Memory changes in community-based older adults: subjective memory complaints, personal memory and their relationship with Alzheimer’s disease biomarkers

Being a report of an investigation submitted as required for the degree of Doctor of Philosophy at the University of Melbourne

by

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About thirty years ago there was much talk that geologists ought only to observe and not theorise; and I well remember someone saying that at this rate a man might as well go into a gravel-pit and count the pebbles and describe the colours. How odd it is that anyone should not see that all observation must be for or against some view if it is to be of any service!

(Darwin, 1861)
Subjective concerns of memory decline (or subjective memory complaints) are a common phenomenon in the normal population, particularly in older adults. Complaints arise from a negative self-appraisal of memory performance, and form the bridge that connects an individual to clinical attention. The experience of memory failure, whether momentary, gradually progressive, or sudden and acute, is universal and inherently subjective. Within this experiential realm lies rich and complex subjective detail. A threshold exists at which point self-appraised memory dysfunction becomes intolerable, and most individuals seek diagnostic resolution for their symptoms.

Alzheimer’s disease (AD) is the most common form of dementia, which is characterised by early impairment in objective memory performance, and gradual accrual of in vivo biological markers. The current trend in the literature is to assume a monotonic relationship between memory complaint severity and level of objective memory impairment, but in general studies have been unable to find a consistent association. The relationship between subjective memory complaining and biomarkers of AD, such as neocortical β-amyloid (Aβ) burden, measured via positron emission tomography (PET) imaging, and brain atrophy, measured via magnetic resonance imaging (MRI), is gathering pace. Brain atrophy in the medial temporal lobes (MTL) is consistently related to memory complaining, but the literature relating to neocortical Aβ burden is less clear; recent studies have shown a relationship, but the effect sizes are small.

Autobiographical (ABM) and personal semantic memories (PSM), along with their autonoetic re-experiencing, form the foundation of everyday personal memory. An assessment of personal memory impairment does not feature in the mainstream diagnostic approach to mild cognitive impairment (MCI), the clinical transitional stage prior to a diagnosis of AD. ABM, or the highly contextualised details related to a personal event, are consistently found to be impaired in individuals with MCI, but the pattern of impairment of PSM is less understood. As the most ecologically valid form of memory, it is possible that a breakdown in ABM and PSM is the main driver for subsequent memory complaining. To the candidate’s knowledge, there is no literature which has yet examined a possible connection between memory complaining and personal memory function. It is also unclear how markers of AD pathology, such as Aβ burden and brain atrophy, may be related to ABM and PSM, but functional MRI studies of these personal memory systems suggest they are supported by differing functional networks. ABM is related to a core functional network that primarily involves the MTL, frontal, and posterior cingulate regions, while PSM has been attributed to networks in the lateral temporal lobe. The current inquiry is aimed at describing the phenomenological experience of memory change in non-demented older adults in order to elucidate complaints in those at greater risk of AD, such as individuals with evidence of biological markers of AD, or those with MCI. The specific objectives of this these were: 1) to determine cognitive, affective and AD biological
marker correlates of SMCs in healthy older adults and individuals with MCI examined via a commonly-used subjective memory complaint questionnaire (SMCQ), 2) to characterise the phenomenological experiences of memory loss in the earliest stages of Alzheimer’s disease, such as healthy older adults with evidence of AD biological markers and those with MCI, and 3) to examine the pattern of ABM and PSM impairment and its relationship with AD biomarkers in healthy memory complainers and individuals with MCI.

The first study (Chapter 4), investigated memory, affective and AD biomarker correlates of SMC severity as measured via a commonly-used SMCQ, the Memory Assessment Clinics Questionnaire (MAC-Q), in healthy older adults and individuals with MCI. Participants were healthy controls (n = 674) and individuals with MCI (n = 66) in the Australian Imaging, Biomarker and Lifestyle (AIBL) study of ageing, who responded to the MAC-Q. Scores from measures of new learning and retention, as well as mood (anxiety and depression), age, education and diagnostic category, were regressed onto the total MAC-Q score, to determine whether memory would relate to SMC severity over and above the other variables. Diagnostic category, depressive symptomatology, and age, were the strongest correlates. In healthy older adults, the strongest driver of greater MAC-Q score was depressive symptomatology, while in individuals with MCI, the sole correlate was age. Aβ deposition, grey matter volumes, and APOE ε4 carrier status were regressed onto MAC-Q total score in both diagnostic groups, but no correlates were found. A strong relationship between depression and memory complaint severity in healthy older adults aligns with other studies using SMCQs. The relationship with age in MCI supports the notion of an underlying organic driver of memory complaining, and a transition from affectively-driven phenomena.

The second study (Chapter 5), addressed the characterisation of SMCs in different AD-risk groups, such as healthy older adults with high Aβ load, healthy memory complainers (identified by asking “do you have difficulties with your memory, yes or no?”), and individuals with MCI. Healthy control (n = 80) and MCI (n = 43) participants were randomly recruited from the AIBL study for the next three studies. A semi-structured interview was developed by the candidate, in conjunction with supervisor, MS to probe the phenomenological experience of memory loss. A thematic analysis was conducted and meaningful phrases were extracted, and grouped similar phrases into what ultimately became twelve themes. A comparison between healthy individuals with high and low Aβ load showed that greater Aβ deposition was related to greater acknowledgement of a progressive memory decline. Complaint themes in healthy memory complainers closely aligned to those expressed by MCI individuals, suggesting that a single SMC question has the potential to uncover individuals with subjectively similar experiences of memory loss as those with a diagnosed memory dysfunction. Individuals with MCI diverged from healthy memory complainers in their greater acknowledgement of dependency on a significant other, and the implementation of burdensome coping strategies. Thus, an increasing
acknowledgement of dysfunction in daily activities may well signify an interim early stage outcome of accumulating memory problems.

The pattern of ABM and PSM impairment in healthy memory complainers and those with MCI was examined in the third study (Chapter 6). The Episodic Autobiographical Memory Interview, a validated semi-structured interview, measured the spatiotemporal and emotional details of a recent personal event (ABM) and personally factual knowledge from the recent past (PSM). Individuals with MCI showed a deficit in both ABM and PSM, supporting conceptual notions of a dynamic and interactive overlap between these two memory systems. Healthy memory complainers did not show a deficit compared to non-complaining healthy older adults, raising the question as to whether current measures of memory complaining are sensitive to the subjective experience of memory decline. In the fourth and final study, AD biomarkers were considered in relation to personal memory performance, namely ABM, PSM and the conscious re-experiencing connected with ABM (Chapter 7). Aβ deposition, grey matter volumes and APOE ε4 carrier status were regressed onto each form of personal memory. PSM was negatively associated with neocortical Aβ burden in healthy older adults, but neither ABM nor autonoetic consciousness were related to any AD biomarkers. ABM impairment exerted a large magnitude of effect on MCI unlike PSM, so there are potentially other underlying neurodegenerative processes affecting ABM performance.

The prevailing assumption in the literature is to treat subjective memory complaining as a unidimensional proxy for neuropsychological measures of memory impairment. The problem with this assumption is that it does not recognise the complex, and often counter-intuitive, nature of subjective experiences. SMCQs, such as the MAC-Q, are structured as screening tools in that they are non-interactive, non-specific and designed for quick self-administration. This approach provides no diagnostic information over and above a quantified score, and neglects the possibility that phenomenological experiences contain important clinical information. The impairment to both ABM and PSM in MCI, highlighting that both personal memory systems are affected by underlying AD-related neuropathology. Specifically, findings from this thesis suggest that ABM and PSM are affected by differential disease mechanisms, with PSM strongly influenced by neocortical Aβ burden in healthy older adults, and ABM showing a trend towards association with hippocampal volume. Thus, elevated AD biomarkers were found to have an effect on the subjective experience (via complaints) and expression (via autobiographical narratives) of memory, supporting the notion that these phenomena are affected in the early stages of AD. This thesis highlights the subjective experience of memory change in non-demented older adults, which will help to inform future approaches to the clinical evaluation of memory complaints prior to diagnosis.
DECLARATION

The study described in this thesis has not previously been submitted for a degree at this or any other university or tertiary institution. The study undertaken and its interpretation is my own original work, except where due acknowledgement has been made.

I also declare that the sum total of words in this thesis, exclusive of tables, figures, footnotes, references, and appendices is less than 100,000 words.

................................

Rachel F. Buckley
All results involved the contribution of others, as this thesis was conducted as a sub-study within a larger study, the Australian Imaging, Biomarker and Lifestyle (AIBL) study of Ageing. Cognitive data, other than the CANTAB Paired Associate Learning (PAL) task, was collected by researchers employed by the AIBL study. Neuroimaging data was collected and processed by the imaging stream (Prof Chris Rowe, Dr Victor Villemagne and others). Genetic information, namely the 

polipoprotein \( \varepsilon_4 \) allele, was collected by the biomarker stream (Dr Alan Rembach and others). Diagnostic information for each participant was determined by a panel of neurologists, geriatricians, old age psychiatrists and neuropsychologists, chaired by Prof David Ames. The semi-structured interview that was developed for the qualitative analysis in Chapter 5 was created in collaboration with Prof Michael Saling. The PhD candidate collected all data pertaining to the qualitative analysis, autobiographical and personal semantic memory performance, and the non-verbal CANTAB PAL task.

The larger AIBL study commenced 18 months prior to my enrolment in the PhD, but no work included in this thesis was carried out prior to enrolment. No third party editorial assistance was used for the formatting of this PhD thesis.

Each manuscript was drafted entirely by the PhD candidate. The manuscripts involved multiple co-authors, all of whom were involved with the revising and editing process. The most involved co-authors have all agreed to the use of these manuscripts in this thesis, and have provided signed copies of the co-author authorization form.
DEDICATION

Michael John Properzi

This thesis was not possible without the never-ending love and support from my loving partner, Michael. Not only did he continually provide a foundation with which to draw emotional strength, but he provided countless hours of critical analysis, proof-reading and listening to me practice presentations. I cannot simply thank my partner for his support, as this would not do justice to what he has done for me. I feel we have both grown from this PhD experience (both trying and triumphant) and have come out the other side as better, and more intellectually sophisticated, people. I would also like to acknowledge the support from Michael’s immediate family for their love and guidance.

Dallas and Douglas Buckley

My parents have provided unwavering support to my achievements, both academic and extracurricular, throughout my whole life. I am always grateful for their desire to see my flourish and allow me that opportunity under any circumstance. Without your emotional and financial generosity, I would not be able to achieve such intellectual heights. In particular, I thank my mother for being an unfailing rock in my life, and my best friend. I cannot put into words how much you mean to me. I also thank my father for his unwavering interest in my life, his wise counsel, and his continued encouragement to challenge myself and my limits. I can’t thank you both enough; my successes are truly your successes.

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Conference abstracts

**Internationally**


**Nationally**


Invited talks

2014

2013
Trauma Memory Lab Seminar Series - National Center for PTSD, VA Boston Healthcare System, Boston, USA. *Predictors of early memory changes in community-based older adults.* July 18\textsuperscript{th}, 2013.

2011
NARI Research Seminar - NARI/RMH (Royal Park), Melbourne. *Memory is in the mind of the beholder: predictors of memory changes in older adults.* August 2\textsuperscript{nd}, 2011.
Awards

2014
Delegate’s scholarship: Japan Neuroscience Society Conference

2013
Delegate’s scholarship: Alzheimer’s Association International Conference
Travel Scholarship: Melbourne School of Psychological Sciences (MSPS)
Travel Scholarship: The Florey Institutes of Neuroscience and Mental Health
Australian Society for Medical Research (ASMR) Student Symposium: Highly commended oral presentation
MSPS PhD Student Conference: Outstanding presenter award

2011
Delegate’s scholarship: Alzheimer’s Association International Conference

2010
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1.1 Subjective experiences of memory function

The experience of memory failure is an intrinsic part of everyday life. Individuals continually self-appraise memory function against a backdrop of mitigating factors, such as multitasking and stress, and across a multitude of contexts, such as social situations, demanding work environments, and perhaps scrutiny from family, friends, and colleagues. Negative self-appraisals of day-to-day memory capacity, accentuated by subjective assessments of increasingly worsening memory lapses, commonly feature in older adults\(^1\) (Abdulrab & Heun, 2008; Ginó et al., 2010; Jonker, Geerlings, & Schmand, 2000; Ponds, Commissaris, & Jolles, 1997; Reisberg & Gauthier, 2008; Tobiansky, Blizard, Livingston, & Mann, 1995; Vestergren & Nilsson, 2011; Westoby, Mallen, & Thomas, 2009). A growing concern of the significance of memory lapses motivates some to seek clinical attention for the purposes of diagnostic clarification.

The prevalence of subjective memory complaints (SMCs) in community-based non-demented older adults ranges from 25% to 50% (Bassett & Folstein, 1993; Blazer, Hays, Fillenbaum, & Gold, 1997; K. A. Ellis et al., 2009; Gagnon et al., 1994; Jonker et al., 2000; O’Connor, Pollitt, Roth, Brook, & Reiss, 1990; Tobiansky et al., 1995), indicating the salience of memory changes in this group.

The media, whether pre-empting this concern or reacting to contemporary trends, frequently report on commentaries of memory loss in older celebrities. For instance, actor Michael Gambon, a 73-year old thespian who plays Dumbledore in the movie series Harry Potter, expressed fears of forgetting his lines (Daily Mail, 20 April, 2014). His fear, he stated, was not borne out of ‘normal’ memory lapses encountered by stage actors, but had become increasingly more noticeable with age. Gambon claimed that he now favoured theatrical roles with few lines, and preferred to wear an ear piece while on stage (Moss, The Guardian, 22 April, 2014). Gambon, an avid private pilot, also acknowledged that he was now limited to doing ‘circuits and bumps around airfields’, when in the past he ‘flew all round (sic) the UK and over France’. His concerns of dementia, and his acknowledgement of changing functional abilities, became so worrisome that he sought the medical opinion of two doctors, who did not find evidence of a dementia. In a similar vein, comedian Billy Connolly spoke of memory concerns to his audience at a recent comedy gig, when he had to stop twice in the middle of his performance and ask the audience to prompt him. He was quoted as saying during the performance, ‘this is fucking terrifying. I feel like I’m going out of

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\(^1\) For the purposes of the current inquiry, older adults are defined as individuals aged beyond 60 years (Ellis et al., 2009).
my mind’, and acknowledged that his wife had also noticed memory lapses (Archibald, Daily Record, 22 April 2013).2

While SMCs of famous personalities are reported in the media. These stories offer a glimpse into the subjective experience of everyday memory dysfunction associated with earlier stages of dementia. President Ronald Reagan revealed his diagnosis of dementia of the Alzheimer’s type, four years after his final term in office. First-hand accounts from White House aides of the latter stages of Reagan’s presidency, were that the President was ‘inattentive and inept’, and disinterested in general current affairs. Aides were also known to sign off on matters in the President’s place, as he progressively withdrew from everyday presidential affairs. One event, recounted by 1984 Democratic Nominee, Walter Mondale, revealed Reagan’s inability to maintain the thread of an autobiographical narrative during a presidential debate. Of the lapse, Mondale said, ‘I think when you look at that performance there’s some question [as to] whether he wasn’t beginning to lose it.’ (Mayer, New Yorker, 24 Feb 2011).

Gradual memory impairment is associated with lowered independence, and a loss of one’s ‘mind’ and identity (D. Cohen & Eis dorfer, 1986; de Boer et al., 2007). It is clear from these anecdotes that age-associated memory changes loom large in the collective conscience (Commissaris et al., 1993; Laforce Jr & McLean, 2005). In this thesis, I conduct an investigation into the phenomenological experience of memory loss in non-demented community-based older adults, and how this relates to clinical and biological markers of Alzheimer’s disease (AD). The impairment of everyday personal memories, both autobiographical and semantic, will also be explored.

1.2 A pain analogy

In the medical profession, interpreting subjectivity is an inevitable reality. Initial presentation of an individual to a clinician involves the communication of the subjective experience of illness, and it is the clinician’s role to understand and interpret this subjective narrative (Leder, 1990; Wulff, 1999). According to Wulff (1999), medicine involves two worlds; one of measurement and science, and the other of feelings, expressions of unpleasant symptoms, and concern. A patient’s illness sits within the context of their interpretation of, and ability to communicate, that illness. Two hypothetical experiences of the same headache, can elicit overlapping features within a degree of noise (that is, a degree of unique ways of expressing the subjective experience. Subjective phenomena in the medical world are best understood from a diagnostic standpoint when descriptions of the phenomenological experience of the condition are available for reference. Headaches are an appropriate analogy for the

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2 It is important for the reader to note that Billy Connolly has since been diagnosed with Parkinson’s disease, but his direct experience of memory change still stands as an interesting insight into an individual’s subjective appreciation of his cognitive difficulties
present inquiry, as they are historically a well-described phenomenon (Duvoisin, Parker, & Kenoyer, 1961; Liveling, 1873; Selby & Lance, 1960)(Gowers, 1888; Lenton, 1954; Wulff 1963). The subjective experience of pain from cluster headaches, for instance, is described in the following way:

“beginning suddenly and without warning, with a pulling, tugging, or pressing sensation behind one eye. Often the pain spreads to the temple...usually there is a prominent throbbing or pulsating component, synchronous with the pulse. Nasal congestion is frequent...At the peak of the headache the pain is intolerable and incapacitating. In contrast to the victim of migraine, the patient in great distress paces the floor restlessly and is unable to sit still or lie down. ... Some patients contemplated suicide during their headaches, so great was their agony. There is rarely a subsequent fatigue...generally, the patient readily resumes his previous activity” (Duvoisin et al., 1961)

A migraine, on the other hand, is described in this manner:

“The attack would begin with sudden blurring of vision for three or four minutes followed by distressing sensations of circles, lines and zig-zags dancing in front of his eyes for some 30 minutes after which the attack ceased, leaving him exhausted.” (Selby & Lance, 1960)

Although pain is an entirely subjective phenomenon, with variable responses both intra-individually and socioculturally (B. J. Good & Good, 1981; Rey, Wallace, Cadden, & Cadden, 1995), evidence from observations of differing headache conditions allows one to characterise each condition according to similar subjective experiences. It is through the interpretation of these subjective nuances that a clinical picture, and possible diagnoses, can be determined prior to further assessment of the patient.

Common subjective symptomatology in the neuropsychological field is a complaint of memory failure. The clinical semiology, or collection of signs related to a condition (see section 1.3 for expanded definition), of subjective memory complaints in some clinical populations has previously been defined. For example, patients with temporal lobe epilepsy characteristically express a ‘bitter’ or strident memory complaint in the absence of significant memory impairment (O'Shea, 1996; O'Shea, Saling, Bladin, & Berkovic, 1996; Rayner, Wrench, & Wilson, 2010), while Beck (1967) described memory complaints in major depressive disorder as particularly exaggerated for the reality. Kahn stated:
“[They] complain about their memory [and give] such illustrations as forgetting to buy something in the store...These are commonplace incidents of forgetfulness that would be ignored by younger or less depressed persons but they were perceived by depressed older persons as indicating a marked decline in mental functioning.” (Kahn, 1975, p. 1572).

Somewhat counterintuitively, patients in the later stages of dementia of the Alzheimer’s type (DAT), and who present with gross memory dysfunction, are described as having a muted complaint (Cotrell & Schulz, 1993; Martin, 1975; Reisberg et al., 1986; Reisberg, Ferris, de Leon, & Crook, 1982). Amnestic cases, such as Henry Molaison, or H.M., who exhibited severe amnesia due to bilateral resection of the temporal lobes, was aware of his memory problem (Ogden, 2005), but the concern did not align with the extent of his memory impairment (Corkin, 1984). These counterintuitive subjective experiences in the face of either subtle or gross memory dysfunction, highlight the complexities of subjective expressions of memory failure, and raise the question of how the experience of memory loss relates to the ‘objective’ reality of memory function according to performance on neuropsychological tasks of new learning and retention.

