Experimental Neuropsychological Tests of Feature Ambiguity, Attention and Structural Learning: Associations with White Matter Microstructural Integrity in Elderly with Amnesic and Vascular Mild Cognitive Impairment

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List of Abbreviations

AD	Alzheimer's disease
aMCI	amnesic mild cognitive impairment
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANT	attention network test
BVMT	brief visuospatial memory test
DTI	diffusion tensor imaging
FA	fractional anisotropy
FLAIR	fluid attenuated inversion recovery
HC	healthy control
L1	axial diffusivity
MCI	mild cognitive impairment
MD	mean diffusivity
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
NP	Neuropsychological
NP1	neuropsychological inventory 1
NP2	neuropsychological inventory 2
RD	radial diffusivity
ROI	regions of interest
RT	reaction time
SEM	standard error of the mean
TBSS	tract-based spatial statistics
TFCE	threshold-free cluster enhancement
vMCI	vascular mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI) is a transition phase between normal aging and Alzheimer's disease. Individuals with MCI show impairment in cognition as well as corresponding damage to areas of their brain. Performance on tasks such as discriminating objects with ambiguous features has been associated with damage to the perirhinal cortex, while scenes with structural (spatial) elements have been associated with damage to the hippocampus. In addition, attention is regarded as one of the first non-memory domains to decline in MCI. A relatively new MRI technique called diffusion tensor imaging (DTI) is sensitive to white matter microstructural integrity and has been associated with changes due to cognitive decline. 18 MCI (14 amnesic, 4 vascular) and 12 healthy matched controls were assessed in feature ambiguity, attention and structural learning to assess associated deficits in MCI. Associations with white matter microstructural integrity were then investigated. The MCI groups were discovered to perform worse than controls on the test of structural learning. In addition, altered attention networks were found in MCI and were associated with white matter microstructural integrity. No significant differences were found for feature ambiguity. These findings suggest there may be specific damage to the hippocampus while the perirhinal cortex may be preserved in MCI. Furthermore, dysfunction in attention was found to be associated with white matter microstructural integrity. These experimental tests may be useful in assessing dysfunction in MCI and identifying degeneration in white matter microstructural integrity. Further studies with larger sample sizes are needed to validate these findings.

1. Introduction

Alzheimer's disease (AD) is an insidious, progressive, degenerative disease associated with severe memory deficits and significant decline in one or more other cognitive domains (Ballard et al., 2011; Bishop, Lu, & Yankner, 2010). Age is the most relevant risk factor in the majority of cases and is consequently, especially prevalent in the elderly (Lindsay et al., 2002). Our ageing population means there is growing concern about the increasing number of people being affected by AD. In 2005, the worldwide incidence of AD was estimated at 24.3 million and forecasted to double every 20 years, reaching 81 million people by 2040 (Ferri et al., 2005). While there is no cure for AD, pharmaceutical treatments for dementia are available, such as cholinesterase inhibitors. Unfortunately, these have shown modest success in slowing down the progression of AD (Singh & O'Brien, 2009) and also have adverse side-effects (Lanctot et al., 2003). Patients with AD eventually require intensive care which puts considerable burden on their families and healthcare providers (Ernst & Hay, 1994). Very little is known about the disease in its early stages. It is imperative more information is uncovered about the cause and progression of the disease, to reduce the prevalence in the future.

1.1 Mild cognitive impairment

Mild Cognitive Impairment (MCI) is a transition phase between normal aging and Alzheimer's disease (R. C. Petersen, 2004). Individuals with MCI are able to conduct activities of daily living but show mild to modest cognitive impairments beyond that expected of someone their age. These individuals are at risk in developing dementia (Devanand et al., 2008). Many case of MCI are considered a prodromal form of AD with conversion rates estimated to be from 10% to 15% per year (Brooks & Loewenstein, 2010) compared to cognitively healthy controls who convert at 1% to 2% each year (Tierney et al., 1996). However, MCI is an unstable state with up to 40% reverting back to normal levels of cognition over a few years (Larrieu et al., 2002). As such, MCI has been of particular interest to researchers in developing interventions and therapies to combat cognitive impairment as well as identifying biomarkers which distinguish decline into dementia.

The instability of MCI makes diagnosis difficult. For example, the commonly used screen, the mini-mental state examination, does not discriminate MCI converters to dementia from MCI non-converters (Misra, Fan, & Davatzikos, 2009). Changes to the MCI criteria and concept have been introduced to improve it prognostic quality. An important development was the classification of subtypes of MCI, such as the amnesic MCI subtype (aMCI) (R. C. Petersen et al., 2001). For aMCI, individuals are required to report a subjective memory complaint and show abnormal memory domain dysfunction beyond that of their healthy peers. Additionally, they must remain relatively unimpaired in other domains of cognition and have preserved activities of daily functioning to exclude dementia (R. C. Petersen, 2004). Patients who meet these criteria for aMCI are suggested to be the most likely to progress to AD. Non-amnesic MCI patients are suggested to have deficits in other cognitive domains and are instead more likely to develop other dementias or to have comorbid etiologies (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). MCI with vascular features (vMCI) appears to be another common type of MCI. Frisoni, Galluzzi, Bresciani, Zanetti, and Geroldi (2002) classified the presence of vascular features in MCI and found these patients to follow a slightly different course with a worse outcome. MCI patients with vascular features showed accelerated deterioration in frontal tests such as in the Wisconsin card sorting and word fluency, and in overall health. Vascular features are becoming increasingly relevant to the diagnosis of AD (Provenzano et al., 2013). To best identify MCI individuals most likely to convert to AD, detailed neuropsychological testing beyond an initial screen coupled with one or more biomarkers remain the best indicators for conversion (Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011).

1.2 Attention in MCI

Although deficits in the memory domain have been most associated with MCI and AD, attention may be the first non-memory domain to be affected (Perry & Hodges, 1999; Perry, Watson, & Hodges, 2000). Attention has been linked directly to problems in activities of daily function (a prerequisite for a dementia diagnosis) and may be linked to overall cognitive state. Additionally, deficits in attention and executive function appear to be characteristic in those during dementia onset (Li et al., 2012;

Silveri, Reali, Jenner, & Puopolo, 2007). Sheridan and Hausdorff (2007) found attention deficits relating to executive dysfunction in AD to be a significant risk factor for falls in AD due to a negative effect on motor behavior. Despite the significance of attentional deficits in MCI and AD, the majority of research has largely neglected the attention domain and focused on the memory and visuospatial domains instead (Romberg, Bussey, & Saksida, 2013).

One way to conceptualize attention is to associate different processes with three major networks, each corresponding to functional and anatomical areas of the brain (Cabeza & Nyberg, 2000). These networks are called the alerting, orienting and executive attention networks and were introduced by Posner and Petersen (1990) as part of their cognitive neuroscience model of attention. When damaged, each is expected to show impaired function relevant to their specific attention network (Berger & Posner, 2000). Although these networks are linked to the overarching attention process, support that the components of attention are generally independent also comes from brain activation studies (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). An explanation of the networks is detailed in the following subsections.

1.2.1 Alerting network

The alerting network is believed to help maintain an individual's awareness of salient environmental stimuli. Regions of the thalamus, right frontal and parietal lobes of the brain have been implicated based on activations found during vigilance tasks (Coull, Frith, Frackowiak, & Grasby, 1996). This network is modulated by the locus coeruleus-norepinephrine neurotransmitter system which has been found to be active following a warning signal (Aston-Jones & Cohen, 2005).

There are a number of approaches to studying the alerting network but tonic alertness has been a useful technique. In this method, participants are exposed to an alerting tone prior to response to a target. This warning tone evokes a new state that involves preparing for the stimulus target and a change from the resting state. If a quicker response is anticipated to a target, then the reaction time following the warning should improve (S. E. Petersen & Posner, 2012).

1.2.2 Orienting network

The orienting network is activated in the selection of a target among several sensory stimuli. The process of shifting attention from one target to another corresponds to this network. Regions of the parietal and frontal lobes, the temporo-parietal junction, and the ventral frontal cortex appear to be related to shifts in orienting attention (Corbetta & Shulman, 2002). Modulation by the cholinergic system has been implicated in this network (Sarter, Bruno, & Givens, 2003). For example, Davidson and Marrocco (2000) showed that an addition of an anticholinergic drug directly into the intraparietal cortex impaired the ability of monkeys to shift attention to a target.

The orienting network is usually assessed in humans by using pre-cuing stimuli before the onset of a target. These paradigms were originally developed by Posner (1980) and assess the benefit of attending to cued stimuli in the same position as the preceding target compared to an invalidly or neutrally cued position not in the same position as a preceding target.

1.2.3 Executive network

The executive attention network is involved in self-regulation, planning, error detection and conflict resolution tasks. The anterior cingulate cortex and the lateral prefrontal cortical areas have been associated with the executive network (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). This network is modulated by the dopaminergic system (Roesch-Ely et al., 2005). As executive impairments are common in early AD, impairments in this domain are beginning to be especially studied in MCI (Stokholm, Vogel, Gade, & Waldemar, 2006). Rainville, Lepage, Gauthier, Kergoat, and Belleville (2012) found executive dysfunction in MCI participants on a tower of London task, where they made more rule breaking errors. The degree of impairment was associated with the rate of decline in cognition.

Assessment of the executive network is often assessed through conflict resolution, such as in the Stroop interference and flanker tasks. The flanker task requires participants to respond to a

central target stimulus (normally in the form of an arrow) while ignoring incongruent flanking distractors (arrows pointing in the opposite direction) (Gamboz, Zamarian, & Cavallero, 2010).

1.2.4 The attention network test

The attention network test (ANT) is a computerized attention task designed to assess these three attention networks. The basic task was first introduced by Fan, McCandliss, Sommer, Raz, and Posner (2002), and combines an alerting tone, pre-cueing and flanker paradigm. In this task, participants are assessed on the executive network by responding to a central arrow while being flanked by four distracting arrows that can be either congruent or incongruent. The orienting network is assessed by a visual cue prior to presentation of the target. In valid cue conditions, the visual cue precedes the target in the exact location. In the invalid condition, the cue is presented in a different location. The alerting network is assessed by producing a tone or no tone prior to the onset of the visual cue. Assessment of each network is obtained from calculating the difference of the reaction times between the two conditions of each attention network.

The ANT has been used to assess attention in ageing. Gamboz et al. (2010) found a decline in the measure of the alerting network but not in the orienting and executive networks in older adults. This has been shown recently in aMCI where selective impairment in the alerting aspect of attention are evident (Martella et al., 2014). Mahoney, Verghese, Goldin, Lipton, and Holtzer (2010) supported this theory of diminished alerting, but also showed that age and blood pressure were negatively associated with the executive attention network. In AD, the ANT has revealed impaired conflict resolution in the executive network but relatively preserved alerting and orienting networks (Fernandez-Duque & Black, 2006). The interactions between the attention networks may serve as a better indicator of impairment in attention. Fuentes et al. (2010) found that in healthy elderly, the trials involving an alerting signal improved both the response times to the orienting cue and to the target, despite an invalid cue or distracting flankers. This alerting effect which improved response times in the other networks of healthy controls was not beneficial in AD patients. Dysfunction in the

interactions between the networks such as the alerting with the orienting and executive networks may be an indicator of impairment. However, the additions of vascular features in MCI appear to have a severe effect on the orienting network. Fernandez et al. (2011) showed a vastly reduced orienting effect in vMCI patients and attributed this to a failure of the participants to summon attention to a cued location.

1.3 Feature ambiguity

The medial temporal lobe (MTL), and the contributing cortical structures such as the perirhinal cortex have been regarded as a single declarative memory system with little role in other functions (Squire, Stark, & Clark, 2004). In this model, damage to the MTL only produces deficits in forms of declarative memory (Squire & Wixted, 2011). There has been much debate over the ensuing years with one competing theory that some of the cortical MTL, especially the perirhinal cortex is essential for discriminating perceptually and semantically ambiguous objects (Bussey, Saksida, & Murray, 2006; Graham, Barense, & Lee, 2010). For example, in an MRI study, the perirhinal cortex was found to be associated with performance on a perceptual and semantically confusable object test (Kivisaari, Tyler, Monsch, & Taylor, 2012). Importantly, this effect was not seen in the entorhinal cortex and the hippocampus. The hippocampus, however, has been associated with visual discrimination of complex spatial scenes rather than ambiguous object discrimination (Lee, Yeung, & Barense, 2012). Mundy, Downing, Dwyer, Honey, and Graham (2013) conducted a further study on functional MRI and found complex spatial (structural) scenes was associated with activity in the hippocampus, whereas, discrimination of ambiguous faces was involved in the perirhinal cortex. The basis for these competing views comes primarily from lesion studies, which are relevant to the idea that degeneration in the parahippocampal cortex (perirhinal and lateral entorhinal regions, especially) is among the earliest structures to be affected by AD neuropathology (Gallagher & Koh, 2011). Tests of feature ambiguity are relevant to this current study as anterior MTL atrophy is present to varying degrees in aMCI (Lerch et al., 2005).

Bussey, Saksida, and Murray (2003) found that lesions to the perirhinal cortex of rhesus monkeys resulted in impairment in complex visual object discrimination (a high degree of feature ambiguity) whereas no difference was found for a low degree of feature ambiguity. In human studies of MTL damage, Barense et al. (2005) reported that patients with MTL damage were unable to discriminate between objects of high feature ambiguity. By contrast, patients with damage restricted to the hippocampal formation instead, were able to perform as well as controls on the feature ambiguous discrimination task and further support the idea of functional specialization.

The ability of MCI participants to discriminate objects of feature ambiguity may be a useful indicator to damage in the MTL, particularly the perirhinal cortex, independent of the hippocampus. Newsome, Duarte, and Barense (2012) found MCI participants to be impaired in high perceptual ambiguity conditions but performed similar to controls in low ambiguity conditions. The conditions vary in difficultly by the elements that make up each target. In the minimum ambiguity conditions, targets contain elements which are unique. In maximum ambiguity conditions, the elements which make up the target also appear separately in non-targets. It is only when these elements are paired together, that these elements make up a correct target. Tests which assess performance in discriminating feature ambiguity may be promising indictors of increased vulnerability to interference in discriminating targets and non-targets due to the perirhinal cortex.

1.4 Structural learning

In rats, hippocampal damage impairs a class of configural problems known as structural learning (Aggleton, Sanderson, & Pearce, 2007). In configural tasks, targets are made up of a specific combination of elements, rather than any single element alone. Configural tasks can be constructed to contain spatial elements or non-spatial elements. For example, in a simple positive patterning configural task, elements A- and B- are non-targets when presented separately but are correct targets when presented together (AB+). Another common configural task is the game ‘paper, scissors, rock’. In this game, paper trumps rock but not scissors, and scissors trumps paper but not

rock. Elements in this game appear both as correct and incorrect depending on their pairing with another element.

Structural learning, like all configural tasks, contains elements which are combined in correct targets and incorrect targets. However, unlike other configural tasks, structural learning contains an additional spatial or temporal feature which helps distinguish combinations of elements as targets or non-targets. An example of a spatial feature is the elements AB+ and BA-. Both elements A and B appear in targets and non-targets. However, the elements are only correct when arranged in a specific orientation (AB+) and not the other (BA-). It is this feature in a configural task which appears to be sensitive to damage in the hippocampus in rats (Aggleton, O'Mara, et al., 2010). Sanderson, Pearce, Kyd, and Aggleton (2006) created lesions in the hippocampus of rats and tested them on an array of configural tasks. In the configural tasks with no spatial feature, performance of rats was not impaired. However, in the structural learning tasks, rats with hippocampal lesions showed impaired ability compared to controls. This demonstrates the importance of the hippocampus in solving configural tasks with spatial elements.

In human amnesic cases of hippocampal pathology, impairment in the recognition of object locations occurs when the viewpoint is changed. This indicates hippocampal damage is functionally necessary to an individual's ability to remember spatial features within a scene (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). Accumulating evidence has attributed the hippocampus not only with memory, but also discrimination of complex spatial scenes independent of deficits in working or long-term memory (Lee et al., 2012). de Rover et al. (2011) found hippocampal dysfunction in MCI associated with fMRI involving a visuospatial pairing task. During low memory loads, MCI patients showed greater activation of the hippocampus compared to controls. This indicates a compensatory mechanism in the hippocampus to acquire additional resources to complete the task. However, this activation effect was reversed in the high memory load task and indicates dysfunction in the hippocampus in unsuccessfully completing a complex visuospatial pairing

task. Lee, Levi, Davies, Hodges, and Graham (2007) found atrophy in AD was linked with ability to discriminate tests of spatial scenes but showed preservation of object discrimination which was consistent with brain pathology. Structural learning tasks may be useful in assessing hippocampal pathology in MCI.

1.5 Neural correlates in MCI

The exact cause of degeneration is unknown in MCI, although brain autopsies have shown resemblance to those with very mild AD (Morris et al., 2001). This suggests MCI pathology may be a prodromal form of AD pathology. Advances in technology have allowed researchers to look more closely in the underlying pathology of MCI in vivo. MRI techniques have allowed detailed analysis of the brains of a number of MCI cases which was not possible in the past. Comparisons of brain atrophy in the hippocampus, entorhinal cortex, whole brain and ventricle size have shown greater rates of atrophy in MCI who converted to AD (Du et al., 2001; Jack et al., 2004). This was consistent with neurofibrillary pathology which had been found to occur in these regions (Markesbery, 2010). Lower volumes of both grey and white matter and more pronounced periventricular small-vessel pathology have also been observed (Misra et al., 2009). The rate of accelerated atrophy appears to be related to pathologic state and suggests pathology accelerates as the disease progresses. Those with AD suffer the greatest accelerated loss in the hippocampus followed by MCI then healthy aging (Jack et al., 2000; Schuff et al., 2009).

In an fMRI study of a visual encoding task, the medial temporal lobe and parahippocampal gyrus was found to have increased activation in MCI participants with greater clinical impairment even after controlling for atrophy (Dickerson et al., 2004).This is proposed to be a compensatory mechanism to the accumulating neurodegenerative pathology. Additionally, the degree of activation in the hippocampus is predictive of the degree to which individuals will demonstrate future cognitive decline regardless of the degree of cognitive impairment and hippocampal volume (Miller et al., 2008).

Although brain pathology appears to be a biomarker of future decline, there appears to be a considerable degree of heterogeneity in individuals between and within the same cognitive category (Delano-Wood et al., 2009; Schneider, Arvanitakis, Leurgans, & Bennett, 2009). This poses a problem for biomarkers using brain pathology as predictors of progression. Heterogeneous pathology has been observed in MCI, AD and even in healthy aging adults (Bennett et al., 2006). An explanation to the discrepancy between cognition and pathology is the concept of cognitive reserve (Brickman et al., 2011; Stern, 2009). Factors such as a high level of education in early and midlife, diet, a cognitively stimulating career and particular leisure activities appear to protect from cognitive impairment despite significant brain pathology (Whalley, Deary, Appleton, & Starr, 2004). A combination of neuropsychological testing and measures of brain pathology are likely the best predictors for converting MCI.

1.6 Diffusion tensor imaging and white matter pathology

Diffusion tensor imaging (DTI) is an MRI imaging technique sensitive to microstructural white matter changes. This technique is relatively new and is associated with numerous degenerative processes such as neuronal loss, gliosis, deterioration of axonal membranes and myelin sheaths, reduced axonal fibre density, cell density and integrity of microtubules and neurofilaments (Beaulieu, 2002; Le Bihan, 2003). Furthermore, white matter pathology using DTI has been shown to be compromised in early and prodromal forms of AD (Rose, Janke, & Chalk, 2008), independent of grey matter atrophy (Bosch et al., 2012). Zhuang et al. (2010) investigated whole brain white matter tracts using DTI in aMCI and non-amnesic MCI and found that white matter pathology in aMCI was consistent with pathology in early AD. DTI may be a useful indicator for predicting those at risk of onset to dementia. Interestingly, DTI has been associated with performance on the ANT in healthy adults. Niogi, Mukherjee, Ghajar, and McCandliss (2010) found fractional anisotropy (FA) to be associated with distinct white matter tracts consistent with the three attention networks and suggests white matter integrity may modulate these networks.

DTI is based on water diffusion in axons. In healthy white matter, water diffusion is anisotropic and travels in one direction along the length of the axon. This is described by three principal vector directions (λ_1, λ_2, and λ_3). These directions correspond to the three primary axis of an ellipsoid which represents water diffusion in a three-dimensional space. The diffusivity along the principal axis (λ_1) is also called axial diffusivity (L1 for simplicity). This direction of diffusion runs parallel along the direction of the axon. The two other axes (λ_2 and λ_3), run perpendicular to L1 and are usually averaged to produce a measure of radial diffusivity (RD). Most studies employing DTI report a measure called fractional anisotropy (FA) and mean diffusivity (MD). FA provides a measure of the strength of directionality of diffusion, while MD provides a translational measure of diffusion. In intact white matter, the direction of diffusion is promoted along the principal axis (L1) of axons while perpendicular diffusion (RD) is obstructed. Damage to white matter results in an increase in MD and a reduction of FA due to damage to cellular barriers which prevent free diffusion (Stebbins & Murphy, 2009). Abnormalities in the myelin sheath have been most associated with RD measures (Song et al., 2005), while lowered L1 has been associated with neuronal dysfunction (Kinoshita, Ohnishi, Kohshi, & Yokota, 1999).

Although most DTI studies report FA and MD, principal diffusion indices such as L1 and RD have been neglected. Boespflug et al. (2014) found that L1 and RD measures combined with FA and MD are more sensitive in describing white matter microstructural integrity in MCI than FA and MD alone. While FA and MD describe the shape of a diffusion ellipsoid, L1 describes the diffusivity along the axon and RD describes diffusion perpendicular to the axon. In another study, MCI participants showed greater RD than controls in the bilateral parahippocampal white matter, which was also correlated with memory function (Y. Wang et al., 2012). This highlights the importance on assessing all measures of diffusivity to gain a complete picture of white matter microstructural integrity.

White matter microstructural pathology in MCI and AD has gained interest recently due to increasing evidence of the association with cognitive impairment. Kantarci et al. (2011) found that

performance in cognitive domains was associated with distinct patterns of cortical and white matter diffusivity in older adults. Additionally, pathology in white matter has been linked with activities of daily living (Yoon et al., 2013) and also grey matter atrophy in MCI (Bosch et al., 2012). In contrast, Salat et al. (2010) demonstrated that degeneration of hippocampal white matter in the MTL was independent of hippocampal atrophy. Microstructural white matter changes have been found to be distinctive in the hippocampus and posterior cingulate of aMCI and early AD and, as a result, may be linked to impairment in memory (Hong et al., 2013).

