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Autobiographical Memory and the Default Mode Network in Mild Cognitive Impairment

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ABBREVIATIONS

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
aMCI	amnesic mild cognitive impairment
AMI	autobiographical memory interview
BVMT	brief visual memory test
CDR	clinical dementia rating scale
CVLT	California verbal learning test
DMN	default mode network
DRS	dementia rating scale
FOV	field of vision
GOF	goodness of fit
ICA	independent component analysis
IPC	inferior parietal cortex
ITC	inferior temporal cortex
JLO	judgement of line orientation
LST	Lesion segmentation toolbox
MCI	mild cognitive impairment
MMSE	mini mental state exam
MoCA	Montreal cognitive assessment
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
MTL	medial temporal lobe
nMCI	non-amnesic mild cognitive impairment
NP1	neuropsychological inventory 1
NP2	neuropsychological inventory 2
PCC	posterior cingulate cortex
SDMT	symbol digit modality test
SPM	statistic parametric mapping
TOPF	test of premorbid functioning
VAT	visual association test
VSOP	visual object and space perception
WML	white matter lesion

Individuals with mild cognitive impairment (MCI) show variable impairment in autobiographical memory function, source memory function and reduced integrity in the brain's default mode network (DMN). There is overlap between the DMN, such as the medial posterior cortical hub, and brain regions that are active when participants recall autobiographical memories. To assess the association between autobiographical memory and the DMN, 14 MCI and eleven age and education-matched healthy control participants were assessed using the autobiographical memory interview (AMI) and underwent resting state *f*MRI scans. The same participants underwent a test of source memory which assessed both recognition and source memory. The MCI group showed significantly increased semantic as well episodic memory impairments using the AMI, evident across the lifespan for episodic memory but not for childhood semantic memory. Significantly poorer DMN connectivity, using a goodness of fit index (GOF) of the DMN template, was evident in the MCI group. MCI participants showed poorer performance on both recognition and source memory relative to HC participants. A modest association between AMI semantic memory (r=0.4) scores, but not episodic memory scores (r=0.09), and DMN connectivity was found in these participants. For future study the predictive value of MR imaging in the DMN of MCI participants should be explored.

Chapter 1. Introduction

1.1 Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a neurodegenerative disorder marked by a decline in cognitive ability below that expected of someone of a similar age and is thought to be an intermediate stage between normal aging and dementia (Ritchie, 2004). Recent work subdivides MCI into two types, amnesic MCI (aMCI) and non-amnesic MCI (nMCI). Amnesic MCI affects memory whereas a less common non-amnesic MCI (nMCI) affects any non-memory area of cognitive functioning (Petersen, 2004). These MCI types are each subdivided into single domain and multiple domain MCI (Gauthier et al., 2006), in terms of whether one domain or multiple domains of cognitive function show impairments. A variety of diagnostic criteria have been used when assessing individuals for MCI. The most commonly used diagnostic criteria, however, are those derived from Petersen (2004). Petersen's criteria are geared toward detecting aMCI as a prodromal condition for Alzheimer's disease (AD) where the individual must show a subjective memory complaint, abnormal memory functioning for their age group, be relatively unimpaired in other areas of cognition and not have significant impairment in activities of daily living so that they do not meet criteria for dementia.

Worldwide prevalence rates of MCI vary, ranging from 3.1% to 35% (Ritchie, 2004; Seeher, Low, Reppermund, & Brodaty, 2013). This range of prevalence is likely because of differing terminology and therefore diagnostic criteria between studies. Individuals with MCI convert to dementia at an annual rate of between 6 and 25%, which is up to 5 times greater than the normally aging population who have an annual conversion rate of between 0.5% and 4% (Jin, Pelak, & Cordes, 2012a; Knopman, Boeve, & Petersen, 2003). MCI can, however, stay stable and not progress to dementia or can revert back so that individuals affected by MCI return to

normal functioning (Buckner, Andrews-Hanna, & Schacter, 2008). Due to this ambiguity of prognosis for MCI, opportunities exist to assess which factors contribute to the stabilizing and reversal of symptoms. As a consequence, detailed neuropsychological testing beyond an initial screen, as well as measures of one of more biomarker, is desirable to capture individuals who are highly likely to progress (Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011).

1.2 Autobiographical Memory in MCI

There are two components of autobiographical memory, episodic memory and semantic memory. Episodic memory requires mentally projecting back in time to reconstruct details about personal events. This remembering is often accompanied with a feeling of re-experiencing emotions (Spreng & Grady, 2010). Semantic memory, by contrast, is the recall of factual information devoid of unique personal experiences. This disconnection between episodic and semantic memory (Svoboda, McKinnon, & Levine, 2006) allows both components of autobiographical memory to be assessed separately. Episodic autobiographical memory is regarded as the first type of memory to become impaired in people with MCI. Typically memory for the source of this information becomes impaired, which includes dates and times of the personal events experienced. Semantic memory is thought to stay relatively unimpaired in MCI, at least until the later stages and progression to dementia.

There have been very few studies investigating the status of autobiographical memory in MCI and these studies have reported inconsistent results. Healthy controls have been found to recall significantly more details when episodic memory retrieval is tested compared to aMCI participants (Murphy, Troyer, Levine, & Moscovitch, 2008). aMCI participants performed significantly better at episodic memory recall than participants with AD (Leyhe, Muller, Milian,

Eschweiler, & Saur, 2009), highlighting MCI as an intermediate stage between normal aging and dementia.

When examining semantic memories healthy control participants and aMCI participants were both significantly better than AD participants at recalling details, but there was no significant difference between the performance of healthy controls and aMCI (Murphy et al., 2008). This result shows a relative sparing of semantic memory in aMCI. In one study, aMCI participants actually recalled more semantic details than healthy controls (Gamboz et al., 2010), which could indicate a compensatory mechanism for the loss of episodic memory. Contrary to this finding, Tramoni et al (2012) found MCI participants recalled fewer semantic details than healthy controls, although the pattern of details recalled across time was similar in both groups; recall for recent semantic details was better for recent time than for childhood or early adulthood.

Recall of recent episodic events was also poorer for aMCI participants than that for events in childhood and early adulthood (Irish, Lawlor, O'Mara, & Coen, 2010; Leyhe et al., 2009). This is the same pattern found in dementia, where recent memory shows the greatest deficits (Leyhe et al., 2009). A greater deficit of episodic memory recall in middle adulthood has been found in MCI (Irish et al., 2010). This is contrary to the normally aging population where an increase in detail has been found (Janssen, Chessa, & Murre, 2005).

The differences found in level of recall of semantic and episodic memory might be attributed to the particular autobiographical memory test used. A range of different tests are used to assess autobiographical memory that may influence the pattern of results. With the autobiographical memory interview (AMI) (Kopelman, Wilson, & Baddeley, 1989), recall of semantic details appears to be poorer in aMCI individuals (Leyhe et al., 2009; Tramoni et al.,

2012). The AMI requires participants to recall episodic and semantic memories separately, in comparison other studies that required participants to recall a memory and assessment of the semantic and episodic components was later done when scoring (Kopelman et al., 1989; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Piolino, Desgranges, & Eustache, 2000). The scoring for the AMI is, therefore, more objective and consistent for comparison across individuals and groups.

1.2.1 Neural Correlates of Autobiographical Memory

Reviews of *f*MRI activation patterns in autobiographical memory have reported that prefrontal cortex, medial temporal lobes, temporal cortex, temporoparietal junction, retrosplenial/posterior cingulate cortex and cerebellum were consistent areas of activation across studies (Milton, Butler, Benattayallah, & Zeman, 2012; Svoboda et al., 2006). It is thought that prefrontal involvement is necessary for the conscious re-experience of episodic memory (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). The activation in the prefrontal lobe is predominantly left-lateralized in the ventrolateral prefrontal region, and is associated with strategic retrieval and verification (Fletcher & Henson, 2001). The medial temporal lobe (MTL) includes the hippocampus, parahippocampus, perirhinal and entorhinal cortex. The MTL shows the most consistent activation across studies of autobiographical memory, with the hippocampus showing activation in the majority of studies (Svoboda et al., 2006). As is well known the MTL are affected early in AD and damage to the MTL is associated with memory deficits (Clark & Squire, 2010), therefore it is expected there may be some deficit in autobiographical memory functioning in MCI.

1.3 Source Memory

Source memory is the ability to recall when and where information was learnt or an event experienced. Deciding what the source of a given memory can be unconscious and made without any intentional thought. When this process is made with intentional thought it becomes more strategic. Inferences can be made about the source of the memory based on other information, because of this the source can be misattributed (Johnson, Hashtroudi, & Lindsay, 1993). For source memory to be accurately and successfully recalled the quality of an individual memory must be of a higher quality than one where the source is not recalled accurately.

Source memory can be divided into three different types. The first is reality, where there is differentiation between self-generated and other-generated sources. The second is external, where there is differentiation between two separate external sources. The third is internal, where the differentiation is between two separate self-generated sources (El Haj, Fasotti, & Allain, 2012). The most commonly tested source memory is external, where individuals are presented with external stimuli and at a later point in time are asked what the source of those stimuli was.