1.3 The clinical semiology of a complaint

The term semiology originates from the Greek word σήμειον, or sign, and, in the medical profession, is used to represent signs that emanate from a condition. The most common neurological reference is in the field of epilepsy, where the term clinical semiology concerns the subjective and behavioural phenomena arising from ictal seizure events (Lüders et al., 1998). For the purposes of the current study, clinical semiology will be used in relation to subjective memory complaining to refer to the subjective signs relating to a complaint, both verbally and non-verbally. More specifically, the clinical semiology of the complaint will relate to what the individual is saying, and how they say it. Memory complaining is founded entirely on overt communication of the individual’s subjective experience, so the term clinical semiology is appropriate in this case.

1.4 Subjective memory complaints: an historical perspective

Subjective memory complaint symptomatology has featured in a range of conditions, and is a particularly predominant feature of ageing. Subjective memory complaints were originally considered as a benign symptom of ageing or the malignant harbinger of a neurodegenerative syndrome (Kral, 1962). Kral (1962) introduced the term ‘benign senescent forgetfulness’ to define the development in older adults of an awareness of everyday memory lapses. Mild memory problems were argued to be experiences of ‘minor and variable errors in orientation, difficulties in recalling, at
times, names and dates of the past which were available at other times’ (O’Brien, 1999, p. 282). More specific guidelines for ageing were proposed, named age-associated memory impairment, by Crook and colleagues (1986) to attempt to characterise the phenomenon of subjective experiences of decline in otherwise healthy older adults. The important feature of the age-associated memory impairment criteria was the proposal of representative memory complaints related to the condition, such as, difficulty remembering names after introduction, misplacing objects, forgetting multiple items at the supermarket or multiple tasks to be completed, difficulty recalling postcodes and telephone numbers, or inability to recall information after a delay or interruption. It is unclear, however, how these complaints were derived. The age-associated memory impairment diagnostic criteria (Blackford & La Rue, 1989) were translated into the Diagnostic and Statistical Manual of Mental Disorders IV criteria, but has been replaced with the advent of newer diagnostic criteria of older age cognitive impairment not yet dementia (DeCarli, 2003 - for a review). Crook and colleagues’ (1992) initial conceptualisation of memory complaints has endured, however, through their widely-used memory complaint questionnaire (Glodzik-Sobanska et al., 2007; Hänninen et al., 1995; Hänninen et al., 1994; Mattos et al., 2003; M. Reid et al., 2011), the Memory Assessment Clinics Questionnaire (Crook et al., 1992), which will be discussed in Chapter 2, and feature in Chapter 4.

Clinical staging tools, used to indicate the severity of a dementing condition, also include memory complaint symptomatology as an early stage phenomenon prior to objective cognitive decline. The Global Deterioration Scale for Age-Associated Cognitive Decline and Alzheimer’s disease (Reisberg et al., 1982) includes a second stage of mild forgetfulness, which manifests as an awareness and concern of memory loss but no significant deficits in activities of everyday living. This second stage was intended to identify individuals who are at greater risk of future cognitive decline. The authors suggested that complaints could include a difficulty in recalling names that were previously known to them or just after introduction, an inability to remember where objects were placed, and a difficulty remembering appointments. These clinical features, when present, marked a possible stepping stone on the pathway to future cognitive impairment (Reisberg, Gordon, McCarthy, Ferris, & de Leon, 1985). These preceding conceptualisations of memory complaints recognised the significance of an individual’s experience of memory loss, but limited the clinical semiology to generalised themes that were not evolved from a scientific investigation into the subjective experience. What is clear from these early forays into the clinical semiology, is that these symptoms of memory complaining in cognitively healthy older adults does not necessarily presage onset of AD (Crook et al., 1986; Reisberg et al., 1986; Reisberg et al., 1982), hence the development of terms referring to a benign form of senescent forgetfulness (Kral, 1962). Thus, subsequent to these initial steps towards defining the phenomenon, focus turned to the predictive quality of subjective memory complaints, in both their prognostic value for progression to AD, and their association with neuropsychological measures of new learning and retention (Abdurab & Heun, 2008; Jessen et al., 2014; Jonker et al., 2000).
1.5 Current concepts of a subjective memory complaint

The current trend of subjective memory complaints is to quantify the subjective phenomenon via questionnaires to ascertain the predictive value of the complaint (for reviews see: Abdulrab & Heun, 2008; Jessen et al., 2014; Jonker et al., 2000). Quantification is primarily based on measuring the presence or severity of the complaint (Abdulrab & Heun, 2008; Reisberg & Gauthier, 2008). That is, questionnaire data are used to develop global scores with continuous metric properties to quantify the severity of memory complaints (Amariglio, Townsend, Grodstein, Sperling, & Rentz, 2011; Hohman, Beason-Held, Lamar, & Resnick, 2011; Jorm et al., 2004). Alternatively, arbitrary cut-off scores can also be developed for metric scales in which individuals can be classified as memory complainers, if their score exceeds this value (Bartley et al., 2012; Jessen et al., 2010; Lautenschlager, Flicker, Vasikaran, Leedman, & Almeida, 2005). The assumption is that a monotonic relationship exists between memory complaints and objective evidence of memory impairment via tasks of new learning and retention (Blackford & La Rue, 1989; Derouesné et al., 1989; McGlone et al., 1990; Sunderland, Watts, Baddeley, & Harris, 1986). Outcomes on subjective memory complaint questionnaires (SMCQs) have not shown a consistent relationship with objective memory performance (Ahmed, Mitchell, Arnold, Dawson, et al., 2008; Bolla, Lindgren, Bonaccorsy, & Bleecker, 1991; Derouesné, Lacomblez, Thibault, & Le Poncin, 1999; Jungwirth et al., 2004; Lenehan, Klekociuk, & Summers, 2012; McGlone et al., 1990; Mendes et al., 2008; Minett, Dean, Firbank, English, & O’Brien, 2005; O’Connor et al., 1990; Purser, Fillenbaum, & Wallace, 2006; Stewart et al., 2008; Sunderland et al., 1986; Taylor, Miller, & Tinklenberg, 1992), particularly in the face of a strong relationship with affective symptomatology, such as depression (Aarts et al., 2010; Abdulrab & Heun, 2008; Blazer et al., 1997; Chin, Oh, Seo, & Na, 2014; Clarnette, Almeida, Förstl, Paton, & Martins, 2001; Jonker et al., 2000; Jorm et al., 2004; Jungwirth et al., 2004; Kahn, Zarit, Hilbert, & Niederehe, 1975; Lenehan et al., 2012; McGlone et al., 1990; Minett et al., 2005; O’Connor et al., 1990; Schmand, Jonker, Geerlings, & Lindeboom, 1997; Smith, Petersen, Ivnik, Malec, & Tangalos, 1996; Zandi, 2004; Zlatar, Moore, Palmer, Thompson, & Jeste, 2014). This failure for SMCQs to be related to memory performance is argued to be a result of poor criterion validity of subjective memory complaint phenomena as a prognostic measure of future memory decline (Bolla et al., 1991; Jorm et al., 1994; Lenehan et al., 2012; A. J. Mitchell, 2008a, 2008b; Purser et al., 2006; Riedel-Heller, Matschinger, Schork, & Angermeyer, 1999). As can be evidenced from the observations of complaints in temporal lobe epilepsy, major depressive disorder, AD and amnestic populations, it is clear that subjective experiences do not necessarily align in a dose-response manner with impairment on neuropsychological measures of new learning. It is problematic, therefore, to assume that SMCQs, with either binary or global score outcomes, can account for the counter-intuitive, idiographic and complex nature of subjective experiences.
A review conducted by Abdulrab and Heun (2008) argued that studies were vastly heterogeneous in the way they conceptualised memory complaining. Not only were studies using a vast array of different subjective memory complaint measures (discussed at length in Chapter 2), but also their recruitment methods were varied. The authors proposed the following operationalised criteria for standardised selection of memory complainers who were at risk of future cognitive decline; (1) older age at presentation (at least over the age of 50); (2) the presence of a complaint over a period of time (approximately six months); (3) an unfavourable comparison to previous memory function; (4) ability to provide examples of memory lapses; (5) the endorsement of frequent memory lapses (at least once a week); and (6) normal activities of daily living.

The authors made additional note of the onset of the complaint, which they argued might allude to the underlying pathology, for instance, gradual complaint onset might indicate DAT, while a staggered onset might indicate vascular pathology. A non-essential feature of the complaint was the support of a significant other’s (or other close informant) report and the spontaneous seeking of medical attention for the memory complaint. Abdulrab and Heun’s (2008) criteria departed from previous conceptualisations about memory complaints because of their attempt to operationalise participant selection, and standardise the terminology and classification of individuals with a complaint. None of these criteria are remarkable, as they appear in various diagnostic guidelines of preclinical AD (Derouesné, Kalafat, Guez, Malbezin, & Poitrenaud, 1994; Reisberg et al., 1986; Sperling et al., 2011), and particularly in the diagnosis of MCI (Albert et al., 2011; Gauthier et al., 2006; Petersen, 2004; Petersen et al., 2001; Petersen et al., 1999; Winblad et al., 2004). A description of the subjective elements of a complaint that accompanied a more malignant form was not presented.

This approach to the development of a common framework for operationalising memory complaints was extended by a working group, the Subjective Cognitive Decline Initiative (Jessen et al., 2014). Firstly, Jessen and colleagues (2014), called for the standardization of both the terminology, which they suggested to be ‘subjective cognitive decline’, and the features of a complaint that indicate preclinical AD. Current terminology is variable, with studies referring to subjective memory complaints, subjective memory impairment, subjective cognitive impairment, and similar variants. The authors argued that the term ‘complaint’ insinuated help-seeking behaviour, so they suggested decline’ as an alternative to refer to a concern that acknowledges change but does not presuppose formal help-seeking. Secondly, Jessen and colleagues (2014) proposed similar criteria to Abdulrab and Heun’s (2008) for isolating healthy older adults with subjective memory complaints that are higher risk of future conversion to AD. The point of conceptual departure was to include supplementary criteria regarding abnormal AD biomarkers or the presence of a genetic risk factor for AD, apolipoprotein E epsilon ε4 (APOE ε4). Preclinical AD workgroups, such as the Alzheimer’s Association Preclinical Alzheimer’s Disease...
Workgroup (Sperling et al., 2011), the US National Institute on Aging-Alzheimer’s Association (NIA-AA; Albert et al., 2011; McKhann et al., 2011), and the International Working Group (IWG; Dubois et al., 2010; Dubois et al., 2007), have proposed that the preclinical stage is primarily defined by evidence of abnormal AD biomarkers, such as \( \beta \)-amyloid (A\( \beta \)) burden and tau-related neurodegeneration, in the absence of objective cognitive impairment according to neuropsychological tasks. Jessen and colleagues (2014) recognised this increased risk of presenting with evidence of AD biomarkers, but called for an additional acknowledgement that evidence of subjective cognitive decline in these individuals strengthens the likelihood of future conversion to AD. Attenuated interest in subjective memory complaints by preclinical workgroups may well arise from the unresolved debate of whether complaints, as measured by SMCQs, are related to neuropsychological measures of memory in the face of a strong relationship with depressive symptomatology (Abdulrab & Heun, 2008; Benito-León, Mitchell, Vega, & Bermejo-Pareja, 2010; Chin et al., 2014; Clarinette et al., 2001; Hertzog, Dixon, & Hultsch, 1990; Jorm et al., 1997; Jorm, Christensen, Korten, Jacomb, & Henderson, 2001; Paradise, Glozier, Naismith, Davenport, & Hickie, 2011; Riedel-Heller et al., 1999; Schofield et al., 1997; Smith et al., 1996; Steinberg et al., 2013), which will be discussed further in Chapter 2.

With reference to Jessen and colleagues’ (2014) term “subjective cognitive decline”, this thesis will refer to the term “subjective memory complaint” for the following reasons; the term ‘memory’ adequately represents the focus of this thesis, which is on subjective assessments of memory loss. In this circumstance, the use of the term ‘cognitive’ is too inclusive and non-specific for the scope of this study. In addition, this thesis will use the term ‘complaint’ as this study is an investigation of the existence of concerns in non-demented individuals, including those with MCI who must present with a complaint as part of their diagnosis.

### 1.6 Everyday personal memories: an aspect of subjective memory

Mild cognitive impairment (MCI) forms the clinical intermediate stage between being classified as cognitively healthy and a diagnosis of dementia of the Alzheimer’s type (Gauthier et al., 2006; Petersen et al., 1999; Winblad et al., 2004). The current psychometric parameters for MCI diagnosis focus primarily on performance on neuropsychological tasks of new learning and retention, in conjunction with the presence of a memory concern and no evidence of ‘significant’ impairment in activities of daily living. Neuropsychological memory tasks, such as list and short-story learning tasks, are laboratory constructed to tap into episodic and semantic memory function. The ecologically valid memory systems that are measured-by-proxy via these tasks are autobiographical and personal semantic memories (Zelinski, Gilewski, & Thompson, 1980), but direct evaluation of everyday personal memories, do not form a part of the mainstream diagnostic approach to MCI. Everyday personal memories involve autobiographical and personal elements (Conway, 1996, 2006; Tulving, 1983, 1985,
1989, 2002), as well as the re-experiencing of personal events (or autonoetic consciousness, Conway & Pleydell-Pearce, 2000; Wheeler, Stuss, & Tulving, 1997). Autobiographical memory (ABM) involves highly contextualised emotional and spatiotemporal details connected to an event (Tulving, 1983, 2002), while personal semantic memory (PSM) involves self-related factual knowledge that is shared at a level that is limited to those who know the individual (Brewer, 1996; Robinson & Swanson, 1990; Tulving, 1989). A unique feature of an autobiographical narrative is the ability to actively relive the experience (Tulving, 1985), referred to as autonoetic consciousness. Autonoetic consciousness is the ability to mentally travel forwards and backwards in time (Wheeler, Stuss, & Tulving, 1997). It is an important quality for self-referential memory, not only for the re-experiencing of retrograde memories but also for the formulation of future plans and goals (Conway, 1995; 1996; Tulving, 1985; Wheeler, Stuss & Tulving, 1997).

Most likely, the sole gauge of memory function that an individual has access to is their ability to consolidate and retrieve everyday personal memories. It is therefore important to consider measures of ABM and PSM as another perspective of an individual’s phenomenological experience of memory change. Changes in these memory systems are likely to result in negative self-appraisal of memory, and therefore might provide a rationale for the presence of a memory concern. ABM and PSM represent the archetypal function of the medial temporal lobes (MTL: Addis, Moscovitch, Crawley, & McAndrews, 2004; Conway, 1990, 1996, 2005; Conway & Pleydell-Pearce, 2000; Gilboa et al., 2005; Moscovitch, 2008; Moscovitch et al., 2005; Svoboda, McKinnon, & Levine, 2006; Tulving, 1983). Studies of ABM and PSM performance in those with MCI, suggest that ABM is impaired compared performance in healthy older adults (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Gilboa et al., 2005; Greene, Hodges, & Baddeley, 1995; Hou, Miller, & Kramer, 2005; Irish, Lawlor, O’Mara, & Coen, 2010; Ivanoiu, Cooper, Shanks, & Venneri, 2006; Kopelman, 1994; Kopelman, Wilson, & Baddeley, 1989; Leyhe, Müller, Milian, Eschweiler, & Saur, 2009; Murphy, Troyer, Levine, & Moscovitch, 2008), but there is no consensus on PSM impairment (Irish et al., 2010; Kazui, Hashimoto, Hirono, & Mori, 2003; Murphy et al., 2008). In addition, no studies have yet investigated whether episodic or personal semantic elements of autobiographical narratives are compromised in healthy older memory complainers in comparison with healthy older adults without a concern.

### 1.7 Consideration of Alzheimer’s disease biomarkers

The term Alzheimer’s disease refers to the neurobiological components and underlying pathological trajectory of the disease, while dementia of the Alzheimer’s type refers to the clinical syndrome of the dementia. While these terms are sometimes used interchangeably in the literature, for the purposes of this thesis, the term dementia of the Alzheimer’s type will be used to refer to the clinical presentation, while the term
Alzheimer’s disease will be referred to as the pathological entity. Alzheimer’s disease involves two hallmark pathologies: the aggregation of insoluble Aβ protein to form extracellular amyloid plaques (Braak & Braak, 1991), and the hyperphosphorylation of tau protein to form neurofibrillary tangles (Braak & Braak, 1991, 1997). In vivo neuroimaging measures of AD pathology provide an avenue for identifying the influence of Aβ deposition and brain atrophy on subjective memory complaining. There is some evidence to suggest that subjective memory complaints, measured via SMCQs, are related to neocortical Aβ burden (Amariglio et al., 2012; Perrotin, Mormino, Madison, Hayenga, & Jagust, 2012), but this finding is far from conclusive. Much stronger evidence exists for a relationship between medial temporal lobe atrophy and greater memory complaint severity (Jessen et al., 2006; Stewart et al., 2008; van der Flier et al., 2004). In individuals with DAT, poor ABM performance is associated with bilateral medial temporal atrophy and anterolateral temporal neocortex. PSM, on the other hand, is associated with atrophy in the temporal neocortex, often bilaterally (Gilboa et al., 2005). Studies of ABM and PSM, on the other hand, have not investigated an influence of Aβ burden on poor performance, but poor ABM performance has been associated with bilateral medial temporal atrophy and anterolateral temporal neocortex, in individuals with dementia of the Alzheimer’s type. PSM, on the other hand, is associated with atrophy in the temporal neocortex, often bilaterally (Gilboa et al., 2005). Functional imaging of healthy adults suggests the ABM-PSM system as a cognitive entity is underpinned by a neural network involving medial and lateral temporal, prefrontal, and posterior parietal cortices (Addis, Moscovitch, et al., 2004; Cabeza & St Jacques, 2007; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Levine, 2004; Maguire, 2001; Niki & Luo, 2002; Svoboda et al., 2006).

The relationship between AD biomarkers and measures of new learning and retention is more widely studied, with the literature showing a consistent relationship between brain atrophy and memory task performance (Corsi, 1972; Delaney, Rosen, Mattson, & Novelley, 1980; Fink et al., 1996; Frisk & Milner, 1990; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Ojemann & Dodrill, 1985; Vyhnalek et al., 2014; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001) on memory. Some studies also show a relationship with neocortical Aβ burden (Bennett et al., 2005; Lim, Ellis, Ames, et al., 2013; Mormino et al., 2009; Rentz et al., 2011; Rentz et al., 2010; Sperling et al., 2013), but this relationship is complex, and will be discussed further in Chapter 2.

Assessment of everyday personal memories is an ecologically valid measure of memory that has been shown to tap into functions of the temporal lobe (Addis et al., 2004; Cabeza et al., 2004; Gilboa et al., 2004; Levine et al., 2004; Maguire, 2001; Niki et al., 2002; Svoboda et al., 2006), and currently does not form a part of the mainstream diagnostic approach to MCI. Diagnosis is informed, in part, by performance on neuropsychological measures of new learning and retention (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006; Fowler, Saling, Conway, Semple, & Louis,
2002; Petersen, 2004; Petersen et al., 2001; Winblad et al., 2004). These tasks are measures of veridical learning and recall that are sensitive, to varying degrees, to future progression to AD (Albert, Moss, Tanzi, & Jones, 2001; Collie & Maruff, 2000; de Jager, Hogervorst, Combrinck, & Budge, 2003; de Jager, Milwain, & Budge, 2002; Fowler et al., 2002; Lehrner et al., 2005; Nestor, Scheltens, & Hodges, 2004; Rabin et al., 2009; Salmon & Bondi, 2009; Salmon et al., 2002; Swainson et al., 2001) and have been shown to be strongly related to volumetric and functional neuroimaging measures of brain atrophy, particularly in the medial temporal lobe (Corsi, 1972; Delaney et al., 1980; Fink et al., 1996; Frisk & Milner, 1990; Nyberg et al., 1996; Ojemann & Dodrill, 1985; Vyhnalek et al., 2014; Yonelinas et al., 2001).