1.7 Aim

This current study examined the performance of amnesic and vascular MCI compared to healthy controls on tasks which assess attention, feature ambiguity and structural learning. Performance on these tasks was then assessed for association with white matter microstructural integrity. It was hypothesized that the MCI groups would show altered attention networks compared to controls, and impaired performance in feature ambiguity and structural learning. For white matter microstructural integrity, the MCI groups were hypothesized to show lowered fractional anisotropy and axial diffusivity, and increased mean and radial diffusivity, compared to controls, consistent with damage to white matter microstructural integrity. In the association of white matter microstructural integrity across the tests, impaired performances were hypothesized to be associated with lower FA and L1, and greater MD and RD.

2. Method

2.1 Participants

Participants were recruited following ethics approval from the Regional Health and Disability Ethics Committee Upper South A. Six hundred and nine older volunteers were assessed on a brief neuropsychological screen. Of these, two hundred and twenty-one were excluded due to medications that may affect cognition such as anticholinergics and benzodiazepines (Bierman et al., 2007; Weston, Weinstein, Barton, & Yaffe, 2010); medical disorders such as stroke, neurological conditions and diabetes (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001); and very old age (>85 years). Based on scores from the brief neuropsychological screen (Table 2-1), participants were divided into seven categories ranging from MCI-6 (very likely to have MCI) to HC-1 (very likely to be aging normally).

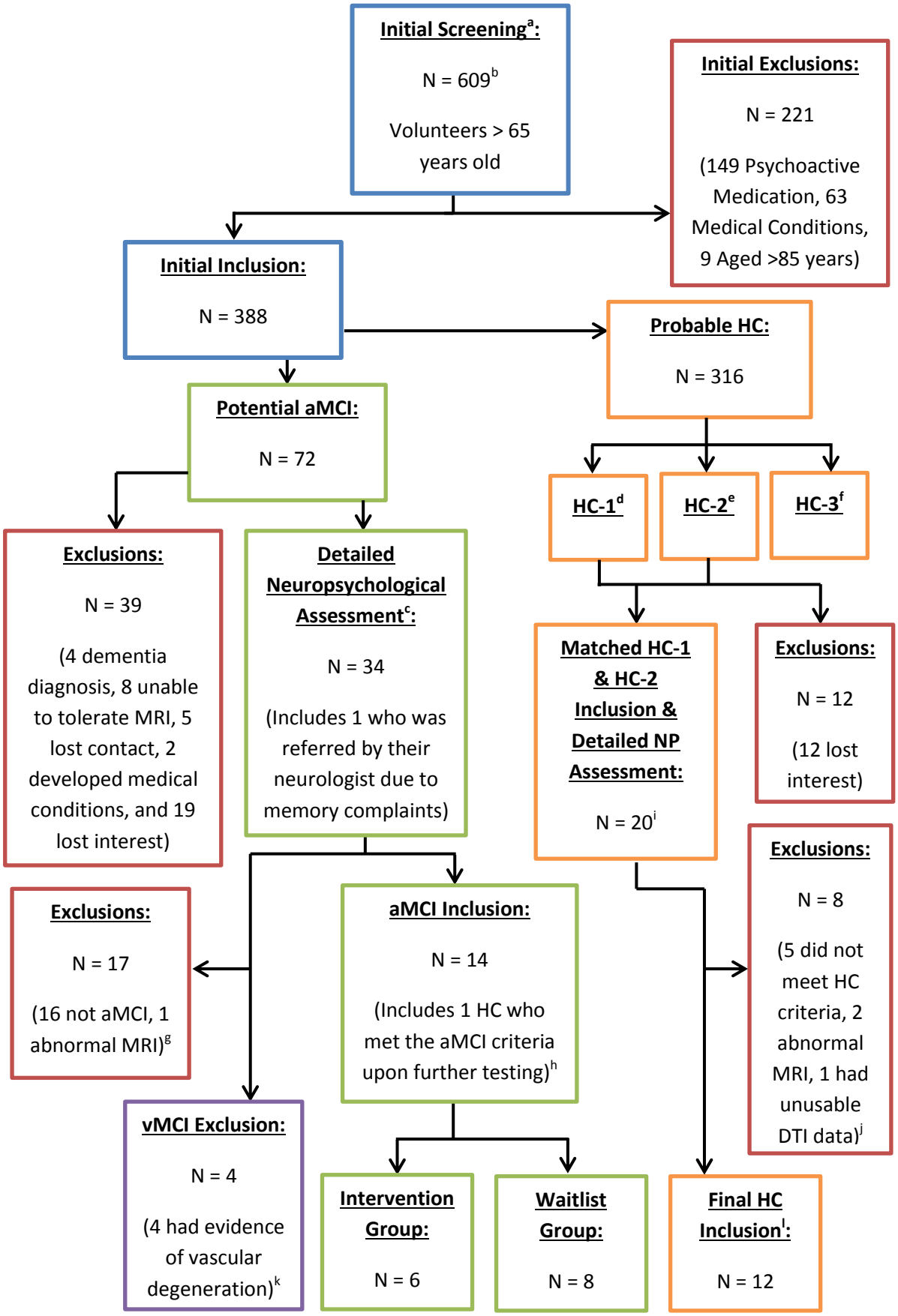
Table 2-1

Criteria for group following initial screen

Group	Preliminary Criteria for Inclusion after Brief Neuropsychological Screen
HC-1	MoCA >25 All neuropsychological scores >-0.7
HC-2	MoCA >25 Some neuropsychological scores <-0.7 but >-1.3
HC-3	MoCA < 26 No neuropsychological scores < -1.3 or MoCA > 25 One neuropsychological test score < -1.3.
MCI-3	MoCA <26 One neuropsychological score <-1.3
MCI-4	MoCA >25 Two neuropsychological scores <-1.3
MCI-5	MoCA <26 One neuropsychological score <1.3 AND one neuropsychological score <-0.7
MCI-6	MoCA <26 Two neuropsychological scores <-1.3

Participants who were likely to be MCI (MCI-3, MCI-4, MCI-5, MCI-6) then received more detailed neuropsychological testing to establish their MCI status. Of the seventy two participants in the likely MCI categories, thirty nine were unable to take part in further testing leaving thirty four to undergo a full neuropsychological battery (see Figure 2-1 for a detailed summary of the inclusion criteria). Eighteen participants were identified to match the following criteria for a diagnosis of MCI: 1) An objective memory loss measured by neuropsychological scores at -1.5 SD below their age and education adjusted norms or an equivalent "impaired score" on the Rivermead Story Recall, a profile score of 1 (borderline) was used; a score of <19 was used for Delayed Recall RI-48 Selective Reminding Test. 2) A global score of <26 on the Montreal Cognitive Assessment (MoCA), a scaled score of 7 or 8 on the Dementia Rating Scale (DRS-2) or a score of >9 on the Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog). 3) A subjective memory complaint by the participant or an informant. 4) Deterioration of cognitive scores obtained from the previous screening test. 5) A score of 0 or 0.5 on the Clinical Dementia Scale with preserved activities of daily living to exclude dementia. Following the MRI scan, 4 participants in the aMCI group were reclassified as vascular MCI (vMCI) due to evidence of vascular disease as reported by an experienced neuroradiologist.

Figure 2-1 *Summary of Inclusion Criteria*



Notes:

a. *Using MoCA, Rey Complex Copy and Immediate recall, Trails A.*
b. *Response to local newspapers, NZBRI website.*
c. *Based on further screening (NP1) using MoCA, Rey Complex copy, immediate and delayed recall, Trails A and B, Digit Span, Clinical Dementia Rating (CDR) scale, Dementia Rating Scale (DRS-2), Judgement of Line Orientation (JLO), D-KEFS: Stroop test, letter fluency, category fluency and switching, Action Fluency, SDMT, CVLT and BVMT; and NP2 including ADAS-Cog, Rivermead Story Recall, Design Fluency, Visual Association Test (VAT) and RI-48 Selective Reminding Test.*
d. *MoCA > 25, all neuropsychological scores >-0.7.*
e. *MoCA > 25, all neuropsychological scores > -1.3 but one score below -0.7.*
f. *MoCA < 26, no neuropsychological scores < -1.3 or MoCA > 25 but one neuropsychological test score < -1.3.*
g. *One participant was excluded due to a non-vascular cyst.*
h. *Final aMCI criteria: 1) An objective memory impairment on two or more memory tests using either, < -1.5 SD below standardised age-corrected normative data, or a profile score of 1 on the Rivermead Story Recall (immediate or delayed) or a recall score of < 19 on the Adams Selective Reminding test (delayed recall); 2) at least one impaired global mental status score from MoCA (<26), DRS-2 (scaled score < 9), and ADAS-Cog (> 9); 3) subjective memory complaints by participant or informant on the CDR; and 4) exclusion of dementia based on CDR < 1 plus essentially preserved activities of daily living judged by significant other and/ or the interviewer. Random allocation to intervention or waitlist group was based on memory scores, age, and availability for the initial phase of enrichment.*
i. *HC -1 and HC -2 who were selected to match the final aMCI for age, sex and education. Includes 1 aMCI who in detailed testing was found to have healthy cognition.*
j. *One had a non-vascular cyst, one had evidence of atrophy in the precuneus.*
k. *4 aMCI participants following the MRI scan were reclassified as vascular MCI due to evidence of vascular disease as reported by an experienced neuroradiologist.*
l. *Final criteria for HC: MoCA > 25, no memory score < -1.5 in sessions 1 and 2 of detailed NP testing but any single score at -1.5 SD on any other test permitted.*

aMCI = Amnesic Mild Cognitive Impairment; vMCI = Vascular Mild Cognitive Impairment; HC = Healthy Control; MoCA = Montreal Cognitive Assessment; D-KEFS = Delis-Kaplan Executive Function System; ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subtest.

Twenty healthy controls were sourced from the 'likely to be aging normally' groups (HC-1, HC-2) who were matched to the likely MCI participants based on age, gender and education (Table 2-2). Healthy controls then undertook the full neuropsychological battery. Nine were excluded for not meeting the healthy control criteria.

Table 2-2

Demographics of participants in each group

Group	Healthy Controls (n=12)		aMCI Participants (n=14)		vMCI Participants (n=4)	
	Mean	SD	Mean	SD	Mean	SD
Male:Female	7:5		8:6		3:1	
Age	76.41	3.50	75.21	4.42	78.00	4.97
Years of Education	12.83	2.59	13.07	2.84	13.00	3.46

2.2 Neuropsychological Tests

2.2.1 Standardised Neuropsychological Tests

2.2.1.1 Global Functioning

Global functioning was assessed using The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (Sano et al., 2011), the Dementia Rating Scale (DRS)(Greenaway, Duncan, Hanna, & Smith, 2012), the Clinical Dementia Rating Scale (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), and the Advanced Clinical Solutions Test of Premorbid Functioning (TOPF) (Pearson, 2009).

2.2.1.2 Learning and Memory

Assessment of learning and memory was conducted using the short form of the California Verbal Learning Test (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000), the Brief Visual Memory Test (BVMT)

(Benedict, 1988), the Rey-Osterrieth Complex Figure (Meyers & Meyers, 1995), the Rivermead Story Recall (Baek et al., 2011), the RI-48 Selective reminding Test (Hanseeuw & Ivanoiu, 2011), and the Visual Association Test (VAT) (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002).

2.2.1.3 Executive Function

Executive function was assessed with Trails B, Action Fluency (Piatt, Fields, Paolo, & Troster, 2004) and items from the Delis-Kaplan Executive Function System (D-KEFS) which were: Letter Fluency Test, Category Fluency, Fluency Switching, Stroop Colour Word Interference and Design Fluency Switching (Delis, Kaplan, & Kramer, 2001).

2.2.1.4 Attention, Processing Speed and Working Memory

Assessment of this domain employed Trails A, The Symbol Digit Modality Test (written and oral), the D-KEFS Stroop colour and word naming (Delis et al., 2001), Number Cancellation (ADAS-Cog), and Digit Span (Wechsler, 2008a, 2008b).

2.2.1.5 Visuospatial Function

Visuospatial function was assessed with Matrix Reasoning, the Rey-Osterrieth Complex Figure Copy (Meyers & Meyers, 1995), the Visual Object and Space Perception (VOSP) (silhouettes only) (Warrington & James, 1991), Judgement of Line Orientation (JLO) (Benton, Hannay, & Varney, 1975), MMSE Pentagons, and the BVMT (copy section) (Benedict, 1988).

2.2.1.6 Language

Assessment of Language was conducted with the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and the Token Test (Snitz et al., 2009).

2.2.2 Experimental Neuropsychological Tests

Three experimental neuropsychological tests were presented using E-Prime™ 2.0.8.90, a stimulus presentation software, and displayed on a Viewsonic™ 22” flat screen monitor with responses recorded on a Cedrus® serial response box with labelled response keys (“L” for left and “R” for right).

External speakers were used for the Attention Network Test, which required an audio output for the "alerting tone" condition.

2.2.2.1 Feature Ambiguity

The feature ambiguity test, adapted from Barense et al. (2005), required participants to discriminate between different levels of complex ambiguous patterns. Following a fixation cross consisting of 1500ms, pairs of beetles (target and non-target, randomised to left and right) were presented adjacent to each other for a maximum of 15s (if no button press was made). After this time limit, red text consisting of "No Response Detected" would be presented on a blank screen, followed by the next trial. Participants were required to select the correct target beetle from the pairs by either pressing the associated left or right response button. Participants received feedback immediately after each button press in the form of a blue "Correct" or a red "Incorrect" displayed in the centre of the screen.

There were three levels of perceptual ambiguity (minimum, intermediate and maximum feature ambiguity). Beetles varied in features by either their body pattern, legs or both (see Figure 2-2 for an example of these levels). In the minimum condition, none of the beetles contained any features that were ambiguous (features such as legs and body patterns were unique to target and non-target beetles). In the intermediate condition, half of the features were ambiguous (one feature was unique to target and non-target beetles while the other feature was common between target and non-target beetles). In the maximum condition, all features were ambiguous (i.e. both features for targets also appeared separately in non-targets). A beetle would appear correct only if the target contained both correct legs and body. These features would appear separately in incorrect beetles.

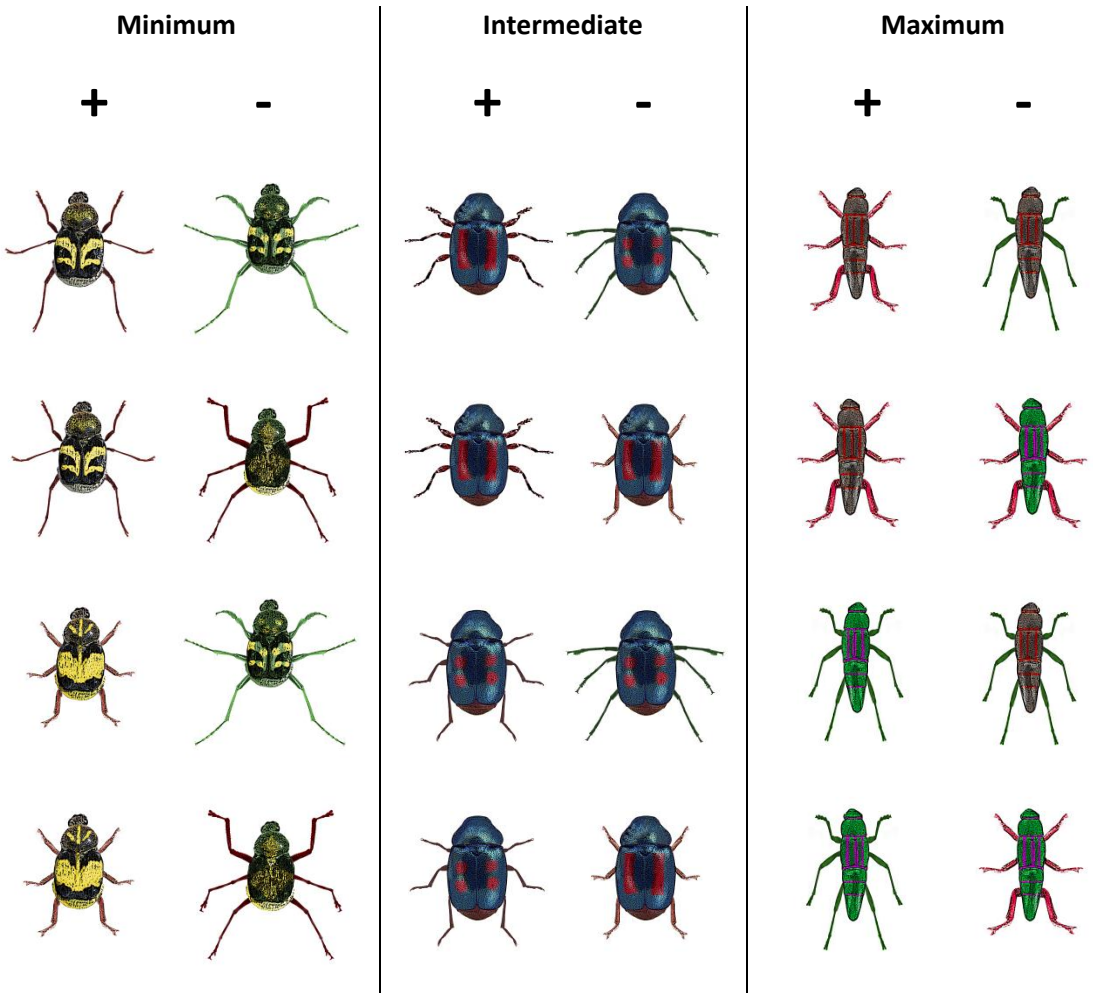


Figure 2-2 *An example of beetles used in the feature ambiguity test. The left and right positions of correct beetles were varied on presentation.*

Completion of each ambiguity condition was achieved by eight consecutive correct trials in a block of eight trials to a maximum of 56 trials (7 blocks of 8 trials). Once the condition was completed, a “thank you” page would appear with the participant allowed to take a brief break before continuing the rest of the test. The presentation order of the ambiguity conditions was randomised across participants. Pairs of beetles appeared twice in each block of 8 (i.e. once on the right and the left). The specific order of pairs was randomised.

To reduce practice effects and memorising of beetles for subsequent visits, 5 sets of test beetles were created for each of the 5 visits required for monitoring the participants over the

cognitive enrichment intervention (not included in this thesis). Participants were assigned to a Latin square to determine which order of beetles they would be exposed to over 5 time points.

2.2.2.2 Attention Network Test

The Attention Network Test, originally devised by Fan et al. (2002), is an attention test with a focus on assessing alerting, orienting and executive attention measures. These networks are generally functionally independent from each other and display brain activation relating to specific attention tasks (Fan et al., 2005). The alerting network is associated with maintaining sustained alertness; the orienting network is activated in tasks that require switching of attention from one stimulus to another; and the executive network is involved in attention tasks requiring conflict resolution such as in a Stroop interference task (Fuentes et al., 2010). This study uses an adapted form of this test introduced by Callejas, Lupianez, and Tudela (2004).

On all trials, a neutral display consisting of horizontal rows of 5 boxes were presented above and below a central fixation cross. For the visual cue (in a visual cue trial), the outline of the central box in the appropriate row was increased for 50ms from 1 pixel to 4 pixels in width. In trials with an alerting tone, a 50 ms beep at 2000 Hz was played (see Figure 2-3 for a visual representation of the experimental procedure which shows a tone trial with a visual cue).

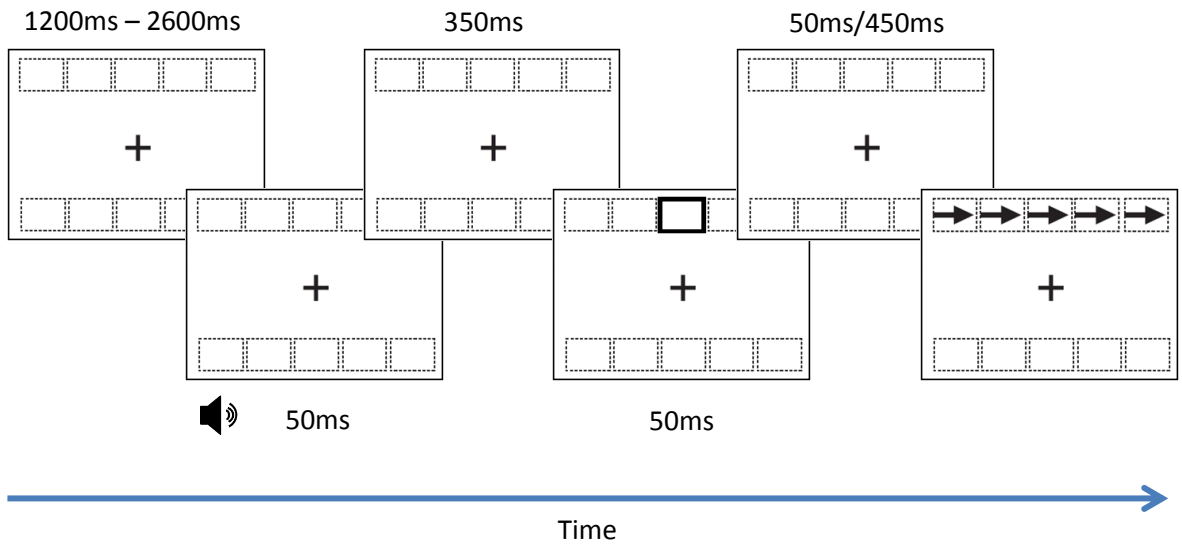


Figure 2-3 *Experimental Procedure of the Attention Network Test*

Trials consisted of the neutral display presented for a random, variable duration between 1200 and 2600 ms. An alerting tone (tone condition) or an empty audio file (no–tone condition) would be played for 50 ms. After 350 ms, the visual cue then appeared either in the box directly above or below the fixation cross or not at all (no cue condition). The cued condition consisted of trials where the visual cue appeared in the same box as the ensuing target. The uncued condition consisted of trials where the visual cue appeared on the other side of the fixation cross prior to the ensuing taget. Five arrows presented within each of the five boxes in a row would then appear randomised for above or below the fixation cross after an interval of 50 ms (stimulus onset asynchrony, SOA = 100) or 450 ms (SOA = 500). Participants were required to respond to the central target arrow in the row and ignore the flanking arrows which could either be pointing the same direction (congruent) or pointing in the opposite direction (incongruent). Participants were asked to respond as quickly as possible without making any mistakes.