Evidence from studies examining AD patients has shown both recognition memory and external source memory to be impaired, which is found when the stimulus presented is visually as pictures or printed words and verbally as different voices reading sentences aloud (Dalla Barba, Nedjam, & Dubois, 1999; Dodson et al., 2011). In addition Dodson et al. (2011) also measured participants' confidence of both their recognition and source judgements and found that participants with AD lacked awareness of the accuracy of their decisions. A comparison group of healthy controls showed more confidence in accurate decisions than incorrect responses.

While still impaired, internal source memory tends to be less impaired than external source memory in AD (El Haj et al., 2012). This implies that AD participants will be more impaired on tests of source memory than tests of autobiographical memory which examines internal source memory as opposed to external source memory.

Although no studies have directly investigated source memory in MCI, evidence shows when recalling an autobiographical memory, individuals with MCI have an impairment recalling the dates and places of events (or internal source memory) (Kopelman, Wilson, & Baddeley, 1990). Therefore it is possible to infer that within the MCI population source memory will be poorer than for normally aging individuals. Confidence in accuracy of recognition and source decisions should also show a deficit.

1.4 Default Mode Network

As explained below, one potentially important neural system in this regard is the default mode network (DMN). The default mode network is a network in the brain that shows high resting state activity when an individual is not engaged in any specific cognitive task (Wu et al., 2011). Activities such as future thinking, past remembering, mental imagery and mind wandering are all associated with the DMN (Buckner et al., 2008; Kim, 2012). The DMN is the primary network associated with spontaneous cognition, as seen in the strong correlation between stimulus independent thought and DMN activity (Buckner et al., 2008).

1.4.1 Anatomy of the default mode network

The key nodes in the default mode network of the brain include the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), inferior parietal cortex (IPC), inferior temporal cortex (ITC) and, in some descriptions, the hippocampal formation (Buckner et al., 2008; Wu et al.,

2011). In individuals with MCI a reduction of grey matter volume is seen bilaterally in the medial temporal cortex, hippocampus, thalamus, insular cortex and in parts of the inferior parietal lobe (Sorg et al., 2007).

1.4.2 The Default Mode Network in Mild Cognitive Impairment

A range of differences are found in the DMN in people with mild cognitive impairment, which include reduced activity, changes in connectivity between different areas (Wu et al., 2011) and reduced white and grey matter (Sorg et al., 2007). There is a progressive deterioration when comparing the DMN of healthy aging, aMCI and demented participants (Hafkemeijer, van der Grond, & Rombouts, 2012). Healthy aging individuals have more activation of the DMN than MCI and demented participants and MCI have more activation of the DMN than demented participants. This appears to mirror the cognitive deterioration during the progression towards dementia and again highlights MCI as an intermediate stage between normal aging and dementia.

1.4.2.1 Reduced Activity

In individuals with MCI, reduced activity is found in the PCC, medial prefrontal cortex (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005), superior parietal lobe and the right prefrontal cortex (Sorg et al., 2007). The reduced activity and profusion abnormalities in the posterior cingulate cortex even before the onset of dementia may be related to impairment in episodic memory (Wu et al., 2011). One study, however, reported an increase in activity is also found in the superior left frontal gyrus, dorsal medial prefrontal cortex, left parietal lobe and medial temporal gyrus, which suggests a possible compensation for the decreased activity in the areas of the default mode network in some aMCI patients (Qi et al., 2010). The integrity of the

DMN can be viewed on a continuum with healthy aging individuals showing the most integrity, MCI participants showing lower integrity and AD participants showing the lowest integrity, moreover, MCI participants showing lower integrity in the DMN were found to be more likely to convert to AD (Petrella et al., 2011).

1.4.2.2 Disrupted Functional Connectivity

Studies with MCI participants have shown decreased connectivity between the hippocampus and the prefrontal cortex and a change in connection direction between the right and left hippocampus and the right and left IPC (Wu et al., 2011). This evidence suggests a reorganisation between the prefrontal cortex and the posterior cingulate cortex in the DMN in MCI.

The posterior cingulate cortex is a crucial node in the default mode network. Studies have shown a disruption between the connection of the PCC and the temporal lobe in MCI participants (Wang et al., 2012). A positive association has also been found between scores on the Mini Mental State Exam (MMSE) and functional connectivity in between precuneus and the posterior cingulate cortex in MCI participants (Wang et al., 2012). That is, higher MMSE scores are indicative of stronger functional connectivity between the precuneus and PCC.

1.5 The Neural Overlap between the DMN and Autobiographical Memory

There is overlap between crucial nodes of the DMN and the neural correlates of autobiographic memory. As discussed above the MTL is essential for memory and is an important component in both autobiographical memory and the DMN, the decrease of activity in the MTL is therefore associated with the loss of memory functioning in AD and MCI. The PCC is another major node

in the DMN (Buckner et al., 2008) and is also implicated in autobiographical memory (Milton et al., 2012).

1.6 The Current Study

The current study examined both autobiographical and source memory in individuals with MCI and in healthy controls (HC). The AMI was used to more objectively assess semantic and episodic components of autobiographical memory. It was expected individuals with MCI would show deficits in both autobiographical and source memory. It was also expected there would be a positive correlation between scores on the AMI and source memory tests. The neural correlates of autobiographical memory within the default mode network were examined using resting state *f*MRI in a 3 T scanner at the New Zealand Brain Research Institute. It was expected that there would be a decrease in the integrity of the DMN in participants with MCI relative to HC participants and the integrity of this system would be associated with episodic autobiographical memory scores.

Chapter 2. Method

2.1 Participants

Previous research has experienced difficulty finding MCI participants. Here, a screening study first assessed 609 older volunteers on various cognitive measures (figure 1). Two hundred and twenty one participants were excluded due to medications, medical disorders and very old age. Participants were then divided into 10 different groups, ranging from "MCI-6" (likely to have MCI) to "HC-1" (likely to be aging normally) based on scores on the initial screening neuropsychological tests. Those classified MCI-3, MCI-4, MCI-5, MCI-6 were deemed likely to be possible MCI while HC-1 and HC-2 were deemed likely to be

healthy controls (see table 1 for specific criteria). Eighty six potential MCI participants were then contacted, 47 participants of whom were not suitable, leaving 39 that were assessed, of the latter, 14 participants met the criteria for MCI (see figure 1). Twenty healthy controls (HC) were contacted who were matched to these MCI participants, based on age, gender and education (see table 2 for summary of participants), and assessed on the same neuropsychological tests as the MCI participants. Eleven of these HC met the study criteria and were included (Fig 1).

Table 1

Groups and Criteria of Participants after Initial Screening

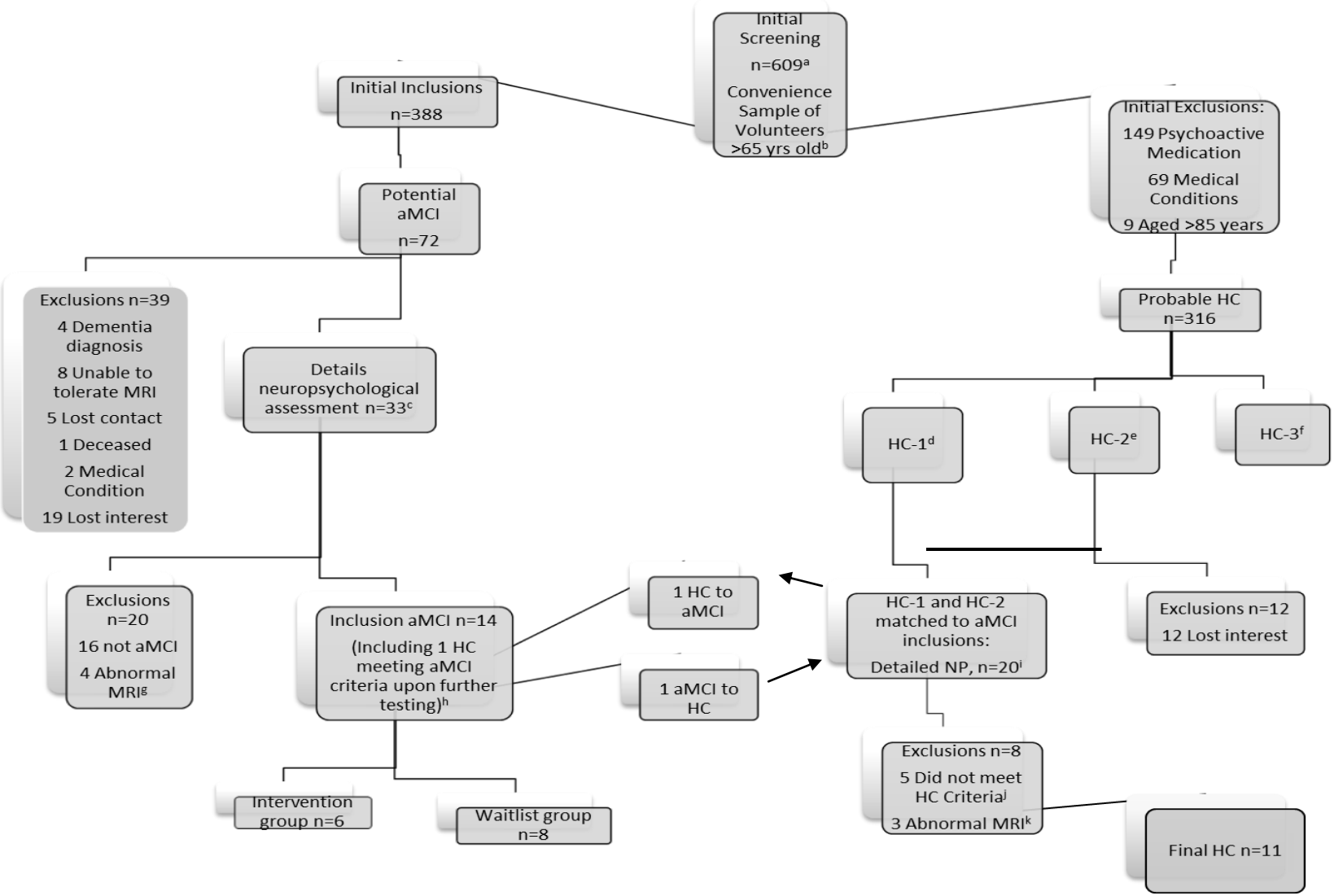
Group	Criteria
HC-1	MoCA >25 All neuropsychological* scores >-0.7
HC-2	MoCA >25 Some neuropsychological* scores <-0.7
HC-3a	MoCA <26 All neuropsychological* scores >-0.7
HC-3b	MoCA <26 One neuropsychological* score <-0.7
HC-3c	MoCA >25 One neuropsychological* score <-1.3
HC-3d	MoCA <26 Two neuropsychological* scores <-0.7
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

