective techniques are highly desirable tools for AD early detection. Data generated from imaging studies are radically changing

how we perceive the disease and this will influence future diagnosis criteria/guidelines and treatment. A combination of diagnostic markers, imaging, CSF and clinical data is an emerging strategy in diagnosing AD.

1.6 Differential diagnosis

Diagnosis gets more complicated when there are coexisting conditions or when the pathologies and symptoms of other dementias overlap with those of AD such as is the case with frontotemporal dementia (FTD) and vascular dementia (VaD). Early accurate diagnosis is critical for the understanding and management of the disease as different types of dementia require different care plans. The closest deterioration observed in other neurodegenerative disorders are in semantic dementia (SD), a sub-type of FTD and VaD. Clarifying the impairments in MCI due to AD will help with differentiating between these disorders.

Although FTD is clinically different from AD, it is a challenge to distinguish FTD from early AD. In fact, people with FTD meet the clinical criteria for probable or possible AD (Siri, Benaglio, Frigerio, Binetti, & Cappa, 2001) even though it is also pathologically different. It is even harder to distinguish between the two in a patient younger than 65 years when the disease is in its earliest stage. The patterns of cortical atrophy differ in the two dementias. There is a decrease in whole brain volume in both FTD and AD but the brain volume loss is higher in FTD and this is noticeable even over a span of approximately 3 years (Whitwell et al., 2008). In SD, shrinkage of the left anterior temporal lobe including the temporal pole and association cortex is more accentuated than the right side (Garrard & Hodges, 2000).

Ventricular expansion is observed in both dementias but again it is more so in FTD although this measure is not good to differentiate between the two forms (Whitwell et al., 2008). Hippocampal atrophy is more severe in AD but atrophy of the entorhinal cortex is similar in the two types. In FTD more atrophy in the anterior part of the hippocampus is observed while the posterior region is similar to that observed in healthy people (Laakso et al., 2000).

Both dementia groups perform similar to each other on neuropsychological tasks and an overlap in clinical performance in observed (Siri et al., 2001). A difference in constructional abilities and calculations is observed between the two groups where FTD patients perform better (Mendez et al., 1996). On the other hand Grossi et al., (2002) explored a wide range of visuospatial and constructional abilities in patients with FTD and they reject the clinical claim that these abilities are preserved in FTD and suggest that these functions cannot reliably discriminate this patient population from AD. Temporal memory is not affected by age, a task dependent on the hippocampus, and can discriminate patients with AD from healthy controls and FTD patients with 87.5% sensitivity and 91.4% specificity (Bellassen, Igloi, de Souza, Dubois, & Rondi-Reig, 2012).

A possible way of differentiating the two dementias is by monitoring cognitive decline and functional behaviour because patients with FTD have a faster decline as well as a greater deterioration of performance in activities of daily living which can be seen over a year (Rascovsky et al., 2005). FTD patients also have slightly shorter survival from disease onset till death compared to AD, approximately 8 years and 9 years respectively (Rascovsky et al., 2005).

In a meta-analysis to establish the optimal test that discriminates AD from FTD it was reported that AD tend to do worse on tasks that assess orientation, memory and global cognition while patients with FTD perform worse on verbal ability tests and semantic memory assessments (Hutchinson & Mathias, 2007). They found a 32-48% overlap on the optimal discriminating tasks between the two types of dementia. This suggests that neuropsychological tests are not sensitive enough to discriminate between the two types of dementia and differential diagnosis is not accurate enough. Clinical testing requires further investigation to develop a reliable differential diagnostic measure.

VaD is the second most common type of dementia in the elderly after Alzheimer's disease. Both VaD and AD are progressive, insidious diseases making it difficult to distinguish between the two dementias unless there is prior history of clinical strokes available. Neuropsychological tests have low accuracy for differential diagnosis (Matioli & Caramelli, 2010). Additional neuroimaging data and clinical information will help with the diagnosis.

1.7. Treatment

Currently, there is no cure for AD but there are both pharmacological and non-pharmacological treatments that help with the cognitive, behavioural and psychiatric symptoms. Various clinical trials are looking for new treatments that would ideally alter or even stop the course of the disease.

1.7.1 Pharmacological treatment

Current treatment is based on the cholinergic hypothesis of AD which proposes that neurochemical deficit in cholinergic neurons and the loss of cholinergic neurotransmission is the responsible factor for the cognitive dysfunction experienced in the disease (Bartus, Dean, Beer, & Lippa, 1982). The pharmacological treatment approved by the Food and Drug Administration and licensed in the UK for clinical use are the acetyl cholinesterase inhibitors (ACHEIs), donepezil, galantamine and rivastigmine, which are mostly beneficial during the early stages of the disease although higher doses of donepezil are also being used for later stages. Memantine, a NMDA receptor antagonist, is sometimes offered instead of the ACHEIs or for patients in late stages of the disease (NICE, 2011).

Donepezil was the first to be introduced as a symptomatic treatment for AD, followed by rivastigmine and galantamine (Deardorff, Feen, & Grossberg, 2015). All three ACHEIs work by inhibiting the enzyme acetylcholinesterase and therefore prevent the breakdown of acetylcholine. Although no major treatment difference is reported for the three agents, it might vary from one patient to another and a change in drug agent could be viable for some patients (Hwang, Ahn, Kim, & Kim, 2016). ACHEIs exert a beneficial effect on cognition where it is sometimes preserved or even slow down the rate decline (Black et al., 2007; Hwang et al., 2016; Rogers, Doody, Mohs, & Friedhoff, 1998). In a mouse model that mimics early onset AD, galantamine also seem to lower the levels of amyloid plaques in the hippocampus and the entorhinal cortex (Bhattacharya, Haertel, Maelicke, & Montag, 2014). Positive effects on other core symptoms of AD such as language and attention are also observed (Ferris & Farlow, 2013; Metzger, Ehlis, Haeussinger, Fallgatter, & Hagen, 2015). Mixed results regarding beneficial effects of ACHEIs on behavioural and neuropsychiatric

symptoms have been presented with most of the studies reporting a modest improvement while others reported no difference (Rodda, Morgan, & Walker, 2009). Memantine is a drug mostly offered for later disease stages. Being an NMDA receptor antagonist, it acts on the glutamatergic system and functions by blocking NMDA receptor channels. Memantine treatment is a safe drug and has shown positive effects on patients with moderate and severe AD (Reisberg et al., 2006). Positive treatment effects of memantine are seen in improved cognition, better engagement in activities of daily living and improvement in behaviour especially in patients with agitation and aggression (Gauthier, Wirth, & Mobius, 2005; Reisberg et al., 2006; Tariot et al., 2004).

Despite the benefits offered by the current drugs, none of them can halt or at least alter substantially the course of the disease and the effects are short lived. Clinical drug studies are working on developing novel pharmacological treatments that work effectively as disease modifying agents. Hence, the aim is to develop drugs that target the hallmarks of the disease and have the ability to change the neuropathological patterns of amyloid and tau proteins (Salomone, Caraci, Leggio, Fedotova, & Drago, 2012). New drug treatment is being driven by the amyloid cascade hypothesis and the tau hypothesis (Sugino et al., 2015).

1.7.2 Non-pharmacological treatment

Several forms of non-pharmacological therapy have been recently proposed and investigated in AD. One of the most promising forms of therapy that is beneficial for cognitive functioning is cognitive stimulation training. Cognitive stimulation is an important approach for patients during the early stages of the disease. It improves global cognitive performance, decreases depression levels and improves neuropsychiatric symptoms (D'Onofrio et al., 2015; Spector et al., 2003). The rate of cognitive decline is slower when

cognitive stimulation is used in addition to pharmacological treatment (O. Matsuda, 2007).

Regular cognitive stimulation therapy seems to offer similar benefits to those produced by

pharmacological treatment (Spector et al., 2003). A positive factor of cognitive training is

that the therapeutic sessions can be tailored according to the disease. In a recent study by

De Marco and colleagues (2016), a one month computerised cognitive stimulating

programme was designed to train the DMN, a vulnerable structure in AD. Findings from the

study suggested that such training increased functional connectivity between the posterior

cingulate cortex and areas in the temporal and parieto-occipital regions. Cognitive decline

can also be slowed down or improved through Transcranial magnetic stimulation therapy

(Liao et al., 2015; Penolazzi et al., 2015).

Mindfulness training is a new technique being associated with neuroprotective

effects that could improve cognitive function in people with AD with the possibility of

slowing down the progression rate of the disease. Mindfulness is a type of meditation which

involves the psychological process of focusing one's attention on the internal and external

experiences in the present moment. In a study on long term meditators it was reported that

age-related atrophy of the left hippocampal subiculum was reduced compared to people

with no meditation experience (Kurth, Cherbuin, & Luders, 2015). The authors suggest that

the positive effect could simply be due to the mental training required for meditation that

counteracts the GM loss or that meditation reduces stress and therefore reduces the

inflammatory process related to stress. A small pilot study using a six week mindfulness-

based training programme on older adults with sleep complaints found GM increase in the

precuneus (Kurth, Luders, Wu, & Black, 2014) while another pilot study based on an 8 week

mindfulness based stress related intervention reported an increase in GM in the

hippocampus, posterior cingulate cortex, temporo-parietal junction and the cerebellum (Holzel et al., 2011). These structures are associated with the functioning of learning and memory. A pilot study on patients with MCI was also conducted and found an increase in functional connectivity between the posterior cingulate cortex and the medial prefrontal cortex and left hippocampus. Furthermore, a decrease in hippocampal volume atrophy was also reported (Wells et al., 2013). Although the positive effects of mindfulness practise seem promising for AD, the studies conducted were mainly on healthy people and all consisted of a small sample size. Therefore, mindfulness based stress reduction programmes require further investigation.

Patients with AD find it easier to recall memories from distant past than recently formed ones and old memories can be retrieved and relieved through reminiscence therapy. Reminiscence therapy is the retrieval of old memories to improve one's mental health and psychological well-being (Chiang et al., 2010; Moral, Terrero, Galan, & Rodriguez, 2015). This form of therapy can be done in individual or group sessions by discussing, sharing and re-living personal experiences. This therapy improves socialisation and communication, alleviates depression, and improves the feeling of loneliness, boosts self-esteem, and improves life satisfaction overall in old healthy people (Chiang et al., 2010; Moral et al., 2015). Same positive effects are experienced in people with AD. In a case study of an 88 year old patient with AD and depressive mood, after 2 months of therapy there was a positive change in mood, improved cognitive function and attention, and better blood flow (Tanaka et al., 2007). Group therapy on people with dementia also reported positive findings where patients' quality of life was improved with reported lower levels of depression and anxiety (Azcurra, 2012).

1.8 Conclusion

AD is a complex disease affecting millions of people. A lot of work has been carried out in the field of AD yet much more is needed to understand the disease and be able to diagnose and treat it. Improving the ability to differentiate between the dementia types and being able to detect individuals at risk of developing AD before the onset of clinical symptoms, would be a major step towards improving the current burden and widespread situation of the disease. It would also aid in the development of a disease modifying drug to cure AD. The purpose of this research project is to explore subtle cognitive decline that is present during the early stages and refine tests accordingly as a means of reaching better diagnosis. The following chapter will review the literature on language impairment due to a decline in semantic memory, since there is evidence that these two functions might be impaired in the preclinical phase of the disease and very subtle impairment might not be detected due to limitations of current assessment methods.

Chapter 2:

Language impairment and

semantic memory decline

2.1 Introduction

A large percentage of the neuropsychology assessment for dementia (CERAD battery) is based on linguistic skills that assess different cognitive functions. The highly complex processing of language requires the synchronisation of several neural areas for an adequate performance, which makes it a useful tool to track cognitive dysfunction. It is also suggested that linguistic measures are reliable and replicable means for the detection of cognitive decline (Biundo et al., 2011; Venneri et al., 2011). This centrality of language to cognition has led to a growing interest in language and its alterations in pathological ageing due to AD.

An early decline in linguistic abilities has been reported in Alzheimer's disease (AD) studies and such changes precede the manifestation of any other clinical symptom. Furthermore, this decline in language functioning is a good discriminator of normal ageing and pathological ageing prodromal to AD (K. E. Forbes-McKay & Venneri, 2005). Linguistic measures as a diagnostic tool for AD is a relatively new research area and requires further investigation to establish linguistic patterns present in early AD possibly during the presymptomatic phase, and how such patterns are differentiated from those in healthy ageing. Normative data can be developed by tracking normal decline in healthy ageing and deviations from it; consequently this information can be implemented in linguistic tasks used during clinical testing. This will facilitate the detection of subtle cognitive changes during the window period between predementia and the onset of clinical dementia. The importance of linguistic measures as an early cognitive marker, the models proposed to explain the neural structures responsible for a well-functioning language system, the sub-

components that make up the system and the linguistic changes in healthy ageing and AD will be reviewed in the remainder of this chapter.

2.2 Language decline preceding clinical onset.

Cognitive decline is experienced both in healthy and pathological ageing hence, it is of critical importance to develop markers that are able to distinguish between the two types of ageing. Impoverishment of spontaneous speech and writing may be a good clinical tool to detect cognitive decline caused by AD pathology (K. E. Forbes-McKay & Venneri, 2005), which could facilitate early detection and differential diagnosis. Diachronic structural analysis of speech and written language is evidence that a decline in linguistic abilities precedes cognitive decline and the manifestations of any clinical symptoms (Cuetos et al., 2007). Ronald Reagan and Iris Murdoch were both diagnosed with AD years after poor linguistic skills were manifested in their speech and writings (Garrard et al., 2005; Le, Lancashire, Hirst, & Jokel, 2011). The longitudinal Nun's study (Snowdon, 1986) has also contributed important insight to this area. Autobiographies written by the nuns in their early life were analysed for linguistic abilities and generated results suggested that linguistic skills in early life were a good predictor of AD development later in life (D. A. Snowdon, Greiner, & Markesbery, 2000).

Although analysing diaries, novels and public speaking cannot be used for testing, standardised linguistic tasks have been developed and are used in clinical settings. There has been a shift from laboratory based language tasks to clinical tasks that reflect real life conversations and abilities (Cuetos et al., 2007; K. E. Forbes-McKay & Venneri, 2005). These tests have also been used for research purposes to help the understanding of impairments

characterising AD in order to develop better markers and therapeutic methods. A variety of linguistic neuropsychological tests that assess different aspects of cognition are used for the screening of early AD symptoms that occur during the preclinical or MCI phase, these tests will be discussed in detail later on in this chapter.

2.3 The language system

Language enables people to communicate with each other by the transfer and exchange of information; this could be done through speech, writing, signing or braille (Jackson, 2010). For the purpose of this project, the literature will focus solely on language through speech. Language is an unconscious and effortless process yet the underlying neural mechanism is a complex one and involves the coordination of different brain structures and pathways to convey appropriate messages, and interpret and comprehend receptive messages. The processes involved in transmitting a message are: the retrieval of the right words and the knowledge of the appropriate grammatical rules to structure sentences, the production of the right sounds which depend on the brain and vocal cords in the glottis, and the awareness of the social and cultural setting of the listener. There are approximately 6,900 identified languages (Jackson, 2010) and although they are made up of different sounds and words they all share similar sub-components that form the language system.

Language is based on a tripartite architecture: utterance, interpretation and construction (S. Hickok, 2015) and is made up of sub-components that are interrelated in a way to create meaningful sentences. The main components that form the tripartite nature of language processing are syntax, the rules that govern sentence structure, phonology the

components associated with sounds and their usage within a language, and semantics, the meaning and interpretation of words and sentences. All this information about a word is stored in a mental lexicon. The other sub-components are morphology, which is the form and structure of words in a language, and pragmatics, the relationship between linguistic expressions and their users. For the most part, all this knowledge is subconscious but disruption in any of the above sub-systems would produce impairment in language.

2.3.1 Language processing

Language processing is the way words are used to communicate thoughts and ideas and how these words are processed and understood, in other words it is how the brain constructs, transmits, and understands language. Various models have been proposed to explain as best as they can the processing mechanism involved in the production and understanding of language. Most of the early information that formed the classical model of language comes from lesion studies and aphasiology, and this model focused on Wernicke's area and Broca's area as the structures responsible for language processing. With the introduction of neuroimaging (NI) studies it became possible to investigate the neural bases of language in cognitively healthy brains through experimental neuro-linguistic paradigms. This has led to the formation of contemporary language models which build on the traditional view, but suggest that the language system is far more extended than it was thought to be and involves the recruitment and interaction of various cortical and subcortical substrates (Bernal, Ardila, & Rosselli, 2015; Ford, McGregor, Case, Crosson, & White, 2010; Tomasi & Volkow, 2012).

The most prominent cortical regions associated with the processing of language remains Broca's area, the region concerned with speech production, and Wernicke's area,

the core node associated with receptive speech. Broca's area is formed by the pars triangularis (Brodmann area 44) (BA 44) and pars opercularis (BA 45) of the inferior frontal gyrus (IFG), commonly located in the left hemisphere in close proximity to the motor cortex and the Wernicke's area is situated at the posterior part of the superior temporal gyrus (STG) (BA 22) and extends around the lateral sulcus in the parietal lobe situated between the auditory and the visual cortex. These two main structures are connected and receive information through the fibre tracts referred to as the arcuate fasciculus (AF). Together these three areas form the neural language loop in the fissure of Sylvius.

The classical model of language processing is the Wernicke-Lichtheim-Geschwind model, based on Broca's (1861, 1865), Wernicke's (1874/1977) and Lichtheim's (1885) work and modified by Geschwind (1965) later on in the 20th century (Poeppel & Hickok, 2004). According to this model, language is processed through a series of seven components; the above mentioned core nodes and the primary auditory, visual and motor cortex. Within this model language is considered to be a left lateralized function in the peri-sylvian area, but this model has some limitations and does not fully explain the neurobiology of linguistic processes. Primitive work that derived this model focused on single word processing but language is much more complex than that and a good model should incorporate natural speech rather than single words, and dynamic networks of brain region-connectivity of the core nodes with other neural substrates need to be take into consideration (Hagoort & Indefrey, 2014). More so, the main areas required for language processing interact with other areas and a well-functioning language system forms circuits that are not exclusively used for language, but are definitely required for a well-functioning system, most

commonly, attention, working memory and the Theory of Mind network which is required for good interpretation of receptive language (Hagoort & Indefrey, 2014).

With the advanced technology and novel ways of studying language, contemporary models aim to create a theory that is more accurate, computationally explicit and has a biological explanation for the production and comprehension of language (Poeppel & Hickok, 2004). Recent studies deviate from the traditional view by implying that language is not a localized and lateralized function, and indeed there are more infrastructures involved than the three main components. The language network of BA 44 consists of 16 clusters. The first 6 clusters of activation are well established language areas but the other 10 are non-specialised subcortical areas (Bernal et al., 2015).

A study (Mirman et al., 2015) that tried to bring together the traditional and contemporary theories of language and brain found that there are two major divisions within the language system, meaning (semantic) versus form (phonology) and recognition (language input) versus production (language output). Semantic processing takes place in the extra-sylvian regions with language output being processed in the left anterior temporal lobe while language input happens in the region where the uncinate fasciculus, inferior fronto-occipital fasciculus and anterior thalamic radiations all converge. Phonological processing happens in the peri-sylvian regions with speech production in the supra sylvian and speech recognition in the infra-sylvian regions. This is similar to the dual pathway model of speech processing (G. Hickok & Poeppel, 2000).

The neuroanatomical model of dual pathway implies that language processing involves two parallel anatomical routes (Saur et al., 2008); the dorsal route (maps sound to articulation) that involves the interaction between the superior temporal and premotor

region and the ventral route (sound to meaning) (G. Hickok & Poeppel, 2000, 2007) which involves the interaction between middle and inferior temporal regions and the ventrolateral prefrontal cortex (Saur et al., 2008). This model forms the basis of various subsequent neuropsychological models.

Brain function is well explained through connectivity models. The language network is organized around the central axis of the main nodes, Broca's and Wernicke's areas, but the network is extended and involves the bilateral caudate nucleus, left putamen and subthalamic nucleus (Tomasi & Volkow, 2012). Broca's region is not just a syntax processing area as described by the traditional language model and therefore needs to be characterized in more general terms. It is involved in what Hagoort (2014) describes as unification, "the assembly of pieces stored in memory into larger structures, with contributions from context" (Hagoort, 2013, p.1). Broca's area has structural connectivity with BA 9, BA 8 and BA 6. The anterior part of Broca's area connects to BA 9, which is important for memory, emotion, verbal and intentions among other functions and BA 8 is critical for the management of uncertainty, while the posterior part of Broca's area connects to BA 6, the neural area responsible for the planning of complex, coordinated movements (Ford et al., 2010).

2.4 Language changes in healthy ageing

Language is the most resilient function to cognitive ageing. A decline in linguistic abilities becomes present in late adulthood during the 7th decade (Kemper, Marquis, & Thompson, 2001). Due to the widespread connections and extensive neural substrates underlying the language system individual sub-components are affected differently and

follow a different time and rate of decline with some of the components remaining stable or even improving across the lifespan. Ageing studies on linguistic abilities highlight the importance of isolating and analysing each linguistic sub-component individually to explore the pattern of age-related changes ideally over repeated assessments.

2.4.1 Neural and language changes in ageing

The prefrontal cortex (PFC) is responsible for various language related actions such as the initiation of speech, word concept monitoring and cognitive control for the selection of appropriate words (Thompson-Schill, D'Esposito, & Kan, 1999). An age-reduction in cerebral oxygenation in the PFC is present during retrieval of words (Kahlaoui et al., 2012), but a healthy brain compensates for the frontal decrease by recruiting additional bilateral activation (Cabeza, 2002; Cabeza, Anderson, Locantore, & McIntosh, 2002) and increasing activation in the middle temporal gyrus (Brassen et al., 2009). Decrease in frontal activation and increase in middle temporal gyrus is also associated with reduced GM density of the PFC and medial temporal lobe, this compensatory mechanism depends on the structural integrity of the two areas (Brassen et al., 2009).

Structural deterioration of tissue and disruption of cortical networks due to a decline in axonal integrity play a critical role in changes in language performance in older adults (Madhavan, McQueeny, Howe, Shear, & Szaflarski, 2014). White matter (WM) integrity of the superior longitudinal fusciculus (SLF) which connects the temporo-parietal language areas to the frontal region starts declining after the age of 30 (Westlye et al., 2010) with more decline happening at the anterior portion of the SLF; furthermore, the pattern of decline between males and females differs and affects language functioning differently

(Madhavan et al., 2014). A disturbance of the structural integrity of cerebral fibre tracts (corpus callosum) also causes a dysfunction in language (Griebe et al., 2011).

There is a discrepancy between neural changes and language performance. Behavioural changes are less than what is expected considering the age-related brain changes. This could be due to compensatory mechanisms which are present in well-functioning older people. Asymmetric reduction of the dorsolateral PFC in older adults (Manenti, Brambilla, Petesi, Miniussi, & Cotelli, 2013) is thought to be one of the compensation mechanism to counteract ageing, showing no predominance between left and right hemispheres, serves for better word finding abilities (Manenti et al., 2013). Studies that show reduction in functional asymmetry in the PFC led to the development of the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Cabeza, 2002). This model implies that the PFC in a healthy brain is less lateralized in older adults as a response to ageing effects. With age, older people have difficulty using specialized language neural mechanisms so instead they engage other mechanisms that could serve the same function (Cabeza et al., 2002).

2.4.2 Changes in language performance in healthy ageing

Language functioning is relatively preserved in healthy ageing and communication is still efficient especially because of all the reorganization and compensatory mechanisms happening during late adulthood, but this does not mean that the language system does not undergo changes with age. Contrary to this belief, language performance is altered and some changes are noticeable and cause frustration. The major difficulty experienced by older adults especially during the later years is word retrieval (Heine, Ober, & Shenaut, 1999). The impairment in naming is not the only change but it is the most prominent feature

as it disrupts communication. There are other language features that decline with time

which is apparent in changes in discourse pattern but other areas go through very subtle or

no change at all, in fact some also improve. The main question is to what extent are

language changes a result of changes in the linguistic system itself. The majority of the

language changes are a response to changes in cognitive functions that are required for the

processing of speech such as working memory and attention rather than the linguistic

system itself (Glisky, 2007; Kemper et al., 2001).

2.4.2.1 Discourse

Spoken discourse remains quite stable up until the age of seventy (Nippold,

Cramond, & Hayward-Mayhew, 2014) when late-life decline in syntactic complexity and

propositional content starts being observed, this is associated with a decline in working

memory (Kemper et al., 2001). During spontaneous speech older adults tend to use simpler

grammatical forms that are less memory demanding (Kynette & Kemper, 1986). A decrease

in functional connectivity within specialised syntax network and a shift in hemispheric

connection responsible for grammatical rules are also observed in ageing. Younger adults

rely on dorsal fibres that connect the frontal and temporal cortical areas while older adults

rely on the ventral tracts that connect the inferior frontal region to the anterior temporal

region (Antonenko et al., 2013). On the other hand, older adults produce similar length of

utterances and number of sentence fragments (Kemper, 1987). Although there is a slight

change in spoken language in ageing, the decline is compensated by using fewer syntactic

complex sentences rather than shortening sentences or using filler words (Kemper, 1987).

Fewer complex sentences, lower volume, slower speech and less precise articulation,

mark the qualitative differences in discourse between young and older adults, but,

regardless of these distinctions, older adults have good conversation skills. The other feature that inhibits speech and declines with advanced ageing is the access and lexical retrieval of appropriate items. Older adults complain about not being able to remember certain words (Schmitter-Edgecombe, Vesneski, & Jones, 2000) most often these are nouns, especially proper nouns, possibly due to their uniqueness and lower frequency than other words (Evrard, 2002). In experimental settings this feature can be tested using a picture naming task where the participant is expected to accurately name the stimuli presented. A large decline in naming performance is observed after the age of 70, but subtle changes in naming are thought to start earlier on (Mackay, Connor, Albert, & Obler, 2002; Nicholas, Obler, Albert, & Goodglass, 1985). Picture naming requires the functioning of the semantics and phonological components in addition to the recognition of visual perception. Recognition and semantic stages seem to be well intact across all ages and the only beneficial cues for older adults are phonemic ones (Nicholas et al., 1985). When retrieval of verbs and nouns were compared, a disadvantage for the latter was found (Nicholas et al., 1985), a problem that high functioning people can cover by the use of circumlocutions, word substitutions and reformulations (Nicholas et al., 1985; Schmitter-Edgecombe et al., 2000).

A similar linguistic change that older adults tend to frequently experience is word finding problems commonly known as the tip-of-the-tongue phenomenon (ToT). This is the partial recall of a word and the imminent feeling of word retrieval combined with a temporary inability to retrieve and produce the word. ToT is a phonological retrieval deficit, when both the lexical and semantic information of a word is accessed (Burke, Mackay, Worthley, & Wade, 1991). This phonological retrieval problem becomes worse with age

(Burke et al., 1991) and is associated with an age-related decrease in GM density in the left insula (Shafto, Burke, Stamatakis, Tam, & Tyler, 2007).

It is well documented that word finding difficulties are independent of memory function (Schmitter-Edgecombe et al., 2000) and the problem is not related to the semantics of language, which is confirmed by the fact that older adults do not benefit from semantic cues during naming difficulties. Indeed, vocabulary recognition remains well stable or even improves across the lifespan. Vocabulary is acquired through experience and, therefore, it is sensible to say that in a healthy brain vocabulary increases with maturity. This increment in vocabulary is reflected in the use of more diverse words and better discourse skills. Some studies that explored naming performance in different age groups also report a better performance for individuals between the ages of 50s and 60s (Schmitter-Edgecombe et al., 2000) before the initiation of difficulties with phonological processing.

2.4.2.2 Language comprehension

Comprehension is spared of major ageing effects. Compared to young people, elderly individuals show increased activation of inferior frontal regions that are not specialised for language comprehension, this compensates for the decreased activation of frontal areas that sub-serve processing of speech comprehension (Peelle, Troiani, Wingfield, & Grossman, 2010). Changes in auditory processing are subtle. Both hearing loss as well as changes in higher cognitive functioning that are required for the processing of speech in addition to language specialized networks are common in the ageing population. All these age-related changes make the comprehension of speech more problematic especially in noisy environment. Difficulty in understanding language becomes worse when it requires fast processing, working memory and executive functioning (Baddeley, 2003; Waters &

Caplan, 2005), cognitive functions that decline with age and therefore understanding speedy speech and sentences with complex syntax becomes challenging with increasing age (Schneider, Daneman, & Pichora-Fuller, 2002).

2.5 Language changes in AD

Due to the early marked atrophy of frontal and temporal lobes in AD, it is expected that linguistic abilities start deteriorating earlier on in the disease. As in healthy ageing the sub-components of language have a different temporal phase of decline during the course of the disease. Longitudinal analysis of connected discourse and experimental tasks that resemble real life conversations, such as spontaneous speech, narration and description of scenes (Cuetos et al., 2007; Hier, Hagenlocker, & Shindler, 1985; Vuorinen, Laine, & Rinne, 2000), provide a lot of information about the language deficit in AD and how it differentiates from that in healthy ageing.

Linguistic changes in verbal expression are present during preclinical AD. Studies of genetically at risk individuals suggest that subtle changes in natural language is present before any clinical symptoms are present and these small difficulties develop into severe problems that cause a disruption in spoken language. During the early stage of the disease articulation and melodic line is not affected much and the length and number of sentences is similar to that expected from a healthy individual matched for age and education (K. Forbes-McKay, Shanks, & Venneri, 2013), but later on AD patients tend to produce fewer words in a given time, they speak slower than controls, have higher numbers of stutters, fewer self-corrections and engage in incomplete conversations (Boye, Grabar, & Thi Tran, 2014). Patients with mild to moderate AD also produce more word finding delays, semantic

paraphasias, empty phrases and indefinite sentences (K. Forbes-McKay et al., 2013). Language comprehension is relatively preserved in AD although patients have difficulties understanding syntactically complex sentences and, although this is true for healthy ageing, the difficulty is more pronounced in AD even during the MCI stage. Patients with early AD show difficulty in understanding both literal and non-literal speech, the difference in performance depends on the complexity of the task; the more complex the discourse is the worse the performance (Cardoso, Silva, Maroco, de Mendonca, & Guerreiro, 2014).

In summary, linguistic changes in AD are good to track disease progression (Ahmed, Haigh, de Jager, & Garrard, 2013). The most dominant problems are related to the semantics of language followed by lexical difficulties (Ahmed et al., 2013; Boye et al., 2014). Language impairment observed earlier on in the disease are mainly semantic errors which are then accompanied by phonological, visual and motoric aspects of speech but this is not until later on when cortical degeneration starts spreading to the frontal lobes, the neural substrates responsible for phonological processing and motor output (K. Forbes-McKay et al., 2013). The above literature suggests that the earliest impairments are semantically related which is a change absent in healthy ageing and therefore could be a good cognitive measure to differentiate between the two types of ageing. The remaining of the chapter will focus on studies that explored semantic impairment in AD.

2.5.1 Semantics of language

Different linguistic tasks can be used to assess different aspects of semantics. The category fluency task (CFT) is the most commonly used test to assess residual semantic skills in patients with AD. This test requires patients to generate as many words as possible in a limited time for a given category; this task depends on various cognitive processes and

requires access to both semantic content and processing (Koenig, Smith, & Grossman, 2010). It requires updating and inhibitory processes relying on working memory so as not to generate the same words repeatedly and suppress intrusions. Cognitive flexibility is also required to disengage and engage in different subcategories (known as switching).

The CFT have been used for different reasons, one of them being to assess temporal characteristics of recall and the structure of semantic memory. (Asymptomatic) ε4 carriers generate fewer items than healthy participants (Rosen et al., 2005). In a study which looked at different strategies used in CFT to establish which technique best discriminates healthy ageing and AD, it was found that the best discriminator is the score of total number of words generated during a given time, where healthy individuals who later on developed dementia produce fewer words five years before the onset of disease (Raoux et al., 2008). Category switching (the shift between different subcategories which relies on the prefrontal lobe processes) and clustering (the number of novel switched sub-categories) are also good measures to discriminate between the two types of ageing (Haugrud, Crossley, & Vrbancic, 2011), 2011). During the early stages there is no difference in repetitions (intrusions), this suggests that working memory is not impaired at this stage (Raoux et al., 2008). AD patients produce fewer words, smaller cluster sizes and less switching compared to healthy people. People with memory complaints also produce fewer words and smaller cluster sizes compared to people with no memory deficits but no difference in switching was observed between the two groups (Fagundo et al., 2008). Therefore, cluster size is a better predictor of early AD. A longitudinal study that followed up people with memory complaints found that after 2 years they had greater alterations in semantic fluency and in cluster size than those who did not develop dementia (Fagundo et al., 2008). Furthermore, a change in word

characteristics and amount of word produced is observed in a clinical setting (K. E. Forbes-McKay & Venneri, 2005; Hodges & Patterson, 1995). Studies using the category fluency task have also predicted changes in behavioural and psychological symptoms in patients (Stopford, Snowden, Thompson, & Neary, 2008).

A more scientific and advanced scoring system for the verbal fluency task is speech graph analysis (SGA). Text is represented as a graph, words are represented by nodes and edges represent the temporal link between words. Healthy participants had more nodes, a network with larger diameter and less dense compared to mild cognitive impairment (MCI) and AD groups (Bertola et al., 2014). The MCI group performed worse than healthy individuals but significantly better than the AD group. This suggests that, SGA is a good method to discriminate further the groups (although perhaps not so practical). SGA correlates with global cognitive performance, as the cognitive performance gets worse, the networks become denser, diameters become smaller, paths become shorter and numbers of nodes and edges become smaller (Bertola et al., 2014).

Verbal description tests were initially developed for patients with aphasia but are now also used for AD patients. Cuetos and his colleagues (2007) used this test and assessed semantic units, objective situations, inferences, total number of sentences, average length of sentences, ratio of open class words to close class words, total number of simple verb forms as opposed to compound verb forms and, as in previous studies, these authors found that the best variable for AD diagnosis was semantic units (Hier et al., 1985). With the use of the picture description task it was recently found that patients with AD produce more indefinite terms, repair fewer errors, and they generate sentences that are less

grammatically complex than healthy matched controls (K. E. Forbes-McKay & Venneri, 2005).

The Boston naming task is another test originally developed for aphasia screening where subjects are required to generate the common name of a drawing. 'Forgetting words' is an early symptom in AD, referred to as anomia which is a common symptom observed during the early stages of the disease. Word-retrieval is the most affected aspect of language in early AD/MCI. And although word retrieval is also present in healthy ageing, the retrieval problem is of a different nature from that observed in AD. Patients with AD show both lexical and semantic deficits on this test. They have difficulty accessing words and naming objects (Balthazar, Martinelli, Cendes, & Damasceno, 2007) and also tend to produce the superordinate of the item rather than the subordinate, for example saying animal instead of a tiger (Hodges & Patterson, 1995; Hodges, Salmon, & Butters, 1990). This suggests difficulty in verifying semantic attributes of concepts and retrieving the semantic category of that object. An association is also noted between naming living and non-living things and sex of participants. This could be due to gender based familiarity effects (Marra, Ferraccioli, & Gainotti, 2007). Men tend to perform better in non-living subcategories while women do better in living subcategories (Gainotti, 2005; Laiacona, Allamano, Lorenzi, & Capitani, 2006). This is still debatable and needs further research.

Impairment of both objects as well as naming famous faces is present in the early stages of AD, with a greater decline for naming faces; such task, therefore, might be a good test to include in the battery of AD screening. An impairment was found both in semantic knowledge of objects as well as that of famous people. In the case of the famous people

category the impairment in naming is associated with an impairment in semantic knowledge (Joubert et al., 2010).

Language retrieval in patients with AD is influenced by various lexical attributes of words such as age of acquisition (AoA) (Cuetos, Herrera, & Ellis, 2010), imageability and typicality (K. Sailor, Antoine, Diaz, Kuslansky, & Kluger, 2004). When these characteristics were studied for the optimal discrimination of the disease, the AoA was the most sensitive parameter being able to classify 88% of the patients and 95% of controls (Cuetos, Rosci, Laiacona, & Capitani, 2008; K. E. Forbes-McKay & Venneri, 2005). In a study where the role of AoA on word recognition was explored, results showed that patients made more errors and recognised less words that were acquired later in life than those acquired earlier (Cuetos et al., 2010). Familiarity is another variable that discriminates healthy from AD (Cuetos et al., 2008). Variables that are better preserved in AD are items with high-relevance and non-sensory features (Marques, Cappa, & Sartori, 2011) although this is debatable.

2.6 Semantic memory

The semantics of language represents the stored knowledge and meaning of words acquired through experience. People accumulate information in the semantic store through experience, including general facts, concepts and meanings of words. The cognitive area that stores this knowledge is termed semantic memory (SM) and it is responsible for one's behaviour, communication, initiation of speech and other daily activities which require reasoning, problem solving and planning as it provides knowledge and facts about all objects and aspects encountered in everyday life. All this information is useful to understand stimuli

and inform actions accordingly. The semantic system is connected to brain areas that are more expanded in humans compared to non-humans (Sherwood, Subiaul, & Zawidzki, 2008). These networks include the parietal, temporal and prefrontal heteromodal association areas (Binder, Desai, Graves, & Conant, 2009). It is suggested that brain areas involved in semantic processing are areas with high-level integrative processes and that receive processed, multimodal and supramodal input. Additionally, the semantic system is mainly lateralized to the left hemisphere with some bilateral representation (Binder et al., 2009).

Several descriptions of SM were proposed which have some differences in the description of its function but there is a general agreement that SM is more than a storage of memorized facts and knowledge about the world. The most recognized theory is that postulated by Quillian (1969) who proposed that SM is a highly categorically structured network of concepts, words and images that are retrieved in order to infer, comprehend, and transmit thoughts (Collins & Quillian, 1969; Tulving, Donaldson, & Bower, 1972).

Studies on deficits in SM help the understanding of how semantic knowledge is stored in the brain. Several models have been proposed to attempt an explanation of how semantic information is organised. One of the first models is the domain-specific model (Caramazza & Shelton, 1998), which advocates that there are distinct neural mechanisms responsible for the storage of living and non-living items. A further subdivision of this model suggests that information is organised depending on their sensory and functional features (Warrington & Mccarthy, 1987; Warrington & Shallice, 1984), with living items being differentiated by their visual appearance while inanimate objects are recognised by their functional properties. A different view on SM is the connectionist view (Rumelhart &

McClelland, 1986) which implies that semantic features could be either distinctive (unique) or non-distinctive (shared). Distinctive features are those factors associated with less than 2 concepts while non-distinctive features are common to many concepts. Therefore, the latter are highly intercorrelated with numerous strong links while distinctive features have few weak interconnections. It is thought that these interconnections are lost with disease related changes and non-distinctive features are more resilient to AD damage (Duarte, Marquie, Marquie, Terrier, & Ousset, 2009) (Flanagan, Copland, Chenery, Byrne, & Angwin, 2013).

2.6.1 Semantic representation and semantic control

Processing semantic information is referred to as semantic cognition which, in a healthy brain involves two interacting but separable components (Binder et al., 2009). The two components of SM involved are semantic representation, the stored information within the memory store and semantic control, the access and retrieval of conceptual knowledge. The former process is an automatic one while the latter is an executive process. Both processes are necessary to discriminate and choose the appropriate information regarding a particular concept from the vast amount of information available for a single concept. These two processes work together but the anatomical structures involved are thought to be distinct (Binder et al., 2009; Whitney, Kirk, O'Sullivan, Ralph, & Jefferies, 2011), therefore, impairment in disease may affect different neural systems and processes. As stated above patients suffering from dementia of Alzheimer's type are impaired on a battery of clinical tests that require semantic knowledge (Hodges, Salmon, & Butters, 1992; Perri, Zannino, Caltagirone, & Carlesimo, 2012); the question addressed here is whether the impairment is due to a loss of stored semantic knowledge or to an impairment in accessing stored

semantic information and secondary to executive deficits. Studies have been carried out in order to understand better the underlying principles of SM impairments in AD, yet the deficit is still not clear.

NI studies in people with brain injuries that affect SM have contributed substantially to the information available regarding the neuroanatomical structures involved in semantic storage and control. The brain areas that have a crucial role in semantic storage of information are the left anterior and midventral lateral regions which include the anterior inferior temporal gyrus, anterior fusiform gyrus and the anterior superior temporal sulcus (Binney, Embleton, Jefferies, Parker, & Ralph, 2010).

The left temporal and frontal cortex are the brain areas responsible for semantic control (Badre & Wagner, 2007; Bedny, McGill, & Thompson-Schill, 2008). There are two processes that could be used when one encounters a stimulus: a bottom-up approach (automatic) or a top-down process (controlled). In the latter, once the brain encounters a stimulus, retrieval of knowledge from semantic memory is necessary. NI studies have suggested that the anatomical substrate responsible for this process is the left IFG (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Whitney, Grossman, & Kircher, 2009). After related information is retrieved from the vast amount of information present, the selection process takes place and the area implicated in this process is the left mid ventrolateral prefrontal cortex (Badre et al., 2005). Therefore the left inferior prefrontal cortex is important for controlling retrieval of semantic knowledge, specifically its anterior part (BA 47/45) (Badre & Wagner, 2007; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001).

Transcranial magnetic stimulation studies have been conducted to distinguish the brain areas involved in semantic control and semantic storage (Whitney et al., 2011).

Semantic control is associated with a distributed network in left IFG and posterior middle temporal gyrus. The posterior middle temporal gyrus together with the IFG are important areas for the regulation of knowledge retrieval. Damage to both areas lead to disruption of executively demanding semantic decisions only (Whitney et al., 2011). Ambiguity tests used to study executive aspects of SM during functional MRI suggested that the posterior lateral temporal cortex is important for retrieval of meanings of words stored in SM while the left ventrolateral prefrontal cortex is important for mastering the executive task involved in choosing the appropriate context meaning for specific words (Bedny et al., 2008).

2.7 Conclusion

Early detection of verbal changes may aid in early diagnosis and intervention of the disease. What previous studies do not address is the nature of semantic deficits, therefore whether the impairments are due to loss of stored semantic knowledge or executive dysfunction. More knowledge and insight regarding this issue needs to be gathered and analysed. This will help in having a more solid diagnostic tool that can distinguish AD from both healthy ageing and other neurodegenerative disorders. A possible way to clarify the nature of semantic impairment in AD patients is to differentiate between executive and automatic language abilities to see if these aspects of linguistic skills are differentially affected by the disease. It is possible to investigate these different aspects of language by modifying clinically standardized tests in a way to test the different aspects of SM. A more in-depth exploration of semantic impairment in prodromal and early AD will allow for a more specific clinical marker which might aid differential diagnosis between the different types of ageing.

Chapter 3:

Aims and objectives

3.1 Introduction

As discussed in chapter 1, experimental research suggests that the neuropathological changes that cause the dementia associated with Alzheimer's disease (AD) appear years before the onset of clinical symptoms and are, therefore, already present during the preclinical stage, possibly decades before the manifestation of the clinical symptoms that accompany full blown dementia. Clinical data support this view and imply that subtle cognitive changes are also present during the predementia phase in parallel with the biological changes. Clinical detection of these subtle cognitive changes, however, is challenging because these early disease-related changes are difficult to differentiate from those observed in normal ageing and because available instruments lack the necessary sensitivity. Recent studies on language in AD suggest that early decline in linguistic abilities due to semantic difficulties is manifested by AD patients earlier on in the course of the disease, a change that is not a characteristic of normal age decline. Although the optimal diagnosis is through neuropsychological testing, these tests lack the sensitivity to detect the early signs of neurodegeneration and there are no distinctive features which would allow a differentiation from normal age-related decline. This is due to two main challenges: the overlap between healthy and pathological decline and the effect of high levels of education that mask any elusive changes.

As highlighted in chapter 2, an early language decline associated with semantic memory (SM) impairment is reported in AD. The nature of this impairment is still unknown. Further research is needed, therefore, to explore the different aspects of SM to understand better the cause of impairment, whether it is due to a degradation of semantic representation (automatic functioning) or due to a disruption in the executive aspects of the

process of retrieval of semantic information (executive functioning), and the neural areas responsible for this deficit. Refining clinical language tasks that tap into semantic memory will help in providing more in-depth information about the memory component and the impairment associated with it and it will increase the sensitivity of the tests to detect the earliest signs of the disease.

The main objective of this study is to modify standard linguistic tests and design novel ones to assess the different aspects of SM and collect normative data from healthy individuals. A small construct validity study will also be carried out in which scores of healthy older adults and patients on the novel tasks will be correlated with grey matter density values derived from high resolution magnetic resonance imaging (MRI) images. Following this, the tasks will be used to investigate the nature of SM impairment in patients at different stages of the disease. Additionally, these tests will also be used on patients with early AD. In doing so this research will aim to establish the type of impairment in AD and how this differentiates from healthy ageing. To this end a small pilot study will be carried out to test the clinical usability of these new tasks and to gather indications on whether they have the potential to detect dissociations in the impairments underlying performance in early AD.

3.2 The aims of this study are to:

3.2.1 Assess the living and non-living category impairment

The aim of this study is to explore the degradation of specific categories in spontaneous word production in early AD patients by looking at the dissociation between living and non-living categories. The pattern of impairment in MCI prodromal to AD will be compared to cognitively healthy participants and other types of dementia to establish differential patterns that might aid in early diagnosis. The temporal gradient of spontaneous word production will also be explored. The findings of this study are reported in chapter 4, study 4.1 and 4.2.

3.2.2 Modify and devise novel language tasks

This study will focus mainly on the modification and generation of linguistic tasks which tap into semantic representation and semantic control. Parts of these tests will require more executive functioning than standard clinical tasks which should allow a better detection of earlier symptoms. These tests will eventually be used in the assessment of patients during clinical testing. Once the instructions and scoring procedures for the tests are developed, they will be piloted on a number of people to ensure that instructions are clear and the testing runs smoothly. The finding of this preliminary work are reported in chapter 5, study 5.1.

3.2.3 Obtain normative data for the novel tests

The modified and the newly designed tests for this study will be administered to a large

sample of healthy native English speakers from different backgrounds and educational levels

in order to eliminate any possible bias. This will generate substantial normative data and will

allow the comparison of the performance of AD patients against that of healthy matched

controls. The finding of this study are reported in chapter 5, study 5.2.

3.2.4 Testing construct validity through anatomical validation

Distinct neuroanatomical structures are involved in semantic cognition in a well-functioning

brain and the disease may affect different neural systems and processes at different stages

and with different severities. The crucial areas in semantic storage of knowledge are the left

anterior and mid-ventral lateral regions of the brain while the left frontal and temporal

cortex are responsible for semantic control. In this study high resolution three dimensional

structural images of the brain will be acquired with MRI to explore and establish the neural

substrates that correlate with the different semantic components used during semantic

processing. Data will be collected from healthy individuals and patients and the data will be

correlated with grey matter density values using the technique of Voxel Based

Morphometry (VBM). This data will generate information about brain areas involved in the

execution of these novel tasks and this will shed light into the processes that are affected by

AD to establish the relationship between cell loss and breakdown of formation in semantic

memory. The purpose is to verify that the newly devised tests of automatic and executive

functioning of semantic memory rely on those specific brain structures which are more

vulnerable to AD neurodegeneration and which are affected by this disease in its earliest

neuropathological development. The findings of this anatomical validation study are reported in study 5.3 in chapter 5.

3.2.5 Assess age related SM decline

SM is well preserved in ageing and tests relying on the functioning of SM are able to discriminate between the two types of ageing (McGeown et al., 2009). The new tests will be administered to a large sample group of young, middle and old adults. The results from this study will highlight any age-related decline in the different components of SM. The findings of this study are presented in chapter 5 study 5.4.

3.2.6 Assess SM impairment in patients with MCI prodromal to AD

It is well known that SM is impaired during the early stages of the disease with mixed results presented by recent studies regarding the nature of impairment (Arroyo-Anllo, Bellouard, Ingrand, & Gil, 2011; Hodges & Patterson, 1995; Kirchberg et al., 2012; Lipinska & Backman, 1996; Mardh, Nagga, & Samuelsson, 2013; Nebes, Martin, & Horn, 1984). Therefore, further research is required to acquire concrete evidence on the nature of this type of memory deficit. This chapter will focus on establishing the nature of impairment and whether there is a difference in performance on tests that assess semantic control and those that assess semantic representation between normal ageing and AD. The findings of this pilot study are reported in chapter 5, study 5.5.