In total, participants were presented with 288 trials divided into 3 blocks of 96. These combined all the experimental conditions (alerting/no alerting tone, cued/uncued/no-cue,

congruent/incongruent and SOA = 100/SOA = 500) There were 24 experimental conditions in total with 12 trials for each. Participants were given rest periods every 48 trials.

Participants were provided a practice before taking part in the full ANT. This consisted of 10 trials with additional blocks of 10 new trials until an accuracy of at least 9 were correct within a block and no responses with a greater reaction time of 2500 ms was achieved. “Correct” and “Incorrect” feedback was given for the practice trials in the space between the fixation cross and the corresponding squares.

2.2.2.3 Structural Learning

Participants for this structural learning test were required to learn a familiar visual stimulus (such as a breakfast setting) and all the features within it and then to discriminate this stimulus from others that contained the same key features but arranged in a different spatial array. This test was adapted from Aggleton et al. (2007), and is a specific configural learning task which directly engages the hippocampus. Similar to the feature ambiguity test, participants were presented with 2 pictures of a scene adjacent to each other and then required to decide on the correct target picture (left or right). The test in the second session was altered due to the floor effect identified in the first session.

Participants were first presented with a fixation cross (1500ms) followed by a pair of pictures (target and non-target) for a maximum of 20s. If no button press was detected, a blank screen with “no response detected” would appear in red for 1500ms. If a button was pressed, a feedback page (1500 ms) was shown with a blue “Correct” or a red “Incorrect” in the centre of the screen.

For the first session, the structural learning test required participants to complete three tasks: a structural learning test and two control tests consisting of a simple discrimination test and transverse patterning test. The order of presentation for the tests was randomised. Criteria for termination of each test were either: a) 8 correct trials in a block or b) completion of 7 blocks of 8 trials (56 trials in total).

Structural learning consisted of the same two pictures of a common visual array. Three objects of interest would be used in total with only two shown at a time in each picture. Instead of one object that changed, up to two objects would change in each picture. The objects of interest could appear either on the right or left side within each picture. In total there were 6 unique pairing of objects (i.e. AB, AC, BA, BC, CA, CB) and 18 pairing of pictures in total, including the target on both sides (i.e. AB-BA, AB-AC, AB-CB). The positioning of the two objects was important as a picture would only be "correct" if the pairs of objects were orientated the correct way within each picture (either on the left or the right). For example, in Figure 2-4, the 'spread' was only correct if it was on the left of the picture and paired with the 'Marmite'. When the 'spread' appeared on the left but paired with another object such as the 'syrup', the picture was incorrect. The reverse orientation of the 'spread' and 'Marmite' was incorrect. To further add to the difficulty of this task, the correct position of an object would switch to the opposite side when paired with another object. The 'spread' when paired with the 'syrup' was correct only if the spread was on the right. Hence, an object would appear correct and incorrect in a particular position depending on the second object pairing. Pictures in each block of 8 trials were selected randomly from the total 18 pairing combinations. A pairing combination, if selected in a block, would not appear again in that block.

Figure 2-4 *A sample of pictures used in the structural learning task in the first session (NP2)*

The simple discrimination task consisted of two identical pictures of a common visual array (i.e. a breakfast scene) but with a unique object of interest (see Figure 2-5). This task was designed to control for general random selection. One of the pictures would be arbitrarily assigned the "correct" target while the other would be the "incorrect" non-target. In total there were two picture combinations for this task (a pairing with the target on the left and a pairing with the target on the right). The target would appear an equal number of times on the left and right in a block of trials. Target location was randomised but would not appear in the same position more than twice in a row.

Figure 2-5 *Example of a Simple Discrimination Task*

Transverse patterning is a configural learning task which appears similar to structural learning both visually and in difficulty but has been observed to not be sensitive to hippocampal damage (Sanderson et al., 2006). The transverse patterning task was composed of one object of interest in each picture of a common visual array. In total, 3 different objects were used in this test. Each object appears both as correct and incorrect once depending on which object they are paired with in the opposing picture. For example, in Figure 2-6, the picture of the 'green tea' was correct when paired with the picture of the 'coffee' but incorrect when paired with the picture of the 'Nesquik'. The common game 'Paper-scissors-rock' is based on the rule of transverse patterning.

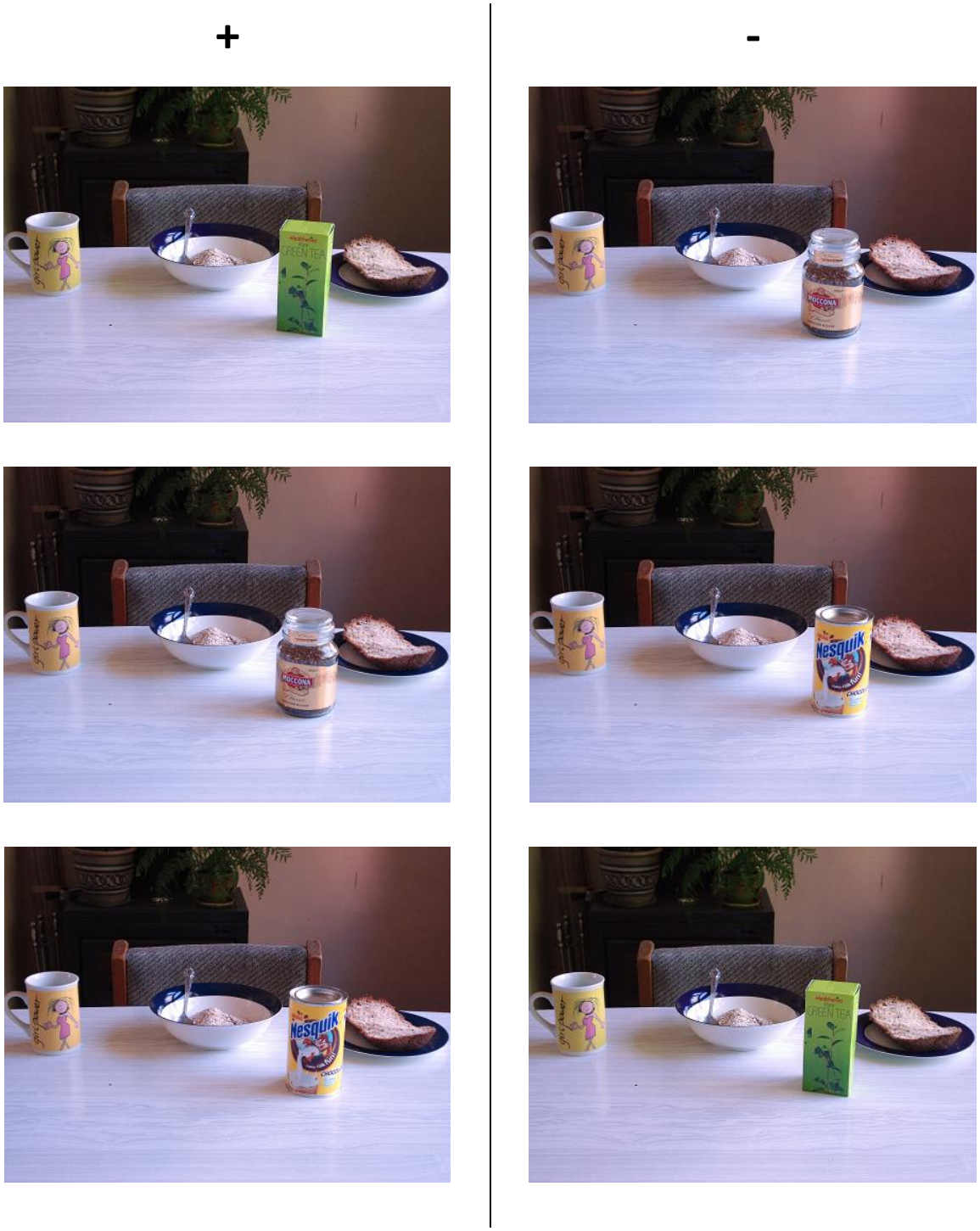


Figure 2-6 *Example of a Transverse Patterning Task*

2.3 *Procedure*

2.3.1 *Standardised Neuropsychological Testing*

Participants undertook standardised neuropsychological testing in three sessions of approximately three hours each after initial screening. The first two sessions, labelled 'Neuropsychological Inventory 1' (NP1) and 'Neuropsychological Inventory 2' (NP2) were used primarily for confirmation of participants with MCI and contained a variety of tasks from different domains. The third 'Baseline' session included additional neuropsychological tests and was conducted just prior to the start of a 16 week cognitive intervention programme (not covered in this thesis). The order of the administration of the tests in each session was taken into consideration to prevent contamination from overlapping memory assessments. Additionally, verbal tests were interchanged with non-verbal tests. All neuropsychological assessments were done at the New Zealand Brain Research Institute by a trained member of the research group.

2.3.2 Experimental Neuropsychological Testing

The experimental Neuropsychological Tests were administered as part of both NP2 and the third 'Baseline' test session. Participants completed the tests in a dedicated computer room at the New Zealand Brain Research Institute. The order of the experimental tests consisted of the Feature Ambiguity test followed by the Attention Network test and Structural Learning group of tests respectively. Each test contained their own set of instructions on screen at the beginning of the experiment except for the Structural Learning test which had additional instructions in a booklet explained by the assessor to circumvent the anticipated difficulty of the test.

Participants were assigned to a Latin square during NP2 to counterbalance the order they each received the different forms of Feature Ambiguity and Structural Learning tests. Participants were planned to be assessed with experimental neuropsychological testing at 5 different time points: 1) NP2; 2) Baseline testing; 3) Midpoint or 8 weeks into the cognitive intervention programme; 4) Endpoint or 16 weeks into the cognitive intervention programme; and 5) Follow-up. This thesis will

only focus on experimental neuropsychological data collected from NP2 and the third Baseline session.

For baseline testing, transverse patterning was excluded from the experiment, leaving simple discrimination and structural learning. The maximum of 7 blocks of 8 trials was changed to 5 blocks of 12 trials (participants had to correctly guess 12 correct in a block to finish the experiment early). The increase in the number of trials per block was changed to minimise participants completing the task by only remembering one structural orientation and guessing the others. Additionally, pictures of the same objects were only shown paired together (i.e. AB+ was only paired with BA-). This reduced the number of available pairings to just the 'mirrors' of each other. In total there were 3 pairing combinations, 6 including the pictures on the opposite side. The reduced number of pairings was done to make the task easier and was more in line with the animal study done by Aggleton, Albasser, Aggleton, Poirier, and Pearce (2010).

2.3.3 Magnetic Resonance Imaging (MRI)

2.3.3.1 Acquisition

Participants received MRI brain scans after their NP2 assessment and prior to baseline assessment. Diffusion tensor imaging (DTI) was the focus of this thesis. The time taken for this scan was 12:10 and formed part of a longer 1.5 hour scanning session consisting of additional structural and functional imaging acquisitions. Participants were asked to remain still during the DTI sequence.

Images were acquired on a 3-tesla General Electric HDxt scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. Microstructural integrity was measured using a 2-dimensional diffusion-weighted, spin-echo, echo planar imaging sequence with diffusion weighting in 64 uniformly distributed directions (b = 1,000 s/mm^2) and 8 acquisitions without diffusion weighting (b = 0 s/mm^2): echo time (TE)/repetition time (TR) = 96/10,000 ms, flip angle = 90°, acquisition matrix = 128 x 128 x 74, field of view = 250mm, slice thickness = 2mm, voxel size 1.95 x 1.95 x 2mm^2, ungated, acquired AC-PC.

A T1-weighted (spoiled gradient recalled echo; TE/TR =2.8/6.6 ms, inversion time = 400 ms, flip angle 15°, acquisition matrix = 256 x 256 x 170, field of view = 250mm, slice thickness = 1mm, voxel size = 250/256 × 250/256 × $1mm^3$) was acquired as part of the larger research project and to rule out gross anatomical abnormalities. A T2-weighted, fluid-attenuated inversion recovery sequence (FLAIR:TE/TR = 105/9,000 ms, inversion time = 2,250 ms, slice thickness 3mm, gap = 1.5mm) were also acquired to rule out recent cerebrovascular accidents.

2.3.3.2 MRI Pre-processing

Pre-processing and statistical analyses were performed using tract-based spatial statistics (TBSS) (Smith et al., 2006) in FSL (FMRIB Software Library 5.0.2; www.fmrib.ox.ac.uk/fsl). Diffusion-weighted images were corrected for motion and eddy current distortion. Absolute and relative motion was quantified for each participant by taking the mean of the eddy current estimated mean displacement across the 12:10 (72 volumes), using a publicly available script. The diffusion tensor was calculated at each voxel using DTIFIT and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1) and radial diffusivity (RD) were produced. Brain extraction was performed using BET. All FA images were aligned to a common space (FMRIB58 FA template) using the nonlinear registration tool FNIRT and a mean FA image created. The mean FA image was thinned (FA > 0.25) to create a mean FA skeleton that represented the centres of all principal white matter tracts common to the group. Each participant's aligned FA image was then projected onto this common skeleton. This procedure minimises misalignment which is more prevalent in standard registration procedures (Smith et al., 2006). The non-linear warps and skeleton projection were then applied to MD, L1 and RD images to create three separate skeletons representing MD, L1 and RD values.

2.3.3.3 Statistical Analyses

A permutation-based inference tool for nonparametric statistical thresholding (FSL's "randomise") was used for voxel-wise statistics on the skeletonised images. Pairwise group differences were assessed between HC, MCI and vMCI with age, sex, years of education and relative motion as

covariates. Individual multiple regression models with age, sex, years of education and relative motion as covariates investigated the association between FA, MD, L1 and RD with each domain of the experimental neuropsychological scores (attention network test, feature ambiguity and structural learning). For each contrast, the null distribution was generated over five thousand permutations with the α level set at $p < 0.05$ and corrected for multiple comparisons using threshold-free cluster enhancement (Smith & Nichols, 2009).

3. Results

3.1 Standardised Neuropsychological Tests

Table 3-1 summarizes the demographics of the three groups and z-score means of each cognitive domain based on the battery of standardised neuropsychological tests. Analysis of variance (ANOVA) confirmed a significant group effect for all cognitive domains. There were no significant group differences for age and education. As planned by the selection process, both MCI groups showed below average performance in the learning and memory domain. The vMCI group also showed poorer performance on the visuospatial and language domains. Post hoc analyses using Newman-Keuls tests ($p < 0.05$) confirmed significant differences between the healthy control group and both MCI groups for the executive function, processing speed, visuospatial domains and especially learning and memory. The visuospatial domain was the only domain to show any significant difference between aMCI and vMCI. Language showed a significant difference between healthy controls and vMCI only.

Table 3-1

Demographic and group mean (SD) z-scores of each cognitive domain

	Healthy Controls	aMCI	vMCI
N	12	14	4
Male:Female	7:5	8:6	3:1
Age	76.41(3.50)	75.21(4.42)	78.00(4.97)
Years of Education	12.83(2.59)	13.07(2.84)	13.00(3.46)
Executive Function[a*b**]	1.09(0.56)	0.24(0.71)	-0.17(0.93)
Working Memory and Processing Speed[a*b*]	0.75(0.40)	0.11(0.58)	0.01(0.47)
Learning and Memory[a***b***]	1.20(0.79)	-1.13(0.61)	-0.93(0.48)
Visuospatial[a**b***c*]	0.68(0.46)	-0.26(0.61)	-0.95(0.55)
Language[b*]	0.17(0.34)	-0.09(0.64)	-0.71(0.91)

Significant analysis of variance/Newman-Keuls between:
[a]HC and aMCI,
[b]HC and vMCI,
[c]aMCI and vMCI
**p < 0.05, **p < 0.01, ***p < 0.001*

3.2 Experimental Neuropsychological Tests

3.2.1 Feature Ambiguity

Mean (± SEM) errors to criteria of the feature ambiguity test, for each group, in the first session are shown in Figure 3-1. A repeated measures ANOVA (group × degree of feature ambiguity) revealed no significant group difference [$F(2,27) = 1.90$, $p = 0.17$ ns], a significant effect for feature ambiguity [$F(2,54) = 8.35$, $p < 0.001$], but no interaction between group and feature ambiguity [$F(4,54) < 1.0$]. Newman-Keuls tests on feature ambiguity revealed the mean errors for the maximum ambiguity (M = 22.41, SEM ± 2.51) to be greater than the errors for the minimum ambiguity (M = 11.33, ± 2.59; $p < 0.001$) and intermediate ambiguity (M = 14.34 ± 2.29; $p = 0.002$), which did not differ. A significant Levene's test was observed for the minimum and maximum ambiguity conditions across groups. However, Friedman's non-parametric ANOVA confirmed a significant difference for feature ambiguity [$\chi^2(2) = 14.31$, $p < 0.001$].

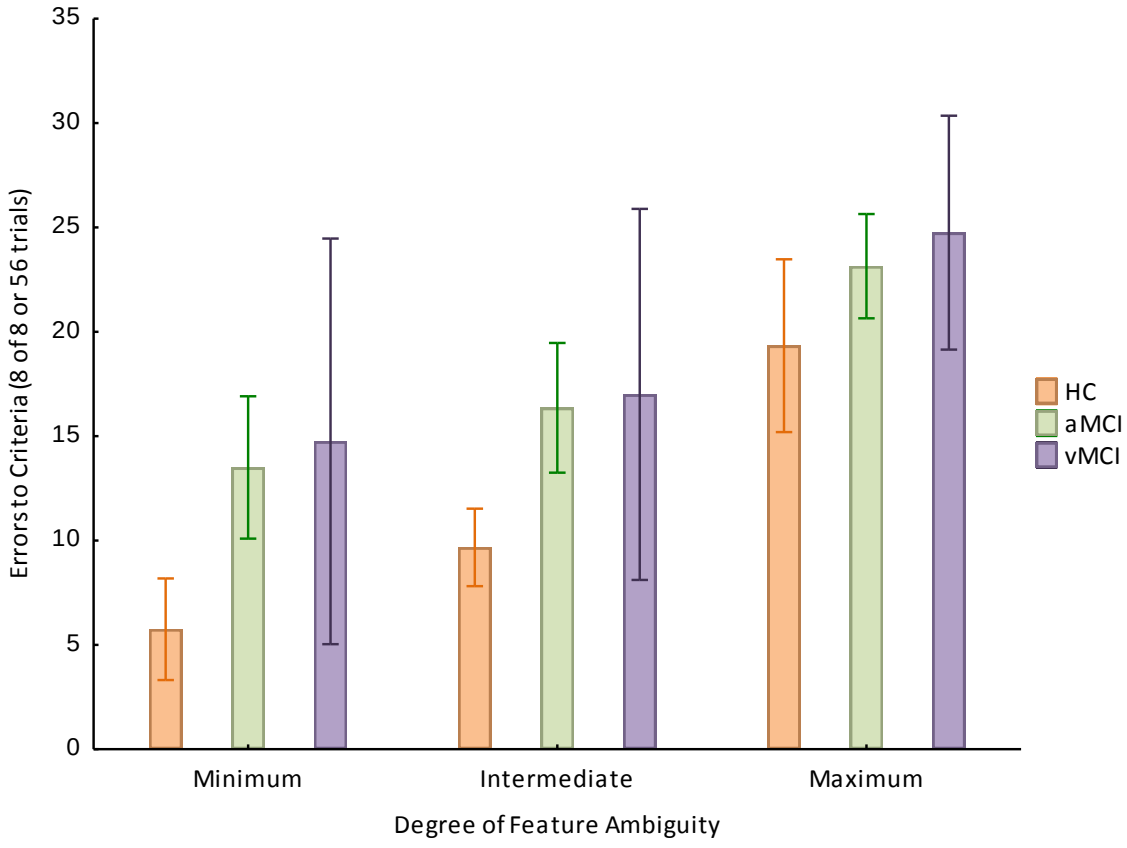


Figure 3-1 *Mean errors to criteria for each of the levels of ambiguity across cognitive status from the first session (NP2). Error bars denote +/- standard error.*

Means errors (± SEM) for the second session of the feature ambiguity test (just prior to the enrichment part of the study) are shown in Figure 3-2. Two participants (one from the healthy controls and one from the aMCI) declined to take part in this test. Repeated measures ANOVA conducted with the remaining participants produced the same conclusions as found for the first session. As in the first session, there were no significant effects for group [$F(2,25) = 1.85$, $p = 0.18$ ns], a significant effect of feature ambiguity [$F(2,50) = 21.48$, $p < 0.001$], and no significant interaction between group and feature ambiguity [$F(4,75) < 1$]. Post hoc analyses again showed that the maximum feature ambiguity was significantly greater in the mean number of errors compared to minimum feature ambiguity ($p < 0.001$), and intermediate feature ambiguity ($p < 0.001$), which again did not differ.