* For details on specific neuropsychological tests administered see materials

Inclusion criteria for participants in the final MCI group were objective memory loss measured by neuropsychological test scores at -1.5 SD below the age and education adjusted norms. Where Z scores were unavailable (for example the Rivermead story recall test), a profile score of 1 (borderline) or a score of <19 on delayed recall IR31 (Selective Reminding Test) were used as inclusion criteria. These participants also were required to have (a) one global score from <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 ADAS-cog; (b) a subjective memory complaint by the participant or an informant; (c) deterioration of cognitive scores obtained from a previous

screening test; a score of 0 or 0.5 on the Clinical dementia rating scale (CDR) and essentially preserved activities of daily living to exclude dementia.

Fig 1. Process of Participant Selection



a Using MoCA, Rey Complex Copy, Rey Complex 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 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. Confirmatory tests (NP2) included ADAS-Cog, Rivermead story recall, design fluency, visual association test (VAT) and RI-48 selective reminding test (see method for further detail).

d HC-1, MoCA > 25 and all NP test scores > -0.7 (25^{th} percentile).

e HC-2, MoCA > 25 and all NP test scores >-1.3 but one score < -0.7

f HC-3, MoCA < 26 but no NP test scores < -1.3 or MoCA > 25 but one NP test score < -1.3.

g Three had evidence of vascular disease; one had a non-vascular cyst.

h Final aMCI criteria: (1) Objective memory impairment on two or more memory tests, using either > -1.5SD (7^{th} percentile) below standardised age-corrected normative data or a profile score of 1 on Rivermead Story Recall (immediate or delayed counted once) or a recall score < 19 on the Adams Selective Reminding Test (delayed recall); (2) at least one impaired one global mental status score from MoCA (<26), DRS-2 (scaled score of <9) and ADAS-Cog (>9); (3) subjective memory complaints by participant or informant on the Clinical Dementia Rating scale; and (4) exclusion of dementia based on CDR < 1.0 plus essentially preserved activities of daily living judged by significant other and / or the researcher interview. Stratified random allocation to intervention or waitlist was based on memory scores, age, plus availability for the initial phase of enrichment.

i HC selected from HC-1 and HC-2 who matched the final aMCI for age, sex and education

j Final HC criteria, MoCA >25, no memory score >-1.5 in sessions 1 and 2 of detailed NP testing, but any single score at -1.5SD on any other test permitted (n = 14 for latter).

k One had a non-vascular cyst; One had evidence of atrophy in the precuneus;

aMCI = amnesic mild cognitive impairment; HC = healthy control; MoCA = Montreal Cognitive Test; D-KEFS = Delis and Kaplan Executive Function System; ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subtest.

Table 2

Age, Education and Gender of Participants

	MCI participants (n=14)		Healthy Controls (n=14)		*t*
	Mean	SD	Mean	SD	
Male:Female	8:6		7:7		
Age	75	4.34	75.93	3.38	0.64
Years of Education	13.27	2.84	12.93	2.46	-0.34

2.2 Standard Neuropsychological Tests

Before participants completed the AMI they underwent a battery of neuropsychological tests to assess their cognitive status. As outlined below the battery included tests for global functioning, tests of learning and memory, executive functioning, attention (including processing speed and working memory), visuospatial functioning, and language function. Several different tests were administered for each domain (see fig 1). The tests were administered by a trained member of the project team in a quiet room at the New Zealand Brain Research Institute (NZBRI).

2.2.1.1 Global Functioning

The Montreal cognitive assessment (MoCA) (Nasreddine et al., 2005), the 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) were also administered.

2.2.1.2 Learning and Memory

Learning and memory was examined using the short form of the California verbal learning test (CVLT) (Delis, Kramer, Kaplan, & Ober, 2000), Brief visual memory test (BVMT) (Benedict, 1988), Rey-Osterrieth complex figure (Meyers & Meyers, 1995), Rivermead story recall (Baek et al., 2011), RI-48 selective reminding test (Hanseeuw & Ivanoiu, 2011), and the visual association test (VAT).

2.2.1.3 Executive Function

To assess executive function participants completed Trails B , D-KEFS letter fluency test, category fluency, fluency switching, action fluency (Piatt, Fields, Paolo, & Troster, 2004), colour word interference (Delis, Kaplan, & Kramer, 2001) and the D-KEFS design fluency (switching).

2.2.1.4 Attention, Processing Speed and Working Memory

This domain included Trails A, Symbol Digit Modality Test (written and oral versions), Delis-Kaplan stroop task (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 functioning was tested using matrix reasoning, the Rey-Osterrieth complex figure copy (Meyers & Meyers, 1995), the visual object and space perception (VSOP) silhouettes only (Warrington & James, 1991), judgement of line orientation (JLO) (Benton, Hannay, & Varney,

1975), pentagons and the copy section of the Brief visuospatial memory test (BVMT)(Benedict, 1988).

2.2.1.6 Language

Language was assessed using the Boston naming test (Kaplan, Goodglass, & Weintraub, 1983) and the token test (Snitz et al., 2009).

2.2.2 Autobiographical Memory Interview (AMI)

Participants were tested using the AMI (Kopelman et al., 1989) after assessment at baseline just prior to the intended enrichment programme (not part of this master's thesis). The AMI requires participants to recall semantic details and autobiographical incidents from three different periods of time (childhood, early adult life and recent life).Each period is divided into three sub categories of events that are common to the time period. For example the 'childhood' period is divided into three categories: before school begins, primary school and secondary school'.

Each (sub) section begins with semantic questioning, participants are asked questions such as the name of the first school the participant attended, dates of children's birthdays and where the previous Christmas was spent. Each section contains a question asking for three names of people present during the period of time, for example names of friends or teachers during secondary school. Prompts, such as 'your form teacher?' were provided if the participant is unable to answer.

Participants were then asked to provide a specific, detailed autobiographical memory related to the particular time frame. Prompts such as 'Involving a teacher?' were given if the participant could not think of a specific incident.

2.2.3 Source Memory

Source memory was tested using a procedure adapted from (Dodson et al., 2011). During an encoding phase participants were presented with 30 random trivia sentences both visually (on a computer screen) and verbally (through speakers) spoken by a male voice or a female voice. Participants were instructed to pay careful attention to the statement and the voice reading it. Immediately following the encoding phase participants were tested with 60 sentences, the 30 from the encoding phase and 30 new distractor sentences. After each presentation participants were given a forced choice recognition new or old. If old was selected, participants were asked if a male voice or a female voice read the sentence; if new was selected, the next sentence was presented. After each old/new and male/female decision participants were asked to rate their confidence level of a scale from 1 to 5, participants were instructed to make full use of the scale. Five different versions, each with different statements but the same male and female voices, were created to remove any potential bias created by statements.

2.3 Procedure

This study was approved by the Upper South A Ethics Committee of the New Zealand Ministry of Health and informed consent was obtained from participants prior to the screening session.

2.3.1 Neuropsychological Tests

In order to further determine participants' cognitive status neuropsychological tests were administered over two standardised 3 hour test sessions, neuropsychological inventory 1 (NP1) and neuropsychological inventory 2 (NP2), both session contained a variety of tests from each of the above domains and verbal tests were varied with non- verbal tests in each session.

Contamination of the memory tests was taken into consideration when the order of test administration was decided. NP1 and NP2 were held prior to a baseline testing session that included addition neuropsychological tests. The testing and data collection were performed by three of the group's investigators.