1.8 Scope and aim

This thesis is predominantly focused on investigating the subjective experience of perceived memory failures, both in terms of their expression in the form of a complaint and as an autobiographical narrative, and how this relates to neuropsychological measures of memory and AD biomarkers. The prevailing underlying supposition, that subjective experiences of memory loss are related isomorphically to objective evidence of memory dysfunction, is untenable as a conceptual standpoint with which to embark on an investigation of prognosis. As demonstrated above, subjective memory complaints can be counter-intuitive, with an internal logic that requires clinical evaluation. It is the inherently rich, descriptive quality of subjective experiences, which have the potential to inform diagnosis. It is worth stating at this point that the aim of this research is to characterise subjective memory complaints, but not to develop a diagnostic marker.

This thesis includes seven additional chapters, split into three broad sections. The first section comprises both Chapters 2 and 3. In Chapter 2, a literature review will discuss the three topic areas of interest in this thesis; current perspectives on subjective memory complaining, memory (namely, ABM, PSM and measures of new learning and retention), and AD biomarkers. First, the literature concerning subjective memory complaining in non-demented older adults will be discussed, with a particular focus on the most common methods of memory complaint measurement. Everyday autobiographical and personal semantic memories will then be introduced as a form of subjective memory. In vivo biological markers of Alzheimer’s disease will be introduced and discussed in relation to subjective memory complaints and neuropsychological measures of new learning and retention. The final section of the literature review will draw these topics of interest together in order to introduce the broad aims of the thesis and subsequent hypotheses. Chapter 3 will include the methodological aspects of this thesis, and a detailed discussion of each measure, and statistical analyses.
The second section includes the four experimental studies, Chapters 4 to 7. Chapter 4 contains an investigation of the strongest drivers of subjective memory complaint severity as measured via a widely-used questionnaire. In particular, this chapter focuses on measures of new learning and retention, affective and AD biomarker variables in healthy older adults and individuals with MCI. In Chapter 5, I will introduce a new perspective in the examination of subjective memory complaints. A semi-structured interview was developed and used to assay the nature and form of a memory complaint. A thematic analysis, using qualitative techniques used in a study of the psychosocial impact of surgical treatment of intractable epilepsy (Wilson et al., 1999), was conducted in order to determine what themes are prominent in a complaint in non-demented older adults. Levels of complaint theme endorsement was established in those who are classified as cognitively normal and those who have a diagnosis of MCI. Healthy older controls were also subsequently divided according to high and low Aβ burden to determine whether different phenomenological characterisations exist. Chapter 6 focuses on subjective experiences of personal memory in the form of autobiographical narratives, to investigate the pattern of ABM and PSM impairment in individuals with MCI. Chapter 7 included a consideration of the influence of AD biomarkers on autobiographical and personal semantic memory impairment. Much of the literature has focused on the relationship between AD biomarkers and veridical measures of memory, so measures of new learning and retention will be used as a benchmark to contrast against the influence of AD biomarkers on ABM and PSM.

The third section, Chapter 8, comprises a general discussion and conclusion and future directions chapters. I will discuss all findings within the context of all the other chapters and the literature as a whole. This thesis will end with a brief conclusion, discuss the broad implication of these findings, and provide recommendations for future directions in research.
Subjective memory complaints have been studied in many clinical populations such as MCI (Ahmed, Mitchell, Arnold, Dawson, et al., 2008; Crowe et al., 2006; Gallassi, Bisulli, Oppi, Poda, & Di Felice, 2008; Glodzik-Sobanska et al., 2007; Lam, Lui, Tam, & Chiu, 2005; Lautenschlager et al., 2005; Lenehan et al., 2012; A. J. Mitchell, 2008a; Reisberg & Gauthier, 2008; Roberts, Clare, & Woods, 2009; Sinforiani, Zucchella, & Pasotti, 2007; Werheid, Ziegler, Klapper, & Kuhl, 2010), major depressive disorder (Grön, Bittner, Schmitz, Wunderlich, & Riepe, 2002; Kahn et al., 1975), patients with a range of neurological disorders, such as temporal lobe epilepsy (Hall, Isaac, & Harris, 2009; O'Shea, 1996; O'Shea et al., 1996; Rayner et al., 2010), traumatic brain injury (Kinsella et al., 1996), and first-ever clinical lacunar syndrome (Anderson, Saling, & Donnan, 2008), patients with cancer (Cull et al., 1996), Parkinson’s disease (Erro et al., 2014), or chronic pain (Schnurr & MacDonald, 1995), stroke (van Rijsbergen, Mark, de Kort, & Sitskoorn, 2014), perimenopause (Weber & Mapstone, 2009), individuals with major depressive disorder who have received electroconvulsive therapy (Coleman et al., 1996; Prudic, Peyser, & Sackeim, 2000), and patients who undergo coronary artery bypass surgery (Newman et al., 1989). It is clear from this range of disparate neurological, somatic and psychiatric conditions, that memory complaining is a ubiquitous phenomenon that can emerge from organic and psychogenic origins.

2.1 Current methods of measurement

Current SMC measures present in a similar format to screening tools, as they predominantly capture the presence (Bartley et al., 2012; Bassett & Folstein, 1993; Blazer et al., 1997; Calley et al., 2010; Comijs, Deeg, Dik, Twisk, & Jonker, 2002; Comijs, Dik, Deeg, & Jonker, 2004; Crowe et al., 2006; K. A. Ellis et al., 2009; Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; Glodzik-Sobanska et al., 2007; Herzog & Rodgers, 1989; Heun, Kockler, & Ptok, 2003; Jessen et al., 2010; Jessen et al., 2007; Kurt, Yener, & Oguz, 2011; Lautenschlager et al., 2005; Luck et al., 2010; Mattos et al., 2003; Minett, Da Silva, Ortiz, & Bertolucci, 2008; Minett et al., 2005; Riedel-Heller et al., 1999; Schofield et al., 1997; St John & Montgomery, 2002; Tsai, Green, Benke, Silliman, & Farrer, 2006; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007) or severity (Ahmed, Mitchell, Arnold, Dawson, et al., 2008; Amariglio et al., 2011; Bolla et al., 1991; Clarinette et al., 2001; Ginó et al., 2010; Hohman et al., 2011; Jessen et al., 2007; Jorm et al., 2004; Jorm et al., 1994; Jorm et al., 1997; Jorm et al., 2001; Jungwirth et al., 2004; Kim et al., 2006; Lam et al., 2005; Langlois & Belleville, 2013; Lenehan et al., 2012; Maestu et al., 2011; Mendes et al., 2008; Minett et al., 2005; Montejo et al., 2013; Pearman & Storandt, 2004; Pearman & Storandt,
2005; Ponds & Jolles, 1996; Schmand, Jonker, Hooijer, & Lindeboom, 1996; Stewart et al., 2001; Troyer & Rich, 2002) of a memory complaint. Screening tools like these are appealing for their ease of administration (Folstein, Folstein, & McHugh, 1975), their ability to be administered to large at-risk populations (Herman, 2006), and because they do not require expert administration or scoring (Reisberg, 2007; Reisberg et al., 1982; Snaith & Zigmond, 1983; Yesavage et al., 1983). A multitude of subjective memory complaint measures exist, so for the purposes of this thesis, only those that are commonly used will be described, and a list of which can be found in Table 1.

One common method is to use a single question with the purpose of dichotomizing healthy individuals into complainers and non-complainers, such as ‘Do you have difficulties with your memory, yes or no?’ (Crowe et al., 2006; Ellis, et al., 2009; Geerlings, et al., 1999; St John & Montgomery, 2002; Tsai, et al., 2006; van Oijen, et al., 2007). Some researchers have suggested that this method limits the sensitivity or validity of subjective memory complaints (Jungwirth et al., 2004), and has the potential to inflate the prevalence of complaining (Ginó et al., 2010). Other studies champion the method’s ecological validity, as it imitates the reality of an interview with a general practitioner (Clarnette et al., 2001; St John & Montgomery, 2002). St John and Montgomery (2002) found an association, albeit weak, between memory complaints and progression to dementia using this method. The authors argued that using a lengthier questionnaire was not necessary, but would serve to strengthen the relationship. Some researchers argue alternatively that this measure might be over-inclusive, with a heterogeneity resulting in the dilution of a population more likely to progress to dementia of the Alzheimer’s type (DAT) (Edwards, Lindquist, & Yaffe, 2004).

Using a similar question, longitudinal studies have found an approximately tripled conversion rate (from ~1% to ~3%) to an MCI diagnosis in healthy memory complainers in comparison to healthy non-complainers over an 18-month follow-up (Elfgren, Gustafson, Vestberg, & Passant, 2010; K. A. Ellis et al., 2014; Jessen et al., 2010; Lehrner et al., 2005). Although a greater conversion rate is reported, studies like Ellis and colleagues’ (2014) have reported a substantial amount of fluctuation in responses to this question at follow-up, with 30% of non-complainers reporting a complaint at follow-up, and 25% of complainers reversing their concern (K. A. Ellis et al., 2014). A limitation with this measure is highlighted from this finding, as it is unclear why individuals were initially concerned for their memory, and why they retracted their negative self-appraisal. There is no way to determine the individual’s rationale behind this change. It is possible that upon an initial assessment the individual received positive feedback about their memory, which allayed their fear of dementia (Ahmed, Mitchell, Arnold, Dawson, et al., 2008; Kessler, Bowen, Baer, Froelich, & Wahl, 2012; Kessler, Südhof, & Frölich, 2014), but these SMCQs are non-interactive and so cannot provide more information beyond the simple flagging of an individual’s memory concern.
Likert-scale SMCQs are also common, where scores on questionnaire items can be combined to create an aggregate total score (Ahmed et al., 2008; Amariglio et al., 2011; Bolla et al., 1991; Ginó et al., 2007, 2010; Clarnette et al., 2001; Hohman et al., 2011; Jessen et al., 2007; Jorm et al., 1994; 1997; 2001; 2004; Jungwirth et al., 2004; Kim et al., 2006; Lam et al., 2005; Langlois & Belleville, 2013; Lenahan et al., 2012; Maestu et al., 2011; Mendes et al., 2008; Minett et al., 2005, 2008; Montejo et al., 2012, 2013; Pearman et al., 2004, 2005; Ponds & Jolles, 1996; Stewart et al., 2001; Schamd et al., 1996; Troyer & Rich, 2002). The outcome forms an individual’s complaint severity. A large range of questionnaires exist in this form (see Table 1), but they differ according to the way items are worded, the scenarios that are probed, and the length of the questionnaire. It is still unclear whether outcomes on these measures are comparable across studies (Abdulrab & Heun, 2008; A. J. Mitchell, 2008a). Some researchers argue that differing methods of measurement in a variety contexts could produce divergent analyses and conclusions about memory complaints (A. J. Mitchell, 2008a, 2008b; Mol, van Boxtel, Willems, & Jolles, 2006). Relating back to the notion of screening tools, these SMCQs are defined by their pre-set questionnaire items, which do not provide further information about areas of particular concern, and do not allow an individual to express nuanced issues relating to an item.

Lengthier SMCQs exist that can provide multiple aggregate scores on a variety of scales. These scales are predominantly relate to different memory score factors, which are created using factor analysis or clustering techniques (Hertzog, Dixon, Schullenberg, & Hultsch, 1987; Hertzog, Hultsch, & Dixon, 1989; Zelinski & Gilewski, 1988). These factors then represent their own scale within the questionnaire. For instance, the Metamemory Questionnaire (Zelinski et al., 1980) involves nine scales that are argued to measure a general rating of memory, frequency of forgetting in various situations, ability to remember occurrences recent or remote in time, importance placed on forgetting in various situations, frequency of using various mnemonics, ability to recall what is read in a novel, and the effort expended to avoid forgetting. The Multifactorial Memory Questionnaire, on the other hand, measure overall contentment of one’s memory ability, perception of everyday memory ability, and use of everyday strategies (Lenahan et al., 2012; Troyer & Rich, 2002). Dixon and Hultsch (1983) created the Metamemory in Adulthood questionnaire, which included several scales from factor analysis: Strategy, Task, Change, Affect, Achievement, Capacity, and Locus. Some have argued as to whether some of these SMCQs provide orthogonal scales, as questionnaires such as the Multifactorial Memory Questionnaire, show unconvincing loading of items in the original psychometric parameters of the scale (Hertzog et al., 1987; Hertzog et al., 1989).

As a screening tools, SMCQs gather the presence and/or severity of the memory concern (Goldberg, 1985), but can provide no further diagnostic information (Herman, 2006) because these measures are non-interactive and involve pre-set items.
In some studies, the subjective memory complaint is not measured, but is assumed to exist simply because the participants was recruited from a memory clinic (Archer et al., 2010; Edwards et al., 2004; Elfgren et al., 2010; Erk et al., 2011; Hurt, Burns, & Barrowclough, 2011; Hurt, Burns, Brown, & Barrowclough, 2010; Kearney-Schwartz et al., 2009; Lehrner et al., 2005; Manes, Serrano, Calcagno, Cardozo, & Hodges, 2008; O'Brien et al., 1992; Vestberg, Passant, & Elfgren, 2009). While these studies refer to this group as healthy memory complainers, they are distinct from healthy memory complainers from community-based studies in the following ways; a) recruitment from a memory clinic increases the incidence and severity of SMCs (Abdulrab & Heun, 2008; Edwards et al., 2004; Jessen et al., 2014; Jonker et al., 2000; Kessler et al., 2014), and b) changes their relationship with mood and cognition (Elfgren et al., 2010; Jonker et al., 2000; Vesterberg et al., 2009). In a cohort derived from a memory clinic, the incidence of memory complaints is considered to be more inflated and more severe (Abdulrab & Heun, 2008; Jonker et al., 2000). A recent qualitative analysis of formal help-seeking in healthy individuals with complaints found a qualitatively greater memory concern than those who do not seek clinical attention for their concern (Begum et al., 2012). Studies of healthy participants recruited from memory clinics also report much stronger relationship between depression and SMCs than those from community-based studies (Elfgren et al., 2010; Jonker et al., 2000; Vesterberg et al., 2009), although not all studies agree (Zlatar et al., 2014). The issue of participant recruitment is not within the scope of this thesis, but does raise the notion of divergent phenomenological experiences of memory loss different sample populations, which cannot be explored with screening tools.

2.1.1 Demographic, affective, cognitive and neuropathological correlates of subjective memory complaints

Subjective memory complaints are complex and multifaceted, and as such, relate to a range of factors in healthy older adults, such as affective symptomatology (Abdulrab & Heun, 2008; Chin et al., 2014; Clarnette et al., 2001; Paradise et al., 2011; Smith et al., 1996), education (van Oijen et al., 2007), age (Craik, 1994; Crook et al., 1986; Reisberg & Gauthier, 2008; St John & Montgomery, 2002), vascular risk factors, such as smoking and hypercholesterolaemia (Paradise et al., 2011), white matter hyperintensity (Kearney-Schwartz et al., 2009; Minett et al., 2005), glucose metabolism (Scheef et al., 2012), grey matter volumes (Striepens et al., 2010; Jessen et al., 2006; Saykin et al., 2006; Stewart et al., 2008; van der Flier et al., 2004), neocortical β-amyloid (Aβ) burden (Amariglio et al., 2012; Barnes et al., 2006) or cerebrospinal (CSF) fluid concentrations of Aβ40-42 (van Harten et al., 2012; Visser et al., 2009), apolipoprotein E ε4 (APOE ε4) genetic risk (Striepens et al., 2011), personality factors, such as neuroticism and conscientiousness (Pearman & Storandt, 2004; L. M. Reid & Maclullich, 2006), and subjective health status (Blazer et al., 1997; St John & Montgomery, 2002). The most predominant driver of memory complaints in healthy older adults is depressive symptomatology (Aarts et al., 2010; Abdulrab & Heun, 2008; Blazer et al., 1997; Chin et al., 2014; Clarnette et al., 2001; Jonker et al.,
2000; Jorm et al., 2004; Jungwirth et al., 2004; Kahn et al., 1975; Lenehan et al., 2012; McGlone et al., 1990; Minett et al., 2005; O’Connor et al., 1990; Schmand et al., 1997; Smith et al., 1996; Zandi, 2004; Zlatar et al., 2014), leading some researchers to argue that subjective memory complaints should be considered solely as an indicator of depressive symptomatology rather than an underlying organic disorder (Bolla et al., 1991; Gurland et al., 1976; Lenehan et al., 2012; M. Reid et al., 2011).

### 2.1.2 A question of prognostic utility

A large body of the literature on subjective memory complaints focuses on the quantification of the experience of memory loss, in the form of SMCQs, and operationalised within a predictive framework. As such, focus is predominantly placed on the relationship between subjective memory complaints and neuropsychological measures of new learning and retention. The results are mixed, with some studies reporting a modest association, after taking into account the effects of depression and age (Gagnon et al., 1994; Hertzog, Park, Morrell, & Martin, 2000; Jonker et al., 2000; Lam et al., 2005; Langlois & Belleville, 2013; Pearman & Storandt, 2004; Rouch et al., 2008; Zelinski, Gilewski, & Anthony-Bergstone, 1990). Others show a relationship, which does not survive the unique effect of depression (Benito-León et al., 2010; Chin et al., 2014; Hertzog et al., 1990; Jorm et al., 1997; Jorm et al., 2001; Riedel-Heller et al., 1999; Schofield et al., 1997; Steinberg et al., 2013). Yet others have found no relationship (Ahmed, Mitchell, Arnold, Dawson, et al., 2008; Bolla et al., 1991; Derouesné et al., 1999; Jungwirth et al., 2004; Lenehan et al., 2012; McGlone et al., 1990; Mendes et al., 2008; Minett et al., 2005; O'Connor et al., 1990; Purser et al., 2006; Stewart et al., 2008; Sunderland et al., 1986; Taylor et al., 1992), leading some researchers to question the prognostic utility of memory complaints (Bolla et al., 1991; Lenehan et al., 2012; A. J. Mitchell, 2008a, 2008b; Purser et al., 2006).

Longitudinal studies report more consistent findings in favour of a negative relationship (Geerlings et al., 1999; Glodzik-Sobanska et al., 2007; Hohman et al., 2011; Jessen et al., 2010; Jorm et al., 2001; O’Brien et al., 1992; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010; St John & Montgomery, 2002), although effect sizes are often reported as small (Hohman et al., 2011; Jorm et al., 2004). Jonker and colleagues (2000) argue that the lack of a consistent relationship is because of the mixed approaches to sampling. As discussed earlier, memory complaints of healthy older adults attending memory clinics can be more strongly underpinned by affect compared with healthy older adults recruited from the general community. Alternatively, some researchers have argued that a lack of relationship is the result of the use of memory tasks that cannot detect subtle memory impairment (Coley, Ousset, Andrieu, Matheix Fortunet, & Vellas, 2008; Dik et al., 2001; Jorm et al., 2001).
Memory complaints feature as a diagnostic criterion of MCI (Gauthier et al., 2006; Petersen et al., 1999; Winblad et al., 2004). Criteria for the classification of MCI also include predominantly normal activities of daily living, poor performance on one or more cognitive tasks compared to the norm for their age, and no evidence of dementia (Morris, 1993; Petersen et al., 1999; Reisberg et al., 1982; Winblad et al., 2004). While a memory complaint forms an integral component of MCI diagnosis, neither Winblad and colleagues (2004) nor Petersen and colleagues (Petersen et al., 2001; Petersen et al., 2009; Petersen et al., 1999) elucidate the clinical semiology of a memory complaint. Staging instruments, such as the Clinical Dementia Rating scale (Morris, 1993) and the Global Deterioration Scale (Reisberg et al., 1982), include memory complaining in their respective intermediary stages (which were defined two decades prior to proposal of the MCI diagnosis), but again do not define the clinical semiology. At the questionable dementia stage (stage 0.5), for instance, the Clinical Dementia Rating scale alludes to a “consistent slight forgetfulness”, but does not provide more information about the nature and form of the complaint. The Global Deterioration Scale (Reisberg et al., 1982) is more forthcoming, suggesting the following types of complaints in individuals with MCI: word or name-finding difficulties, the inability to function in high-performing jobs or to handle complex tasks, the inability to retain the thread of an argument or passage of a book, issues with getting lost when travelling to a new destination, issues with remembering names upon initial introduction or issues with poor concentration. To the author’s knowledge, this is the only clinical rating instrument to suggest types of memory complaints that can feature in MCI.