Chapter 4:
The category dissociation debate in
Alzheimer's disease

4.0 The category dissociation debate in AD

Cognitive science has been trying to understand and model how conceptual knowledge is stored in semantic memory (SM) and if this reflects the organizational structure of the world. One way of exploring this phenomenon is through the category-specific semantic impairment, that is, the disproportionate impairment for items belonging to a specific category compared to items from another category. The most commonly presented dissociation is that between living and non-living categories. This impairment has been explored in patients with brain lesions, but recent studies have focused on Alzheimer's disease (AD) since an early SM deficit is well documented. Category dissociation is of interest in the field of AD diagnosis as the sensitivity of clinical tests can be increased by establishing and incorporating words that are first affected during the disease. Until now, contradictory results have been generated from the AD population, but the majority of studies detected a disadvantage for living items (Silveri, Cappa, Mariotti, & Puopolo, 2002; Zannino, Perri, Carlesimo, Pasqualetti, & Caltagirone, 2002). Specific-category impairment remains a debatable matter in AD and requires further investigation. Establishing the impairment pattern in early AD will not only be useful for a better understanding of the SM deficit caused by this disease, but it would also contribute to its earlier diagnosis. This chapter will address the mixed results generated from AD studies taking into account the main theories proposed to explain the living and non-living dissociation, and aims to investigate the impairment using a different methodological approach from that previously applied.

A common explanation for this semantic dissociation is the sensory-functional theory, first introduced by Warrington and colleagues (Warrington & Mccarthy, 1987; Warrington & Shallice, 1984). This theory suggests that the differential performance on the

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two categories is due to the fact that different types of information contribute to the identification of items from the distinct categories. In their study on Herpes Simplex Encephalitis patients with damage to the temporal lobe, Warrington and Shallice (1984) found that non-living items relied on functional features while items from the living category, particularly animals, relied on sensory/perceptual attributes. It is suggested that the functional system has evolved more than the sensory system and therefore is more resistant to neural damage (Caramazza & Shelton, 1998). Furthermore, categories that are an exception to the rule generate different results; for example, the non-living category of musical instruments (members of the category are distinguished through sensory information) is less preserved than the living category of body parts (functional attributes required to distinguish between different body parts) (Barbarotto, Capitani, & Laiacona, 2001). This assumption is supported by a computational model of a simplified SM that attributes codes to living and non-living items according to their visual and functional features. The impairment reported in this study was dependent on whether the applied lesions affected visual or functional information (Farah & McClelland, 1991). Furthermore, evidence from a longitudinal study on AD patients suggests that knowledge of living items deteriorates at a faster rate compared to non-living items, and this semantic domain appears to be a good predictor of 'concept loss' (Garrard et al., 2001).

Contradictory behavioural results have been generated and despite that the mixed results could be genuinely related to the disease pathology and its heterogeneity some studies attribute them to the extraneous variables presented by the experimental procedures and stimuli used. The most common test used to assess category impairment is the standardized line drawing confrontation naming task of Snodgrass and Vanderwart

(1980). Patients with AD are able to name more non-living items compared to living ones (Silveri et al., 2002; Zannino et al., 2002). However, the same performance pattern is observed in cognitively healthy individuals suggesting that line drawings of living items put the category at a disadvantage (Montanes, Goldblum, & Boller, 1995; Zannino, Perri, Caltagirone, & Carlesimo, 2007). Members from the living category require more semantic processing than non-living items due to their high degree of overlapping features (Zannino, Perri, Pasqualetti, Caltagirone, & Carlesimo, 2006). Additionally, colour information plays a major role in discriminating living items while it has no effect on non-living ones (Zannino et al., 2007), therefore, using black and white line drawings is detrimental to the living category with the possibility of exaggerating the extent of the impairment.

Colour is highly relevant for semantic processing but it is not the only sensory variable that influences the performance on the confrontation naming test. Patients with AD as well as healthy adults perform worse on naming drawings of high visual complexity and this distinction is only visible for living items (Montanes et al., 1995). Studies that control for extraneous factors report a reverse pattern, and sometimes absence of category-specific impairment. This was the case when semantic relevance, the contribution of semantic features for concept representation, was experimentally manipulated by Sartori and colleagues (2007) to explore its effect on the category dissociation. Greater impairment for non-living items was also observed during an explicit semantic task later on in the disease progression, when patients showed normal priming for the animal category but reduced priming for artefacts (Hernandez, Costa, Juncadella, Sebastian-Galles, & Rene, 2008). This is suggestive of animals having more shared features (Garrard et al., 2001) which tend to intercorrelate with each other (Devlin, Gonnerman, Andersen, & Seidenberg, 1998).

Psycholinguistics is another contributing factor to the performance on semantic tasks. Variables of words are better predictors of AD performance compared to category effect (Garrard et al., 2001; Moreno-Martinez, Goni-Imizcoz, & Spitznagel, 2011) and as discussed in chapter 2 it is widely accepted that words acquired earlier in life, higher in lexical frequency, familiarity, imageability and typicality are relatively better preserved throughout the disease progression (Cuetos et al., 2010; K. E. Forbes-McKay, Ellis, Shanks, & Venneri, 2005; K. Sailor et al., 2004). The previously mentioned advantage of body parts over musical instruments can also be interpreted in the light of this assumption. A gender difference in performance has also been reported in studies on category impairment. Research samples consisting of higher proportions of females yield larger category effect sizes (Laws, Adlington, Gale, Moreno-Martinez, & Sartori, 2007). This difference is attributed to a category familiarity bias with males performing better on naming living items while females excel in artefacts (Marra et al., 2007).

The storage and organization of semantic information has also been investigated by neuroimaging research to understand the neural substrates responsible for the category impairment. The main question raised through theories from category-specific impairment is whether the semantic system is a unitary one or a segregated one with distinct neural areas responsible for specific category domain. The preponderant view supports the assumption that semantic knowledge is represented by a distributed system responsible for both living and non-living categories with semantic information from both categories stored in common areas (Devlin et al., 2002). Other studies that support a unitary system suggest that the category-specific impairment is a result of a complex interaction of semantic features, the amount of shared or distinctive features, and the correlation between features

attached to a given item; all these characteristics tend to favour the preservation of non-living items (Tyler, Moss, Durrant-Peatfield, & Levy, 2000). Rather than having distinct areas involved in the storage of semantic knowledge it is the processing of semantic information that makes use of different brain regions, namely the right medial temporal lobe for living items and the left medial temporal gyrus for non-living items (Brambati et al., 2006).

Neuroimaging data are as inconsistent as behavioural data which could be due to false positives and nuisance variables present in the procedures applied in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A minority of studies have found some evidence of a specialised segregated neural system for different category domain. Supporting the sensory-functional theory, studies show that healthy people recruit different neural areas for the distinct categories although more than one area seems to be responsible for the same category. Living categories rely on left ventral temporal-occipital and frontal cortex (Grossman et al., 2003; Moore & Price, 1999) and non-living categories depend on posterolateral temporal, lateral frontal and prefrontal areas (Cappa, Perani, Schnur, Tettamanti, & Fazio, 1998; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Grossman et al., 2003). The disadvantage for living items is suggested to be due to early and severe damage to the temporal neocortical regions. A recurrent finding is that the left anterior medial temporal pole is associated with semantic processing of animals (Devlin et al., 2002; Gainotti, 2000) while the left posterior middle temporal gyrus is activated when processing tools (Devlin et al., 2002). These areas are affected by AD pathology at the early stages of the disease (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; H. Braak & Braak, 1991) and in fact different substrates from those used in healthy people are activated in brains with AD. To counteract the pathophysiological changes, a compensatory

mechanism is thought to be present for the living category of animals; patients tend to use

the posterior portions of the ventral temporal cortex which is adjacent to the area activated

in healthy adults (Grossman et al., 2003).

4.1: An investigation of category-specific impairment in early AD using the category fluency task

4.1.1 Introduction

A definite impairment in the semantic system is present in early AD but the pattern of impairment and whether the living or non-living category has an advantage over the other is still not clear. The literature can be grouped into two main assumptions; impairment due to a 'disproportionate degradation of a dedicated neural substrate', functional or perceptual (Caramazza & Shelton, 1998; Warrington & Shallice, 1984), and the assumption that some categories have less common features and are, therefore, more demanding than others and hence are affected first as cognitive reserve starts decreasing (Rumelhart & McClelland, 1986). Meanwhile, other studies attribute any category dissociation to the methodology of the study (Zannino et al., 2007) which raises critical questions about the presence of a true category dissociation. This study tries to contribute to this debate by comparing living and non-living categories using the category fluency test (CFT), a task that assesses residual semantic skills.

As mentioned above the most common test used to explore the category dissociation in AD is confrontation naming which presents methodological issues. CFT is another widely used clinical diagnostic task in AD to assess SM and language impairment as it is a reliable discriminator between early AD and healthy ageing. CFT requires the participant to generate items constraint by a category in 60 seconds. The most used category in clinical settings is 'animals,' with the 'fruits', and 'cities' categories used for more extensive examination. In order to properly execute this task, two main areas of the brain are required; the frontal area, to organise information, initiate response, monitor previous

responses and inhibit inappropriate information, and the temporal lobe which is required to access and integrate the information stored in the semantic store. A good performance on the CFT requires more functioning of the temporal lobe compared to the frontal region (Henry & Crawford, 2004). CFT involves similar neural substrates to those required for confrontation naming (Grogan, Green, Ali, Crinion, & Price, 2009; Zhang et al., 2013) to complete the task, these are areas that experience changes and reduced metabolism in AD (Melrose et al., 2009). The difference between the two tests is that CFT eliminates extraneous stimuli bias such as colour, visual complexity, and the possibility of unknown knowledge presented by confrontation naming task, by assessing information stored in the mental lexicon through spontaneous speech.

Initially, when CFT was introduced as a diagnostic tool, the performance was based on the total score of the generated items during the 60s, and this is still the only score considered during a clinical neuropsychological assessment. But research has delved into more depth regarding the performance of AD patients on CFT and found that clustering and switching are good discriminators of healthy ageing and early AD (Haugrud et al., 2011). Analysing and comparing words produced by patients and healthy people reveal a difference between the psycholinguistics of the words produced between the two groups (see section 2.5.1). The impoverishment in SM which seems to be more pronounced for living items is expected to be reflected on CFT with patients performing better in categories whose items have higher frequency, are acquired earlier on in life, and are more familiar.

Another way of analysing performance on CFT is by looking at the temporal gradient of word production. Fernaeus and colleagues (2008) demonstrated for the first time that time interval gives critical information for an AD diagnosis. The importance of marking

words in short intervals during the 60s is emerging as an important feature of clinical testing. Multiple cognitive processes and distinct anatomical structures are required during the CFT. The temporal cortex, where semantic information is stored, is the main cortical area involved in this test but the frontal area is also critical for the execution of this test (Baldo & Shimamura, 1998; Henry & Crawford, 2004). Apart from the retrieval of semantic information, the CFT requires strategic control and self-monitoring of information to prevent intrusions and perseverations; all these strategies rely on the functioning on the frontal lobe. In a healthy brain, the number of words produced after the first 15s declines in comparison to the first quartile (Venegas & Mansur, 2011). It has been stated that the first 30s of the performance on the CFT have a significant power for predicting diagnosis of dementia in AD and this specific period is enough for diagnostic purposes (Fernaeus et al., 2008). This is still a new technique explored by using solely the 'animal' category and therefore requires further investigation.

The present study aims to address the lack of agreement regarding the category specific impairment. This will be done by analysing differences between retrieving exemplars from a living category and from a non-living one using the CFT in patients with mild cognitive impairment (MCI) who are in the prodromal phase of AD. This study would be the first one to explore the degradation of specific categories in spontaneous word production rather than in naming pictures. Confrontation naming tasks require the pre-selection of items and are based on the assumption that any difference between categories is related to the negative effects of neuropathology. However, the possibility remains that any of the observed effects might reflect an artefact of material selection and modality of testing rather than representing a selective impairment within aspects of semantic

representation selective for specific object categories. Matched controls will be used to explore whether a greater impairment for a specific category is only present in MCI prodromal AD or if healthy subjects show a similar pattern of impairment. Numerous studies suggest a strong link between word attributes and CFT performance. Hence, in this study the frequency and age of acquisition (AoA) of the words generated by the research sample were also analysed to investigate whether linguistic properties have an effect on the living and non-living performance. Another aim of this study is to establish whether there is a temporal gradient in spontaneous word production for both healthy controls and patients and whether access to peoples' own vocabulary is time limited in AD. We hypothesize that the living category will be more impaired since we are exploring the early stages of the disease when pathology is mostly severe at the medial temporal structures. The task becomes harder by time, exhaustion of semantic information typical of that category is expected and therefore it is assumed that the number of items generated decreases by time.

4.1.2 Methodology

4.1.2.1 Participants

This study is based on data collected retrospectively from the Memory and Dementia Clinic database at the Royal Hallamshire Hospital in Sheffield between 2011 and 2015. A total of 21 patients (8 males, 13 females) and 19 cognitively healthy controls (CH) (6 males, 13 females) were included in the study. Selected patients had a diagnosis of amnestic and non-amnestic MCI according to current general clinical criteria (Petersen et al. 2001). The diagnosis was based on extensive neurological, psychiatric and neuropsychological

examinations supported by longitudinal follow up. All patients met the clinical criteria for MCI (Petersen et al. 2001) experiencing cognitive impairment with spared functional activities of daily living. All patients scored above 24 on the Mini Mental State Examination (MMSE) and both MCI of the amnestic and non-amnestic type were included as the purpose of the study was to draw inferences about the performance on different semantic categories. The control group included cognitively healthy (CH) participants who volunteered to take part in dementia research studies. Participants were only included if they had no history of cerebrovascular disease, brain damage, epilepsy, substance abuse and psychiatric disorders. To eliminate any bias resulting from language barriers, all participants were native English speakers.

4.1.2.2 Materials and procedure

A standardized CFT was administered to both the patient and control groups. Participants were asked to name as many exemplars from a category as they could think of in 60 seconds. The categories included 'cities', 'animals', 'fruits' and 'things people wear' (TPW). For the purpose of this study the 'animals' category was used as the living semantic category, while items produced in the 'TPW' category were used as the non-living category. The 'fruits' category was later on included in the analysis to explore categories within the same domain.

All items mentioned by the participants were noted down at 15s intervals (4 quartiles: 1-15s (T1), 16-30s (T2), 31-45s (T3), 46-60s (T4)). The rules listed below were used for data scoring. Repeated words (perseverations) were only counted ones and appropriate answers used for the wrong category (intrusions) were not counted. When a superordinate category was produced (example bird, coat) it was not scored if representatives of it

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(example robin, raincoat) were also produced. In the case of the animal category, baby versions of an animal were not counted if the adult name was also listed (example: cat, kitten). The total number of unique words was generated for the whole 60s. In addition, each quartile was scored separately.

AoA values were obtained from a list of 30,121 singular words compiled using a web-based crowdsourcing technology (Kuperman, Stadthagen-Gonzalez, & Brysbaert, 2012). The data were collected from respondents aged between 15 and 82 years. This web-based database offers high validity and reliability when compared to other databases collected in more controlled laboratory studies. Nine words generated during the present study were not part of the database. SUBTLEX-UK database (van Heuven, Mandera, Keuleers, & Brysbaert, 2014) was used to obtain the frequency values of the generated words. This database is based on a corpus of 201.7 million words from subtitles of 45,099 broadcasts. Nine channels from the British Broadcasting Corporation (BBC) were used to compile the list. In the present study the Harmonic Mean for the first 5 words produced by each participant was calculated. One of the participants generated less than 5 words on the 'fruits' category and therefore the mean for 4 words were calculated. This was possible since the main interest lies in the properties of the words rather than the performance.

4.1.2.3 Statistical analysis

Parametric tests were used in the comparison between the performance of CH controls and MCI patients as the data had no outliers, they were normally distributed, and the homogeneity of variance was the same for both groups on all categories. An independent-samples t-test was carried out to determine differences between groups. To test for group differences between the categories a 2 x 3 ANOVA was used. A repeated

measure analysis was carried out to explore within subject differences between the living and non-living category and MANOVA was used to compare the two groups on the words generated across the 4 quartiles.

For the analysis and comparisons of the psycholinguistics of words (Frequency and AoA) a 2 x 3 ANOVA was implemented. One of the CH participants was an outlier and therefore was removed. Although some of the variables were non-normally distributed (Animals (AoA) and TPW (Frequency) for MCI and Animals (AoA and TPW (AoA) for patients (more information in result section), the sample size used was more than 15 participants and the skewness and kurtosis was checked. All analyses were performed using IBM SPSS statistics 22.

4.1.3 Results

4.1.3.1 Demographics and clinical variables

In total, data from 21 patients (38% males) and 19 CH controls (32% males) were analysed and reported in this study. The two groups were matched for age, years of education (YoE) and gender. The mean age of the control group (M = 67.26, S.D = 12.78) was slightly higher than that of the patient group (M = 66.29, S.D = 10.81) and the mean YoE for the control group (M = 13.16, S.D = 3.96) was similar to that of the patient group (M = 13.05, S.D 2.84). None of the factors were significantly different. The two groups did not differ in gender either (χ^2 (1, *N* = 40) = .186, *p* = .666). The only value that differed between the two groups was the MMSE score which was higher for controls (M= 28.79, S.D = 1.08) than for patients (M = 26.05, S.D = 1.32). Table 4.1 summarizes the mean scores and significance values for the demographic and clinical characteristics.

Table 4.1: *t*-test values and significance levels for the demographic and clinical variables of patients and CH participants

	MCI (n=21)	CH (n=19)	*T*	Sig. (2-tailed)
Mean Age (SD)	66.29 (10.81)	67.26 (12.78)	.262	.795
Mean YoE (SD)	13.05 (2.84)	13.16 (3.96)	.102	.919
Mean MMSE (SD)	26.05 (1.32)	28.79 (1.08)	7.13	.000

CH: Cognitively healthy, MCI: Mild cognitive impairment, MMSE: Mini Mental State Examination, YoE: Years of Education

4.1.3.2 Group and category effect on the total score of generated words between MCI patients and CH controls

The mean scores and SD values for the generated words on each category by the two groups are summarized in Table 4.2 and Figure 4.1. A 2 x 3 ANOVA, group (MCI and CH) x category (fruits, animals and TPW) was conducted. This revealed a significant main effect for group [F (1,114) = 31.308, p < .001] with the MCI group generating fewer words in all three categories compared to the CH group. The greatest difference between the performance of the two groups was recorded for the living 'fruits' category *t*(38) = 4.41, *p* < .001, followed by the 'animals' category *t*(38) = 2.90, *p* < .01, and the non-living category, 'TPW' *t*(38) = 2.56, *p* < .05.

Table 4.2: The mean values and SD scores for the total items generated by the two groups for Fruits, Animals and TPW

	MCI		Controls	
	Mean	S.D	Mean	S.D
Fruits	10.33	3.18	15.58	4.31
Animals	14.71	4.33	18.58	4.09
TPW	16.71	5.04	20.26	3.49
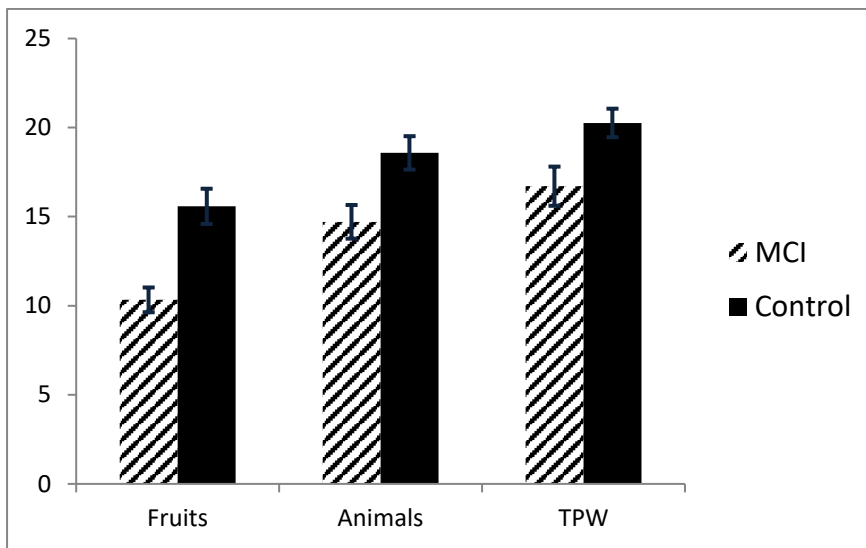
Figure 4.1: A bar graph showing the mean scores and standard error for the generated items on the three categories.

A significant main effect of category was also reported [$F_{(2, 114)}$ = 18.608, $p < .001$]. Post hoc comparisons with Bonferroni adjustment showed a significant difference between fruits and animals ($p < .001$) and fruits and TPW ($p < .001$) but no significant difference was present between animals and TPW ($p = .145$). There was no significant interaction between group and category on the CFT performance [$F_{(2, 114)}$ = .477, $p = .622$].

4.1.3.3 Psycholinguistic effect on living and non-living performance

AoA and Frequency of the first five words produced by all the participants in this research study were obtained and analysed. This part of the study was carried out to investigate the effect of word attributes on the performance of the CFT and to establish any differences between the living and non-living categories. Shapiro-Wilk test was performed to check for normality. Six variables (AoA for Animals, Fruits and TPW, and Frequency of animals, fruits and TPW) for each group were used. The data for the AoA of Animals ($p < .05$) and AoA of TPW ($p < .01$) from the Control group and AoA of animals ($p < .01$) and

Frequency of TPW (p < .05) from the MCI group was not normally distributed but the skewness and kurtosis were less than moderately skewed. For this reason and other explanations discussed in section 4.1.2.3 parametric tests were used for this part of the study. Table 4.3 represents the degree of skewness and kurtosis for the non-normally distributed data.

Table 4.3: Skewness and kurtosis values for the non-normally distributed data

	Variables	Skewness (S.E)	Kurtosis (S.E)
Control group	AoA_Animals	1.008 (.536)	0.016 (1.04)
	AoA_TPW	1.208 (.536)	0.253 (1.04)
MCI group	AoA_Animals	1.361 (.501)	0.901 (.972)
	Freuqency_TPW	0.974 (.501)	0.256 (.972)

The harmonic mean of the first 5 words generated by individual MCI participants was compared to those generated by participants in the control group. A group (MCI and CH) x category (Animals, Fruits and TPW) ANOVA was performed to analyse the effect of AoA on category and group. The MCI group produced words that were acquired slightly earlier than those produced by the healthy group. The mean values and SD of mean AoA of the generated words are summarised in Table 4.4 The difference in the mean AoA was not significant for any of the categories but the smallest difference was observed in the non-living 'TPW' category [$t(37) = 1.068$, $p = 0.292$]. The largest difference between the group's AoA was present for the 'Fruits' category [$t(37) = .513$, $p = 0.571$] with the 'animals' category [$t(37) = 0.513$, $p = 0.571$] falling in the middle.

Table 4.4 Mean values and SD for the AoA of animals, fruits and TPW

	Controls	MCI
	Mean (SD)	Mean (SD)
Animals	4.09 (.414)	3.80 (.329)
Fruits	4.24 (.335)	4.18 (.298)
TPW	4.72 (1.18)	4.38 (.780)

A main significant difference was reported for category F (2,116) = 6.383, $p < .01$. Bonferroni post hoc tests revealed that the 'animals' category (M = 4.03, SD .370) contained words that were earlier acquired than words generated in the 'TPW' category (M = 4.54, SD 0.985), this was a significant difference ($p < .01$). No significant difference was reported between the AoA of 'Fruits' (M = 4.21, SD = 0.312) and 'TPW' (M = 4.54, SD = 0.985) ($p = 0.070$) and between 'Animals' and 'Fruits' ($p = .972$). No interaction between category and group was reported [$F(2,116) = .532$, $p = 0.589$].

The same statistics were applied for the frequency variable to see if this had any influence on CFT performance and if there were any differences between the words produced on the distinct categories. A 2 (group) x 3 (category) ANOVA with frequency as a dependent variable was conducted. The mean values and SD for the first 5 words generated by each participant are summarized in Table 4.5. The difference in performance between the two groups was not significant for any of the categories. The MCI group generated words with higher frequency for the 'fruits' ($p = 0.400$) and 'TPW' ($p = 0.370$) categories, the opposite pattern was present for the 'animals' category ($p = 0.665$) where the MCI group produced a mean of lower frequency. A significant difference between categories was also observed [F (2,116) = 63.05, < 0.001]. Items generated in the 'Animals' category (M = 5284.95) had a much higher mean frequency than fruits (M=1418.66) and TPW (M =1288.524). Bonferroni

post hoc analysis showed a significant difference between both animals and fruits ($p <$ 0.001) and animals and TPW ($p < 0.001$). The difference in frequency between 'TPW' and 'Fruits' was not of significance value ($p = 1.000$). Figure 4.2 shows frequency differences between the three categories. No category by group interaction was found for this word attribute [$F (2,116) = 0.848$, $p = 0.431$].

Table 4.5: Mean values and SD for the frequency of the first 5 words generated by each participant in both groups.

Categories	Controls Mean (SD)	MCI Mean (SD)
Animals	5429.97 (2840.66)	5044.45 (2742.59)
Fruits	1287.60 (557.66)	1485.28 (861.52)
TPW	1222.21 (1127.90)	1572.05 (1295.67)
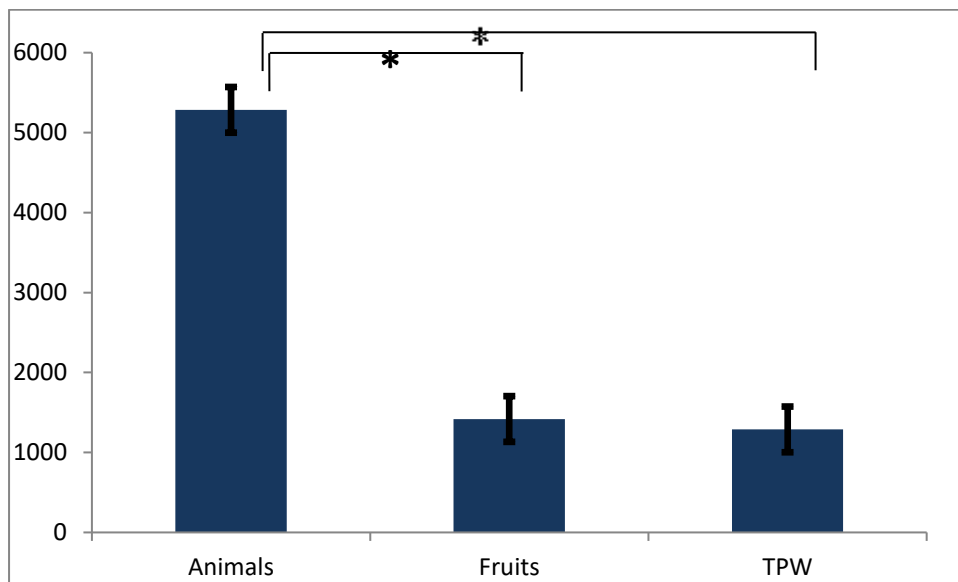
Figure 4.2: A graph representing the mean values of the frequency of words with error bars. *Significant difference ($p < 0.001$) between the frequency of the categories

4.1.3.4 Differences in generated words across time

The words generated at 15s timepoints (T1, T2, T3, T4) of the two sample groups were compared and analysed to investigate any differences between the two types of ageing. The three categories were explored separately. The largest mean difference between the two groups was reported for the 'fruits' category. In this category a significant difference was present for the first 45s with increasing difference. T1 [$F_{(1,38)}$ = 6.14, $p < 0.05$, T2 [$F_{(1, 38)}$ = 6.55, $p < 0.05$], and T3 [$F_{(1, 38)}$ = 11.47, $p < 0.01$]. For the 'animals' category the mean number of words generated at each timepoint was less for the MCI group compared to the CH group and a significant difference was observed during T3 [$F_{(1,38)}$ = 4.26, $p < 0.05$] and T4 [$F_{(1,38)}$ = 8.67, $p < 0.01$]. Although the MCI group produced fewer words during all 4 timepoints of the 'TPW' category compared to the CH group, the difference was much less compared to the previous living categories. A significant difference was only observed during the last 15s, T4 [$F_{(1,38)}$ = 5.31, $p < 0.05$]. Table 4.6 Summarizes the mean values and significance level of each timepoint.

Table 4.6 mean values and p-values of generated words across time

	Fruits			Animals			TPW		
	Mean MCI	**Mean CH**	**p-Value**	**Mean MCI**	**Mean CH**	**p-value**	**Mean MCI**	**Mean CH**	**P-value**
T1	6.14	7.68		7.29	7.95		7.33	8.05	
	(1.71)	(2.21)	0.018	(1.71)	(1.72)	0.229	(2.08)	(2.59)	0.332
T2	2.05	3.32		3.67	4.16		4.14	5.00	
	(1.11)	(1.95)	0.015	(2.48)	(1.92)	0.491	(2.35)	(1.67)	0.196
T3	1.05	2.89		2.24	3.26		2.71	3.42	
	(1.28)	(2.11)	0.002	(1.45)	(1.70)	0.046	(1.55)	(1.90)	0.203
T4	1.10	1.68		1.52	3.21		2.52	3.79	
	(1.09)	(1.57)	0.172	(1.33)	(2.23)	0.005	(1.97)	(1.44)	0.027

Shaded cells represent the significant values

4.1.3.5 Time point differences within group

Individual time points were analysed and compared to investigate changes in the number of words generated per 15s intervals. A repeated measure analysis was performed to explore the temporal gradient in spontaneous word production. The CH group generated the highest number of words during the first 15s (T1) on all categories (Fruits: M= 7.68, SD=2.21, Animals: M=7.95, SD=1.72), TPW: M=8.05, SD=2.59). The largest decline in number of words generated is between T1 and T2 with the highest mean difference of 4.36 for the 'fruit' category, followed by 'animals' with a mean difference of 3.79 words and 'TPW' with a 3.05 mean word difference. The number of words produced by the CH group decreased across the 60s and the least number of generated words was reported for T4 both in the 'fruits' category (M = 1.68, SD = 1.57) which was also the lowest number of words out of the three categories, and 'animals' category (M = 3.21, SD = 2.23). A slight increase of 0.37 in the non-living 'TPW' category (M = 3.79, SD = 1.44) was reported between T3 and T4. The mean number of words generated at every 15s are displayed in Figure 4.3 and the percentage distribution of the produced words is presented in Table 4.7. A significant difference was reported for comparisons between the different time points for 'fruits' [F (3,54) = 35.83, $p < 0.001$], 'animals' [F (3, 54) = 27.91], $p < 0.001$ and 'TPW' [F (3, 54) = 20.82, $p < 0.001$]. Post hoc Bonferroni comparisons reported differences between T1 and all the other 15s intervals ($p < 0.001$). The significant values for each time point comparison for the CH group is presented in Table 4.8.
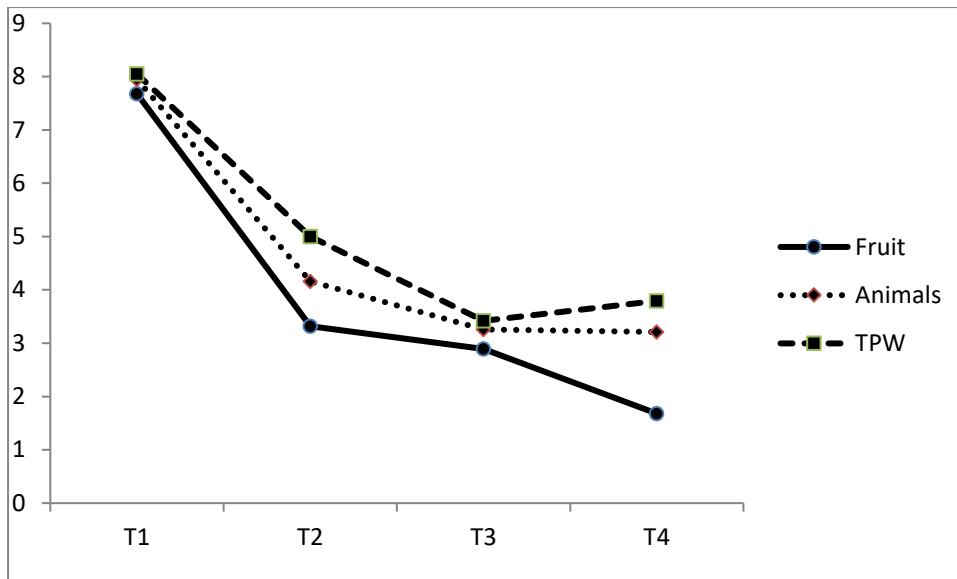
Figure 4.3: Line graph showing the mean number of words generated across 15s interval for the Control group on the three categories.

Same as for the CH group, the MCI group generated most words during T1 (0-15s) on all categories (Fruit: M=6.14, SD = 1.71, Animals: M=7.29, SD = 1.71, TPW: M=7.33, SD = 2.08). The largest decline in number of words produced was between T1 and T2. For the 'fruits' category there was a mean difference of 4.09 words, for animals there was a 3.62 difference and for TPW it was a mean difference of 3.19 words. The performance on T2, T3 and T4 was similar. Between T2 and T3 there was a mean difference of 1 word for the 'fruits' category, and 1.43 for the animals and TPW categories, while an even smaller difference was observed between T3 and T4 with a mean difference of 0.05, 0.72 and 0.19 words for the 'fruits', 'animals' and 'TPW' respectively. The mean number of words generated at every 15s and percentage distribution are displayed in Figure 4.4 and Tables 4.7 and 4.8 respectively. A significant difference was present for comparisons between the different time points for fruit [$F_{(3, 60)}$ = 82.16, $p < 0.001$], animals [$F_{(3,60)}$ = 50.40, $p < 0.001$] and TPW [$F_{(3, 60)}$ = 31.84, $p < 0.001$). Bonferroni comparisons reported a significant difference between T1 and all other time points ($p < 0.001$), T2 and T3 ($p < 0.05$) and T2 and T4 ($p < 0.05$) for the fruit

category. For the animal category a significant difference was presented between T1 and the three other time points ($p < 0.001$) and T2 and T4 ($p < 0.01$), and for TPW a significant difference was present between T1 and the three other time points ($p < 0.001$) and between T2 and T3 ($p < 0.05$). The significant values for each time point comparison for the MCI group is presented in Table 4.8.
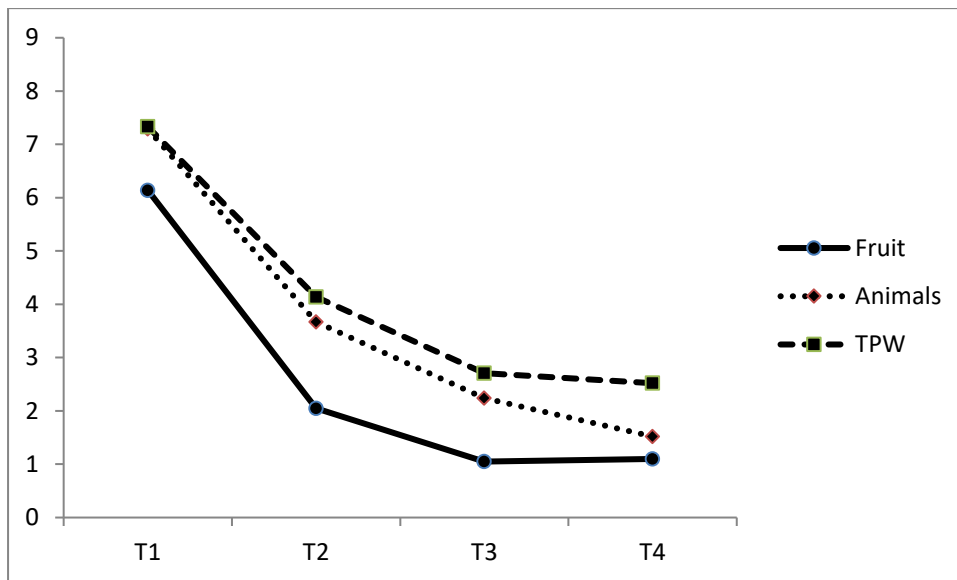
Figure 4.4 : Line graph showing the mean number of words generated across 15s interval for the MCI group on the three categories

Table 4.7: Percentage distribution of the generated words

	Controls:				MCI:		
	Fruit	**Animals**	**TPW**		**Fruit**	**Animals**	**TPW**
T1	49	43	39		59	50	44
T2	21	22	25		20	25	25
T3	19	18	17		10	15	16
T4	11	17	19		11	10	15

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Table 4.8: Comparisons between generated words across 60s in 15s intervals.

	Category					
	Fruits		**Animals**		**TPW**	
Time interval	**Controls**	**MCI**	**Controls**	**MCI**	**Controls**	**MCI**
T1 x T2	0.00	0.00	0.00	0.00	0.00	0.00
T1 x T3	0.00	0.00	0.00	0.00	0.00	0.00
T1 x T4	0.00	0.00	0.00	0.00	0.00	0.00
T2 x T3	1.00	0.02	0.55	0.13	0.08	0.05
T2 x T4	0.12	0.01	0.68	0.01	0.07	0.05
T3 x T4	0.35	1.00	1.00	0.58	1.00	1.00

Shaded boxes represent significant results

4.1.4 Discussion

Both behavioural as well as neuroimaging studies have contributed to the category dissociation debate. The combined findings from previous studies have produced contradicting results which together form an important question that still needs to be addressed: 'Is the living and non-living category specific impairment in AD a genuine dissociation?' Establishing an impairment pattern would be beneficial for the improvement of clinical diagnosis as testing material would be modified to increase the sensitivity of current assessment.

The present study made use of the CFT as a measure of semantic memory. Two living categories (Animals and Fruits) and a non-living category (TPW) were used for testing. The global test scores from a sample of 40 people (21 MCI patients and 19 controls) were used for the first part of the study in which differences between living and non-living items were

investigated. For the second part of the study, the number of words produced per 15s from the same test and sample was taken into consideration. This was done to establish whether spontaneous word production has a temporal gradient and if this changes during the early stages of the disease. In addition, AoA and frequency, two most common word attributes that influence lexical access and noun production in AD, were obtained for the first 5 words produced by each participant. This was done to further explore the effect of lexical properties on the living and non-living categories.

Consistent with previous AD studies on SM functioning, the present findings confirm the degradation of semantic information (K. Forbes-McKay et al., 2013; Vogel, Gade, Stokholm, & Waldemar, 2005). A decline in semantic functioning starts early on in the course of AD (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006) and increases with the disease progression (Hodges & Patterson, 1995; Weiner, Neubecker, Bret, & Hynan, 2008). Patients with AD perform poorly on a number of distinct tests that assess SM but the CFT is regarded as the optimal diagnostic tool to differentiate early AD from healthy ageing (Adlam et al., 2006; Joubert et al., 2010; Murphy, Rich, & Troyer, 2006). With respect to the findings in this study a general worse performance for the MCI group was observed on all three categories when compared to their healthy matched controls. This suggests that all the categories are sensitive to the SM impairment present during the earliest stage of the disease. In support of this claim, patients performed best in the 'TPW' category and yet its total score was still able to differentiate between healthy ageing and early AD. Performance comparison of the three categories showed that the difference between the two types of ageing was mostly pronounced for the living categories with the 'Fruits' category being

more sensitive to the impairment than the 'Animals' category. This confirms that living items are harder to retrieve compared to non-living ones**.**

A disadvantage for living categories is the most reported finding in the literature (Silveri et al., 2002; Zannino et al., 2002) as expected from clinical observations; nonetheless the opposite pattern or no dissociation has also been found in research settings (Hernandez et al., 2008; Sartori et al., 2007). The patterns observed in this study are similar to the former ones in that a different degree of category impairment was present, with lower scores for living categories, but the difference was independent of whether the category is a living or a non-living one. A significant difference was observed between 'fruits' and 'TPW', as well as 'Fruits' and 'animals' but the difference between 'animals' and 'TPW' was not sufficient for significance. The same pattern to a lesser extent was also present in the healthy group.

It has been argued that testing procedures have influenced previous results putting living items at a disadvantage (Montanes et al., 1995; Tippett, Meier, Blackwood, & Diaz-Asper, 2007; Zannino et al., 2007). This study has an advantage over previous research as the CFT eliminates biases such as the disadvantages of line drawings, lack of colour and visual complexity that are present in confrontation naming test. Furthermore, CFT assess residual semantic skills and is purely based on the access and retrieval of words from the mental lexicon. In saying that, different categories contain words with different lexical properties (Silveri et al., 2002).

Psycholinguistics is known to influence the performance of semantic tasks. Both the AoA and frequency values have an effect on noun retrieval and production (Cuetos, Arce, Martinez, & Ellis, 2015; Cuetos et al., 2010; Rodriguez-Ferreiro, Davies, Gonzalez-Nosti,

Barbon, & Cuetos, 2009; Tippett et al., 2007). Hence, the choice of the two word-attributes used for this study. The results established here show that words generated by patients during the early stage of the disease are earlier acquired than the words produced by their matched controls. Early AoA is one of the characteristics of AD speech (K. E. Forbes-McKay et al., 2005; K. M. Sailor, Zimmerman, & Sanders, 2011) which is prominent in the CFT (K. M. Sailor et al., 2011). With regards to frequency of words, patients produced higher frequency words on the 'fruits' and 'TPW' categories while the opposite was observed for the 'animals' category. The differences between the two groups were not significant for neither the AoA nor the frequency. Several explanations could justify this outcome. It might be a bias due to the small sample size (to detect a significant difference with a statistical power of 0.95 a sample size of around 600 individuals would be required) but it could also be due to the fact that during the first 15s it is easier to retrieve information that is of high frequency and earlier AoA even for healthy participants. Additionally, the patient sample consisted of people in the MCI phase, the stage when certain aspects of cognitive functioning are still preserved and therefore results are expected to be similar to that of the healthy sample.

The most interesting results established in this study came from category comparisons for the frequency and AoA values. A large discrepancy for both of the word attributes was present between 'animals' and the other two categories which had similar values. Nouns retrieved from the category 'animals' had higher frequency and earlier AoA. Considering that living categories have words with higher frequency and earlier AoA (Silveri et al., 2002), it is expected that patients perform better on such categories. Yet, this is not the case for most studies including the present one. This suggests that a greater impairment is present for living items compared to non-living ones, but words with high frequency and

early AoA are preserved and easier to retrieve hence, the non-significant results between the total score of 'animals' and 'TPW'.

Temporal gradient of word production is a new technique important for AD diagnosis (Fernaeus et al., 2008). Comparing the two sample groups on each time point suggest that the poorer the performance the more time points with significant differences. While poor performance differs from the beginning of the test (as observed in the 'fruits' category), better performance differs during the second part, or even during the last 15 seconds of the test (as seen in the 'TPW' category). Therefore, the score from the first part of the test cannot replace the total score for all categories, as previously suggested (Venegas & Mansur, 2011).

Looking at the temporal gradient of spontaneous speech from the individual groups seems that vocabulary is time limited since the highest percentage of words were produced during the first 15s for both groups. The same temporal pattern emerged in a study on healthy participants (Venegas & Mansur, 2011). A decline in words produced is observed across time but this was more pronounced for the MCI group. For the proper execution of CFT, multiple cognitive processes and distinct anatomical structures are involved. The first few seconds of the task, during the time point when most words are generated, is mainly dependent on the temporal cortex where semantic information is stored (Binder & Desai, 2011). The rest of the task is dependent on cognitive abilities involved in planning, self-monitoring and adjustment which is associated with the frontal region (Siddiqui, Chatterjee, Kumar, Siddiqui, & Goyal, 2008). From these results it can be concluded that MCI patients who are in the prodromal stage of AD struggle more on the second part of the test than the first part and the difficulty during the second part of the test increases by time since a

difference in time point is observed between almost all the time points. This pattern is not similar to that observed in healthy ageing.

Although care was taken to eliminate any factors that might bias the results some could not be helped which presents some limitations to the study. Matching of patients and controls was ensured but the sample size used was relatively small. The patient group was made up of amnestic and non-amnestic MCI and the rate of conversion from MCI to AD is still unknown. Since different categories may have different characteristics that will impact the storage and retrieval of items and therefore affect the performance on CFT, more categories should be explored. Lexical properties of the full list of words produced by the two groups would be interesting to analyse to explore differences between the first set and second set of produced words.

In conclusion, these findings demonstrate that semantic memory is a good clinical marker for early AD. The three categories used in this study can all be used in clinical settings since they discriminate the two groups, but living items are more sensitive to the earliest stages of the disease. New insight on the living and non-living category debate suggests that the impairment is not solely related to the category type but lexical properties play an important role. Spontaneous speech production is time limited but patients struggle more on the executive functioning part of the test than the actual access of semantic information since they perform worse during the second part of the CFT as seen in the results section Table 4.8.

4.2: CFT performance for differential diagnosis of AD

4.2.1 Introduction

Frontotemporal dementia (FTD) and vascular dementia (VaD) are two common types of dementia often misdiagnosed for AD. FTD is a general term used for diseases that affect mainly the frontal and temporal lobes, two areas also affected early in AD that are responsible for semantic memory and executive functioning, although their involvement is not selective and atrophy is seen more globally in AD. VaD, the second most prevalent age-related dementia, is associated with cognitive decline due to cerebrovascular pathologies (Gorelick et al., 2011). Early signs of VaD commonly go unnoticed and may later be misdiagnosed for AD once cognitive decline gets severe and Alzheimer-type lesions are present. Therapeutic interventions vary from one dementia subtype to another, this makes differential diagnosis highly critical. Studies have highlighted cognitive differences between the aforementioned distinct types of dementia but discriminating between them is still a challenge especially during the early stages. This is due to the overlapping of disease pathologies, phenotypical variations and the similarities in clinical manifestation. An effective diagnostic test pattern able to discriminate the dementia subtypes will allow for a more accurate diagnosis, and hence better prognosis.

There is controversial evidence regarding the degree of differential impairment between FTD and VaD in comparison to AD cognitive profiles, especially when it comes to memory deficits. Similar impairment is expected in the three dementia subtypes due to pathologies affecting similar brain regions underlying performance on specific dementia tests. Language impairment due to SM dysfunction is an early main feature of all three subtypes (Canning, Leach, Stuss, Ngo, & Black, 2004; Laisney et al., 2009; Vuorinen et al.,

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2000; Q. Zhao, Guo, & Hong, 2013). The language impairment observed in VaD is very similar to that in AD. It is reported that VaD are more impaired on SM compared to AD (Graham, Emery, & Hodges, 2004; Matioli & Caramelli, 2010) but this is not always the case (Bentham, Jones, & Hodges, 1997; Crossley, D'Arcy, & Rawson, 1997) and SM tasks might not have high accuracy in differentiating between the two types of dementia (Matioli & Caramelli, 2010).

The SM course of impairment in FTD is also similar to that in AD (Laisney et al., 2009) but the rate of deterioration is thought to be higher in patients with FTD compared with those with AD (Binetti, Locascio, Corkin, Vonsattel, & Growdon, 2000; Rascovsky et al., 2002). Furthermore, word finding problems are presented earlier in FTD than in AD (Binetti et al., 2000). Despite the small differences between FTD and AD, both groups are impaired on confrontation naming with some studies reporting no difference between the performance of the two diagnostic groups (Perri et al., 2012). Similarities and differences in naming performance can be observed when comparing object and action naming where the latter is more challenging to perform. On such tests both subtypes are more impaired on action naming compared to object naming but the difference is more pronounced in FTD (Cappa, Binetti, et al., 1998). Despite the differences reported between the two groups, some literature suggests that the current language tasks and SM memory tests are not sensitive enough to differentiate between the two groups (Diehl & Kurz, 2002; Looi & Sachdev, 1999; Siri et al., 2001).

The CFT is a widely used diagnostic tool due to its power in discriminating dementia from healthy ageing. All the three dementia subtypes are impaired on semantic fluency during the early stages of the disease (Canning et al., 2004; Libon et al., 2009; Q. Zhao et al.,

2013). The most common index used, both for clinical as well as research purposes, is the total score of items generated in 60 seconds. Although this index serves its purposes in detecting dementia, its ability to discriminate between the subtypes is very low. Indeed, most research studies report similar performance both between VaD and AD (Canning et al., 2004; Crossley et al., 1997; Traykov et al., 2005) as well as between FTD and AD (Ramanan, Narayanan, Perpetua D'Souza, Malik, & Ratnavalli, 2015). On the contrary, a differential pattern has also been observed on the performance of the semantic category 'Animals' in a study with a relatively large sample size of patients with FTD and AD. The findings from this study suggest that CFT contributes to the differential diagnosis of the two dementia subtypes (Diehl et al., 2005). A difference between VaD and AD was also reported in one study which compared the number of perseverations. The findings reported higher perseverations for AD compared with VaD (Traykov et al., 2005). A difference in the clustering and switching indices of CFT has also been reported between VaD and AD in a mandarin based study (Q. Zhao et al., 2013).

Research on living and non-living category impairment in VaD and FTD is limited and none of the studies have explored the category specific impairment using the CFT. Furthermore, the few studies on FTD found in the literature focus on a specific group, most commonly the semantic dementia group. A case study with a patient with SD suggests that the category impairment shows an advantage for living things on a naming task (Lambon Ralph, Howard, Nightingale, & Ellis, 1998). This is partially supported by a study that made use of a sorting task where an advantage for 'Fruits' and 'Vegetables' categories was reported compared with animals, tools and kitchenware (Merck et al., 2013). A study with patients with the semantic variant of primary progressive aphasia, another type of FTD,

reported an impairment in natural objects rather than manufactured ones using a judgement test (Libon et al., 2013).