2.3.2 Autobiographical and Source Memory

The autobiographical memory interview (AMI) was administered in each participants' home. Answers were recorded as close to verbatim as possible and with the permission of each participant interviews were recorded using a Zoom H4N voice recorder. Each interview lasted approximately 30 minutes.

The test of source memory was assessed twice, once during NP 2 in a quiet room at the New Zealand Brain Research Institute and once in participant's homes during baseline testing. Participants were randomly assigned one version of the test for NP2 and one of four different versions of the test (containing different statements) for baseline assessment. Each source memory assessment took approximately 20 minutes to complete.

2.3.3 Imaging

Participants had an MRI after NP2 and prior to baseline at the NZBRI. Anatomic (T1- and T2-weighted), functional resting state, and field map images were acquired on a 3 tesla General Electric HDx scanner with an eight channel head coil. Structural MR images included a T1-weighted, three-dimensional spoiled gradient echo recalled (SPGR) acquisition (TE/TR=2.8/6.6 ms, TI=400 ms, flip angle=15^0, acquisition matrix=256×256×170, FOV=250 mm, slice thickness=1 mm, voxel size=0.98×0.98×1.0 mm^3) and a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence for classification of white matter hyperintensities (TE/TR/TI =

105/9000/2250 ms, 3 mm slices with 1.5 mm gap, 33 slices, FOV = 220 mm, acquisition matrix = 320 × 320). Resting state functional images were acquired using a two-dimensional gradient echo, echo planar imaging (EPI) sequence (TE/TR=35/3000ms, flip angle 90^0, acquisition matrix=64×64×44, FOV=220mm, slice thickness=3mm, number of slices=44, space between slices=0mm, voxel size=3.4×3.4×3mm^3, interleaved, bottom-top, planned 20^0 above the anterior commissure-posterior commissure line). A field map was acquired using two 2D gradient recalled echo images (TE1/TE2=5.3/7.6ms, TR=475ms) to assist the correction for distortion due to susceptibility inhomogeneity.

The resting state images are the focus of this thesis. These images were acquired over 8:12 minutes as part of a longer, 1.5-hour scanning session in which several other types of images were also acquired. During the functional resting state acquisition, participants were instructed to close their eyes and keep as still as possible throughout the scanning procedure.

2.3.3.1 Preprocessing

In each subject, white matter lesions were quantified using the Lesion Segmentation Toolbox (LST) (Schmidt et al., 2012). This technique allows automatic detection of T2 hyperintensities based on a T2 FLAIR and T1-weighted image, resulting in a total white matter lesion (WML) load for each subject (measured in ml). WMLs (which appear hypointense on T1-weighted SPGR images) were then automatically filled (using LST) on the T1-weighted SPGR image with intensities of normal appearing white matter to minimize grey matter misclassifications during structural segmentation.

Structural T1-weighted SPGR images were pre-processed using VBM8 (dbm.neuro.uni-jena.de/vbm8), a toolbox of statistical parametric mapping software (SPM8)

(www.fil.ion.ucl.ca.uk/spm), in Matlab 7.10.0 (R2010a, Mathworks, Massachusetts, USA). After lesion filling, structural images were intensity bias corrected, tissue classified and registered using linear and non-linear transformations (DARTEL), within a unified model (Ashburner & Friston, 2005). GM segments for each subject were modulated using non-linear components of the normalisation only, thereby preserving actual tissue values locally in order to account for individual brain size globally.

Using a field map produced using the Fieldmap toolbox in SPM8, functional images were then realigned (motion-corrected to the first functional volume) and unwarped (to minimise susceptibility distortions), and a mean functional image was produced. This was followed by slice timing correction. All functional images for each subject were coregistered the T1-weighted image using the mean functional image as the source image. Coregistered functional images were then normalised using the deformation fields generated from the structural registration and warping process. Finally, normalised resting state images were smoothed with an 8 mm isotropic Gaussian kernel.

2.3.3.2 Identifying the Default Mode Network

Independent component analysis (ICA) was used to decompose the imaging dataset into a number of statistically independent spatial maps, each with its own time course (McKeown et al., 1998). As a result of ICA, the sum of the statistically independent spatial maps, multiplied by the time courses of each component, approximates the original signal. Group ICA and subsequent processing were performed following methods set out in Petrella et al. (2011). In short, preprocessed images were analysed with software for group independent component analysis using default values (Group ICA of fMRI Toolbox [GIFT], v2.0e, available at

http://icatb.sourceforge.net/gift/gift_startup.php). The number of components estimated for each subject was 25.

To sort which of the 25 components from the ICA represented the DMN, group components were sorted in GIFT using correlations across voxels with "ref_default_mode", a standard DMN template included with the GIFT package. The component with the closest match to the DMN, that is the highest spatial correlation, was selected. The individual DMN component maps were then z scored using the following formula:

$$C_z(X) = (C(X) - \mu_c)/\sigma_c$$

where $C(X)$ are the component weightings, μ_c is the mean and $C_z(X)$ is the z scored component weighting.

To quantify the similarity between the DMN of subjects with MCI and healthy individuals, a Goodness-of-Fit (GOF) index was calculated. This GOF index was based on a DMN template derived from the group of healthy controls. First, a one-sample *t* test of the healthy control subjects' default mode component was run in SPM8, and results were corrected for multiple comparisons using a false discovery rate correction ($p<0.05$) and cluster extent threshold of 10. Positive values that survived correction for multiple comparisons defined the DMN template; this healthy template was used to make a binary mask that was in turn used to calculate the GOF index. The GOF was calculated in Matlab using the following equation:

$$GOF = mean(DMNcomponent[INmask]) - mean(DMNcomponent(OUTmask))$$

or, the mean z score of all voxels (of each individual's identified DMN component) within the DMN mask minus the mean z score of all voxels (of each individual's identified DMN

component) outside the mask, among all voxels inside the brain. (Greicius, Srivastava, Reiss, & Menon, 2004). For display purposes, a similar DMN template for the MCI group was also created, using a one-sample *t* test of the MCI subjects' default mode component.

Chapter 3. Results

3.1 Descriptive Statistics

Means (and standard deviation) for various domains (based on aggregate scores within each domain) of neuropsychological tests for healthy controls and MCI group are shown in table 3. The healthy control group performed significantly better for the domains of processing speed, learning and memory, visuospatial ability and language, but not executive function. As expected based on the selection criteria, learning and memory showed the largest between group effect.

Table 3

Means and Standard Deviations of Global Domain Scores for MCI and Healthy Control Participants

Cognitive Domain	MCI Mean Global Score (SD) (n=14)	Healthy Control Mean Global Score (SD) (n=11)	*t* score
Executive Function	0.14 (0.73)	1.08 (0.52)	-0.45
Processing	0.08 (0.53)	0.78 (0.37)	-4.33**
Learning and Memory	-1.03 (0.61)	1.17 (0.66)	-10.06*
Visuospatial	-0.39 (0.64)	0.76 (0.42)	-5.75**
Language	-0.22 (0.71)	0.22 (0.30)	-2.24*

* p<.05, **p<.01

Means and standard deviations for individual neuropsychological tests are displayed in table 4. Additional assessments were undertaken but the assessments shown are the ones that were included for purposes of establishing cognitive status. *t* scores are also shown, the majority showing a difference between the HC participants and the MCI participants. .

Table 4

Means and Standard Deviation of Neuropsychological Test Scores that Determined Cognitive Status for MCI and HC Participants

Neuropsychological Domain	Neuropsychological Test[a, b]	MCI Mean (SD) (n=14)	HC Mean (SD) (n=11)	*t Score*
Global Function	MoCA-Age Adjusted	22.5 (2.88)	27.45 (1.97)	-4.88***
	DRS2-Scaled Score	9.43 (1.74)	13.36 (1.80)	-5.52***
	ADAS-Cog	13.95 (3.94)	4.69 (2.47)	7.19***
Learning and memory	CVLT-Total Recall	-0.25 (0.94)	1.72 (0.48)	-6.32***
	CVLT-Short Delay	-0.68 (1.33)	2.27 (1.46)	-5.27***
	CVLT-Long Delay	-0.54 (0.87)	1.32 (0.81)	-5.46***
	BVMT-Total Recall	-1.88 (0.74)	0.34 (0.96)	-6.64***
	BVMT-Delayed	-1.71 (1.09)	0.37 (0.81)	-5.28***
	Rey- Immediate Recall	-1.66 (0.81)	1.59 (1.03)	-8.82***
	Rey-Delayed Recall	-1.68 (0.81)	1.32 (1.25)	-7.27***
	Rivermead Story Recall-Immediate Raw Score	4.50 (2.36)	8.50 (3.07)	-3.68***
	Rivermead Story Recall-Delayed Raw Score	3.00 (2.45)	7.14 (2.78)	-3.95***
	RI-48 Selective Reminding-	38.21 (6.73)	45.09 (2.98)	-3.15**