The severity of memory complaints peak around the diagnostic stage of MCI and attenuate at the mid to late stages of DAT (Förstl & Kurz, 1999; Jungwirth et al., 2004; Reisberg et al., 1986; Reisberg & Gauthier, 2008), found in Figure 1. Clinical anecdotal evidence suggests that individuals with DAT declare that all is well with their memory (Martin, 1975), often leading to over-estimation of memory ability (Clare, Whitaker, & Nelis, 2010; Green, Goldstein, Sirockman, & Green, 1993; Grut et al., 1993). Reisberg and colleagues (1986) argued that this attenuated complaint was a coping strategy or form of psychological defence, however, it is also possible that these individuals gradually lose a sense of conscious awareness of their memory impairment as the disease progresses (Grut et al., 1993; McDaniel, Edland, & Heyman, 1995; McGlynn & Kaszniak, 1991; Reisberg et al., 1985). The experience of memory loss in DAT is outside the scope of the present inquiry, but the ‘inverted U’ model presented by Reisberg and colleagues (1985) serves to highlight the potential for stage-associated memory complaint clinical semiology.
2.1.4 Characterising at-risk memory complaints

A small collection of studies has recognised the importance of characterising the types of complaint that might represent better predictors of cognitive decline (Amariglio et al., 2011; Bolla et al., 1991; Langlois & Belleville, 2013; Tobiansky et al., 1995). These studies were focused on using SMCQs to identify complaint types in psychometric terms. Tobiansky and colleagues (1995), for instance, examined whether particular SMCQ items were better predictors of diagnostic outcome (either major depressive disorder or dementia) in a community-recruited sample. They reported that positive responses to SMCQ items relating to particular memory lapses (for instance, forgetting what they are attending to) was more than five times more likely to indicate future progression to dementia. SMCQ items relating to the embarrassment of a suspected memory impairment, on the other hand, were four times more likely to relate to depression. The authors noted that this partial dissociation between items was possibly indicative of qualitatively divergent complaint phenomenology between the two groups. Bolla and colleagues (1991) suggested that a greater responses to the item ‘frequency of forgetting while reading newspapers and magazines’ in healthy older adults had a significant but small association with delayed recall of a short story ($R^2 = 0.02$). In a large cross-sectional study, Amariglio and colleagues (2011) found that items such as ‘an overall awareness of memory changes’ or ‘getting lost’ were associated with a greater likelihood of cognitive impairment (assessed via the brief Telephone Interview for Cognitive Status) in healthy older adults, after accounting for age and depression. The authors also reported a dose-response effect, such that more complaints related to a higher likelihood of cognitive impairment. Langlois and Belleville (2013) used data reduction techniques to identify seven factors of complaint items from a 62-item SMCQ, the Self-Evaluation Questionnaire (Van der Linden, Wyns, Coyette, von Frenckell, & Seron, 1989). The factor defined as ‘memory failures
with consequence’ related to less functional autonomy (as measured via the Instrumental Activities of Daily Living), and with poor performance on word list learning, but with only a small effect size ($R^2 = 0.06$). These findings, while small in number, suggest that certain types of complaints, as measured via SMCQs, may well align more closely with cognitive and functional impairment, while others might signify affect-driven responses. An underlying problem with using SMCQs to characterise at risk complaints is that these measures are non-interactive and items are pre-set. This results in responses that provide no information over and above the quantified score, and neglects the rich, descriptive detail gained from qualitative narratives, which have the potential to shed light on group-level phenomenological differences of memory change in pathological and non-pathological ageing.

### 2.1.5 Summary

The current method of measuring subjective memory complaints is to quantify the presence or severity of the concern for the purposes of prediction. The assumption is that more severe memory complaints will translate to poorer memory performance in a monotonic fashion. In light of inconsistent findings, and a strong relationship with depressive symptomatology, some studies have questioned the validity of SMCQs (Blackford & La Rue, 1989; Derouesné et al., 1994; McGlone et al., 1990; M. Reid et al., 2011), and yet others have questioned subjective memory complaints as a reliable concept in early detection of DAT (Lenehan et al., 2012; A. J. Mitchell, 2008b; Purser et al., 2006). The issue with this underlying assumption, is that subjective memory complaints are multidetermined, as demonstrated by the multiple cognitive, demographic and affective correlates, and often counter-intuitive, as evidenced by the ‘inverted-U’ model. The assessment of memory complaints as a simple unidimensional score within an SMCQ neglects the rich phenomenological experience attached to memory self-appraisal. In addition, the operationalized criteria set out by Jessen and colleagues (2014) and Abdulrab and Heun (2008) aim to standardize future subjective memory complaint studies, but provide no qualitative description of the clinical semiology of the complaints in the earliest clinical stages of the disease. This type of analysis is important to provide insight into the interim early stage outcome of accumulating memory deficits in individuals with MCI.
<table>
<thead>
<tr>
<th>Questionnaire name</th>
<th>SMC measurement description</th>
<th>Reference(s)</th>
</tr>
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<tbody>
<tr>
<td>No questionnaire</td>
<td>Enrolled through a linked memory clinic or hospital</td>
<td>Archer et al., 2010; Elfgren et al., 2010; Erk et al., 2011; Hurt et al., 2010, 2011; Kearney-Schwartz et al., 2009; Lerhner et al., 2005; Lojo-Seoane et al., 2014; Manes et al., 2008; O’Brien et al., 1992; Palm et al., 2013; Sinforiani et al., 2007; van Harten et al., 2013</td>
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<tr>
<td>No name: one question</td>
<td>Do you worry about your memory? or Do you feel like your memory is becoming worse?</td>
<td>Bartley et al., 2012; Bassett et al., 1993; Blazer et al., 1997; Calley et al., 2010; Comijs et al., 2002, 2004; Crowe et al., 2006; Dik et al., 2001; Ellis et al., 2009; Geerlings, et al., 1999; Herzog &amp; Rodgers, 1989; Heun et al., 2003; Jessen et al., 2007, 2010; Kurt et al., 2011; Lautenschlager et al., 2005; Luck et al., 2010; Minett et al., 2005, 2008; Reidel-Heller et al., 1999; Schofield et al., 1997; St John et al., 2002; Tsai et al., 2006; van Oijen, et al., 2007;</td>
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<td>Questionnaire name</td>
<td>SMC measurement description (cont.)</td>
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<tr>
<td>No name: one question</td>
<td>Comparison of your memory compared to other people of same age. 5-point Likert scale response.</td>
<td>Aarts et al., 2010;</td>
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<td>Ganguli et al., 2004;</td>
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<td>Johansson et al., 1997</td>
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<td>No name: four questions</td>
<td>With unknown Likert-scale Responses</td>
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<td>On the whole, do you think that your memory is good or poor?</td>
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<td>Do you think you have problems with your memory that make your life more difficult?</td>
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<td>Do you think that your memory has gotten worse during the past 2 years?</td>
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<td>On the whole, do you think that you have problems remembering things that you want to do or say?</td>
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<td>Johansson et al., 1997</td>
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<tr>
<td>Subjective Memory Decline Scale</td>
<td>Five questions (using 3-point Likert scale)</td>
<td>Jessen et al., 2007;</td>
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<td></td>
<td>Has your memory become any worse in some areas compared to earlier in life?</td>
<td>Jorm et al., 1994;</td>
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<td></td>
<td>Do you have more trouble remembering things that have happened recently?</td>
<td>Jorm et al., 1997;</td>
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<td>Are you worse at remembering where belongings are kept?</td>
<td>Jorm et al., 2001;</td>
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<td></td>
<td>Do you have trouble recalling conversations a few days later?</td>
<td>Jorm et al., 2004;</td>
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<td>Do you have more trouble remembering appointments and social arrangements?</td>
<td>Jungwirth et al., 2004;</td>
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<td>*Lam et al., 2005 involved slightly different questions along the same theme</td>
<td>Lam et al., 2005</td>
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<tr>
<td>Memory Assessment Clinics Questionnaire (MAC-Q)</td>
<td>6-item questionnaire reflecting five specific situations and one global SMC item. It uses a five-point Likert scale.</td>
<td>Fornazzari et al., 2009;</td>
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<td>Gallassi et al., 2008;</td>
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<td>Mattos et al., 2003;</td>
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<td>Minett et al., 2005, 2008;</td>
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<td>Amariglio et al., 2011;</td>
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<td>O’Connor et al., 1990</td>
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<tr>
<td>No name: seven questions</td>
<td>Binary responses to each question:</td>
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<td>Have you recently experienced any change in your ability to remember things?</td>
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<td>Do you have more trouble than usual remembering a short list of items, such as a shopping list?</td>
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<td>Do you have trouble remembering things from one second to the next?</td>
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<td>Do you have much more trouble than usual remembering recent events?</td>
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<td>Do you have any difficulty in understanding or following spoken instructions?</td>
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<td>Do you have more trouble than usual following a group conversation or plot in a TV program due to your memory?</td>
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<td></td>
<td>Do you have trouble finding your way around familiar streets?</td>
<td></td>
</tr>
<tr>
<td>Questionnaire name</td>
<td>SMC measurement description (cont.)</td>
<td>Reference(s)</td>
</tr>
<tr>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Geriatric Mental State Schedule (GMS)</td>
<td>Seven-item measure with a maximum score of 10, rates the presence and severity of memory difficulties, recent forgetfulness of names and objects, and efforts to remember things</td>
<td>Kim et al., 2006; Stewart et al., 2001</td>
</tr>
<tr>
<td>Subjective Memory Scale</td>
<td>8 items derived from the Cognitive Difficulties Scale (McNair &amp; Kahn, 1983) with a 3-point Likert scale</td>
<td>Dérouesne et al., 1989, 1999;</td>
</tr>
<tr>
<td>Ten questions (with binary response)</td>
<td>Regarding everyday memory problems experienced in the preceding month, summed to a total of ten.</td>
<td>Geerlings et al., 2008</td>
</tr>
<tr>
<td>SMC scale</td>
<td>Answer ten individual items concerning difficulties with day-to-day scenarios (scoring between 0-21)</td>
<td>Schamd et al., 1996; Ginó et al., 2007, 2010; Mendes et al., 2008; Silva et al., 2014</td>
</tr>
<tr>
<td>Memory questionnaire (MQ)</td>
<td>12-item questionnaire probing recent changes in memory in different daily tasks with 4-point Likert scale</td>
<td>Harwood et al., 1998, 2004</td>
</tr>
<tr>
<td>Prospective Retrospective Memory Questionnaire (PRMQ)</td>
<td>16-item questionnaire is a measure of self-reported minor memory problems with 5-point Likert scale (scoring between 16 and 80)</td>
<td>Crawford et al., 2003; Crawford et al., 2006; Steinberg et al., 2013</td>
</tr>
<tr>
<td>Cambridge Memory Complaints Questionnaire (CMCQ)</td>
<td>20-item questionnaire with binary choice (yes/no) representative of everyday situations. It uses a five-point Likert scale.</td>
<td>Ahmed et al., 2008;</td>
</tr>
<tr>
<td>Cognitive Failure Questionnaire (CFQ)</td>
<td>25-item questionnaire asking questions relating to memory lapses in everyday activities.</td>
<td>Broadbent et al., 1982; Hohman et al., 2011; Sunderland et al., 1983; Maestu et al., 2011; Montejo et al., 2012, 2013; Collins &amp; Abeles, 1996; Levy-Cushraan &amp; Abeles, 1998; Pearman et al., 2004, 2005; Ponds &amp; Jolles, 1996</td>
</tr>
<tr>
<td>Memory Failures of Everyday (MFE) test</td>
<td>28-item questionnaire investigating different aspects of everyday memory using either a 9-point or 3-point Likert-scale</td>
<td></td>
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<tr>
<td>Memory Assessment Clinics Self-Rating Scale (MAC-S)</td>
<td>49-item questionnaire assessing Ability to remember and Frequency of occurrence of SMCs. It uses a five-point Likert scale.</td>
<td></td>
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<tr>
<td>Metamemory questionnaire (MMQ)</td>
<td>5-point Likert scale involving nine memory scales (general rating of memory, frequency of forgetting in various situations, ability to remember occurrences recent or remote in time, importance placed on forgetting in various situations, frequency of using various mnemonics, ability to recall what is read in a novel, and effort expended to avoid forgetting</td>
<td>Bolla et al., 1991; Hertzog et al., 1987; 1989</td>
</tr>
<tr>
<td>Questionnaire name</td>
<td>SMC measurement description (cont.)</td>
<td>Reference(s)</td>
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</tr>
<tr>
<td>Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)</td>
<td>CAM-COG is a subsection of the CAMDEX</td>
<td>Clarnette et al., 2001; Montejo et al., 2013; Roth et al., 1986;</td>
</tr>
<tr>
<td>Multifactorial Memory Questionnaire (MMQ)</td>
<td>Probes three dimensions of memory complaining: Contentment (18 items), Ability (20 items), Strategy (19 items) involving a 5-point Likert scale.</td>
<td>Lenehan et al., 2012; Troyer &amp; Rich, 2002; Chin et al., 2014d</td>
</tr>
<tr>
<td>Self-evaluation questionnaire (QAM)</td>
<td>62-item questionnaire using a 6-point Likert scale</td>
<td>Langlois &amp; Belleville, 2013; van der Linden et al., 1989;</td>
</tr>
<tr>
<td>Memory Functioning Questionnaire (MFQ)</td>
<td>64-item questionnaire using a 5-point Likert scale. *Crane et al., 2007, Crowe et al., 2006 and Parisi et al., 2011 used a shortened version which involved a 7-point Likert-scale</td>
<td>Crane et al., 2007; Crowe et al., 2006; Gilewski, et al., 1990; Hertzog et al., 2000; Parisi et al., 2011; Small et al., 2001; Taylor et al., 1992; Werheid et al., 2010; Zelinski et al., 1990</td>
</tr>
<tr>
<td>Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS)</td>
<td>87-item questionnaire involving self- and information-rating items. Assesses changes over the last 12 months on daily habits, personality, and motor functioning. A 4-point Likert-scale (scoring between 0-348)</td>
<td>Caselli et al., 2009; 2014</td>
</tr>
<tr>
<td>Metamemory in Adulthood (MIA)</td>
<td>108 statements with 5-point Likert scale response probing memory functioning and general knowledge of memory processes</td>
<td>Dixon et al., 1988; Ponds &amp; Jolles, 1996</td>
</tr>
<tr>
<td>Global Deterioration Scale (GDS)</td>
<td>Stage 2: the presentation of a SMC with no objective cognitive impairment. *Reisberg et al., 2010 also used the Brief Cognitive Rating Scale (BCRS; Reisberg &amp; Ferris, 1988) as a categorical analysis of SMCs</td>
<td>Glodzik-Sobanska et al., 2007; Mosconi et al., 2008; Reisberg et al., 1987, 2010;</td>
</tr>
</tbody>
</table>

**Note:** a Variations exist for this question but the intent is the same, b Asked about specific situations, c The first question was ‘Do you have complaints about your memory in the last 2.5 years?’ (sic), d This questionnaire was modified
2.2 The subjective experience of memory: autobiographical and personal semantic memory

Memory is most commonly assessed via veridical measures of new learning and retention that tap into medial temporal lobe (MTL) function (see Section 2.3). Arguably, the most ecologically valid assessment of memory, however, is via personal everyday memories (Kopelman, 1987). The assessment of the retrieval of everyday personal memories does not form a part of the mainstream diagnostic approach to MCI, and the rationale is most likely because of issues of validation (Brewer, 1992; Kopelman, 1987), quantification and assessment (J. R. Hodges, 1995; Elizabeth K Warrington, 1996). Nevertheless, changes in everyday personal memory function is the sole gauge of memory function available to individuals prior to seeking clinical attention (Leyhe, Müller, Eschweiler, & Saur, 2010; Leyhe et al., 2009; Seidl, Lueken, Thomann, Geider, & Schröder, 2011). Personal memory can be broken into two conceptually different but dynamically interactive systems, autobiographical memory (ABM) and the attached autonoetic experience, and personal semantic memory (PSM).

2.2.1 Relationship between autobiographical and personal semantic memory

ABM forms a part of the declarative memory system (Irish et al., 2010; Kopelman & Kapur, 2001; Tulving, 1983). Essential elements of ABM involve remembering the details of the event as they took place within a temporospatial and emotional context, with rich accompanying visual imagery (Irish, Lawlor, O’Mara, & Coen, 2011). This visual imagery forms a part of the self-referential nature of personal memory, or autonoetic consciousness (Wheeler, Stuss & Tulving, 1997), and is an important conceptual foundation of ABM (Conway, 1990, 1996, 2005; Conway & Pleydell-Pearce, 2000; Greenberg & Rubin, 2003). Souchay and Moulin (2009) argue that autonoesis underpins the ‘re-experiencing’ of a memory, where the ability to remember involves a conscious, effortful state of recollection, and is distinct from familiarity or ‘knowing’(Tulving, 1985; Yonelinas, Otten, Shaw, & Rugg, 2005). Conway (2006) attaches a sense of cognitive feeling to this consciousness, that is, an individual holds a sense of themselves in the past that is attached to the event-specific knowledge of the memory. Personal semantic memory (PSM), on the other hand, refers to personally relevant knowledge or facts about the individual (Brewer, 1996; Robinson & Swanson, 1990). This type of information can be repeated over time and across multiple contexts (Linton, 1982), and is shared by individuals with overlapping autobiographical experiences (Greene & Hodges, 1996; Westmacott, Black, Freedman, & Moscovitch, 2004). General semantic memory sits in contrast to PSM, as it encompasses abstracted knowledge that is shared at a societal level (Tulving, 1985). These distinctions of each form of personal memory (that is, ABM, autonoetic consciousness, and PSM) have
been found to be differentially affected in clinical populations, such as individuals with MCI (see section 2.2.2).

One conceptualisation of personal memory, put forth by Conway (1990, 1995, 1996) and Conway and Pleydell-Pearce (2000), proposes that ABM and PSM are conceptually inter-related and therefore difficult to disentangle. The authors argue that personal memory is dynamically assembled within a self-referential memory system comprised of three parts: the first consists of thematic and temporal knowledge that sits within the framework of lifetime periods, such as ‘when I was dating X’. The second part, general events, sit within lifetime periods and refer to more specific memories that could exist as one-off or repeated events, such as ‘our first date’ or ‘eating dinner at our favourite restaurant’, respectively. They could also feature in multiple lifetime periods such as ‘when I was living in X’ and ‘when I had my hair dyed blue’. This example exposes the ‘symbiotic’ relationship between ABM and PSM, which becomes particularly salient when reviewing the literature on ABM and PSM dysfunction in individuals with MCI.