Although studies on the category specific impairment in AD are also limited, vast information is available regarding the topic. SM impairment gets progressively worse with AD severity (Garrard et al., 2001; Hodges & Patterson, 1995), but it is questionable if a shift or a pronounced category specific impairment becomes present during the transition from predementia to the dementia stage. A computational model of the semantic system suggests an early mild disadvantage for non-living concepts which is later replaced by a definite disadvantage for living concepts (Devlin et al., 1998). Both this pattern as well as the reversed pattern has been observed in cross-sectional patient studies (Gonnerman, Andersen, Devlin, Kempler, & Seidenberg, 1997; Montanes, Goldblum, & Boller, 1996), while a longitudinal study by (Garrard et al., 2001) on patients with probable AD found that living items deteriorate at a faster rate and non-living concepts were favoured throughout the four year follow up, although the difference between the two categories was minimal.

CFT might not be the current optimal test for differential diagnosis but considering its diagnostic power and the early disrupted semantic memory present in all three types of dementia it is important to analyse it further and establish a pattern that could separate the three subtypes. The number of words produced in 15s intervals could also present a novel different pattern to the total score. In this study we investigated the difference in performance between the three groups, AD, FTD and VaD. Comparisons between MCI and the other groups were also conducted, primarily to explore the shift from early stages to late stages of AD. This study was mainly designed to establish performance patterns from the three distinct, yet clinically similar, dementia subtypes to facilitate differential diagnosis.

As in the previous sub-chapter (Chapter 4.1), temporal gradient will be analysed for a detailed performance pattern of the three groups. We expect the three dementia subtypes to be impaired on the CFT with the AD and FTD groups performing worse than the other two groups with a more pronounced disadvantage for living items in the AD group and a disadvantage for non-living things in the FTD group.

4.2.2 Methodology

4.2.2.1 Participants

Retrospective data from 74 patients were included in this study. The sample was divided into four groups including, 21 MCI prodromal AD (8 males, 13 females - same participants as those used in chapter 4.1), 23 patients with AD (8 males, 15 females), 13 patients with FTD (6 Males, 7 Females) and 17 patients with VaD (11 males, 6 females). All patients were clinically tested and diagnosed in the Memory and Dementia Clinic at the Royal Hallamshire Hospital in Sheffield. Patients with MCI were experiencing cognitive decline but functional activities of daily living were spared. The clinical criteria proposed by Petersen et al.,(2001) were used to diagnose clinically patients with MCI. Patients in the AD sample group met the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical criteria for probable dementia due to AD (McKhann et al., 2011). The FTD group consisted of a heterogeneous group who met the clinical criteria proposed by the Lund and Manchester group "Clinical and neuropathological criteria for frontotemporal dementia" (The Lund and Manchester Groups, 1994). Patients with VaD met the NINDS-AIREN criteria (Roman et al., 1993).

4.2.2.2 Materials and procedures

The four groups were compared using the same testing material and procedures as in the previous study. Please refer to section 4.1.2.2

4.2.2.3 Statistical analysis

Both parametric and non-parametric tests were used as the homogeneity of variance was violated in some instances and the data were not always normally distributed. Further information on the models used will be provided in the results section. IBM SPSS statistics 22 was used for all analyses.

4.2.3 Results

4.2.3.1 Demographics and clinical variables

Participants were matched for demographics. The mean values and SD of age, YoE and MMSE score is presented in Table 4.9. No significant difference was present for age [$F_{(3,69)}$ = 0.974, p = 0.410], YoE [$F_{(3,69)}$ = 1.947), p = .130], and gender (χ^2 (3, N = 73) = 4.16, p = .245) between groups. A Significant difference was present for the MMSE score (H (3) = 34.15, p = .0.00], MCI > VaD > FTD > AD, with a mean rank of 56.74 for the MCI group, 38.32 for the VaD group, 33.79 for the FTD group, and 19.67 for the AD group. The MCI group (Median = 26.00, IQR = 2) had a significantly higher median score than the AD group (Median = 20.00, IQR = 6), $p < 0.01$, and the FTD group (Median = 21.00, IQR = 10.25), p = 0.016, and the VaD group (Median = 23.00, IQR = 4), p = 0.045. The VaD group had a significantly higher score than the AD group, p = 0.035 but no significant difference was

present between the VaD and FTD groups, p = 1.00. No difference was present for the FTD and AD groups, p = 0.363

Table 4.9: Mean (SD) and p-values for age, YoE and MMSE score of the four groups

	AGE	YoE	MMSE
MCI (n = 21)	66.29 (10.81)	13.05 (2.84)	26.05 (1.32)
AD (n = 23)	65.30 (11.28)	11.48 (2.76)	18.39 (4.34)
FTD (n = 13)	63.00 (11.84)	11.17 (3.16)	21.08 (5.50)
VaD (n = 17)	69.76 (10.49)	13.06 (3.34)	22.71 (3.85)

4.2.3.2 Group and category effects on the total score of words

A two-way analysis of variance was conducted on the influence of group and category on the total score of the CFT with the MMSE score as a covariate. The group variable consisted of the four groups and the category included three levels, 'Animals', 'Fruits' and 'TPW'. The mean values of the total score obtained on each of the three categories for each group is presented in Figure 4.5. Levene's test indicated unequal variances (F = 2.25, p = 0.013) so the square root transformation was used on the data to account for heteroscedasticity. A significant main effect for group was found in the square root of the data [F (3, 206) = 13.32, p < 0.001] indicating a performance difference between the groups. The MCI group (M = 13.92, SD = 4.97) performed significantly better than the VaD (M = 9.98, SD = 4.33), p = 0.004, AD (M = 7.30, SD = 3.27), p < 0.001 and FTD (M = 6.92, SD = 3.68), p = 0.004. VaD performed significantly better than FTD, p = 0.005 but similarly to the AD group (p = 1.00). No significant difference was present between FTD and AD (p = 0.167). A significant main effect for category was also present [F (2, 206 = 21.67, p <0 0.001]. Post hoc Bonferroni comparisons revealed a significant difference between Animals (M = 10.16, S.D = 4.82) and

Fruits (M= 7.55, S.D = 3.48), $p < 0.001$, and TPW (M = 11.59, S.D = 5.67) and Fruits ($p < 0.001$), but no significant difference was present for Animals and TPW ($p = 0.077$). The interaction effect between group and category was not significant [F (6, 206) = 0.681, p = 0.665].
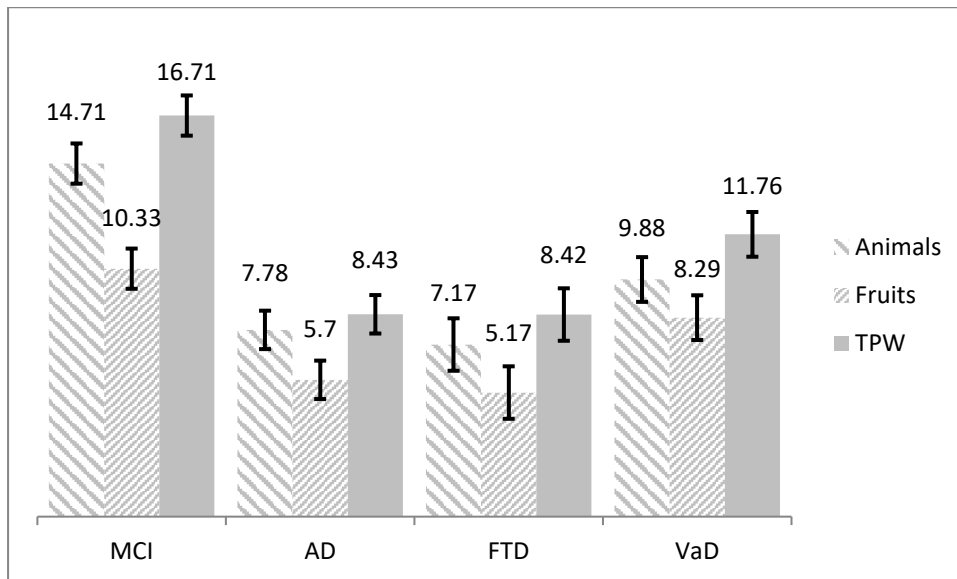
Figure 4.5: A bar graph comparing the groups' mean values (S.E bars) of the total scores for each category

A general linear model with MMSE as a covariate was carried out to explore the impact of different categories on the different groups and their performance. The means of each group on the three categories are presented in Figure 4.5. A statistically significant difference between groups based on category was present [F (9,160) = 2.64, $p = 0.007$, Wilk's $\lambda = 0.715$, partial $\eta^2 = 0.106$]. Given the significance of the overall test the univariate main effects were examined. A significant difference between the groups was present for the Animals category [F (3, 68) = 6.24, $p = 0.001$]. Bonferroni comparisons revealed a significant difference between the MCI group and FTD ($p = 0.001$), AD ($p = 0.017$), and VaD

(*p* = 0.023). No statistical difference was present between the subtypes of dementia. A main

effect was also present for the fruit category [F (3, 68) = 4.47, *p* = 0.006]. A significant

difference was only present for the MCI group and the FTD group (*p* = 0.004). A significant

main effect was also present for the TPW category [F (3, 68) = 5.08, *p* = 0.003] with post hoc

Bonferroni comparisons revealing a significant performance difference between MCI and

FTD (*p* = 0.003) and MCI and AD (*p* = 0.018). The *p* – values for each pairwise Bonferroni

comparison are summarized in Table 4.10.

Table 4.10: The *p* – values from Bonferroni post hoc comparisons between groups for each category

Groups	Categories		
	Animals	**Fruits**	**TPW**
MCI – AD	0.02	0.16	0.02
MCI – FTD	0.00	0.00	0.00
MCI – VaD	0.02	1.00	0.11
FTD – AD	1.00	0.93	1.00
FTD – VaD	0.72	0.06	0.63
AD – VaD	1.00	1.00	1.00

*Shaded cells present significant values

4.2.3.3 Time point differences within group

A repeated measures MANOVA was carried out to compare the effect of time on

performance during the 60s split in 15s quartiles (T1, T2, T3, T4). The mean values and SD

are summarised in Table 4.11 and Figure 4.6. The mean number of words generated by the

MCI group on the Animals category was highest during T1 (M = 7.29, SD = 1.71) followed by

a large decline in T2 (M = 3.67, SD = 2.48), and similar performance in T3 (M = 2.24, SD = 1.45) and T4 (M = 1.52, SD = 1.33). A significant difference of time was present for this category [F (3, 60) = 57.98, $p < 0.001$]. A difference was revealed between the first 15s and the rest of the time [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. A difference between mid-test and the end of the 60s was also present [T2 and T4 ($p = 0.007$)]. P – values of each pairwise Bonferroni comparison are displayed in Table 4.12. The highest score for the Fruits category was achieved in T1 (M= 6.14, SD = 1.71) and similar performance was observed in T2 (M = 2.05, SD = 1.12), T3 (M= 1.05, SD = 1.28) and T4 (M = 1.10, SD = 1.09). A significant difference of time was present for the performance on the Fruits category [F (3, 60) = 82.16, $p < 0.001$] with a statistical difference observed between all points except for the last 30s [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$), T2 and T3 ($p = 0.02$), T2 and T4 ($p = 0.013$). The performance pattern of the MCI group on TPW category was similar to the other two categories with the highest score observed in T1 (M = 7.33, SD = 2.08), followed by T2 (M = 4.14, SD = 2.35) T3, (M = 2.71, SD = 1.55) and T4 (M = 2.52, SD = 1.97). A significant effect of time on performance was present for TPW category [F (3, 60) = 31.84, $p < 0.001$]. A statistical significance was observed during all time points except between T3 and T4 [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$), T2 and T3 ($p = 0.045$), T2 and T4 ($p = 0.046$).
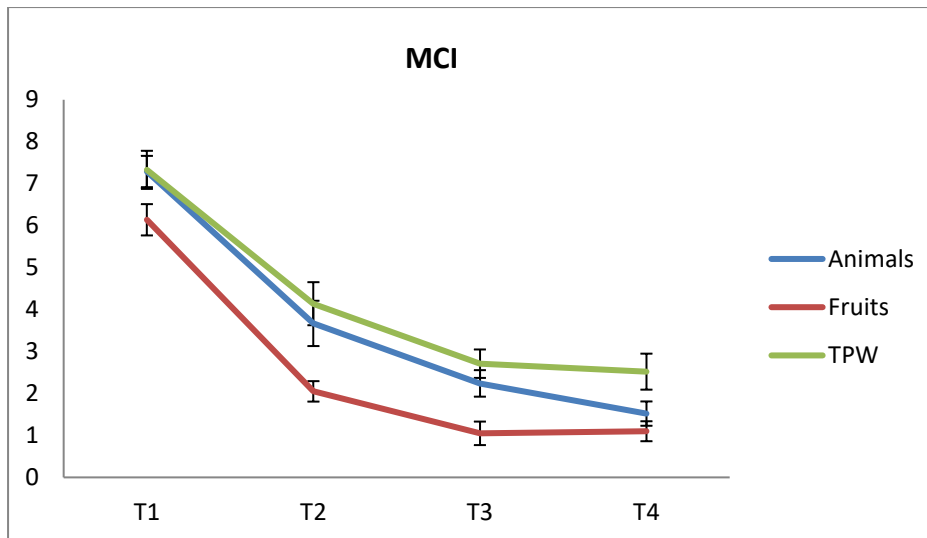
Figure 4.6 Bar line representing the mean values (SE bars) of the MCI group obtained during the test at 15s intervals.

The mean number of words generated by the AD group on the animal category was highest during T1 (M = 3.83, SD = 1.59) followed by T2 (M = 1.52, SD = 1.24) while exhibiting similar values in T3 (M = 1.22, SD = 1.09) and T4 (M = 1.22, SD = 1.38). The mean values and SD are summarised in Table 4.11 and Figure 4.7. An overall effect of time on performance was present [F (3, 66) = 22.40, $p < 0.001$], but the only significant difference between time points was present between the first 15s and all the other time points [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. All p – values are summarized in Table A (please refer to appendix). The amount of words generated on the Fruits category was less than those generated in the Animals category but the pattern was similar. T1 (M = 3.91, SD = 1.38) had the highest number of word production. T2 (M = 0.78, SD = 0.80), T3 (M = 0.65, SD = 0.94) and T4 (M = 0.35, SD = 0.65) had similar low production of words. An overall effect of time was also significant for the Fruits category. The assumption of sphericity was violated, $\chi2(5)$ = .526, p - 0.21, therefore degrees of freedom were corrected using Greenhouse-

Geisser ($\varepsilon = 0.705$) [$F_{(2.12, 46.55)} = 83.84$, $p < 0.001$]. Bonferroni comparisons revealed a significant difference between T1 and the three other quartiles [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. The mean number of words produced on the TPW category was similar to those produced on the Animals category, T1 (M = 4.43, SD = 2.19), T2 (M = 1.83, SD = 1.34), T3 (M = 1.00, SD = 0.85) and T4 (M = 1.17, SD = 1.27). An overall effect of time on performance was present [$F_{(3, 66)} = 31.93$, $p - 0.000$]. A significant difference was observed between the first quartile and the rest [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)].
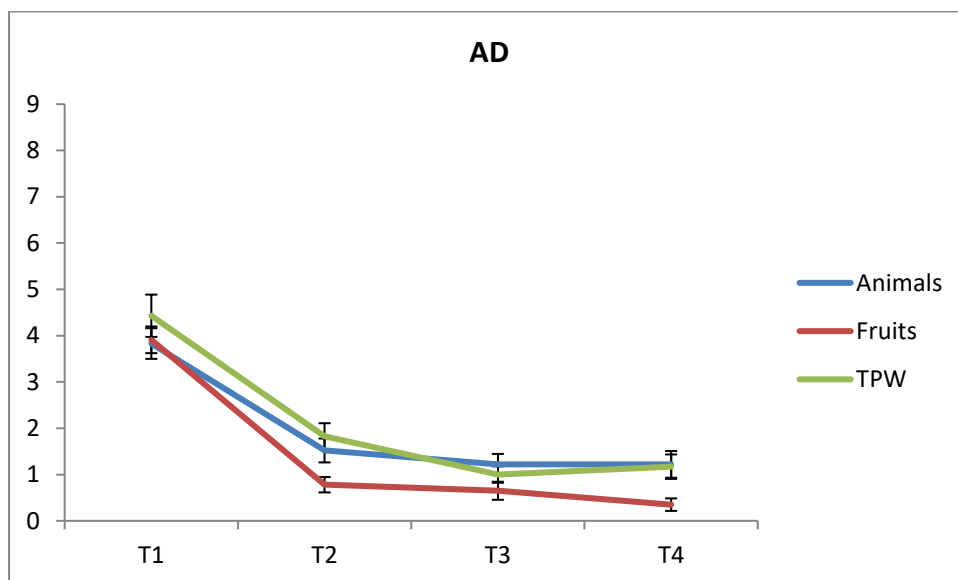
Figure 4.7 Bar line representing the mean values (SE bars) of the AD group obtained during the test at 15s intervals.

The mean number of words on the Animals category from the FTD group is presented in Figure 4.8. Most of the words were produced during T1 (M=4.08, SD = 1.38). A similar number of words was produced in the remaining time points T2 (M= 1.17, SD = 1.19), T3 (M= 0.92, SD = 1.00) and T4 (M=1.00, SD = 1.04). A significant effect of time was observed

for this category [$F_{(3, 33)} = 34.29$, $p < 0.001$]. Post hoc analysis revealed a significant difference between T1 and the three other quartiles [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. No other significant differences were present. All p-values from the post hoc Bonferroni comparisons are summarized in Table A (Please refer to Appendix). Fewer words were produced for the Fruits category with a mean of less than 1 word produced during the last 30s; T1 (M = 3.67, SD = 1.88), T2 (M = 1.08, SD = 0.669), T3 (M= 0.17, SD = 0.112) and T4 (M = 0.25, SD = 0.452). The Mauchly's test indicated that the assumption of sphericity had been violated $\chi^2(5) = .106$, $p = 0.001$, hence the degrees of freedom were corrected using Green-Geisser estimates of sphericity ($\varepsilon = 0.481$). The results show that performance was significantly affected by the temporal gradient [$F_{(1.442, 15.86)} = 29.39$, $p < 0.001$]. Post hoc Bonferroni comparisons showed a significant difference between T1 and the rest of the time points [T1 and T2 ($p = 0.002$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)] as well as T2 and T3 ($p = 0.028$). The remainder of the time points did not significantly differ and results are presented in Table A (Please refer to Appendix). For the TPW category, FTD patients performed best during T1 (M = 3.75, SD = 1.96), while the performance for T2 (M = 1.50, SD = 1.45), T3 (M = 1.42, SD = 1.24) and T4 (M = 1.75, SD = 1.49) was similar. Assumption of sphericity was violated $\chi^2(5) = .153$, $p = 0.003$, therefore the degrees of freedom were corrected using Green-Geisser estimates of sphericity ($\varepsilon = 0.568$). Results showed an overall impact of time on performance [$F_{(1.71, 18.75)} = 10.16$, $p = 0.002$], but pairwise Bonferroni comparisons revealed that the only significant difference was between T1 and T2 ($p < 0.001$) and T1 and T3 ($p = 0.006$).
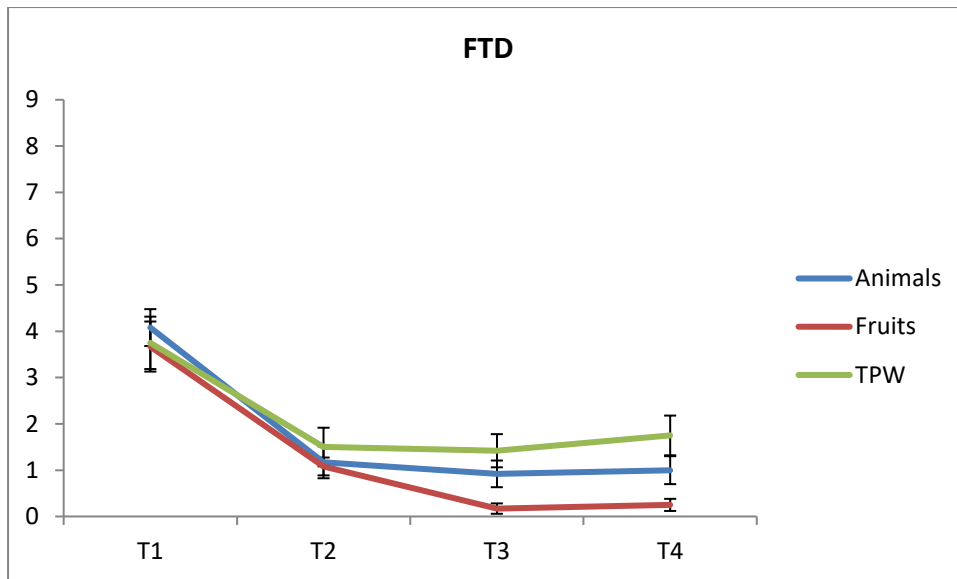
Figure 4.8: Bar line representing the mean values (SE bars) of the FTD group obtained during the test at 15s intervals.

The mean values of the words generated by the VaD group on the three categories are presented in Figure 4.9 and summarised in Table 4.11. For the Animals category, the highest number of words was generated in T1 (M = 5.06, SD = 2.36). This was followed by T2 (M = 2.12, SD = 1.58) with similar mean numbers presented in T3 (M = 1.12, SD = 1.17) and T4 (M = 1.59, SD = 1.70). An overall significant difference was observed in this category [$F_{(3, 48)}$ = 21.01, $p < 0.001$]. Bonferroni post hoc analysis revealed a statistical difference between T1 and the other three quartiles [T1 and T2 ($p = 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. The remainder of the pairwise's p – values are presented in Table A (please refer to Appendix). The number of words generated in T1 (M = 5.00, SD = 1.77) on the fruits category is much higher than the number generated during T2 (M = 1.53, SD = 1.13), T3 (M = 1.00, SD = 0.935) and T4 (M = 0.76, SD = 1.20). The assumption of sphericity was violated $\chi^2(5) = .381$, $p = 0.015$. This was corrected using Green-Geisser estimates of sphericity ($\varepsilon = 0.629$). Results revealed a significant impact of time on performance [$F_{(1.89, 30.21)}$ = 49.52, $p < 0.001$] with a significant difference between the first 15s and the remainder of

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the test time [T1 and T2 ($p < 0.001$), T1 and T3 ($p = < 0.001$), T1 and T4 ($p = 0.000$)] and T2 and T4 ($p = 0.018$)]. The remainder of the p-values are presented in Table A (please refer to Appendix). The VaD group generated the biggest number of words on the TPW category; T1 (M = 5.76, SD = 1.89), T2 (M =2.53, SD = 1.63), T3 (M = 2.06, SD = 1.64) and T4 (M = 1.41, SD = 1.28). Performance of TPW was affected by time [F (3, 48) = 39.99, $p < 0.001$], with significant differences present between T1 and the rest of the time points [T1 and T2 ($p < 0.001$), T1 and T3 ($p < 0.001$), T1 and T4 ($p < 0.001$)]. The remainder of the p – values are presented in Table A (please refer to Appendix).
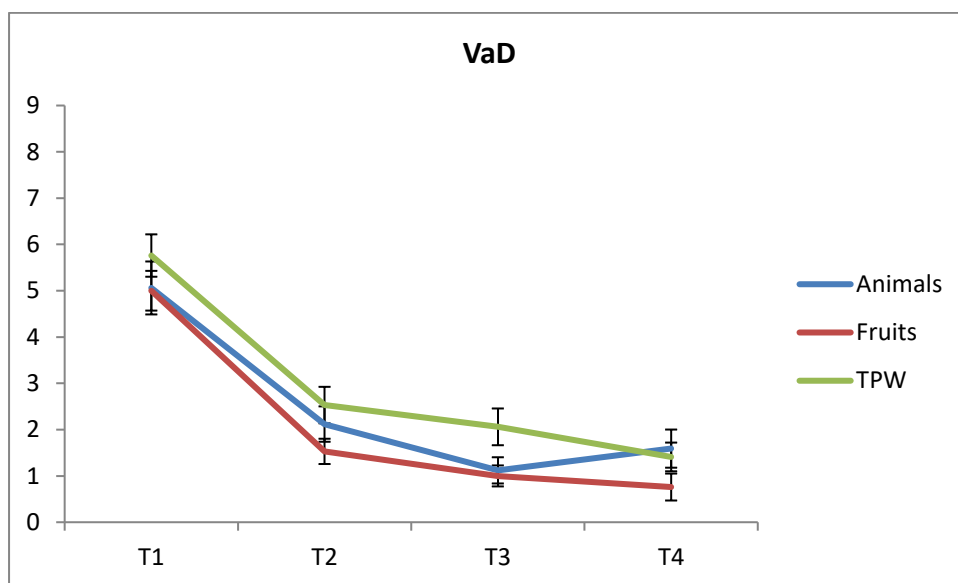
Figure 4.9 Bar line representing the mean values (SE bars) of the VaD group obtained during the test at 15s intervals.

Table 4.11: Mean values and SD for the number of words generated per 15s by each group on the three categories: (A) Animals (B) Fruits (C) TPW.

(A) Animals	MCI	AD	FTD	VaD
T1	7.29 (1.71)	3.82 (1.59)	4.08 (1.38)	5.06 (2.36)
T2	3.67 (2.48)	1.52 (1.24)	1.17 (1.19)	2.12 (1.58)
T3	2.24 (1.45)	1.22 (1.09)	0.92 (1.00)	1.12 (1.17)
T4	1.52 (1.33)	1.22 (1.38)	1.00 (1.04)	1.59 (1.70)

(B) Fruits	MCI	AD	FTD	VaD
T1	6.14 (1.71)	3.91 (1.38)	3.67 (1.88)	5.00 (1.77)
T2	2.05 (1.12)	0.78 (0.80)	1.08 (0.67)	1.53 (1.13)
T3	1.05 (1.28)	0.65 (0.94)	0.17 (0.389)	1.00 (0.94)
T4	1.10 (1.09)	0.35 (0.65)	0.25 (0.45)	0.76 (1.20)

(C) TPW	MCI	AD	FTD	VaD
T1	7.33 (2.08)	4.43 (2.19)	3.75 (1.96)	5.76 (1.89)
T2	4.14 (2.35)	1.83 (1.34)	1.50 (1.45)	2.53 (1.63)
T3	2.71 (1.55)	1.00 (0.85)	1.42 (1.24)	2.06 (1.64)
T4	2.52 (1.97)	1.17 (1.27)	1.75 (1.49)	1.41 (1.28)

4.2.3.4 Group differences in generated words across time

Rank analysis of covariance was carried out to analyse the difference in performance

between groups during 15s interval (T1, T2, T3, T4). This model was used since most of the

ANCOVA assumptions were violated. And the mean number of words produced by each group is summarised in Table 4.11. A statistically significant difference between groups was found for T1 on the animal category [$F_{(3,69)}$ = 7.935, $p < 0.001$]. Bonferroni post hoc tests revealed that the MCI group produced more words than AD ($p = 0.001$), and FTD ($p < 0.001$). *P* – values are shown in Table 4.12. An overall significant difference was also present for T2 in the same category [$F_{(3,69)}$ = 5.39, $p = 0.002$], but a significant difference was only detected between MCI and FTD ($p = 0.005$) and AD and FTD ($p = 0.029$). All the *p* – values are presented in Table 4.12. A borderline significant difference was found for T3 [$F_{(3,69)}$ = 2.77, $p = 0.048$], but post hoc Bonferroni analysis revealed no significant differences between either of the group pairs. *P* – values are summarized in Table 4.12. No significant difference was observed for T4 [$F_{(3,69)}$ = 0.808, $p = 0.0494$]. Performance was similar for all the groups during the four quartiles and no significant differences between groups were observed for the fruits category, T1 [$F_{(3,69)}$ = 2.01, $p = 0.121$], T2 [$F_{(3,69)}$ = 1.14, $p = 0.340$], T3 [$F_{(3,69)}$ = 2.453, $p = 0.071$] and T4 [$F_{(3,69)}$ = 0.74, $p = 0.534$]. Same as in the Fruits category the performance for TPW was similar for all the groups. The only overall significant difference was observed on T1 [$F_{(3,69)}$ = 2.820, $p = 0.045$], but Bonferroni post hoc test revealed that none of the pairwise comparisons reached significance level. No significant difference between groups was observed in T2 [$F_{(3,69)}$ = 2.39, $p = 0.076$], T3 [$F_{(3,69)}$ = 0.767, $p = 0.517$] and T4 [$F_{(3,69)}$ = 0.584, $p = 0.627$]. All *p*-values are presented in Table 4.12.

Table 4.12: *p*-values for group comparison using Bonferroni post hoc analysis for (A) Animals, (B) Fruits and (C) TPW. Shaded cells represent significant values.

(A) Animal Category	T1	T2	T3	T4
MCI - AD	0.00	1.00	0.69	1.00
MCI - FTD	0.00	0.01	0.11	1.00
MCI - VaD	0.06	0.06	0.12	1.00
FTD - AD	1.00	0.03	1.00	1.00
FTD - VaD	0.45	1.00	1.00	1.00
AD - VaD	1.00	0.35	1.00	1.00

(B) Fruit Category	T1	T2	T3	T4
MCI - AD	1.00	0.64	0.88	0.85
MCI - FTD	0.16	1.00	0.37	0.50
MCI - VaD	1.00	1.00	0.60	0.97
FTD - AD	0.27	1.00	0.06	0.82
FTD - VaD	0.29	1.00	0.02	0.73
AD - VaD	1.00	1.00	0.94	0.99

(C) TPW Category	T1	T2	T3	T4
MCI - AD	1.00	1.00	1.00	1.00
MCI - FTD	0.06	0.06	1.00	1.00
MCI - VaD	1.00	1.00	1.00	1.00
FTD - AD	0.11	0.45	1.00	1.00
FTD - VaD	0.11	0.44	1.00	1.00
AD - VaD	1.00	1.00	1.00	1.00

Shaded cells represent significant differences

4.2.4 Discussion

SM impairment is a prominent feature of preclinical AD, making it critical for the early diagnosis of the disease, but differential diagnosis through this cognitive dysfunction is a challenge since it is not exclusive to AD. This study aimed to look at shifting patterns from early to late stages of AD and attempted to establish a discriminating pattern between the three most prevalent dementia subtypes, AD, FTD and VaD, using the CFT. The total scores from two living categories (Animals and Fruits) and one non-living category (TPW) were analysed. In addition, the number of words generated per 15s within and between groups were also analysed to investigate the temporal gradient of impaired SM.

The findings from this research study confirm the progressive deterioration from the early stages (MCI) to the late stages (AD) of the disease documented in previous studies (Hodges & Patterson, 1995; Weiner et al., 2008). An overall difference in the total score on all categories is observed between the MCI and the AD stage. The pattern of living and non-living dissociation is qualitatively similar in the two groups with higher scores recorded for the MCI group. Consistent with a longitudinal study that explored the living and non-living dissociation in AD (Garrard et al., 2001), this study established that patients perform better on non-living categories but the difference does not always reach significance level (as observed in Animals and TPW). This is true for both the MCI as well as the AD groups. These results are in accordance with evidence from neuroimaging studies which suggest a segregated neural system with living items depending on the temporal neocortical areas (Devlin et al., 2002; Gainotti, 2000; Grossman et al., 2003; Moore & Price, 1999) and the non-living items associated with the posterolateral temporal, lateral frontal and prefrontal areas (Cappa, Perani, et al., 1998; Damasio et al., 1996; Grossman et al., 2003). Additionally,

this study also suggests that a performance difference could also exist for two categories of the same type (as observed between Animals and Fruits). This could be hypothetically explained using the psycholinguistics data from the previous chapter and other studies suggesting that AD patients have good compensatory mechanisms for the category Animals (Grossman et al., 2003) compared to the Fruits category.

Despite that patients in the MCI group generated more words on all categories compared to those in the AD group, a significant difference was only present for the Animals and TPW categories. In contrast, the Fruits category did not differentiate the two groups. This implies that this category deteriorates quicker than the other two categories, hence, it is more sensitive to the degradation of SM caused by AD pathology. Indeed, considering its sensitivity to SM impairment this study supports the use of the Fruits category in research and clinical settings to identify people at risk of converting from the MCI stage to clinical AD.

As expected an overall better performance from the MCI group was observed when compared to FTD and VaD groups. The performance comparison between the groups on the total scores of the three distinct categories gives insight regarding the degradation of semantic information belonging to different categories. All three categories differentiate MCI from FTD, but MCI and VaD are only differentiated by the Animals category. This implies that while FTD seems to be more impaired on all categories compared to the other groups, VaD is impaired on the Animals and Fruits categories while TPW category is more preserved than that observed in the other groups. In saying that, although VaD performed better than AD, the difference was not sufficient to reach significance level. The similarity in performance observed in this study for VaD and AD is comparable to other studies (Bentham et al., 1997; Crossley et al., 1997), but different from other studies that report a

better performance for VaD compared to AD (Graham et al., 2004). An overall difference between the performance of VaD and FTD was observed, but this was not reflected on individual categories. New tasks assessing SM are required to improve the efficiency of differential diagnosis as the current tests are not sufficient (Matioli & Caramelli, 2010).

The data were further analysed for the temporal gradient pattern of CFT performance present in the dementia subtypes. In all the groups, word production decreases and becomes more effortful over time. This had been previously observed in both healthy and patients with mild impairments (Fernaeus et al., 2008; Raboutet et al., 2010; Weakley, Schmitter-Edgecombe, & Anderson, 2013). Analysing individual groups, a different pattern of temporal gradient was observed between the MCI group and the groups of dementia. While the MCI group showed a significant difference between almost all time points except for the last few seconds, the three other groups showed a difference between the first 15s and the remainder of the 60s. The highest number of words were produced during the first 15s followed by a large decline after the 15s which remained constant for the remaining 45s.

A dynamical model of word production for the CFT was proposed by Raboutet et al., (2010). This model suggests that both automatic as well as controlled retrieval processes are required during the initial stages of the test. This means that both semantic processing as well as executive functioning are necessary for a high quality performance. With time, word production becomes more challenging and limits the processes that are dependent on the executive component. In the light of this model, the present results may hint towards a more disrupted executive functioning in patients with MCI and a disruption in both executive and semantic functioning in the three dementia subtype. In the light of this

model, the present results may hint towards a more disrupted executive functioning in patients with MCI and a disruption in both executive and semantic functioning in the three dementia subtype.

Group comparisons on 15s time points provide minimal relevant information with regards to differential diagnosis. This is expected when a small number of words are produced. Differences were only observed in the Animals category between MCI and AD during the first 15s suggesting a greater semantic impairment between the two stages of the disease, and between MCI and FTD during the first 30s which is expected considering the overall fewer production of words by the FTD compared to MCI. A difference was also observed between the AD and FTD groups during the second 15s quartile. This could either imply that SM impairment is worse for FTD than AD mid-point through the test, or could simply be an artefact.

The power of findings in this study might be affected by the small sample size. More significant differences could emerge with a larger sample size which could be useful in discriminating between the different types of dementia. An additional limitation of this study is the heterogeneous nature of the groups. Despite that all the sub-groups of FTD and VaD experience SM problems some sub-groups might have greater impairments than others biasing the results.

In conclusion, these results confirm that SM dysfunction gets worse with disease progression which is sufficient to differentiate MCI from AD. Out of the three categories used in this study, the Fruits category is the most sensitive to the deterioration of SM in AD making it useful in detecting people at risk of converting from MCI to AD. Furthermore, the results confirm that SM impairment is also a clinical feature of FTD and VaD which is

reflected on the CFT, especially on the living categories. Although the CFT is a powerful diagnostic tool in dementia diagnosis, it lacks power in differentiating between dementia subtypes.

4.3 Conclusions

This study confirms a progressive degradation of SM present for both living and non-living categories but this is more pronounced for the living category of Fruits. A better compensatory mechanism might be present for the category Animals which might mask the difference between Animals and TPW categories. An explanation for the lack of difference between these two categories could be due to the word attributes of the items belonging to each category. The Animals category contains words with higher frequency and earlier AoA compared to the Fruits and TPW categories.

Clearly, categories vary in their word features and this has an effect on the sensitivity of the category in dementia in general. This makes further research on different categories necessary. In addition to the living and non-living categories, mixed ones should also be analysed. The current notion is that the Fruits category is more sensitive to SM impairment and might be good practise to use this category in short dementia tests which are being administered both in clinical as well as in research settings.

It can be concluded that the temporal gradient of word production is a relatively new technique which provides relevant information regarding the nature of SM impairment. Vocabulary is time limited and word generation becomes less and more effortful across the 60s of the CFT. These findings imply that the initial problem during the early stages of the disease is a dysfunction in retrieval of semantic knowledge. An additional problem of loss of

semantic knowledge is present later on as the disease progresses. The temporal gradient in all dementia subtypes is characterised by both a loss of semantic knowledge as well as difficulties with retrieval of semantic information.

Overall, the CFT is reliable in discriminating between both healthy and mild impairment, and between mild impairment and dementia, but further research and improvement on the CFT is required to increase its effectiveness in differentiating between the dementia subtypes.

Chapter 5:

The automatic and executive functioning of semantic memory

5.0 The nature of SM impairment in AD

Detailed neuropsychological testing is currently the most appropriate approach to reach an accurate diagnosis of Alzheimer's disease (AD) in clinical settings. Although clinical testing is reported to be less sensitive than biological markers, it is thought that neuropathological alterations are accompanied by subtle changes in cognitive processes that could be detected by highly sensitive clinical tests. Such tests can be developed once a good understanding of the earliest symptoms of this disease is reached and of how these relate to neuroanatomical changes. A thorough understanding of the association between pathology and resulting cognitive deficit in the early stages of the disease would help refining assessment methods so that these might have the necessary sensitivity to detect even the slightest alteration. The early stage of AD is now referred to as preclinical AD, that is, the phase during which an unhealthy brain presents biological changes without any clinical symptoms (Jack et al., 2011). This view could change if clinical tests can overcome any compensation that the neural system undergoes to cope with the neuropathological changes and have the ability to detect subtle cognitive dysfunction.

Semantic memory (SM) dysfunction is an early impairment that serves as a good clinical marker in AD. Recent research suggests that SM deficits are present decades before the clinical diagnosis of AD (Cuetos et al., 2007; Garrard et al., 2005; Le et al., 2011; D. A. Snowdon et al., 2000). The problem is that current tests are not sufficiently sensitive to detect such early subtle changes in this type of memory. There are some questions that still need to be addressed in order to understand the nature of SM impairment. One of the main questions is regarding the functioning of SM. SM is made up of two components (Binder et al., 2009; Whitney et al., 2011), semantic representation (automatic component) and semantic control (executive component). The first component refers to the storage of

semantic information while the second part represents the access and retrieval of information (a detailed description of SM and semantic cognition is reviewed in chapter 2, please see sub-section 2.6). The question that could aid in early diagnosis is whether the impairment observed in patients with AD is due to a deficit in semantic control or to a loss of semantic knowledge. Deficits in SM are reflected in the language system (please refer to chapter 2); hence, a possible way to answer the question on the nature of AD related impairments is by using language tasks that can differentiate the executive and automatic components of SM.

A common view is that a degraded semantic store is the underlying cause of impairment in AD, even during the early stages of the disease (Hodges & Patterson, 1995). One of the early studies supporting the theory of a degraded semantic store based their findings on three notions; patients are more impaired on less familiar items, superordinate knowledge is still preserved, and there are item-by-item consistent errors (Hodges et al., 1992). Item-by-item consistency, the usage of the same stimuli across different tasks, is a commonly used methodology to attempt to clarify the mechanism breakdown behind SM impairment in AD (Hodges et al., 1992; Mardh et al., 2013). Consistent errors for the same stimuli presented on different tests suggest that the impairment is due to loss of semantic knowledge rather than difficulties with the access and retrieval processes. In-depth studies regarding the breakdown of the semantic system report that some aspects of knowledge are more impaired than others (Hornberger, Bell, Graham, & Rogers, 2009). Knowledge about physical attributes and sensory features of a concept is important information for the naming of an item (Garrard et al., 2005). Such information is degraded earlier on during the disease progression (Garrard et al., 2005; Kirchberg et al., 2012). Furthermore, semantic

information of distinctive features is more impaired than shared features (Garrard et al., 2005) making it more vulnerable to insidious disease pathology.

The possibility that the deficits detected in early AD may reflect more than a degraded semantic system has also been implied. Both old and recent studies have suggested that the SM impairment is an access/retrieval problem rather than loss of information (Arroyo-Anllo et al., 2011; Lipinska & Backman, 1996; Nebes et al., 1984). Despite that the impairment could be due to an overall deficit in accessing semantic information, an impairment in storage of information cannot be completely ruled out (Laatu, Portin, Revonsuo, Tuisku, & Rinne, 1997). In a study by Duong and colleagues (2006) patients at the early stage of the disease were only impaired on tasks that required semantic control while patients with greater disease severity were impaired on tasks that made use of both semantic control as well as semantic representation.

From the previous literature in AD it can be concluded that the deficits presented by a dysfunctional SM requires further research. The mixed results might be due to the different tasks and stimuli used. Despite that item-by-item consistency is a sound procedure, it does not eliminate the fact that some words are harder to access and retrieve due to their storage properties, regardless of the modality of access. This chapter deals with the cognitive and anatomical correlates associated with SM both in healthy as well as in people with cognitive impairment. This is currently an active area in the field of early AD due to the possibility of SM being used as an early clinical marker. Most of the available tests have been developed a long time ago and some are established to detect deficits in other diseases rather than those leading to AD dementia making them less sensitive than desirable for their usage in dementia clinics. These tests require updating and improvement

for the early stages of AD. The purpose of this chapter is, therefore, twofold: it addresses the question regarding the underlying cause of impairment in SM in AD, and it will propose tests with increased sensitivity to the early impairment present in the preclinical stage of this disease.

Study 5.1 Modifying and devising novel language tasks

5.1.1 Introduction

AD research on clinical diagnosis has focused on memory assessments since memory decline is the most prominent symptom in AD. While early research targeted episodic memory (EM), current studies are shifting towards tests assessing SM (Venneri et al., 2016). The assessment of EM offers diagnostic utility but it lacks sensitivity as similar decline is present in healthy adults. SM functioning in people at risk of developing AD goes through subtle changes that can be differed from those presented in healthy ageing. Hence, understanding the nature of impairment of SM would be beneficial for the earlier diagnosis of AD. The current SM tests used routinely in clinical practise are amongst the optimal tests that have the ability to identify patients in the MCI stage but they are not accurate enough to detect the subtle differences between early AD and normal ageing and are not sufficiently informative about the performance of the two different components of SM. In order to deal with the lack of information and diagnosis we propose a few modified and novel language tests.

Subtle cognitive decline is experienced in daily activities before abnormal scores are presented on clinical tests. These changes do not affect everyday life and are well within the current cut-off scores for normal cognitive functioning, but if well understood and assessed they could be used for earlier detection. The pathological hallmark of AD, the presence of cortical NFT, is initiated in the medial perirhinal cortex (E. Braak et al., 1999) which is the region associated with SM (Didic et al., 2011). It is therefore assumed that SM changes should be detectable around the same time that neurofibrillary tangles (NFT) accumulate in

the perirhinal area, provided that sensitive tests are available. Indeed, a change in semantic measures is associated with medial perirhinal cortex thickness as early as 12 years before the onset of the disease and this gets worse closer to the clinical diagnosis of the disease (dementia stage) (Hirni et al., 2016). This association supports the importance of SM tests as potential diagnostic markers with high ability to distinguish people at risk of developing the disease and healthy individuals.

The motoric aspect of language is well preserved (K. Forbes-McKay et al., 2013) which makes it a good tool to track cognitive impairment (Biundo et al., 2011; Venneri et al., 2011). The two most common linguistic tests used to assess SM in AD are the confrontation naming test (CNT), i.e. the naming of visually presented stimuli, and the category fluency task (CFT), i.e. the generation of words belonging to a semantic category. A common measure of the CNT is the Boston naming test (BNT) produced in 1983 (Kaplan, Goodglass, & Weintraub, 1983) for people with aphasia after stroke. Due to the word finding problems that patients with AD exhibit (Reilly, Peelle, Antonucci, & Grossman, 2011), the BNT, which is made up of 60 black and white line drawings, or a short version of it, is routinely used for AD diagnosis. People with severe neural damage perform badly on the BNT and have difficulties with naming even the easiest stimuli presented (Silagi, Bertolucci, & Ortiz, 2015). The BNT score of patients with moderate to advanced AD pathology can be distinguished from healthy individuals but this is not the case for patients during the early stage of the disease (Katsumata et al., 2015; Testa et al., 2004).

The CFT is the semantic fluency part of the verbal fluency test. This test was initially used for patients with brain injury to assess speed of verbal production and the organisation of one's thinking. CFT makes use of different areas of the brain (Baldo & Shimamura, 1998;

Henry & Crawford, 2004) and it is known for its sensitivity to the earliest effects of AD (Venneri et al., 2011; Venneri et al., 2008) and its accuracy in detecting early AD (Clark et al., 2009). The most common category used in this test is 'Animals' followed by 'fruits' and 'cities'. Other categories are sometimes used for research purposes. Same as the CNT, the CFT is useful in discriminating AD from healthy ageing and sometimes it also detects very mild dementia (Gomez & White, 2006) although demographic variables, especially education, have an impact on CFT performance which might reduce the sensitivity of the test (Kawano et al., 2010).

The lack of sensitivity for early diagnosis is a major limitation for both tests. Originally these tests were not designed for the diagnostic use of Alzheimer's disease and additionally, society's educational level has increased since the introduction of these tests (Eurostat). High education levels have the tendency to mask clinical deficits presented during early AD when cognitive functioning is only mildly effected by the disease (Vadikolias et al., 2012). Recent research has also suggested that subtle cognitive impairment in language due to semantic memory is present decades before the onset of the disease (Albert et al., 2014; Wilson et al., 2012). Hence, novel tests have to be conceived having people with higher education as the target and earlier stages of the disease.

This study has two purposes: the main aim is to modify and devise new tests that can aid in answering the question regarding the impairment of SM and improve the assessment of executive and automatic functioning in early AD; and the second aim is to provide clinical tests that are more sensitive than the current ones that could aid in detecting the disease at an earlier stage than possible at present. Overall, this will help the establishment of the type

of impairment present in early AD and whether this is different from healthy ageing and other neurodegenerative diseases.

5.1.2 Methodology

5.1.2.1 Procedure

Devising the final battery of tests involved two parts, a qualitative and a quantitative part. Initially the stimuli were discussed with a small number of people who helped in eliminating stimuli that were misinterpreted, too difficult or ambiguous. The second part consisted of a pilot study of 64 healthy volunteers aged between 20 and 90 years with a mean age of 60.72 (S.D = 16.94, Range 20-90) and mean YoE of 15.69 years (S.D = 2.63, Range 10 – 22) who completed the whole set of tests. Screening for intact mental status was confirmed by the performance on the mini mental state examination (MMSE) and the Raven Coloured Progressive Matrices. The testing consisted of two sessions held at least one week apart to avoid practise effect. Test order was organised so that half of the group did the first part of the testing in the first session and the other half did the second part of the testing in the first session. The results from this pilot study were used to form the final battery of tests which can be found in the Appendix. Research approval was given by the Medical School Ethics of the University of Sheffield and all participants gave informed consent.

5.1.2.2 Modified CFT

Eighteen different categories were used for the modified CFT (Figure 5.1). Eight of the categories belonged to the living class, 6 belonged to the non-living class and 4 were mixed. The original test addresses mainly the automatic functioning of SM while the current test consists of categories that are more specific and require more executive functioning. Eight

categories were presented during the first session while the other 10 were presented during the second session in a random order. The modified CFT differs from the original test in that it requires more executing functioning, more thinking, knowledge and education which makes it appropriate for people at the early stage of the disease with high education. Participants were asked to name as many items they could think of from a given category in 60 seconds.