	Immediate			
	RI-48 Selective Reminding-Delayed	17.86 (5.95)	30.27 (5.37)	-5.40***
	VAT	-0.93 (0.97)	0 (0)	-3.57**
Executive function	Trails B	0.54 (1.16)	1.11 (0.51)	-1.54
	Letter Fluency	0.19 (1.25)	1.00 (1.78)	-1.33
	Category Fluency	0.62 (1.23)	2.00 (0.88)	-3.15**
	Category Fluency-Switching	0.07 (0.88)	1.12 (0.85)	-3.01**
	Action Fluency	0.02 (0.84)	0.73 (0.47)	-2.48*
	Stroop-Colour Word Interference	0.21 (1.29)	1.12 (0.45)	-2.46*
	Design Fluency-Switching	0.19 (1.34)	1.15 (0.89)	-2.05
Attention, Processing Speed and Working Memory	Trails A	0.75 (0.60)	1.34 (0.28)	-3.27**
	SDMT-Written	-0.36 (0.82)	1.09 (0.97)	-4.05***
	SDMT-Oral	-0.50 (0.62)	0.91 (0.80)	-4.97***
	Stroop-Colour Naming	-0.22 (1.09)	0.69 (0.57)	-2.51*
	Stroop-Word Naming	0.26 (0.98)	0.76 (0.65)	-1.44
	Design Fluency-Filled Dots	0.52 (1.14)	0.85 (0.71)	-0.83

	Design Fluency-Empty Dots	0.31 (1.19)	0.64 (0.80)	-.078
Visuospatial Function	Matrix Reasoning	0.17 (1.13)	1.12 (1.16)	-2.07*
	Rey-Copy	-1.42 (0.83)	0.09 (0.48)	-5.31***
	VSOP-Raw Score	18.21 (4.87)	23.55 (3.70)	-3.01**
	JLO	0.49 (0.58)	0.82 (0.46)	-1.52
	Pentagons-Raw Score	9.36 (1.34)	9.91 (0.30)	-1.34
	BVMT-Copy Raw Score	10.93 (1.07)	11.45 (0.52)	-1.49

*p<.05, **p<.01, ***p<.001

a For abbreviations see section 2.2

b Where score type is not specified age and education z scores have been analysed

3.2 Autobiographical Memory (AMI)

Table 5

Means, Standard Deviations and t-scores of AMI Episodic scores for MCI and Healthy Control Participants at Each Time Period

		Mean	SD	*t*
Childhood	MCI (n=14)	4.86	1.70	-1.76
	HC (n=11)	5.91	1.14	
Early Adulthood	MCI (n=14)	5.07	1.39	-2.84*
	HC (n=11)	6.45	0.93	
Recent Life	MCI (n=14)	5.07	1.50	-2.25*
	HC (n=11)	6.18	0.75	

*$p<.05$

Means (and standard deviation) for episodic autobiographical memory are described in Table 4. Factorial ANCOVA controlling for age and education showed a main effect of group with HC participants recalling significantly more detail on episodic autobiographical memory, F (1,21) = 9.78, $p<.01$ (Figure 2). There was no significant effect of time period, age or education on episodic autobiographical memory. There were no significant interactions between episodic memory score and time, age, education or group.

Fig 2. *AVCOVA Showing Differences between Means of Childhood, Early Adulthood and Recent Life Periods Episodic Memory of MCI and HC (Controlling for Age and Education)*

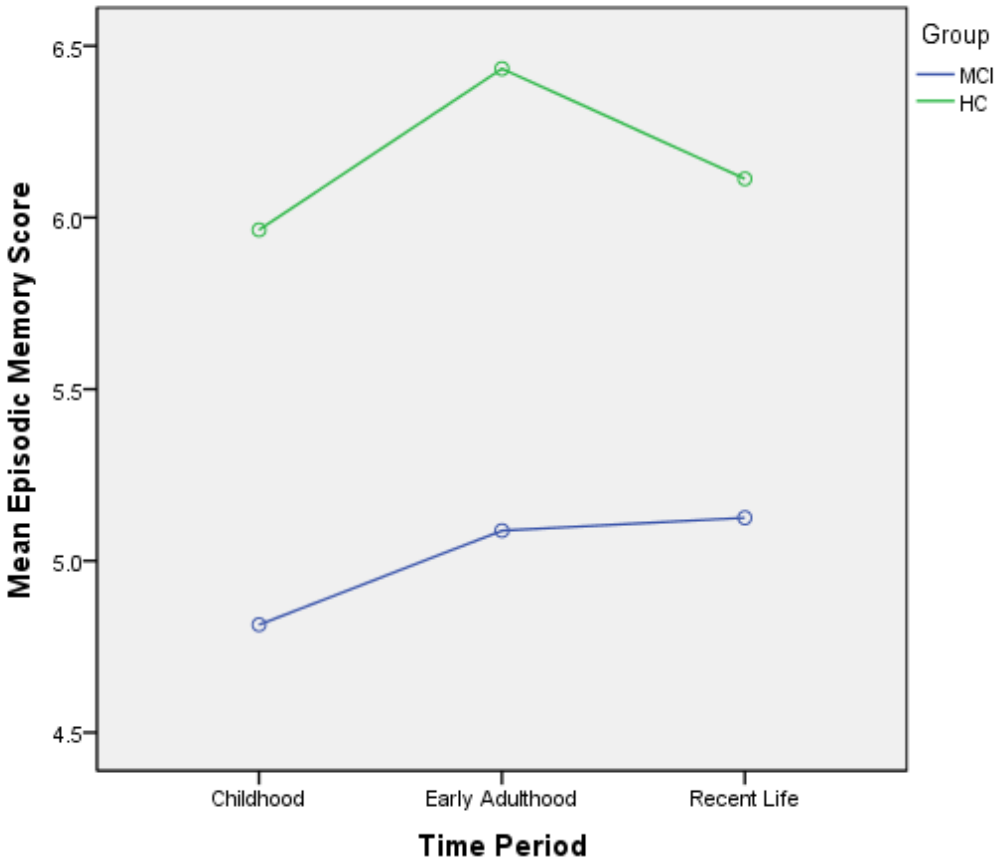


Table 6

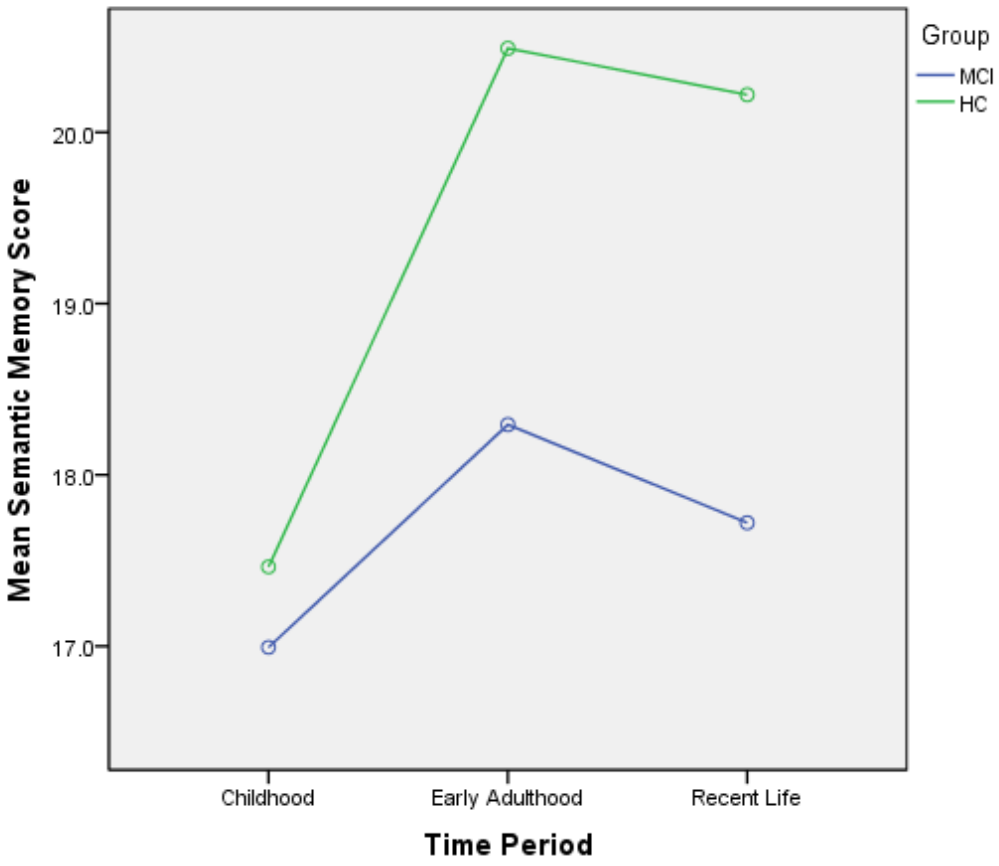
Means, Standard Deviations and t-scores of AMI Semantic scores for MCI and Healthy Control Participants at Each Time Period

		Mean	SD	*t*
Childhood	MCI (n=14)	16.95	2.13	-0.75
	HC (n=11)	17.5	1.18	
Early Adulthood	MCI (n=14)	18.32	2.24	-2.87*
	HC (n=11)	20.46	1.15	
Recent Life	MCI (n=14)	17.71	2.13	-3.56*
	HC (n=11)	20.23	2.14	

*$p<.01$

Means (and standard deviations) for semantic memory are described in Table 5. Factorial ANCOVA was carried out to assess the difference between HC and MCI at each time period for semantic memory. Results show, controlling for age and education, a main effect of group and HC participants recalled significantly more detail on semantic autobiographical memory recall scores, $F(1,21) = 9.77$, $p<.01$ (Figure 3). There was no significant effect of time period, age or education on semantic autobiographical memory. A significant interaction was found between time period and group $F(1,21)=4.75$, $p<.05$, showing poorer recall of childhood semantic details than recall of early adulthood and recent life.