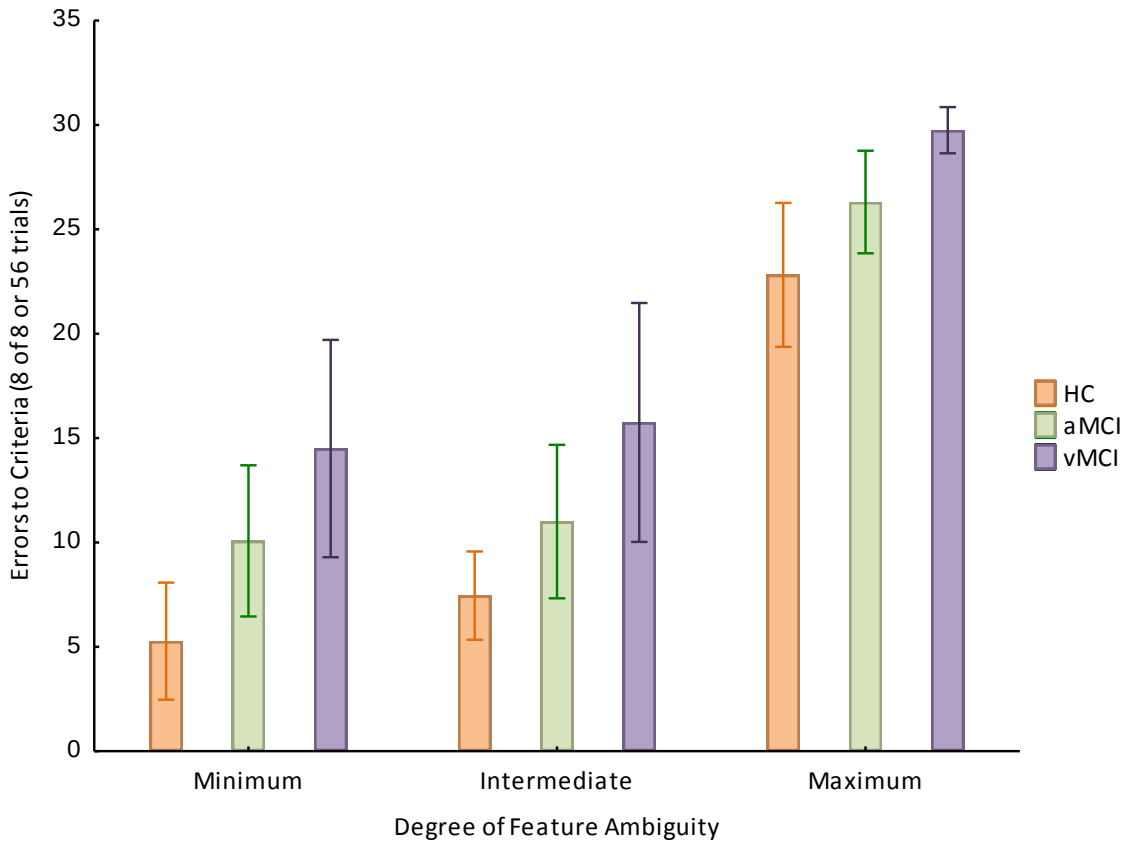


Figure 3-2 *Mean errors to criteria for each of the levels of ambiguity across cognitive status from the second session (Baseline). Error bars denote +/- standard error.*

The two feature ambiguity sessions were then assessed together in a repeated measures ANOVA to better test the effect of group and to determine if there were any practice effects across sessions. There was no main effect for session [$F(1,25) < 1$] or interaction with group [$F(2,25) < 1$]. A significant main effect for feature ambiguity was again observed [$F(2,50) = 24.96$, $p < 0.001$]. However, group did not differ [$F(2,25) = 2.21$, $p = 0.13$], nor did the interaction for feature ambiguity and group [$F(4,50) < 1$].

3.2.2 Attention Network Test

3.2.2.1 First Session (NP2)

Mean reaction times (SEM) for the three groups across the different experimental conditions are displayed in Table 3-2. One aMCI did not complete this test. Two separate analyses were conducted as per Fernandez et al. (2011). The first was constructed to investigate interactions involving orienting (visual cue) effects; and the second, to investigate interactions involving alerting (tone) and congruency.

Table 3-2

Mean reaction times (standard error) (ms) for each experimental condition for the three groups in the first session

Group	SOA	Congruency	Alerting tone			No Alerting tone		
			Cued	No Cue	Invalid Cue	Cued	No Cue	Invalid Cue
HC	100	Congruent	640(47)	635(45)	731(37)	649(40)	696(41)	735(41)
N = 12		Incongruent	681(73)	715(87)	792(72)	708(89)	756(69)	814(80)
	500	Congruent	607(37)	644(36)	697(38)	615(41)	687(42)	726(39)
		Incongruent	648(88)	707(83)	787(82)	664(97)	743(80)	792(79)
aMCI	100	Congruent	686(45)	739(43)	806(36)	756(39)	790(39)	833(40)
N = 13		Incongruent	749(70)	816(84)	891(69)	808(86)	844(66)	884(77)
	500	Congruent	663(35)	721(34)	810(37)	682(39)	783(41)	829(37)
		Incongruent	725(84)	804(80)	885(79)	771(93)	873(77)	910(75)
vMCI	100	Congruent	799(81)	896(78)	924(65)	802(70)	813(71)	831(72)
N = 4		Incongruent	1080(127)	1233(151)	1264(124)	1257(155)	1117(119)	1205(138)
	500	Congruent	736(63)	797(62)	864(66)	806(70)	929(73)	867(67)
		Incongruent	1058(152)	1205(144)	1312(142)	1153(168)	1177(138)	1301(136)

For the first analysis, repeated measures ANOVA was conducted on valid cue and invalid cue trials only. No cue trials were excluded to better assess the interactions between orienting (visual cue) effects with alerting (tone) and congruency (trials with no visual cue were irrelevant when assessing interactions with the orienting (visual cue) effect). Participants were quicker when responding to congruent (M = 754 ms, SEM = 27.52) than incongruent (M = 922 ms, SEM = 59.93) stimuli [$F(1,26) = 15.88$, $p < 0.001$]. They were also faster to respond following an alerting tone (M = 826 ms, SEM = 40.24) than no tone (M = 850 ms, SEM = 43.07) [$F(1,26) = 13.95$, $p < 0.001$]. An even larger orienting effect was also found with faster reaction times following a valid cue (M = 781 ms, SEM = 44.52) than an invalid cue (M = 895 ms, SEM = 39.25) [$F(1,26) = 96.74$, $p < 0.001$]. The SOA effect was smaller than for the other manipulations but reaction times were significantly faster at the longer (500 ms) SOA (M = 829 ms, SEM = 42.16) than the shorter (100 ms) SOA (M = 847 ms, 41.21) [$F(1,26) = 7.26$, $p = 0.012$]. Groups showed a significant difference in overall reaction time [$F(2,26) = 3.83$, $p = 0.035$]. Further post hoc analyses with Newman-Keuls showed that the vMCI group (M = 1016 ms) took significantly longer to respond than the HC ($M = 705$, $p = 0.014$) and aMCI (M = 793, $p = 0.038$) groups.

There was a significant interaction for congruency and group [$F(2,26) = 4.22$, $p = 0.026$] (Figure 3-3). The vMCI group showed a greater effect of incongruency than the HC and aMCI groups.

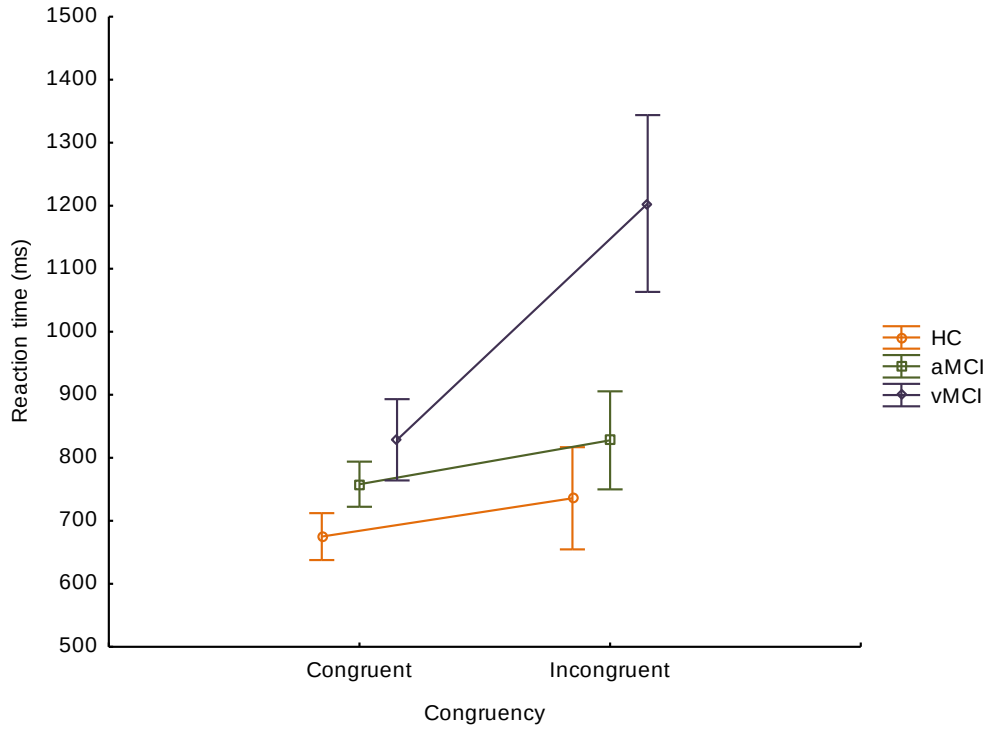


Figure 3-3 Mean reaction times for congruent and incongruent trials for the three groups. Error bars denote +/- standard error.

There was an interaction for congruency and cue (Figure 3-4). The incongruency effect was greater in the invalid cue condition than the cued [$F(1,26) = 8.59$, $p = 0.007$]. Trials requiring participants to switch from an invalid cue and then respond to an incongruent stimulus resulted in longer reaction times as opposed to having to respond to a valid cue and an incongruent stimulus or an invalid cue and a congruent stimulus.

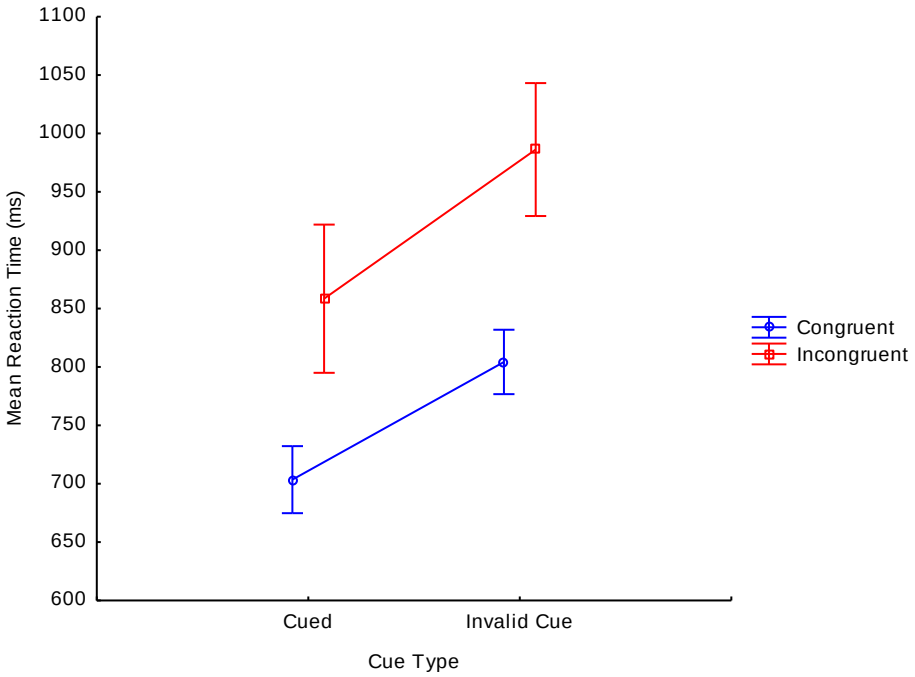


Figure 3-4 Mean reaction times for cued and invalid cue across congruent and incongruent trials. Error bars denote +/- standard error.

Figure 3-5 shows the significant interaction between alerting tone and cue [$F(1,26) = 21.49$, $p < 0.001$]. The cue effect of lower reaction time was greater when following the alerting tone than no tone, while invalid cue conditions did not benefit from an alerting tone. Additionally, a three way interaction between tone, cue and group was observed [$F(2,26) = 8.41$, $p = 0.002$] (Figure 3-6). This interaction is best interpreted as a change in the degree of the previous interaction between tone and cue. The HC group was the least affected by the tone × cue interaction whereas this was greater in aMCI group and greater still in vMCI group.

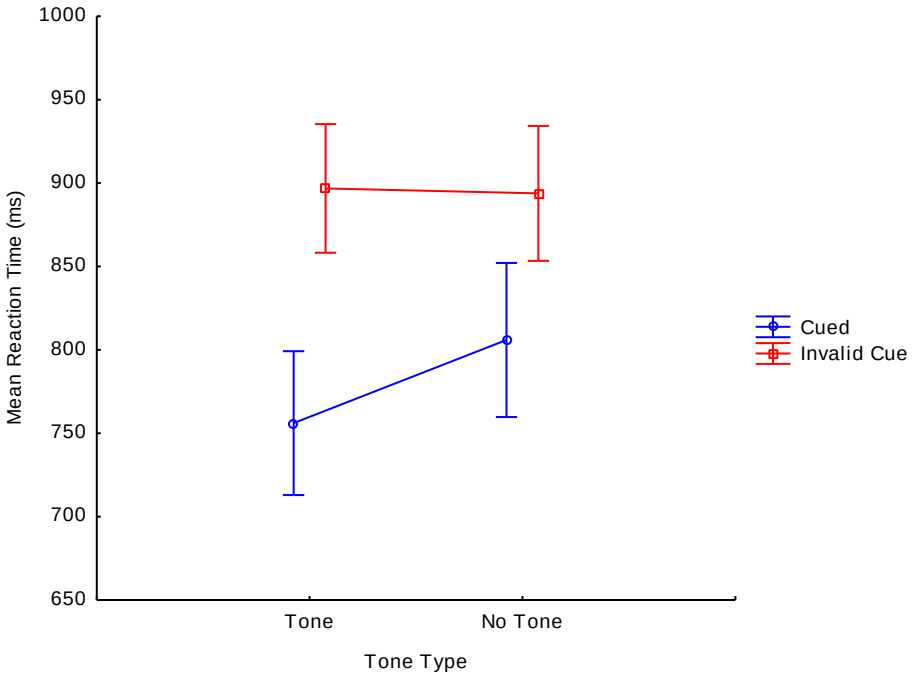


Figure 3-5 Mean reaction times for tone and cue trials. Error bars represent +/- standard error.

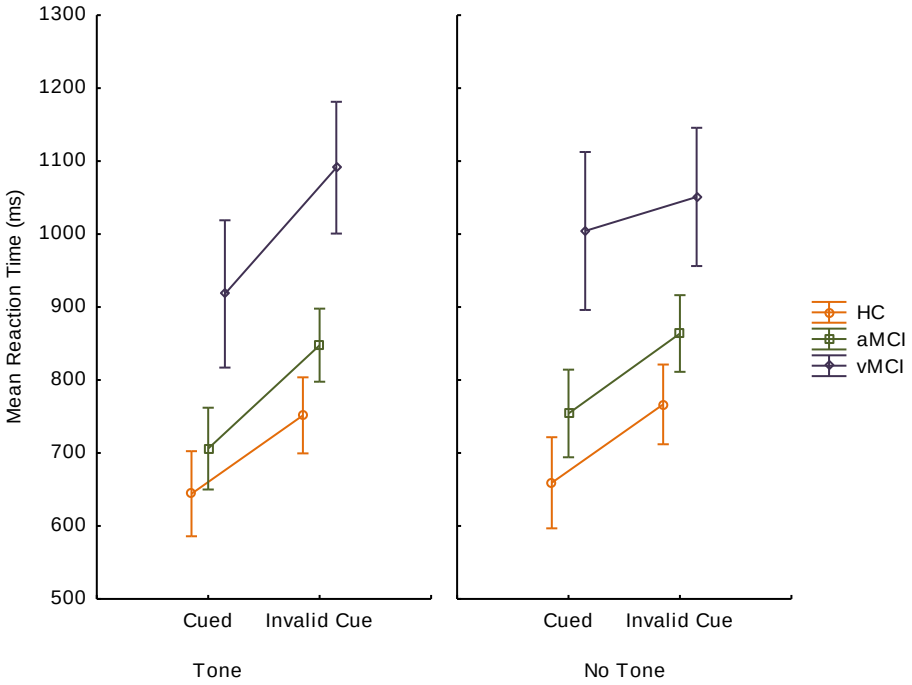


Figure 3-6 Mean reaction time for tone and cue trials across group. Error bars denote +/- standard error.

Significant interactions were also observed for SOA × cue [$F(1,26) = 11.99$, $p = 0.002$], SOA × congruency × cued [$F(1,26) = 4.27$, $p = 0.049$], and SOA × alerting tone × cue [$F(2,26) = 4.82$, $p = 0.037$). However, no significant SOA interactions was found involving group [$F(2,26) < 1$] and so this factor is not discussed further.

For the second analysis, only trials with no visual cue (no-cue) were assessed in a repeated measures ANOVA to study potential interactions between alerting tone and congruency which excludes any alerting effects produced by the visual cues. There was a significant difference for group [$F(2,26) = 4.01$, $p = 0.03$]. Further post hoc with Newman-Keuls revealed the vMCI group to have a significantly longer reaction time (M = 1021 ms) than HC (M = 698 ms, $p = 0.012$) and aMCI (M = 796 ms, $p = 0.040$). The HC and aMCI groups did not significantly differ ($p = 0.35$). As per the analyses conducted on the trials involving cues, significant effects were also observed for congruency [$F(1,26) = 18.80$, $p < 0.001$] and tone [$F(1,26) = 5.44$, $p = 0.028$]. However no significant effect for SOA was observed [$F(1,26) < 1$].

Figure 3-7 shows the significant interaction between congruency and alerting tone [$F(1,26) = 5.40$, $p = 0.028$] in trials without a visual cue (no cue). Incongruent trials were unaffected by tone, whereas, congruent trials produced quicker responses following an alerting tone than no tone.

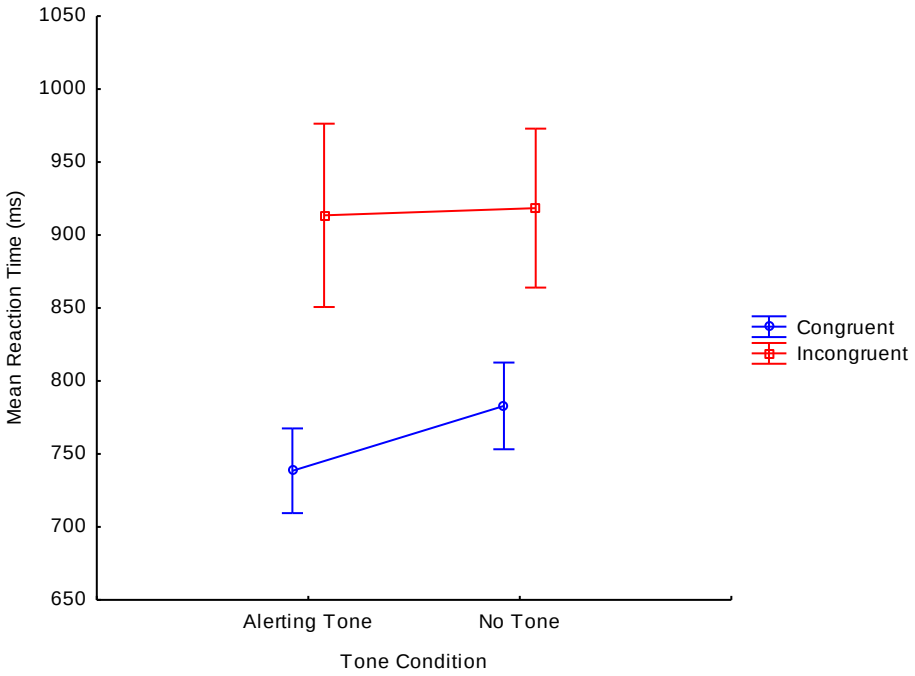


Figure 3-7 Mean reaction times for tone and congruency trials with no visual cue. Error bars denote +/- standard error.

There were significant interactions between group and congruency [$F(2,26) = 3.95$, $p = 0.032$], in addition to, group and tone [$F(2,26) = 3.80$, $p = 0.036$]. Figure 3-8 shows the interaction between group and congruency; the vMCI group were affected more strongly by incongruency than the aMCI and HC groups. Figure 3-9 displays the interaction between group and alerting tone. Decreased reaction time was evident for the HC and aMCI groups when a preceding alerting tone was presented, but not for the vMCI group.

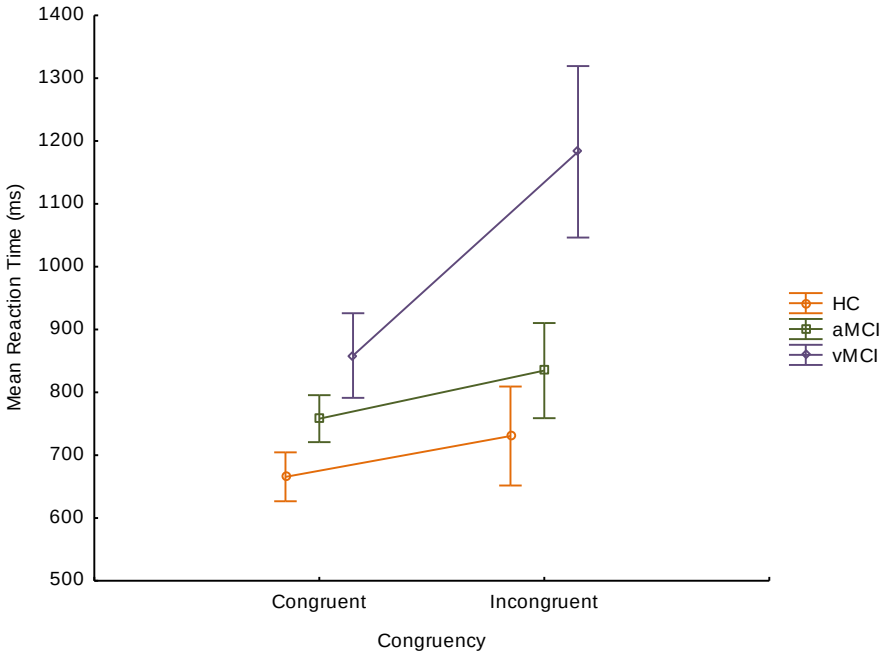


Figure 3-8 Mean reaction times for congruency across group. Error bars denote ± standard error.

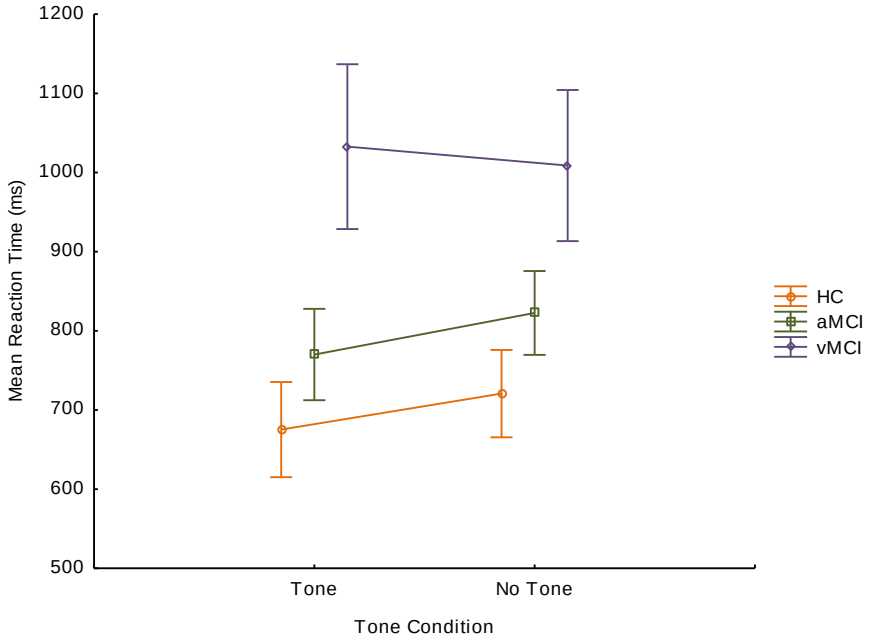


Figure 3-9 Mean reaction times for tone condition across group. Error bars denote ± standard error.