Natural categories:
Animals without a tail Vegetables without seeds
Artificial categories:
Items that melt when heated Sports that do not use a ball
Mixed categories:
Identical but separate items that come in pairs Items that can fly

Figure 5.1: Exemplars of the categories used for the modified CFT

5.1.2.3 Modified CNT

Sixty objects were photographed in total (Figure 5.2). A photo of the whole object and part of an object was captured and printed using a dimension of 10cm x 10cm. The concept of presenting the whole and part of an object allows for the testing of automatic and executive functioning of semantic memory. The naming of whole objects requires automatic functioning while naming part of an object requires executive functioning as the participant needs to make sense of what they are seeing before retrieving the word and naming it. The

pictures included 30 living items and 30 non-living items since category type seems to affect performance in AD. Living items consisted of different kinds of animal (land animals, insects, and aquatic animals), plants and fruits, while non-living items consisted of clothing items, tools, utensils and furniture. The 120 photographs were divided into two sessions and presented pseudo-randomly. In one session, part of the object was presented and in the second sessions the whole object was presented or vice versa. Participants were told that some pictures were whole objects while others were parts of an object and they were asked to give the name of the whole object even when part of the object was presented (for example saying 'dog' when a dog's ear was presented). The two things that make the current test different from the original is the photographic pictures rather than black and white line drawings which seem to put certain pictures at a disadvantage (Montanes et al., 1995; Moreno-Martinez & Rodriguez-Rojo, 2015) and the presentation of part of an object which allows for the testing of executive functioning.
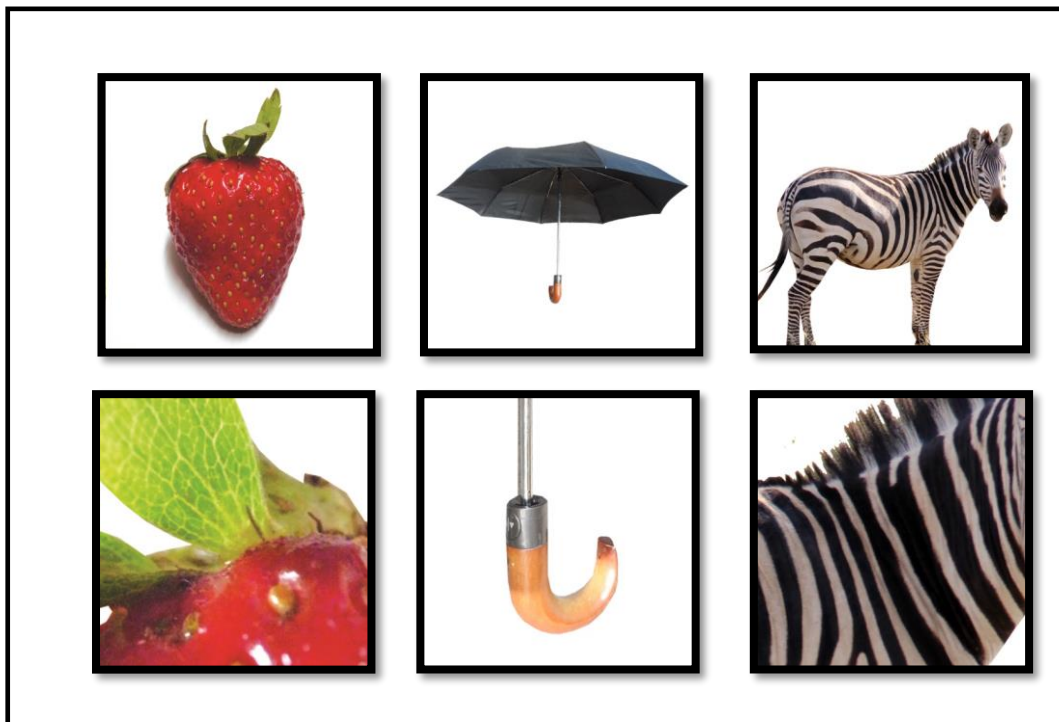
Figure 5.2: Exemplars of the stimuli presented as part of the modified CNT. Top row represents automatic functioning test stimuli and bottom pictures represent executive functioning test stimuli.

5.1.2.4 Sentence completion test

A sentence completion test (SCT) (Figure 5.3) was added to the testing material to assess language comprehension. Forty fill-in-the-blanks sentences were designed for the purpose of this test. As the CNT, this test consisted of two parts, 20 sentences had a figurative meaning (to assess automatic functioning) and the other 20 were literal sentences (that assess executive functioning). Three words were given as an option to complete the sentence and each set of options were used for a literal sentence and a figure of speech. In half of the sentences, the missing words contained the figurative or literal meaning of the sentences (Figure 5.3 example 1) while in the other half of the sentences it did not (Figure 5.3 example 2). Twenty sentences were presented during the first session and the other 20 were presented during the second session. The participants were told that some sentences were literal and some were figurative sentences and were instructed to choose a word from the three options presented that fitted best to complete the sentence.

Example 1:

Spilled Dropped Gobbled

a) I <u>spilled</u> the beans accidentally on the table while cooking.

b) Martina finally <u>spilled</u> the beans about the affair.

Example 2:

Sleep Cry   Scream

a) Babysitting is a breeze when you have a child like Suzie, all she does is <u>sleep.</u>

b) Claire would not <u>sleep</u> before we read a bedtime story together.

Figure 5.3: Exemplars of the sentences used for the SCT.

5.1.3. Results

5.1.3.1 Selection of categories for the CFT

A Pearson correlation was carried out to explore the relationship between individual categories, age and years of education (YoE). This will help in the selection of categories for the final test. Table 5.1 reports the *r* values and *p*-values for all the categories. YoE had the most impact on performance with a mild to moderate effect on eight of the categories. A negative mild effect of age was present for three of the categories and a mild effect of gender was only present for two of the categories. The categories, 'Animals that could be grey in colour' and 'household items that only work with electricity' were the only categories that were influenced by both age and education. Please refer to Table 5.1 for results. The mean values for each category were also taken into consideration for the selection process; these are presented in Figure 5.4.

Table 5.1 Correlations between demographic variables and category scores

Category	Age		YoE		Gender	
	r	*p*	*r*	*P*	*r_{bp}*	*P*
Animals without a tail	-0.189	0.134	0.186	0.141	-0.071	0.577
Separate items that come in pairs	-0.127	0.317	0.021	0.866	0.204	0.106
Items that melt when heated	0.125	0.324	0.147	0.247	0.039	0.758
Items that can fly	0.061	0.634	0.083	0.515	0.062	0.624
Fruit and vegetables that come in different colours	-0.063	0.619	0.229	0.069	0.026	0.838
Items fastened with a zip	0.042	0.743	0.184	0.145	0.032	0.803
Animals that are larger than humans	-0.055	0.666	**0.293**	**0.019***	-0.157	0.216
Vegetables without seeds	-0.031	0.809	0.068	0.593	**0.322**	**0.009****
Circular objects	0.118	0.354	-0.006	0.965	**0.270**	**0.031***
Animals that could be grey in colour	**-0.253**	**0.043***	**0.353**	**0.004****	0.057	0.656
Sports that do not use a ball	-0.230	0.067	**0.276**	**0.027***	0.20	0.877
Sharp objects that cut	-0.153	0.229	**0.317**	**0.011***	0.015	0.904
Two legged animals	-0.034	0.788	**0.392**	**0.001***	-0.025	0.843
Animals that live in water and on land	**-0.317**	**0.011***	0.175	0.166	0.086	0.501
Items with four legs	0.048	0.704	0.198	0.117	0.143	0.260
Household items that only work with electricity	**-0.306**	**0.014***	**0.504**	**0.000****	0.111	0.384
Animals that can swim and fly	-0.020	0.874	**0.297**	**0.018***	0.021	0.872
Different types of houses	-0.010	0.937	**0.248**	**0.048***	0.050	0.693

*Significant level <0.05　　****Significant level <0.01**
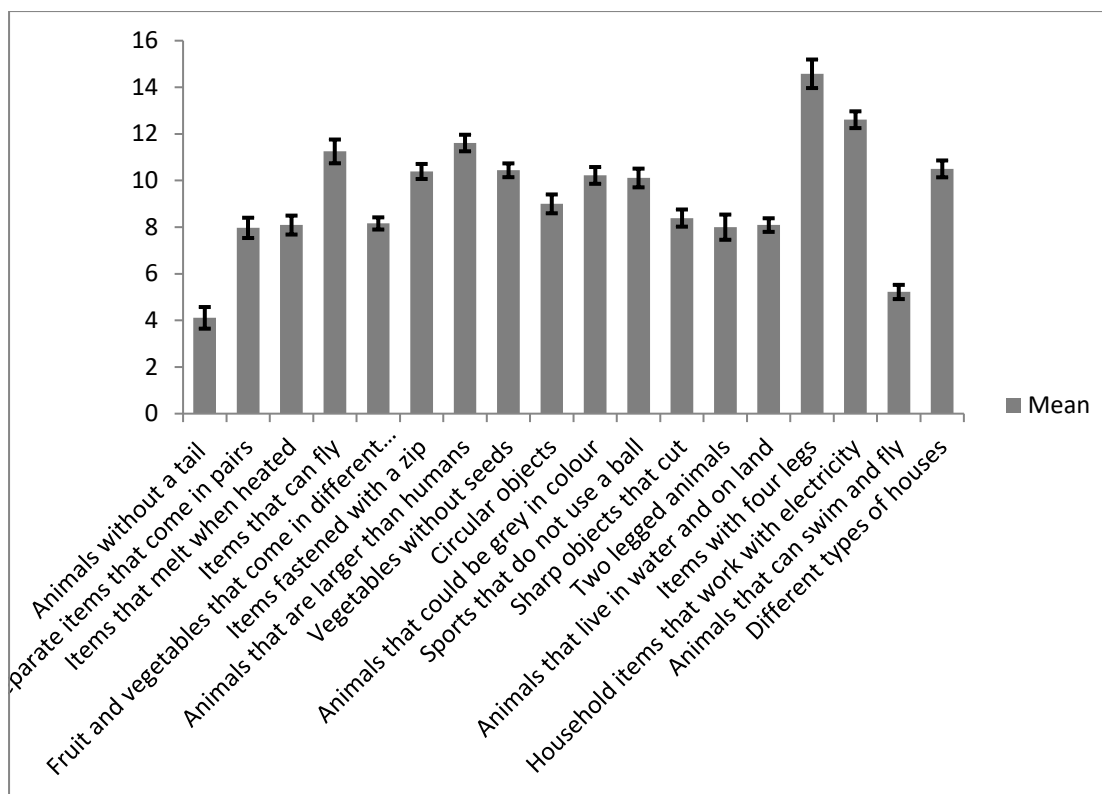
Figure 5.4: A graph representing the mean values (SE) obtained for each category

5.1.3.2 Performance on the CNT

The percentages of correct answers for each picture were documented. These values are presented in Figure 5.5. Participants performed better when the whole picture was presented but some stimuli such as 'Antelope' were hard to retrieve even when the whole picture was presented. Chosen pictures had a correct percentage between 80 and 100%. Reasons for wrong answers were mostly due to difficulties retrieving non-familiar words and presentation of ambiguous pictures.
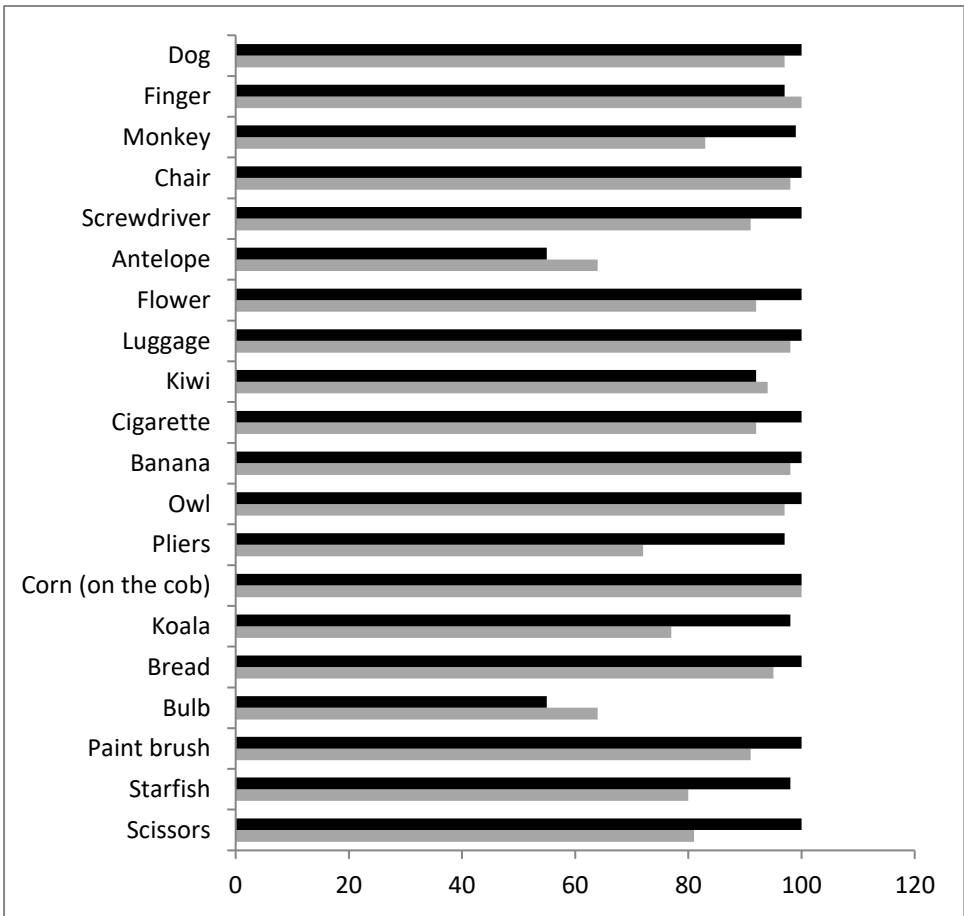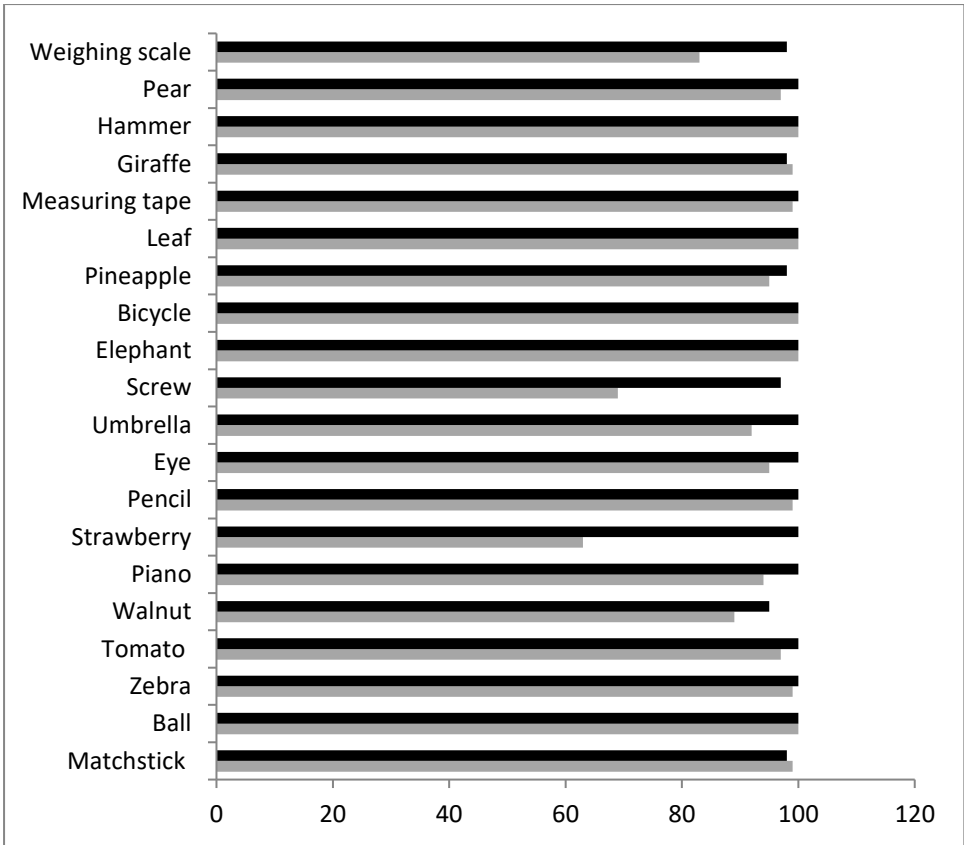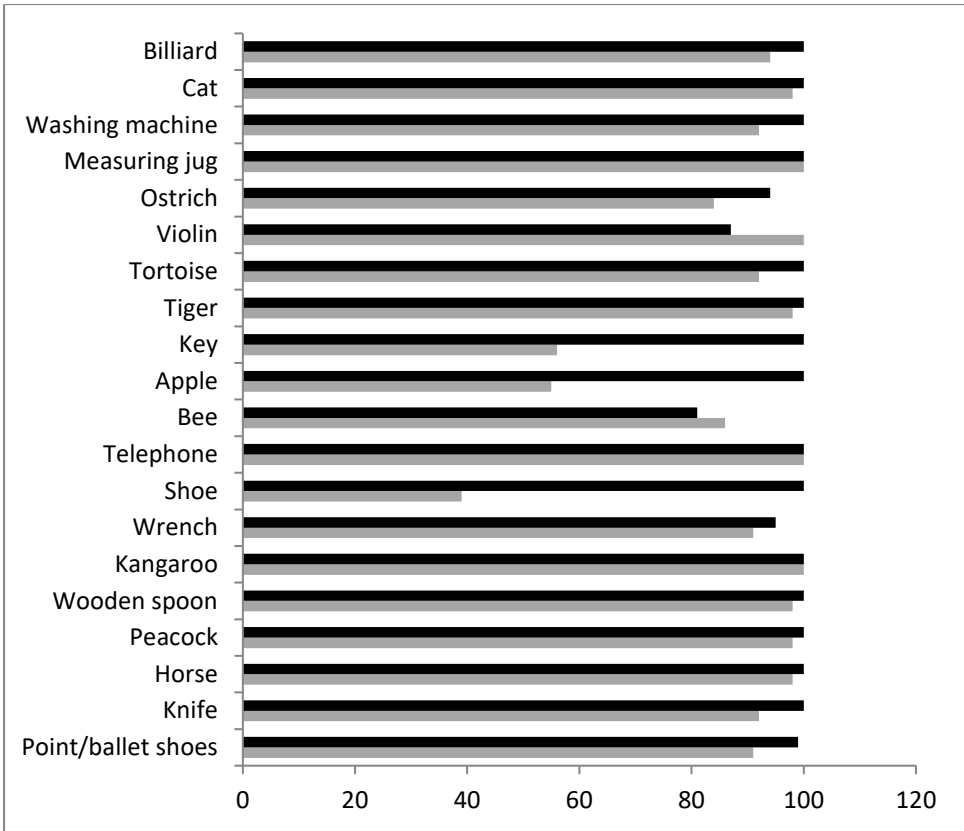
Figure 5.5 Bar graphs representing the percentage of correct responses for each picture. The black line represents automatic functioning (Whole picture) and the grey line represents executive functioning (part of picture).

5.1.3.3 Performance on the SCT

Text readability was measured using an online tool (http://www.webpagefx.com/tools/read-able/check.php). The automated readability index was used since it is designed for English text. Each sentence was analysed for the average grade level, a readability index test for English text, the total number of words that make up a sentence and the percentage of complex words present in the sentence. This information is presented in Table B (please refer to appendix) together with the percentage of correct answers.

An independent samples *t*-test was carried out to compare the readability measures of literal sentences (LS) (executive component) and sentences with figures of speech (FOS)

(automatic component). It is important that the two types of sentences are matched for lexical properties. The mean scores and SD are reported in Table 5.2. No significant difference was reported between the two types of sentences in none of the readability variables; average grade level [t(38) = -0.44, p = 0.67], reading index [t(38) = -0.79, p = 0.43], the total number of words [t(38) = 1.38, p = 0.176] and the percentage of complex words [t(38) = -0.304, p = 0.763].

Table 5.2 The mean scores (SD) of readability features for the two types of sentences

Readability feature	FOS	LS
Grade level	6.20 (2.88)	6.60 (2.95)
Reading index	4.57 (3.54)	5.44 (3.44)
No. of words	15.90 (6.55)	13.55 (3.91)
Percentage of complex words	7.45 (7.90)	6.76 (6.25)

5.1.3.4 Comparisons between young and old adults

Participants were divided into two groups according to their age, the young adult group (N = 31) was made up of people younger than 65 years and the old adult group (N = 33) consisted of individuals over the age of 65 years. An independent sample t-test was carried out to compare differences between the two groups on the total score of the CFT. A non-significant difference was present where young adults (M = 51.29, SD = 11.10) performed slightly better than the older age group (M = 48.64, SD = 9.73), [t(62) = 1.02, p = 0.312].

Due to non-normal data generated for the CNT and SCT the Mann-Whitney U Test was used to explore differences between the two groups for each testing session. Results from the CNT indicated that the score for the young group (Median = 58, Range = 53-60) was significantly higher than that for the old group (Median = 55, Range = 43-60) during the first session [U = 275.5, p = 0.001]. The same pattern was observed for the second session, where the young group (Median = 58, Range = 54-60) performed significantly better than the old group (Median = 56, Range = 38-60), [U = 264.5, p = 0.001]. Similar performance was present on the SCT for the two groups. For the first session the score for the young adults (Median = 19, Range = 14-20) did not differ from that generated by the old adult group (Median = 19, Range = 15-20), [U = 493.5, p = 0.798]. During the second session, the correct answers generated by the young age group (Median 19, Range = 17-20) were very similar to those generated by the older age group (Median = 19, Range = 16-20), [U = 439.5, p = 0.300].

5.1.4 Discussion

This study reports preliminary data collection from 64 healthy participants between the ages of 20 and 90 years. The aim was to ensure that the testing material was appropriate for the target group and testing instructions were clear. Additionally, this pilot study was conducted as part of the selection process of the stimuli to be included in the final testing material to be used for normative data collection and patient testing (in the following chapters). Comparisons between young and old adults on the three tests were also administered since we were interested in differential patterns between age-related changes and pathological changes due to AD.

Six categories were chosen for the final CFT test. Due to the category specific impairment reported in the literature (Garrard et al., 2001; Silveri et al., 2002; Zannino et al., 2002), varied categories were chosen. Two of them require the production of living items, another two require the retrieval of non-living nouns, and the last two consist of the production of both living and non-living words. The standard CFT currently used in clinical routine is highly influenced by age, education and gender (Brickman et al., 2005). To improve this task, it was ensured that the categories chosen were free from demographic influences. Results from the comparison between young and older individuals on this test confirm that older adults perform similar to younger adults even though more executive functioning is required. The selected categories are presented in Appendix 7.1.

The selection of the 40 photograph (20 living and 20 non-living, 20 pictures of whole object and 20 pictures consisting of part of an object) for further analysis was based on the percentage of correct answers, which varied between 80% and 100%. This guarantees that the stimuli were not ambiguous and healthy people did not have problems with the retrieval of the words. A significant difference between young and older adults emerged in this pilot study. An age effect is highly documented in normative studies on CNT (Patricacou, Psallida, Pring, & Dipper, 2007). An effort to reduce the impact of age was made by choosing photographs that were correctly named by both adult groups. Please refer to Appendix 7.2 for the full set of photographs used in the CNT.

There were no differences between the readability features of the sentences with FOS and LS. The sentences were chosen depending on the percentage of correct answers. The sentences below 80% correct answers were eliminated and the rest were chosen among those with high percentages and those with low percentages. Previous studies claim

that the system involved in language comprehension is the most stable system in old age (Peelle et al., 2010; Silagi et al., 2015). This is also supported in this study were young and old adults showed similar performance. The selected 20 sentences (10 LS and 10 FOS) are presented in Appendix 7.3.

In conclusion, this chapter offers promising testing material that can be used for the understanding of early SM impairment through language tasks. The similar performance between healthy young and old individuals suggests that these tests are appropriate for the clinical detection of pathological changes present in AD.

Study 5.2: Obtaining normative data for the novel semantic memory tests

5.2.1 Introduction

Distinctive clinical features present during the preclinical AD phase are yet to be established. The current inability to detect people with AD pathology that will go on to develop full blown clinical dementia is the driving force for most research including the present one. The newly modified tests presented in the previous sub-chapter (Study 5.1) were designed on the basis of recent research (Jack et al., 2010) and the revised version of the guidelines and clinical criteria for diagnosing AD (McKhann et al., 2011) which introduced the 'preclinical' concept and confirmed the idea that pathological changes including cognitive functioning are present before the clinical onset of the disease. New and modified clinical tests require the important process of normative data collection before they can be applied in clinical routine and used as diagnostic tools.

The term 'normative data' refers to a collection of test scores obtained from the administration of tests to a large cohort that is representative of the general population of interest. Normative scores are collected to define the boundaries between normal and abnormal performance in the population of interest of cognitively healthy individuals. Pathological performance can only be determined by comparing such performance to a cognitively normal reference group that shares similar demographics. Poorer performance than that reported for the normative group would imply abnormal functioning and would require further investigation and interpretation.

The lack of proper normative data results in misdiagnosis. It is commonly agreed that performance on cognitive tests is affected by demographic variables such as age, gender,

socioeconomic status and YoE (Beeri et al., 2006), especially tests assessing memory

(Ganguli et al., 2010; Inouye, Albert, Mohs, Sun, & Berkman, 1993). Most studies on the

correlation between demographic factors and cognitive performance demonstrate that the

number of years in education has the highest effect on performance (Beeri et al., 2006;

Passos et al., 2015), while gender is the least influential variable (Tripathi, Kumar, Bharath,

Marimuthu, & Varghese, 2014). Yet, clinical tests still lack such data for certain age groups

(mostly over the age of 85), minorities and nationalities which makes it difficult for clinicians

to provide accurate diagnosis.

Most cognitive tests, including the modified tests used in this study, CFT, CNT SCT

are based on intrinsic performance which can be highly affected by age, YoE and gender.

Both age as well as education have an impact on the final MMSE score (Ishizaki et al., 1998),

a test that is commonly used to assess global cognitive functioning in clinical and research

settings. Age and education effects were also reported for other common tests used for

diagnosis such as the Modified Card Sorting Test (Caffarra, Vezzadini, Dieci, Zonato, &

Venneri, 2004), the short version of Raven's progressive matrices (Caffarra, Vezzadini,

Zonato, Copelli, & Venneri, 2003), The Pyramids and Palm Trees test (Callahan et al., 2010;

Gamboz, Coluccia, Iavarone, & Brandimonte, 2009), and the Trial making test (Tombaugh,

2004).

Age and education are associated with performance on the CFT, with an increase in

age and lower education, generating less number of total words (Brickman et al., 2005). In a

study on the link between demographic variables and performance it was reported that age

correlated negatively with total score but clustering (the number of words produced that

belong to a sub category, for example 'farm animals' when the category 'animals' is given)

correlated positively with increasing age (Lanting, Haugrud, & Crossley, 2009) which is thought to be due to the large number of stored semantic (verbal) knowledge. Age is also found to have an impact on the switching (the switch between one cluster and another) results, while YoE correlate negatively with both switching and the total score (Brucki & Rocha, 2004). Although most studies do not show gender effect on CFT performance and the total score is not influenced by this factor (Brickman et al., 2005; Brucki & Rocha, 2004; Lanting et al., 2009), males seem to produce larger clusters while females have more switches (Lanting et al., 2009).

Although age has an impact on CNT (Patricacou et al., 2007) such as the Boston naming task (BNT), naming is relatively stable across the years with a slight decrease in the older adult ages (Welch et al., 1996). Formal education has a strong positive impact on the BNT (Patricacou et al., 2007). Additionally, scores on BNT seem to be more preserved in adults with more YoE (Welch, Doineau, Johnson, & King, 1996). An age by education interaction has also been reported with higher age and lower education obtaining lower scores on picture naming (Welch et al., 1996). Contrary to this, a lack of an education effect on the BNT has also been reported in the literature (Hall, Vo, Johnson, Barber, & O'Bryant, 2011). Gender effect is not frequently reported to have an impact on the performance of CNT (Patricacou et al., 2007), but a gender bias is sometimes reported (Hall et al., 2011; Welch et al., 1996), with males performing better than females (Hall et al., 2011).

In clinical routine, verbal comprehension is commonly assessed with the Token Test. Although less normative studies are available on this test compared to the CFT and CNT, the pattern of influence of demographic variables is similar to that observed in the previous tests. No gender effect on verbal comprehension is reported but age and education both

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play a role in the performance on the Token Test (Pena-Casanova et al., 2009). In a normative study on young individuals (between 18 and 49), age did not play a significant role but education did (Aranciva et al., 2012). It is suggested that formal education has more of an impact than age on this cognitive task (Moreira et al., 2011).

From the available literature it can be concluded that the common tests used in dementia clinics are all influenced by the background of the individual. This highlights the importance of using normative scores when assessing patients for an accurate diagnosis. The main aim of this study was to collect norms from healthy English speakers for the newly devised tests to be used as cut off scores for normal semantic functioning. In addition, the impact of three common demographic variables, age, YoE and gender, on performance was examined for each test.

5.2.2. Methodology

5.2.2.1 Participants

Initially one hundred and seventy-six participants, between the ages of 20 and 90 years, volunteered to take part in this study. The volunteers were recruited through adverts in public places, mainly, The University of Sheffield and The University of Third Age, religious groups, charities and partners of dementia patients visiting the memory clinic. Participants underwent a detailed interview regarding their background, medical history and current health conditions. The MMSE test and The Coloured Raven's Progressive Matrices (Raven's test) were also administered to ensure that the participant's global cognitive performance and fluid intelligence were within the healthy norms. Exclusion criteria consisted of treatment for psychiatric symptoms, history of transient ischemic attacks, seizures and

convulsions, head injuries and substance abuse problems. Forty eight out of the total 176 participants were not included in the study as they either fulfilled the exclusion criteria or did not attend the full testing session. Participants were also eliminated if English was not their native language. All participants had the opportunity to read through the information sheet and ask questions regarding the study before giving informed consent to participate in the study. Ethical approval for the study was granted by The Medical School Ethics of University of Sheffield (SMBRER255).

5.2.2.2 Materials and procedures

The SM assessment included the newly modified CFT, CNT and SCT with the stimuli selected from the pilot study (study 5.1) Please see Appendix. Participants were administered all three modified tests in addition to the standardised MMSE and The Raven's test.

The CFT consisted of 6 categories in total of which two were living categories, two non-living and two mixed categories. Participants were asked to name as many exemplars they could think of from a given category in 60 seconds. The following rules were used for scoring: perseverations were only counted once, intrusions were not counted, a superordinate category was not scored if representatives of it were also produced, but only one representative was considered when more than one with the same name was produced (for example: football, tennis ball and basketball).

The CNT consisted of 40 photographed pictures (20 living and 20 non-living) half of the pictures consisted of whole objects (automatic functioning) and the other half contained half of an object (executive functioning). The participants were shown the set of pictures,

and were required to identify and name the objects presented. A point for each correct answer was scored.

The SCT consisted of 20 incomplete sentences. Ten of the sentences involved figures of speech (automatic functioning) and the other 10 were literal sentences (executive functioning). Participants were required to complete the sentences by choosing one of the three optional words provided with each sentence. A point for each correct answer was scored.

5.2.3. Results

5.2.3.1 Demographics

The age of participants ranged between 20 and 90 years with a mean age of 58.45 (SD = 18.48). The mean YoE was 16.07 (Range = 10 - 27, SD =2.92). Forty-two of the participants were males and 86 were females. The descriptive statistics and screening tests of participants stratified by decades are presented in Table 5.3. For the purpose of descriptive data and means of test scores, participants were separated into 7 decades: 20 – 30, 31 – 40, 41 – 50, 51 – 60, 61 – 70, 71 – 80, 81 – 90. The mean score for the modified CFT, CNT and SCT and their individual components for each decade were calculated and presented in Tables 5.4, 5.5 and 5.6 respectively.

Table 5.3: Demographics of participants separated by each decade

Decade	20-30 (N=16)	31-40 (N=9)	41-50 (N=10)	51-60 (N=17)	61-70 (N=41)	71-80 (N=27)	81+ (N = 8)
Age (Range, SD)	23.44 (20-30, 2.53)	33.56 (31-37, 2.30)	45.50 (41-50, 3.37)	54.76 (51-59, 2.93)	66.17 (61-70, 66.17)	75.22 (71-80, 2.74)	84.25 (81-90, 3.10)
M/F ratio	7/9	3/6	3/7	5/12	12/29	10/17	2/6
YoE	16.94 (13-19, 1.88)	17.89 (13-27, 4.17)	17.10 (11-21, 3.25)	17.00 (13-22, 2.60)	15.44 (10-20, 2.72)	15.52 (10-20, 2.47)	14.18 (11-23, 4.09)
MMSE (Range, SD)	29.63 (27-30, 0.81)	29.33 (28-30, 0.71)	29.20 (27-30, 1.03)	28.82 (27-30, 0.81)	29.15 (27-30, 0.79)	28.93 (26-30, 1.17)	28.50 (27-30, 0.93)
Raven's (Range, SD)	33.93 (32-36, 1.10)	33.89 (29-36, 2.20)	33.33 (30-36, 1.87)	34.25 (30-36, 1.44)	33.02 (26-36, 2.81)	32.60 (26-36, 2.71)	30.13 (25-34, 3.56)

Table 5.4: Mean scores (SD) of individual categories and total score for the CFT for each decade

Decade	20-30 (N=16)	31-40 (N=9)	41-50 (N=10)	51-60 (N=17)	61-70 (N=41)	71-80 (N=27)	81+ (N = 8)
Animals without a tail	4.50 (3.05)	3.44 (3.43)	7.50 (5.68)	3.88 (2.85)	4.12 (3.26)	2.78 (2.29)	3.00 (2.14)
Separate items that come in pairs	9.44 (3.72)	6.00 (2.34)	7.30 (2.50)	7.06 (3.23)	7.05 (3.85)	7.85 (4.63)	6.75 (2.25)

Items that melt when heated	7.25 (4.07)	6.33 (1.12)	8.60 (3.41)	8.06 (3.36)	8.59 (3.20)	8.07 (2.93)	6.00 (2.27)
Items that that can fly	10.75 (3.62)	9.67 (2.12)	12.00 (5.56)	11.59 (2.90)	13.66 (4.42)	11.67 (4.57)	10.13 (4.19)
Fruit and Vegetables that come in different colours	8.50 (2.53)	9.67 (1.87)	7.70 (1.57)	9.41 (2.29)	8.22 (2.38)	8.00 (2.20)	7.38 (2.93)
Items fastened with a zip	10.13 (2.63)	7.67 (1.80)	10.40 (2.99)	9.88 (2.89)	10.63 (2.89)	9.67 (2.13)	8.88 (2.70)
Total Score	50.56 (13.27)	42.89 (6.67)	53.50 (15.02)	49.71 (7.48)	52.24 (11.96)	48.11 (9.92)	42.13 (7.85)

Table 5.5: Mean scores (SD) of the total score and the score for the executive and automatic tasks for the modified CNT for each decade

Decade	20-30	31-40	41-50	51-60	61-70	71-80	81+
Executive functioning	19.50 (0.73)	19.67 (0.50)	19.80 (0.42)	19.59 (0.71)	19.15 (0.94)	18.44 (1.37)	16.38 (3.34)
Automatic functioning	19.81 (0.54)	19.89 (0.33)	19.80 (0.42)	19.65 (0.70)	19.46 (0.87)	19.26 (0.66)	18.50 (1.51)
Total score	39.31 (0.87)	39.56 (0.53)	39.60 (0.52)	39.24 (0.90)	36.61 (1.45)	37.70 (1.64)	34.88 (4.42)

Table 5.6: Mean scores (SD) of the total score and the score for the executive and automatic tasks for the SCT for each decade

Decade	20-30	31-40	41-50	51-60	61-70	71-80	81+
Executive functioning	9.56 (0.73)	9.44 (1.01)	9.60 (0.70)	9.94 (0.24)	9.61 (0.67)	9.63 (0.49)	9.50 (0.76)
Automatic functioning	9.69 (1.01)	9.78 (0.67)	9.80 (0.42)	9.82 (0.39)	9.88 (0.33)	9.63 (0.56)	9.38 (0.74)
Total score	19.25 (1.18)	19.33 (1.66)	19.40 (0.84)	19.76 (0.44)	19.49 (0.81)	19.26 (0.71)	18.88 (1.13)

5.2.3.2 The influence of age, education and gender on the newly modified tests

Spearman rank order correlation was used as the data did not reach normal distribution. The correlation was run to determine the relationship between test scores of 128 participants and the demographic variables age and YoE. The *rho* and significance values are presented in Table 5.7. No strong associations were present between the scores on the modified tests and age and YoE. A moderate negative correlation with statistical significance was present between the scores of the CNT and age: [Executive score r_s (128) = -0.441, $p <$ 0.001, Automatic score r_s (128) = -0.429, $p = 0.000$ and total score r_s (128) = -0.519, $p <$ 0.001], and a weak positive correlation was also present between age and the Executive score [r_s (128) = 0.203, $p = 0.021$] and the total score [r_s (128) = -0.188, $p = 0.034$]. Age correlated negatively with the automatic score of SCT [r_s (128) = -0.209, $p = 0.018$] and the total score of SCT [r_s (128) = -0.184, $p = 0.038$]. Age and education did not correlate with the total score of the CFT, and the only category performance that showed a negative association with age [r_s (128) = -0.195, $p = 0.020$] and a positive association with education [r_s (128) = -0.179, $p = 0.043$] was 'Animals without a tail'. A Point-Biserial Correlation was

carried out to determine the association between gender and the scores on the tests. No statistically significant correlations were found except for one of the categories used in the CFT 'Items that melt when heated' [r_{pb} (128) = 0.57, p = 0.051]. Results are presented in Table 5.8.

Table 5.7: Correlations between tests scores with age and YoE.

Tests	Age		YoE	
	Rho	*P*	*Rho*	*P*
CFT				
Animals without a tail	-0.195	0.020*	0.179	0.043*
Separate items that come in pairs	-0.145	0.100	0.79	0.377
Items that melt when heated	0.052	0.557	0.146	0.101
Items that can fly	0.092	0.300	0.112	0.206
Fruit and vegetables that come in different colours	-0.13	0.143	0.037	0.679
Items fastened with a zip	0.011	0.905	0.001	0.995
Total score	-0.055	0.537	0.16	0.071
CNT				
Executive functioning Picture naming	-0.441	0.000*	0.203	0.021*
Automatic functioning picture naming	-0.429	0.000*	0.147	0.098
Total score	-0.519	0.000*	0.188	0.034*
SCT				
Executive functioning Sentence completion	-0.082	0.360	0.072	0.416
Automatic functioning sentence completion	-0.209	0.018*	0.134	0.133
Total score	-0.184	0.038*	0.106	0.235

* Statistically significant correlation

Table 5.8: Correlations between tests scores with gender.

Tests	Gender	
	r_{pb}	*P*
CFT		
Animals without a tail	0.15	0.867
Separate items that come in pairs	0.098	0.147
Items that melt when heated*	0.569	0.051
Items that can fly	0.491	0.061
Fruit and vegetables that come in different colours	0.041	0.645
Items fastened with a zip	0.149	0.094
Total score	0.136	0.125
CNT		
Executive functioning Picture naming	0.031	0.731
Automatic functioning picture naming	-0.013	0.881
Total score	0.017	0.848
SCT		
Executive functioning Sentence completion	0.160	0.072
Automatic functioning sentence completion	0.067	0.449
Total score	0.135	0.128

* Statistically significant correlation

The statistically significant correlated factors were entered in an enter regression model to predict tests performance from demographic variables. A significant regression equation was found for the executive score of the CNT [F (2, 125) = 13.36, p = 0.000, r^2 = 0.176. Age was a significant predictor [p = 0.000] but YoE were not [p = 0.212]. A significant equation was also found for the Automatic score [F (2, 125) = 9.61, p = 0.000 with an r^2 of 0.133. Age added statistically significantly to the prediction [p = 0.000], YoE did not [p =

0.434]. The same prediction pattern was observed for the total score of the CNT where a significant regression equation was found [F (2, 125) = 17.21, p = 0.000, r^2 = 0.216] with a significant prediction by age [$p < 0.001$] but not YoE [$p = 0.196$]. It can be concluded that age is the only significant predictor of the three scores on the CNT.

Age was not a significant predictor of the automatic score on the SCT [F (1, 126) = 0.345, p = 0.557, r^2 = 0.003] and it was not a predictor of the total score either [F (1, 126) = 0.147, p = 0.702, r^2 = 0.001]. The regression equation for the category 'Animals without a tail' was not statistically significant [F (2, 125) = 2.694, p = 0.720, r^2 = 0.041]. Neither age [p = 0.165] nor YoE [p = 0.171] can significantly predict the score on this category. The regression analysis for the category 'Items that melt when heated' was also not statistically significant when tested with gender as a predictor of performance [F (1, 126) = 0.326, p = 0.569, r^2 = 0.003]. In conclusion, age, YoE and gender do not influence the scores of the SCT and the CFT.

5.2.4. Discussion

This study presents normative data for the newly modified SM tests that assess the different components of SM, executive functioning (semantic control) and automatic functioning (semantic representation). The data were collected from an English speaking cohort between the ages of 20 and 90 years. In addition, the study explored the influential effects of age, YoE and gender on the total scores of the three tests as well as the scores on the individual parts of the tests.

The performance observed by the 7 decade groups were similar on all three linguistic tests. The least variation in performance was observed on the SCT which assess language comprehension, a cognitive function known to remain stable in healthy ageing (Silagi et al., 2015). This was followed by CNT which showed a similar pattern of decline found in previous studies (Connor, Spiro, Obler, & Albert, 2004; Hodgson & Ellis, 1998; Tsang & Lee, 2003), and the CFT where the best performance group was the one between 41 and 50 years followed by the 61-70 years' group. This highlights the stability of semantic knowledge and confirms previous studies that suggest an increase in word knowledge across age (Salthouse, 2014; Stolwyk, Bannirchelvam, Kraan, & Simpson, 2015).

Normative studies on the standardised tests used in dementia clinics report demographic effects on the performance of clinical tests (Ganguli et al., 2010), with the strongest influence contributed by age and formal education (Beeri et al., 2006; Passos et al., 2015; Tripathi et al., 2014). These studies stress the importance of normative data for accurate diagnostic information and increase awareness about the possibility of external influence. The present study reports weak links between age, YoE and gender with the performance on the new tests, and the only significant predictor was age on the performance of the modified CNT, where increase in age correlated with a decrease in test score. Increasing age has been previously linked to worse performance on confrontation naming. This is mainly due to the normal decline in executive functioning required for the completion of this test (Silagi et al., 2015) which results in an impairment during the 7th decade (Mackay et al., 2002). This impairment in healthy ageing is confirmed by the present study where a decline in performance was mostly observed in the task that requires more semantic control. Furthermore, a greater difference between the automatic and the

executive scores was present for individuals older than the age of 71 years and this discrepancy increased further over the age of 81 years.

A strong link between age and YoE with the performance on the standardised CFT has also been reported (Brickman et al., 2005). The current study does not report similar findings. A weak correlation between age and YoE was only present for one of the categories, while a slight gender bias was present on another category, but none of these factors survived the regression model. The new version of the CFT test is different from the original one in that it requires more executive functioning, but it also requires access to a wider semantic store. While the younger population are expected to do better on the first task, older adults have a more extensive vocabulary (Kave & Yafe, 2014). In fact, in a study assessing clustering scores, a positive correlation was found with age where an increase in age leads to larger clusters (Lanting et al., 2009). The decline in executive functioning and increase in vocabulary in older adults as opposed to better executive functioning and limited semantic information could explain the results found in this study.

A very weak association between age and the newly devised SCT was the only link found with this test and age was not a predictor of the performance score. This suggests that like the CFT, the new SCT is free from demographic bias. Previous findings from normative studies exploring demographic impact on language comprehension tests report both an age and an education effect (Moreira et al., 2011; Pena-Casanova et al., 2009).

A number of limitations should be outlined for this study as they might influence the generalisability of the findings. One of the limitations is the sample size which is less than that desirable for a normative study. The recruitment of further volunteers would be needed to add value to this study. The participants who volunteered to participate in this

study are mostly highly educated people who are physically and mentally very active. Although the level of education is generally increasing and adults are more active, these normative data might have a wider application as the sample might be more representative of future generations, but this does not exclude the fact that the data might be skewed. As expected, recruiting older individuals was harder than younger ones and while a good number between 60 and 80 years were recruited, very few people over the age of 81 years volunteered for the study. Studies on the oldest old group are becoming increasingly important since people live longer and the risk of developing AD increases after the 8th decade.

In conclusion, normative data are beneficial for both clinicians and researchers in determining whether a performance is considered as normal or pathological. The only bias found in this study was age on the CNT. No other demographic effects were present for the other two tests. The newly modified tests have no education bias, which is one of the strongest predictors of the performance on the original tests. Therefore, the new tests can be applied to individuals of both sexes from different educational levels. Additionally, these tests can be used for further clinical research.

Chapter 5.3: Neuroanatomical correlates of automatic and executive semantic tasks

5.3.1 Introduction

The pattern of GM atrophy in AD mirrors the build-up pattern of NFT (H. Braak & Braak, 1995; H. Matsuda, 2013). It starts in the transentorhinal and entorhinal regions spreading to the hippocampus and neocortical regions (H. Matsuda, 2013; Thompson et al., 2003; P. Wang et al., 2015). Reduced GM density in the medial and lateral temporal areas especially in the parahippocampal gyri bilaterally and left fusiform gyrus are present earlier on in the disease (Busatto et al., 2003). Strong correlations are reported between GM density values in the medial and lateral temporal lobes and cognitive memory scores. GM volumes in prefrontal and temporal cortices are also associated with the performance on tasks involving executive functioning (de Jong et al., 2008; Garrido et al., 2002; D. Zheng et al., 2014).

The processing of SM is a complex system that can be separated into two components for research purposes. Semantic representation (automatic functioning) and semantic control (executive functioning) are two highly interdependent processes required for a healthy semantic cognition. Clinical tasks and procedures to examine the two processes separately have been previously designed and applied in research. Neuroimaging studies show that despite their dependency the two processes depend on distinct neuroanatomical structures.

Representation of semantic knowledge is stored in a distributed network including structures in the parietal, temporal and prefrontal cortex (Binder et al., 2009). Object identification elicits different parts of the brain depending on what the object is. The ventral

occipitotemporal cortex is important for the recognition of object form, lateral temporal cortex is required for motion and ventral premotor cortex is important for use-associated motor movements (Martin & Chao, 2001). A recent study (Huth, de Heer, Griffiths, Theunissen, & Gallant, 2016) on the storage of semantic information mapped the semantic system from data collected through a 2 hour listening comprehension of narrative stories. A total of 10, 470 words grouped into 12 categories were used to form a human word atlas. Generated results suggest that semantic information is organised in a domain specific manner and both cerebral hemispheres are equally involved with 77 semantic areas on the left and 63 on the right. Semantic areas reported included the lateral and medial parietal cortex, superior and inferior prefrontal cortex (PFC) and lateral and ventral temporal cortex. Therefore, an object or a word has semantic information stored in various parts of the brain. For example, the word 'tiger' has information about the visual features of orange and black stripes, the sensory feature of the roaring sound and the emotional connotation of a dangerous animal. More than one area could be selective for a particular representation (Huth et al., 2016) and recollecting the meaning of a word would require the engagement of such areas.

During a semantic related task, semantic information is retrieved from the storage area followed by a selection process to choose relevant information. This involves the engagement of the left anterior ventrolateral prefrontal cortex (VLPFC) of semantic knowledge, and the mid-VLPFC for the selection of appropriate semantic information (Badre et al., 2005; Demb et al., 1995). Additionally, posterior middle temporal gyrus and the intraparietal sulcus are also documented structures to be recruited when the demand of

semantic selection and therefore executive functioning increases (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012).

The purpose of this anatomical validation is to explore and verify the anatomical structures that correlate with the two distinct processes of SM, using a voxel-based correlation analysis on 3D structural MRI scans of the brain of both healthy as well as patients. The main aims of this study were to confirm that the newly modified SM tests of automatic and executive functioning (proposed in study 5.1) rely on the anatomical structures of interest, that is, the specific brain regions that are more vulnerable to AD pathology. Correlations between score tests and grey matter density values in the medial temporal areas and frontal regions are expected for the tests to be recruiting desirable anatomical features.

5.3.2 Methodology

5.3.2.1 Participants

The study sample included twenty-seven participants with varying degree of cognitive functioning. Twenty participants (5 males, 15 females) were healthy volunteers and seven participants (3 males, 4 females) were patients with mild to severe dementia. Patients were recruited through the memory clinic at the Royal Hallamshire Hospital. Their mean age was 64 years (SD = 13.35, Range 32-88) and their mean years of education was 15 years (SD = 2.93, Range 10-23). All participants underwent extensive neuropsychological screening in addition to the novel SM tests and structural MRI scanning. Five of the participants with MCI and 1 with AD fulfilled the clinical criteria proposed by Petersen et al.,

(2001) The remaining participant fulfilled the FTD criteria proposed by Lund and Manchester group "Clinical and neuropathological criteria for frontotemporal dementia." (The Lund and Manchester Groups," 1994). Healthy volunteers were recruited through the University of Third Age, charity and religious groups in Sheffield as well as partners of patients who visited the memory clinic. A brief interview was conducted to gather health information from healthy participants. Exclusion criteria included psychiatric disorders, brain injury, epilepsy, cerebrovascular disease and history or current substance abuse. All participants provided informed consent for the involvement in the study. Ethics approval for the study was granted by the Medical School of Sheffield (SMBRER255) and Sheffield Regional NHS ethics (12/YH/0474).