Fig 3. ANCOVA Showing Differences between Childhood, Early Adulthood and Recent Life Semantic Memory of MCI and HC Participants (Controlling for Age and Education)



3.3 Source Memory

Table 7

Means and Standard Deviations of Number of Correct Responses on Source Memory Measures for HC and MCI Participants

	Recognition Memory Score (old/new decision)		Source Memory Score (male/female decision)	
	MCI Mean (SD) (n=14)	HC Mean (SD) (n=11)	MCI Mean (SD) (n=14)	HC Mean (SD) (n=11)
NP 2	51.15 (6.28)	57.00 (3.55)	29.23 (6.92)	34.09 (6.76)
Baseline	46.27 (6.72)	58.00 (2.65)	25.45 (10.30)	37.86 (3.13)

Means and standard deviations for recognition memory (old/new statement) and source memory (male/female voice) are presented in table 6. A two tailed *t*-test for independent means was carried out to determine if HC and MCI differed in their performance of recognition (accuracy of old/new decision) memory on source memory. Homogeneity of variance was violated, when this was corrected for a significant difference was found between HC and MCI groups, t=-2.86, p<.01. A two tailed *t*-test for independent means was conducted to determine whether there was a difference between HC and MCI performance on recalling if a male or female voice had previously spoken the statement. Results showed MCI participants performed significantly poorer at recalling the source of information, t=-2.86, p<.01.

At baseline testing participants were given one of four versions of the source memory test. A one way ANOVA was carried out to assess if the different versions had an effect on scores. Results showed there was no main effect of test version, $F(3,13)$=.35, p=.80,n.s. A main

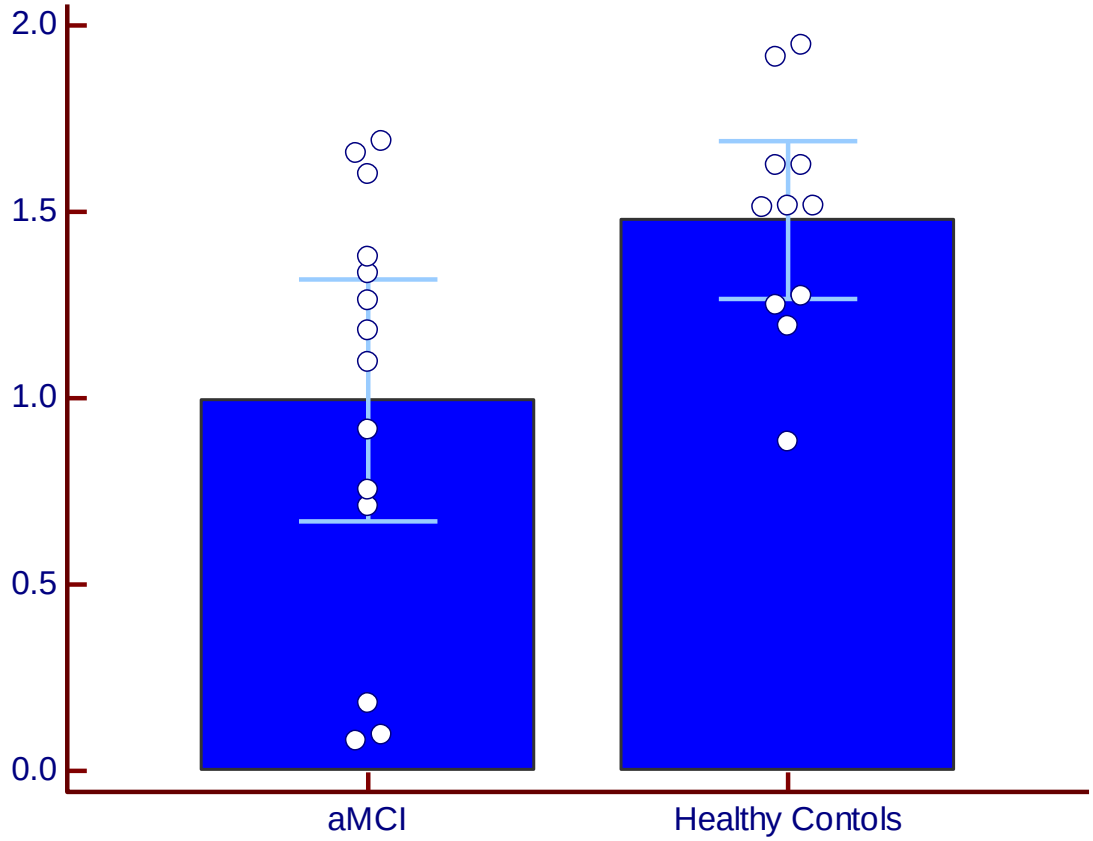
effect of group was found on both recognition ($F(1,16)=19.05$, $p<.001$) and source memory ($F(1,16)=7.90$, $p<.05$) showing HC performed significantly better at recalling statements already seen and if a male or female spoke the statement.

To determine if participants' performance changed between NP2 and baseline assessment a one way ANOVA was performed. Results showed participants did not show a change in the recognition task between NP2 and baseline assessment, $F(1,16)=.42$, $p=.53$, n.s. Participants also did not show a difference with identifying the source of information, i.e. the male or female accuracy, $F(1,16)=3.52$, $p=.08$,n.s.

3.4 Default Mode Network

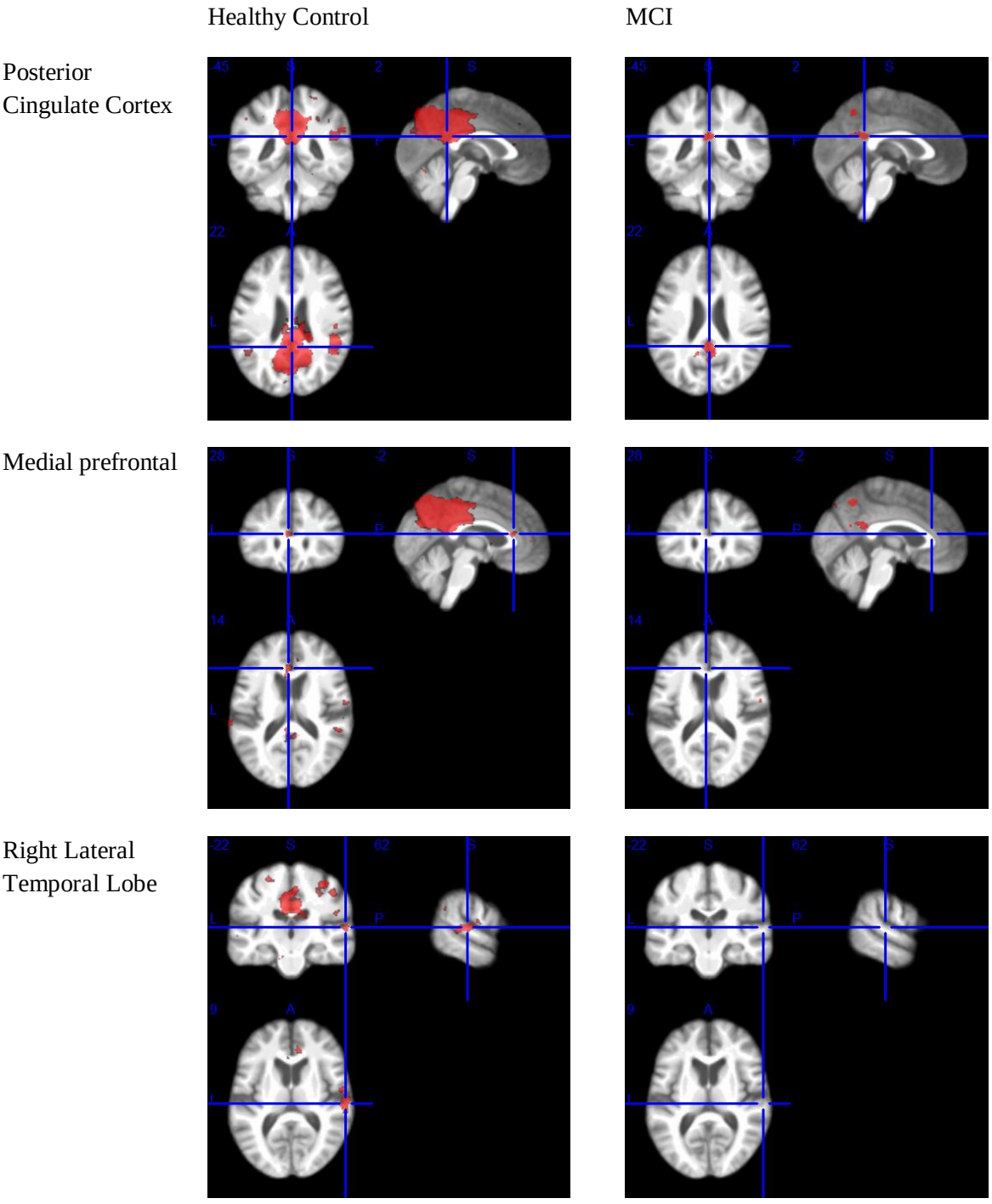
Goodness of fit was used to assess resting state activation of participants default mode network. A two tailed *t*-test showed the MCI group had significantly poorer GOF compared to the HC group, $t=2.54$, $p<.05$.