2.2.2 Autobiographical memory in MCI and DAT

The literature examining the effects of MCI and DAT on personal memory function is relatively small, but studies show ABM dysfunction compared to healthy older adults (Addis, McIntosh, et al., 2004; Barnabe et al., 2012; Gilboa et al., 2005; Greene et al., 1995; Hou et al., 2005; Irish et al., 2010; Ivanoiu et al., 2006; Kopelman, 1994; Kopelman et al., 1989; Leyhe et al., 2009; Murphy et al., 2008; Seidl et al., 2011). A temporal gradient exists, with earlier childhood memories more ‘resilient’, while more recent memories are significantly affected (Greene et al., 1995; Irish, Hornberger, et al., 2011; Irish, Lawlor, Coen, & O'Mara, 2011; Irish et al., 2010; Kopelman & Bright, 2012; Kopelman et al., 1989; Piolino et al., 2003; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1988). The extent of retrograde ABM loss is argued to be related to the amount of damage to the medial temporal lobe (MTL), as evidenced by amnestic patients with hippocampal lesions (for a review see, Nadel & Moscovitch, 1997). Considering this preferential loss of recent ABMs in individuals with MCI, this thesis will focus on recent personal memory dysfunction in individuals with MCI. To the candidate’s knowledge, ABM function has not been studied in healthy older memory complainers, so this will be investigated in the present inquiry.

A pertinent question is how ABM performance in individuals with MCI is affected by AD pathology. To answer this question, one must first review the structural and functional imaging literature of ABM function in healthy adults. Structural studies suggest that hippocampal morphology influences autobiographical recall in MCI, although in regionally specific areas and not globally (Thomann et al., 2012). Reviews of functional magnetic resonance imaging (fMRI) studies investigating ABM functional networks highlights a “core” network involving the medial and lateral
temporal lobe, medial and ventrolateral prefrontal cortices (PFC), temporoparietal junction, retrosplenial/posterior cingulate cortex, and the cerebellum (Cabeza & St Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). These regions were argued to specialise in processes unique to the phenomenological re-experiencing of an event, and other generalised networks such as working memory and attention. Maguire (2001) reviewed both fMRI and positron emission topography (PET) studies and reported an overall pattern of medial and left-lateralised activation associated with ABM recall. A consistent finding in the functional imaging literature is that the recollective element related to ABM predominantly recruits hippocampal activity (for a review see, Eichenbaum, Yonelinas, & Ranganath, 2007), or parahippocampal activity (Levine, 2004; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). Taken together, these findings suggest that ABM recruits a diverse network for successful functioning, but the MTL region is undeniably central to the mnemonic processing of highly contextualised personal experiences (Piolino et al., 2008; Svoboda et al., 2006).

2.2.3 Autonoetic consciousness in MCI and DAT

Individuals with MCI and DAT also exhibit a deficit in the autonoetic recollection of ABMs (Irish, Lawlor, O’Mara, et al., 2011; Piolino et al., 2003). Irish and colleagues (2011) suggest that this deficit, which was also found in the healthy older adults in comparison with healthy middle-aged adults, might arise as a result of changes in prefrontal cortical function (Moscovitch, 1992; West, 1996). Remember/know (R/K)³ paradigms assess whether an individual feels that they ‘know’ the information (involving a familiarity with the information in the absence of further recollection) or whether they can recall particulars about the information, and are the most popular method of measuring autonoetic consciousness in patients with DAT (Dalla Barba, Mantovan, Ferruzza, & Denes, 1997; Piolino et al., 2003; Piolino et al., 2006). Studies using this paradigm have found reduced remember responses compared to know responses in patients with DAT (Dalla Barba et al., 1997; Piolino et al., 2003; Piolino et al., 2006). The problem is whether this paradigm measures the unique contribution of autonoesis to the memory (Irish, Lawlor, O’Mara, & Coen, 2008), as this paradigm does not elicit further responses from the individual about the act of recollection. A measure developed by Irish and colleagues (2008), probes different elements of autonoetic consciousness, such as the vividness of the imagery, viewer perspective, the continuity of the imagery, emotional re-experiencing, and overall re-experiencing of the event. Using this measure, the authors found that individuals with MCI exhibited impairments in the ability to generate vivid, self-referential visual imagery and to re-experience the original emotion of ABMs. The present inquiry will also use this measure to determine the pattern of impairment of autonoetic consciousness in MCI and healthy memory complainers, and how this system relates to AD biomarkers.

³ Remember/know paradigms involve a list of items that an individual endorses that they know conceptually (i.e. semantic connection) or in an episodic sense. (Tulving, 1989)
Neural correlates of the self-referential qualities of autonoetic consciousness are consistently conceptualised in the prefrontal cortex (Conway, 2005; Conway & Pleydell-Pearce, 2000; J. R. Hodges, 1995; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Patients with frontal lobe damage show fewer remember responses in the R/K paradigm (Levine et al., 1998; Levine, Freedman, Dawson, Black, & Stuss, 1999), and fMRI studies have found that self-referential processing and monitoring (functions of autonoetic consciousness) is related to activation in the lateral and ventromedial PFC (Cabeza & St Jacques, 2007; Yonelinas, 2002). Further evidence has been found in a fluoro-deoxyglucose positron emission tomography (FDG-PET) study of patients with DAT, where ‘remember’ responses were reduced compared to healthy controls, and subsequently related to glucose hypometabolism in the frontal lobes (Rauchs et al.). This association with the frontal regions may well have implications for influence of AD biomarkers on autonoetic consciousness.

2.2.4 Personal semantic memory in MCI and DAT

The level of impairment in PSM, as well as the rationale for its dysfunction in MCI, remains unclear. Some studies of individuals with MCI and DAT have reported a relatively spared PSM in the face of ABM impairment (Greene et al., 1995; Meulenbroek, Rijpkema, Kessels, Rikkert, & Fernandez, 2010; Murphy et al., 2008; Seidl et al., 2011). Greene, Hodges and Baddeley (1995) found impaired recall of ABM narratives in individuals with mild DAT, but relatively preserved recall of PSM. A study of individuals with MCI similarly reported a reduction of contextual (internal) details and elevation of incidentally-associated semantic (external) details within a personal narrative in comparison to healthy older adults (Murphy et al., 2008), a finding which has been mirrored, to a lesser extent, in healthy older adults in comparison with younger adults (Levine et al., 2002). Other studies, on the other hand, report that individuals with MCI and DAT are impaired in both ABM and PSM, particularly for recent memories (Irish, Hornberger, et al., 2011; Irish, Lawlor, Coen, et al., 2011; Kazui et al., 2003; Leyhe et al., 2009).

The functional imaging literature of PSM is sparse but most studies suggest the recruitment of the lateral temporal cortex (Gilboa et al., 2005; Kapur, 1999; Maguire, 2001; Moscovitch et al., 2005; Svoboda et al., 2006; Tulving, 2002). Addis and colleagues (2004) found activation of the hippocampal formation during PSM in their fMRI study of healthy adults, supporting Conway’s (1995; 1996) theory that of a dynamic interaction between ABM and PSM. These findings highlight the need to clarify the level of impairment of PSM in individuals with MCI, and whether different mechanisms of disease relate to each system.
2.2.5 Summary

Taking the literature as a whole, the following questions emerge: what is the pattern of ABM and PSM impairment in healthy memory complainers and individuals with MCI, and how are deficits in personal forms of memory influenced by AD biomarkers? An understanding of the breakdown of personal memory in the earliest stages of pathological ageing will aid the understanding of the likely antecedents of subjective memory complaints. SMCQs probe elements of personal memory lapses in items such as ‘do you put your keys down and forget where they are a little while later?’ (Amariglio et al., 2011; Crook et al., 1992; Jessen et al., 2007; Jorm et al., 1994), and ‘do you have problems with remembering things that you want to do or say?’ (Johansson, Allen-Burge, & Zarit, 1997), but have not formally investigated personal memory function in healthy memory complainers. In addition, while the neural correlates of ABM, PSM and autonoetic consciousness have been elucidated in functional imaging studies, research has yet to be conducted on the influence of AD neuropathology, such as β-amyloid burden and brain atrophy on each system.

2.3 Neuropsychological markers of new learning and retention

To reiterate a point made earlier, measures of ABM and PSM are ecologically valid measures of memory, but they do not form the main diagnostic approach to memory performance in MCI, which is the domain of neuropsychological tests of new learning and retention. These tasks are primarily characterised by paradigms that tap into the recall of verbal or nonverbal information over a short and long delay (Salmon & Bondi, 2009). The sensitivity and specificity of a clinical diagnosis of MCI using neuropsychological markers in conjunction with a clinical assessment is relatively high, between approximately 65% and 94% for both (Albert et al., 2001; Collie & Maruff, 2000; de Jager et al., 2003; Gauthier et al., 2006; Lehrner et al., 2005; Mura et al., 2013; Nestor et al., 2004; Rabin et al., 2009; Salmon et al., 2002). Test sensitivity to future progression to DAT is variable, with some new learning and retention paradigms particularly sensitive (Arnáiz & Almkvist, 2003; de Jager et al., 2003; Fowler et al., 2002; Mura et al., 2013). The following sections will illustrate the relationship that measures of new learning and retention have with MTL, and then discuss a particularly sensitive and early neurocognitive marker of future progression to DAT, arbitrary associative learning.

2.3.1 Neural correlates of measures of new learning and retention

Studies converge on the notion that paradigms of new learning and retention rely on MTL integrity (Bird & Burgess, 2008; Chan et al., 2001; Vyhnalek et al., 2014), the initial site of tau-related neurodegeneration in the topographical staging of AD pathology (Braak & Braak, 1991). Patients with amnesia, related to various forms of damage to the MTL, are characteristically impaired on these forms of memory tasks
Patients with unilateral anterior temporal lobectomy, particularly with excisions of the left hippocampus and/or parahippocampus, exhibit poor acquisition and recall of word lists and short prose passages (Barr, 1997; Delaney et al., 1980; Frisk & Milner, 1990; Kapur & Prevett, 2003; Mayes, 1991; Ojemann & Dodrill, 1985; Savage, Saling, Davis, & Berkovic, 2002; Elizabeth K. Warrington & McCarthy, 1988). The severity of the deficit not only relies on the amount of hippocampus excised (Corsi, 1972; Frisk & Milner, 1990) but also the extent of extra-hippocampal or lateral temporal lobe tissue removal (for instance, densely amnestic patient H.M. who underwent extensive bilateral resections of lateral and medial temporal lobe; Baxendale, 1998; Scoville & Milner, 1957; Weniger, Boucsein, & Irle, 2004). fMRI studies also show activation in the MTL when healthy adults participate in memory paradigms (Burianova & Grady, 2007; N. J. Cohen et al., 1999; Fink et al., 1996; Markowitsch, 1995; Nyberg et al., 1996; Yonelinas et al., 2001). Animal lesion studies of the perirhinal cortices (M. J. Buckley & Gaffan, 1998) and the hippocampus (Wallenstein, Hasselmo, & Eichenbaum, 1998), show similar impairments of new learning in tasks of paired associate learning. The MTL is clearly crucial for the encoding and consolidation of newly learned material, and MTL function can be accessed via measures of new learning and retention.

### 2.3.2 Varying sensitivity to early detection of DAT

These psychometric measures have differing levels of sensitivity to the early detection of DAT. The immediate and delayed recall of prose is a common measure of memory impairment used in the diagnosis of MCI (Grundman et al., 2004), and has been reported as a sensitive measure of future conversion to DAT (Rubin et al., 1998; Storandt & Hill, 1989), particularly when using a veridical scoring procedure (Abikoff et al., 1987; Johnson, Storandt, & Balota, 2003). This task includes grammatico-syntactical structure, however, which somewhat reduces the unique variance associated with the MTL (N. C. Ellis, 1996; Haut, Demarest, Keefover, & Rankin, 1994; Hermann, Wyler, Steenman, & Richey, 1988; Kemper, Jackson, Cheung, & Anagnopoulos, 1993; Saling, 2009). Word list-learning paradigms, on the other hand, are more sensitive to memory impairment in individuals diagnosed with MCI (Duara et al., 2011; Fowler et al., 2002; Grundman et al., 2004). Unlike prose paradigms, Saling (2009) argues that word lists possess a greater component of ‘arbitrariness’, as the list includes random permutations of words within semantic categories. It is this level of arbitrariness that is particularly dependent on MTL integrity (Lillywhite et al., 2007; Nestor et al., 2004; Saling, 2009; Wood, Saling, O’Shea, Berkovic, & Jackson, 2000). Lillywhite and colleagues (2007) found that hippocampal T2 relaxation times, a measure of tissue integrity, were linked to the consolidation of newly learned lists of words. List-learning tasks do include a semanticised component, as words are sampled from predefined semantic categories, so, do not solely recruit MTL function. Tasks that include a higher proportion of arbitrariness and less semantic components are those that probe the ability to pair verbal or non-verbal arbitrary pieces of information.
together (Saling, 2009). Paradigms which measure this ability, termed arbitrary associative learning (AAL), have been shown to be the most sensitive and specific neurocognitive marker of conversion to DAT (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Blackwell et al., 2005; Blackwell et al., 2004; Collie & Maruff, 2000; de Jager et al., 2003; de Rover et al., 2011; Fowler et al., 2002; Hannseuu et al., 2011; Harel et al., 2011; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; J. Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009; Rentz et al., 2011; Swainson et al., 2001; Zamboni et al., 2012).

2.3.3 Arbitrary associative learning: a well-established early indicator of DAT

Fowler and colleagues (2001) examined a range of neurocognitive tasks of list-learning, prose learning, and AAL, to determine their level of sensitivity to identifying those with MCI who would progress to DAT over 24 months. While list-learning and short-story learning tasks were able to predict conversion over time, the Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associate Learning (PAL) task, a computerised task that arbitrarily pairs random objects and locations, was able to sensitively classify individuals at baseline who were likely to convert later to DAT. Other studies using the CANTAB PAL also support this level of sensitivity (Ahmed et al., 2008; Blackwell et al., 2004; 2005; de Jager et al., 2003; Lee et al., 2003; Mitchell et al., 2009; Nester, Scheltens & Hodges, 2004). The task also shows high specificity to DAT against highly comorbid conditions such as depression (Swainson et al., 2001). Thus, as a well-established early neurocognitive marker of DAT, AAL is be a suitable choice for measuring memory performance in non-demented older adults.

Studies of temporal lobe epilepsy (TLE) patients and functional neuroimaging studies of healthy adults have provided the clearest insight into the underlying neural correlates of AAL. Patients who have undergone left anterior temporal lobectomy to treat intractable TLE demonstrate significant impairment in recalling arbitrary word pairs (Saling et al., 1993; Wood et al., 2000). More specifically, the rhinal cortices have been implicated in their unique contribution to performance on AAL paradigms in patients with TLE who specifically underwent rhinal cortical resection (Weintrob, Saling, Berkovic, & Reutens, 2007). These findings are also supported by FDG-PET (Weintrob, Saling, Berkovic, Berlangieri, & Reutens, 2002), and MRI T2 relaxometry studies (Lillywhite et al., 2007), that show activation of the rhinal cortices during verbal AAL paradigms. fMRI studies of AAL performance in non-demented adults have also highlighted bilateral activation of various regions of the medial temporal lobe, that is, the entorhinal cortex (Owen, Milner, Petrides, & Evans, 1996), hippocampus and parahippocampal gyrus (de Rover et al., 2011; Strange, Otten, Josephs, Rugg, & Dolan, 2002).
AAL involves the obligatory and rapid uptake of arbitrary information (N. J. Cohen et al., 1999; Eichenbaum, 2000; Moscovitch, 2008; Tulving et al., 1994), and the subsequent automatic binding of converging arbitrary inputs (N. J. Cohen et al., 1999; Eichenbaum, 2000, 2004; Henke, Buck, Weber, & Wieser, 1997; Tulving et al., 1994). Moscovitch (2008) and Cohen et al. (1999) argued for an obligatorily process or of arbitrary information in the environment, regardless of its importance, which they argued to be the specialty of the hippocampal region. Others implicate the rhinal cortices for this role (Fernández & Tendolkar, 2006; Saling, 2009). An elegant study of the neural correlates of AAL by Weintrob and colleagues’ (2002) found that arbitrarily linked word pairs were more closely correlated to FDG-PET uptake in the rhinal cortices than the hippocampus. The salience of the rhinal cortices in relation to AD, and also this thesis, involve post-mortem and imaging findings at the earliest stages of AD, which will be discussed shortly. In brief, Braak and Braak (1991) defined the trans-entorhinal region as the earliest to exhibit neurofibrillary tangles, one of the hallmark AD pathologies. Arbitrary associative learning is therefore an interesting neurocognitive marker of MTL integrity.

2.3.4 Summary

Measures of new learning and retention are a well-established method of investigating MTL function, and are sensitive early indicators of future progression to DAT. This is likely driven by AD-related pathological mechanisms originating in the trans-entorhinal region. AAL paradigms are particularly sensitive to DAT by tapping into rhinal cortical integrity, and are therefore an ideal candidate to measure memory function in non-demented older adults. For the purposes of this thesis, neurocognitive paradigms of new learning and retention, including the CANTAB PAL, word list learning and short story learning, will be used to measure memory function in healthy older adults and individuals with MCI as a comparison against personal memory function (ABM, PSM and autonoetic consciousness).

2.4 Alzheimer’s disease pathology

Both Aβ plaques and neurofibrillary tangles appear decades before manifestation of clinical symptoms (Braak, Thal, Ghebremedhin, & Del Tredici, 2011; Jack et al., 2013; Villemagne et al., 2011), suggesting a long prodromal phase (Amieva et al., 2008). The relationship between these two pathologies is unclear (Masters & Beyreuther, 2006; Mattsson, Blennow, & Zetterberg, 2009), with some findings suggesting an earlier onset of tauopathy (Braak et al., 2011), while others suggest cascade hypotheses that hinge on an initiation of amyloid abnormality (Hardy & Selkoe, 2002; Jack et al., 2013; Masters & Beyreuther, 2006). The topographical distribution of these pathologies follow a loose inverse pattern, such that neurofibrillary tangles become apparent in the limbic midline and work their way outward, while Aβ plaques first appear in the neocortex and work their way towards basal midline structures (Braak & Braak, 1991).
More specifically, initial stages of Aβ deposition begin primarily in the neocortex (excepting the primary sensorimotor cortex), followed by later stages which encroach on the remainder of the neocortex and the hippocampus. Neurofibrillary tangles, on the other hand, appear in the trans-entorhinal cortex, spreading to other limbic areas in individuals with MCI, and finally to the neocortex. For the purposes of this thesis, these initial stages of disparate locations of deposition are of interest as they could contribute to differing manifestations of subjective memory complaints, and impairment of ABM and PSM.

2.4.1 Biological markers of AD via neuroimaging

AD pathological changes can be measured in vivo using neuroimaging techniques. Aβ deposition is commonly measured via PET, via radiotracers that bind predominantly to insoluble neocortical Aβ in the brain (Clark, Schneider, Bedell, & et al., 2011; Klunk et al., 2004; Vandenberghhe et al., 2010). One common radiotracer involving the 11C isotope, 11C-Pittsburgh Compound B (PiB), has been reported extensively in the literature and has been found to align closely with the Braak and Braak (1991) stages of Aβ deposition (Jack et al., 2008; Klunk et al., 2004; C. C. Rowe et al., 2007). The isotope has a very short half-life, which creates feasibility issues involving clinical scanning facilities that require an onsite labs that can create the isotope on demand (Vandenberghhe et al., 2010). New radiotracers with a longer half-life have been introduced that use the 18F isotope, such as florbetapir (Clark et al., 2011; Doraiswamy et al., 2012; Rodrigue et al., 2012) and flutemetamol (Thurfjell, Lundqvist, Buckley, Smith, & Sherwin, 2013; Vandenberghhe et al., 2010). The standard uptake value ratio (SUVR), a unit of measurement used in all radiotracer techniques, signifies the amount of radioactivation from Aβ binding in regions of interest compared to regions unlikely to show Aβ burden (for instance, the cerebellum or pons). SUVR is a continuous measure, with qualitative cut-off points to divide groups into high and low levels of Aβ burden (Clark et al., 2011; Klunk et al., 2004; Rowe et al., 2007; Jack et al., 2008; Thurfjell et al., 2013).