5.3.2.2 Neuropsychological assessment and testing procedure

For the purpose of this study each participant was administered the short version of the modified SM tests: CFT, CNT, the SCT described in chapter 5.1 (please refer to section 5.1.2 for testing materials and procedures), and the MMSE. Scores from the three modified tests were correlated with GM density values obtained from the patients' three dimensional (3D) MRI scan.

5.3.2.3 MRI procedures

High resolution T_1 – weighted structural images of the brain were acquired on a 3 T Philips Ingenia scanner. Voxel dimensions were 1.1 x 1.1 x 6 and the field of view was 250mm, matrix size 256 x 124. A number of preprocessing steps were followed to extract the GM from the 3D T1-weighted structural scans before running the statistical analysis. After checking for global differences in brain shape and reorienting, structural images were segmented into GM, white matter (WM) and cerebrospinal fluid (CSF). The GM segments

were then smoothed and entered into a voxel-based multiple regression model. Voxel based

morphometry (VBM) (Good et al., 2001) was used to quantify GM volume and SPM8 was

used for statistical analysis of the scans (Wellcome Department of Imaging, Neuroscience,

UCL, London, UK). A Linear correlation between GM volumes and the scores from the three

modified tests and the standard CFT was conducted to establish the neural substrates that

correlated with automatic and executive functioning used during semantic processing. The

x, y and *z* coordinates of areas with significant correlations were converted into Talairach

coordinates using a non-linear transform

(http://imaging.mrccbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) and were identified

using the Talairach Daemon Client (http://www.talairach.org/client.html).

5.3.3 Results

5.3.3.1. Behavioural results

The mean values, SD and range for the MMSE and the newly devised tests for the

sample group are presented in Table 5.9. On both the modified CNT and SCT, participants

performed better on the automatic functioning task. An independent *t*-test was carried out

to explore whether the differences were significant. For the modified CNT, scores on the

automatic task (M = 19.11, SD =1.25) were significantly higher than scores on the executive

task (M = 17.63, SD = 2.93), [*t* (27) = -2.41, *p* = 0.02]. The mean scores on the executive part

of the test (M = 9.41, SD = 0.97) was not significantly worse than the automatic functioning

(M = 9.63, SD = 0.56) [*t* (27) = -0.13, *p* = 0.31].

Table 5.9: Mean scores (SD) of participants and patients on the modified and standard tests

Test	Type	Mean	(SD)	Range
MMSE		28.04	2.01	23-30
Modified CFT		42.89	12.99	14-65
Modified CNT	Automatic	19.11	1.25	16-20
	Executive	17.63	2.93	10-20
SCT	Automatic	9.63	0.56	8-10
	Executive	9.41	0.97	6-10

5.3.3.2 GM correlations

A VBM multiple regression analysis for GM volume and the mean score for each test were run with age and GM fraction inserted as covariates. All reported results survived the cluster-level Family-Wise Error-corrected ($p < 0.001$, $p < 0.01$). For the modified CFT significant positive correlations were present between GM density values and the right STG, middle temporal gyrus, and inferior temporal gyrus (ITG), left middle temporal gyrus, right parahippocampal gyrus, uncus and anterior cingulate, supramarginal gyrus, and inferior parietal lobule (IPL), right IFG, middle frontal gyrus and superior frontal gyrus (SFG) and left IFG and middle frontal gyrus, right rectal and orbital gyrus, left SFG, left insula.

The scores on the automatic functioning test of the CNT showed positive correlations with GM densities in the right parahippocampal gyrus and sub-gyral, right insula, right IFG, right STG, right precentral gyrus, right middle temporal gyrus. The scores on the executive functioning test of the CNT showed positive correlations with GM volume

in the right precentral gyrus, sub-gyral, supramarginal gyrus, IPL, right SPL, precuneus, left paracentral lobule, right superior occipital gyrus, right STG, right cingulate gyrus, right IFG, right insula, right SFG, right middle frontal gyrus, right orbital gyrus, and right extra nuclear. None of the clusters for the automatic and executive functioning tests of the SCT survived the FWE in. Table 5.10 and figure 5.6 show the correlations between GM and the semantic tests.

Table 5.10: Areas of significant correlations between GM volume and the newly devised tests. This table represents the first 5 peaks from each cluster for each test. Additional peaks spreading to the left side were also present but these had lower level of significance

Brain area	Right/left	Brodmann's area	Talairach Co-ordinates			Peak-level-Z score
			X	Y	Z	
CFT: Cluster 1:						
(FWE < 0.001)						
Superior temporal gyrus	R	22	51	-50	14	4.38
Supramarginal gyrus	R	40	57	-53	30	4.31
Supramarginal gyrus	R	40	61	-45	32	4.05
Supramarginal gyrus	R	40	53	-57	34	3.98
Inferior parietal lobe	R	40	51	-54	40	3.67
CFT: Cluster 2						
(FWE < 0.001)						
Parahippocampal gyrus	R	36	30	-37	-7	4.05
Inferior temporal gyrus	R	20	32	-2	-37	3.75
Parahippocampal gyrus	R	36	34	-24	-14	3.62
Inferior frontal gyrus	R	47	18	16	-24	3.60
Middle frontal gyrus	R	11	26	30	-18	3.58

CNT: Automatic

Cluster 1

(FWE <0.001)

Region			x	y	z	
Sub-gyral	R	Hippocampus	34	-28	-10	4.84
Parahippocampal gyrus	R	Amygdala	32	-7	-20	4.45
Parahippocampal gyrus	R	Amygdala	30	-7	-20	4.43
Parahippocampal gyrus	R	34	22	1	-12	3.71
Inferior frontal gyrus	R	47	16	11	-21	3.52

CNT: Executive

Cluster 1

(FWE < 0.01)

Region			x	y	z	
Postcentral gyrus	R	3	30	-30	59	4.42
Supramarginal gyrus	R	40	61	-41	32	3.96
Inferior parietal lobule	R	40	48	-46	50	3.68
Precuneus	R	19	30	-70	37	3.64
Postcentral gyrus	R	2	61	-27	38	3.49

CNT: Cluster 2

(FWE < 0.05)

Region			x	y	z	
Superior temporal gyrus	R	*	53	0	0	3.55
Inferior frontal gyrus	R	11	24	34	-17	3.46
Inferior frontal gyrus	R	47	50	19	-8	3.30
Superior temporal gyrus	R	22	57	-4	4	3.21
Insula	R	13	44	6	0	3.13

Fig**ure 5.6:** Figures of GM correlations with (A) Modified CFT, (B) Automatic CNT, (C) Executive CNT
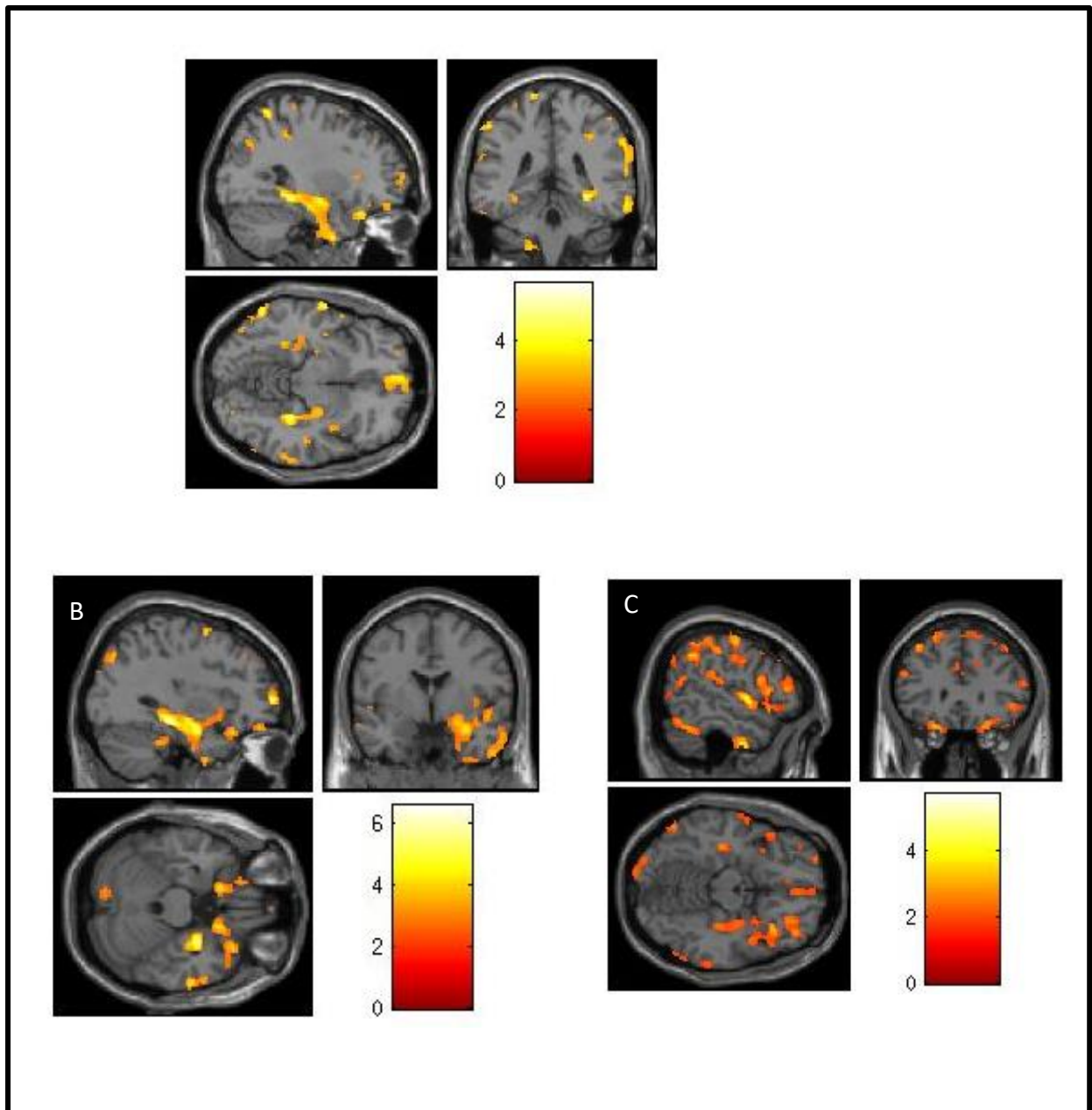
5.3.4 Discussion

The study was carried out to establish the brain areas responsible for the execution of the newly modified tests. In addition, this study was a validation study (construct validity check) to verify that the tests depend on brain structures that are vulnerable to early pathology and are affected earlier on in the disease progression. Indeed, this study has confirmed that some of the areas involved in the modified CFT and CNT are areas that are well-documented to experience cell loss and build-up of NFT. Moreover, this study confirms the widely distributed semantic system (Binder et al., 2009) and the involvement of various areas in the linguistic semantic tasks.

The CFT and CNT together require the use of mainly frontal and temporal lobes, including the medial temporal cortex, and parietal and occipital cortex. The areas involved in the newly modified CFT are the temporal areas bilaterally, and the medial temporal regions including the right parahippocampal, uncus and anterior cingulate; the frontal cortex bilaterally, left insula and right rectal and orbital gyri. These are structures that have previously been reported in studies on neural correlates of the standard CFT (Grogan et al., 2009; Rodriguez-Aranda et al., 2016; Zhang et al., 2013). An exception from some previous studies is the recruitment of the cerebellum that was not involved in the present test (Grogan et al., 2009; Rodriguez-Ferreiro et al., 2009).

For the standard CNT the structural correlates underlying the execution of the standard CNT are similar to those associated with the CFT except for the frontal lobe which does not seem to influence performance on the CNT (Zhang et al., 2013). The structural correlates underlying the execution of the BNT in old age are bilateral temporal lobes, and left hippocampi and parrahippocampal gyri (Zhang et al., 2013). These are areas important

for semantic processing that are damaged earlier on during AD (H. Braak & Braak, 1995). The fusiform gyrus is also associated with the performance on naming (Zhang et al., 2013). An association between loss in the left fusiform gyrus and naming difficulties has been reported in people who receive a clinical diagnosis of AD, 12 months prior to diagnosis (Pravata et al., 2016). The same neural pattern was observed on the execution of the automatic functioning task of CNT. In the present study associations between scores and GM density values in the Automatic CNT scores and right parahippocampal gyrus, sub-gyral and insular, important for language, Right precentral gyrus, IFG, STG, middle temporal gyrus were shown. A different pattern of structural correlates emerged for the performance on the executive task of the CNT. Associations between scores and neural substrates were shown for the right precentral gyrus, sub-gyral and supramarginal gyrus, inferior and superior parietal lobes, precuneus, superior occipital gyrus, STG, cingulate gyrus, the frontal area and the left paracentral lobule. The difference between the automatic and executive tasks is that the latter requires more functioning of the frontal region which is also observed in the CFT, which is currently considered as the optimal semantic test.

A difference highlighted in the present study relative to other studies using the CNT is the lateralisation of the right hemisphere. This was not expected as the group was mainly made up of older adults but a study on older adults was found, that gives importance to the right hemisphere (Obler et al., 2010). This goes against the Hemispheric Asymmetrical Reduction in older adults model (Cabeza, 2002).

It is important to highlight some limitations for this study. Data from voxel based correlation should be taken with a degree of caution given the nature of the variables. Moreover, the sample group was made up of a relatively small and heterogeneous group.

This might be the reason for the lack of cluster correlation with GM analyses. Given the mixed composition of the sample (including both healthy and participants with dementia) one could argue that the findings might reflect the difference in severity between the two groups rather than a link with semantic impairment. If that were the case no difference should have been seen between the different semantic variables, and similar findings should have been detected with all semantic variables. Separate analyses with reasonably sized sample would have been ideal, nevertheless the differential results obtained in the different semantic variables are most likely a genuine reflection of the differential effects that anatomical damage has on the different semantic variables. A more homogenous sample group would be desirable for this study with the recruitment of young adults to see if there are any changes between young and old neural patterns for the performance of these tasks as well as the recruitment of a more homogenous patient sample. Although the small and mixed sample size makes the study less reliable, the generated data fulfil the purpose of the study which is to verify the anatomical structures required for the new tasks.

In summary, these tasks require the use of areas that are of most interest due to their low resistance to AD pathology. These include the medial temporal area, temporal region and frontal region. Additionally, these newly devised tasks require the involvement of more areas in general. Any atrophy in any of the neural regions would impair performance. Due to the higher demand on frontal regions, it is expected that these tests are more sensitive relative to current tests and might be better at identifying people at risk of developing the disease. Future studies would be required to explore functional patterns during such tasks. Disconnections between areas might influence performance early on in the disease progression.

Study 5.4. Semantic memory performance in healthy ageing

5.4.1 Introduction

The major challenge for an AD clinical marker is its sensitivity in distinguishing early symptoms from age-related decline. The most prominent symptoms of early AD are likewise experienced in healthy ageing. Such deficits are reported in episodic memory, executive function and attention (Buckner, 2004; Kirova, Bays, & Lagalwar, 2015; Nyberg, Backman, Erngrund, Olofsson, & Nilsson, 1996). Although a degree of cognitive decline is physiological in healthy ageing, some cognitive functions are relatively well preserved. SM is one of the age-resilient cognitive functions (Lacombe, Jolicoeur, Grimault, Pineault, & Joubert, 2015; Nyberg et al., 1996; Spaniol, Madden, & Voss, 2006); this feature adds potential to SM as an early clinical marker for AD.

SM can be assessed by measuring semantic knowledge, which is also referred to as word knowledge or vocabulary. Semantic knowledge is acquired through experience; the number of words stored in SM, therefore, is expected to be positively associated with age. Conclusions from a meta-analysis on experimental research on cognitive functioning, report an age effect on vocabulary scores favouring older adults (P. Verhaegen, Borchelt, & Smith, 2003) who seem to have a more stable and elaborate semantic storage than young adults. Word knowledge does increase with age, but a slight decrease is also common during and after the 6th decade (Salthouse, 2014), and this is mainly observed in linguistic semantic tasks such as confrontation naming and semantic fluency. These changes are attributed to secondary processes required for a given task such as a decline in processing speed, working memory, attention and executive functioning (Elgamal, Roy, & Sharratt, 2011; Glisky, 2007;

Kemper et al., 2001), which lead to the slowing down of the mechanism involved in word retrieval (Kave & Mashal, 2012).

Word knowledge (automatic functioning) and word retrieval (executive functioning) are separate but interdependent processes required for linguistic semantic tasks. Studies show that older adults perform better than younger adults on tests based on word knowledge (Stolwyk et al., 2015) due to their extensive vocabulary. This performance is reversed on tests that require word retrieval, although the difference between the young and older adults is less pronounced for the latter mechanism (Kave & Yafe, 2014). This is supported by behavioural studies exploring CFT performance in different age groups. CFT requires associative and retrieval mechanisms in addition to working memory (Siddiqui et al., 2008) and it seems that in younger individuals this multi-functional process is more efficient than in older people (Stolwyk et al., 2015).

The above decline is further confirmed by neuroimaging studies reporting age-related changes in brain activation patterns (Lacombe et al., 2015; Manenti et al., 2013; Meinzer et al., 2009). In a study looking at the performance of young and old adults on the CFT, it was found that older people make use of additional right middle and inferior-frontal brain areas instead of the left areas observed in younger adults, this is thought to reduce the efficiency of word-retrieval (Meinzer et al., 2009). On the other hand, high performing older adults are thought to reduce prefrontal asymmetry (compared to younger adults) to counteract age-related changes, which seems to be beneficial for better word finding abilities in old age (Manenti et al., 2013).

It can be implied that language comprehension is preserved for longer compared to language production. Language comprehension abilities in healthy old adults are similar to

those in young adults (Silagi et al., 2015). One of the few differences observed across time is that older adults require more time to understand and make sense out of a sentence, but an age effect is mainly present for the processing of complex sentences (Silagi et al., 2015). Multiple cognitive processes are involved in the understanding of language (DeDe & Knilans Flax, 2016) and these can be commonly affected by age-related changes. Such components are working memory, executive functioning and meta-comprehension in the case of reading comprehension (De Beni, Borella, & Carretti, 2007; Silagi et al., 2015). These changes are counteracted by expert language skills acquired through experience as well as neural compensations which allow normal functioning of the language comprehension system (De Beni et al., 2007; DeDe & Knilans Flax, 2016; Peelle et al., 2010).

Although some aspects of linguistic function are subjected to age-related changes, language tasks that assess SM are considered to be well preserved in healthy ageing and hence, good clinical tools to detect AD symptoms. This is why tests like CFT, CNT and SCT are of interest when it comes to AD assessment. The main aim of this chapter is to explore the performance of older adults on the modified tests presented in the previous sub-chapters and how this compares to that of young adults. From previous literature we expect a similar performance between the different groups of adulthood since SM is well preserved across age. It is expected that old adults would perform slightly worse than younger adults due to the decline in executive functioning and processing speed. As SCT requires the understanding of language and has no time limit, we expect that the performance on this test would not vary across the different age groups.

5.4.2. Methodology

5.4.2.1 Participants

The participants recruited for the collection of normative data were also part of this study to explore the performance of different adult groups on the novel tests. The hundred and twenty-eight native English speakers were divided into three groups according to their age; 30 participants formed the young adults group (aged younger than 45 years), 35 participants were part of the middle adults group (over 45 and younger than 65 years), and 63 participants were part of the older adults group (65 years or older). The sample was made up of healthy volunteers with no subjective cognitive complaints. Global cognitive functioning and fluid intelligence were measured using the MMSE and the Raven's Progressive Matrices. Exclusion criteria included psychiatric symptoms, history of transient ischemic attacks, seizures and convulsions, head injuries, and substance abuse problems. These were ruled out using a detailed interview regarding previous and current medical history. Ethical consent was granted by the Medical School Ethics Committee of the University of Sheffield.

5.4.2.2 Materials and Procedures

SM performance from the different age groups was compared using the newly modified testing material and procedures introduced in the previous study. For the CFT 6 categories (2 living, 2 non-living and 2 mixed) we administered to the participants. The CNT was made up of 20 pictures of whole objects (automatic functioning) and 20 pictures of part of an object (executive functioning). The SCT consisted of fill-in-the-blank sentences. 10 sentences were LS and 10 were FOS. (More information regarding the testing material and procedure is provided in section 5.1.2).

5.4.3 Results

5.4.3.1 Demographics

The mean, SD and range values of age, number of years of education, MMSE and Raven's progressive matrices scores are reported in Table 5.11 together with the groups' gender ratio. As required by this study a significant difference in age was present between the three groups [F (2,125) = 467.09, p = 0.000]. No significant difference for the male-to-female ratio was reported for the groups [χ^2 (2, N = 128) = 0.44, p = 0.80]. A difference in YoE was reported between the young and old adult groups [p = .002] with the younger sample group having approximately two more years of education. No significant difference was reported between the number of YoE of the young and middle age groups [p = 0.54] and the middle age and old groups [p = 0.12]. The clinical scores for each participant were above the cut-off scores for normal performance but small differences were present between the three groups. An overall difference was reported for the MMSE score F (2,125) = 3.23, p = 0.04] but Bonferroni post hoc tests reported no significant difference between neither of the group pairs, young and middle age groups [p = 0.96], young and old groups [p = 0.58], middle age and old group [p = 1.00]. A significant difference was also present between the young and old groups [p = 0.01] and the middle age and old groups [p = .007]. There was no difference between young and middle age adults [p = 0.96].

Table 5.11: Mean (SD, range) values and range for the demographics and clinical data of the three groups.

	Young adults	Middle adults	Old adults
No. of participants	30	35	63
Age	29.67 (SD = 7.74, Range = 20-44)	56.91 (SD = 5.66, Range = 46-64)	73.00 (SD=6.08, range = 65-90)
Gender	11M 19F	12M 23F	19M 44F
YoE	17.40 (SD = 2.82, range = 13-27)	16.46 (SD = 2.76, range = 10-22)	15.23 (SD = 2.82, range = 10-23)
MMSE	29.47 (SD = 0.78, range = 27-30)	28.97 (SD = 0.86, range = 27-30)	28.98 (SD = 1.01, range = 26-30)
Raven's	33.79 (SD = 1.70, range = 29-36)	33.91 (SD = 1.84, range = 27-36)	32.94 (SD = 3.03, range = 25-36)

5.4.3.2 Modified confrontation naming test

The data ware non-normally distributed and therefore the non-parametric Kruskal-Wallis test was used for this part of data analysis. Although education was slightly lower in the older group in comparison to the younger group, in the normative study presented in Study 5.2 it was reported that YoE had no influential effect on the test scores and therefore Kruskal-Wallis H test could be carried out. The median and range for each part of the test are reported in Table 5.12. There was a statistically significant difference in performance score for the executive test component between the three groups [$\chi^2(2)=23.06$, $p = 0.000$] with a mean rank score of 81.03 for the young group, 76.91 for the middle age group and

49.73 for the old group. Post hoc Bonferroni comparisons revealed a significant difference between the young and the old group [p = 0.000] and between the middle age and the old group [p < 0.001] but no significant difference was present between the young and the middle age groups [p = 0.631]. A statistically significant difference was also present for the automatic test component [$\chi^2(2)$=20.29, p < 0.001] with a mean rank score of 81.57 for the young group, 72.09 for the middle age group and 52.16 for the old group. A significant difference was present between the young and old group [p <0.001] and the middle age and old group [p =0.009] but no difference was revealed between the young and middle age group [p =0.687]. Similar results to the individual components were present for the total score where an overall significance level was reached for the three groups [$\chi^2(2)$=31.06, p < 0.001] with a mean rank score of 87.02 for the young group, 76.64 for the middle age adult group and 47.03 for the old adult group. Bonferroni comparisons showed a significant difference between the young and old group [p =0.000] and middle age and old group [p < 0.001]. No statistically significant difference was present between young and middle age adult groups [p =0.729].

Table 5.12: The median (Range) for each test component and the total score on the modified CNT for the three adult groups.

CNT	Young adults	Middle adults	Old adults
Executive score	20 (18-20)	20 (18-20)	19 (11-20)
Automatic score	20 (18-20)	20 (18-20)	19 (15-20)
Total score	40 (38-40)	39 (38-40)	38 (26-40)

Further analyses were carried out to compare total performance scores between each separate decade starting from the 2nd decade up to the 8th decade (20-30, 31-40, 41-50, 51-60, 61-70, 71 -80, 81+). Kruskal-Wallis test showed an overall significant difference [$\chi^2(6)$=36.13, p = 0.000] with mean ranks of 80.91 for the 2nd decade, 87.89 for the 3rd decade, 89.60 for the 4th decade, 78.35 for the 5th decade, 64.66 for the 6th decade, 40.93 and 26.25 for the 7th and 8th decades respectively. Bonferroni comparisons revealed a significant difference between the 2nd and 7th decade [p =0.007], 3rd and 7th decade [p = 0.013], 4th and 7th decade [p = 0.005] and 5th and 7th decade [p = 0.014]. The same decades, 2nd, 3rd, 4th, and 5th, showed a significant difference with the 8th decade [p = 0.009], [p = 0.008], [p = 0.004] and [p = 0.014] respectively. Similar performances were observed between the first 5 decades, after which a slight decline is present with a further decline after the 8th decade.

5.4.3.3 Modified category fluency test

A MANCOVA was carried out to compare the performance of the three adult groups on the modified CFT. Each category was analysed separately with YoE entered as a covariate to eliminate any education bias. Figure 5.7 represents the mean scores of the three groups on each category and Figure 5.8 represent the total score of the CFT. A significant main effect for group was found [F (14, 238) = 2.22, p = 0.008]. Similar results on individual categories were found for the three groups. Exploring each category separately a significant difference was present on two of the categories, 'Items that melt when heated' and 'Items that can fly' where the older adult group performed significantly better than the young adult group [p = 0.05] and [p = 0.01] respectively. No significant difference was present for

the other categories, 'Animals without a tail' [*p* = 0.055], 'Separate items that come in pairs'

[*p* = 0.552], 'Fruit and vegetables that come in different colours' [*p* = 0.389] and 'Items

fastened with a zip [*p* = 0.285]. The middle age group (M=52, SD =12.69) generated most

words in total followed by the old group (M= 49.19, SD = 10.15) and the young group (M =

47.80, SD = 11.49), but the difference was not statistically significant [*p* = 0.218]. The

covariate, YoE, was not significantly related to the category performance [*F* (7, 118) = 1.49, *p*

= 0.177].
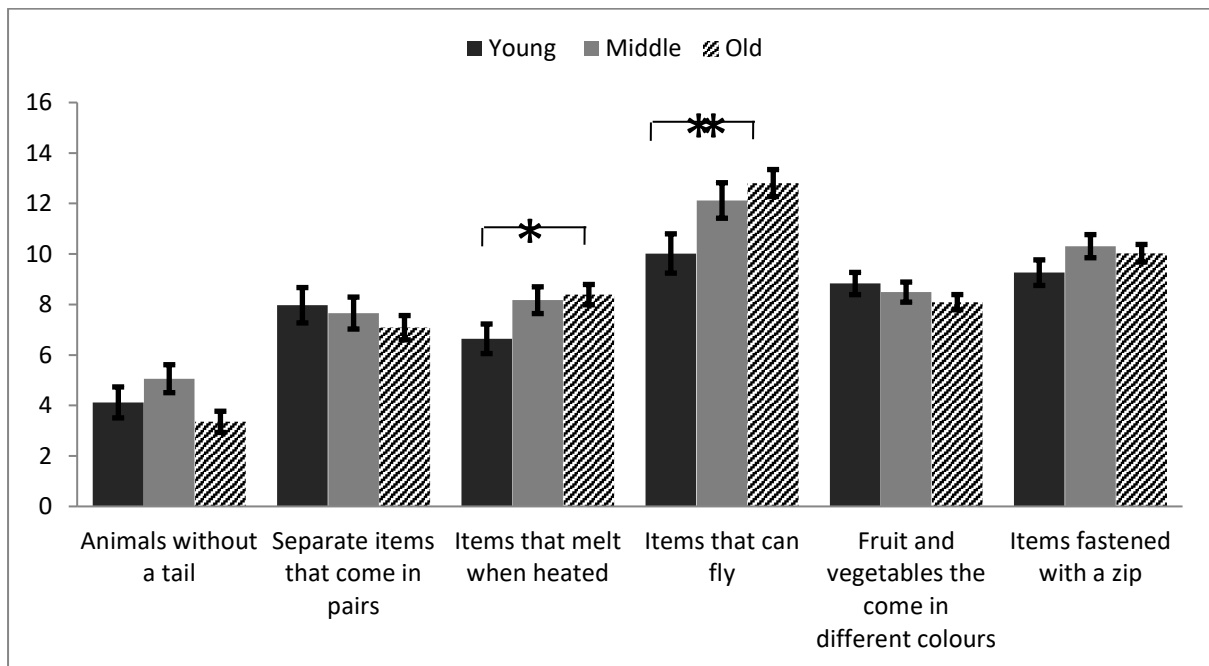
Figure 5.7: A graph representing the mean scores (S.E) of the three groups on the individual categories presented in the modified CFT.

* Significant difference *p* < 0.05
** Significant difference *p* <0.01
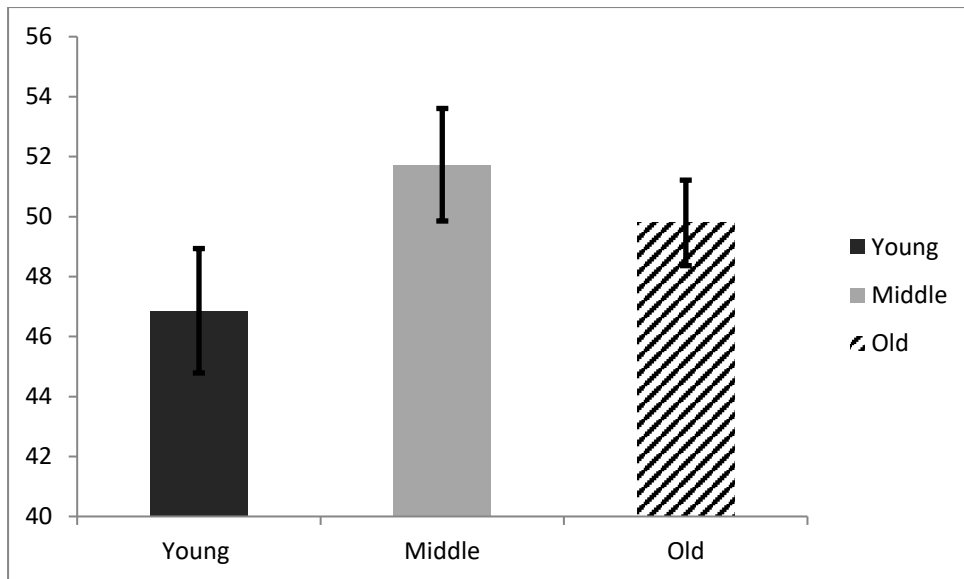
Figure 5.8. A graph representing the mean total score of the modified CFT for the young, middle age and old adult groups.

5.4.3.4 Sentence completion test

Due to the non-normal distribution of data, Kruskal-Wallis test was used for the comparison of the three adult groups on the performance of the SCT. The median scores and range for each test and the total score are presented in Table 5.13. The Kruskal-Wallis H test showed no significant difference for the executive component of the SCT [$\chi^2(2)$=3.55, p = 0.170] where mean ranks scores were 60.85 for the young adult group, 72.51 for the middle age group and 61.80 for the older group. No statistically significant difference was found for the automatic component [$\chi^2(2)$=3.14, p = 0.208] with mean rank score of 68.33, 68.64 and 60.37 for the young, middle age and old groups respectively. No significant difference was present for the total score of the test either [$\chi^2(2)$=3.59, p = 0.166], where mean rank scores were 65.98 for the young group, 72.31 for the middle age group and 59.45 for the old group.

Table 5.13: The median (Range) for each test component and the total score on the modified SCT for the three adult groups.

SCT	Young adults	Middle adults	Old adults
Executive score	10 (6-10)	10 (9-10)	10 (8-10)
Automatic score	10 (7-10)	10 (7-10)	10 (8-10)
Total score	20 (15-20)	20 (17-20)	20 (17-20)

5.4.4 Discussion

A different clinical performance pattern for healthy ageing and AD would be highly beneficial in establishing a tool that could discriminate between the two types of ageing during the early stages of the disease. The primary aim of this study was to explore the performance of young and old adults across 7 decades on the newly modified tasks. Similar performance for different age groups would confirm the stability of SM in healthy ageing and support the use of linguistic SM tests for early AD diagnosis. Overall, findings from this study do suggest a stable semantic system with a slight decline in old age which was mostly pronounced in picture naming abilities.

Despite the evidence of an extensive semantic store in old age which is indicated by various clinical tests such as word-definition tasks and reading tests, a difference in performance on naming is still reported in most aging studies (Connor et al., 2004; Mackay et al., 2002; Tsang & Lee, 2003; C. Verhaegen & Poncelet, 2013). Therefore, a change in performance for older adults on the CNT administered in this study was expected. Performance is stable until the age of 70 years and from there onwards a slight decline is observed. A study exploring the mechanism deficit underlying SM impairment suggests that the decline in naming is due to processing speed rather than a decline in semantic memory (Spaan, 2015). In the current study, older participants (aged 71 years and over) exhibited

similar performance on the automatic and executive tests with a slight disadvantage for the latter, and relative to the other adult groups the performance on both tests differed significantly. This study confirms previous findings (Mackay et al., 2002; Nicholas et al., 1985; Schmitter-Edgecombe et al., 2000) that in healthy ageing a change in naming abilities starts around the 7th decade which is further pronounced after the 8th decade. Considering that naming impairment starts earlier on in the AD process (Verma & Howard, 2012), this test would still be beneficial in identifying pathological cognitive functioning from healthy ageing.

The results from the CFT suggest that verbal knowledge reaches its peak during middle adulthood and declines slightly after that although it is relatively preserved across the years and can be considered better than that in younger adults. This is evident in the higher number of words generated by the middle age and older adults. Age has been previously reported to have a negative influence on the performance of the CFT (Brickman et al., 2005; Mathuranath et al., 2003), however, a positive effect has also been reported for clustering scores in CFT (Lanting et al., 2009) which suggests a large, stable semantic storage. A decline in processing speed and executive functioning seems to be responsible for the decline in performance on the CFT (Spaan, 2015). This is not supported by the current study, where older adults performed as well as young adults even though more executive functioning is required. An explanation for this finding could be that these categories are more specific than previously used categories and therefore require a more extensive vocabulary that younger people might lack. All three groups performed qualitatively the same and can be confirmed that on categories that generate the greatest number of words, the older group performed better than the other two groups.

Language comprehension is the most spared cognitive function in healthy ageing and is aided by neural compensation (Peelle et al., 2010). Multiple cognitive processes are involved when it comes to reading and understanding a sentence, including recognising words, building up of a mental representation of the relationship between words, and giving relevant meaning to words (DeDe & Knilans Flax, 2016). Age-related changes associated with reading comprehension are working memory and metacognitive knowledge (De Beni et al., 2007) which, although they have an effect on understanding sentences, the changes are minimal and not detectable in daily living. The findings in the present study are in line with this, since older adults performed slightly worse than the younger participants but the difference did not reach significance levels.

A few limitation factors need to be taken into consideration. As mentioned in the previous chapters the participants who volunteered to take part in this study are not only highly educated but they also keep their brain engaged by participating in cognitively stimulating activities such as learning a new language or instrument and participating in history classes as well as social activities such as gaming and hiking groups. Another limitation is the level of tasks. Close to ceiling effects were observed for the younger groups, this could not be avoided since the tests were designed for patients with AD and mainly older adults, therefore, testing material had to be appropriate for this population as difficult tests might cause frustration.

In conclusion, semantic performance remains stable until the age of 70 years followed by a slight decline. Performance on executive functioning is slightly worse than that observed on automatic functioning, but the difference is minimal. Language comprehension is the most preserved function assessed in this study while naming abilities

are the most impaired in old age. The similarities in performance between different ages

suggest that these tests could be a potentially good tool to track cognitive decline in AD. The

tests that would probably contribute most in AD diagnosis would be the modified CFT since

a good performance is exhibited by people in their middle and old adulthood relative to

young healthy adults.

Study 5.5 Assessing SM impairment in patients with MCI prodromal AD: A pilot study

5.5.1 Introduction

More importance has been given to research on detecting early symptoms of AD and establishing methods that can identify people at risk of developing the disease. It is commonly agreed that subtle cognitive decline are present decades before the clinical onset of the disease (Amieva et al., 2005). Semantic deficits are present during the early stages of the disease, with some studies reporting its presence one to two decades before clinical diagnosis (Garrard et al., 2005; Le et al., 2011; D. A. Snowdon et al., 2000; Vogel et al., 2005). On the contrary, SM is well preserved in healthy ageing (McGeown et al., 2009) and can be beneficial in discriminating between the two types of ageing. Increasing research is claiming that SM measures could be beneficial clinical tools for the diagnosis of early AD (Cuetos et al., 2007; Cuetos et al., 2010; Venneri et al., 2016) if these tests are sensitive enough in detecting the subtle changes experienced during the preclinical stage of the disease.

Two commonly impaired SM tests are the CFT and the CNT with the former having higher sensitivity to AD pathology (Balthazar et al., 2007). CFT shows a decline in performance before clinical diagnosis (Howieson et al., 2008) which makes it a powerful diagnostic test. In a longitudinal study investigating the cognitive profile of AD, starting from the healthy stage through to the clinically diagnosed stage, the authors reported a change in CFT four years before the onset of the disease (Mistridis, Krumm, Monsch, Berres, & Taylor, 2015). CNT is also impaired and gets worse with disease progression (Silagi et al., 2015). The pattern of naming errors changes and the number of no responses increases (Silagi et al.,

2015) especially for names with low frequency and late acquired words (Cuetos et al., 2015).

CNT is a good research tool to understand SM impairment in AD but it is less useful for

diagnostic purposes during the early stages of the disease (Katsumata et al., 2015; Testa et

al., 2004; Vogel et al., 2005). Although both the above tests assess SM, they involve

different processes to reach the appropriate answer and while the CNT is mostly relying on

semantic information, the CFT requires executive functioning in addition to the involvement

of semantic memory. The different mode of assessment required for the two tests could be

the explanation for the variation in performance.

As described in the previous chapters, SM is made up of two components, semantic

representation (automatic functioning) and semantic control (executive functioning).

Deficits in both components have been previously documented in AD studies. Some studies

described the impairment as loss of semantic knowledge (Hodges et al., 1992; Mardh et al.,

2013), in particular, information about sensory and physical attributes of items (Garrard et

al., 2005; Kirchberg et al., 2012) and distinctive, non-shared features (Flanagan et al., 2013;

Garrard et al., 2005). Other studies implied problems with the retrieval processes of

semantic information (Arroyo-Anllo et al., 2011; Lipinska & Backman, 1996) and it is

suggested that such impairment is present before the degradation of semantic information

(Duong et al., 2006).

A semantic task requires the retrieval of semantic information which in turn involves

a strategic search of stored representation in the semantic storage in the medial temporal

lobe. During an automatic semantic task the search would give rise to one memory but

during an executive task the search would give rise to more than one semantic

representation/memory which will be maintained in working memory by the PFC. In order

to perform the task well according to a given context, the dorsolateral PFC is then responsible for the comparison of the retrieved information and to match it to the retrieval criteria (Simons & Spiers, 2003).

The main question addressed in this chapter is whether the impairment of SM is related to a deficit in automatic functioning, executive functioning or both semantic components. This study contributes to the understanding of the nature of impairment of SM in early AD by establishing a pattern of impairment on a small sample size and to explore whether this is different from that presented in healthy ageing. A secondary aim of this study was to assess whether the newly modified tests proposed in the previous chapters were more sensitive than the current used semantic tests by comparing results from the current standardised tests and the newly modified ones. We hypothesised that patients with a diagnosis of early AD (MCI prodromal AD) will be distinguished from age-matched healthy volunteers mainly by tasks measuring executive functioning and the novel tests will be more sensitive in discriminating the two types of ageing. Emerging patterns from this pilot study will determine whether the study is worth applying to a larger sample size.

5.5.2 Methodology

5.5.2.1 Participants

Nineteen participants, 8 patients with MCI and 11 cognitively healthy controls (CH) were recruited for this study. All participants in the patient group were recruited through the Memory and Dementia Clinic at the Royal Hallamshire Hospital in Sheffield and had a diagnosis of MCI prodromal AD according to the clinical criteria proposed by Petersen et al., (2011). Although all participants were in the early stage of the disease, two of the patients

had even milder symptoms and performed within normal cut-off scores in certain tests such as the MMSE. The diagnosis of these two patients was later confirmed by a follow up session. The control group included matched CH participants who volunteered to participate in Alzheimer's Disease research studies. Exclusion criteria included non-native speakers, history of cerebrovascular disease, brain injury, epilepsy, substance abuse and psychiatric disorders or treatment. Ethics approval for the study was granted by the Medical School of Sheffield (SMBRER255) and Sheffield Regional NHS ethics (12/YH/0474).

5.5.2.2 Materials and procedure

Both groups were administered the modified CFT, CNT and SCT. Please refer to Section 5.4.2.2 for detailed instructions regarding the testing material and procedures used in this study. In addition to the modified tests, participants were also tested on the current clinical standardised CFT and CNT. For the CFT participants were requested to list as many items that could think of in 60 seconds on three given categories, 'Animals', 'Fruits' and 'Cities.' The total raw score of the three categories was used for the purpose of this study. The short version of the Boston naming task was used as the standardised CNT. Participants were requested to name presented stimuli which consisted of 20 black and white drawings

5.5.3 Results

5.5.3.1 Demographics and clinical status

Patients and healthy participants were matched for age, YoE and gender. An independent sample *t*-test was carried out to compare demographics and neuropsychological performance between the two groups. The mean (SD, range) age, YoE and gender ratios of both groups are reported in Table 5.14. There was no significant difference between age [*t*

(17) = -0.861, p = 0.401], YoE [t (17) = 1.69, p = 0.110] and gender [χ^2 (1, N = 19) = 0.833, p = 0.361]. The two groups were also compared on MMSE to assess the global cognitive function and the standardized SM tests. The mean values (SD, Range) are presented in table 5.14. A significant different was reported for MMSE score [t (8.31) = 3.15, p = 0.013], standardized CFT score [t (17) = 6.72, p =0.000]. No difference was reported for the performance on the standardized CNT [t (16) = 0.45, p =0.66].

Table 5.14: The mean values (SD, Range) of age, YoE, neuropsychological scores, and gender ratios for the patient with MCI, and healthy participants group.

	Patients with MCI	Healthy participants
No. of participants	8	11
Age	70.63 (SD = 10.32, Range = 56-88)	66.64 (SD = 9.71, Range = 52-86)
Gender	2M 6F	5M 6F
YoE	13.00 (SD = 2.84, range = 10-18)	15.00 (SD = 2.32, range = 10-18)
MMSE*	25.13 (SD = 3.09, range = 20-30)	28.73 (SD = 1.10, range = 26-30)
Standardized CFT*	34.00 (SD =11.34, range = 19-58)	65.64 (SD = 9.19, range 52-81)
Standardized CNT	19.13 (SD = 0.83, range = 18-20)	19.30 (SD = 0.82), range = 18-20)

* A significant difference between the two groups was present

5.5.3.2 Executive and automatic functioning: Within and across group differences

A two-way ANOVA was administered to assess the performance of executive and automatic functioning within the groups. This will give insight to whether one of the two components

is more impaired than the other and whether the pattern of impairment is different between the two groups. For this analysis the modified CNT and SCT were assessed and the model consisted of executive and automatic functioning as the type of semantic measure, and patients with MCI and healthy participants as the group types.

For the first model, the scores from the modified CNT were analysed. The mean scores and SD values for each group are reported in Table 5.15. A main effect for the type of semantic measure yielded an F ratio of [F (1,34) = 11.54, p =0.002] indicating a significant difference between executive (M = 17.21, SD = 2.59) and automatic functioning (M= 19.11, SD = 1.15). A significant main effect for the group type was also present [F (1,34) = 7.88, p = 0.008] indicating a significant difference between the performance of patients (M = 17.19, SD = 2.64) and healthy participants (M = 18.86, SD = 1.52). No significant interaction between group and semantic measure was present [F (1,34) = 2.01, p = 0.165].

For the second model the scores from the modified SCT were analysed. The mean scores and SD values for each group are reported in Table 5.15. A significant main effect was present for group type [F (1,34) = 4.52, p =0.04], but no significant impact was found for the semantic type [F (1,34) = 2.63, p = 0.114]. The interaction between the effect of group and the semantic measure was not significant either [F (1,34) = 2.63, p = 0.114].

Table 5.15: Mean (SD) scores for executive and automatic modified CNT and SCT for the patients and healthy groups.

Test	SM type	Patients MCI Mean (SD)	Healthy Mean (SD)
CNT	Executive	15.75 (2.91)	18.27 (1.79)
	Automatic	18.63 (1.30)	19.45 (0.93)
SCT	Executive	8.62 (1.41)	9.64 (0.50)
	Automatic	9.50 (0.76)	9.64 (0.50)

Performance on the CFT from the patients' group was compared to that of the healthy group by a simple independent sample t-test for the six categories. The modified CFT requires more executive functioning than the standard test but the six categories vary in difficulty level. These results will give insight into the pattern of impairment in exercising executive functioning for CFT and whether the two groups exhibit similar performance on individual categories. The mean values and SE bars are presented in a graph (Figure 5.9). The patient group performed worse than the healthy control group on all six categories. A significant difference in performance was present for most of the categories; Items fastened with a zip [t (17) = 2.45, p = 0.025], Animals without a tail [t (17) = 2.67, p = 0.017], Items that can fly [t (17) = 3.71, p = 0.002] and Fruit and vegetables that come in different colours [t (17) = 2.964, p = 0.009]. No significant difference was present for Separate items that come in pairs [t (17) = 1.106, p = 0.284] and Items that melt when heated [t (17) = 1.017, p = 0.323].
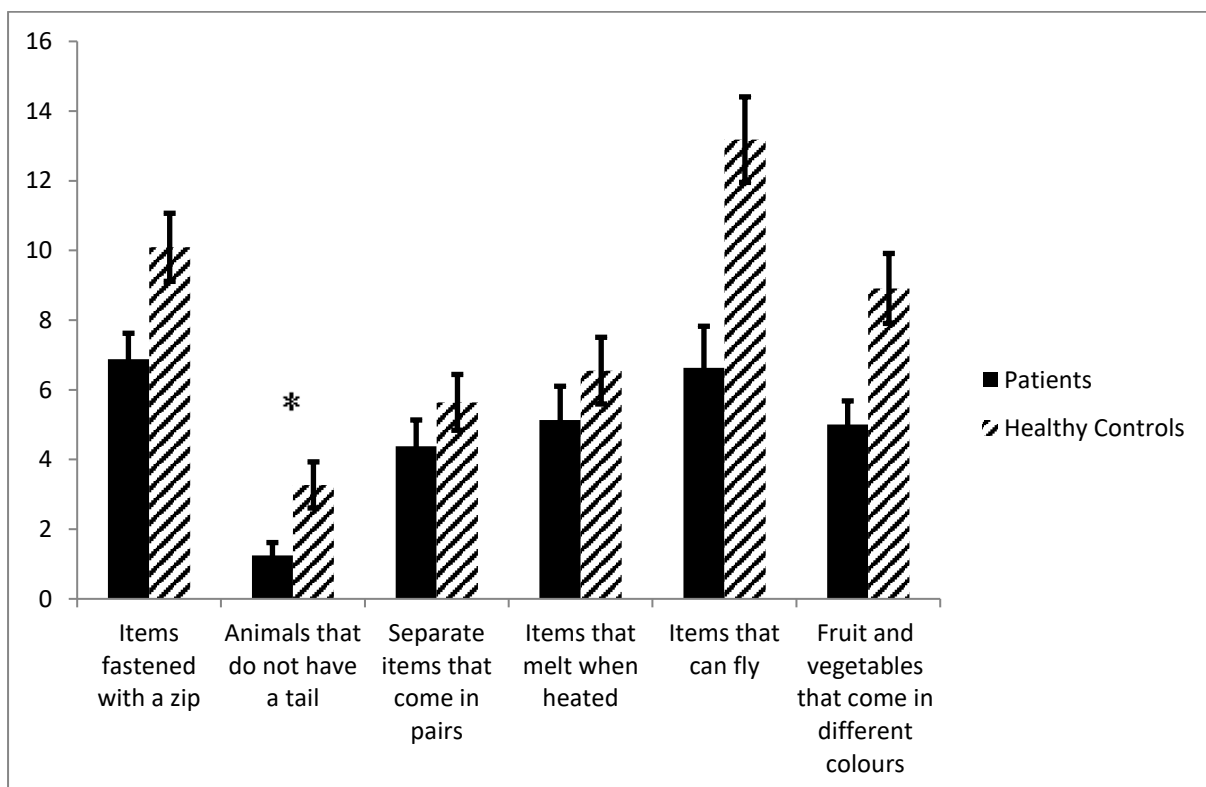
Figure 5.9: A graph representing the mean values with standard error of each category for the two groups. The solid black bars represent the patients' mean scores while the patterned bars represent the healthy controls' mean scores.
* Significant difference between the two groups.