Fig 4. aMCI and HC Default Mode Network GOF Values

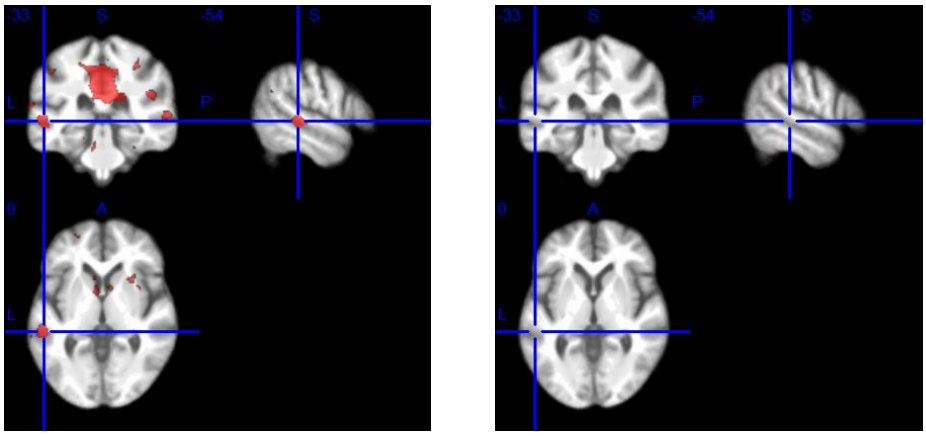


An ANCOVA with age and education as covariates produced the same results (group, $F(1,24)=5.66$, $p<.05$). Age and education did not show significant correlations with GOF. Voxel-wise differences were evident in all regions of the DMN (Figure 4).

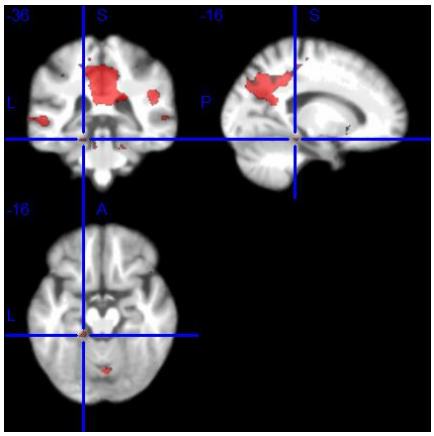
Fig 5. Specific Regions of Activation in the Default Mode Network in HC (Left) and MCI (Right)

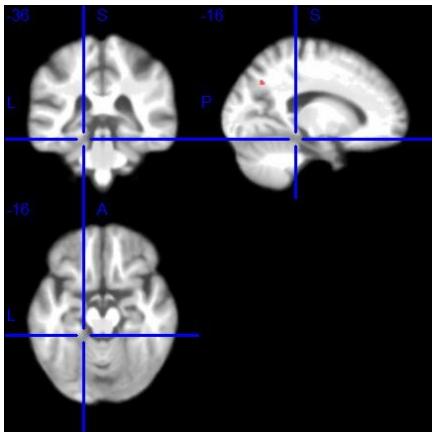


Left Lateral Temporal Lobe

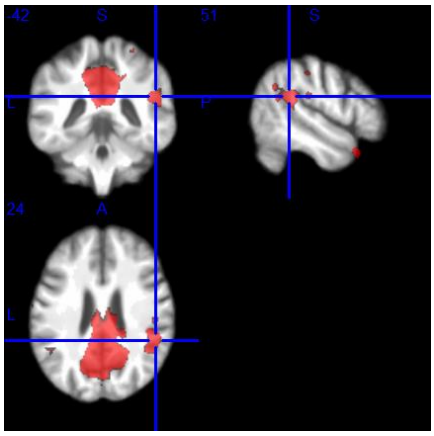


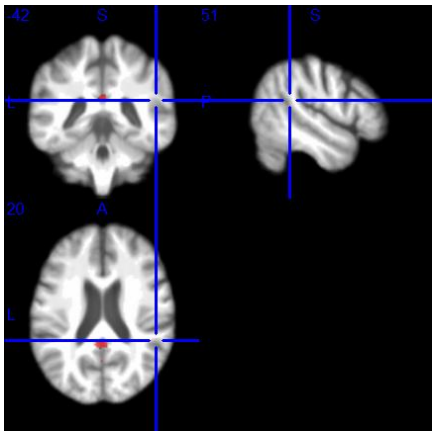
Parahippocampal Gyrus





Right Angular gyrus





Left Angular gyrus

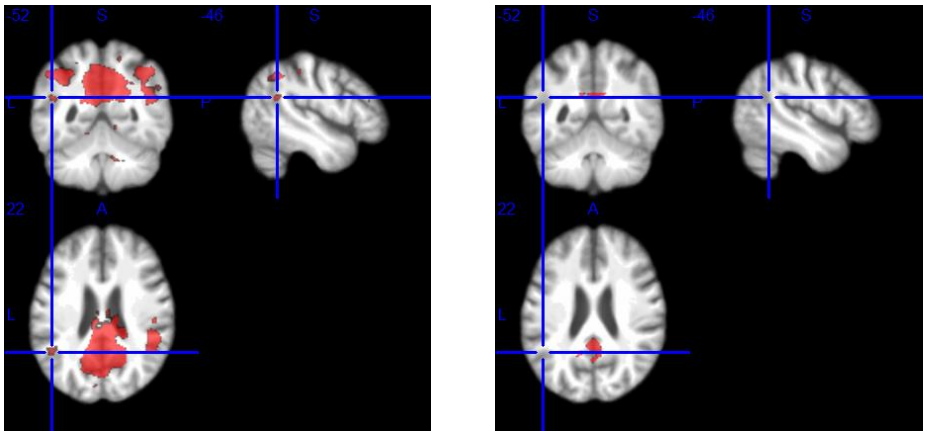


Figure 5. The Default Mode Network (DMN) template identified in the healthy elderly controls derived from the resting state fMRI component that most closely resembled a standard default mode template, following the analytic procedures of Petrella et al (2011). Colour overlay represents regions in the healthy control group that met the criterion of a one-sample t-test corrected for multiple comparisons using the false discovery rate (FDR) error correction ($p<0.05$) and cluster extent threshold of 10. The cross-hairs display local regions of interest. Right: By contrast, areas of DMN activity in the aMCI group, as defined by a one-sample t-test, FDR-corrected $p<0.05$, were markedly restricted throughout the brain and evident only in the retrosplenial cortex and parts of the precuneus. In summary, substantially reduced DMN was evident in the aMCI group. A Goodness of Fit Index (GOF) was derived for each individual, expressed by the mean z-score of all voxels within the healthy control DMN template minus the mean z-score of all voxels outside the this mask. Group differences between the GOF index are displayed in Figure 4.

Correlations between the GOF measure and global cognitive domain scores were carried out. A significant correlation was found between GOF and global learning and memory, r=.41, p<.05. No significant correlations were found between GOF and global visuospatial (r=.319, p=.120, n.s.), global executive function (r=.24, p=.26, n.s.), globalprocessing speed (r=.22, p=.30, n.s.) or global language (r=.08, p=.72, n.s.). A correlation between AMI episodic memory

and GOF was preformed, results were not significant (r=.09, p=.67, n.s.) showing no association between recall of episodic memory and default mode network GOF. A correlation between AMI semantic memory and GOF was performed and a significant result (r=.44, p<.05) showing a moderate association between semantic memory recall and default mode network GOF was found. Correlations between source memory (male/female voice decision) and GOF for NP2 (r=.24, p=.26, n.s.) and baseline (r=.43, p=.08, n.s. and r=.37, p=.14, n.s. respectively) were all found to be non-significant. The correlation of recognition memory (old/new statement decision) and GOF was found to be significant, r=.44, p<.05.

Chapter 4. Discussion

Episodic and semantic autobiographical memory was assessed in both HC and MCI participants and a significant difference was found between the groups on both measures. The difference found in episodic autobiographical memory was expected and supports the hypothesis that MCI participants would have poorer scores relative to HC participants. MCI participants also showed lower semantic autobiographical memory. As expected, MCI participants also showed significantly poorer recognition memory for old/new statements as well as poorer source memory (male/female voice identification). A GOF measure taken of DMN also showed that the DMN of the MCI has poorer functional connectivity than was evident in the HC participants. Nonetheless, no significant correlations were found between the GOF measure of the DMN and episodic or semantic autobiographical memory scores.