Finally, each component attention network effect was calculated for each participant to investigate the association with group without the influence of overall reaction time (Fernandez et al., 2011). These values were used later in the brain imaging analyses. The alerting effect was calculated for each participant by subtracting tone trials from no tone trials (no tone trials – tone trials); the orienting effect was calculated by subtracting valid cue trials from invalid cue trials (invalid cue trials – valid cue trials); and the executive effect was calculated by subtracting congruent conditions from the incongruent conditions (incongruent – congruent). Means of each effect from the first session are presented in Table 3-3.

Table 3-3

Mean (SD) reaction times of each attention network effect and number of errors from the first session

	HC	aMCI	vMCI
Alerting	25.17(32.64)	38.93(22.53)	7.47(35.61)
Orienting	106.78(40.40)	125.67(40.33)	109.75(114.40)
Executive	62.18(27.74)	71.98(35.05)	358.11(540.18)
Errors	1.75(1.71)	2.54(3.28)	9.00(11.80)

Three one-way ANOVAs were conducted to determine if there was a group effect on the three attention networks. There was no significant alerting [$F(2,26) = 2.00$, $p = 0.16$] or orienting effect [$F(2,26) < 1$]. The executive effect showed a significant difference for group [$F(2,26) = 4.23$, $p = 0.026$]. However, a significant Levene's test was detected in this ANOVA. Accordingly, a Kruskal-Wallis non-parametric test was conducted and revealed no significant executive effect for group [$\chi^2(2) = 2.38$, $p = 0.30$]. The number of errors also significantly differed across the three groups [$F(2,26) = 3.71$, $p = 0.038$]. However, a Kruskal-Wallis was again conducted due to a significant Levene's test and found no significant difference for the number of errors for each group [$\chi^2(2) < 1$].

3.2.2.2 Second session (baseline)

Means (± SEM) from the second session of the ANT are presented in Table 3-4. One HC and two aMCI declined to complete the ANT in this session.

Table 3-4

Means (SEM) for the second session of the Attention Network Test.

Group	SOA	Congruency	Alerting tone			No Alerting tone		
			Cued	No Cue	Invalid Cue	Cued	No Cue	Invalid Cue
HC	100	Congruent	615(32)	681(40)	725(34)	682(41)	725(44)	737(45)
N = 11		Incongruent	673(39)	703(48)	809(37)	718(44)	771(44)	804(39)
	500	Congruent	602(32)	636(34)	706(43)	634(38)	724(40)	740(43)
		Incongruent	638(47)	724(43)	790(43)	683(37)	746(46)	779(45)
aMCI	100	Congruent	724(31)	796(39)	814(32)	788(40)	847(42)	850(43)
N = 12		Incongruent	802(37)	853(46)	911(36)	856(42)	881(42)	934(37)
	500	Congruent	677(31)	764(32)	821(41)	733(37)	791(38)	824(41)
		Incongruent	780(45)	859(41)	951(41)	766(36)	912(44)	965(43)
vMCI	100	Congruent	672(54)	739(67)	851(56)	777(69)	810(73)	812(74)
N = 4		Incongruent	808(64)	905(79)	926(62)	789(73)	940(72)	950(65)
	500	Congruent	683(54)	738(56)	832(72)	761(63)	722(67)	826(72)
		Incongruent	730(79)	847(71)	948(71)	772(62)	862(77)	967(75)

Repeated measures ANOVA on the second session of the ANT (excluding no-cue trials) produced significant main effects for alerting tone [$F(1,24) = 11.60$, $p = 0.002$], valid cue [$F(1,24) = 125.68$, $p < 0.001$], congruency [$F(1,24) = 27.95$, $p < 0.001$] and SOA [$F(1,24) = 6.10$, $p = 0.021$] similar to those found in the first session. Significant interactions between congruency × cue [$F(1,24) = 15.65$, $p < 0.001$], alerting tone × cue [$F(1,24) = 6.47$, $p = 0.018$] and SOA × cue [$F(1,24) = 4.81$, $p = 0.038$] also matched those found for the first session. The main effect of group, however, became non-significant [$F(1,24) = 3.33$, $p = 0.053$ ns]. The interaction between group and congruency was

also non-significant [$F(2,24) < 1$] along with the interaction involving group, tone and cue [$F(1,24) < 1$].

For the second analysis involving only trials with no visual cue (no cue), significant main effects for tone [$F(1,24) = 21.39$, $p < 0.001$] and congruency [$F(1,24) = 20.76$, $p < 0.001$] remained. However, the main effect for group was no longer significant [$F(2,24) = 3.08$, $p = 0.064$ ns]. Additionally, previous interactions involving group were no longer significant. These include the interaction between group with congruency [$F(2,24) = 1.65$, $p = 0.21$ ns] and group with tone [$F(2,24) < 1$].

Means and standard deviation for each ANT effect from the second session are presented in Table 3-5. Again, there were no significant differences between group with alerting [$F(2,24) < 1$], orienting [$F(2,24) < 1$] or executive [$F(2,24) = 1.13$, $p = 0.34$ ns] effects. The number of errors was also non-significant [$F(2,24) = 1.67$, $p = 0.21$ ns].

Table 3-5

Mean (SD) reaction times of each attention network effect and the number of errors for the second session

	HC	aMCI	vMCI
Alerting	36.58(41)	33.06(34)	25.89(17)
Orienting	105.17(38)	118.10(55)	140(60)
Executive	52.37(24)	84.89(90)	101.77(41)
Errors	1.45(1.92)	1.42(3.40)	4.25(3.20)

To assess practice effects, t-tests for dependent means were conducted for global reaction time, errors and each of the attention effects across each session (Table 3-6). No significant effects were found for any of the measures across the two sessions.

Table 3-6

Means (SD) for each of the attention network effects across the two sessions

Effect	Session 1	Session 2	*t*	*p*
Alerting	29.98(30.48)	33.43(34.43)	-0.59	0.56
Orienting	115.85(55.14)	116.06(49.16)	-0.02	0.99
Executive	111.70(213.30)	74.26(65.08)	0.95	0.35
Global RT	795.70(220.37)	779.22(126.28)	0.53	0.60
Error	3.15(5.30)	1.85(2.92)	1.23	0.23

3.2.3 Structural Learning

Means (± SEM) for the first session of the structural learning test are displayed in Figure 3-10 (a score of 28 was equivalent to chance). One aMCI participant declined to complete this assessment. A one-way ANOVA showed no significant effect of group [$F(2,26) = 0.566$, $p = 0.57$ ns] but poor performance even in many HC suggests that the lack in sensitivity in separating HCs from MCI may be attributed to the difficulty of the task.

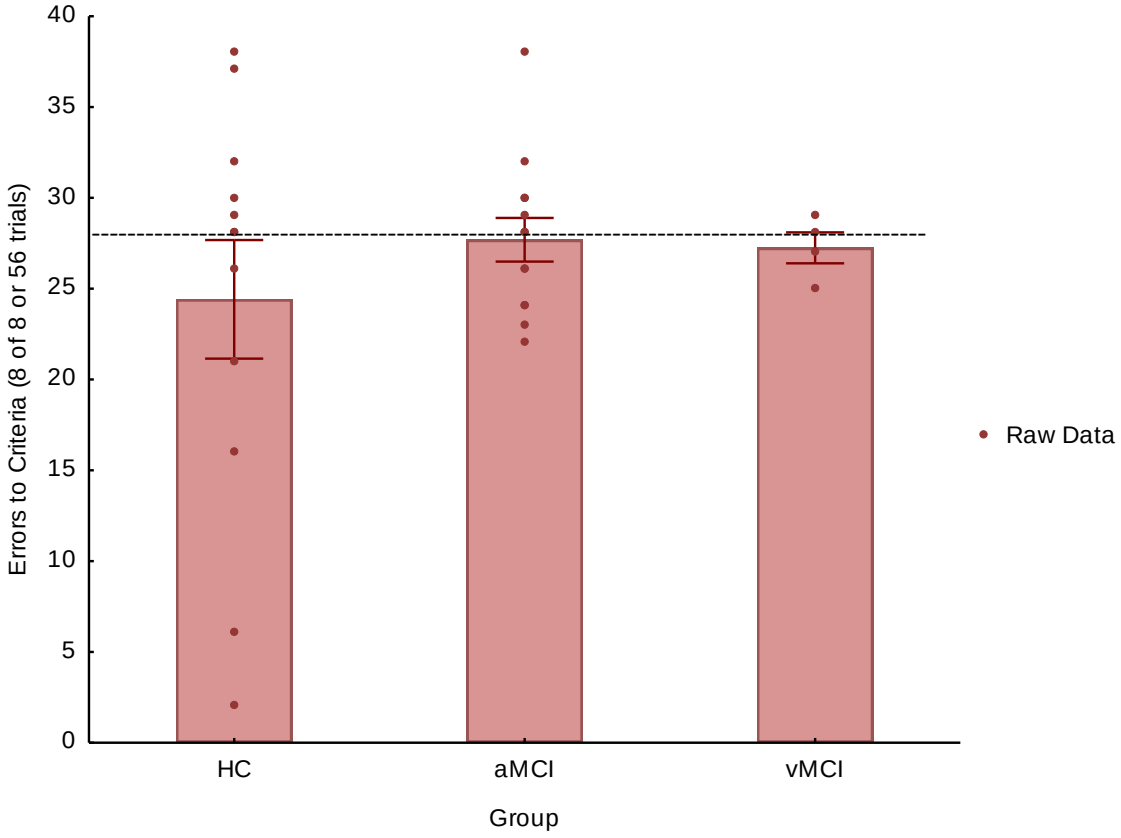


Figure 3-10 *Mean errors to criteria for each group in the first session (NP2) of the structural learning test. Error bars denote ± standard error. The broken line represents the number of errors if made by chance.*

For the second session (at baseline) of the structural learning test, the experimental procedure was altered to display only mirrored structural orientations of objects and extended to 5 blocks of 12 trials (60 trials in total). Means (± SEM) are displayed in Figure 3-11 (a score of 30 was equivalent to chance). One HC and two aMCI declined to complete this test. Analysis of variance showed a

significant effect of group [$F(2,24) = 6.14$, $p = 0.007$]. Post hoc analyses with Newman-Keuls procedure revealed a lower number of errors for healthy controls compared to both aMCI ($p = 0.029$) and vMCI ($p = 0.012$) groups.

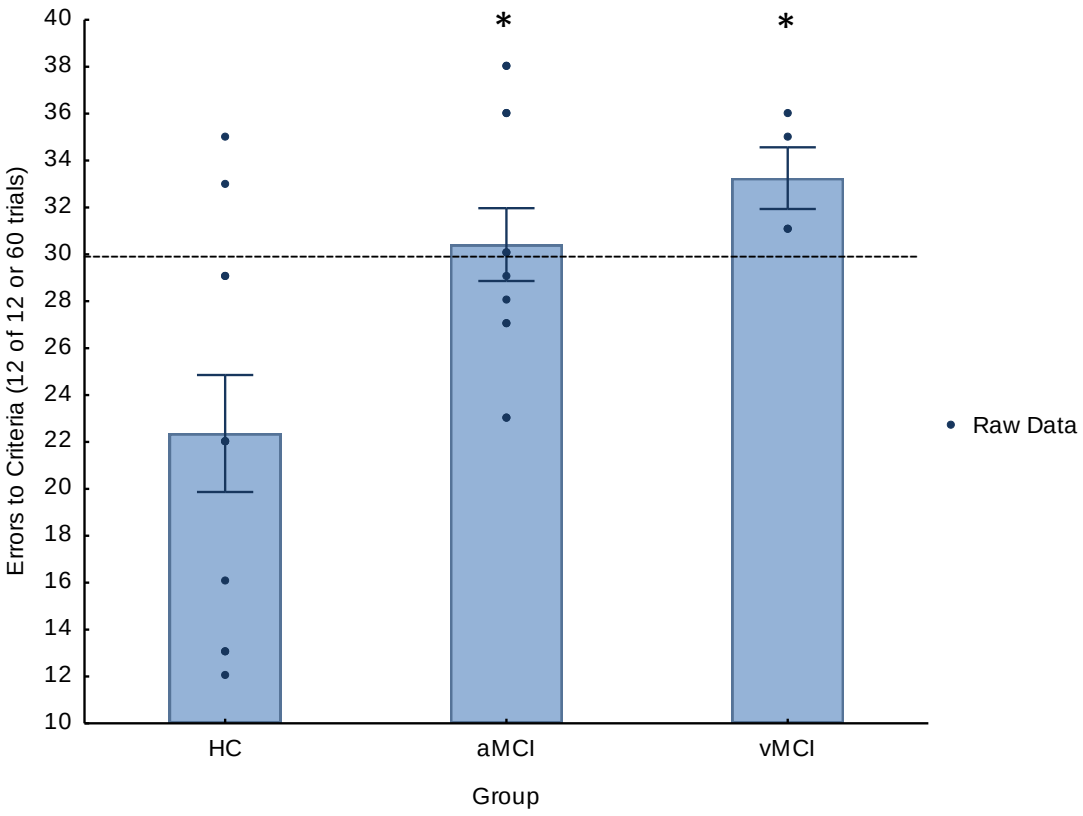


Figure 3-11 *Mean errors to criteria for each group in the second session of the structural learning test. Error bars denote ± standard error. The broken line represents the number of errors if made by chance.*
**p < 0.05 vs HC*

3.2.3.1 Control tests for structural learning

Means and standard deviations for the simple discrimination and transverse patterning tests are displayed in Table 3-7. One-way ANOVA on the first session (NP2) revealed no significant differences between the three groups in the simple discrimination task [$F(2,26) = 2.75$, $p = 0.08$ ns], and the transverse patterning task [$F(2,26 < 1$]. For the second session, a significant effect was found for the simple discrimination task [$F(2,23) = 6.82$, $p = 0.005$]. Post hoc with Newman-Keuls revealed the vMCI to have a greater number of errors to criteria compared to HCs ($p = 0.002$) and aMCI ($p = 0.003$). A

Kruskal-Wallis ANOVA was conducted due to a significant Levene's test and confirmed a significant difference for errors [$\chi^2(2) = 10.64$, $p = 0.005$]. Transverse patterning was not conducted in the second session due to apparent floor effects in the first session.

Table 3-7

Means (SD) of errors to criteria of control tests for structural learning

	HC	aMCI	vMCI
Simple Discrimination (First Session)	0.67(0.78)	2.08(2.10)	2.75(3.10)
Transverse Patterning (First Session)	25.75(9.78)	24.62(10.31)	25.25(2.87)
Simple Discrimination (Second Session)	0.55(0.82)	3.45(8.82)	20.50(20.37)*

$*p < 0.05$

3.3 Diffusion Tensor Imaging

3.3.1 TBSS Group Comparisons

Pairwise contrasts between HC, aMCI and vMCI were conducted within an ANCOVA model with age, sex, years of education and relative motion as covariates across FA, MD, L1 and RD. The results were corrected for multiple comparisons using threshold-free cluster enhancement ($p < 0.05$) and displayed on the study-specific mean white matter skeleton (green) which represents the centres of the principal white matter tracts. This skeleton was overlaid on top of the Montreal Neurological Institute (MNI152) T1-weighted template. Relative to healthy controls, no significant differences in FA, MD and both L1 or RD was found in aMCI. However, differences were identified in the vMCI group compared to HC and aMCI groups.

3.3.1.1 Fractional anisotropy

Figure 3-12 shows reduced FA in the right superior corona radiata of the vMCI group compared to the healthy controls. Decreases in FA were more evident in the comparison between the vMCI and aMCI groups (Figure 3-13).

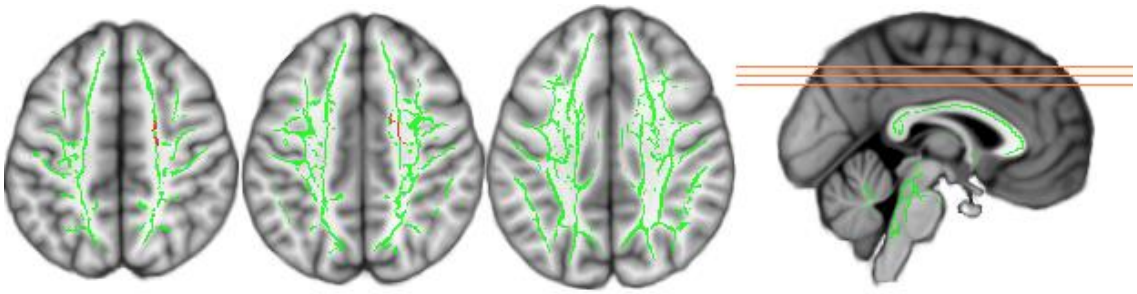


Figure 3-12 Reduced fractional anisotropy in the right superior corona radiata of the vMCI group compared to the HC group. The orange lines in the sagittal view on the right represent the location of the axial slices. Threshold free cluster enhancement (TFCE) – corrected $p < 0.05$.

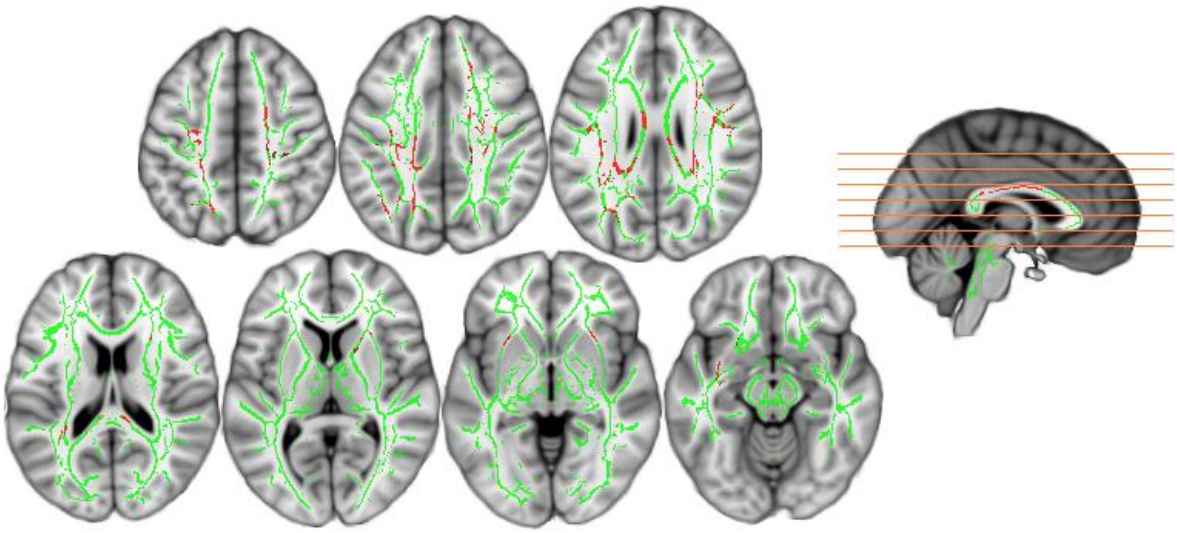


Figure 3-13 Reduced fractional anisotropy in the left inferior fronto-occipital fasciculus, external capsule, right anterior limb of internal capsule, corpus callosum, and superior corona radiata of the vMCI group compared to the aMCI group. The orange lines in the sagittal view on the right represent the location of the axial slices. TFCE – corrected $p < 0.05$.

3.3.1.2 Mean diffusivity

There were no significant differences in mean diffusivity between aMCI and HC. The vMCI group again showed MD differences in comparison to HC and aMCI groups. Relative to healthy controls, the vMCI group showed widespread areas of larger mean diffusivity indicating microstructural white matter damage Figure 3-14. Interestingly, when compared with the aMCI group the localisation became unilateral with greater mean diffusivity appearing on the left side (Figure 3-15).

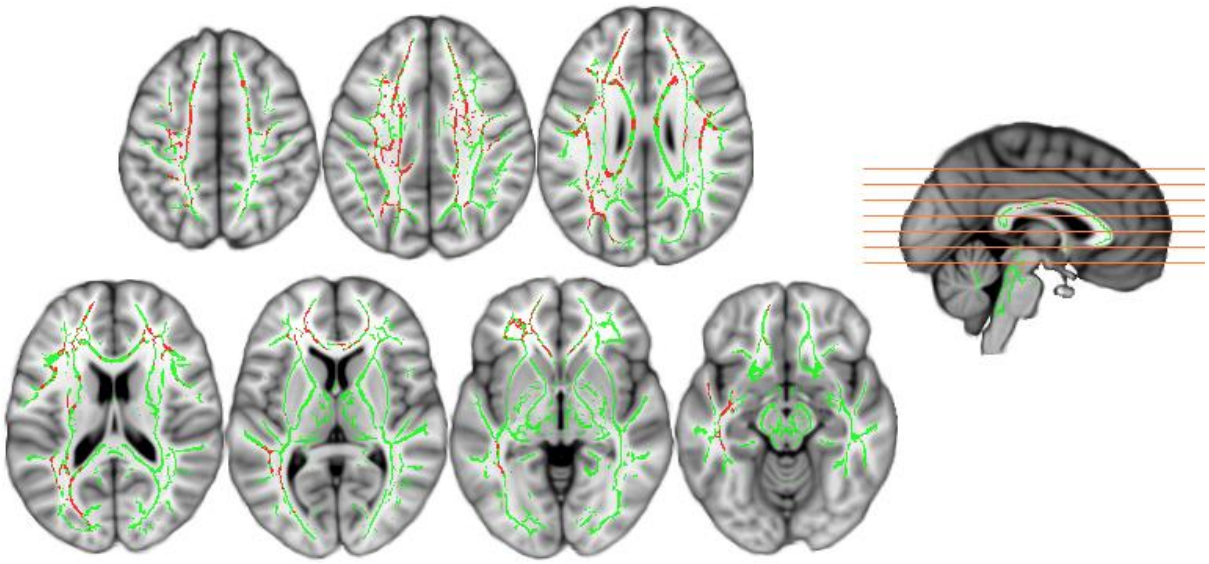


Figure 3-14 Increased mean diffusivity in the superior corona radiata, cingulum, superior longitudinal fasciculus, anterior corona radiata, corpus callosum, left external capsule and the left inferior longitudinal fasciculus of the vMCI group compared to the HC group. TFCE – corrected $p < 0.05$.