5.5.3.3. Performance difference between the two groups on standardised and novel tests.

An independent *t*-test was also performed to identify differences between test scores for the standard and novel tests. For the modified CNT and SCT the scores for the different semantic measures were taken into consideration to assess whether one of the types is more sensitive in discriminating the two types of ageing. The performance of the patients' group was always poorer than that of the healthy control group but similar performance was exhibited in the SCT and the standardised CNT. The mean scores and SD are presented in Table 5.16. A significant performance difference was present for the executive measure of modified CNT [t (17) = 2.338, p = 0.032], and the total score of the modified CNT [t (17) = 2.381, p = 0.029]. No significant difference was present for the automatic measure on this test [t (17) = 1.622, p = 0.123]. No statistical significance was reported for the standardised CNT [t (17) = 0.445, p = 0.662]. The performance of the two groups differed significantly on the modified CFT [t (17) = 4.437, p = 0.000] as well as the standard CFT [t (17) = 6.721, p = 0.000]. Performance on the SCT was similar in the two groups with no significant difference on either of the measures, [t (17) = 1.943, p = 0.087] and [t (17) = 0.181, p = 0.666] for executive and automatic measures respectively nor for the total test score [t (17) = 1.673, p = 0.113].

Table 5.16: Mean values and SD of the two groups on tests

Tests	Score type	Patients Mean (SD)	Healthy controls Mean (SD)
	Executive*	15.75 (2.91)	18.27 (1.79)
Modified CNT	Automatic	18.63 (1.30)	19.45 (0.93)
	Total*	34.38 (3.74)	37.73 (2.41)
Standard CNT	Total	19.13 (0.835)	19.30 (0.835)
Modified CFT	Total*	29.25 (9.39)	47.64 (8.57)
Standard CFT	Total*	34.00 (11.34)	65.64 (9.19)
	Executive	8.63 (1.41)	9.64 (0.50)
SCT	Automatic	9.50 (0.76)	9.64 (0.50)
	Total	18.13 (2.03)	19.27 (0.90)

 * Significant difference in performance

5.5.4. Discussion

This pilot study addressed the SM impairment debate by using modified tests to optimise the identification of subtle semantic decline. Increasing the sensitivity of the tests involved the assessment of the two SM components, semantic representation (automatic functioning) and semantic control (executive functioning) separately. This study contributes to the understanding of semantic memory impairment in AD by establishing whether one of the two components is more impaired than the other and whether tests targeting an individual semantic component can be applied for better and earlier diagnosis.

The Modified CNT and SCT allowed for the direct comparison of executive and automatic functioning of SM. Anomia is a prominent clinical feature of patients with AD (Balthazar et al., 2007; Silagi et al., 2015), yet in this study the performance on the current standardised CNT showed no difference between the scores of patients and age matched healthy participants. Various versions of the 60 item Boston naming test exist and, although

they all have the ability to discriminate healthy people from people with dementia, this ability gets less useful during the early stages of the disease (Katsumata et al., 2015), furthermore, its diagnostic utility is not helpful until the late stages of the disease when patients enter the moderate to severe stages (Testa et al., 2004). This is also observed in the current research study. Despite its lack of sensitivity for early detection of AD, detailed research on confrontation naming in AD shows that picture naming is a major impairment in AD, especially when more challenging stimuli are presented. This instigated the modification of this test as part of this study. Indeed, the modified test had the ability to discriminate people during the MCI stage from healthy ageing; therefore, it is more sensitive to subtle changes than the current versions used in clinical settings. In addition, when the total score was separated into individual automatic and executive functioning scores, the two types of ageing only differed significantly on the executive score. This suggests that executive functioning is impaired before automatic functioning and, although the latter is worse than that observed in healthy ageing, such measure is not sensitive enough to discriminate between early AD and healthy ageing.

Language comprehension is more preserved compared to language production. Currently, the test used for the assessment of language comprehension is the Token Test. Although it offers a good assessment of the patient's auditory comprehension, it is not an appropriate test for the detection of patients with AD or to discriminate these patients from healthy individuals (Paula, Bertola, Nicolato, Moraes, & Malloy-Diniz, 2012). This was also observed in the current study. Although patients performed slightly worse than their matched healthy controls on the modified SCT, the test was not able to discriminate

between the two types of ageing and the executive and automatic scores did not differ significantly.

CFT is a useful test to detect AD (Cerhan et al., 2002) and it is considered as the optimal clinical test in discriminating AD from healthy ageing even during the early stages of preclinical dementia (Clark et al., 2009). One of the reasons for its high sensitivity to cognitive impairment in AD could be that it is not a pure assessment of SM, it relies highly on the semantic storage in the temporal lobe and on the contribution of mediotemporal structures to retrieval, but it also requires executive functioning. A shortcoming of this test is that education level has an impact on performance (Kawano et al., 2010) where poor performance during the early stages of the disease could be masked by high education levels. This led to the design of the modified version of the CFT which requires more executive functioning than the standard test. Results from the current study report poorer performance on the new test compared to the standard one where both patients as well as their matched controls generate fewer words. This new test involves a more challenging semantic retrieval process which makes it less susceptible to compensation by high education and could be a potential test in identifying early impairment even for highly educated individuals.

The pattern of impairment exhibited on the three tests suggests a more impaired executive component of SM. Therefore, the processes required in the access and retrieval of semantic knowledge are impaired before loss of semantic information is present. Although some previous studies report an impairment due to loss of semantic information (Hodges et al., 1992; Mardh et al., 2013) other studies suggested that the impairment appears mainly because of a degraded system (Arroyo-Anllo et al., 2011; Lipinska & Backman, 1996; Nebes

et al., 1984). The mixed results could be in the variation of the sample types and the methodology applied. But a study that explored SM impairment in both early and late AD implied that an impairment in executive functioning was present before automatic functioning (Duong et al., 2006). Hence, considering that the focus of this study was on early impairment and symptoms, the pattern of impairment with a more disturbed executive system is as expected.

Studies report that distinct neuroanatomical areas are responsible for automatic and executive functioning (Binder et al., 2009; Whitney et al., 2011). The left temporal cortex is important for the automatic component, that is, the storage of semantic information, while the left prefrontal cortex is responsible for the executive part, therefore, the ability to choose and retrieve the appropriate context meaning (Badre & Wagner, 2007; Bedny et al., 2008; Wagner et al., 2001). Hence, one can conclude that, for most activities in daily living, semantic cognition involves the interaction of the frontal and temporal areas. The interaction between the two regions is important for memory functioning and the disconnection of the ventrolateral prefrontal cortex and medial temporal cortex can have an impact on tasks that require more effort (Simons & Spiers, 2003).

The function of the temporal lobe has been highlighted in studies of memory functioning in AD, but less importance is given to the frontal cortex which could be responsible for earlier impairment in semantic tasks. Recent neuroimaging studies on MCI pathologies suggest both an early structural as well as functional impairment in the frontal cortex (Niu et al., 2013; L. Wang et al., 2009; Yeung et al., 2016). Frontal cortical thinning is observed during the early stages of the disease (L. Wang et al., 2009; H. Zhao et al., 2015) and it is associated with poor performance on SM tests (Woodward & Woodward, 2009)

and, while confrontation naming is more associated with the temporal region, the CFT is highly associated with the frontal area (Ahn et al., 2011). During semantic fluency fMRI task, healthy individuals exhibit a left lateralization of frontal activation which is not present in people with MCI and it is implied that this underlies the poorer performance in CFT (Yeung et al., 2016). Left lateralised frontal activation has been reported to have a role in memory control and retrieval which is reflected in research that looked at cortical activation in the CFT (Yeung et al., 2016). These studies provide support for an early frontal dysfunction that underlies the executive impairment observed in this study.

Although the pattern of SM impairment and functioning is similar between the two types of ageing, the large discrepancy in executive scores still has the ability to discriminate patients from healthy individuals. This study is particularly interesting when it comes to the modified CNT as it is able to distinguish very early AD from healthy ageing which could be obtained by using solely the executive part of the test.

In conclusion, executive functioning seems to be impaired earlier on compared to automatic functioning of SM. This could be due to the interaction and involvement of the different brain regions that are required and hence, it is the processes involved in semantic cognition rather than loss of semantic knowledge that are impaired first in AD. SM tests that require the use of the frontal cortex in addition to the temporal area might be more sensitive than those relying exclusively on the latter. It is important to take into consideration that the findings are obtained from a small sample group and a larger study needs to be conducted to confirm the results.

Considering the emergent pattern among the small sample size, it can be confirmed that these tests might be more sensitive than the current tests and worth applying it to a

larger sample size. Ideally asymptomatic participants who are at risk of developing the disease should be considered as a research sample for further studies. Furthermore, it would be good to include patients at different stages of the disease and establish whether impairment pattern changes with disease progression. If the results from this pilot study are replicated in a larger study the tests can eventually be used as part of the assessment. Clinical tests are desirable for AD diagnosis. They are non-invasive and relatively easy and cheap to administer. Moreover, no risks or harm are associated with such tests and are therefore ideal markers for such a vulnerable population. These modified tests can increase the sensitivity of clinical neuropsychological assessment with the possibility of identifying people at risk of developing the disease during the time point when they could mostly benefit from the increasing possibilities of therapies. Such tests would allow for the recruitment of a more homogeneous clinical sample rendering the prospect of developing a disease modifying treatment more likely.

5.6 Conclusions

The aim of this study was to design new testing material that can give a better understanding of the semantic memory impairment present in early AD as well as possibly provide tests that are more sensitive to AD pathology. Compared to the standard tests, the newly modified tasks have less age, education and gender bias. In fact, the only impact was age on the performance on the CNT. Therefore, these tests can be applied to people from various backgrounds.

These tests confirm the stability of SM across age with a slight decline during the 7th and 8th decade. This further supports previous studies claiming that linguistic SM tests are good tools to detect cognitive impairment in AD that could differentiate patients from

healthy adults. The test that is mostly sensitive to age-related changes is the CNT while the most resilient system is that involved in reading comprehension.

Both the performance on the automatic functioning and that on the executive functioning are worse than the performance observed in healthy ageing but the difference in scores on the executive tests are larger than those for the automatic tests. This suggests that the SM impairment observed during the early stages of the disease is due to damage to the processes involved in the access and retrieval of semantic knowledge. Moreover, the difference between the performance of early AD and healthy ageing is a quantitative one. Both types of ageing perform less well on executive tasks compared to automatic tasks. The CFT is the optimal clinical diagnostic test. The SCT is only beneficial to test the level of language comprehension, no diagnostic utility emerged from this study. Both the modified CFT and the CNT are more sensitive to early impairment compared to the standard tests.

Chapter 6:

General Discussion

This research project was motivated by the lack of diagnostic tools for early Alzheimer's disease (AD). This area is receiving more importance as the number of elderly people living with dementia is on the increase. Considering the current treatment options and the need for a more accurate diagnostic criterion, it is highly critical to detect people who are at risk of developing the disease before the presence of severe irreversible neural damage. Early accurate diagnostic tests would also be beneficial for clinical trials and research studies where a more homogenous patient group would generate more precise findings that can be applied to the population living with AD.

Semantic memory (SM), a defining feature of human behaviour is a target cognitive feature in AD diagnosis research. It is important for one's behaviour as it is responsible for communication and initiation of speech, it provides meaning to actions and language, and provides the flexibility for interpretation in different contexts. SM impairment is a common symptom in various neurological diseases including dementia of the Alzheimer's type (Garrard, Perry, & Hodges, 1997; Hodges & Patterson, 1995; Kazui & Takeda, 2011). Indeed, increasing research on AD suggests an early impairment in AD (Arango-Lasprilla et al., 2007; Cuetos et al., 2007) which could be beneficial in identifying people at risk of developing clinical dementia. Previous research has explored deficits in SM through linguistic measures generating useful information as well as mixed results that require further research.

The purpose of the present study was to explore further the nature of SM impairment present in AD and establish how this differs from semantic performance observed in healthy ageing to help improve clinical testing. The study consisted of two main parts that made use of different sample groups and techniques to address two common controversies in neuropsychological research. The first study (Chapter 4) addressed the question regarding the dissociation between living and non-living. The category specific impairment has been

studied mostly using confrontation naming test (CNT) with black and white line drawings which has been reported to put living items at a disadvantage. The present study made use of the category fluency test (CFT) with two living categories ('Animals' and 'Fruits') and a non-living category (Thing people wear). To our knowledge this is the first study to assess category dissociation through CFT. This carries the advantage of assessing residual knowledge and eliminates any biases that can put categories at a disadvantage such as the previously reported visual difficulties (Montanes et al., 1995; Sartori et al., 2007; Zannino et al., 2007) or lack of vocabulary knowledge. Retrospective data from patients with mild cognitive impairment (MCI) prodromal AD were compared to a healthy sample group and a group of patients with more severe stages of AD. Additionally, the MCI group was also compared to other dementia types that experience semantic impairment, including frontotemporal dementia (FTD) and vascular dementia (VaD).

The findings from this study confirm a more degraded system for living category although this cannot be explained solely by a category effect. Previous studies on the loss of semantic knowledge have attributed the impairment to lexical features with some studies claiming that variables of words are better predictors of AD than category (Cuetos et al., 2010; K. E. Forbes-McKay et al., 2005; Garrard et al., 2001; Moreno-Martinez et al., 2011; K. Sailor et al., 2004). In this study, the frequency and age of acquisition (AoA) of words were compared for the three categories and results show that categories with words that are higher in frequency and earlier acquired (such as those present in the category 'Animals') are more preserved and easier to generate. Hence, even though living categories seem to be more impaired, the performance outcome is highly influenced by lexical features. This sheds light on the importance of considering word attributes when designing research methods as well as clinical tests for early diagnosis.

Furthermore, this study gives insight into the temporal gradient of vocabulary. Word production decreases over time and becomes more effortful; therefore, vocabulary is time limited. This pattern was observed both in patients with semantic impairment as well as healthy individuals. Although patients during the mild cognitive impairment stage (MCI) perform better than other types of dementia with semantic impairment, the current CFT is not always appropriate for differential diagnosis.

The second part of the project (Chapter 5) addressed the argument whether semantic memory impairment is due to loss of semantic knowledge or due to a damaged semantic system for word access and retrieval. In addition, this test aimed to produce novel tests that could provide more sensitivity to early diagnosis. To reach the goal of this study, standard clinical tests (CFT and confrontation naming test (CNT) were modified and a new sentence completion test (SCT) was designed to test the executive (semantic control) and automatic (semantic representation) components of SM separately. The initial stage of this study involved the designing of the tests (Study 5.1) and the collection of normative data (Study 5.2). An important outcome from this part of the study was the reduction of demographic influences on the tests. Apart from the CNT which had an age effect, the tests were free from any age, gender and education bias.

Findings regarding the performance of old adults on the new tests confirm previous research (Lanting et al., 2009; Stolwyk et al., 2015; P. Verhaegen et al., 2003) that semantic knowledge is not affected by age and older adults perform as well as young adults on tests that rely on word knowledge. SM is a stable system in healthy ageing (McGeown et al., 2009) with most studies on healthy people (Mackay et al., 2002; Nicholas et al., 1985; Schmitter-Edgecombe et al., 2000; Spaan, 2015) including the present one reporting a slight decrease after the age of 70 years. It has been reported that the underlying cause for the

decline is not due to the semantics of language (Elgamal et al., 2011; Glisky, 2007; Kemper et al., 2001) and indeed older adults perform worse on tasks that require more executive functioning of SM.

A pilot study (study 5.5) comparing the performance of healthy individuals and patients with early AD was also carried out to explore the nature of impairment in AD and to assess the sensitivity of these tests compared to the standard ones. Findings suggest that tests requiring the executive functioning of SM are impaired before automatic functioning which could be explained by the early structural and functional damage in the frontal cortex as well as in the medial temporal area (Thompson et al., 2003; P. Wang et al., 2015). As suggested by the anatomical study, these areas are required for a good performance on the new tests. Considering that these tests rely on the functioning of various parts of the brain, it would be beneficial to explore the activation pattern during test performance. An assumption would be that performance that requires the involvement of several brain areas would be more impaired than tests that assess one area due to the early disconnections between distinct brain regions. The neuroanatomical validity study (Study 5.3) confirm that the newly modified tests rely on areas damaged in the early stages of the disease. These areas include the frontal and temporal areas including the parahippocampal gyrus and the uncus.

Comparisons of performance on the standard and new tests suggest that the latter seem to be better at detecting people at risk of developing AD. This could be due to the involvement of various neural areas where a reduction of grey matter volume is experienced earlier on. These tests need to be applied to a larger sample group to confirm results.

6.1 Conclusions

Semantic memory remains stable and world knowledge increases and gets better by age and experience. On the contrary, a progressive degradation of SM for both living and non-living categories is present, with the impairment present during the early stages of the disease. Similar patterns of decline are observed in healthy and AD but it is much more exaggerated in AD. This confirms that semantic tests are good clinical tools for the discrimination between healthy ageing and early AD. Conclusions from both studies together suggest that both the executive and the automatic functioning of semantic memory are impaired but the former is impaired before and tests that make more use of executive functioning might be more sensitive to mild AD pathology. The CFT is the most sensitive test for early AD impairment and its sensitivity increases if more executive load of the semantic system is required. Degradation of semantic knowledge is highly influenced by word attributes, with words that are higher in frequency and have an early AoA being better preserved. These findings contribute to the understanding of the SM impairment observed in AD. The pattern of impairment established can be used as a foundation for future research. Moreover, it provides information regarding the optimal clinical tools for the detection of AD and gives directions in the design of new tests to increase sensitivity of clinical testing.

6.2 Limitations

Some limitations need to be highlighted which can be improved with further research to support the present findings. The main limitation for both parts of the study was the small sample sizes that decrease the credibility of the findings. For the first study, even though it

was a retrospective study, limited data was present for one of the categories that was included for research purposes. For the second study, emails and adverts were sent out and although a large number of healthy volunteers were recruited, some participants were not willing to come for the complete testing session or data could not be used for the study as they fulfilled the exclusion criteria which decreased the number of people in the normative study. The patient sample group was especially small but finding the right patient is harder than a healthy participant and access to patients was more limited. However, the findings confirm that the newly designed tests could be more sensitive than the current ones and beneficial in clinical testing, therefore it is worth taking it further and applying it to larger research groups. Another limitation with regards to the healthy research group is that participants were highly active people and most of them had high levels of education. The method of recruitment used made it hard to target people unless they were interested in dementia studies and the majority of these were highly educated people or people having relative with AD. In saying that, people are getting more active and the education level has definitely increased, so, despite the skewed data, the level of education of the sample group is highly representative of the education level of the current and future population. A larger number of people in the MRI study would also be desirable but funding was limited and the sample recruitment had to be done through another study. Another limitation is that the patient sample group were not as homogenous as desired. In Chapter 4 study 1 both amnestic and non-amnestic patients were included in the study. Although this was sufficient for the purpose of this study further studies should aim to explore the impairment in separate groups to generate more accurate data.

A limitation for the test design also needs to be highlighted. High performing young adults performed very well on two of the tests that are newly designed and a close to ceiling

effect was reached. This was difficult to avoid as the tests were mainly designed for patients with AD and the older population. Both groups perform less well than the healthy young group and therefore harder stimuli could have caused frustration and lack of compliance to finish the testing sessions. Moreover, the high performance in healthy young ageing still offers a discrimination pattern between healthy ageing and early AD and therefore the purpose of the test was still fulfilled.

6.3 Future work

This study highlights the optimal and least relevant tests for an early diagnosis in AD; it also proposes modified versions of current tests to improve early diagnosis and provides information about the degradation of semantic knowledge. This information can be used as foundation for future work to increase the sensitivity of clinical diagnosis in early AD. In the first study, the importance of word attributes was highlighted. Considering the influences of lexical properties on retrieval of nouns, further research on different categories is required. This would generate data on the underlying mechanism of semantic loss and possibly on the organisation of semantic knowledge. This would lead to the design of testing material that has higher sensitivity to early impairment present in preclinical AD. The temporal gradient of SM is a new area of investigation which requires further research. This study analysed the pattern in the first 30 seconds of the CFT. Future work could explore this in the whole 60s rather than 30s to establish differences between healthy and pathological time limit of word knowledge.

Studies with larger number of participants and a more homogenous group of AD are definitely required to increase the reliability of the work presented in this thesis.

Additionally, the sensitivity of these tests can be further supported if the tests are

administered to people in the preclinical stage with subtle cognitive changes due to AD or to

people who are genetically at risk of developing the disease. Positive results from larger

studies could be used to introduce these new tests in the battery of clinical dementia tests

for earlier detection of people at risk of developing clinical symptoms of AD.

Chapter 7:
Appendix

Table A: The *p* -values obtained from pairwise Bonferroni comparisons for the four 15s quartiles on each category, for (A) MCI, (B) AD, (C) FTD and (D) VaD

(A)

MCI	Animals	Fruits	TPW
1 x 2	0.00	0.00	0.00
1 x 3	0.00	0.00	0.00
1 x 4	0.00	0.00	0.00
2 x 3	0.13	0.02	0.05
2 x 4	0.01	0.01	0.05
3 x 4	0.58	1.00	1.00

(B)

AD	Animals	Fruits	TPW
1 x 2	0.00	0.00	0.00
1 x 3	0.00	0.00	0.00
1 x 4	0.00	0.00	0.00
2 x 3	1.00	1.00	0.14
2 x 4	1.00	0.34	0.55
3 x 4	1.00	1.00	1.00

(C) FTD

(C) FTD	Animals	Fruits	TPW
1 x 2	0.00	0.00	0.00
1 x 3	0.00	0.00	0.01
1 x 4	0.00	0.00	0.10
2 x 3	1.00	0.03	1.00
2 x 4	1.00	0.10	1.00

(D)

VaD	Animals	Fruits	TPW
1 x 2	0.00	0.00	0.00
1 x 3	0.00	0.00	0.00
1 x 4	0.00	0.00	0.00
2 x 3	0.28	0.02	1.00
2 x 4	1.00	0.01	0.05

Table B: The percentage of correct answers and readability information for each sentence.

Matched FOS/LS	% of correct answers	Grade level	Automated reading index	No.of words	%of complex words
F1	75	5	2.2	16	6.25
L1	98	7	5.1	16	6.25
F2	100	6	6.1	21	0
L2	81	4	2.5	16	0
F3	98	5	3.0	12	8.33
L3	98	3	2.2	16	0
F4	94	2	-0.9	12	0
L4	92	7	4.4	8	12.50
F5	98	4	3.8	8	0
L5	100	2	0.9	7	0
F6	100	6	4.6	12	8.33
L6	100	7	6.3	11	9.10
F7	100	5	1.1	12	8.33
L7	100	4	2.5	16	0
F8	100	10	7.9	8	25
L8	69	8	7.1	10	10
F9	97	11	7.4	15	27
L9	94	10	11.7	17	5.88
F10	100	8	8.8	24	4.17
L10	84	13	13.5	24	12.5
F11	94	2	-0.1	16	0
L11	91	3	2.1	13	0
F12	80	6	3.1	14	7.1
L12	84	12	9.3	13	23
F13	98	6	6.1	13	0
L13	80	7	5.4	12	8.3
F14	77	5	5.8	22	0
L14	100	6	3.7	14	7.1
F15	100	0	-4	9	0
L15	95	7	5.7	16	6.2
F16	98	9	9.2	29	10.3
L16	100	10	9.6	15	13.3
F17	98	7	4.7	14	7.1
L17	100	6	2.9	10	10
F18	100	9	7.1	15	13.3
L18	94	6	3	9	11.1
F19	94	9	7.8	14	14.3
L19	100	4	3.4	12	0
F20	100	9	7.6	32	9.4
L20	100	6	7.5	16	0

FOS/F: Figure of speech
LS/L: Literal sentence

7.1 Category fluency test

	Items that melt when heated	Items that can fly	Fruit and vegetables that come in different colours
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

	Items fastened with a zip	Animals without a tail	Separate items that come in pairs
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

7.2 Confrontation naming test
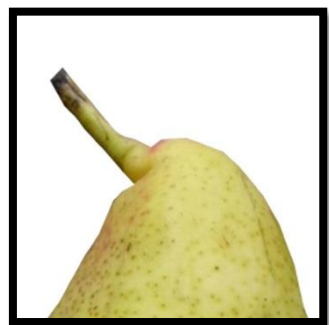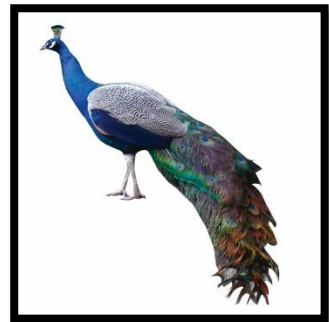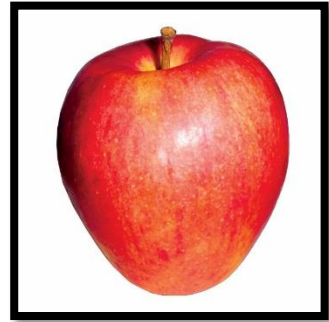
Answer sheet

No.	Part (P) or whole (W)	Picture
1	W	Pencil
2	W	Bulb
3	P	Umbrella
4	W	Tiger
5	P	Walnut
6	P	Dog
7	P	Pineapple
8	P	Giraffe
9	P	Weighing scale
10	W	Pliers
11	P	Cigarette
12	P	Tomato
13	W	Starfish
14	P	Bicycle
15	W	Washing machine
16	W	Wasp/bee
17	P	Screwdriver
18	W	Apple
19	P	Kangaroo
20	W	Knife
21	W	Peacock
22	W	Flower
23	P	Chair
24	W	Violin
25	P	Pear
26	W	Screw
27	P	Banana

28	P	Painting brush
29	P	Elephant
30	W	Sweetcorn/ corn on the cob
31	P	Leaf
32	W	Shoes
33	P	Zebra
34	W	Kiwifruit
35	W	Strawberry
36	P	Bread
37	W	Koala
38	W	Spanner/ wrench
39	W	Scissors
40	P	Piano

P =   / 20

W =   /20

7.3 Sentence Completion Test

Choose the word that fits best

1. Could you please ask your guests to _____ it down? I'm trying to do some work.
   - A. Keep
   - B. Lower
   - C. Hold

2. Both brothers were travelling in the _____ boat as their father.
   - A. Same
   - B. Different
   - C. Opposite

3. Martina finally _____ the beans about the affair.
   - A. Gobbled
   - B. Spilled
   - C. Dropped

4. My parents are worried about the new group of students they're hosting, because they're an _____ group.
   - A. Adventurous
   - B. Cautious
   - C. Hazardous

5. Rachel: "it is definitely too warm in here"

   Edward: "you can _____ that again"
   - A. Read
   - B. Write
   - C. Say

6. She can _____ the biscuit, I'm not eating anymore
   - A. Take
   - B. Share
   - C. Nip

7. Rob will be _____ when he finds out that he doesn't need to re-take the exam.
   - A. Anxious
   - B. Delighted
   - C. Disappointed

8. I thought she was _____ because she was insistent on beating around the bush.
   - A. Annoying
   - B. Disturbing
   - C. Adorable

9. I offered to _____ for the meal because she paid for the previous one.
   - A. Manage
   - B. Control
   - C. Pay

10. You should _____ your tongue because Lucy wouldn't want to hear that news.
    A. Hold
    B. Lower
    C. Retain

11. Steve will be _____ a Spanish course to improve his language before moving to Bolivia.
    A. Facilitating
    B. Holding
    C. Attending

12. I don't need an answer now, I think you should _____ on it and let me know during the next meeting.
    A. Sleep
    B. Rest
    C. Lie

13. His extensive lab skills, knowledge and experience make him an _____ in biology.
    A. Natural
    B. Amateur
    C. Expert

14. I think you _____ the nail on the head with that description.
    A. Bang
    B. Slam
    C. Hit

15. £500 is my _____ offer, now the ball is in your court.

    A. Final

    B. Initial

    C. Starting

16. In reading about the increase in crime rate for this area, I found the figures _____ .

    A. Disgusting

    B. Socking

    C. Soothing

17. He needs to _____ his socks up if he wants to graduate.

    A. Push

    B. Pull

    C. Twist

18. Michael might _____ his leg again if he takes up skiing so soon after his accident.

    A. Crack

    B. Break

    C. Burn

19. Mark bent over backwards to _____ his wife.

    A. Distract

    B. Please

    C. Upset

20. Claire is not looking forward to starting work on Monday as she did not _____ any of the instructions given during the induction course.

    A. Identify

    B. Grasp

    C. Understand

2. Answer sheet

1	FOS	Keep	**Lower**	Hold
2	LS	**Same**	Different	Opposite
3	FOS	Gobbled	**Spilled**	Dropped
4	LS	**Adventurous**	Cautious	Hazardous
5	FOS	Read	Write	**Say**
6	LS	**Take**	Share	Nip
7	LS	Anxious	**Delighted**	Disappointed
8	FOS	**Annoying**	Disturbing	Adorable
9	LS	Manage	Control	**Pay**
10	FOS	**Hold**	Lower	Retain
11	LS	Facilitating	Holding	**Attending**
12	FOS	**Sleep**	Rest	Lie
13	LS	Natural	Amateur	**Expert**
14	FOS	Bang	Slam	**Hit**
15	FOS	**Final**	Initial	Starting
16	LS	Disgusting	**Socking**	Soothing
17	FOS	Push	**Pull**	Twist
18	LS	Crack	**Break**	Burn
19	FOS	Distract	**Please**	Upset
20	LS	Identify	Grasp	**Understand**

Figure of speech (FOS) =   /10

Literal sentences (LS) =   /10

7.4 Ethical approval 12/YH/0474

The University Of Sheffield.

The Medical School.

2 May 2013

Ms Caroline Carta
Department of Neuroscience
N Floor
Royal Hallamshire Hospital

Medical School Office
Ms Jean Lazenby
Research Ethics Administrator
Beech Hill Road
Sheffield   S10 2RX

Telephone: +44 (0) 114 271 2237
Fax: +44 (0) 114 271 3892
Email: j.lazenby@sheffield.ac.uk

Dear Caroline

PROJECT TITLE: 'Piloting a new approach to testing executive and automatic aspects of language and collecting normative data in a large sample of healthy participants' – SMBRER255

I am pleased to inform you that on 30 April 2013 the School's Ethics Reviewers **approved** the above-named project on ethics grounds, on the basis that you will adhere to and use the following documents that you submitted for ethics review:

i)   Ethics application form [approved – 30 April 2013]
ii)   Participant Information Sheet [approved – 30 April 2013]
iii)   Advert [approved – 30 April 2013]
iv)   Consent Form [approved – 30 April 2013]
v)   Neuropsychological Assessment[approved – 30 April 2013]
vi)   Raven Test [approved – 30 April 2013]

If during the course of the project you need to deviate from the above-approved documents please inform me. The written approval of the School's Ethics Review Panel will be required for significant deviations from or significant changes to the above-approved documents. If you decide to terminate the project prematurely please inform me.

Yours sincerely

Jean Lazenby
School Research Ethics Administrator

The Medical School Ethics Application Form For Staff and Postgraduate Researchers

This form has been approved by the University Research Ethics Committee (UREC)

Tick as appropriate

Complete this form if you are a **member of staff or a postgraduate research student** who plans to undertake a research project which requires ethics approval via the University Ethics Review Procedure.

X

or

Complete this form if you plan to submit a **'generic' research ethics application** (i.e. an application that will cover several sufficiently similar research projects). Information on the 'generic' route is at: http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/approval-procedure/review-procedure/generic-research-projects.html

PLEASE NOTE THAT YOUR DEPARTMENT MAY USE A VARIATION OF THIS FORM: PLEASE CHECK WITH THE ETHICS ADMINISTRATOR IN YOUR DEPARTMENT

This form should be accompanied, where appropriate, by all Information Sheets / Covering Letters / Written Scripts which you propose to use to inform the prospective participants about the proposed research, and/or by a Consent Form where you need to use one.

Further guidance on how to apply is at:
http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/approval-procedure/review-procedure

Guidance on the possible routes for obtaining ethics approval (i.e. on the University Ethics Review Procedure, the NHS procedure and the Social Care Research Ethics Committee, and the Alternative procedure) is at:
http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/approval-procedure/ethics-approval

Once you have completed this research ethics application form in full, and other documents where appropriate, check that your name, the title of your research project and the date is contained in the footer of each page and email it to the Ethics Administrator of your academic department. Please note that the original signed and dated version of 'Part B' of the application form should also be provided to the Ethics Administrator in hard copy.

Ethics Administrators are listed at:
http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/approval-procedure/review-procedure/3.1-3.1.2.html

SMBRER255 Approved 30.04.13 **Date:**
Name of applicant:
Research project title:

1

University Research Ethics Application Form

I confirm that I have read the current version of the University of Sheffield 'Ethics Policy Governing Research Involving Human Participants, Personal Data and Human Tissue', as shown on the University's research ethics website at: http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/index.html

| X |

Part A

A1. **Title of Research Project:** Piloting a new approach to testing executive and automatic aspects of language and collecting normative data in a large sample of healthy participants.

A2. **Contact person** (normally the Principal Investigator, in the case of staff-led research projects, or the student in the case of supervised-postgraduate researcher projects):

Title: Ms   First Name/Initials: Caroline   Last Name: Carta
Post: PhD student   Department: Neuroscience
Email: ccarta1@sheffield.ac.uk   Telephone: 01142711597

A2.1. **Is this a postgraduate researcher project?**
If yes, please provide the Supervisor's contact details:

Prof. Annalena Venneri
Department of Neuroscience
University of Sheffield
Tel. +44-114-2713430
e-mail: a.venneri@sheffield.ac.uk

A2.2. **Other key investigators/co-applicants** (within/outside University), where applicable:

Please list all (add more rows if necessary)

Title	Full Name	Post	Responsibility in project	Organisation	Department
Prof.	Annalena Venneri	Professor of clinical neuropsychology	Primary supervisor	University of Sheffield	Neuroscience

A3. **Proposed Project Duration:**

Start date: 2013   End date: 2015

A4. **Mark 'X' in one or more of the following boxes if your research:**

	involves *no* access to identifiable personal data **and** *no* direct contact with participants
	involves adults with mental incapacity or mental illness
	involves prisoners or others in custodial care (e.g. young offenders)
	involves children or young people aged under 18 years
	involves using samples of human biological material collected before for another purpose
	involves taking new samples of human biological material (e.g. blood, tissue) *
	involves testing a medicinal product *

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	involves taking new samples of human biological material (e.g. blood, tissue) *
	involves additional radiation above that required for clinical care *
	involves investigating a medical device *

* If you have marked boxes marked * then you also need to obtain confirmation that appropriate University insurance is in place. The procedure for doing so is entirely by email. Please send an email addressed to insurance@shef.ac.uk and request a copy of the 'Clinical Trial Insurance Application Form'.

University Research Ethics Application Form

It is recommended that you familiarise yourself with the University's Ethics Policy Governing Research Involving Human Participants, Personal Data and Human Tissue before completing the following questions. Please note that if you provide sufficient information about the research (what you intend to do, how it will be carried out and how you intend to minimise any risks), this will help the ethics reviewers to make an informed judgement quickly without having to ask for further details.

A5.   **Briefly summarise:**

i.   **The project's aims and objectives:**
(this must be in language comprehensible to a lay person)

The main aim of this project is to establish normative performance for a novel testing approach to identify executive (i.e. requiring the use of a strategy to produce words) and automatic aspects (does not require any strategies) of language and how these aspects of language are affected by the process of healthy ageing. The establishment of norms in this field would be invaluable to better understand the differences between healthy ageing and pathological ageing related cognitive decline.

The objective of this study is to modify and standardise tests used in clinical settings that assess semantic abilities which take into account the executive and automatic aspects of language and devise novel instruments to improve the assessment of these aspects of language for future clinical applications.

ii.   **The project's methodology:**
(this must be in language comprehensible to a lay person)

A sample of 250 healthy participants, male and female, over the age of 18, across a range of educational backgrounds will be recruited in total for the pilot study and subsequent normative study. Participants will be tested with the MMSE test and with the Raven Coloured Progressive Matrices (Please find attached a copy of the tests). This will assess the global functioning of participants and screen for intact mental status. Additionally, participants will be given tests that consist of modified versions of standardised clinical tests. These will include:
- **The category fluency task**: name as many animals as possible in 1 minute
Modified version of test: Name as many two legged animals as possible in 1 minute.
- **Object naming:** name presented objects
Modified version of test: A part of an object is presented and the subject is asked to name the object.
- **Sentence comprehension:** subjects are asked to complete simple or idiomatic sentences.
- **Semantic categorization:** selection of the appropriate category for a stimulus between two typical categories such as birds-mammals vs selection of the appropriate category for a stimulus between two less typical categories such as flying animals and non-flying animals.

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- **Semantic association:** selection of the most appropriate pair of associated pictures. Direct strong semantic link example palm-beach vs low more distant association example pyramid-palm.

Regression analyses will be used to analyse the data collected to identify the influence of socio-demographic variables such as age, gender, and education on performance on tests and to establish parameters of normal variation for performance on the modified tests.

A6. What is the potential for physical and/or psychological harm / distress to participants?

There is no potential for physical or psychological harm; however, some, especially the older ones, might experience some discomfort due to the length and time taken to complete the tests. To reduce any distress testing will be planned with frequent breaks and spread over more than one session not exceeding 60 minutes to overcome tiredness, and location will be chosen accordingly to accommodate the participants.

A7. Does your research raise any issues of personal safety for you or other researchers involved in the project? (especially if taking place outside working hours or off University premises)

In general no issues of personal safety will be raised for anyone involved in the study but some of the data might be collected from outside the University premises.

If yes, explain how these issues will be managed.

Interview sessions will be scheduled in advance and the supervisor will be kept informed about the schedule and location. A contact system will be established so that either the supervisor or someone from the research team will know the whereabouts of the researcher. Contact with one of the team members will be made before the session starts and when the session finishes.

The researcher will make sure that a mobile phone or other means of communication will be easily accessible in the unlikely event that help, or further assistance, will be needed.

A8. How will the potential participants in the project be:

i. **Identified?**

Advertisements with purpose of research and the researcher's contact details will be distributed through emails and printed posters. Interested individuals will be able to contact the researcher through these adverts. Once the individual contacts the researcher more information about the study will be given and if potential participants are still interested and meet the criteria, they will be invited to be part in the study.

ii. **Approached?**

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Potential participants will be approached by researcher after they would have contacted the researcher through advertisements.

iii.   **Recruited?**

Participants will be approached by direct advertisements distributed in social places and advertisements by electronic mail.

A9.   **Will informed consent be obtained from the participants?**

                                                          YES ☒   NO ☐

If informed consent or consent is <u>NOT</u> to be obtained please explain why.
Further guidance is at:
http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/policy-notes/consent

A9.1.   This question is only applicable if you are planning to obtain informed consent:
How do you plan to obtain informed consent? (i.e. the proposed process?):

Participants will be asked to read a study information sheet and sign a consent form after having familiarised themselves with details regarding the study. The form will also include their details of involvement and any debriefing.

A10.   **What measures will be put in place to ensure confidentiality of personal data, where appropriate?**

The data will be stored safely and will be retained for 5 years. The data will also be anonymised and identified by an alphanumeric code.

A11.   **Will financial / in kind payments (other than reasonable expenses and compensation for time) be offered to participants?** (Indicate how much and on what basis this has been decided)

No.

A12. Will the research involve the production of recorded media such as audio and/or video recordings?

YES ☒ NO ☐

A12.1. This question is only applicable if you are planning to produce recorded media:
How will you ensure that there is a clear agreement with participants as to how these recorded media may be stored, used and (if appropriate) destroyed?

The audio recording will only be used by the researcher for transcription and scoring. An audio consent form which asks for permission for audio use will be given and signed by the participants. The consent form will also outline that participants will not be identified and recorded media will be destroyed as soon as scoring is completed.

Guidance on a range of ethical issues, including safety and well-being, consent and anonymity, confidentiality and data protection are available at:
http://www.shef.ac.uk/ris/gov_ethics_grp/researchethics/policy-notes

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University Research Ethics Application Form
Part B – The Signed Declaration

Title of Research Project: Piloting a new approach to testing executive and automatic aspects of language and collecting normative data in a large sample of healthy participants.

I confirm my responsibility to deliver the research project in accordance with the University of Sheffield's policies and procedures, which include the University's *'Financial Regulations'*, *'Good Research Practice Standards'* and the *'Ethics Policy Governing Research Involving Human Participants, Personal Data and Human Tissue'* (Ethics Policy) and, where externally funded, with the terms and conditions of the research funder.

In signing this research ethics application form I am also confirming that:

- The form is accurate to the best of my knowledge and belief.

- The project will abide by the University's Ethics Policy.

- There is no potential material interest that may, or may appear to, impair the independence and objectivity of researchers conducting this project.

- Subject to the research being approved, I undertake to adhere to the project protocol without unagreed deviation and to comply with any conditions set out in the letter from the University ethics reviewers notifying me of this.

- I undertake to inform the ethics reviewers of significant changes to the protocol (by contacting my academic department's Ethics Administrator in the first instance).

- I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of personal data, including the need to register when necessary with the appropriate Data Protection Officer (within the University the Data Protection Officer is based in CiCS).

- I understand that the project, including research records and data, may be subject to inspection for audit purposes, if required in future.

- I understand that personal data about me as a researcher in this form will be held by those involved in the ethics review procedure (e.g. the Ethics Administrator and/or ethics reviewers) and that this will be managed according to Data Protection Act principles.

- If this is an application for a 'generic' project all the individual projects that fit under the generic project are compatible with this application.

- **I understand that this project cannot be submitted for ethics approval in more than one department, and that if I wish to appeal against the decision made, this must be done through the original department.**
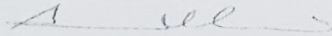
Name of the Principal Investigator (or the name of the Supervisor if this is a postgraduate researcher project):
Prof. Annalena Venneri

If this is a postgraduate researcher project insert the student's name here:
Caroline Carta

Signature of Principal Investigator (or the Supervisor):

Date: 06/02/13

Email the completed application form (and if relevant, other documents) to medschoolethics@sheffield.ac.uk and provide a signed, hard copy of 'Part B' to

Sara Watkinson, Research Ethics Administrator,
Medical School, Beech Hill Road, Sheffield, S10 2RX

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Health Research Authority

NRES Committee Yorkshire & The Humber - Sheffield

Yorkshire and the Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050128

28 December 2012

Professor Annalena Venneri
Professor of Clinical Translational Neuropsychology
University of Sheffield, Department of Neuroscience
Medical School, N Floor, Rm N130
Beech Hill Road
Royal Hallamshire Hospital, Sheffield
S102RX

Dear Professor Venneri

Study title:	**Assessment of age and disease related cognitive impairment in normal volunteers and people with degenerative and vascular brain disease and assessment of the potential neuroplastic effect of non pharmacological treatment**
REC reference:	12/YH/0474
IRAS project ID:	84442

Thank you for your letter of 19 December 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Rachel Bell, nrescommittee.yorkandhumber-sheffield@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		18 September 2012
GP/Consultant Information Sheets	1.0	18 September 2012
Investigator CV		
Participant Consent Form: Patient 1	2	19 December 2012
Participant Consent Form: Patient 2	2	19 December 2012
Participant Consent Form: Volunteer 1	2	19 December 2012
Participant Consent Form: Volunteer 2	2	19 December 2012
Participant Information Sheet: Patient 1	2	19 December 2012

Participant Information Sheet: Patient 2	2	19 December 2012
Participant Information Sheet: Volunteer 1	2	19 December 2012
Participant Information Sheet: Volunteer 2	2	19 December 2012
Protocol		
REC application		
Response to Request for Further Information		19 December 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

[signature: R Bell]

Chapter 8:

References

Aboud, O., Mrak, R. E., Boop, F., & Griffin, S. T. (2012). Apolipoprotein epsilon 3 alleles are associated with indicators of neuronal resilience. *BMC Med, 10*, 35. doi:10.1186/1741-7015-10-35

Adam, S., Bonsang, E., Grotz, C., & Perelman, S. (2013). Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease. *Clin Interv Aging, 8*, 377-390. doi:10.2147/CIA.S39921

Adlam, A. L., Bozeat, S., Arnold, R., Watson, P., & Hodges, J. R. (2006). Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex, 42*(5), 675-684.

Ahmed, S., Haigh, A. M., de Jager, C. A., & Garrard, P. (2013). Connected speech as a marker of disease progression in autopsy-proven Alzheimer's disease. *Brain, 136*(Pt 12), 3727-3737. doi:10.1093/brain/awt269

Ahn, H. J., Seo, S. W., Chin, J., Suh, M. K., Lee, B. H., Kim, S. T., . . . Na, D. L. (2011). The cortical neuroanatomy of neuropsychological deficits in mild cognitive impairment and Alzheimer's disease: a surface-based morphometric analysis. *Neuropsychologia, 49*(14), 3931-3945. doi:10.1016/j.neuropsychologia.2011.10.010

Albert, M., Soldan, A., Gottesman, R., McKhann, G., Sacktor, N., Farrington, L., . . . Selnes, O. (2014). Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. *Curr Alzheimer Res, 11*(8), 773-784.

Alzheimer, A. (1906). Über einen eigenartigen schweren Erkrankungsprozeβ der Hirnrinde. . *Neurol Central., 25:1134.*

Amieva, H., Jacqmin-Gadda, H., Orgogozo, J. M., Le Carret, N., Helmer, C., Letenneur, L., . . . Dartigues, J. F. (2005). The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. *Brain, 128*(Pt 5), 1093-1101. doi:10.1093/brain/awh451

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., . . . Dartigues, J. F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. *Brain, 137*(Pt 4), 1167-1175. doi:10.1093/brain/awu035

Andreasen, N., Minthon, L., Vanmechelen, E., Vanderstichele, H., Davidsson, P., Winblad, B., & Blennow, K. (1999). Cerebrospinal fluid tau and Abeta42 as predictors of development of Alzheimer's disease in patients with mild cognitive impairment. *Neurosci Lett, 273*(1), 5-8.

Andreasen, N., Vanmechelen, E., Vanderstichele, H., Davidsson, P., & Blennow, K. (2003). Cerebrospinal fluid levels of total-tau, phospho-tau and A beta 42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. *Acta Neurol Scand Suppl, 179*, 47-51.

Antonenko, D., Brauer, J., Meinzer, M., Fengler, A., Kerti, L., Friederici, A. D., & Floel, A. (2013). Functional and structural syntax networks in aging. *Neuroimage, 83*, 513-523. doi:10.1016/j.neuroimage.2013.07.018

Apostolova, L. G., Green, A. E., Babakchanian, S., Hwang, K. S., Chou, Y. Y., Toga, A. W., & Thompson, P. M. (2012). Hippocampal atrophy and ventricular enlargement in normal aging, mild cognitive impairment (MCI), and Alzheimer Disease. *Alzheimer Dis Assoc Disord, 26*(1), 17-27. doi:10.1097/WAD.0b013e3182163b62

Aranciva, F., Casals-Coll, M., Sanchez-Benavides, G., Quintana, M., Manero, R. M., Rognoni, T., . . . Pena-Casanova, J. (2012). Spanish normative studies in a young adult population (NEURONORMA young adults Project): norms for the Boston Naming Test and the Token Test. *Neurologia, 27*(7), 394-399. doi:10.1016/j.nrl.2011.12.016

Arango-Lasprilla, J. C., Cuetos, F., Valencia, C., Uribe, C., & Lopera, F. (2007). Cognitive changes in the preclinical phase of familial Alzheimer's disease. *J Clin Exp Neuropsychol, 29*(8), 892-900. doi:10.1080/13803390601174151

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex, 1*(1), 103-116.

Arroyo-Anllo, E. M., Bellouard, S., Ingrand, P., & Gil, R. (2011). Effects of automatic/controlled access processes on semantic memory in Alzheimer's disease. *J Alzheimers Dis, 25*(3), 525-533. doi:10.3233/JAD-2011-110083

Attems, J., Quass, M., Jellinger, K. A., & Lintner, F. (2007). Topographical distribution of cerebral amyloid angiopathy and its effect on cognitive decline are influenced by Alzheimer disease pathology. *J Neurol Sci, 257*(1-2), 49-55. doi:10.1016/j.jns.2007.01.013

Azcurra, D. J. L. S. (2012). A reminiscence program intervention to improve the quality of life of long-term care residents with Alzheimer's disease. A randomized controlled trial. *Revista Brasileira De Psiquiatria, 34*(4), 422-433. doi:10.1016/j.rbp.2012.05.008

Backman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain, 124*(Pt 1), 96-102.