Significant differences were found between HC and MCI participants on episodic autobiographical memory. Many studies have previously shown that MCI patients show poorer episodic autobiographical memory (Gamboz et al., 2010; Murphy et al., 2008; Tramoni et al.,

2012), even when more lenient criterion are used. (Leyhe et al., 2009) used a weaker cutoff score to classify MCI participants and using the AMI found HC participants to be significantly better at recalling episodic memory. Only two other studies have used the AMI to assess episodic memory in MCI (Leyhe et al., 2009), these both found similar results to the current study. One of these studies found a temporal gradient, where more remote events are recalled with greater detail than recent memories (Leyhe et al., 2009; Tramoni et al., 2012). The hippocampus is implicated in the consolidation of new memories (Squire, Cohen, & Nadel, 1984), therefore, deficits in recent memory could be reflective of the hippocampal degeneration found in MCI and to a greater extent in AD (Celone et al., 2006). An increase in recall is evident in early adulthood compared with childhood and recent life, an effect called the reminiscence bump, which is a common finding in other studies examining autobiographical memory (Janssen et al., 2005). The current study did not find an interaction between group and time showing no significant evidence of either a temporal gradient or a reminiscence bump, rather the MCI group showed a general lowering of scores of episodic autobiographical memory recall. The current study did not find significant effects of time, however, the HC group are following the general trend of the reminiscence bump and it is possible with more statistical power that this could be a significant finding. Similar to the current study, neither Leyhe et al. (2009) or Tramoni et al. (2012) found an effect of a reminiscence bump in their studies, it is possible that this effect does not exist in MCI groups.

Semantic autobiographical memory was also found to be significantly better in the HC group than in the MCI group. Results from previous studies have been varied, some show a relative sparing (Gamboz et al., 2010; Murphy et al., 2008) of semantic memory in aMCI while others show deficits in semantic memory functioning (Tramoni, et al., 2012). Each of the above

studies that examined semantic autobiographical memory function used different tests and it could be this factor that is producing the inconsistent results. Where the AMI has been used, studies have shown a decrease in both semantic and episodic memory functioning in MCI groups (Tramoni et al., 2012), implying that perhaps the AMI is a more sensitive measure of semantic autobiographical memory. Levine et al. (2002) argues it is not possible to separate episodic from semantic autobiographical memory, in order to produce a richer narrative both types of memory are essential. Accordingly, assessing and scoring these two components of autobiographical memory separately is not possible. The differences found in semantic memory do seem to be dependent on the type of test administered; the AMI could be artificially finding an effect that is not actually there. On the other hand tests such as that by Levine may not be sensitive enough. An effect of time was found where all participants showed worse performance at recalling childhood semantic autobiographical details compared with early adulthood or recent life. This is the exact opposite of the temporal gradient that would be expected, however, a reminiscence bump is evident. A recent study found evidence that the reminiscence bump can apply to semantic memories as well as episodic autobiographical memories (Janssen, Rubin, & Conway, 2012).

This study found the MCI group to have significantly poorer GOF index of the DMN compared with the HC group. This finding is reflected in the lower neuropsychological scores, particularly in the learning and memory domain where there is a correlation with the GOF index. The GOF index did not correlate with autobiographical memory, this was an unexpected finding given the overlap between major nodes of the DMN and neural correlates of autobiographical memory. For example, the posterior cingulate cortex is a major node of the DMN and has been found to be involved in autobiographical memory (Milton et al., 2012), the current study found

very clear visual differences (in brain imaging data) between the MCI group and HC group (see fig 5). Voxel wise differences between the HC group and the MCI group were found in each major node of the DMN. Visually the voxel-wise differences found in this study seem large, this could be a result of having highly functioning HC participants (see section 4.1 below). The MTL has been associated with autobiographical memory function. In the current study decreases in functional activity and episodic and semantic autobiographical memory in the MCI group were found, although no correlation was found between the GOF index of the DMN other studies have found an association between MTL functioning and autobiographical functioning. In a study that examined both whole-brain and region of interest analysis Jin, Pelak, Curran, Nandy, and Cordes (2012b) found differences in functional activation between an MCI group and a HC group, specifically they found decreases in the MTL activity in both encoding and recognition tasks. Since the current study used resting state MRI and Jin et al. (2012b) used functional MRI to investigate the DMN the disparity in results could be a function of the type of scan acquired. Poorer connectivity in the DMN of MCI participants have been found to be predictive of cognitive decline and progression to AD. Using *f*MRI Petrella et al. (2011) found GOF indices to be correlated in MCI conversion to AD, those MCI participants with a lower GOF at baseline were more likely to convert to AD over the course of 2 or 3 years. Unlike the current study Petrella et al. (2011) used *f*MRI which affects any conclusions drawn from comparisons with the current study. A recent study that followed participants with AD and MCI for 2 years found MCI participants that had converted to AD during the 2 year period did not show a significant difference from AD participants when examining the resting state functional activity in the PCC and precuneus at initial assessment. Participants with MCI that had stayed stable over time did show significantly more resting state functional connectivity compared to AD participants,

although not significantly different, the study also found the regional values of MCI to be in between HC participants and AD participants (Binnewijzend et al., 2012). Combined these studies show the possibility of adding MR imaging as part of diagnosis for MCI.

Pronounced effects were found between the HC group and the MCI group on a test of source memory. MCI were found to be significantly poorer compared with HC participants at recognition of statement (old/new decision) and at identifying if the male or female had spoken the statement (or the source of the information). Although there are no other studies that examine source memory in MCI participants these results would be expected as MCI is an intermediate stage between normal aging and AD. Individuals with AD have been found to be impaired in recognition memory (Dalla Barba et al., 1999; Dodson et al., 2011), it is expected that MCI participants would show this same impairment as the results of the current study do. MCI participants were also found to be significantly poorer at identifying the source of information, again AD participants have been found to be impaired in source memory (El Haj et al., 2012) and it is expected that MCI would also follow this pattern. The current study used a truncated version of the protocol from Dodson et al. (2011), where the number of statements read for encoding and the number of distractor statements was smaller and MCI still showed poorer scores.

4.1 Limitation and Future Directions

The HC participants in this study had been specifically chosen because their cognitive score are above average (z score above 0). This is particularly evident in the mean scores of the learning and memory domain where the HC group score above the mean, which could influence the group comparisons made between groups and also brings into question whether or not the HC group really are representative of the general (healthy aging) population. This has generally been a

function of the volunteers available to be included as participants in the study (see fig 1 for reasons for inclusion/exclusion), for future study a greater variation in participants would potentially be more representative of the cognitive function of the healthy aging population.

Different studies use a variety of cut-off scores to classify MCI, for example (Leyhe et al., 2009) used a more lenient cut-off score of <1 and still found the HC group were significantly better at recalling episodic and semantic autobiographical memory. The current study used a cut off of <-1.5, which tends to be what most papers use to define MCI (Gamboz et al., 2010; Murphy et al., 2008), in more than one measure of cognition which reduces any potential false positives (Ingraham & Aiken, 1996; Jak et al., 2009; Palmer, Boone, Lesser, & Wohl, 1998; Teng, Tingus, Lu, & Cummings, 2009).

Semantic autobiographical memory has been assessed using three main assessments and the results found in MCI participants have varied. Only one study has sought to directly compared different tests of semantic autobiographical memory and it found that the type of test does have an impact on results (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012). Thought this comparison was limited to the AMI and Levine's Autobiographical Interview, future studies should take into account the differences found between tests.

Source memory has not been studied in MCI previously. Although it was expected (and found that) this type of memory would follow the same progressive impairment as found in other types of memory, such as autobiographical, this is as yet unknown and should be explored more fully including HC, MCI and AD participants in order to draw comparisons.

This study has included a comparison of the main nodes of the DMN, but owing to time restraints a full statistical analysis of the differences between the HC group and the MCI group

has not been completed. Therefore, although it is possible to see the differences between the HC group and the MCI group in Figure 5, statistical voxel-wise comparisons were not made. The goodness of fit index showed that overall connectivity of the DMN was significantly different between the MCI and HC groups, but clearer differences may be apparent when connectivity in localised regions are analysed. Similarly, a voxel-based analysis of correlations of connectivity with AMI scores, even within selected DMN regions such as the medial posterior cortex, might more clearly show whether autobiographical memory is associated with DMN activity. This is important for areas such as the medial prefrontal cortex where the MCI group show no resting state functional activity and the HC group show a small amount of resting state activation. Continuing to track participants to assess what factors contribute to the progression to dementia would contribute further to this field of study and should be considered for further research.

4.2 Concluding Remarks

The above study examined autobiographical memory in relation to the default mode network in HC participants and MCI participants. MCI participants were found to have lower DMN integrity and to be impaired on both semantic and episodic autobiographical memory relative to HC participants. The findings of this study support the majority of current research which show deficits in memory and deterioration in the DMN, and, thereby, evidence is added to the theory of MCI as a prodromal phase of dementia. Semantic memory should also be directly compared across the AMI with Levine et al. (2002) and Piolino et al. (2000) assessments, further comparing these three assessments in HC participants, MCI participants and also AD participants. For future study the predictive value of MR imaging in the DMN of MCI participants should be explored.

Chapter 5. References

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