Brain atrophy, on the other hand, is measured via structural MRI. Studies have shown a direct association between brain structural changes in each diagnostic stage and the temporal staging of neurofibrillary tangles (Ferreira, Diniz, Forlenza, Busatto, & Zanetti, 2009; Jack et al., 1997; Schroeter, Stein, Maslowski, & Neumann, 2009; Schuff et al., 2009; Tondelli et al., 2011; Whitwell et al., 2007). It is important to note that functional changes, particularly in the posterior cingulate and retrosplenial cortices, are thought to precede structural changes observed in these regions (Nestor, Fryer, Ikeda, & Hodges, 2003). For the purposes of this review, and considering the biomarker modalities that will be used, structural changes will be discussed at length. Both PET and MRI will feature in various chapters of this thesis as measures of AD pathology (see Methods chapter for more detail).
2.4.2 Hypothetical dynamic model of biomarkers

Jack and colleagues (2010; 2013) developed a model of the dynamic temporal sequence of biomarker abnormality as an individual progressed from healthy status to being diagnosed with MCI and then DAT. The original model hypothesized that abnormal elevation of Aβ biomarkers occurs early in the clinical disease process, followed by tau-mediated neurodegeneration (see Figure 2). The greatest rate of neocortical Aβ deposition is apparent in the earliest stages of the disease, that is, in healthy older adults and those with MCI, with a levelling off at the DAT stage (Villemagne et al., 2013), thus displaying a sigmoidal relationship (Jack et al., 2013; Jack et al., 2010). Neurodegenerative processes resulting in brain structural changes, however, were argued to appear at a much attenuated level healthy older adults and become significantly more pronounced at the MCI diagnostic level, and maintain a rapid rate in DAT. The dynamic model proposed in 2010 recognised the appearance of cognitive impairment, but did not include subjective memory complaining at the earliest stages. The updated hypothetical model included a threshold for the level of detection of biomarkers and clinical symptoms (see Figure 2, Jack et al., 2013), and was supported by evidence from real data arising from the AIBL study (Villemagne et al., 2013). This detection threshold is of particular interest for the present inquiry, as it suggests some amount of clinicopathological symptomatology that exists just below current levels of detection.

![Figure 2. Dynamic model of biomarkers as they become abnormal over time and across diagnostic stages (adapted from Jack et al., 2013)](image)

2.4.3 Genetic influence of apolipoprotein E epsilon 4 (APOE ε4)

The genetic risk for sporadic AD, apolipoprotein E epsilon 4 (APOE ε4), is related to an earlier onset of clinicopathological abnormalities (Jack et al., 2013; Jack et al., 2010). The exact role of APOE ε4 in the pathological cascade is unclear (Jiang et al., 2008), but some studies suggest an involvement in the proteolytic clearance of soluble
Aβ40-42, and thus playing a role in Aβ homeostasis (Hardy & Selkoe, 2002; Jiang et al., 2008; Poirier, 2000). Carrying APOE ε4 is strongly associated with Aβ burden (Lim, Ellis, Ames, et al., 2013; Pike et al., 2007; Poirier, 2000; Rodrigue et al., 2012; C. C. Rowe et al., 2014; Strittmatter et al., 1993; Villemagne et al., 2011), and has also been associated with hippocampal and entorhinal cortical atrophy (Schuff et al., 2009; Stewart et al., 2011; Striepens et al., 2011), increased white matter hyperintensities (de Leeuw et al., 2004; Steffens, Trost, Payne, Hybels, & MacFall, 2003), and reduced glucose metabolism in regions of interest in AD (Cherbuin, Leach, Christensen, & Anstey, 2007; During, Osorio, Elahi, Mosconi, & de Leon, 2011; Small et al., 2000; Small et al., 1995).

The proposed pathological mechanism of APOE ε4 is in the lack of clearing of extracellular debris, which leaves soluble Aβ to accumulate in extracellular space and subsequently aggregate into insoluble Aβ plaques (Hardy & Selkoe, 2002; Jiang et al., 2008; Poirier, 2000). Greater neocortical Aβ burden in APOEε4 carriers is therefore unsurprising, and should be included as a covariate when examining the influence of neocortical Aβ burden on clinical symptomatology.

2.4.4 Summary

In vivo AD biomarkers, such as PET and MRI, will be used in this thesis as a measure of AD neuropathology. In particular, these measures will be used to examine their influence on subjective memory complaints and personal memory function in non-demented older adults, with APOEε4 used as a covariate. The final section of this literature review will address studies that have investigated elements of these relationships.

2.5 AD biomarkers relationship with subjective memory complaints and neuropsychological measures of memory

2.5.1 Subjective memory complaints

Neocortical Aβ burden

Studies of the relationship between neocortical Aβ burden and subjective memory complaints has only recently started to gain momentum (Amariglio et al., 2012; Barnes, et al., 2006; Chételat et al., 2010; Jorm et al., 2004; Mielke et al., 2012; Perrotin, et al., 2012). Post-mortem studies of healthy older memory complainers show elevated levels of AD pathology, both Aβ plaques and neurofibrillary tangles, in comparison to non-complainers, even after accounting for depression and chronic

There are two predominant forms of Aβ, the Aβ42 which has 42 residues and the Aβ40 which has 40 residues. These two isoforms tend to form mixed fibrils that interlace and form plaques, and are the most common form of Aβ plaque to be measured in AD research (Gu & Guo, 2013).
illness (Barnes et al., 2006). Perrotin and colleagues (2012) found that healthy older adults with high Aβ load felt less confident in their overall memory function. Amariglio and colleagues (2012) found a relationship between higher Aβ load and a more severe complaint according to a composite of multiple subjective memory complaint measures (see Table 1), and that Aβ load was associated to complaints specifically pertaining to memory and executive function SMCQ items. Meilke and colleagues (2012) found that in a classification model of high and low Aβ load in healthy older adults, the best predictors were APOEε4 carrier status and age, but the inclusion of subjective memory complaint severity increased the strength of the model to a small but significant extent. Some studies do not report any relationship between memory complaints and Aβ burden (Pike et al., 2011; Rodda et al., 2010), or only report a relationship in carriers of APOEε4 (Rowe et al., 2010). An important point is that studies that do show a relationship, report a small to moderate effect size (between approximately 0.1 to 0.4), suggesting that this relationship is complex and requires further examination.

**Brain atrophy**

Subjective memory complaints in healthy older adults have been consistently associated with reduced brain volume, particularly in regions that are affected early in pathological process (Jessen et al., 2006; Peter et al., 2014; Saykin et al., 2006; Stewart et al., 2008; Striepens et al., 2010; van der Flier et al., 2004). For instance, Jessen and colleagues (2006) noted that healthy memory complainers showed reduced entorhinal cortical volume compared with non-complainers. Other studies have shown that hippocampal atrophy is related to more subjective memory complaints in healthy older adults (Stewart et al., 2008; van der Flier et al., 2004). In addition, an AD-like pattern of grey matter atrophy has also been found in healthy older memory complainers (Peter et al., 2014; Saykin et al., 2006), particularly in those who were Aβ positive (Chételat et al., 2010). Supporting these findings, Archer and colleagues (2010) found that healthy memory complainers who progress to MCI have increased rates of grey matter atrophy over a period of one year in comparison to those who maintain their healthy status. Taken together, these findings indicate that subjective memory complaints are an early marker of AD-related neurodegeneration, and are particularly influenced by the medial temporal lobe but there is mounting evidence for AD-related patterns of grey matter volume changes.

**APOE ε4**

APOE ε4 has an unclear influence on subjective memory complaining, with some studies showing that healthy APOEε4 carriers complain more about their memory (Dik et al., 2001; Laws et al., 2002; Mosconi et al., 2008; Small et al., 1999; Striepens et al., 2011; van der Flier et al., 2008), while other studies have found no modifying effect (Bartley et al., 2012; Clarnette et al., 2001; Harwood, Barker, Ownby, Mullan, & Duara, 2004; Lautenschlager et al., 2005). Healthy older APOEε4 carriers with memory complaints show altered glucose metabolism, and AD-like levels of CSF Aβ42
and tau (Mosconi et al., 2008). Healthy older APOEε4 carriers also show greater longitudinal hippocampal volume reduction compared to non-carriers (Stewart et al., 2008). The literature seems to suggest that APOEε4 plays an indirect mediatory role with subjective memory complaints, particularly through its influence on Aβ.

2.5.2 Measures of new learning and retention

Neocortical Aβ burden

As objective memory performance is not the primary focus of this thesis, the reader will be directed to noteworthy studies investigating the relationship between measures of new learning and retention and AD biomarkers. Studies show an elevation of AD biomarkers across the diagnostic span (Fjell et al., 2010; Hansson et al., 2006; Jack et al., 2008; C. C. Rowe et al., 2010; C. C. Rowe et al., 2007; Whitwell et al., 2007) during the DAT stage (Jack et al., 2013; Jack et al., 2010; Villemagne et al., 2013). Studies using cognitive screening tools, such as the Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-Cog), have found a relationship between longitudinal cognitive decline and greater Aβ burden (Doraiswamy et al., 2012). Studies using more sensitive measures of new learning and retention have found memory function, in both healthy older adults (Rentz et al., 2011; Rentz et al., 2010; Sperling et al., 2013) and individuals with MCI (Harrington et al., 2013), is influenced by neocortical Aβ deposition. A relationship in healthy controls has not always been supported (Aizenstein, Nebes, Saxton, & et al., 2008; Harrington et al., 2013; Jack et al., 2008; Pike et al., 2007), placing doubt on whether elevated AD biomarkers in healthy older adults are influencing subtle memory changes. One rationale for the unclear relationship is that current measures of memory are not sensitive enough to detect subtle cognitive changes (de Jager et al., 2003; Harrington et al., 2013). Most studies use composite memory scores to measure memory changes (Harrington et al., 2013; Lim et al., 2013; Pike et al., 2007), which are not targeted measures of memory, as they combine the unique variance from a range of different memory measures (K. Rowe, 2002). Interestingly, studies using more sensitive measures of new learning and retention, such as an AAL paradigm, have found Aβ burden in healthy older adults is related to memory impairment (Rentz et al., 2011), lending support to the argument that Aβ burden is having a subtle effect on memory performance. An alternative explanation is that Aβ load only has an impact when other AD risk factors are present, such as APOEε4 (Bennett et al., 2005; Lim, Ellis, Ames, et al., 2013) or subjective memory complaints (Rolstad et al., 2011). Lim and colleagues (2013) reported that healthy older APOEε4 carriers were the only group to show a relationship between neocortical Aβ burden and visual and verbal episodic memory performance. Rolstad and colleagues (2011) found that CSF Aβ42 levels were associated with poorer general semantic and working memory only in healthy memory complainers. Individuals with MCI are also at greater risk of further cognitive decline if they carry the APOE ε4 allele in addition to being Aβ positive (Daw et al., 2000; Dik et al., 2000; Lautenschlager et
What is clear from these findings is the existence of an impact of Aβ burden on memory performance, particularly when an individual carries APOEε4.

Brain atrophy
In individuals with MCI, brain atrophy has a well-established relationship with poorer performance on measures of new learning (Fox, Scahill, Crum, & Rossor, 1999; Jack et al., 2013; Jack et al., 2010). Volume reduction in the entorhinal cortex (de Leon et al., 2001; Dickerson et al., 2001), hippocampus (Hanseeuw et al., 2011; Troyer et al., 2012; Tupler et al., 2007), and overall MTL grey matter (Glodzik et al., 2011), is associated with memory dysfunction. Tupler and others (2007) reported a stronger relationship of APOE ε4 on cognitive impairment in healthy controls over and above that of hippocampal volume. This finding was supported by Striepens and colleagues (2011) who showed that carrying APOE ε4 had an effect on both memory performance and hippocampal volume in healthy memory complainers compared to non-complainers. Thus, the influence of MTL atrophy has a clear demonstrable influence on memory impairment, with some indication of mediation according to APOE ε4 carrier status.

2.5.3 Summary and diagrammatic cognitive model
Although the literature suggests a relationship between subjective memory complaints and neocortical Aβ burden in the early clinical stages of the disease, it has so far been reported in conjunction with attenuated effect sizes, suggesting that the relationship is complex. This is the first study to investigate the clinical semiology of memory complaining in individuals with evidence of neocortical Aβ burden. A relationship between memory complaints and MTL atrophy appears more robust, perhaps highlighting an awareness of memory loss that aligns closely to AD-related neurodegeneration. While ABM and PSM have not been studied at length in relation to AD biomarkers, there is evidence that neuropsychological measures of memory are adversely related to both Aβ burden and brain atrophy, particularly if the individual is a carrier of APOE ε4.

The following diagram depicts the theoretical cognitive model of subjective memory complaining, and how this may be influenced by components of personal memory (ABM/PSM/autonoetic consciousness), and underlying biomarkers of AD.
2.6 Research questions and aims

Subjective memory complaints are an important phenomenon in their own right as they form the bridge connecting an individual to clinical attention. SMCQs canvas the presence or severity of a complaint, with the aim of quantifying the subjective experience for the purposes of determining their predictive value. The underlying assumption is that subjective memory complaints have a dose-response relationship with memory impairment. A failure to find a consistent relationship between these two variables has resulted in the interpretation that memory self-appraisal is not a valid measure of an individual’s memory function, and thus should not form an MCI diagnostic criterion (Lenehan et al., 2012; Purser et al., 2006). As described earlier, memory complaints are often counter-intuitive, and thus require idiographic and interactive methods to elucidate their nuanced aspects. Subjective memory complaints, memory function (both autobiographical memory and new learning and retention), and AD biomarkers are all significant components of the clinicopathological landscape at the earliest stages of the disease. This inquiry seeks to clarify a number of issues surrounding memory change in non-demented older adults,
that is, the clinical semiology of subjective experiences of memory loss, the pattern of personal memory impairment, and the relationship of both of these subjective phenomena with cognitive, affective and biomarker factors.

Chapter 4 presents an investigation of the relationships between cognition, affect, AD biomarkers, and memory complaint severity, as measured via a commonly-used SMCQ, the MAC-Q (see Table 1). The next study builds on the work presented in the previous chapter by focusing on characterising the phenomenological experience of memory loss in those at risk of AD, that is, individuals with MCI and/or those with high Aβ burden (Chapter 5). In Chapter 6, I investigate the pattern of impairment in ABM and PSM in healthy memory complainers and individuals with MCI, to determine whether a breakdown in personal memory aligns with our current understanding of memory impairment in MCI. Finally, Chapter 7 presents findings that examine the potentially disparate AD pathological mechanisms underlying the impairment of episodic and semantic elements of personal memory in individuals with MCI.
CHAPTER THREE: Method

The studies in this thesis are cross-sectional, incorporating both quantitative (Chapters 4, 6 and 7) and qualitative (Chapter 5) research designs. The study presented in Chapter 4 examines the relationship between memory complaints canvassed via a commonly-used Likert-style questionnaire, memory performance, affect and AD biomarkers in non-demented older adults. Chapter 5 describes the development and implementation of a semi-structured interview, which characterises the phenomenological experience of memory complaints in pathological and non-pathological aging. The objective of Chapter 6 is to ascertain the pattern of impairment in episodic and semantic elements of autobiographical narratives in healthy memory complainers and individuals with MCI. Chapter 7 assesses the relationship between autobiographical memory, personal semantic memory and autonoetic consciousness, and AD biomarkers, to determine whether these memory systems are affected by differing underlying neurocognitive mechanisms. This methods chapter will first outline the methods and quantitative research designs of Chapters 4, 6 and 7, and then cover the qualitative analysis of Chapter 5.

3.1 Participants

For this thesis, eighty healthy older controls ($M_{age} = 75.61$ years, $SD = 6.9$, range = 66 to 95 years) and 44 individuals with MCI ($M_{age} = 79.63$ years, $SD = 6.9$, range = 67 to 94 years) were recruited from the Australian, Imaging, Biomarkers and Lifestyle (AIBL) flagship study of ageing. The AIBL study’s recruitment procedure has been reported in detail previously (K. A. Ellis et al., 2009) and is outlined below. Participants were recruited from both the Melbourne and Perth AIBL study sites.

3.2 Recruitment

The larger AIBL ageing study

Human Research Ethics Committee approval for the larger AIBL study was obtained in Victoria from St Vincent’s Hospital and the Austin Hospital, and Hollywood Private Hospital in Western Australia. The studies in this thesis were also approved through the University of Melbourne and amendments were passed through the hospitals to conduct these studies. The aspects of assessment directly relevant to this thesis took approximately one hour to complete (including the qualitative interview). The larger AIBL study of ageing is a longitudinal study that involves follow-up assessments every 18 months. At the time of recruitment of the current study, the 36 month assessment for the larger AIBL study had commenced. The AIBL study’s baseline recruitment procedure has been outlined in previous literature (K. A. Ellis et al., 2009; K. A. Ellis et al., 2010; K. A. Ellis et al., 2014). The healthy control (HC) cohort is a convenience
sample recruited primarily via media appeal, and also via information distributed through treating specialists. Individuals with MCI, were primarily referred from a geriatrician, geriatric psychiatrist, neuropsychologist or other medical professional, but could also be diagnosed from the general community. Individuals responded by phoning in their interest, and all participants were administered an initial telephone screening questionnaire. Telephone questions were focused on basic demographic data (age and gender), medical history (of previous diagnoses of dementia, psychiatric disorders, Parkinson’s disease, stroke, cancer, cardiovascular diseases, diabetes, head injury, sleep apnoea and average daily alcohol intake). The screening questionnaire was not conducted beyond the baseline time point, though some elements of it (i.e. current medical and medication history and current alcohol use) were repeated in parts of the follow up assessments. At each time point, individuals were asked whether they noticed any difficulty with their memory function (with the question, “do you have difficulties with your memory?” with a binary yes or no answer elicited). If HCs responded in the affirmative, they would be placed in the subjective memory complaining group. HCs in the AIBL cohort, who underwent PET imaging, were enriched with APOE ε4 carriers, although the overall proportion of APOE ε4 carriers in the AIBL baseline cohort was consistent with levels reported in other large Australian studies (Corbo & Scacchi, 1999; R. N. Martins et al., 1995).

To be considered for the AIBL study, individuals had to be over 60 years old. Exclusion criteria for the larger AIBL study were as follows: a diagnosis or history of non-AD dementia, schizophrenia, history of sleep apnoea, bipolar disorder, current depression (either through diagnosis or if an individual attained a Geriatric Depression Scale (GDS; Yesavage et al., 1983) score of greater than 5), Parkinson’s disease, cancer within two years, stroke, uncontrolled diabetes or current daily alcoholic intake of two standard drinks per day for women and four for men, epilepsy, or previous head injury with greater than one hour of post-traumatic amnesia. As the larger AIBL cohort had already implemented basic exclusion criteria at baseline, the current study did not perform a telephone screen. The exclusion criteria for the current study were an elevated GDS score of above 5 and a diagnosis of any dementia at the 36 month time point. This information could be gathered from the existing AIBL study database.

The current thesis

Participants for this thesis were recruited from the larger AIBL study of ageing at the start of AIBL’s 36-month follow-up. Only 18-month diagnostic classification information was available for the purposes of identifying HC and MCI participants (Ellis et al., 2014). At the 18 month follow-up, there were 692 HC and 82 MCI available to be contacted from the AIBL study. A power analysis, using G*Power: Statistical Power Analyses for Windows and Mac (Faul, Erdfelder, Lang, & Buchner, 2007) determined that for analyses involving the subjective memory complaint
questionnaire, the MAC-Q, 80 HC and 80 MCI were required. This was based on power estimates derived from previous use of the MAC-Q which demonstrated a large within-subjects effect size when comparing healthy memory complainers and non-complainers (Cohen’s d = 0.8, a priori sample size assuming alpha = 0.05 and power = 0.80; Hänninen et al., 1994). As a total of 82 MCI participants were available from the larger AIBL study, a decision was made to recruit 80 HC and 80 MCI.