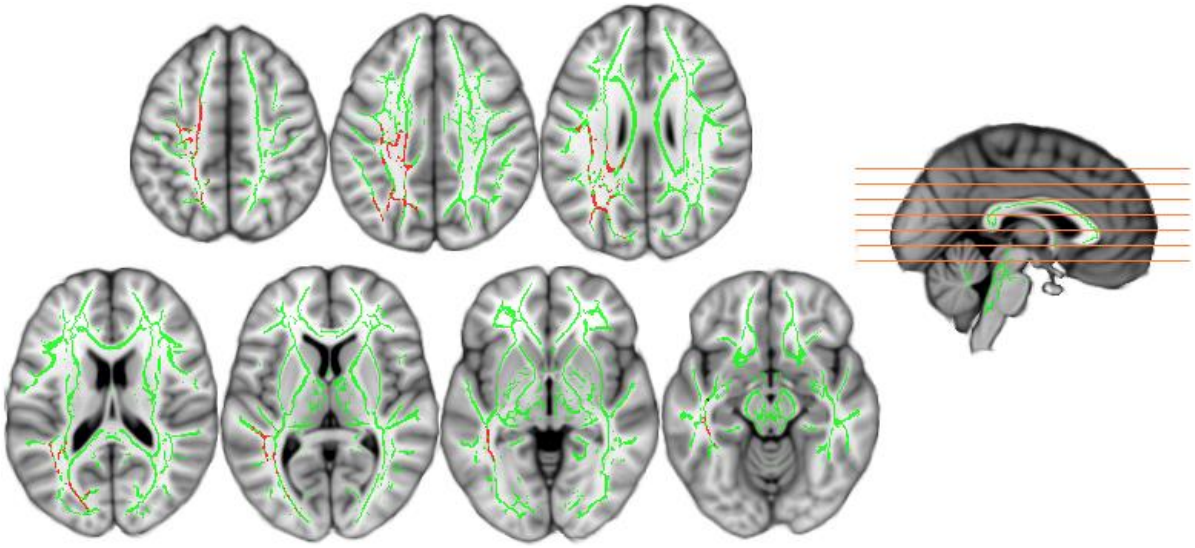


Figure 3-15 Increased mean diffusivity in the left superior corona radiata, left corticospinal tract, left forceps major, left posterior thalamic radiation, left retrolenticular part of internal capsule and left inferior longitudinal fasciculus of vMCI group when compared with the aMCI group. TFCE – corrected $p < 0.05$.

3.3.1.3 Axial diffusivity

There were no significant differences in the axial diffusivity measure for the three groups.

3.3.1.4 Radial diffusivity

The vMCI group showed significantly greater radial diffusivity compared with the healthy control group (Figure 3-16). Greater radial diffusivity was also observed for the vMCI group when compared with the aMCI group (Figure 3-17). However, there were no differences for the HC and aMCI groups.

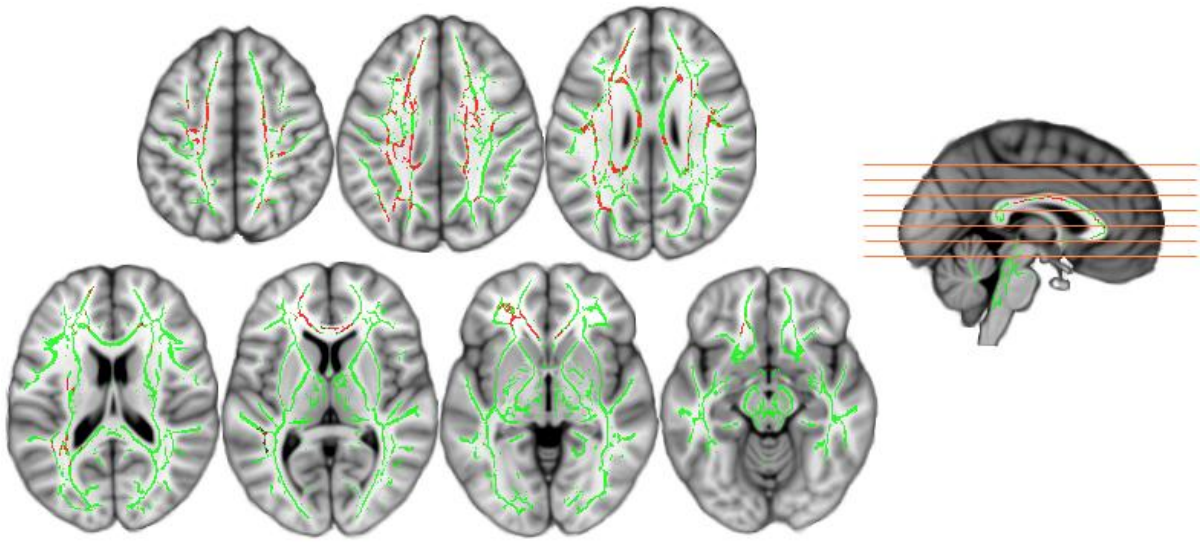


Figure 3-16 Increased radial diffusivity in the corticospinal tract, superior longitudinal fasciculus, superior corona radiata, corpus callosum, left external capsule and left posterior thalamic radiation of the vMCI group when compared with the HC group. TFCE – corrected $p < 0.05$.

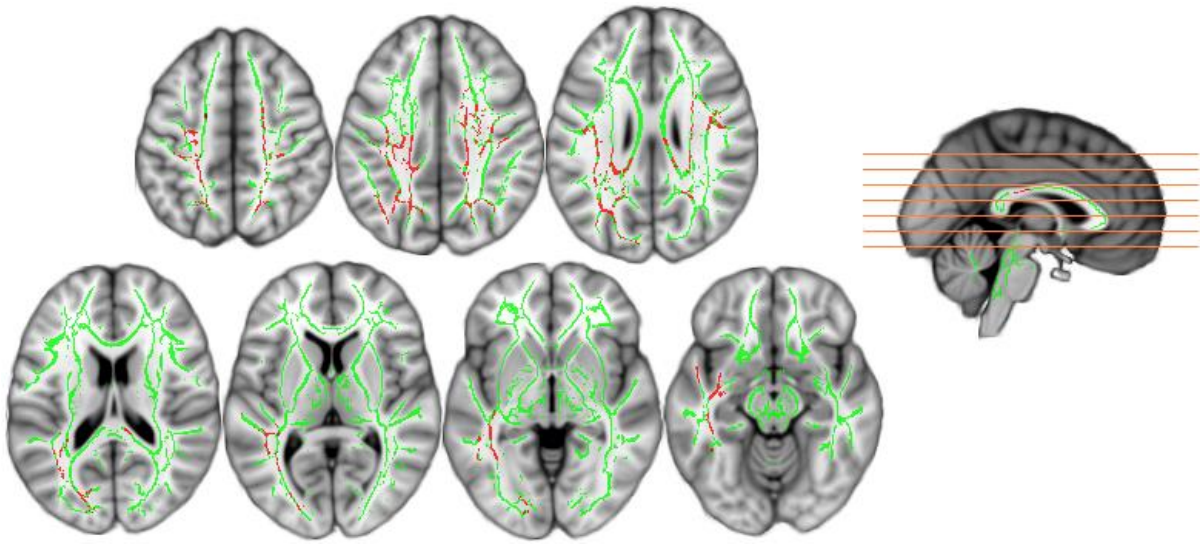


Figure 3-17 Increased radial diffusivity in the corticospinal tract, superior corona radiata, superior longitudinal fasciculus, corpus callosum, left posterior corona radiata, left external capsule and left sagittal stratum of the vMCI group compared with the aMCI group. TFCE – corrected $p < 0.05$.

3.3.2 Association of white matter microstructural integrity with global and domain specific standardised neuropsychological test z-scores.

Global z-score was run in 4 separate multiple regressions with age, sex, years of education and relative motion as covariates to assess the association with FA, MD, L1 and RD. Global z-score showed no significant association with white matter microstructural integrity for any of these four measures.

Each individual cognitive domain z-score was then investigated for association with FA, MD, L1 and RD with age, sex, years of education and relative motion as covariates. Individual executive function, processing speed and working memory, learning and memory, and visuospatial domains were not associated with any of the measures of white matter microstructural integrity. However, the language domain was positively associated with FA (Figure 3-18).

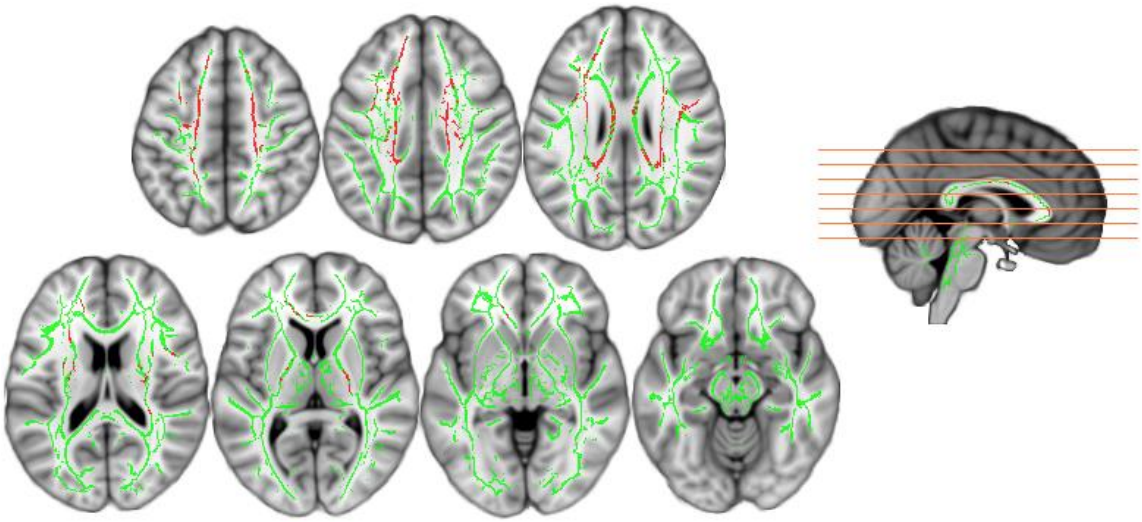


Figure 3-18 Significant positive associations in the superior corona radiata, anterior corona radiata, posterior corona radiata, superior longitudinal fasciculus, corpus callosum, posterior limb of internal capsule and external capsule between the z-scores for the language domain and FA. TFCE – corrected $p < 0.05$.

3.3.3 Association of white matter microstructural integrity with scores from the experimental neuropsychological tests

3.3.3.1 Modelling missing data

There were a small number of data points missing from the experimental neuropsychological tests (one aMCI participant declined to complete the ANT and the structural learning test in the first session; one HC and two aMCI participants declined to complete the ANT and structural learning tests, and one HC and one aMCI declined to complete the feature ambiguity test in the second session). To make use of the imaging and experimental data, missing neuropsychological values were predicted for association with FA, MD, L1 and RD.

Missing experimental neuropsychological scores were generated by predictions using multiple regression. First, the participant with the missing value was removed. Age, sex, education, MoCA and previous session score (or an appropriate standardised test substitute) were entered into a multiple regression as explanatory variables. Based on the fit of this model, explanatory variables (age, sex, education, MoCA score and previous experimental neuropsychological score or an appropriate substitute) were used to predict a suitable value for use in investigating the association with FA, MD, L1 and RD. Details of each regression for predicting missing scores are as follows:

Equation 1: ANT Alerting/Orienting/Executive (NP2)

$$Z'_{(ANT\ domain)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{Digit\ Span})(Z_{Digit\ Span}) + (\beta_{ANT\ domain})(Z_{ANT\ domain})$$

Equation 2: ANT Global Reaction Time (NP2)

$$Z'_{(Global)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{Digit\ Span})(Z_{Digit\ Span}) + (\beta_{Global})(Z_{Global})$$

Equation 3: Structural Learning (NP2)

$$Z'_{(SL)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{BVMT})(Z_{BVMT}) + (\beta_{SL})(Z_{SL})$$

Equation 4: ANT Alerting/Orienting/Executive/Global (Baseline)

$$Z'_{(ANT\ domain)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{Previous\ ANT\ score})(Z_{Previous\ ANT\ score}) + (\beta_{ANT\ domain})(Z_{ANT\ domain})$$

Equation 5: Feature Ambiguity (minimum/intermediate/maximum) (Baseline)

$$Z'_{(Feature\ Amb)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{Previous\ score})(Z_{Previous\ score}) + (\beta_{Predicting\ Score})(Z_{Predicting\ Score})$$

Equation 6: Structural Learning (Baseline)

$$Z'_{(SL)} = (\beta_{Age})(Z_{Age}) + (\beta_{Sex})(Z_{Sex}) + (\beta_{Education})(Z_{Education}) + (\beta_{MoCA})(Z_{MoCA}) + (\beta_{BVMT})(Z_{BVMT}) + (\beta_{SL})(Z_{SL})$$

3.3.3.2 Association of the attention network test with white matter microstructural integrity

Mean reaction time, and the alerting, orienting and executive effects of the attention network test were investigated for association with FA, MD, L1 and RD for both test sessions independently. Multiple regressions were conducted with age, sex, education and motion as covariates. There was a very localized significant association of mean reaction time with L1 in the first session (Figure 3-19) but no association for FA, MD or RD. Additionally, no associations were found with regard to the mean reaction time in the second session across FA, MD, L1 or RD.

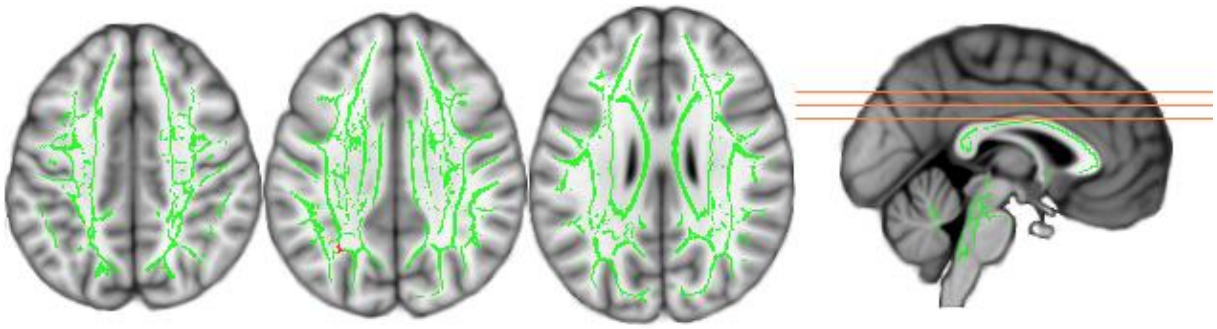


Figure 3-19 Significant association of L1 in the left inferior longitudinal fasciculus with mean reaction time from the first session of the ANT. TFCE – corrected $p < 0.05$.

The first session of the ANT showed no association for the alerting and orienting effects in FA, MD, L1 or RD. However, the executive effect showed similar areas of association in MD, L1 and RD (Figure 3-20) to the L1 association with mean reaction time (Figure 3-19).

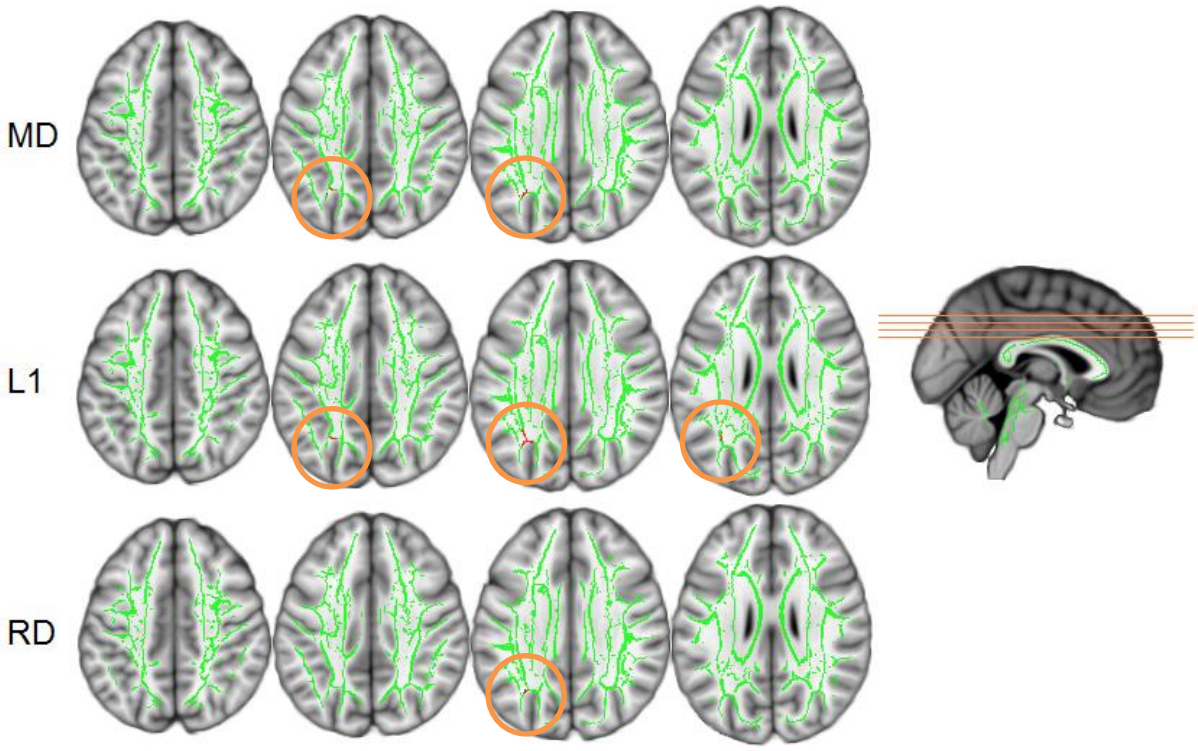


Figure 3-20 Significant association of the executive effect with MD, L1 and RD in the left inferior longitudinal fasciculus. TFCE – corrected $p < 0.05$.

For the second session, there was a negative association in the alerting effect with areas in the left forceps minor and anterior corona radiata in RD (Figure 3-21). However, no associations were discovered for FA, MD or L1. Additionally, no associations were observed for the orienting and executive effects across FA, MD, L1 or RD.

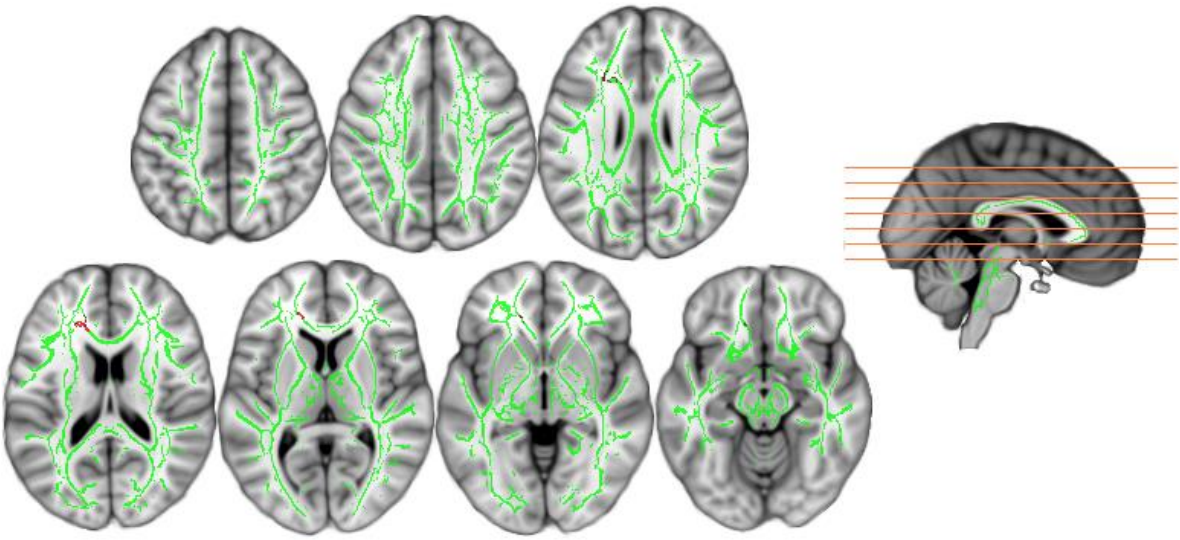


Figure 3-21 Significant association of the second session alerting effect with RD in the left forceps minor and left anterior corona radiata. TFCE – corrected $p < 0.05$.

3.3.3.3 Association of feature ambiguity with white matter microstructural integrity

Errors to criteria for the minimum, intermediate and maximum feature ambiguity conditions from each session were used independently to assess the association with FA, MD, L1 and RD. No significant associations were found for each of the feature ambiguity conditions for both sessions.

3.3.3.4 Association of structural learning with white matter microstructural integrity

Errors to criteria for the two sessions of the structural learning test were used to investigate the association with FA, MD, L1 and RD. There were no significant association for structural learning across all measures of white matter microstructural integrity.

4. Discussion

This research aimed to examine the value of experimental computerized neuropsychological tests in identifying deficits in feature ambiguity, attention and structural learning in elderly participants with mild cognitive impairment compared to matched controls. Performances on these computerized tests were then investigated for association with white matter microstructural integrity using tract based spatial statistics (TBSS) derived from DTI MRI.

4.1 Standardised neuropsychological testing

Standardised neuropsychological tests were able to differentiate between HC and the MCI groups by identifying deficits in learning and memory in MCI. The groups also differed in executive function, working memory, processing speed, and visuospatial domains. Differences in learning and memory and the other domains were consistent with the inclusion criteria for MCI in this study.

Few studies have explored the association of whole brain white matter microstructural integrity with cognitive domains. In the current study, microstructural integrity of the primary white matter skeleton was not associated with cognition with the exception of language. In contrast, Rose et al. (2006) found associations with global neuropsychological performance with FA and MD values using similar DTI techniques. The researchers used neuropsychological tests which were sensitive to MCI. This included the Boston naming test which was included as one of the two language domain tests in this current study. The finding that participants who scored higher in the language domain showed greater FA in a number of white matter tracts was particularly interesting as increased FA indicates preserved white matter. The language domain may be a reliable indicator of white matter microstructural integrity in the elderly and may provide an early indicator for Alzheimer's disease.