Baddeley, A. (2003). Working memory and language: an overview. *Journal of Communication Disorders, 36*(3), 189-208. doi:10.1016/S0021-9924(03)00019-4

Badre, D., Poldrack, R. A., Pare-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron, 47*(6), 907-918. doi:10.1016/j.neuron.2005.07.023

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia, 45*(13), 2883-2901. doi:10.1016/j.neuropsychologia.2007.06.015

Bailly, M., Destrieux, C., Hommet, C., Mondon, K., Cottier, J. P., Beaufils, E., . . . Ribeiro, M. J. (2015). Precuneus and Cingulate Cortex Atrophy and Hypometabolism in Patients with Alzheimer's Disease and Mild Cognitive Impairment: MRI and (18)F-FDG PET Quantitative Analysis Using FreeSurfer. *Biomed Res Int, 2015*, 583931. doi:10.1155/2015/583931

Baldo, J. V., & Shimamura, A. P. (1998). Letter and category fluency in patients with frontal lobe lesions. *Neuropsychology, 12*(2), 259-267.

Ball, M. J. (1978). Topographic distribution of neurofibrillary tangles and granulovacuolar degeneration in hippocampal cortex of aging and demented patients. A quantitative study. *Acta Neuropathol, 42*(2), 73-80.

Ball, M. J., & Lo, P. (1977). Granulovacuolar degeneration in the ageing brain and in dementia. *J Neuropathol Exp Neurol, 36*(3), 474-487.

Balthazar, M. L., Martinelli, J. E., Cendes, F., & Damasceno, B. P. (2007). Lexical semantic memory in amnestic mild cognitive impairment and mild Alzheimer's disease. *Arq Neuropsiquiatr, 65*(3A), 619-622.

Barbarotto, R., Capitani, E., & Laiacona, M. (2001). Living musical instruments and inanimate body parts? *Neuropsychologia, 39*(4), 406-414.

Bartus, R. T., Dean, R. L., 3rd, Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science, 217*(4558), 408-414.

Beauquis, J., Pavia, P., Pomilio, C., Vinuesa, A., Podlutskaya, N., Galvan, V., & Saravia, F. (2013). Environmental enrichment prevents astroglial pathological changes in the hippocampus of APP transgenic mice, model of Alzheimer's disease. *Exp Neurol, 239*, 28-37. doi:10.1016/j.expneurol.2012.09.009

Bedny, M., McGill, M., & Thompson-Schill, S. L. (2008). Semantic Adaptation and Competition during Word Comprehension. *Cerebral Cortex, 18*(11), 2574-2585. doi:10.1093/cercor/bhn018

Beeri, M. S., Schmeidler, J., Sano, M., Wang, J., Lally, R., Grossman, H., & Silverman, J. M. (2006). Age, gender, and education norms on the CERAD neuropsychological battery in the oldest old. *Neurology, 67*(6), 1006-1010. doi:10.1212/01.wnl.0000237548.15734.cd

Bellassen, V., Igloi, K., de Souza, L. C., Dubois, B., & Rondi-Reig, L. (2012). Temporal order memory assessed during spatiotemporal navigation as a behavioral cognitive marker for differential Alzheimer's disease diagnosis. *J Neurosci, 32*(6), 1942-1952. doi:10.1523/JNEUROSCI.4556-11.2012

Bentham, P. W., Jones, S., & Hodges, J. R. (1997). A comparison of semantic memory in vascular dementia and dementia of Alzheimer's type. *Int J Geriatr Psychiatry, 12*(5), 575-580.

Berisha, V., Wang, S., LaCross, A., & Liss, J. (2015). Tracking discourse complexity preceding Alzheimer's disease diagnosis: a case study comparing the press conferences of Presidents Ronald Reagan and George Herbert Walker Bush. *J Alzheimers Dis, 45*(3), 959-963. doi:10.3233/JAD-142763

Bernal, B., Ardila, A., & Rosselli, M. (2015). Broca's area network in language function: a pooling-data connectivity study. *Front Psychol, 6*, 687. doi:10.3389/fpsyg.2015.00687

Bertens, D., Knol, D. L., Scheltens, P., Visser, P. J., & Alzheimer's Disease Neuroimaging, I. (2014). Temporal evolution of biomarkers and cognitive markers in the asymptomatic, MCI, and dementia stage of Alzheimer's disease. *Alzheimers Dement*. doi:10.1016/j.jalz.2014.05.1754

Bertola, L., Mota, N. B., Copelli, M., Rivero, T., Diniz, B. S., Romano-Silva, M. A., . . . Malloy-Diniz, L. F. (2014). Graph analysis of verbal fluency test discriminate between patients with Alzheimer's disease, mild cognitive impairment and normal elderly controls. *Front Aging Neurosci, 6*, 185. doi:10.3389/fnagi.2014.00185

Bertram, L. (2011). Alzheimer's genetics in the GWAS era: a continuing story of 'replications and refutations'. *Curr Neurol Neurosci Rep, 11*(3), 246-253. doi:10.1007/s11910-011-0193-z

Bhattacharya, S., Haertel, C., Maelicke, A., & Montag, D. (2014). Galantamine slows down plaque formation and behavioral decline in the 5XFAD mouse model of Alzheimer's disease. *PLoS One, 9*(2), e89454. doi:10.1371/journal.pone.0089454

Biagioni, M. C., & Galvin, J. E. (2011). Using biomarkers to improve detection of Alzheimer's disease. *Neurodegener Dis Manag, 1*(2), 127-139. doi:10.2217/NMT.11.11

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn Sci, 15*(11), 527-536. doi:10.1016/j.tics.2011.10.001

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cerebral Cortex, 19*(12), 2767-2796. doi:10.1093/cercor/bhp055

Binetti, G., Locascio, J. J., Corkin, S., Vonsattel, J. P., & Growdon, J. H. (2000). Differences between Pick disease and Alzheimer disease in clinical appearance and rate of

cognitive decline. *Archives of Neurology, 57*(2), 225-232. doi:DOI 10.1001/archneur.57.2.225

Binney, R. J., Embleton, K. V., Jefferies, E., Parker, G. J. M., & Ralph, M. A. L. (2010). The Ventral and Inferolateral Aspects of the Anterior Temporal Lobe Are Crucial in Semantic Memory: Evidence from a Novel Direct Comparison of Distortion-Corrected fMRI, rTMS, and Semantic Dementia. *Cerebral Cortex, 20*(11), 2728-2738. doi:10.1093/cercor/bhq019

Biundo, R., Gardini, S., Caffarra, P., Concari, L., Martorana, D., Neri, T. M., . . . Venneri, A. (2011). Influence of APOE Status on Lexical-Semantic Skills in Mild Cognitive Impairment. *Journal of the International Neuropsychological Society, 17*(3), 423-430. doi:10.1017/S135561771100021x

Black, S. E., Doody, R., Li, H., McRae, T., Jambor, K. M., Xu, Y., . . . Richardson, S. (2007). Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology, 69*(5), 459-469. doi:10.1212/01.wnl.0000266627.96040.5a

Blocq P. , M. G. (1982). Sur les lésions et la pathogénie de l'épilepsie dite essentielle. *Sem. Med, 12*, 445–446.

Borroni, B., Colciaghi, F., Corsini, P., Akkawi, N., Rozzini, L., Del Zotto, E., . . . Padovani, A. (2002). Early stages of probable Alzheimer disease are associated with changes in platelet amyloid precursor protein forms. *Neurol Sci, 23*(5), 207-210. doi:10.1007/s100720200042

Bouras, C., Hof, P. R., Giannakopoulos, P., Michel, J. P., & Morrison, J. H. (1994). Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: a quantitative evaluation of a one-year autopsy population from a geriatric hospital. *Cereb Cortex, 4*(2), 138-150.

Boye, M., Grabar, N., & Thi Tran, M. (2014). Contrastive conversational analysis of language production by Alzheimer's and control people. *Stud Health Technol Inform, 205*, 682-686.

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., & Braak, H. (1999). Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Eur Arch Psychiatry Clin Neurosci, 249 Suppl 3*, 14-22.

Braak, H., & Braak, E. (1991). Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. *Brain Pathol, 1*(3), 213-216.

Braak, H., & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging, 16*(3), 271-278; discussion 278-284.

Brambati, S. M., Myers, D., Wilson, A., Rankin, K. P., Allison, S. C., Rosen, H. J., . . . Gorno-Tempini, M. L. (2006). The anatomy of category-specific object naming in neurodegenerative diseases. *J Cogn Neurosci, 18*(10), 1644-1653. doi:10.1162/jocn.2006.18.10.1644

Brassen, S., Buchel, C., Weber-Fahr, W., Lehmbeck, J. T., Sommer, T., & Braus, D. F. (2009). Structure-function interactions of correct retrieval in healthy elderly women. *Neurobiol Aging, 30*(7), 1147-1156. doi:10.1016/j.neurobiolaging.2007.10.005

Brickman, A. M., Paul, R. H., Cohen, R. A., Williams, L. M., MacGregor, K. L., Jefferson, A. L., . . . Gordon, E. (2005). Category and letter verbal fluency across the adult lifespan: relationship to EEG theta power. *Archives of Clinical Neuropsychology, 20*(5), 561-573. doi:10.1016/j.acn.2004.12.006

Brucki, S. M., & Rocha, M. S. (2004). Category fluency test: effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. *Braz J Med Biol Res, 37*(12), 1771-1777. doi:/S0100-879X2004001200002

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208. doi:10.1016/j.neuron.2004.09.006

Burke, D. M., Mackay, D. G., Worthley, J. S., & Wade, E. (1991). On the Tip of the Tongue - What Causes Word Finding Failures in Young and Older Adults. *Journal of Memory and Language, 30*(5), 542-579. doi:Doi 10.1016/0749-596x(91)90026-G

Busatto, G. F., Garrido, G. E., Almeida, O. P., Castro, C. C., Camargo, C. H., Cid, C. G., . . . Bottino, C. M. (2003). A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiol Aging, 24*(2), 221-231.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2004). Modified Card Sorting Test: normative data. *J Clin Exp Neuropsychol, 26*(2), 246-250. doi:10.1076/jcen.26.2.246.28087

Caffarra, P., Vezzadini, G., Zonato, F., Copelli, S., & Venneri, A. (2003). A normative study of a shorter version of Raven's progressive matrices 1938. *Neurol Sci, 24*(5), 336-339. doi:10.1007/s10072-003-0185-0

Callahan, B. L., Macoir, J., Hudon, C., Bier, N., Chouinard, N., Cossette-Harvey, M., . . . Potvin, O. (2010). Normative data for the pyramids and palm trees test in the Quebec-French population. *Arch Clin Neuropsychol, 25*(3), 212-217. doi:10.1093/arclin/acq013

Canning, S. J., Leach, L., Stuss, D., Ngo, L., & Black, S. E. (2004). Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. *Neurology, 62*(4), 556-562.

Cappa, S. F., Binetti, G., Pezzini, A., Padovani, A., Rozzini, L., & Trabucchi, M. (1998). Object and action naming in Alzheimer's disease and frontotemporal dementia [see comment]. *Neurology, 50*(2), 351-355.

Cappa, S. F., Perani, D., Schnur, T., Tettamanti, M., & Fazio, F. (1998). The effects of semantic category and knowledge type on lexical-semantic access: a PET study. *Neuroimage, 8*(4), 350-359. doi:10.1006/nimg.1998.0368

Caramazza, A., & Shelton, J. R. (1998). Domain-specific knowledge systems in the brain: The animate-inanimate distinction. *Journal of Cognitive Neuroscience, 10*(1), 1-34. doi:Doi 10.1162/089892998563752

Cardoso, S., Silva, D., Maroco, J., de Mendonca, A., & Guerreiro, M. (2014). Non-literal language deficits in mild cognitive impairment. *Psychogeriatrics, 14*(4), 222-228. doi:10.1111/psyg.12101

Cerhan, J. H., Ivnik, R. J., Smith, G. E., Tangalos, E. C., Petersen, R. C., & Boeve, B. F. (2002). Diagnostic utility of letter fluency, category fluency, and fluency difference scores in Alzheimer's disease. *Clin Neuropsychol, 16*(1), 35-42. doi:10.1076/clin.16.1.35.8326

Chen, Y., Chen, K., Zhang, J., Li, X., Shu, N., Wang, J., . . . Reiman, E. M. (2015). Disrupted functional and structural networks in cognitively normal elderly subjects with the

APOE varepsilon4 allele. *Neuropsychopharmacology, 40*(5), 1181-1191. doi:10.1038/npp.2014.302

Chiang, K. J., Chu, H., Chang, H. J., Chung, M. H., Chen, C. H., Chiou, H. Y., & Chou, K. R. (2010). The effects of reminiscence therapy on psychological well-being, depression, and loneliness among the institutionalized aged. *Int J Geriatr Psychiatry, 25*(4), 380-388. doi:10.1002/gps.2350

Clark, L. J., Gatz, M., Zheng, L., Chen, Y. L., McCleary, C., & Mack, W. J. (2009). Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. *Am J Alzheimers Dis Other Demen, 24*(6), 461-468. doi:10.1177/1533317509345154

Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. (1994). *J Neurol Neurosurg Psychiatry, 57*(4), 416-418.

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci, 58*(2), 176-180.

Collins, A. M., & Quillian, M. R. (1969). Retrieval Time from Semantic Memory. *Journal of Verbal Learning and Verbal Behavior, 8*(2), 240-&. doi:Doi 10.1016/S0022-5371(69)80069-1

Connor, L. T., Spiro, A., 3rd, Obler, L. K., & Albert, M. L. (2004). Change in object naming ability during adulthood. *J Gerontol B Psychol Sci Soc Sci, 59*(5), P203-209.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., . . . Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921-923.

Crossley, M., D'Arcy, C., & Rawson, N. S. (1997). Letter and category fluency in community-dwelling Canadian seniors: a comparison of normal participants to those with dementia of the Alzheimer or vascular type. *J Clin Exp Neuropsychol, 19*(1), 52-62. doi:10.1080/01688639708403836

Cuetos, F., Arango-Lasprilla, J. C., Uribe, C., Valencia, C., & Lopera, F. (2007). Linguistic changes in verbal expression: a preclinical marker of Alzheimer's disease. *J Int Neuropsychol Soc, 13*(3), 433-439. doi:10.1017/S1355617707070609

Cuetos, F., Arce, N., Martinez, C., & Ellis, A. W. (2015). Word recognition in Alzheimer's disease: Effects of semantic degeneration. *J Neuropsychol*. doi:10.1111/jnp.12077

Cuetos, F., Herrera, E., & Ellis, A. W. (2010). Impaired word recognition in Alzheimer's disease: the role of age of acquisition. *Neuropsychologia, 48*(11), 3329-3334. doi:10.1016/j.neuropsychologia.2010.07.017

Cuetos, F., Rosci, C., Laiacona, M., & Capitani, E. (2008). Different variables predict anomia in different subjects: a longitudinal study of two Alzheimer's patients. *Neuropsychologia, 46*(1), 249-260. doi:10.1016/j.neuropsychologia.2007.07.011

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther, 6*(4), 37. doi:10.1186/alzrt269

Cunnane, S., Nugent, S., Roy, M., Courchesne-Loyer, A., Croteau, E., Tremblay, S., . . . Rapoport, S. I. (2011). Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition, 27*(1), 3-20. doi:10.1016/j.nut.2010.07.021

D'Onofrio, G., Sancarlo, D., Addante, F., Ciccone, F., Cascavilla, L., Paris, F., . . . Pilotto, A. (2015). A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. *Int J Geriatr Psychiatry, 30*(9), 965-975. doi:10.1002/gps.4247

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature, 380*(6574), 499-505. doi:10.1038/380499a0

De Beni, R., Borella, E., & Carretti, B. (2007). Reading comprehension in aging: the role of working memory and metacomprehension. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 14*(2), 189-212. doi:10.1080/13825580500229213

de Jong, L. W., van der Hiele, K., Veer, I. M., Houwing, J. J., Westendorp, R. G., Bollen, E. L., . . . van der Grond, J. (2008). Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain, 131*(Pt 12), 3277-3285. doi:10.1093/brain/awn278

De Marco, M., Meneghello, F., Duzzi, D., Rigon, J., Pilosio, C., & Venneri, A. (2016). Cognitive stimulation of the default-mode network modulates functional connectivity in healthy aging. *Brain Res Bull, 121*, 26-41. doi:10.1016/j.brainresbull.2015.12.001

De Strooper, B. (2007). Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease. *EMBO Rep, 8*(2), 141-146. doi:10.1038/sj.embor.7400897

Deardorff, W. J., Feen, E., & Grossberg, G. T. (2015). The Use of Cholinesterase Inhibitors Across All Stages of Alzheimer's Disease. *Drugs Aging, 32*(7), 537-547. doi:10.1007/s40266-015-0273-x

DeDe, G., & Knilans Flax, J. (2016). Language comprehension in aging. In H. H. wright (Ed.), *Cognition, Language and Aging*. Amsterdam/Philadelphia: John Benjamins Publishing Company.

Delbeuck, X., Van der Linden, M., & Collette, F. (2003). Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev, 13*(2), 79-92.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci, 15*(9), 5870-5878.

Devlin, J. T., Gonnerman, L. M., Andersen, E. S., & Seidenberg, M. S. (1998). Category-specific semantic deficits in focal and widespread brain damage: a computational account. *J Cogn Neurosci, 10*(1), 77-94.

Devlin, J. T., Russell, R. P., Davis, M. H., Price, C. J., Moss, H. E., Fadili, M. J., & Tyler, L. K. (2002). Is there an anatomical basis for category-specificity? Semantic memory studies in PET and fMRI. *Neuropsychologia, 40*(1), 54-75.

Di Marco, L. Y., Marzo, A., Munoz-Ruiz, M., Ikram, M. A., Kivipelto, M., Ruefenacht, D., . . . Frangi, A. F. (2014). Modifiable lifestyle factors in dementia: a systematic review of longitudinal observational cohort studies. *J Alzheimers Dis, 42*(1), 119-135. doi:10.3233/JAD-132225

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., . . . Buckner, R. L. (2009). The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex, 19*(3), 497-510. doi:10.1093/cercor/bhn113

Dickerson, B. C., Goncharova, I., Sullivan, M. P., Forchetti, C., Wilson, R. S., Bennett, D. A., . . . deToledo-Morrell, L. (2001). MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiol Aging, 22*(5), 747-754.

Didic, M., Barbeau, E. J., Felician, O., Tramoni, E., Guedj, E., Poncet, M., & Ceccaldi, M. (2011). Which memory system is impaired first in Alzheimer's disease? *J Alzheimers Dis, 27*(1), 11-22. doi:10.3233/JAD-2011-110557

Diehl, J., & Kurz, A. (2002). Frontotemporal dementia: patient characteristics, cognition, and behaviour. *International Journal of Geriatric Psychiatry, 17*(10), 914-918. doi:10.1002/gps.709

Diehl, J., Monsch, A. U., Aebi, C., Wagenpfeil, S., Krapp, S., Grimmer, T., . . . Kurz, A. (2005). Frontotemporal dementia, semantic dementia, and Alzheimer's disease: The contribution of standard neuropsychological tests to differential diagnosis. *Journal of Geriatric Psychiatry and Neurology, 18*(1), 39-44. doi:10.1177/0891988704272309

Du, A. T., Schuff, N., Amend, D., Laakso, M. P., Hsu, Y. Y., Jagust, W. J., . . . Weiner, M. W. (2001). Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 71*(4), 441-447.

Duarte, L. R., Marquie, L., Marquie, J. C., Terrier, P., & Ousset, P. J. (2009). Analyzing feature distinctiveness in the processing of living and non-living concepts in Alzheimer's disease. *Brain and Cognition, 71*(2), 108-117. doi:10.1016/j.bandc.2009.04.007

Duong, A., Whitehead, V., Hanratty, K., & Chertkow, H. (2006). The nature of lexico-semantic processing deficits in mild cognitive impairment. *Neuropsychologia, 44*(10), 1928-1935. doi:10.1016/j.neuropsychologia.2006.01.034

Eggermont, L. H., Swaab, D. F., Hol, E. M., & Scherder, E. J. (2009). Walking the line: a randomised trial on the effects of a short term walking programme on cognition in dementia. *J Neurol Neurosurg Psychiatry, 80*(7), 802-804. doi:10.1136/jnnp.2008.158444

Elgamal, S. A., Roy, E. A., & Sharratt, M. T. (2011). Age and verbal fluency: the mediating effect of speed of processing. *Can Geriatr J, 14*(3), 66-72. doi:10.5770/cgj.v14i3.17

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi:10.1073/pnas.1015950108

Esiri, M. M., & Wilcock, G. K. (1986). Cerebral amyloid angiopathy in dementia and old age. *J Neurol Neurosurg Psychiatry, 49*(11), 1221-1226.

Evrard, M. (2002). Ageing and lexical access to common and proper names in picture naming. *Brain Lang, 81*(1-3), 174-179.

Fagan, A. M., Mintun, M. A., Mach, R. H., Lee, S. Y., Dence, C. S., Shah, A. R., . . . Holtzman, D. M. (2006). Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann Neurol, 59*(3), 512-519. doi:10.1002/ana.20730

Fagundo, A. B., Lopez, S., Romero, M., Guarch, J., Marcos, T., & Salamero, M. (2008). Clustering and switching in semantic fluency: predictors of the development of Alzheimer's disease. *Int J Geriatr Psychiatry, 23*(10), 1007-1013. doi:10.1002/gps.2025

Farah, M. J., & McClelland, J. L. (1991). A computational model of semantic memory impairment: modality specificity and emergent category specificity. *J Exp Psychol Gen, 120*(4), 339-357.

Fernaeus, S. E., Ostberg, P., Hellstrom, A., & Wahlund, L. O. (2008). Cut the coda: early fluency intervals predict diagnoses. *Cortex, 44*(2), 161-169. doi:10.1016/j.cortex.2006.04.002

Ferris, S. H., & Farlow, M. (2013). Language impairment in Alzheimer's disease and benefits of acetylcholinesterase inhibitors. *Clin Interv Aging, 8*, 1007-1014. doi:10.2147/CIA.S39959

Flanagan, K. J., Copland, D. A., Chenery, H. J., Byrne, G. J., & Angwin, A. J. (2013). Alzheimer's disease is associated with distinctive semantic feature loss. *Neuropsychologia, 51*(10), 2016-2025. doi:10.1016/j.neuropsychologia.2013.06.008

Forbes-McKay, K., Shanks, M. F., & Venneri, A. (2013). Profiling spontaneous speech decline in Alzheimer's disease: a longitudinal study. *Acta Neuropsychiatr, 25*(6), 320-327. doi:10.1017/neu.2013.16

Forbes-McKay, K. E., Ellis, A. W., Shanks, M. F., & Venneri, A. (2005). The age of acquisition of words produced in a semantic fluency task can reliably differentiate normal from pathological age related cognitive decline. *Neuropsychologia, 43*(11), 1625-1632. doi:10.1016/j.neuropsychologia.2005.01.008

Forbes-McKay, K. E., & Venneri, A. (2005). Detecting subtle spontaneous language decline in early Alzheimer's disease with a picture description task. *Neurol Sci, 26*(4), 243-254. doi:10.1007/s10072-005-0467-9

Ford, A., McGregor, K. M., Case, K., Crosson, B., & White, K. D. (2010). Structural connectivity of Broca's area and medial frontal cortex. *Neuroimage, 52*(4), 1230-1237. doi:10.1016/j.neuroimage.2010.05.018

Frisoni, G. B., Fox, N. C., Jack, C. R., Jr., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol, 6*(2), 67-77. doi:10.1038/nrneurol.2009.215

Furgerson, M., Fechheimer, M., & Furukawa, R. (2012). Model Hirano bodies protect against tau-independent and tau-dependent cell death initiated by the amyloid precursor protein intracellular domain. *PLoS One, 7*(9), e44996. doi:10.1371/journal.pone.0044996

Gainotti, G. (2000). What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: a review. *Cortex, 36*(4), 539-559.

Gainotti, G. (2005). The influence of gender and lesion location on naming disorders for animals, plants and artefacts. *Neuropsychologia, 43*(11), 1633-1644. doi:10.1016/j.neuropsychologia.2005.01.016

Gamboz, N., Coluccia, E., Iavarone, A., & Brandimonte, M. A. (2009). Normative data for the Pyramids and Palm Trees Test in the elderly Italian population. *Neurol Sci, 30*(6), 453-458. doi:10.1007/s10072-009-0130-y

Ganguli, M., Snitz, B. E., Lee, C. W., Vanderbilt, J., Saxton, J. A., & Chang, C. C. (2010). Age and education effects and norms on a cognitive test battery from a population-based cohort: the Monongahela-Youghiogheny Healthy Aging Team. *Aging Ment Health, 14*(1), 100-107. doi:10.1080/13607860903071014

Garrard, P., & Hodges, J. R. (2000). Semantic dementia: clinical, radiological and pathological perspectives. *J Neurol, 247*(6), 409-422.

Garrard, P., Lambon Ralph, M. A., Watson, P. C., Powis, J., Patterson, K., & Hodges, J. R. (2001). Longitudinal profiles of semantic impairment for living and nonliving concepts in dementia of Alzheimer's type. *J Cogn Neurosci, 13*(7), 892-909. doi:10.1162/089892901753165818

Garrard, P., Maloney, L. M., Hodges, J. R., & Patterson, K. (2005). The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author. *Brain, 128*(Pt 2), 250-260. doi:10.1093/brain/awh341

Garrard, P., Perry, R., & Hodges, J. R. (1997). Disorders of semantic memory. *J Neurol Neurosurg Psychiatry, 62*(5), 431-435.

Garrido, G. E., Furuie, S. S., Buchpiguel, C. A., Bottino, C. M., Almeida, O. P., Cid, C. G., . . . Busatto, G. F. (2002). Relation between medial temporal atrophy and functional brain activity during memory processing in Alzheimer's disease: a combined MRI and SPECT study. *J Neurol Neurosurg Psychiatry, 73*(5), 508-516.

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *J Neurosci, 23*(27), 9240-9245.

Gauthier, S., Wirth, Y., & Mobius, H. J. (2005). Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int J Geriatr Psychiatry, 20*(5), 459-464. doi:10.1002/gps.1341

Geda, Y. E., Roberts, R. O., Knopman, D. S., Petersen, R. C., Christianson, T. J., Pankratz, V. S., . . . Rocca, W. A. (2008). Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry, 65*(10), 1193-1198. doi:10.1001/archpsyc.65.10.1193

Giannakopoulos, P., Herrmann, F. R., Bussiere, T., Bouras, C., Kovari, E., Perl, D. P., . . . Hof, P. R. (2003). Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology, 60*(9), 1495-1500.

Gibson, P. H., & Tomlinson, B. E. (1977). Numbers of Hirano bodies in the hippocampus of normal and demented people with Alzheimer's disease. *J Neurol Sci, 33*(1-2), 199-206.

Giri, M., Zhang, M., & Lu, Y. (2016). Genes associated with Alzheimer's disease: an overview and current status. *Clin Interv Aging, 11*, 665-681. doi:10.2147/CIA.S105769

Giuffrida, M. L., Caraci, F., Pignataro, B., Cataldo, S., De Bona, P., Bruno, V., . . . Copani, A. (2009). Beta-amyloid monomers are neuroprotective. *J Neurosci, 29*(34), 10582-10587. doi:10.1523/JNEUROSCI.1736-09.2009

Glisky, E. L. (2007). Changes in Cognitive Function in Human Aging. In D. R. Riddle (Ed.), *Brain Aging: Models, Methods, and Mechanisms*. Boca Raton (FL).

Goate, A., Chartier-Harlin, M. C., Mullan, M., Brown, J., Crawford, F., Fidani, L., . . . et al. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature, 349*(6311), 704-706. doi:10.1038/349704a0

Gomez, R. G., & White, D. A. (2006). Using verbal fluency to detect very mild dementia of the Alzheimer type. *Archives of Clinical Neuropsychology, 21*(8), 771-775. doi:10.1016/j.acn.2006.06.012

Gonnerman, L. M., Andersen, E. S., Devlin, J. T., Kempler, D., & Seidenberg, M. S. (1997). Double dissociation of semantic categories in Alzheimer's disease. *Brain Lang, 57*(2), 254-279. doi:10.1006/brln.1997.1752

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., . . . Anesthesia, C. C. S. (2011). Vascular Contributions to Cognitive Impairment and Dementia A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke, 42*(9), 2672-2713. doi:10.1161/STR.0b013e3182299496

Graham, N. L., Emery, T., & Hodges, J. R. (2004). Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *Journal of Neurology Neurosurgery and Psychiatry, 75*(1), 61-71.

Griebe, M., Forster, A., Wessa, M., Rossmanith, C., Bazner, H., Sauer, T., . . . Szabo, K. (2011). Loss of callosal fibre integrity in healthy elderly with age-related white matter changes. *J Neurol, 258*(8), 1451-1459. doi:10.1007/s00415-011-5956-6

Grogan, A., Green, D. W., Ali, N., Crinion, J. T., & Price, C. J. (2009). Structural correlates of semantic and phonemic fluency ability in first and second languages. *Cereb Cortex, 19*(11), 2690-2698. doi:10.1093/cercor/bhp023

Grossi, D., Fragassi, N. A., Chiacchio, L., Valoroso, L., Tuccillo, R., Perrotta, C., . . . Trojano, L. (2002). Do visuospatial and constructional disturbances differentiate frontal variant of frontotemporal dementia and Alzheimer's disease? an experimental study of a clinical belief. *Int J Geriatr Psychiatry, 17*(7), 641-648. doi:10.1002/gps.654

Grossman, M., Koenig, P., Glosser, G., DeVita, C., Moore, P., Rhee, J., . . . f, M. R. I. s. F. m. r. i. (2003). Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. *Brain, 126*(Pt 2), 292-311.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol, 6*(7), e159. doi:10.1371/journal.pbio.0060159

Hagoort, P. (2013). MUC (Memory, Unification, Control) and beyond. *Front Psychol, 4*, 416. doi:10.3389/fpsyg.2013.00416

Hagoort, P., & Indefrey, P. (2014). The neurobiology of language beyond single words. *Annu Rev Neurosci, 37*, 347-362. doi:10.1146/annurev-neuro-071013-013847

Hall, J., Vo, H., Johnson, L., Barber, R. C., & O'Bryant, S. (2011). Boston Naming Test: Gender Differences in Older Adults with and without Alzheimer's Dementia. *Archives of Clinical Neuropsychology, 26*(6), 538-538.

Halliday, G. M., McCann, H. L., Pamphlett, R., Brooks, W. S., Creasey, H., McCusker, E., . . . Harper, C. G. (1992). Brain stem serotonin-synthesizing neurons in Alzheimer's disease: a clinicopathological correlation. *Acta Neuropathol, 84*(6), 638-650.

Hardy, J., & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci, 12*(10), 383-388.

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science, 256*(5054), 184-185.

Harwood, D. G., Sultzer, D. L., Feil, D., Monserratt, L., Freedman, E., & Mandelkern, M. A. (2005). Frontal lobe hypometabolism and impaired insight in Alzheimer disease. *Am J Geriatr Psychiatry, 13*(11), 934-941. doi:10.1176/appi.ajgp.13.11.934

Haugrud, N., Crossley, M., & Vrbancic, M. (2011). Clustering and switching strategies during verbal fluency performance differentiate Alzheimer's disease and healthy aging. *J Int Neuropsychol Soc, 17*(6), 1153-1157. doi:10.1017/S1355617711001196

Health, T. S. N. I. o. P. (2007). Healthy ageing A challenge for Europe.

Heine, M. K., Ober, B. A., & Shenaut, G. K. (1999). Naturally occurring and experimentally induced tip-of-the-tongue experiences in three adult age groups. *Psychol Aging, 14*(3), 445-457.

Henneman, W. J., Sluimer, J. D., Barnes, J., van der Flier, W. M., Sluimer, I. C., Fox, N. C., . . . Barkhof, F. (2009). Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. *Neurology, 72*(11), 999-1007. doi:10.1212/01.wnl.0000344568.09360.31

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology, 18*(2), 284-295. doi:10.1037/0894-4105.18.2.284

Hernandez, M., Costa, A., Juncadella, M., Sebastian-Galles, N., & Rene, R. (2008). Category-specific semantic deficits in Alzheimer's disease: A semantic priming study. *Neuropsychologia, 46*(4), 935-946. doi:10.1016/j.neuropsychologia.2007.11.018

Hickok, G., & Poeppel, D. (2000). Towards a functional neuroanatomy of speech perception. *Trends Cogn Sci, 4*(4), 131-138.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nat Rev Neurosci, 8*(5), 393-402. doi:10.1038/nrn2113

Hickok, S. (2015). The neurobiology of Language. In G. Hickok, and Small, S.L. (Ed.), *Neurobiology of Language* (first ed.). Oxford: Mica Haley.

Hier, D. B., Hagenlocker, K., & Shindler, A. G. (1985). Language Disintegration in Dementia - Effects of Etiology and Severity. *Brain and Language, 25*(1), 117-133. doi:Doi 10.1016/0093-934x(85)90124-5

Hirni, D. I., Kivisaari, S. L., Krumm, S., Monsch, A. U., Berres, M., Oeksuez, F., . . . Taylor, K. I. (2016). Neuropsychological Markers of Medial Perirhinal and Entorhinal Cortex Functioning are Impaired Twelve Years Preceding Diagnosis of Alzheimer's Dementia. *J Alzheimers Dis, 52*(2), 573-580. doi:10.3233/JAD-150158

Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia, 33*(4), 441-459.

Hodges, J. R., Salmon, D. P., & Butters, N. (1990). Differential impairment of semantic and episodic memory in Alzheimer's and Huntington's diseases: a controlled prospective study. *J Neurol Neurosurg Psychiatry, 53*(12), 1089-1095.

Hodges, J. R., Salmon, D. P., & Butters, N. (1992). Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? *Neuropsychologia, 30*(4), 301-314.

Hodgson, C., & Ellis, A. W. (1998). Last in, first to go: age of acquisition and naming in the elderly. *Brain Lang, 64*(1), 146-163. doi:10.1006/brln.1998.1960

Holzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Res, 191*(1), 36-43. doi:10.1016/j.pscychresns.2010.08.006

Hornberger, M., Bell, B., Graham, K. S., & Rogers, T. T. (2009). Are judgments of semantic relatedness systematically impaired in Alzheimer's disease? *Neuropsychologia, 47*(14), 3084-3094. doi:10.1016/j.neuropsychologia.2009.07.006

Howieson, D. B., Carlson, N. E., Moore, M. M., Wasserman, D., Abendroth, C. D., Payne-Murphy, J., & Kaye, J. A. (2008). Trajectory of mild cognitive impairment onset. *Journal of the International Neuropsychological Society, 14*(2), 192-198. doi:10.1017/S1355617708080375

Hutchinson, A. D., & Mathias, J. L. (2007). Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. *J Neurol Neurosurg Psychiatry, 78*(9), 917-928. doi:10.1136/jnnp.2006.100669

Huth, A. G., de Heer, W. A., Griffiths, T. L., Theunissen, F. E., & Gallant, J. L. (2016). Natural speech reveals the semantic maps that tile human cerebral cortex. *Nature, 532*(7600), 453-458. doi:10.1038/nature17637

Hwang, T. Y., Ahn, I. S., Kim, S., & Kim, D. K. (2016). Efficacy of Galantamine on Cognition in Mild-to-Moderate Alzheimer's Dementia after Failure to Respond to Donepezil. *Psychiatry Investig, 13*(3), 341-348. doi:10.4306/pi.2016.13.3.341

Ibach, B., Binder, H., Dragon, M., Poljansky, S., Haen, E., Schmitz, E., . . . Hajak, G. (2006). Cerebrospinal fluid tau and beta-amyloid in Alzheimer patients, disease controls and an age-matched random sample. *Neurobiol Aging, 27*(9), 1202-1211. doi:10.1016/j.neurobiolaging.2005.06.005

Ilmarinen, J. (2012). Promoting active ageing in the workplace. Accessed from https://osha.europa.eu/en/publications/articles/promoting-active-ageing-in-the-workplace/view

Im, K., Lee, J. M., Seo, S. W., Yoon, U., Kim, S. T., Kim, Y. H., . . . Na, D. L. (2008). Variations in cortical thickness with dementia severity in Alzheimer's disease. *Neurosci Lett, 436*(2), 227-231. doi:10.1016/j.neulet.2008.03.032

Ingelsson, M., Fukumoto, H., Newell, K. L., Growdon, J. H., Hedley-Whyte, E. T., Frosch, M. P., . . . Irizarry, M. C. (2004). Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. *Neurology, 62*(6), 925-931.

Inouye, S. K., Albert, M. S., Mohs, R., Sun, K., & Berkman, L. F. (1993). Cognitive performance in a high-functioning community-dwelling elderly population. *J Gerontol, 48*(4), M146-151.

Ishizaki, J., Meguro, K., Ambo, H., Shimada, M., Yamaguchi, S., Hayasaka, C., . . . Yamadori, A. (1998). A normative, community-based study of Mini-Mental State in elderly adults: the effect of age and educational level. *J Gerontol B Psychol Sci Soc Sci, 53*(6), P359-363.

Jack, C. R., Jr., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., . . . Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 257-262. doi:10.1016/j.jalz.2011.03.004

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., . . . Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol, 12*(2), 207-216. doi:10.1016/S1474-4422(12)70291-0

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6

Jackson, H. a. S., P. (2010). Describing Language *An Introduction to the Nature and Function of Language* (second ed.). London: Continuum International Publishing Group.

Jonaitis, E., La Rue, A., Mueller, K. D., Koscik, R. L., Hermann, B., & Sager, M. A. (2013). Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease. *Psychol Aging, 28*(4), 1004-1014. doi:10.1037/a0034838

Joubert, S., Brambati, S. M., Ansado, J., Barbeau, E. J., Felician, O., Didic, M., . . . Kergoat, M. J. (2010). The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia, 48*(4), 978-988. doi:10.1016/j.neuropsychologia.2009.11.019

Juva, K., Verkkoniemi, A., Viramo, P., Polvikoski, T., Kainulainen, K., Kontula, K., & Sulkava, R. (2000). APOE epsilon4 does not predict mortality, cognitive decline, or dementia in the oldest old. *Neurology, 54*(2), 412-415.

Kahlaoui, K., Di Sante, G., Barbeau, J., Maheux, M., Lesage, F., Ska, B., & Joanette, Y. (2012). Contribution of NIRS to the study of prefrontal cortex for verbal fluency in aging. *Brain Lang, 121*(2), 164-173. doi:10.1016/j.bandl.2011.11.002

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia: PA: Lea & Fibiger.

Karran, E., Mercken, M., & De Strooper, B. (2011). The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov, 10*(9), 698-712. doi:10.1038/nrd3505

Katsumata, Y., Mathews, M., Abner, E. L., Jicha, G. A., Caban-Holt, A., Smith, C. D., . . . Fardo, D. W. (2015). Assessing the discriminant ability, reliability, and comparability of multiple short forms of the Boston Naming Test in an Alzheimer's disease center cohort. *Dement Geriatr Cogn Disord, 39*(3-4), 215-227. doi:10.1159/000370108

Kave, G., & Mashal, N. (2012). Age-related differences in word-retrieval but not in meaning generation. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 19*(4), 515-529. doi:10.1080/13825585.2011.638975

Kave, G., & Yafe, R. (2014). Performance of Younger and Older Adults on Tests of Word Knowledge and Word Retrieval: Independence or Interdependence of Skills? *American Journal of Speech-Language Pathology, 23*(1), 36-45. doi:10.1044/1058-0360(2013/12-0136)

Kawano, N., Umegaki, H., Suzuki, Y., Yamamoto, S., Mogi, N., & Iguchi, A. (2010). Effects of educational background on verbal fluency task performance in older adults with Alzheimer's disease and mild cognitive impairment. *Int Psychogeriatr, 22*(6), 995-1002. doi:10.1017/S1041610210000839

Kazui, H., & Takeda, M. (2011). [Language impairment and semantic memory loss of semantic dementia]. *Brain Nerve, 63*(10), 1047-1055.

Kemper, S. (1987). Life-span changes in syntactic complexity. *J Gerontol, 42*(3), 323-328.

Kemper, S., Marquis, J., & Thompson, M. (2001). Longitudinal change in language production: effects of aging and dementia on grammatical complexity and propositional content. *Psychol Aging, 16*(4), 600-614.

Kim, G. H., Jeon, S., Seo, S. W., Kim, M. J., Kim, J. H., Roh, J. H., . . . Na, D. L. (2012). Topography of cortical thinning areas associated with hippocampal atrophy (HA) in patients with Alzheimer's disease (AD). *Arch Gerontol Geriatr, 54*(2), e122-129. doi:10.1016/j.archger.2011.10.013

Kinugawa, K., Schumm, S., Pollina, M., Depre, M., Jungbluth, C., Doulazmi, M., . . . Dere, E. (2013). Aging-related episodic memory decline: are emotions the key? *Front Behav Neurosci, 7*, 2. doi:10.3389/fnbeh.2013.00002

Kirchberg, B. C., Cohen, J. R., Adelsky, M. B., Buthorn, J. J., Gomar, J. J., Gordon, M., . . . Goldberg, T. E. (2012). Semantic distance abnormalities in mild cognitive impairment: their nature and relationship to function. *Am J Psychiatry, 169*(12), 1275-1283. doi:10.1176/appi.ajp.2012.12030383

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *Biomed Res Int, 2015*, 748212. doi:10.1155/2015/748212

Kittner, S. J., White, L. R., Farmer, M. E., Wolz, M., Kaplan, E., Moes, E., . . . Feinleib, M. (1986). Methodological issues in screening for dementia: the problem of education adjustment. *J Chronic Dis, 39*(3), 163-170.

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., . . . Langstrom, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol, 55*(3), 306-319. doi:10.1002/ana.20009

Klunk, W. E., Wang, Y., Huang, G. F., Debnath, M. L., Holt, D. P., & Mathis, C. A. (2001). Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. *Life Sci, 69*(13), 1471-1484.

Koenig, P., Smith, E. E., & Grossman, M. (2010). Categorization of novel tools by patients with Alzheimer's disease: category-specific content and process. *Neuropsychologia, 48*(7), 1877-1885. doi:10.1016/j.neuropsychologia.2009.07.023

Kuperman, V., Stadthagen-Gonzalez, H., & Brysbaert, M. (2012). Age-of-acquisition ratings for 30,000 English words. *Behav Res Methods, 44*(4), 978-990. doi:10.3758/s13428-012-0210-4

Kurth, F., Cherbuin, N., & Luders, E. (2015). Reduced age-related degeneration of the hippocampal subiculum in long-term meditators. *Psychiatry Res, 232*(3), 214-218. doi:10.1016/j.pscychresns.2015.03.008

Kurth, F., Luders, E., Wu, B., & Black, D. S. (2014). Brain Gray Matter Changes Associated with Mindfulness Meditation in Older Adults: An Exploratory Pilot Study using Voxel-based Morphometry. *Neuro, 1*(1), 23-26. doi:10.17140/NOJ-1-106

Kynette, D., & Kemper, S. (1986). Aging and the Loss of Grammatical Forms - a Cross-Sectional Study of Language Performance. *Language & Communication, 6*(1-2), 65-72. doi:Doi 10.1016/0271-5309(86)90006-6

Laakso, M. P., Frisoni, G. B., Kononen, M., Mikkonen, M., Beltramello, A., Geroldi, C., . . . Aronen, H. J. (2000). Hippocampus and entorhinal cortex in frontotemporal dementia and Alzheimer's disease: a morphometric MRI study. *Biol Psychiatry, 47*(12), 1056-1063.

Laatu, S., Portin, R., Revonsuo, A., Tuisku, S., & Rinne, J. (1997). Knowledge of concept meanings in Alzheimer's disease. *Cortex, 33*(1), 27-45.

Lacombe, J., Jolicoeur, P., Grimault, S., Pineault, J., & Joubert, S. (2015). Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. *Brain Lang, 149*, 118-127. doi:10.1016/j.bandl.2015.07.003

Laiacona, M., Allamano, N., Lorenzi, L., & Capitani, E. (2006). A case of impaired naming and knowledge of body parts. Are limbs a separate sub-category? *Neurocase, 12*(5), 307-316. doi:10.1080/13554790601125940

Laisney, M., Matuszewski, V., Mezenge, F., Belliard, S., de la Sayette, V., Eustache, F., & Desgranges, B. (2009). The underlying mechanisms of verbal fluency deficit in frontotemporal dementia and semantic dementia. *J Neurol, 256*(7), 1083-1094. doi:10.1007/s00415-009-5073-y

Lambon Ralph, M. A., Howard, D., Nightingale, G., & Ellis, A. W. (1998). Are Living and Non-living Category-specific Deficits Causally Linked to Impaired Perceptual or Associative Knowledge? Evidence From a Category-specific Double Dissociation. *Neurocase, 4*, 311-338.

Lampert, E. J., Roy Choudhury, K., Hostage, C. A., Rathakrishnan, B., Weiner, M., Petrella, J. R., . . . Alzheimer's Disease Neuroimaging, I. (2014). Brain atrophy rates in first degree relatives at risk for Alzheimer's. *Neuroimage Clin, 6*, 340-346. doi:10.1016/j.nicl.2014.08.024

Langa, K. M. (2015). Is the risk of Alzheimer's disease and dementia declining? *Alzheimers Res Ther, 7*(1), 34. doi:10.1186/s13195-015-0118-1

Lanting, S., Haugrud, N., & Crossley, M. (2009). The effect of age and sex on clustering and switching during speeded verbal fluency tasks. *J Int Neuropsychol Soc, 15*(2), 196-204. doi:10.1017/S1355617709090237

Laws, K. R., Adlington, R. L., Gale, T. M., Moreno-Martinez, F. J., & Sartori, G. (2007). A meta-analytic review of category naming in Alzheimer's disease. *Neuropsychologia, 45*(12), 2674-2682. doi:10.1016/j.neuropsychologia.2007.04.003

Le, X., Lancashire, I., Hirst, G., & Jokel, R. (2011). Longitudinal detection of dementia through lexical and syntactic changes in writing: a case study of three British novelists. *Literary and Linguistic Computing, 26*(4), 435-461. doi:10.1093/llc/fqr013

Leung, K. K., Bartlett, J. W., Barnes, J., Manning, E. N., Ourselin, S., Fox, N. C., & Alzheimer's Disease Neuroimaging, I. (2013). Cerebral atrophy in mild cognitive impairment and Alzheimer disease: rates and acceleration. *Neurology, 80*(7), 648-654. doi:10.1212/WNL.0b013e318281ccd3

Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D. M., Oshima, J., Pettingell, W. H., . . . et al. (1995). Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science, 269*(5226), 973-977.

Liao, X., Li, G., Wang, A., Liu, T., Feng, S., Guo, Z., . . . Mu, Q. (2015). Repetitive Transcranial Magnetic Stimulation as an Alternative Therapy for Cognitive Impairment in Alzheimer's Disease: A Meta-Analysis. *J Alzheimers Dis, 48*(2), 463-472. doi:10.3233/JAD-150346

Libon, D. J., McMillan, C., Gunawardena, D., Powers, C., Massimo, L., Khan, A., . . . Grossman, M. (2009). Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. *Neurology, 73*(7), 535-542. doi:10.1212/WNL.0b013e3181b2a4f5

Libon, D. J., Rascovsky, K., Powers, J., Irwin, D. J., Boller, A., Weinberg, D., . . . Grossman, M. (2013). Comparative semantic profiles in semantic dementia and Alzheimer's disease. *Brain, 136*(Pt 8), 2497-2509. doi:10.1093/brain/awt165

Lipinska, B., & Backman, L. (1996). Feeling-of-knowing in fact retrieval: further evidence for preservation in early Alzheimer's disease. *J Int Neuropsychol Soc, 2*(4), 350-358.

Liu, Y., Yu, C., Zhang, X., Liu, J., Duan, Y., Alexander-Bloch, A. F., . . . Bullmore, E. (2014). Impaired long distance functional connectivity and weighted network architecture in Alzheimer's disease. *Cereb Cortex, 24*(6), 1422-1435. doi:10.1093/cercor/bhs410

Looi, J. C., & Sachdev, P. S. (1999). Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology, 53*(4), 670-678.