Due to the large number of HCs in the AIBL study, a smaller subset of HC participants were randomly sampled from the larger cohort. AIBL identification numbers for HC participants were populated in a Microsoft Excel spreadsheet, and numbered consecutively in a list. Random numbers were subsequently generated in using a publicly available random number generation algorithm (French), and every AIBL ID randomly selected from the program was selected until 80 were obtained for either Melbourne or Perth. The random HC sample for the current study was convenience-based for the following reasons; as a matter of feasibility participants were chosen if they lived within 80 kilometres of the candidate’s Melbourne or Perth residence, as participants could have the choice to be visited in their homes. As 92% of participants in Victoria and 88% of participants in Western Australia lived within this perimeter, it was decided that this would not overly bias the sample. Statistical analyses were run to verify that there was no significant difference between individuals who live within and beyond 80km with regards to general demographic or cognitive variables. Secondly, if an HC or MCI participant, was partnered with another participant in the AIBL study, their partner would also be invited to participate. In the HC group, there were 10 randomly sampled participants with HC partners who agreed to participate. In the MCI group, 4 participants had HC partners, and one couple were both diagnosed with MCI.

As there were 82 MCI participants available to be contacted at the 18-month follow-up, no random sampling was conducted. All participants were contacted and invited to volunteer for the current study.

Melbourne

Healthy controls

Seventy-six HC participants were contacted in Melbourne, and 70 (34 males, 36 females) volunteered to participate. Four HCs declined to participate in this study because of lack of available times or travelling interstate or overseas, and two were unable to be contacted. Recruitment of HC participants in Melbourne was halted once 70 participants had been contacted, as we had exhausted MCI recruitment and decided to concentrate MCI recruitment on the Perth AIBL cohort.

MCI participants
Fifty-six participants were available to be contacted in Melbourne, with 24 MCI participants (9 males, 15 females) agreeing to participate in the current study (see Figure 3 for a diagrammatic description). As 36-month AIBL follow-up assessments were occurring at the same time as the current study’s recruitment, new classifications were made available. Nineteen MCI participants progressed to DAT and one participant to vascular dementia, before they could be contacted for the current study. Four participants lived greater than 80km from Melbourne CBD, three declined to participate in the current study, and one was deceased. On four occasions, individuals who were classified with MCI at the 18 month AIBL follow-up were subsequently reclassified as DAT at the 36 month follow-up occurring soon after they had participated in this study. Since these MCI participants were, in reality, early stage DAT at the time of their assessment in the current study, they were excluded from further analyses. Figure 4A gives a diagrammatic representation of the Melbourne recruitment of participants.

**Perth**

*Healthy controls*

Ten healthy controls (five males and five females) were recruited in Perth. These participants were invited to participate in order to determine whether both HC and MCI groups in Melbourne and Perth were comparable on demographic and cognitive variables.

*MCI participants*

After exhausting the sample of MCI participants in Melbourne, it was necessary to invite MCI participants from the Perth AIBL cohort to participate in the study. Of the twenty-six MCI participants that were available for contact in Perth, 19 (9 males and 10 females) agreed to participate in the current study. Three MCI participants were not able to be contacted, three were not interested in participating, and one cancelled on the day of the appointment and declined to volunteer. Figure 4B gives a diagrammatic representation of the Perth recruitment of participants.
3.3 Classification of MCI

The larger AIBL ageing study

MCI participants were primarily recruited via a referral from their medical practitioner, but they could also be recruited from the community sample that approached the study as a healthy volunteer. A consensus diagnosis would be made for each MCI participant at each time point, conducted under the auspices of an expert clinical review panel of old age psychiatrists, geriatricians, neurologists and clinical neuropsychologists. The classification followed the diagnostic protocol set out by Winblad et al., (2004) and Petersen et al. (1999). All MCI participants or their informants had to present with a complaint, demonstrate largely preserved activities of daily living, and report no significant functional decline in social or occupational spheres. Those who were referred by a medical professional were required to demonstrate performance below 1.5SD age-appropriate norms on at least one neuropsychological task in the AIBL assessment, while those who volunteered initially as a healthy control had to perform below 1.5SD age-appropriate on two or more.
neuropsychological assessments. For the current study, MCI classifications were verified on the AIBL database before contacting the participant.

### 3.4 Neuropsychological measures

#### The larger AIBL ageing study

The neuropsychological battery that was used in the larger AIBL study was administered by research staff who were predominantly neuropsychologists in training. Administration of the neuropsychological battery took approximately 2 hours. Tasks covered a range of cognitive domains, such as verbal and non-verbal memory, executive function, and language. Measures of verbal memory were the California Verbal Learning Test – second edition (CVLT Delis, Kramer, Kaplan, & Ober, 2000), and the Wechsler Memory Scale Logical Memory Story I only (LM D Wechsler, 1997). Non-verbal memory was measured using the Rey Complex Figure Test (RCFT Meyers & Meyers, 1995). Measures of executive function were D-KEFS verbal fluency (Delis, Kaplan, & Kramer, 2001), the Stroop task (Victoria version) (Strauss, Sherman, & Spreen, 2006), and the digit span and digit symbol coding subtests of the Wechsler Adult Intelligence Scale (WAIS D Wechsler, 1997). The shortened version of the Boston Naming Test (BNT Kaplan, Goodglass, & Weintraub, 1983; Mack, Freed, Williams, & Henderson, 1992) was used to measure language. These tasks will be discussed in more detail below.

Two cognitive screening tools, the Mini Mental State Examination (Folstein et al., 1975) and the Clinical Dementia Rating (CDR) scale (Morris, 1993), and an estimate of pre-morbid intelligence was measured using the Wechsler Test of Adult Reading (WTAR), were also included in the battery but were not included in any analysis of this thesis so they will not be dealt with further.

**California Verbal Learning Test (CVLT)**

This is a well-validated neuropsychological task (Baldo, Delis, Kramer, & Shimamura, 2002; Bondi et al., 1995; Collie & Maruff, 2000; Delis et al., 2000; Delis et al., 2005; Donders & Nienhuis, 2007; Rabin et al., 2009) that measures verbal new learning and retention (Salmon & Bondi, 2009). Participants are asked to free recall a list of sixteen words (four words from four different semantic categories) after a short and long delay, and to correctly recognise the words from a list of target and intrusion words. The initial retention variable measures an individual’s ability to learn the 16 words accrued over five trials, and is represented as a T-score. Short delay recall (also referred to as post-interference recall in sections of this thesis) measures the ability to recall words after an intervening trial of another list. Long delay recall measures an individual’s ability to recall words after a delay of approximately 30 minutes. The recognition variable measures an individual’s ability to recognise the studied words in
amongst a list of distractors. All variables were represented as z-scores, excepting the retention variable. For the purpose of this thesis, only the retention, short and long delay recall variables are used.

**Wechsler Memory Scale III - Logical memory (LM; Story 1)**

This is a widely-validated verbal memory task that measures learning and retention of short prose (Collie & Maruff, 2000; Cullum, Butters, Troster, & Salmon, 1990; Helmstaedter, Wietzke, & Lutz, 2009; Marquis et al., 2002; Rabin et al., 2009; D. Wechsler, 2001). This task measures both immediate and delayed recall. The first variable, immediate recall, assesses the individual’s ability to recall details of a short story immediately after it is read aloud. The delayed recall variable measures retention of the short story after approximately 30 minutes has passed. These scores are represented by age-scaled scores. Both of these measures are used in this thesis.

**Rey Complex Figure Test (RCFT)**

The RCFT is a non-verbal task that assesses memory and visuospatial ability (Fowler et al., 2002; Meyers & Meyers, 1995; Shin, Park, Park, Seol, & Kwon, 2006; Troyer et al., 2008). This task requires the participant to copy a complex pattern, and reproduce it after a short and long delay. Participants are also asked to recognise elements of the pattern. The copy variable of the RCFT determines the individual’s ability to reproduce a similar copy of the pattern that they see in front of them. The immediate recall variable requires an individual to draw the complex pattern to the best of their ability immediately after being shown the drawing. The 3 and 30 minute delay variables determine an individual’s ability to redraw the pattern after each period of delay. Finally, the recognition measure assesses an individual’s ability to correctly recognize different elements of the pattern. For the purposes of this thesis, the copy, 30-minute delay and recognition scores are used. These variables are represented as z-scores.

**Delis-Kaplan Executive Function System (D-KEFS) fruit and furniture switching (FFS)**

The fruit and furniture switching task is a verbal fluency task that features in the D-KEFS (Delis et al., 2001), and which measures executive function (Homack, Lee, & Riccio, 2005; Swanson, 2005). It requires the individual to say aloud words within the categories of fruit and furniture, while switching between each category over one minute. These scores are represented as z-scores.

**The Stroop task**
The Stroop task (Trenerry, Crosson, DeBoe, & Leber, 1989) assesses an individual’s ability to correctly read a word or a colour while competing stimuli are presented (for instance, the opposite word or colour). For instance, the individual may need to read the word ‘red’ even though the word is coloured blue. This measure has been validated in older adults as a measure of cognitive flexibility (Spieler, Balota, & Faust, 1996). This thesis will use only the total score, which is calculated as the total of correctly read colours and words before making a mistake within one minute, and is represented as a z-score.

The Boston Naming Test (BNT)

This is a language task that tests the ability to correctly identify objects in pictures (Kaplan et al., 1983). The AIBL study uses a validated and shortened 30-item version (Mack et al., 1992; Saxton et al., 2000). If an item is not recognised by the participant, they are given either a phonemic or semantic prompt. The total score of the BNT represents the total number of objects an individual can name without a phonemic cue, that is, it does not include correct responses made with a prompt. This thesis will include the total score in analyses, which is represented as a z-score.

3.5 Affective measures

Affective screening measures were sent out in the mail prior to the neuropsychological assessment. This included the Geriatric Depression Scale (GDS) and the Hospital Anxiety and Depression Scale (HADS Snaith & Zigmond, 1983).

Geriatric Depression Scale (GDS)

The GDS is a 15-item screening tool for depression in older adults, developed and validated by Yesavage and colleagues (1983). Each question assesses different aspects of depressive symptomatology. The individual is asked to respond according to their observations over the past week. A score above five is considered to be elevated, and requiring further clinical evaluation (Yesavage et al., 1983).

Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated (Bjelland, Dahl, Haug, & Neckelmann, 2002) 15-item questionnaire of anxiety and depression (Snaith & Zigmond, 1983). It requires binary responses of ‘yes’ or ‘no’. The responses that have been highlighted in grey on the coding sheet are given a score of one, with a higher score indicating more depressive or anxious symptomatology. This symptomatology must be experienced within the last week. A score of greater than 11 on either anxiety or depression scores is considered as
clinically elevated or potentially diagnosable upon further clinical investigation (Bjelland et al., 2002).

### 3.6 Subjective memory complaint questionnaire

The AIBL study included a memory complaint questionnaire, the Memory Assessment Questionnaire (MAC-Q Crook et al., 1992) in a package that was sent out to individuals, and was used to determine memory complaint severity.

**Memory Assessment Clinics Questionnaire (MAC-Q)**

The MAC-Q is a brief six-item questionnaire, and is a shortened version of the Memory Assessment Clinics Self-Rating Scale (MAC-S) developed by Crook and Larrabee (1990). It is intended to assess the more generalized notion of “global memory ability” (Abdulrab et al., 2008). MAC-Q scores range from 5 to 35, with a higher score indicating a more severe concern about memory (see Appendix A for the questionnaire). The internal consistency has been reported as moderate (Cronbach’s α = .57) with a strong test-retest reliability of .67 (Crook, Feher, & Larrabee, 1992). The MAC-Q was included for the first time at the 18 month follow-up assessment in the larger AIBL study, and is used in Chapter 4 of this thesis.

### The current thesis

This thesis included three additional measures: a semi-structured qualitative interview of subjective memory complaints (Chapter 5), a measure of autobiographical and personal semantic memory (Chapters 6 and 7), the Episodic Autobiographical Memory Interview (EAMI Irish et al., 2008), and a non-verbal arbitrary associative learning paradigm, the Paired Associates Learning (PAL) task (Robbins et al., 1994), which was used in all experimental chapters.

**Memory complaint semi-structured interview**

The semi-structured interview was developed, using clinical anecdotal experience, to elicit a rich description of an individual’s subjective experience of memory changes. The interview mirrors that of a normal clinical evaluation, and was structured to probe circumstances in which memory lapses were likely to occur (see Appendix B for the interview). It comprised eight different scenarios where memory lapses could occur, and included prompts to elicit responses from the participant. The semi-structured interview was developed, using clinical experience and aligning with previous interviews constructed by supervisor, MS (S. J. Wilson, Saling, Lawrence, & Bladin, 1999), to elicit a rich description of an individual’s subjective experience of memory changes. Prompts focused on the following: a) the subjective frequency of the
occurrence of memory lapses, b) the ability to recall, in detail, the most recent memory lapse, and c) how the individual recovered from the acknowledged memory lapse.

Each of the eight scenarios and probes were given in the same order for every participant. If the participant responded that they did not experience difficulties with a particular scenario, the interviewer would move onto the next question. Some participants would become distracted by a question and divert their response. In this case, the participant was allowed to continue until they finished and then they were moved onto the next response.

The candidate trialled the interview on 10 friends and family between 60 and 70 years of age who were not participants in the AIBL study. These interviews were recorded and transcribed, and notes were taken on how to improve for the next interview. Interviewees were also asked for their feedback on the interviewer’s style in order improve on rapport-building and other interviewing techniques. These interviews were also assessed by the candidate’s supervisor. Administration of the interview took approximately 30 minutes.

**Episodic Autobiographical Memory Interview**

The EAMI is a semi-structured interview that takes approximately 40 minutes to administer, and consists of a personal semantic memory (PSM) section, an autobiographical memory (ABM) section, and an autonoetic consciousness section. Appendix C displays the EAMI in its entirety. These interviews are recorded with the approval of the participant, transcribed, and scored by the interviewer and a blinded clinical neuropsychologist. Inter-rater reliability, as measured by intraclass correlation coefficient, was high for both ABM and PSM sections ($r_{ABM} = 0.92; r_{PSM} = 0.94$).

The PSM section focuses on the participant’s ability to recall recent personally relevant knowledge with precision. The section comprises three items that probe the following: recalling the full names of three friends the individual has only met within the past five years, the name of an establishment they frequent and how to get there from their house, and the exact day, month, year and location of a significant event that has occurred within the past five years. This totals to a maximum score of 14 for the PSM component. In an effort to avoid any compensatory effects that ABM may play on PSM, this section will be administered first.

The ABM section asks participants to recall an important event within the past five years and supply as many details as possible about the event. After a period of free recall, the participant is then probed for areas of ABM recall, highlighted in the Event Details Checklist developed by Moscovitch and colleagues (2000). These areas include event detail, temporal, spatial, sensory, implication of the event, emotion, and thought
recall. Each detail is awarded a maximum score of one point, which is summed to a maximum score of seven points.

The autonoetic consciousness section probes the participant’s autonoetic re-experience of the event from the ABM section. The following questions were asked: a) whether they see the event through first-person perspective (the variable was named perspective), b) whether the images of the event follow in a continuous sequence with no gaps (continuity), c) whether the event is dynamic or like watching a video (image quality), d) whether an individual feels an emotional connection with the memory, and e) did the individual feel that they were reliving the event. Each response had a binary outcome, that is, an individual could respond affirmatively (score of zero) or negatively (score of one) to each question. Negative responses were scored because the research question was focused on whether ABM, PSM or autonoetic consciousness is impacted in individuals with MCI.

For this study, the EAMI is modified to only focus on recent memories (within the past five years). The “recent” memory period is defined as any memory within the past five years (Irish, Hornberger, et al., 2011; Irish et al., 2008, 2010; Irish, Lawlor, O’Mara, et al., 2011). The scope of the present inquiry is to investigate the differences between healthy controls and individuals with MCI on clinically relevant grounds. The most sensitive cognitive indicators of conversion to Alzheimer’s disease involve tests of new learning and retention (Albert et al., 2001; Collie & Maruff, 2000; de Jager et al., 2003; Salmon & Bondi, 2009), which involve “recent” memories, so the intention was to mirror these tests by assessing recent autobiographical and personal semantic memories. Internal consistency for this modified version was calculated and reported in Chapters 6 and 7.

**Paired Associates Learning Task**

The PAL task was administered in the current study, not only due to its sensitivity as an early indicator of DAT, but also because all AIBL neuropsychological measures were used to help classify individuals as healthy, MCI or AD. The PAL task took approximately 15 minutes to complete. The tablet computer is raised on a stand on a table so that the screen faces the individual at an angle of approximately 70°, and is placed approximately 30 cm away. In this task, the participant is required to remember the locations of different patterns on a screen during multiple trials. Six boxes appear on the screen and are randomly “uncovered” to reveal different patterns (see Figure 5). Once all six boxes have been revealed, the patterns are presented in the middle of the screen, and the participant is prompted by the interviewer to correctly identify which one of the six boxes holds each pattern. If all boxes are chosen correctly for each pattern, the participant moves onto the next set of patterns. If an error is made, the trial is repeated until all patterns are matched with their boxes correctly up to a maximum of 10 trials. The clinical version of the PAL, which was used in the
current study, assesses eight stages in total (Robbins et al., 1994). The task commences with only one box concealing a pattern. After two sets involving one pattern, there are two sets involving two patterns, followed by two sets of three patterns, and then one set of six patterns in all six boxes. The final set involves eight patterns in eight boxes. If a correct response is not made after 10 trials, the test is terminated, and an adjusted score is given. This adjusted score allocates the individual the score of the lowest-performing individual that successfully completed the stage. For the purposes of this thesis, the variable that was used was the number of errors at stage 6, as it is most often in the literature (Blackwell et al., 2005; Blackwell et al., 2004; Fowler, Saling, Conway, Semple, & Louis, 1997; Fowler et al., 2002; Swainson et al., 2001), and has been previously validated in MCI populations (Fowler et al., 1997).

![Figure 5](image)

*Figure 5.* A pictorial representation of the PAL task on the CANTAB and is adapted from Nestor, Scheltens & Hodges (2004, p. S36). A = the encoding stage where the boxes are opened one by one to reveal a pattern. B = the retrieval stage where a pattern appears in the middle of the screen and the participant must choose the box they think held the pattern

### 3.7 Neuroimaging measures

Approximately a quarter of participants from the larger AIBL cohort were invited to undergo PET and MRI at baseline (C. C. Rowe et al., 2007). Image acquisition and processing was conducted by the larger AIBL study. The reader is directed to an in depth description of each neuroimaging procedure by Rowe and colleagues (2007; 2010) and Villemagne and colleagues (2013).
Table 2. Cross-tabulation of individuals who participated in an MRI or PET scan at the 18 month time point

<table>
<thead>
<tr>
<th>MRI</th>
<th>PET scan</th>
<th>None</th>
<th>PiB</th>
<th>Flutemetamol</th>
<th>Florbetapir</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>57</td>
<td>9</td>
<td>12</td>
<td>13</td>
<td>91</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>3</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>(HC: 1/MCI: 2)</td>
<td>(HC: 21/MCI: 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>60</td>
<td>39</td>
<td>12</td>
<td>13</td>
<td>124</td>
</tr>
</tbody>
</table>

PET imaging

Aβ imaging with PET was conducted using either $^{11}$C-Pittsburgh Compound B (PiB), $^{18}$F-florbetapir or $^{18}$F-flutemetamol. In the current study, 30 healthy controls and 11 individuals with MCI had PiB-PET imaging data available, while 12 participants (HC = 9, MCI = 3) had $^{18}$F-flutemetamol scans available, and 13 participants (HC = 12, MCI = 1) had $^{18}$F-florbetapir PET scans available for analysis (see Figure 6 for a diagrammatic representation).