4.2 Group comparisons in white matter microstructural integrity

In the group comparisons of FA, MD, L1 and RD, the vMCI group showed lower FA and increased MD and RD compared to the HC and aMCI groups, whereas, no differences were found between the HC and aMCI groups. The lowered FA and greater diffusivity indicates that vascular features in MCI

represent more advanced pathology in white matter microstructural integrity than amnesic MCI with no vascular features. In addition, microstructural damage appears to be weighted towards the left side in the diffusivity measures. This is clear in the aMCI comparison in MD with differences only appearing in the left hemisphere. Consistent with these findings, hippocampal size reductions, especially on the left side, have been observed in MCI (deToledo-Morrell et al., 2004; Pennanen et al., 2004) and may be an additional risk factor to hippocampal reduction (Raz et al., 2005). Furthermore, hippocampal volume reduction has been shown to be predictive of conversion to dementia (Jack et al., 2013; Kantarci & Jack, 2003).

Vascular features may play an additional role in decline in MCI by facilitating hippocampal loss in the left hemisphere. Jacobs et al. (2013) found that poor vascular health was associated with a negative impact on executive functioning and processing speed. Vascular white matter lesions are an independent predictor of conversion to AD and may represent a more destructive pathology than that associated with non-vascular MCI. Provenzano et al. (2013) found that white matter hyperintensities (seen as increased signal intensity in white matter T2-weighted MRI) indicated small-vessel cerebrovascular disease and contributes to the presentation of AD. However, it is uncertain in this current study as to whether cognitive decline due to vascular features and MCI are causally related or independent from each other.

No group differences for aMCI and HC were found for FA, MD, L1 and RD despite the strict study criteria set for inclusion in the aMCI group. Previously, compared to HC, aMCI have exhibited significant reductions in FA and increases in MD in many areas. Previous studies have reported: the left superior frontal white matter; the left lateral temporal lobe; the medial temporal fornix; the parietal lobe; the precuneus and postcentral gyrus; the corpus callosum; the inferior frontoccipital fasciculus, the right superior longitudinal fasciculus; the bilateral posterior thalamic radiation; the posterior, anterior and superior corona radiata; and the internal capsule (Liu et al., 2013; J. H. Wang et al., 2013; Zhang, Xu, Zhu, & Kantarci, 2014; Zhuang et al., 2010). However, these studies have a

much larger sample size than this study and thus a greater likelihood of discovering differences due to the additional power. Axial diffusivity (L1) and radial diffusivity (RD) have been studied to a much lesser degree with the majority of DTI studies electing for just FA and MD. Recent evidence has emerged that axial and radial diffusivity may be more sensitive to underlying pathology in aMCI and AD than just FA and MD alone (Boespflug et al., 2014). In RD, differences have been found in areas of the inferior longitudinal and occipitofrontal fasciculi, the posterior cingulum and the right longitudinal superior and right uncinate fasciculus in aMCI (Bosch et al., 2012). As aMCI is an early diagnosis, small changes to white matter microstructural integrity (i.e. small effect sizes) may not be substantial enough in this current study to show significant differences.

4.3 Feature Ambiguity

Feature ambiguity tests are believed to be sensitive to the cortical regions of the medial temporal lobe (MTL) (Barense et al., 2005; Saksida & Bussey, 2010). It was therefore expected to show significant impairment in the MCI groups. The current study, however, was unable to distinguish the HC group from the aMCI and vMCI groups using this task. In Barense et al. (2005), patients with memory impairment as a result of medial temporal lobe damage were unable to distinguish maximum feature ambiguity objects from each other but were able to distinguish less ambiguous objects. However, amnesic patients with hippocampal damage performed as well as controls across all levels of feature ambiguity despite a similar degree of impairment in formal memory tests compared to the amnesic MTL patients. In the current study, the two sessions of the feature ambiguity test reached the same conclusion and suggested that early memory deficits in the MCI groups may be attributed to subtle hippocampal damage rather than more extensive damage to the MTL region. This is consistent with Salat et al. (2009) who found isolated damage to white matter microstructural integrity in AD to be independent of grey matter atrophy in the MTL.

There have been no previous reported studies investigating the association of white matter microstructural integrity with performance in a visual feature ambiguity task. The relationship

between varying degrees in performance across participants, in each degree of feature ambiguity, was examined with association with white matter microstructural integrity. The current research found no association in performance on feature ambiguity with white matter microstructural integrity. Previous research on feature ambiguity and grey matter found an association with damage to the perirhinal and medial temporal lobes (Graham et al., 2010). This current study, however, did not look exclusively at amnesic patients with obvious MTL lesions. Therefore, performance in the feature ambiguity tasks may not directly reflect underlying white matter microstructural integrity.

There was a discrepancy between the number of errors to criterion in this current study and a similar study by Barense et al. (2005). Comparative inspection of the results showed an unusually low number of trials to criterion in their healthy controls. The HCs in Barense et al. (2005) were learning to distinguish maximum ambiguous stimuli after a mean of 3 errors. In contrast, HCs in this current study were making substantially more mean errors to criteria for the first and second session (19 and 23 respectively). Additionally, in Barense et al. (2005), MTL damaged patients were comparable in the mean number of errors to criterion as the healthy controls in this study. Although Barense et al. (2005) had a much younger sample (M = 48.7), ages is unlikely to be a contributing factor. In Barense, Rogers, Bussey, Saksida, and Graham (2010), a much older control group (M = 62.9) and semantic dementia group (M = 63.2) were achieving around 2 and 11 errors to criterion respectively. The experimental procedure used in the current study was modelled as close as possible to Barense et al. (2005). However, there were some differences in experimental design. Barense et al. (2005) used a touch screen to present stimuli and a tone to inform participants of correct or incorrect responses. This current study required participants to press buttons on a response box to stimuli presented on a computer screen. Participants were given text feedback on screen in the form of “correct” and “incorrect” instead of an auditory tone. Although there were slight differences in methodology, it is unlikely to be the cause of such a large discrepancy in results.

4.4 Attention Networks

The attention network test was used to examine attention performance in the MCI groups compared to HC. Previous findings on the main effects in the congruency (executive), cue validity (orienting) and alerting tone (alerting) were replicated (Fernandez et al., 2011; Martella et al., 2014). With respect to group differences for these attention measures, the vMCI group showed slower reaction times in the executive effect than the HC and aMCI groups. This suggests the executive network may be preserved in aMCI but not in MCI with vascular features. However, inspection of the network effect calculated by the difference scores which control for individual reaction times found no significant difference for the executive network. This indicates the executive effect interaction was driven by long reaction times in the vMCI group. The vMCI group was also unaffected by trials with just an alerting tone (without the influence of visual cues). The alerting tone by itself was unable to improve phasic alertness in vMCI. This lack of ability for the alerting tone to improve response times was supported in the interaction involving alerting tone × visual cue × group. In this interaction, the alerting tone facilitated the visual cue effects in the MCI groups and was particularly evident in the vMCIs. The vMCI, in order to remain alert, required both an alerting and visual cue and explains their slow overall mean reaction times. This group interaction involving the orienting effect and alerting effect reflects dysfunction in maintaining sustained attention in aMCI and vMCI.

Fernandez et al. (2011), found a severe orienting network dysfunction in MCI with subcortical vascular features. These subcortical vMCI patients showed a reduced validity (orienting) effect in comparison to non-vascular MCI and healthy controls. The researchers suggested that this was due in part to a failure of the cue to summon attention to the cued location and was related to vascular damage. However, this severe orienting network dysfunction was not evident in this current study and may be due to a smaller sample than Fernandez et al. (2011).

The two sessions of the ANT varied slightly in the conclusions that were reached. The main effects in the first session for each of the conditions were found to match those in the second

session. However, no interactions for the second session involving group reached significance whereas interactions between group with congruency, cue and alerting were found in the first session. This discrepancy may be due to a lower number of participants who took part in the second session of the ANT than the first session. Additionally, the difference between the two testing sessions may also indicate instability of the attention networks in MCI.

Attention and speed of processing has been associated with white matter hyperintensities (Ylikoski et al., 1993). However, there are no accounts of studies investigating the association between microstructural integrity and the attention networks of elderly. In this current study, the attention network scores from the first session revealed greater mean, axial and radial diffusivity associated with the executive effect in the left posterior inferior longitudinal fasciculus. Additionally, the left inferior longitudinal fasciculus was additionally involved in the L1 association with overall mean reaction time. The overall reaction time of participants may be linked to their ability in responding to congruent and incongruent stimuli. Additionally the posterior location of dysfunction in white matter microstructural integrity was consistent with previous studies on DTI highlighting a breakdown in the posterior regions in aMCI and early AD (Hong et al., 2013; Kavcic, Ni, Zhu, Zhong, & Duffy, 2008; Zhou et al., 2008).

Associations of the second session with white matter microstructural integrity produced a different pattern of results to the first session. Interestingly, the alerting effect showed a negative association with RD in part of the left forceps minor and left anterior corona radiata. The lack of an alerting ability appears to be associated with greater radial diffusivity. This finding reflects the previous conclusion of an alerting network dysfunction in the vMCI group. No other significant attention network effects were found for FA, MD, L1 or RD.

Differences in the association of white matter microstructural integrity with scores from the attention networks at the two time points are not entirely surprising. As the results from the first session to the second session had changed, it is likely any association with white matter

microstructural integrity would as well. The period between the brain scan date and their participation in the tests varied for the sessions. Acquisition of brain imaging was conducted relatively immediately (M = 17 days, SD = 121) after the first session of experimental neuropsychological testing (NP2). However, the second session (baseline) was conducted just prior to a cognitive enrichment intervention and was much further in time from the scan (M= 125 days, SD = 78). The discrepancy of each session from the scan date may be potentially useful as the first session may capture direct associations of white matter microstructural integrity with the attention networks whereas the second session may indicate future decline in cognition based on past microstructural integrity.

4.5 Structural Learning

Animal studies suggest that tests of structural learning reflect specific damage in the hippocampus (Aggleton et al., 2007). This study was the first to assess structural learning on white matter microstructural integrity in older adults. However, this research varied to the animal research in that familiar visual scenes were used instead of simple patterned stimuli. Additionally, the animal studies assessed the ability of relearning after lesions to the hippocampus, while this current study assessed participant's ability to learn new sets of structural rules.

The first session of the structural learning test revealed no differences between the groups, but a floor effect evident. The difficulty of the task was attributed to the comparisons of the structural scenes containing mixed objects. Thus, for the second session, the pairing of the scenes for structural learning was reduced so that only the 'mirrors' of the objects in the structural scenes were paired together. This was in agreement with the previous animal study conducted by Sanderson et al. (2006) (the researchers only paired mirrored stimuli). The change in difficulty resulted in observed differences between the HC and the MCI groups in the second session. The aMCI and vMCI were on average at chance and performed significantly worse than the HC group in this test. Differences in performance suggest the role of the hippocampus in this task may be disrupted in MCI and is

consistent with studies which have found smaller hippocampal volumes in aMCI and early AD (Zhou et al., 2008).

For the transverse patterning and simple discrimination tests, no differences were found for group in the first session. This was hypothesized as the simple discrimination test was designed to assess if participants could discriminate an object in a visual scene and learn a simple rule. This appeared to be the case and shows that participants could respond correctly to the given stimuli. However, participants in general found it very difficult to learn the rule of transverse patterning. This task was a conditional task similar in difficultly to the structural learning test but does not contain features dependent on processing spatial information in the MTL (Sanderson et al., 2006). There are varying conclusions regarding the ability of older adults in learning transverse patterning rules. Reed and Squire (1999) found older adults were able to do transverse patterning problems, albeit after practice and a large number of trials. In contrast, Kumaran et al. (2007) found that configural tasks which have spatial and non-spatial elements such as transverse patterning were both dependent of MTL. Due to the surprising difficulty of the task in the current study, transverse patterning was abandoned in the second session to reduce discomfort for the participants.

In the second session, the simple discrimination task differed from the first as a result of the vMCI group making a greater number of errors than the HC and aMCI groups. This was driven by two participants in the vMCI group and suggests they were guessing for the structural learning test instead of attempting to complete the task successfully. The failure of the vMCI participants in attempting this task suggests a disruption in sustained attention as previously established from the ANT.

The association of structural learning with white matter microstructural integrity revealed no significant correlation for FA, MD, L1 or RD. Although it was expected white matter microstructural integrity would correlate with areas in the hippocampus with structural learning, no associations

were found. Errors to criteria in this test may not reflect the state of the hippocampal white matter microstructural integrity.

4.6 Limitations and future directions

While a good pilot, the major limitation of this study includes the small sample size as briefly mentioned earlier. With such a small sample size, power would be low (the between group effect size with 80% power at $p < 0.05$ would have to be large). A large sample size would have resulted in a greater likelihood of rejecting the null hypothesis, had the research hypothesis been true. Although, tasks such as the feature ambiguity test did not show any significant group differences, they suggested differences for group in the maximum condition. However, participant recruitment was difficult given very few had met our aMCI criteria out of the original screening pool. An improved recruitment screening tool for aMCI prior to the standardised neuropsychological testing is clearly necessary.

Participants obtained for this study were from a convenience sample. Volunteers responded from advertisements in newspapers and magazines. This brings about a bias for individuals who are generally active and interested in research and events in their community. It has been suggested that those who progress onto dementia score high on apathy scales (Teng, Lu, & Cummings, 2007). Individuals who score high in apathy would be unlikely to have responded to participant requests in advertisements. As such, participants in this study may not be representative of the population and are likely to be of slightly higher functioning. However, this bias was also relevant for the healthy control group and direct group comparisons partly control for this bias.

A few of the participants in this study declined to complete a number of the experimental neuropsychological tests. Although this was few in number, the participants who did not take part in the tests were likely to have performed poorly. As a result, the scores predicted for the participants in the analyses with the white matter associations were likely to be conservative estimates.

For the analyses of the attention network test and subsequent associations with white matter microstructural integrity, trials with reaction times for each participant, which were three standard deviations above or below the mean, were not removed. Due to time constraints, this was not corrected and results include the addition of outliers. Despite this limitation, it is unlikely that the conclusions drawn would have changed had the outliers had been removed.

Fernaeus, Ostberg, and Wahlund (2013) found that in a simple attention test, MCI participants did not differ from the controls in the first 3 of the 5 segments of the test. However, inspection of the last 2 segments revealed impairment in MCI compared to the controls. They suggested differences were a result of impairment in sustained attention. Vigilance or sustained attention was not explicitly assessed in this study. Given additional time, this idea would have been possible to investigate as the attention network test is composed of 3 blocks of 96 trials. Additionally, intra-individual reaction times were not investigated. Gorus, De Raedt, Lambert, Lemper, and Mets (2008) found the best predictors for aMCI were the variability in reaction times of complex attention tasks. Examination of the variability of ANT trials containing the incongruent and invalid cue conditions may generate a more comprehensive theory of dysfunction of attention in MCI.

Transverse patterning as a control condition for structural learning did not perform as expected. Instead it appeared very few of even the healthy control participants were able to learn the rule. For future studies involving structural learning, another configural task called biconditional discrimination could be used instead (Aggleton et al., 2007). In this task, elements are paired together within a scene (much like structural learning). However, scenes are correct only when two specific elements are paired together regardless of spatial position. If hippocampal damaged was localized in MCI, it would be expected aMCI would perform poorly on structural learning but as well as controls in biconditional discrimination.

Tract based spatial statistics was used to assess whole brain white matter microstructural integrity. Although useful for identifying changes in microstructural integrity, this technique was

limited to the white matter skeleton. For investigating areas of the MTL with measures such as structural learning, other techniques which combine assessment of grey matter or regions of interest (ROIs) may prove useful in future studies.

The associations of each of the experimental measures were conducted with all participants across the three groups. However, most of the significant group differences were associated with the vMCI group. To properly assess the association of aMCI with white matter microstructural integrity in the experimental neuropsychological tests, the vMCI group should be excluded from future analyses as the vMCI group may be driving the significant associations.

Vascular white matter lesions, which are identified as areas of hyperintense signal on T2 FLAIR images, are abundant in AD patients and is associated with cognitive decline and an independent predictor of conversion to dementia (Provenzano et al., 2013). In this study, the vMCI group was identified based on a neuroradiological screen. However, white matter lesions in the aMCI or HC groups were not quantified and may affect DTI measures. As evidenced by previous research and findings in the vMCI groups, an additional quantitative assessment of white matter lesions may provide a more complete picture of the relationship between attention and white matter integrity in aMCI.

4.7 Conclusion

This study examined the value of experimental computerized neuropsychological tests and the associations with white matter microstructural integrity in elderly with amnesic MCI with and without vascular features. Although feature ambiguity was based on similar human studies, no group differences or associations with white matter microstructural integrity were found. The attention network and structural learning tests, however, provided more interesting conclusions. Results from the ANT suggest a dysfunction in alertness in MCI. Additionally, participants' ability to respond to congruent and incongruent stimuli was associated with white matter microstructural integrity. The revised structural learning test showed distinct differences for group performance but was not

associated with white matter microstructure. The findings from these experimental computerized neuropsychological tests may be useful in assessing dysfunction in MCI and identifying degeneration in white matter microstructural integrity which has been attributed to numerous degenerative processes. Further studies with larger samples are needed to validate the effects observed in this study and to explore possible associations with white matter microstructural integrity with cognitive decline in elderly.

References

Aggleton, J. P., Albasser, M. M., Aggleton, D. J., Poirier, G. L., & Pearce, J. M. (2010). Lesions of the rat perirhinal cortex spare the acquisition of a complex configural visual discrimination yet impair object recognition. *Behav Neurosci, 124*(1), 55-68. doi: 10.1037/a0018320

Aggleton, J. P., O'Mara, S. M., Vann, S. D., Wright, N. F., Tsanov, M., & Erichsen, J. T. (2010). Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur J Neurosci, 31*(12), 2292-2307. doi: 10.1111/j.1460-9568.2010.07251.x

Aggleton, J. P., Sanderson, D. J., & Pearce, J. M. (2007). Structural learning and the hippocampus. *Hippocampus, 17*(9), 723-734. doi: 10.1002/hipo.20323

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci, 28*, 403-450. doi: 10.1146/annurev.neuro.28.061604.135709

Baek, M. J., Kim, H. J., Ryu, H. J., Lee, S. H., Han, S. H., Na, H. R., . . . Kim, S. (2011). The usefulness of the story recall test in patients with mild cognitive impairment and Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 18*(2), 214-229. doi: 10.1080/13825585.2010.530221

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019-1031. doi: 10.1016/S0140-6736(10)61349-9

Barense, M. D., Bussey, T. J., Lee, A. C., Rogers, T. T., Davies, R. R., Saksida, L. M., . . . Graham, K. S. (2005). Functional specialization in the human medial temporal lobe. *J Neurosci, 25*(44), 10239-10246. doi: 10.1523/JNEUROSCI.2704-05.2005

Barense, M. D., Rogers, T. T., Bussey, T. J., Saksida, L. M., & Graham, K. S. (2010). Influence of conceptual knowledge on visual object discrimination: insights from semantic dementia and MTL amnesia. *Cereb Cortex, 20*(11), 2568-2582. doi: 10.1093/cercor/bhq004

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed, 15*(7-8), 435-455. doi: 10.1002/nbm.782

Benedict, R. H. B. (1988). *Brief Visuospatial Memory Test-Revised*. Lutz, Florida, USA: PAR.

Bennett, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., & Wilson, R. S. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology, 66*(12), 1837-1844. doi: 10.1212/01.wnl.0000219668.47116.e6

Benton, A., Hannay, H. J., & Varney, N. R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25*(10), 907-910.

Berger, A., & Posner, M. I. (2000). Pathologies of brain attentional networks. *Neurosci Biobehav Rev, 24*(1), 3-5.

Bierman, E. J., Comijs, H. C., Gundy, C. M., Sonnenberg, C., Jonker, C., & Beekman, A. T. (2007). The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent? *Int J Geriatr Psychiatry, 22*(12), 1194-1200. doi: 10.1002/gps.1811

Bishop, N. A., Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature, 464*(7288), 529-535. doi: 10.1038/nature08983

Boespflug, E. L., Storrs, J., Sadat-Hossieny, S., Eliassen, J., Shidler, M., Norris, M., & Krikorian, R. (2014). Full diffusion characterization implicates regionally disparate neuropathology in mild cognitive impairment. *Brain Struct Funct, 219*(1), 367-379. doi: 10.1007/s00429-013-0506-x

Bosch, B., Arenaza-Urquijo, E. M., Rami, L., Sala-Llonch, R., Junque, C., Sole-Padulles, C., . . . Bartres-Faz, D. (2012). Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. *Neurobiol Aging, 33*(1), 61-74. doi: 10.1016/j.neurobiolaging.2010.02.004

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J. J., Luchsinger, J. A., Yeung, L. K., . . . Stern, Y. (2011). White matter hyperintensities and cognition: testing the reserve hypothesis. *Neurobiol Aging, 32*(9), 1588-1598. doi: 10.1016/j.neurobiolaging.2009.10.013

Brooks, L. G., & Loewenstein, D. A. (2010). Assessing the progression of mild cognitive impairment to Alzheimer's disease: current trends and future directions. *Alzheimers Res Ther, 2*(5), 28. doi: 10.1186/alzrt52

Busse, A., Hensel, A., Guhne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology, 67*(12), 2176-2185. doi: 10.1212/01.wnl.0000249117.23318.e1

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2003). Impairments in visual discrimination after perirhinal cortex lesions: testing 'declarative' vs. 'perceptual-mnemonic' views of perirhinal cortex function. *Eur J Neurosci, 17*(3), 649-660.

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2006). Perirhinal cortex and feature-ambiguous discriminations. *Learn Mem, 13*(2), 103-105; author reply 106-107. doi: 10.1101/lm.163606

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci, 12*(1), 1-47.

Callejas, A., Lupianez, J., & Tudela, P. (2004). The three attentional networks: on their independence and interactions. *Brain Cogn, 54*(3), 225-227. doi: 10.1016/j.bandc.2004.02.012

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215. doi: 10.1038/nrn755

Coull, J. T., Frith, C. D., Frackowiak, R. S., & Grasby, P. M. (1996). A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia, 34*(11), 1085-1095.