Love, S., Nicoll, J. A., Hughes, A., & Wilcock, G. K. (2003). APOE and cerebral amyloid angiopathy in the elderly. *Neuroreport, 14*(11), 1535-1536. doi:10.1097/01.wnr.0000085694.46774.90

Lublin, A. L., & Gandy, S. (2010). Amyloid-beta oligomers: possible roles as key neurotoxins in Alzheimer's Disease. *Mt Sinai J Med, 77*(1), 43-49. doi:10.1002/msj.20160

Lunnon, K., Sattlecker, M., Furney, S. J., Coppola, G., Simmons, A., Proitsi, P., . . . dNeuroMed, C. (2013). A blood gene expression marker of early Alzheimer's disease. *J Alzheimers Dis, 33*(3), 737-753. doi:10.3233/JAD-2012-121363

Lyketsos, C. G., Carrillo, M. C., Ryan, J. M., Khachaturian, A. S., Trzepacz, P., Amatniek, J., . . . Miller, D. S. (2011). Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement, 7*(5), 532-539. doi:10.1016/j.jalz.2011.05.2410

Mackay, A. I., Connor, L. T., Albert, M. L., & Obler, L. K. (2002). Noun and verb retrieval in healthy aging. *J Int Neuropsychol Soc, 8*(6), 764-770.

Madhavan, K. M., McQueeny, T., Howe, S. R., Shear, P., & Szaflarski, J. (2014). Superior longitudinal fasciculus and language functioning in healthy aging. *Brain Res, 1562*, 11-22. doi:10.1016/j.brainres.2014.03.012

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus, 16*(12), 1091-1101. doi:10.1002/hipo.20233

Malnar, M., Kosicek, M., Bene, R., Tarnik, I. P., Pavelin, S., Babic, I., . . . Hecimovic, S. (2012). Use of cerebrospinal fluid biomarker analysis for improving Alzheimer's disease diagnosis in a non-specialized setting. *Acta Neurobiol Exp (Wars), 72*(3), 264-271.

Manenti, R., Brambilla, M., Petesi, M., Miniussi, C., & Cotelli, M. (2013). Compensatory networks to counteract the effects of ageing on language. *Behav Brain Res, 249*, 22-27. doi:10.1016/j.bbr.2013.04.011

Mardh, S., Nagga, K., & Samuelsson, S. (2013). A longitudinal study of semantic memory impairment in patients with Alzheimer's disease. *Cortex, 49*(2), 528-533. doi:10.1016/j.cortex.2012.02.004

Marques, J. F., Cappa, S. F., & Sartori, G. (2011). Naming from definition, semantic relevance and feature type: the effects of aging and Alzheimer's disease. *Neuropsychology, 25*(1), 105-113. doi:10.1037/a0020417

Marra, C., Ferraccioli, M., & Gainotti, G. (2007). Gender-related dissociations of categorical fluency in normal subjects and in subjects with Alzheimer's disease. *Neuropsychology, 21*(2), 207-211. doi:10.1037/0894-4105.21.2.207

Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: structure and processes. *Curr Opin Neurobiol, 11*(2), 194-201.

Mathuranath, P. S., George, A., Cherian, P. J., Alexander, A., Sarma, S. G., & Sarma, P. S. (2003). Effects of age, education and gender on verbal fluency. *J Clin Exp Neuropsychol, 25*(8), 1057-1064. doi:10.1076/jcen.25.8.1057.16736

Matioli, M. N., & Caramelli, P. (2010). Limitations in differentiating vascular dementia from Alzheimer's disease with brief cognitive tests. *Arq Neuropsiquiatr, 68*(2), 185-188.

Matsuda, H. (2013). Voxel-based Morphometry of Brain MRI in Normal Aging and Alzheimer's Disease. *Aging Dis, 4*(1), 29-37.

Matsuda, O. (2007). Cognitive stimulation therapy for Alzheimer's disease: the effect of cognitive stimulation therapy on the progression of mild Alzheimer's disease in patients treated with donepezil. *Int Psychogeriatr, 19*(2), 241-252. doi:10.1017/S1041610206004194

Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., . . . Ageing, C. (2013). A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet, 382*(9902), 1405-1412. doi:10.1016/S0140-6736(13)61570-6

Mattsson, N., & Zetterberg, H. (2009). Alzheimer's disease and CSF biomarkers: key challenges for broad clinical applications. *Biomark Med, 3*(6), 735-737. doi:10.2217/bmm.09.65

McGeown, W. J., Shanks, M. F., Forbes-McKay, K. E., & Venneri, A. (2009). Patterns of brain activity during a semantic task differentiate normal aging from early Alzheimer's disease. *Psychiatry Res, 173*(3), 218-227. doi:10.1016/j.pscychresns.2008.10.005

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease:

recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J. D., Moseley, M., Fleischman, D., . . . Stebbins, G. T. (2006). White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiol Aging, 27*(5), 663-672. doi:10.1016/j.neurobiolaging.2005.03.026

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., . . . Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. *J Cogn Neurosci, 21*(10), 2007-2018. doi:10.1162/jocn.2009.21219

Melrose, R. J., Campa, O. M., Harwood, D. G., Osato, S., Mandelkern, M. A., & Sultzer, D. L. (2009). The neural correlates of naming and fluency deficits in Alzheimer's disease: an FDG-PET study. *Int J Geriatr Psychiatry, 24*(8), 885-893. doi:10.1002/gps.2229

Mendez, M. F., Cherrier, M., Perryman, K. M., Pachana, N., Miller, B. L., & Cummings, J. L. (1996). Frontotemporal dementia versus Alzheimer's disease: differential cognitive features. *Neurology, 47*(5), 1189-1194.

Mephon-Gaspard, A., Boca, M., Pioche-Durieu, C., Desforges, B., Burgo, A., Hamon, L., . . . Pastre, D. (2016). Role of tau in the spatial organization of axonal microtubules: keeping parallel microtubules evenly distributed despite macromolecular crowding. *Cell Mol Life Sci, 73*(19), 3745-3760. doi:10.1007/s00018-016-2216-z

Merck, C., Jonin, P. Y., Vichard, H., Boursiquot Sle, M., Leblay, V., & Belliard, S. (2013). Relative category-specific preservation in semantic dementia? Evidence from 35 cases. *Brain Lang, 124*(3), 257-267. doi:10.1016/j.bandl.2013.01.003

Metzger, F. G., Ehlis, A. C., Haeussinger, F. B., Fallgatter, A. J., & Hagen, K. (2015). Effects of cholinesterase inhibitor on brain activation in Alzheimer's patients measured with functional near-infrared spectroscopy. *Psychopharmacology (Berl), 232*(23), 4383-4391. doi:10.1007/s00213-015-4066-z

Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., & Schwartz, M. F. (2015). Neural organization of spoken language revealed by lesion-symptom mapping. *Nat Commun, 6*, 6762. doi:10.1038/ncomms7762

Mistridis, P., Krumm, S., Monsch, A. U., Berres, M., & Taylor, K. I. (2015). The 12 Years Preceding Mild Cognitive Impairment Due to Alzheimer's Disease: The Temporal Emergence of Cognitive Decline. *Journal of Alzheimers Disease, 48*(4), 1095-1107. doi:10.3233/Jad-150137

Molinuevo, J. L., Gomez-Anson, B., Monte, G. C., Bosch, B., Sanchez-Valle, R., & Rami, L. (2011). Neuropsychological profile of prodromal Alzheimer's disease (Prd-AD) and their radiological correlates. *Arch Gerontol Geriatr, 52*(2), 190-196. doi:10.1016/j.archger.2010.03.016

Montanes, P., Goldblum, M. C., & Boller, F. (1995). The naming impairment of living and nonliving items in Alzheimer's disease. *J Int Neuropsychol Soc, 1*(1), 39-48.

Montanes, P., Goldblum, M. C., & Boller, F. (1996). Classification deficits in Alzheimer's disease with special reference to living and nonliving things. *Brain Lang, 54*(2), 335-358. doi:10.1006/brln.1996.0079

Montembeault, M., Rouleau, I., Provost, J. S., Brambati, S. M., & Alzheimer's Disease Neuroimaging, I. (2016). Altered Gray Matter Structural Covariance Networks in Early Stages of Alzheimer's Disease. *Cereb Cortex, 26*(6), 2650-2662. doi:10.1093/cercor/bhv105

Moore, C. J., & Price, C. J. (1999). A functional neuroimaging study of the variables that generate category-specific object processing differences. *Brain, 122 (Pt 5)*, 943-962.

Moral, J. C. M., Terrero, F. B. F., Galan, A. S., & Rodriguez, T. M. (2015). Effect of integrative reminiscence therapy on depression, well-being, integrity, self-esteem, and life satisfaction in older adults. *Journal of Positive Psychology, 10*(3), 240-247. doi:10.1080/17439760.2014.936968

Moreira, L., Schlottfeldt, C. G., de Paula, J. J., Daniel, M. T., Paiva, A., Cazita, V., . . . Malloy-Diniz, L. F. (2011). Normative study of the Token Test (short version): preliminary data for a sample of Brazilian seniors. *Revista De Psiquiatria Clinica, 38*(3), 97-101.

Moreno-Martinez, F. J., Goni-Imizcoz, M., & Spitznagel, M. B. (2011). Domain or not domain? That is the question: longitudinal semantic deterioration in Alzheimer's disease. *Brain Cogn, 77*(1), 89-95. doi:10.1016/j.bandc.2011.05.006

Moreno-Martinez, F. J., & Rodriguez-Rojo, I. C. (2015). On Colour, Category Effects, and Alzheimer's Disease: A Critical Review of Studies and Further Longitudinal Evidence. *Behav Neurol, 2015*, 960725. doi:10.1155/2015/960725

Mosconi, L., Mistur, R., Switalski, R., Tsui, W. H., Glodzik, L., Li, Y., . . . de Leon, M. J. (2009). FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 36*(5), 811-822. doi:10.1007/s00259-008-1039-z

Mosconi, L., Sorbi, S., de Leon, M. J., Li, Y., Nacmias, B., Myoung, P. S., . . . Pupi, A. (2006). Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *J Nucl Med, 47*(11), 1778-1786.

Murphy, K. J., Rich, J. B., & Troyer, A. K. (2006). Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *J Int Neuropsychol Soc, 12*(4), 570-574.

Nebes, R. D., Martin, D. C., & Horn, L. C. (1984). Sparing of semantic memory in Alzheimer's disease. *J Abnorm Psychol, 93*(3), 321-330.

Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., . . . Beach, T. G. (2012). Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol, 71*(5), 362-381. doi:10.1097/NEN.0b013e31825018f7

Nelson, P. T., Jicha, G. A., Schmitt, F. A., Liu, H., Davis, D. G., Mendiondo, M. S., . . . Markesbery, W. R. (2007). Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity. *J Neuropathol Exp Neurol, 66*(12), 1136-1146. doi:10.1097/nen.0b013e31815c5efb

Nicholas, M., Obler, L., Albert, M., & Goodglass, H. (1985). Lexical retrieval in healthy aging. *Cortex, 21*(4), 595-606.

Nippold, M. A., Cramond, P. M., & Hayward-Mayhew, C. (2014). Spoken language production in adults: examining age-related differences in syntactic complexity. *Clin Linguist Phon, 28*(3), 195-207. doi:10.3109/02699206.2013.841292

Niu, H. J., Li, X., Chen, Y. J., Ma, C., Zhang, J. Y., & Zhang, Z. J. (2013). Reduced frontal activation during a working memory task in mild cognitive impairment: a non-invasive near-infrared spectroscopy study. *CNS Neurosci Ther, 19*(2), 125-131. doi:10.1111/cns.12046

Nyberg, L., Backman, L., Erngrund, K., Olofsson, U., & Nilsson, L. G. (1996). Age differences in episodic memory, semantic memory, and priming: relationships to demographic, intellectual, and biological factors. *J Gerontol B Psychol Sci Soc Sci, 51*(4), P234-240.

Obler, L. K., Rykhlevskaia, E., Schnyer, D., Clark-Cotton, M. R., Spiro, A., 3rd, Hyun, J., . . . Albert, M. L. (2010). Bilateral brain regions associated with naming in older adults. *Brain Lang, 113*(3), 113-123. doi:10.1016/j.bandl.2010.03.001

Okonkwo, O. C., Schultz, S. A., Oh, J. M., Larson, J., Edwards, D., Cook, D., . . . Sager, M. A. (2014). Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology, 83*(19), 1753-1760. doi:10.1212/WNL.0000000000000964

Padurariu, M., Ciobica, A., Mavroudis, I., Fotiou, D., & Baloyannis, S. (2012). Hippocampal neuronal loss in the CA1 and CA3 areas of Alzheimer's disease patients. *Psychiatr Danub, 24*(2), 152-158.

Parihar, M. S., & Brewer, G. J. (2010). Amyloid-beta as a modulator of synaptic plasticity. *J Alzheimers Dis, 22*(3), 741-763. doi:10.3233/JAD-2010-101020

Parnetti, L., Lanari, A., Silvestrelli, G., Saggese, E., & Reboldi, P. (2006). Diagnosing prodromal Alzheimer's disease: role of CSF biochemical markers. *Mech Ageing Dev, 127*(2), 129-132. doi:10.1016/j.mad.2005.09.022

Passos, V. M. D., Giatti, L., Bensenor, I., Tiemeier, H., Ikram, M. A., de Figueiredo, R. C., . . . Barreto, S. M. (2015). Education plays a greater role than age in cognitive test performance among participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Bmc Neurology, 15*. doi:ARTN 19110.1186/s12883-015-0454-6

Patricacou, A., Psallida, E., Pring, T., & Dipper, L. (2007). The Boston Naming Test in Greek: Normative data and the effects of age and education on naming. *Aphasiology, 21*(12), 1157-1170. doi:10.1080/02687030600670643

Paula, J. J., Bertola, L., Nicolato, R., Moraes, E. N., & Malloy-Diniz, L. F. (2012). Evaluating language comprehension in Alzheimer's disease: the use of the Token test. *Arq Neuropsiquiatr, 70*(6), 435-440.

Pedersen, N. L., Gatz, M., Berg, S., & Johansson, B. (2004). How heritable is Alzheimer's disease late in life? Findings from Swedish twins. *Ann Neurol, 55*(2), 180-185. doi:10.1002/ana.10999

Peelle, J. E., Troiani, V., Wingfield, A., & Grossman, M. (2010). Neural Processing during Older Adults' Comprehension of Spoken Sentences: Age Differences in Resource Allocation and Connectivity. *Cerebral Cortex, 20*(4), 773-782. doi:10.1093/cercor/bhp142

Pena-Casanova, J., Quinones-Ubeda, S., Gramunt-Fombuena, N., Quintana, M., Aguilar, M., Molinuevo, J. L., . . . Team, N. S. (2009). Spanish Multicenter Normative Studies (NEURONORMA Project): norms for the Stroop color-word interference test and the Tower of London-Drexel. *Arch Clin Neuropsychol, 24*(4), 413-429. doi:10.1093/arclin/acp043

Penolazzi, B., Bergamaschi, S., Pastore, M., Villani, D., Sartori, G., & Mondini, S. (2015). Transcranial direct current stimulation and cognitive training in the rehabilitation of Alzheimer disease: A case study. *Neuropsychol Rehabil, 25*(6), 799-817. doi:10.1080/09602011.2014.977301

Pereira, J. B., Mijalkov, M., Kakaei, E., Mecocci, P., Vellas, B., Tsolaki, M., . . . AddNeuroMed consortium, f. t. A. s. D. N. I. (2016). Disrupted Network Topology in Patients with Stable and Progressive Mild Cognitive Impairment and Alzheimer's Disease. *Cereb Cortex, 26*(8), 3476-3493. doi:10.1093/cercor/bhw128

Perri, R., Zannino, G., Caltagirone, C., & Carlesimo, G. A. (2012). Alzheimer's Disease and Semantic Deficits: A Feature-Listing Study. *Neuropsychology, 26*(5), 652-663. doi:10.1037/a0029302

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., . . . Winblad, B. (2001). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petrella, J. R., Sheldon, F. C., Prince, S. E., Calhoun, V. D., & Doraiswamy, P. M. (2011). Default mode network connectivity in stable vs progressive mild cognitive impairment. *Neurology, 76*(6), 511-517. doi:10.1212/WNL.0b013e31820af94e

Poeppel, D., & Hickok, G. (2004). Towards a new functional anatomy of language. *Cognition, 92*(1-2), 1-12. doi:10.1016/j.cognition.2003.11.001

Pravata, E., Tavernier, J., Parker, R., Vavro, H., Mintzer, J. E., & Spampinato, M. V. (2016). The neural correlates of anomia in the conversion from mild cognitive impairment to Alzheimer's disease. *Neuroradiology, 58*(1), 59-67. doi:10.1007/s00234-015-1596-3

Prodan, C. I., Ross, E. D., Vincent, A. S., & Dale, G. L. (2007). Coated-platelets correlate with disease progression in Alzheimer disease. *J Neurol, 254*(4), 548-549. doi:10.1007/s00415-006-0323-8

Qiu, C., Kivipelto, M., Aguero-Torres, H., Winblad, B., & Fratiglioni, L. (2004). Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry, 75*(6), 828-833.

Raboutet, C., Sauzeon, H., Corsini, M. M., Rodrigues, J., Langevin, S., & N'Kaoua, B. (2010). Performance on a semantic verbal fluency task across time: dissociation between clustering, switching, and categorical exploitation processes. *J Clin Exp Neuropsychol, 32*(3), 268-280. doi:10.1080/13803390902984464

Rak, M., Del Bigio, M. R., Mai, S., Westaway, D., & Gough, K. (2007). Dense-core and diffuse Abeta plaques in TgCRND8 mice studied with synchrotron FTIR microspectroscopy. *Biopolymers, 87*(4), 207-217. doi:10.1002/bip.20820

Ramanan, S., Narayanan, J., Perpetua D'Souza, T., Malik, K. S., & Ratnavalli, E. (2015). Total output and switching in category fluency successfully discriminates Alzheimer's disease from Mild Cognitive Impairment, but not from frontotemporal dementia. *Dement Neuropsychol, 9*(3), 251-257.

Raoux, N., Amieva, H., Le Goff, M., Auriacombe, S., Carcaillon, L., Letenneur, L., & Dartigues, J. F. (2008). Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: results from the PAQUID longitudinal study. *Cortex, 44*(9), 1188-1196. doi:10.1016/j.cortex.2007.08.019

Rascovsky, K., Salmon, D. P., Ho, G. J., Galasko, D., Peavy, G. M., Hansen, L. A., & Thal, L. J. (2002). Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology, 58*(12), 1801-1808.

Rascovsky, K., Salmon, D. P., Lipton, A. M., Leverenz, J. B., DeCarli, C., Jagust, W. J., . . . Galasko, D. (2005). Rate of progression differs in frontotemporal dementia and Alzheimer disease. *Neurology, 65*(3), 397-403. doi:10.1212/01.wnl.0000171343.43314.6e

Rasmusson, D. X., Carson, K. A., Brookmeyer, R., Kawas, C., & Brandt, J. (1996). Predicting rate of cognitive decline in probable Alzheimer's disease. *Brain Cogn, 31*(2), 133-147. doi:10.1006/brcg.1996.0038

Reilly, J., Peelle, J. E., Antonucci, S. M., & Grossman, M. (2011). Anomia as a Marker of Distinct Semantic Memory Impairments in Alzheimer's Disease and Semantic Dementia. *Neuropsychology, 25*(4), 413-426. doi:10.1037/a0022738

Reiman, E. M., Chen, K., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., . . . Hardy, J. (2005). Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci U S A, 102*(23), 8299-8302. doi:10.1073/pnas.0500579102

Reisberg, B., Doody, R., Stoffler, A., Schmitt, F., Ferris, S., & Mobius, H. J. (2006). A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol, 63*(1), 49-54. doi:10.1001/archneur.63.1.49

Riley, K. P., Snowdon, D. A., Desrosiers, M. F., & Markesbery, W. R. (2005). Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. *Neurobiol Aging, 26*(3), 341-347. doi:10.1016/j.neurobiolaging.2004.06.019

Rodda, J., Morgan, S., & Walker, Z. (2009). Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. *Int Psychogeriatr, 21*(5), 813-824. doi:10.1017/S1041610209990354

Rodrigue, K. M., Kennedy, K. M., Devous, M. D., Sr., Rieck, J. R., Hebrank, A. C., Diaz-Arrastia, R., . . . Park, D. C. (2012). beta-Amyloid burden in healthy aging: regional distribution and cognitive consequences. *Neurology, 78*(6), 387-395. doi:10.1212/WNL.0b013e318245d295

Rodrigue, K. M., & Raz, N. (2004). Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *J Neurosci, 24*(4), 956-963. doi:10.1523/JNEUROSCI.4166-03.2004

Rodriguez-Aranda, C., Waterloo, K., Johnsen, S. H., Eldevik, P., Sparr, S., Wikran, G. C., . . . Vangberg, T. R. (2016). Neuroanatomical correlates of verbal fluency in early Alzheimer's disease and normal aging. *Brain Lang, 155-156*, 24-35. doi:10.1016/j.bandl.2016.03.001

Rodriguez-Ferreiro, J., Davies, R., Gonzalez-Nosti, M., Barbon, A., & Cuetos, F. (2009). Name agreement, frequency and age of acquisition, but not grammatical class, affect object and action naming in Spanish speaking participants with Alzheimer's disease. *Journal of Neurolinguistics, 22*(1), 37-54. doi:10.1016/j.jneuroling.2008.05.003

Rogers, S. L., Doody, R. S., Mohs, R. C., & Friedhoff, L. T. (1998). Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med, 158*(9), 1021-1031.

Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., . . . et al. (1993). Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology, 43*(2), 250-260.

Rosen, V. M., Sunderland, T., Levy, J., Harwell, A., McGee, L., Hammond, C., . . . Lefkowitz, C. (2005). Apolipoprotein E and category fluency: evidence for reduced semantic access in healthy normal controls at risk for developing Alzheimer's disease. *Neuropsychologia, 43*(4), 647-658. doi:10.1016/j.neuropsychologia.2004.06.022

Rumelhart, D. E., & McClelland, J. L. (1986). *Parallel Distributed Processing: Explorations in the Microstructure of Cognition* (Vol. 1). Cambridge: MIT Press.

Sabuncu, M. R., Desikan, R. S., Sepulcre, J., Yeo, B. T., Liu, H., Schmansky, N. J., . . . Alzheimer's Disease Neuroimaging, I. (2011). The dynamics of cortical and hippocampal atrophy in Alzheimer disease. *Arch Neurol, 68*(8), 1040-1048. doi:10.1001/archneurol.2011.167

Sailor, K., Antoine, M., Diaz, M., Kuslansky, G., & Kluger, A. (2004). The effects of Alzheimer's disease on item output in verbal fluency tasks. *Neuropsychology, 18*(2), 306-314. doi:10.1037/0894-4105.18.2.306

Sailor, K. M., Zimmerman, M. E., & Sanders, A. E. (2011). Differential impacts of age of acquisition on letter and semantic fluency in Alzheimer's disease patients and healthy older adults. *Q J Exp Psychol (Hove), 64*(12), 2383-2391. doi:10.1080/17470218.2011.596660

Salomone, S., Caraci, F., Leggio, G. M., Fedotova, J., & Drago, F. (2012). New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. *Br J Clin Pharmacol, 73*(4), 504-517. doi:10.1111/j.1365-2125.2011.04134.x

Salthouse, T. A. (2014). Quantity and structure of word knowledge across adulthood. *Intelligence, 46*, 122-130.

Sartori, G., Gnoato, F., Mariani, I., Prioni, S., & Lombardi, L. (2007). Semantic relevance, domain specificity and the sensory/functional theory of category-specificity. *Neuropsychologia, 45*(5), 966-976. doi:10.1016/j.neuropsychologia.2006.08.028

Saur, D., Kreher, B. W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M. S., . . . Weiller, C. (2008). Ventral and dorsal pathways for language. *Proc Natl Acad Sci U S A, 105*(46), 18035-18040. doi:10.1073/pnas.0805234105

Scheff, S. W., Price, D. A., Schmitt, F. A., & Mufson, E. J. (2006). Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging, 27*(10), 1372-1384. doi:10.1016/j.neurobiolaging.2005.09.012

Scheltens, P. (2009). Imaging in Alzheimer's disease. *Dialogues Clin Neurosci, 11*(2), 191-199.

Schmitter-Edgecombe, M., Vesneski, M., & Jones, D. W. (2000). Aging and word-finding: a comparison of spontaneous and constrained naming tests. *Arch Clin Neuropsychol, 15*(6), 479-493.

Schneider, B. A., Daneman, M., & Pichora-Fuller, M. K. (2002). Listening in aging adults: From discourse comprehension to Psychoacoustics. *Canadian Journal of Experimental Psychology-Revue Canadienne De Psychologie Experimentale, 56*(3), 139-152. doi:DOI 10.1037/h0087392

Schrijvers, E. M., Verhaaren, B. F., Koudstaal, P. J., Hofman, A., Ikram, M. A., & Breteler, M. M. (2012). Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology, 78*(19), 1456-1463. doi:10.1212/WNL.0b013e3182553be6

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med, 1*(1), a006189. doi:10.1101/cshperspect.a006189

Shafto, M. A., Burke, D. M., Stamatakis, E. A., Tam, P. P., & Tyler, L. K. (2007). On the tip-of-the-tongue: neural correlates of increased word-finding failures in normal aging. *J Cogn Neurosci, 19*(12), 2060-2070. doi:10.1162/jocn.2007.19.12.2060

Sherrington, R., Rogaev, E. I., Liang, Y., Rogaeva, E. A., Levesque, G., Ikeda, M., . . . St George-Hyslop, P. H. (1995). Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature, 375*(6534), 754-760. doi:10.1038/375754a0

Sherwood, C. C., Subiaul, F., & Zawidzki, T. W. (2008). A natural history of the human mind: tracing evolutionary changes in brain and cognition. *Journal of Anatomy, 212*(4), 426-454. doi:10.1111/j.1469-7580.2008.00868.x

Shu, N., Liang, Y., Li, H., Zhang, J., Li, X., Wang, L., . . . Zhang, Z. (2012). Disrupted topological organization in white matter structural networks in amnestic mild cognitive impairment: relationship to subtype. *Radiology, 265*(2), 518-527. doi:10.1148/radiol.12112361

Siddiqui, S. V., Chatterjee, U., Kumar, D., Siddiqui, A., & Goyal, N. (2008). Neuropsychology of prefrontal cortex. *Indian J Psychiatry, 50*(3), 202-208. doi:10.4103/0019-5545.43634

Silagi, M. L., Bertolucci, P. H., & Ortiz, K. Z. (2015). Naming ability in patients with mild to moderate Alzheimer's disease: what changes occur with the evolution of the disease? *Clinics (Sao Paulo), 70*(6), 423-428. doi:10.6061/clinics/2015(06)07

Silveri, M. C., Cappa, A., Mariotti, P., & Puopolo, M. (2002). Naming in patients with Alzheimer's disease: influence of age of acquisition and categorical effects. *J Clin Exp Neuropsychol, 24*(6), 755-764. doi:10.1076/jcen.24.6.755.8407

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience, 4*(8), 637-648. doi:10.1038/nrn1178

Singh, V., Chertkow, H., Lerch, J. P., Evans, A. C., Dorr, A. E., & Kabani, N. J. (2006). Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain, 129*(Pt 11), 2885-2893. doi:10.1093/brain/awl256

Siri, S., Benaglio, I., Frigerio, A., Binetti, G., & Cappa, S. F. (2001). A brief neuropsychological assessment for the differential diagnosis between frontotemporal dementia and Alzheimer's disease. *Eur J Neurol, 8*(2), 125-132.

Small, G. (2002). *Neuropsychopharmacology: The Fifth Generation of Progress: An Official Publication of the American College of Neuropsychopharmacology* (5 ed.). Philadelphia, Pennsylvania, 2002 Lippincott, Williams, & Wilkins.

Smith, E. E., Schneider, J. A., Wardlaw, J. M., & Greenberg, S. M. (2012). Cerebral microinfarcts: the invisible lesions. *Lancet Neurol, 11*(3), 272-282. doi:10.1016/S1474-4422(11)70307-6

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol Hum Learn, 6*(2), 174-215.

Snowdon, D. (2007). [Aging with grace: findings from the Nun Study]. *Rinsho Shinkeigaku, 47*(11), 708-709.

Snowdon, D. A., Greiner, L. H., & Markesbery, W. R. (2000). Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease - Findings from the nun study. *Vascular Factors in Alzheimer's Disease, 903*, 34-38. doi:DOI 10.1111/j.1749-6632.2000.tb06347.x

Snowdon, D. A., & Nun, S. (2003). Healthy aging and dementia: findings from the Nun Study. *Ann Intern Med, 139*(5 Pt 2), 450-454.

Sobral, M., Pestana, M. H., & Paul, C. (2015). Cognitive reserve and the severity of Alzheimer's disease. *Arq Neuropsiquiatr, 73*(6), 480-486. doi:10.1590/0004-282X20150044

Soldan, A., Pettigrew, C., Lu, Y., Wang, M. C., Selnes, O., Albert, M., . . . Team, B. R. (2015). Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve

in preclinical Alzheimer's disease. *Hum Brain Mapp, 36*(7), 2826-2841. doi:10.1002/hbm.22810

Spaan, P. E. J. (2015). Episodic and semantic memory functioning in very old age: Explanations from executive functioning and processing speed theories. *Cogent Psychology*, 1-24.

Spaniol, J., Madden, D. J., & Voss, A. (2006). A diffusion model analysis of adult age differences in episodic and semantic long-term memory retrieval. *J Exp Psychol Learn Mem Cogn, 32*(1), 101-117. doi:10.1037/0278-7393.32.1.101

Spears, W., Furgerson, M., Sweetnam, J. M., Evans, P., Gearing, M., Fechheimer, M., & Furukawa, R. (2014). Hirano bodies differentially modulate cell death induced by tau and the amyloid precursor protein intracellular domain. *BMC Neurosci, 15*, 74. doi:10.1186/1471-2202-15-74

Spector, A., Thorgrimsen, L., Woods, B., Royan, L., Davies, S., Butterworth, M., & Orrell, M. (2003). Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br J Psychiatry, 183*, 248-254.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol, 11*(11), 1006-1012. doi:10.1016/S1474-4422(12)70191-6

Stolwyk, R., Bannirchelvam, B., Kraan, C., & Simpson, K. (2015). The cognitive abilities associated with verbal fluency task performance differ across fluency variants and age groups in healthy young and old adults. *J Clin Exp Neuropsychol, 37*(1), 70-83. doi:10.1080/13803395.2014.988125

Stopford, C. L., Snowden, J. S., Thompson, J. C., & Neary, D. (2008). Variability in cognitive presentation of Alzheimer's disease. *Cortex, 44*(2), 185-195. doi:10.1016/j.cortex.2005.11.002

Stoub, T. R., Bulgakova, M., Leurgans, S., Bennett, D. A., Fleischman, D., Turner, D. A., & deToledo-Morrell, L. (2005). MRI predictors of risk of incident Alzheimer disease: a longitudinal study. *Neurology, 64*(9), 1520-1524. doi:10.1212/01.WNL.0000160089.43264.1A

Suckling, J., Simas, T., Chattopadhyay, S., Tait, R., Su, L., Williams, G., . . . O'Brien, J. T. (2015). A Winding Road: Alzheimer's Disease Increases Circuitous Functional Connectivity Pathways. *Front Comput Neurosci, 9*, 140. doi:10.3389/fncom.2015.00140

Sugino, H., Watanabe, A., Amada, N., Yamamoto, M., Ohgi, Y., Kostic, D., & Sanchez, R. (2015). Global Trends in Alzheimer Disease Clinical Development: Increasing the Probability of Success. *Clin Ther, 37*(8), 1632-1642. doi:10.1016/j.clinthera.2015.07.006

Talbot, C., Lendon, C., Craddock, N., Shears, S., Morris, J. C., & Goate, A. (1994). Protection against Alzheimer's disease with apoE epsilon 2. *Lancet, 343*(8910), 1432-1433.

Tanaka, K., Yamada, Y., Kobayashi, Y., Sonohara, K., Machida, A., Nakai, R., . . . Toba, K. (2007). Improved cognitive function, mood and brain blood flow in single photon emission computed tomography following individual reminiscence therapy in an

elderly patient with Alzheimer's disease. *Geriatrics & Gerontology International, 7*(3), 305-309. doi:10.1111/j.1447-0594.2007.00418.x

Tariot, P. N., Farlow, M. R., Grossberg, G. T., Graham, S. M., McDonald, S., Gergel, I., & Memantine Study, G. (2004). Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA, 291*(3), 317-324. doi:10.1001/jama.291.3.317

Testa, J. A., Ivnik, R. J., Boeve, B., Petersen, R. C., Pankratz, V. S., Knopman, D., . . . Smith, G. E. (2004). Confrontation naming does not add incremental diagnostic utility in MCI and Alzheimer's disease. *J Int Neuropsychol Soc, 10*(4), 504-512. doi:10.1017/S1355617704104177

Thal, D. R., Del Tredici, K., & Braak, H. (2004). Neurodegeneration in normal brain aging and disease. *Sci Aging Knowledge Environ, 2004*(23), pe26. doi:10.1126/sageke.2004.23.pe26

Thal, D. R., Del Tredici, K., Ludolph, A. C., Hoozemans, J. J., Rozemuller, A. J., Braak, H., & Knippschild, U. (2011). Stages of granulovacuolar degeneration: their relation to Alzheimer's disease and chronic stress response. *Acta Neuropathol, 122*(5), 577-589. doi:10.1007/s00401-011-0871-6

Thal, D. R., Rub, U., Orantes, M., & Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology, 58*(12), 1791-1800.

Thal, D. R., von Arnim, C., Griffin, W. S., Yamaguchi, H., Mrak, R. E., Attems, J., & Upadhaya, A. R. (2013). Pathology of clinical and preclinical Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci, 263 Suppl 2*, S137-145. doi:10.1007/s00406-013-0449-5

Thompson-Schill, S. L., D'Esposito, M., & Kan, I. P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron, 23*(3), 513-522.

Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., . . . Toga, A. W. (2003). Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci, 23*(3), 994-1005.

Tippett, L. J., Meier, S. L., Blackwood, K., & Diaz-Asper, C. (2007). Category specific deficits in Alzheimer's disease: fact or artefact? *Cortex, 43*(7), 907-920.

Tomasi, D., & Volkow, N. D. (2012). Language network: segregation, laterality and connectivity. *Mol Psychiatry, 17*(8), 759. doi:10.1038/mp.2012.99

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology, 19*(2), 203-214. doi:10.1016/S0887-6177(03)00039-8

Traykov, L., Baudic, S., Raoux, N., Latour, F., Rieu, D., Smagghe, A., & Rigaud, A. S. (2005). Patterns of memory impairment and perseverative behavior discriminate early Alzheimer's disease from subcortical vascular dementia. *J Neurol Sci, 229-230*, 75-79. doi:10.1016/j.jns.2004.11.006

Tripathi, R., Kumar, K., Bharath, S., Marimuthu, P., & Varghese, M. (2014). Age, education and gender effects on neuropsychological functions in healthy Indian older adults. *Dement Neuropsychol, 8*(2), 148-154.

Tsang, H. L., & Lee, T. M. (2003). The effect of ageing on confrontational naming ability. *Arch Clin Neuropsychol, 18*(1), 81-89.

Tulving, E., Donaldson, W., & Bower, G. H. (1972). Organization of memory. United States. Office of Naval Research: Academic Press.

Tyas, S. L., Snowdon, D. A., Desrosiers, M. F., Riley, K. P., & Markesbery, W. R. (2007). Healthy ageing in the Nun Study: definition and neuropathologic correlates. *Age Ageing, 36*(6), 650-655. doi:10.1093/ageing/afm120

Tyler, L. K., Moss, H. E., Durrant-Peatfield, M. R., & Levy, J. P. (2000). Conceptual structure and the structure of concepts: a distributed account of category-specific deficits. *Brain Lang, 75*(2), 195-231. doi:10.1006/brln.2000.2353

Vadikolias, K., Tsiakiri-Vatamidis, A., Tripsianis, G., Tsivgoulis, G., Ioannidis, P., Serdari, A., . . . Piperidou, C. (2012). Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. *Brain Behav, 2*(5), 620-627. doi:10.1002/brb3.88

van Heuven, W. J., Mandera, P., Keuleers, E., & Brysbaert, M. (2014). SUBTLEX-UK: a new and improved word frequency database for British English. *Q J Exp Psychol (Hove), 67*(6), 1176-1190. doi:10.1080/17470218.2013.850521

Veitinger, M., Varga, B., Guterres, S. B., & Zellner, M. (2014). Platelets, a reliable source for peripheral Alzheimer's disease biomarkers? *Acta Neuropathol Commun, 2*, 65. doi:10.1186/2051-5960-2-65

Velayudhan, L., Proitsi, P., Westman, E., Muehlboeck, J. S., Mecocci, P., Vellas, B., . . . dNeuroMed, C. (2013). Entorhinal cortex thickness predicts cognitive decline in Alzheimer's disease. *J Alzheimers Dis, 33*(3), 755-766. doi:10.3233/JAD-2012-121408

Venneri, A., McGeown, W. J., Biundo, R., Mion, M., Nichelli, P., & Shanks, M. F. (2011). The Neuroanatomical Substrate of Lexical-Semantic Decline in MCI APOE epsilon 4 Carriers and Noncarriers. *Alzheimer Disease & Associated Disorders, 25*(3), 230-241. doi:10.1097/WAD.0b013e318206f88c

Venneri, A., McGeown, W. J., Hietanen, H. M., Guerrini, C., Ellis, A. W., & Shanks, M. F. (2008). The anatomical bases of semantic retrieval deficits in early Alzheimer's disease. *Neuropsychologia, 46*(2), 497-510. doi:10.1016/j.neuropsychologia.2007.08.026

Venneri, A., Mitolo, M., & De Marco, M. (2016). Paradigm shift: semantic memory decline as a biomarker of preclinical Alzheimer's disease. *Biomark Med, 10*(1), 5-8. doi:10.2217/bmm.15.53

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., . . . Buschke, H. (2003). Leisure activities and the risk of dementia in the elderly. *N Engl J Med, 348*(25), 2508-2516. doi:10.1056/NEJMoa022252

Verhaegen, C., & Poncelet, M. (2013). Changes in naming and semantic abilities with aging from 50 to 90 years. *J Int Neuropsychol Soc, 19*(2), 119-126. doi:10.1017/S1355617712001178

Verhaegen, P., Borchelt, M., & Smith, J. (2003). Relation between cardiovascular and metabolic disease and cognition in very old age: cross-sectional and longitudinal findings from the berlin aging study. *Health Psychol, 22*(6), 559-569. doi:10.1037/0278-6133.22.6.559

Verma, M., & Howard, R. J. (2012). Semantic memory and language dysfunction in early Alzheimer's disease: a review. *Int J Geriatr Psychiatry, 27*(12), 1209-1217. doi:10.1002/gps.3766

Vinters, H. V., & Gilbert, J. J. (1983). Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. *Stroke, 14*(6), 924-928.

Vliet, E. C., Manly, J., Tang, M. X., Marder, K., Bell, K., & Stern, Y. (2003). The neuropsychological profiles of mild Alzheimer's disease and questionable dementia as compared to age-related cognitive decline. *J Int Neuropsychol Soc, 9*(5), 720-732. doi:10.1017/S1355617703950053

Vogel, A., Gade, A., Stokholm, J., & Waldemar, G. (2005). Semantic memory impairment in the earliest phases of Alzheimer's disease. *Dement Geriatr Cogn Disord, 19*(2-3), 75-81. doi:10.1159/000082352

Vos, S. J., Xiong, C., Visser, P. J., Jasielec, M. S., Hassenstab, J., Grant, E. A., . . . Fagan, A. M. (2013). Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol, 12*(10), 957-965. doi:10.1016/S1474-4422(13)70194-7

Vuorinen, E., Laine, M., & Rinne, J. (2000). Common pattern of language impairment in vascular dementia and in Alzheimer disease. *Alzheimer Disease & Associated Disorders, 14*(2), 81-86. doi:Doi 10.1097/00002093-200004000-00005

Wagner, A. D., Pare-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31*(2), 329-338. doi:Doi 10.1016/S0896-6273(01)00359-2

Wakefield, S. J., McGeown, W. J., Shanks, M. F., & Venneri, A. (2014). Differentiating normal from pathological brain ageing using standard neuropsychological tests. *Curr Alzheimer Res, 11*(8), 765-772.

Wang, L., Goldstein, F. C., Veledar, E., Levey, A. I., Lah, J. J., Meltzer, C. C., . . . Mao, H. (2009). Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. *AJNR Am J Neuroradiol, 30*(5), 893-899. doi:10.3174/ajnr.A1484

Wang, P., Zhou, B., Yao, H., Zhan, Y., Zhang, Z., Cui, Y., . . . Jiang, T. (2015). Aberrant intra- and inter-network connectivity architectures in Alzheimer's disease and mild cognitive impairment. *Sci Rep, 5*, 14824. doi:10.1038/srep14824

Wang, Y., Risacher, S. L., West, J. D., McDonald, B. C., Magee, T. R., Farlow, M. R., . . . Saykin, A. J. (2013). Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. *J Alzheimers Dis, 35*(4), 751-760. doi:10.3233/JAD-130080

Warrington, E. K., & Mccarthy, R. A. (1987). Categories of Knowledge - Further Fractionations and an Attempted Integration. *Brain, 110*, 1273-1296. doi:DOI 10.1093/brain/110.5.1273

Warrington, E. K., & Shallice, T. (1984). Category Specific Semantic Impairments. *Brain, 107*(Sep), 829-854. doi:DOI 10.1093/brain/107.3.829

Waters, G., & Caplan, D. (2005). The relationship between age, processing speed, working memory capacity, and language comprehension. *Memory, 13*(3-4), 403-413. doi:10.1080/09658210344000459

Wattamwar, P. R., & Mathuranath, P. S. (2010). An overview of biomarkers in Alzheimer's disease. *Ann Indian Acad Neurol, 13*(Suppl 2), S116-123. doi:10.4103/0972-2327.74256

Weakley, A., Schmitter-Edgecombe, M., & Anderson, J. (2013). Analysis of verbal fluency ability in amnestic and non-amnestic mild cognitive impairment. *Arch Clin Neuropsychol, 28*(7), 721-731. doi:10.1093/arclin/act058

Weiner, M. F., Neubecker, K. E., Bret, M. E., & Hynan, L. S. (2008). Language in Alzheimer's disease. *J Clin Psychiatry, 69*(8), 1223-1227.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med, 2*(4), a006171. doi:10.1101/cshperspect.a006171

Welch, L. W., Doineau, D., Johnson, S., & King, D. (1996). Educational and gender normative data for the Boston naming test in a group of older adults. *Brain and Language, 53*(2), 260-266. doi:DOI 10.1006/brln.1996.0047

Wells, R. E., Yeh, G. Y., Kerr, C. E., Wolkin, J., Davis, R. B., Tan, Y., . . . Kong, J. (2013). Meditation's impact on default mode network and hippocampus in mild cognitive impairment: a pilot study. *Neurosci Lett, 556*, 15-19. doi:10.1016/j.neulet.2013.10.001

Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjornerud, A., Due-Tonnessen, P., Engvig, A., . . . Fjell, A. M. (2010). Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. *Cereb Cortex, 20*(9), 2055-2068. doi:10.1093/cercor/bhp280

Whalley, L. J., Deary, I. J., Appleton, C. L., & Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev, 3*(4), 369-382. doi:10.1016/j.arr.2004.05.001

Wharton, S. B., Brayne, C., Savva, G. M., Matthews, F. E., Forster, G., Simpson, J., . . . Aging, S. (2011). Epidemiological neuropathology: the MRC Cognitive Function and Aging Study experience. *J Alzheimers Dis, 25*(2), 359-372. doi:10.3233/JAD-2011-091402

Whitney, C., Grossman, M., & Kircher, T. T. (2009). The influence of multiple primes on bottom-up and top-down regulation during meaning retrieval: evidence for 2 distinct neural networks. *Cereb Cortex, 19*(11), 2548-2560. doi:10.1093/cercor/bhp007

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., & Jefferies, E. (2012). Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J Cogn Neurosci, 24*(1), 133-147. doi:10.1162/jocn_a_00123

Whitney, C., Kirk, M., O'Sullivan, J., Ralph, M. A. L., & Jefferies, E. (2011). The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. *Cerebral Cortex, 21*(5), 1066-1075. doi:10.1093/cercor/bhq180

Whitwell, J. L., Jack, C. R., Jr., Pankratz, V. S., Parisi, J. E., Knopman, D. S., Boeve, B. F., . . . Josephs, K. A. (2008). Rates of brain atrophy over time in autopsy-proven frontotemporal dementia and Alzheimer disease. *Neuroimage, 39*(3), 1034-1040. doi:10.1016/j.neuroimage.2007.10.001

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., & Bennett, D. A. (2013). Life-span cognitive activity, neuropathologic burden, and cognitive aging. *Neurology, 81*(4), 314-321. doi:10.1212/WNL.0b013e31829c5e8a

Wilson, R. S., Nag, S., Boyle, P. A., Hizel, L. P., Yu, L., Buchman, A. S., . . . Bennett, D. A. (2013). Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology, 80*(13), 1202-1208. doi:10.1212/WNL.0b013e3182897103

Wilson, R. S., Segawa, E., Boyle, P. A., Anagnos, S. E., Hizel, L. P., & Bennett, D. A. (2012). The natural history of cognitive decline in Alzheimer's disease. *Psychol Aging, 27*(4), 1008-1017. doi:10.1037/a0029857

Woodward, M. C., & Woodward, E. (2009). A national survey of memory clinics in Australia. *Int Psychogeriatr, 21*(4), 696-702. doi:10.1017/S1041610209009156

Yasuno, F., Kazui, H., Morita, N., Kajimoto, K., Ihara, M., Taguchi, A., . . . Kishimoto, T. (2015). Low amyloid-beta deposition correlates with high education in cognitively normal older adults: a pilot study. *Int J Geriatr Psychiatry, 30*(9), 919-926. doi:10.1002/gps.4235

Yeung, M. K., Sze, S. L., Woo, J., Kwok, T., Shum, D. H., Yu, R., & Chan, A. S. (2016). Altered Frontal Lateralization Underlies the Category Fluency Deficits in Older Adults with Mild Cognitive Impairment: A Near-Infrared Spectroscopy Study. *Front Aging Neurosci, 8*, 59. doi:10.3389/fnagi.2016.00059

Yildiz, S. H., Erdogan, M. O., Artan, S., Solak, M., Yaman, M., Ozbabalik, B. D., & Terzi, E. S. (2015). Association of Alzheimer's Disease With APOE and IL-1alpha Gene Polymorphisms. *Am J Alzheimers Dis Other Demen, 30*(8), 756-761. doi:10.1177/1533317512461557

Zannino, G. D., Perri, R., Caltagirone, C., & Carlesimo, G. A. (2007). Category-specific naming deficit in Alzheimer's disease: the effect of a display by domain interaction. *Neuropsychologia, 45*(8), 1832-1839. doi:10.1016/j.neuropsychologia.2006.12.011

Zannino, G. D., Perri, R., Carlesimo, G. A., Pasqualetti, P., & Caltagirone, C. (2002). Category-specific impairment in patients with Alzheimer's disease as a function of disease severity: a cross-sectional investigation. *Neuropsychologia, 40*(13), 2268-2279.

Zannino, G. D., Perri, R., Pasqualetti, P., Caltagirone, C., & Carlesimo, G. A. (2006). (Category-specific) semantic deficit in Alzheimer's patients: the role of semantic distance. *Neuropsychologia, 44*(1), 52-61. doi:10.1016/j.neuropsychologia.2005.04.008

Zetterberg, H., Wahlund, L. O., & Blennow, K. (2003). Cerebrospinal fluid markers for prediction of Alzheimer's disease. *Neurosci Lett, 352*(1), 67-69.

Zhang, H., Sachdev, P. S., Wen, W., Kochan, N. A., Crawford, J. D., Brodaty, H., . . . Trollor, J. N. (2013). Grey matter correlates of three language tests in non-demented older adults. *PLoS One, 8*(11), e80215. doi:10.1371/journal.pone.0080215

Zhao, H., Li, X., Wu, W., Li, Z., Qian, L., Li, S., . . . Xu, Y. (2015). Atrophic Patterns of the Frontal-Subcortical Circuits in Patients with Mild Cognitive Impairment and Alzheimer's Disease. *PLoS One, 10*(6), e0130017. doi:10.1371/journal.pone.0130017

Zhao, Q., Guo, Q., & Hong, Z. (2013). Clustering and switching during a semantic verbal fluency test contribute to differential diagnosis of cognitive impairment. *Neurosci Bull, 29*(1), 75-82. doi:10.1007/s12264-013-1301-7

Zheng, D., Sun, H., Dong, X., Liu, B., Xu, Y., Chen, S., . . . Wang, X. (2014). Executive dysfunction and gray matter atrophy in amnestic mild cognitive impairment. *Neurobiol Aging, 35*(3), 548-555. doi:10.1016/j.neurobiolaging.2013.09.007

Zheng, H., & Koo, E. H. (2011). Biology and pathophysiology of the amyloid precursor protein. *Mol Neurodegener, 6*(1), 27. doi:10.1186/1750-1326-6-27