Davidson, M. C., & Marrocco, R. T. (2000). Local infusion of scopolamine into intraparietal cortex slows covert orienting in rhesus monkeys. *J Neurophysiol, 83*(3), 1536-1549.

de Rover, M., Pironti, V. A., McCabe, J. A., Acosta-Cabronero, J., Arana, F. S., Morein-Zamir, S., . . . Sahakian, B. J. (2011). Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. *Neuropsychologia, 49*(7), 2060-2070. doi: 10.1016/j.neuropsychologia.2011.03.037

Delano-Wood, L., Bondi, M. W., Sacco, J., Abeles, N., Jak, A. J., Libon, D. J., & Bozoki, A. (2009). Heterogeneity in mild cognitive impairment: differences in neuropsychological profile and associated white matter lesion pathology. *J Int Neuropsychol Soc, 15*(6), 906-914. doi: 10.1017/S1355617709990257

Delis, D. C., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function Scale (D-KEFS)*. San Antonio, Texas: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test* (2nd ed.). San Antonio, Texas: Pschological Corporation.

deToledo-Morrell, L., Stoub, T. R., Bulgakova, M., Wilson, R. S., Bennett, D. A., Leurgans, S., . . . Turner, D. A. (2004). MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. *Neurobiol Aging, 25*(9), 1197-1203. doi: 10.1016/j.neurobiolaging.2003.12.007

Devanand, D. P., Liu, X., Tabert, M. H., Pradhaban, G., Cuasay, K., Bell, K., . . . Pelton, G. H. (2008). Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry, 64*(10), 871-879. doi: 10.1016/j.biopsych.2008.06.020

Dickerson, B. C., Salat, D. H., Bates, J. F., Atiya, M., Killiany, R. J., Greve, D. N., . . . Sperling, R. A. (2004). Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol, 56*(1), 27-35. doi: 10.1002/ana.20163

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.

Ernst, R. L., & Hay, J. W. (1994). The US economic and social costs of Alzheimer's disease revisited. *Am J Public Health, 84*(8), 1261-1264.

Fan, J., Flombaum, J. I., McCandliss, B. D., Thomas, K. M., & Posner, M. I. (2003). Cognitive and brain consequences of conflict. *Neuroimage, 18*(1), 42-57.

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *Neuroimage, 26*(2), 471-479. doi: 10.1016/j.neuroimage.2005.02.004

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *J Cogn Neurosci, 14*(3), 340-347. doi: 10.1162/089892902317361886

Fernaeus, S. E., Ostberg, P., & Wahlund, L. O. (2013). Late reaction times identify MCI. *Scand J Psychol, 54*(4), 283-285. doi: 10.1111/sjop.12053

Fernandez-Duque, D., & Black, S. E. (2006). Attentional networks in normal aging and Alzheimer's disease. *Neuropsychology, 20*(2), 133-143. doi: 10.1037/0894-4105.20.2.133

Fernandez, P. J., Campoy, G., Garcia Santos, J. M., Antequera, M. M., Garcia-Sevilla, J., Castillo, A., . . . Fuentes, L. J. (2011). Is there a specific pattern of attention deficit in mild cognitive impairment with subcortical vascular features? Evidence from the Attention Network Test. *Dement Geriatr Cogn Disord, 31*(4), 268-275. doi: 10.1159/000327165

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., . . . Alzheimer's Disease, International. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet, 366*(9503), 2112-2117. doi: 10.1016/S0140-6736(05)67889-0

Fontbonne, A., Berr, C., Ducimetiere, P., & Alperovitch, A. (2001). Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study. *Diabetes Care, 24*(2), 366-370.

Frisoni, G. B., Galluzzi, S., Bresciani, L., Zanetti, O., & Geroldi, C. (2002). Mild cognitive impairment with subcortical vascular features: clinical characteristics and outcome. *J Neurol, 249*(10), 1423-1432. doi: 10.1007/s00415-002-0861-7

Fuentes, Luis J., Fernández, Pedro J., Campoy, Guillermo, Antequera, Martirio M., García-sevilla, Julia, & Antúnez, Carmen. (2010). Attention Network Functioning in Patients with Dementia with Lewy Bodies and Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 29*(2), 139-145.

Gallagher, M., & Koh, M. T. (2011). Episodic memory on the path to Alzheimer's disease. *Curr Opin Neurobiol, 21*(6), 929-934. doi: 10.1016/j.conb.2011.10.021

Gamboz, N., Zamarian, S., & Cavallero, C. (2010). Age-related differences in the attention network test (ANT). *Exp Aging Res, 36*(3), 287-305. doi: 10.1080/0361073X.2010.484729

Gorus, E., De Raedt, R., Lambert, M., Lemper, J. C., & Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. *J Geriatr Psychiatry Neurol, 21*(3), 204-218. doi: 10.1177/0891988708320973

Graham, K. S., Barense, M. D., & Lee, A. C. (2010). Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia, 48*(4), 831-853. doi: 10.1016/j.neuropsychologia.2010.01.001

Greenaway, M. C., Duncan, N. L., Hanna, S., & Smith, G. E. (2012). Predicting functional ability in mild cognitive impairment with the Dementia Rating Scale-2. *Int Psychogeriatr, 24*(6), 987-993. doi: 10.1017/S1041610211002717

Hanseeuw, B., & Ivanoiu, A. (2011). Performance on the RI-48 Cued Recall Test Best Predicts Conversion to Dementia at the 5- and 10-Year Follow-Ups. *Dement Geriatr Cogn Dis Extra, 1*(1), 258-266. doi: 10.1159/000330097

Hong, Y. J., Yoon, B., Lim, S. C., Shim, Y. S., Kim, J. Y., Ahn, K. J., . . . Yang, D. W. (2013). Microstructural changes in the hippocampus and posterior cingulate in mild cognitive impairment and Alzheimer's disease: a diffusion tensor imaging study. *Neurol Sci, 34*(7), 1215-1221. doi: 10.1007/s10072-012-1225-4

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *Br J Psychiatry, 140*, 566-572.

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., Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., . . . Kokmen, E. (2000). Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology, 55*(4), 484-489.

Jack, C. R., Jr., Shiung, M. M., Gunter, J. L., O'Brien, P. C., Weigand, S. D., Knopman, D. S., . . . Petersen, R. C. (2004). Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology, 62*(4), 591-600.

Jacobs, H. I., Leritz, E. C., Williams, V. J., Van Boxtel, M. P., van der Elst, W., Jolles, J., . . . Salat, D. H. (2013). Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. *Hum Brain Mapp, 34*(1), 77-95. doi: 10.1002/hbm.21412

Kantarci, K., & Jack, C. R., Jr. (2003). Neuroimaging in Alzheimer disease: an evidence-based review. *Neuroimaging Clin N Am, 13*(2), 197-209.

Kantarci, K., Senjem, M. L., Avula, R., Zhang, B., Samikoglu, A. R., Weigand, S. D., . . . Jack, C. R., Jr. (2011). Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology, 77*(1), 26-34. doi: 10.1212/WNL.0b013e31822313dc

Kaplan, E, Goodglass, H, & Weintraub, S. (1983). *Boston Naming Test*. Philadelphia: Lee & Febiger.

Kavcic, V., Ni, H., Zhu, T., Zhong, J., & Duffy, C. J. (2008). White matter integrity linked to functional impairments in aging and early Alzheimer's disease. *Alzheimers Dement, 4*(6), 381-389. doi: 10.1016/j.jalz.2008.07.001

King, J. A., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2002). Human hippocampus and viewpoint dependence in spatial memory. *Hippocampus, 12*(6), 811-820. doi: 10.1002/hipo.10070

Kinoshita, Y., Ohnishi, A., Kohshi, K., & Yokota, A. (1999). Apparent diffusion coefficient on rat brain and nerves intoxicated with methylmercury. *Environ Res, 80*(4), 348-354. doi: 10.1006/enrs.1998.3935

Kivisaari, S. L., Tyler, L. K., Monsch, A. U., & Taylor, K. I. (2012). Medial perirhinal cortex disambiguates confusable objects. *Brain, 135*(Pt 12), 3757-3769. doi: 10.1093/brain/aws277

Kumaran, D., Hassabis, D., Spiers, H. J., Vann, S. D., Vargha-Khadem, F., & Maguire, E. A. (2007). Impaired spatial and non-spatial configural learning in patients with hippocampal pathology. *Neuropsychologia, 45*(12), 2699-2711. doi: 10.1016/j.neuropsychologia.2007.04.007

Lanctot, K. L., Herrmann, N., Yau, K. K., Khan, L. R., Liu, B. A., LouLou, M. M., & Einarson, T. R. (2003). Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ, 169*(6), 557-564.

Larrieu, S., Letenneur, L., Orgogozo, J. M., Fabrigoule, C., Amieva, H., Le Carret, N., . . . Dartigues, J. F. (2002). Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology, 59*(10), 1594-1599.

Le Bihan, D. (2003). Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci, 4*(6), 469-480. doi: 10.1038/nrn1119

Lee, A. C., Levi, N., Davies, R. R., Hodges, J. R., & Graham, K. S. (2007). Differing profiles of face and scene discrimination deficits in semantic dementia and Alzheimer's disease. *Neuropsychologia, 45*(9), 2135-2146. doi: 10.1016/j.neuropsychologia.2007.01.010

Lee, A. C., Yeung, L. K., & Barense, M. D. (2012). The hippocampus and visual perception. *Front Hum Neurosci, 6*, 91. doi: 10.3389/fnhum.2012.00091

Lerch, J. P., Pruessner, J. C., Zijdenbos, A., Hampel, H., Teipel, S. J., & Evans, A. C. (2005). Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. *Cereb Cortex, 15*(7), 995-1001. doi: 10.1093/cercor/bhh200

Li, R., Wu, X., Fleisher, A. S., Reiman, E. M., Chen, K., & Yao, L. (2012). Attention-related networks in Alzheimer's disease: a resting functional MRI study. *Hum Brain Mapp, 33*(5), 1076-1088. doi: 10.1002/hbm.21269

Lindeboom, J, Schmand, B, Tulner, L, Walstra, G, & Jonker, C. (2002). Visual association test to detect early dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery & Psychiatry, 73*(2), 126-133. doi: 10.1136/jnnp.73.2.126

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G. B., & McDowell, I. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol, 156*(5), 445-453.

Liu, J., Yin, C., Xia, S., Jia, L., Guo, Y., Zhao, Z., . . . Jia, J. (2013). White matter changes in patients with amnestic mild cognitive impairment detected by diffusion tensor imaging. *PLoS One, 8*(3), e59440. doi: 10.1371/journal.pone.0059440

Mahoney, J. R., Verghese, J., Goldin, Y., Lipton, R., & Holtzer, R. (2010). Alerting, orienting, and executive attention in older adults. *J Int Neuropsychol Soc, 16*(5), 877-889. doi: 10.1017/S1355617710000767

Markesbery, W. R. (2010). Neuropathologic alterations in mild cognitive impairment: a review. *J Alzheimers Dis, 19*(1), 221-228. doi: 10.3233/JAD-2010-1220

Martella, D., Manzanares, S., Campoy, G., Roca, J., Antunez, C., & Fuentes, L. J. (2014). Phasic and tonic alerting in mild cognitive impairment: A preliminary study. *Exp Gerontol, 49*, 35-39. doi: 10.1016/j.exger.2013.11.001

Meyers, J, & Meyers, K. (1995). *The Meyers scoring system for the Rey Complex Figure and the Recognition Trial:Professional Manual*. Odessa, Florida: Psychological Assessment Resources.

Miller, S. L., Fenstermacher, E., Bates, J., Blacker, D., Sperling, R. A., & Dickerson, B. C. (2008). Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. *J Neurol Neurosurg Psychiatry, 79*(6), 630-635. doi: 10.1136/jnnp.2007.124149

Misra, C., Fan, Y., & Davatzikos, C. (2009). Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage, 44*(4), 1415-1422. doi: 10.1016/j.neuroimage.2008.10.031

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol, 58*(3), 397-405.

Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: complementary findings from amnesia and FMRI. *J Neurosci, 33*(25), 10490-10502. doi: 10.1523/JNEUROSCI.2958-12.2013

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53*(4), 695-699. doi: 10.1111/j.1532-5415.2005.53221.x

Newsome, R. N., Duarte, A., & Barense, M. D. (2012). Reducing perceptual interference improves visual discrimination in mild cognitive impairment: implications for a model of perirhinal cortex function. *Hippocampus, 22*(10), 1990-1999. doi: 10.1002/hipo.22071

Niogi, S., Mukherjee, P., Ghajar, J., & McCandliss, B. D. (2010). Individual Differences in Distinct Components of Attention are Linked to Anatomical Variations in Distinct White Matter Tracts. *Front Neuroanat, 4*, 2. doi: 10.3389/neuro.05.002.2010

Pearson. (2009). *Advanced Clinical Solutions for the WAIS-IV/WMS-IV.* San Antonio, TX: Pearson.

Pennanen, C., Kivipelto, M., Tuomainen, S., Hartikainen, P., Hanninen, T., Laakso, M. P., . . . Soininen, H. (2004). Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging, 25*(3), 303-310. doi: 10.1016/S0197-4580(03)00084-8

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain, 122 (Pt 3)*, 383-404.

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia, 38*(3), 252-271.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J Intern Med, 256*(3), 183-194. doi: 10.1111/j.1365-2796.2004.01388.x

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.

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annu Rev Neurosci, 35*, 73-89. doi: 10.1146/annurev-neuro-062111-150525

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

Piatt, A. L., Fields, J. A., Paolo, A. M., & Troster, A. I. (2004). Action verbal fluency normative data for the elderly. *Brain Lang, 89*(3), 580-583. doi: 10.1016/j.bandl.2004.02.003

Posner, M. I. (1980). Orienting of attention. *Q J Exp Psychol, 32*(1), 3-25.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annu Rev Neurosci, 13*, 25-42. doi: 10.1146/annurev.ne.13.030190.000325

Provenzano, F. A., Muraskin, J., Tosto, G., Narkhede, A., Wasserman, B. T., Griffith, E. Y., . . . Alzheimer's Disease Neuroimaging, Initiative. (2013). White matter hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease? *JAMA Neurol, 70*(4), 455-461. doi: 10.1001/jamaneurol.2013.1321

Rainville, C., Lepage, E., Gauthier, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task. *J Clin Exp Neuropsychol, 34*(3), 306-324. doi: 10.1080/13803395.2011.639298

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., . . . Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex, 15*(11), 1676-1689. doi: 10.1093/cercor/bhi044

Reed, J. M., & Squire, L. R. (1999). Impaired transverse patterning in human amnesia is a special case of impaired memory for two-choice discrimination tasks. *Behav Neurosci, 113*(1), 3-9.

Roesch-Ely, D., Scheffel, H., Weiland, S., Schwaninger, M., Hundemer, H. P., Kolter, T., & Weisbrod, M. (2005). Differential dopaminergic modulation of executive control in healthy subjects. *Psychopharmacology (Berl), 178*(4), 420-430. doi: 10.1007/s00213-004-2027-z

Romberg, C., Bussey, T. J., & Saksida, L. M. (2013). Paying more attention to attention: towards more comprehensive cognitive translation using mouse models of Alzheimer's disease. *Brain Res Bull, 92*, 49-55. doi: 10.1016/j.brainresbull.2012.02.007

Rose, S. E., Janke, A. L., & Chalk, J. B. (2008). Gray and white matter changes in Alzheimer's disease: a diffusion tensor imaging study. *J Magn Reson Imaging, 27*(1), 20-26. doi: 10.1002/jmri.21231

Rose, S. E., McMahon, K. L., Janke, A. L., O'Dowd, B., de Zubicaray, G., Strudwick, M. W., & Chalk, J. B. (2006). Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment. *J Neurol Neurosurg Psychiatry, 77*(10), 1122-1128. doi: 10.1136/jnnp.2005.074336

Saksida, L. M., & Bussey, T. J. (2010). The representational-hierarchical view of amnesia: translation from animal to human. *Neuropsychologia, 48*(8), 2370-2384. doi: 10.1016/j.neuropsychologia.2010.02.026

Salat, D. H., Greve, D. N., Pacheco, J. L., Quinn, B. T., Helmer, K. G., Buckner, R. L., & Fischl, B. (2009). Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage, 44*(4), 1247-1258. doi: 10.1016/j.neuroimage.2008.10.030

Salat, D. H., Tuch, D. S., van der Kouwe, A. J., Greve, D. N., Pappu, V., Lee, S. Y., . . . Rosas, H. D. (2010). White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiol Aging, 31*(2), 244-256. doi: 10.1016/j.neurobiolaging.2008.03.013

Sanderson, D. J., Pearce, J. M., Kyd, R. J., & Aggleton, J. P. (2006). The importance of the rat hippocampus for learning the structure of visual arrays. *Eur J Neurosci, 24*(6), 1781-1788. doi: 10.1111/j.1460-9568.2006.05035.x

Sano, M., Raman, R., Emond, J., Thomas, R. G., Petersen, R., Schneider, L. S., & Aisen, P. S. (2011). Adding delayed recall to the Alzheimer Disease Assessment Scale is useful in studies of mild cognitive impairment but not Alzheimer disease. *Alzheimer Dis Assoc Disord, 25*(2), 122-127. doi: 10.1097/WAD.0b013e3181f883b7

Sarter, M., Bruno, J. P., & Givens, B. (2003). Attentional functions of cortical cholinergic inputs: what does it mean for learning and memory? *Neurobiol Learn Mem, 80*(3), 245-256.

Schneider, J. A., Arvanitakis, Z., Leurgans, S. E., & Bennett, D. A. (2009). The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol, 66*(2), 200-208. doi: 10.1002/ana.21706

Schuff, N., Woerner, N., Boreta, L., Kornfield, T., Shaw, L. M., Trojanowski, J. Q., . . . Alzheimer's Disease Neuroimaging, Initiative. (2009). MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain, 132*(Pt 4), 1067-1077. doi: 10.1093/brain/awp007

Sheridan, P. L., & Hausdorff, J. M. (2007). The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. *Dement Geriatr Cogn Disord, 24*(2), 125-137. doi: 10.1159/000105126

Silveri, M. C., Reali, G., Jenner, C., & Puopolo, M. (2007). Attention and memory in the preclinical stage of dementia. *J Geriatr Psychiatry Neurol, 20*(2), 67-75. doi: 10.1177/0891988706297469

Singh, B., & O'Brien, J. T. (2009). When should drug treatment be started for people with dementia? *Maturitas, 62*(3), 230-234. doi: 10.1016/j.maturitas.2008.12.022

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505. doi: 10.1016/j.neuroimage.2006.02.024

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage, 44*(1), 83-98. doi: 10.1016/j.neuroimage.2008.03.061

Snitz, B. E., Unverzagt, F. W., Chang, C. C., Bilt, J. V., Gao, S., Saxton, J., . . . Ganguli, M. (2009). Effects of age, gender, education and race on two tests of language ability in community-based older adults. *Int Psychogeriatr, 21*(6), 1051-1062. doi: 10.1017/S1041610209990214

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage, 26*(1), 132-140. doi: 10.1016/j.neuroimage.2005.01.028

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annu Rev Neurosci, 27*, 279-306. doi: 10.1146/annurev.neuro.27.070203.144130

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annu Rev Neurosci, 34*, 259-288. doi: 10.1146/annurev-neuro-061010-113720

Stebbins, G. T., & Murphy, C. M. (2009). Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. *Behav Neurol, 21*(1), 39-49. doi: 10.3233/BEN-2009-0234

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. doi: 10.1016/j.neuropsychologia.2009.03.004

Stokholm, J., Vogel, A., Gade, A., & Waldemar, G. (2006). Heterogeneity in executive impairment in patients with very mild Alzheimer's disease. *Dement Geriatr Cogn Disord, 22*(1), 54-59. doi: 10.1159/000093262

Teng, E., Lu, P. H., & Cummings, J. L. (2007). Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord, 24*(4), 253-259. doi: 10.1159/000107100

Tierney, M. C., Szalai, J. P., Snow, W. G., Fisher, R. H., Nores, A., Nadon, G., . . . St George-Hyslop, P. H. (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology, 46*(3), 661-665.

Wang, J. H., Lv, P. Y., Wang, H. B., Li, Z. L., Li, N., Sun, Z. Y., . . . Huang, Y. (2013). Diffusion tensor imaging measures of normal appearing white matter in patients who are aging, or have amnestic mild cognitive impairment, or Alzheimer's disease. *J Clin Neurosci, 20*(8), 1089-1094. doi: 10.1016/j.jocn.2012.09.025

Wang, Y., West, J. D., Flashman, L. A., Wishart, H. A., Santulli, R. B., Rabin, L. A., . . . Saykin, A. J. (2012). Selective changes in white matter integrity in MCI and older adults with cognitive complaints. *Biochim Biophys Acta, 1822*(3), 423-430. doi: 10.1016/j.bbadis.2011.08.002

Warrington, E. K., & James, M. (1991). A new test of object decision: 2D silhouettes featuring a minimal view. *Cortex, 27*(3), 370-383.

Wechsler, D. (2008a). *Wechsler Adult Intelligence Scale-Fourth Edition* (4th ed.). San Antonio, Texas: Pearson.

Wechsler, D. (2008b). *Wechsler Adult Intelligence Scale-Fouth Edition: Technical and interpretive manual* (4th ed.). San Antonio, Texas: Pearson.

Weston, A. L., Weinstein, A. M., Barton, C., & Yaffe, K. (2010). Potentially inappropriate medication use in older adults with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci, 65*(3), 318-321. doi: 10.1093/gerona/glp158

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

Ylikoski, R., Ylikoski, A., Erkinjuntti, T., Sulkava, R., Raininko, R., & Tilvis, R. (1993). White matter changes in healthy elderly persons correlate with attention and speed of mental processing. *Arch Neurol, 50*(8), 818-824.

Yoon, B., Shim, Y. S., Kim, Y. D., Lee, K. O., Na, S. J., Hong, Y. J., . . . Yang, D. W. (2013). Correlation between instrumental activities of daily living and white matter hyperintensities in amnestic mild cognitive impairment: results of a cross-sectional study. *Neurol Sci, 34*(5), 715-721. doi: 10.1007/s10072-012-1120-z

Zhang, B., Xu, Y., Zhu, B., & Kantarci, K. (2014). The role of diffusion tensor imaging in detecting microstructural changes in prodromal Alzheimer's disease. *CNS Neurosci Ther, 20*(1), 3-9. doi: 10.1111/cns.12166

Zhou, Y., Dougherty, J. H., Jr., Hubner, K. F., Bai, B., Cannon, R. L., & Hutson, R. K. (2008). Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimers Dement, 4*(4), 265-270. doi: 10.1016/j.jalz.2008.04.006

Zhuang, L., Wen, W., Zhu, W., Trollor, J., Kochan, N., Crawford, J., . . . Sachdev, P. (2010). White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. *Neuroimage, 53*(1), 16-25. doi: 10.1016/j.neuroimage.2010.05.068