A 30 minute acquisition was started 40 minutes post-injection of PiB, 20 minute acquisition was performed 50 minutes post-injection of florbetapir and 90 minutes post-injection of flutemetamol. For PiB-PET, standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV (Klunk et al., 2004; C. C. Rowe et al., 2010; C. C. Rowe et al., 2007), and the resulting tissue ratio termed SUV ratio (SUVR). As advocated by each pharmaceutical company, the whole cerebellum SUV was the reference region for florbetapir (Clark et al., 2011), while for flutemetamol the SUV reference region was the pons (Vandenberghe et al., 2010). Participants who underwent PiB-PET imaging would be classified as Aβ positive (Aβ⁺) when SUVR ≥ 1.5 [21], florbetapir when SUVR ≥ 1.11 (Clark et al., 2011), and for flutemetamol when SUVR ≥ 0.62 (Vandenberghe et al., 2010). For the purposes of this
thesis, the PiB SUVR index was considered as both a continuous variable, and a dichotomous variable (Aβ⁺ or Aβ¯). At the stage of publishing the results chapters for this thesis, continuous SUVRs for florbetapir and flutemetamol were not standardised, and therefore could only be treated a dichotomous variables (Aβ⁺ or Aβ¯). Dichotomous Aβ status is considered as comparable across PiB, flutemetamol and florbetapir (Villemagne et al., 2012).

**MRI**

Of the participants included in this thesis, thirty-three participants (HC = 22, MCI = 11) had MR scans available for analysis. T1-weighted MRIs were segmented into cerebrospinal fluid, grey and white matter. Estimates of grey matter as well as for left and right hippocampal volumes for each participant were calculated (for detailed methods, see Rowe et al., 2010). All volumes were normalized to intracranial volume. 3D T1 MPRAGE and a T2 turbospin echo and FLAIR sequence MRI was acquired for screening and co-registration with the PET images.

**APOE ε4 classification**

APOE ε4 carrier status was determined in all participants. A 0.5mL tube was sent off to pathology labs for APOE genotyping as described previously (Ellis et al., 2009).

**3.8 Procedure for the current study**

The candidate carried out all the additional assessments relevant to this thesis (as outlined in section 3.6). The additional assessments were conducted in the participant’s home, except for one participant who preferred to be assessed in an AIBL assessment room located at the Mental Health Research Institute (MHRI) in Oak Street, Parkville, Victoria. Individuals provided signed informed consent upon arrival after being given time to ask questions about the study. Any other individuals in the home were asked to relocate to another room to allow the participant to focus on the tasks. Six MCI participants requested that their significant other sit in the room with them, and in one instance, the significant other asked to stay in the room. The candidate asked them to stay in the periphery and not answer on behalf of the participant. With the participant’s consent and HREC approval, tape recorders were used to record the interviews, and detailed notes were taken in the interview of the participants verbal and non-verbal responses.

The order of administration of each task was the same for each participant; the EAMI and the semi-structured interviews were administered first, in order to build rapport and lower anxiety the participant may have about the computer task. Following the interview period, and a brief break, the PAL task was administered.
3.9 Statistical analysis

Chapter 4: Factors affecting subjective memory complaints in the AIBL ageing study: biomarkers, memory, affect and age

The aim of the study reported in Chapter 4 was to examine the influence of memory, affect and AD biomarkers on subjective memory complaint severity as measured by a widely-used questionnaire, the MAC-Q.

The CVLT-II retention, short and long delay, LM immediate and delayed recall and RCFT 3 and 30 minute delay variables were data reduced using principal components analysis (PCA), with an orthogonal rotation. Multiple hierarchical regression was used to determine the unique explained variance of each variable on memory complaint severity. The first multiple regression model included both healthy control and MCI participants, with demographic variables (age, diagnosis, education) in the first block, affective variables (GDS, HADS-Anxiety and HADS-Depression) in the second block, and memory factors in the third block. A separate hierarchical regression was run with the healthy control group only, in order to determine driving factors of memory complaint severity in this group. Due to the smaller sample size, a regression model was not used for the MCI group as this would lower the power of the model (Tabachnick & Fidell, 2007). Instead, Pearson product-moment correlations were conducted between memory complaint severity and age, memory variables and affect.

The second set of analyses, investigated the effect of AD biomarkers on memory complaint severity in healthy controls and individuals with MCI. The first block of the model included age, diagnostic category (HC vs MCI), and years of education. The second block included neocortical PiB SUVR, grey matter volume, left and right hippocampal volume and APOEε4 carrier status.

Chapter 5: Phenomenological characterisation of memory complaints in healthy Aβ positive individuals, healthy memory complainers, and those with mild cognitive impairment

The qualitative component of this chapter followed procedures outlined by analyses on psychosocial outcomes of individuals with surgically treated intractable temporal lobe epilepsy (S. J. Wilson et al., 1999). Participant’s responses were transcribed verbatim. Once all data had been collected and transcribed, the candidate and supervisor, MS, read through each interview. By consensus, codes, defined as phrases or sentences that contain a single theme or piece of information (Miles & Huberman, 1994), were extracted. In the context of the current study, codes were considered to be phrases which were meaningful to the person’s experience of their own memory function. These codes were assigned descriptive labels, for example, the phrase ‘I do
things when I think of them’, was labelled as a coping strategy. Discussions between
the coders, the candidate and MS, were held until an expert consensus was reached
for each code (Srikanth et al., 2004). Meticulous notes were kept during discussions in
order to keep track of the decisions surrounding each code. Similar codes were then
grouped into themes, and re-analysed and reconceptualised until a consensus was
reached. The transcripts were scored according to endorsements of each theme on any
of the eight questions such that an individual could possess a maximum score of eight
on each theme. In the derivation of categories, blinding wasn’t necessary, but to
determine whether themes were correctly scored, a clinical neuropsychologist was
given a random selection of 15% of participant’s transcripts to score using the
definitions of themes given to them. We found a strong consensus between the
neuropsychologist’s scoring and that of the candidate and MS.

For the quantitative sections of this chapter, non-parametric tests were used to
determine the difference in the level of complaint theme endorsement. Kruskal-Wallis
$\chi^2$ was used to compare the complaint themes according to diagnostic category (HC
non-memory complainer/HC memory complainer/MCI), while Mann-Whitney $U$ was
used for comparing complaint themes according to amyloid status ($A\beta^+/A\beta^-$).
Spearman rank-order ($\rho$) correlations were used to determine the relationship
between complaint themes, memory measures and depressive symptomatology. Partial non-parametric correlations were calculated between verbal and non-verbal
memory measures and complaint themes, with age and depression score as covariates.

Chapter 6: Personal memory function in mild cognitive impairment
(MCI) and subjective memory complaints

The aim of this chapter was to determine the pattern of ABM and PSM impairment in
healthy memory complainers (HC-SMC) and individuals with MCI in comparison with
healthy older controls without memory complaints (HC-NMC).

A multivariate analysis of variance (MANCOVA) was conducted to determine
how both ABM and PSM were affected by diagnostic category (HC-NMC, HC-SMC and
MCI) while taking into account the unique variance explained by age and depression.
A discriminant function analysis (DFA) was also used to determine the ability of
personal memory measures (ABM and PSM) to differentiate between HC and MCI
groups in comparison to a classification model that used neuropsychological measures
of new learning and retention to differentiate between HC and MCI. Finally, Pearson’s
correlations were conducted to determine the relationship between ABM, PSM and
neuropsychological measures of new learning and retention.

Chapter 7: Association between AD biomarkers and personal
memories
In this study, the objective was to determine the relationship between everyday personal memory systems, namely PSM, ABM and autonoetic consciousness, and AD biomarkers, that is, Aβ burden, grey matter and hippocampal volumes, and APOE ε4 carrier status. This study also investigated the ability of personal memory systems to classify individuals who were either amyloid positive or negative, and compare this against the classification ability of neuropsychological measures of new learning and retention.

PCA was performed on left and right hippocampal volume in order to reduce the issue of multicollinearity (Tabachnick & Fidell, 2007). Logistic regression models were performed to determine the ability of all AD biomarkers to predict each dichotomous autonoetic consciousness variable (perspective, continuity, image quality, emotional connection, and the overall recollective experience of an event). Linear regression models were performed to determine whether AD biomarkers predicted ABM or PSM performance, and these models were compared to the ability of AD biomarkers to predict performance on neuropsychological measures of new learning and retention (such as, CVLT (short and long delay), LM (immediate and delayed recall), and RCFT 30 minute delayed recall). A final step-wise linear regression model was performed to determine which personal or neuropsychological memory measure would best predict PiB SUVR as a continuous measure, while taking into account the unique variance explained by APOE ε4 carrier status.
CHAPTER FOUR: FACTORS AFFECTING SUBJECTIVE MEMORY COMPLAINTS IN NON-DEMENTED OLDER ADULTS: BIOMARKERS, MEMORY, AFFECT, AND AGE

The presence of a subjective memory complaint, either garnered from the individual themselves or an informant, is a criterion of MCI diagnosis (Petersen et al., 1999). Within the context of MCI diagnostic criteria, the subjective memory complaint serves the purpose of gauging an individual’s self-appraisal of their memory function in recent years, in the absence of previous neuropsychological evidence of cognitive function (Petersen et al., 1999). The most common memory complaint measures are those that determine the presence or severity of the complaint via SMCQs (see Table 1). Current conceptions of memory complaints, as measured via SMCQs, is that they relate in a monotonic fashion to neuropsychological measures of memory. The focus of Chapter 4 is to determine how cognitive, affective and AD biomarker variables relate to subjective memory complaint severity in healthy older adults and individuals with MCI.

4.1 The Memory Assessment Clinics Questionnaire

The Memory Assessment Clinics Self-Rating Scale (MAC-S; Crook & Larrabee, 1990), was developed to quantify memory complaint severity. Its lengthy duration prompted the development of the MAC-Q (Crook, Feher & Larrabee, 1992), a six-item shortened version (found in Appendix A). The MAC-Q is widely used in the ageing literature (Antikainen et al., 2001; Barker, Jones, & Jennison, 1995; Derouesné et al., 1994; K. A. Ellis et al., 2009; K. A. Ellis et al., 2014; Glodzik-Sobanska et al., 2007; Hänninen et al., 1995; Hänninen et al., 1994; Mattos et al., 2003; M. Reid et al., 2011), and is argued to assess global memory ability (Crook, Feher & Larrabee, 1992). Studies are mixed on whether higher total MAC-Q scores are related to greater cognitive impairment. Mattos and colleagues (2003) showed that there was no difference in list-learning performance between healthy memory complainers (a score >25 on the MAC-Q) and non-complainers. Similarly, Reid and colleagues (2011) reported that, although the MAC-Q showed high reliability and internal validity, scores were closely related to affect in healthy older adults and not memory function. Glodzik-Sobanska and colleagues (2007), on the other hand, found that inclusion of MAC-Q score significantly improved a classification model for individuals who would cognitively decline over time, with a sensitivity of 61-65% and specificity of 75-76%.

4.2 Memory complaining in relation to neuroimaging AD biomarkers

Neocortical Aβ burden
What is also unclear is whether memory complaints relate to neocortical Aβ burden. There are relatively few studies that have investigated the relationship between neocortical Aβ deposition and memory complaining in healthy older adults, but again results are mixed. Some studies show a relationship (Amariglio et al., 2012; Barnes, Schneider, Boyle, Bienias, & Bennett, 2006; Perrotin et al., 2012), but their reported effect sizes are only small to moderate, suggesting a complex relationship. Barnes and colleagues (2006) conducted post-mortem investigations into the relationship between memory complaints in cognitively normal older adults and AD pathology, namely Aβ plaques and tau tangles. Both levels of Aβ plaques and tau tangles were somewhat related to subjective memory complaints, measured via a questionnaire prior to death, although the effect size was small. They found this relationship survived the unique variance explained by depression, the existence of chronic illness, gender, education and age. Two PiB-PET imaging studies have supported this finding (Amariglio et al., 2012; Perrotin et al., 2012), although these effect sizes were also small, and not all PiB-PET studies have found a relationship (Pike et al., 2011; Rowe et al., 2007). Pike and colleagues (2011) did not find a relationship between memory complaints and neocortical Aβ burden, while Rowe and colleagues (2007) found that only subjective memory complainers who carried APOE ε4 were likely to show higher neocortical Aβ deposition, according to PiB-PET imaging. As such, the relationship between Aβ burden and memory complaints is still unclear.

**Brain atrophy**

More studies have investigated the relationship between brain atrophy and subjective memory complaints (Jessen et al., 2006; Saykin et al., 2006; Stewart et al., 2008; Striepens et al., 2010; van der Flier et al., 2004). Entorhinal cortical (Jessen et al., 2006) and hippocampal volume (Stewart et al., 2008; Tepest et al., 2008; van der Flier et al., 2004), and overall grey matter volume (Archer et al., 2010; Chételat et al., 2010; Saykin et al., 2006) have all been inversely related to greater memory complaint severity in healthy older adults, but no studies have investigated the relationship in individuals with MCI.

### 4.3 Aims of Chapter 4

It is unclear what cognitive, affective and AD biomarker factors drive memory complaint severity in healthy older adults and individuals with MCI, particularly when measured using the MAC-Q. The aim of this chapter is to elucidate these relationships, with objective of shedding light on potential divergent drivers of complaint severity in the diagnostic categories. This chapter was published in *International Psychogeriatrics* (R. Buckley et al., 2013), and will be presented in this format.
Factors affecting subjective memory complaints in the AIBL ageing study: biomarkers, memory, affect and age


Abstract

**Background:** The prognostic value of subjective memory complaints (SMCs) in the diagnosis of dementia of the Alzheimer’s type is unclear. While some studies have found an association between SMCs and cognitive decline, many have found a stronger association with depression, which raises questions about their diagnostic utility.

**Methods:** We examined the cross-sectional association between SMC severity (as measured using the MAC-Q, a brief SMC questionnaire) and affect, memory and Alzheimer’s disease (AD) biomarkers (β-amyloid deposition and the apolipoprotein E ε4 (APOEε4) allele) in healthy older adults controls (HC) (M = 78.74 years, SD = 6.7) and individuals with mild cognitive impairment (MCI) (M = 72.74 years, SD = 8.8). We analysed a sub-set of individuals drawn from the Australian Imaging Biomarkers and Lifestyle (AIBL) Study of Aging.

**Results:** SMCs were more severe in MCI patients as compared to HCs. SMC severity was related to affective variables and the interaction between age and group membership (HC/MCI). Within the HC group, SMC severity was related to affective variables only, while severity correlated only with age in the MCI group. SMCs were not related to cognitive variables or AD biomarkers.

**Conclusion:** SMCs were related to solely by poorer mood (greater depressive and anxious symptomatology) in the cognitively healthy older adults however mean levels were subclinical. This finding argues for the assessment of affective symptomatology in conjunction with cognitive assessment in older memory complainers. Future AIBL research will focus on assessing other AD biomarkers, such as brain atrophy and Aβ plasma markers, in relation to complaint severity. Once our 36-month follow-up data are collected, we propose to assess whether SMCs can predict future cognitive decline.
Introduction

A subjective memory complaint (SMC), preferably corroborated by an informant’s report, is a diagnostic criterion of mild cognitive impairment (MCI) (Petersen et al., 1999; Winblad et al., 2004). An SMC is used as a gauge of memory change that occurs prior to the individual’s first clinical presentation (Petersen, 2004). It is unclear how SMCs relate to the clinicopathological aetiology of dementia of the Alzheimer’s type (DAT) or whether they correlate with objective memory impairment. Objective memory impairment is a prominent feature of MCI (Gauthier et al., 2006) and is considered to be the primary diagnostic consideration for MCI over and above that of the memory complaint (Petersen, 2004). This is because a close relationship exists between cognitive impairment and neuropathology in MCI due to prodromal AD and early DAT (Jack et al., 2010). For instance, the pattern of brain volumetric changes from healthy older individuals to patients with DAT has been paralleled with the neuropathological distribution of tau reported by Braak and Braak (1991). The relationship between cognitive impairment and brain amyloid deposition as measured by 11C-Pittsburgh Compound B positron emission tomography (PiB-PET) imaging (Rowe et al., 2007), is less clear as amyloid deposition occurs years before cognitive symptoms arise (Jack et al., 2010).

Evidence is equivocal as to whether SMCs are predictive of the development of DAT (Jonker et al., 2000). Studies have associated SMCs with putative biomarkers for AD such as apolipoprotein E ε4 allele (APOE ε4) carrier status (Clarnette et al., 2001), brain atrophy (Chételat et al., 2010) and β-amyloid deposition (Rowe et al., 2010). SMCs in healthy older adults are also strongly associated with depression (Clarnette et al., 2001; Ginó et al., 2010; Glodzik-Sobanska et al., 2007; Lautenschlager et al., 2005), leading some researchers to suggest that they are, for the most part, affect-driven.

Most studies consider memory complaints as categorical, but important information can be lost when dichotomizing responses. Thus, we examined memory complaints as a continuous severity measure. Our aim was to examine the contributions of objective memory, affect and AD biomarker variables to complaint severity in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Aging (Ellis et al., 2009). We wanted to examine the different associative factors in healthy older individuals and those with mild cognitive impairment (MCI).

Methods

Participants

All volunteers provided written consent before participating in the study. The methods of recruitment and assessment have been published elsewhere (Ellis et al., 2009). The
study commenced in November 2006. The Human Research Ethics Committees of Austin Health and St Vincent’s Health in Victoria and Hollywood Private Hospital and Edith Cowan University in Western Australia approved the AIBL study. Exclusion criteria at baseline included excessive alcohol consumption, current diagnosis of a dementia other than AD, history of epilepsy or stroke(s), history of other neurological conditions likely to affect cognition (i.e. hypoxia, head injury), current diagnosis of clinical depression satisfying DSM-IV criteria for Major depressive disorder, or a score on the Geriatric Depression Scale (GDS) above 5, or insufficient proficiency in English to complete cognitive tests. A diagnostic review panel of neurologists, geriatricians, old age psychiatrists and neuropsychologists, chaired by DA, made a diagnosis of MCI, when appropriate, according to the diagnostic criteria initially developed by Petersen and colleagues (1999) and revised by Winblad and colleagues (2004). The measure of a memory complaint was based on a single question of, “Do you worry about your memory, yes or no?”. They reviewed all available data, barring the PiB results. MCI participants could not fulfill dementia criteria according to the DSM-IV-TR or ICD-10. If MCI participants were referred by a clinician to the AIBL study with a clinical diagnosis of MCI, they had to demonstrate a score 1.5SD below the relevant normative mean on at least one neuropsychological task within the AIBL psychometric battery for their study status to be considered as MCI. Individuals who initially volunteered as healthy controls had to score 1.5SD below the normative mean on at least two neuropsychological tasks in addition to reporting a memory complaint in order to gain an MCI diagnosis for study purposes. See Ellis et al. (2009) for full details. Participants were included in this study if they responded to the mail-out memory assessment clinics self-rating questionnaire (or the MAC-Q).

**Study design**

**Cognitive assessment**

Participants were seen every 18 months. They were sent various questionnaires to fill in before their neuropsychological assessment (see Ellis et al., 2009 for details). The MAC-Q was added to the AIBL clinical protocol at the 18-month follow-up, thus this was considered to be the baseline time point for data collection of SMC severity. Details of the MAC-Q items can be found in Appendix A (published as supplementary material online attached to the electronic version of this paper at http://www.journals.cambridge.org/ipg). All participants were assessed with a standard neuropsychological battery, which took approximately 2 hours to administer (for details and mean scores see Ellis et al., 2009). Cognitive assessors at both the Melbourne and Perth sites performed neuropsychological testing.

In the current study, a subset of measures collected at the 18-month follow-up was analyzed: complaint severity was measured via the MAC-Q total score (the summation of six Likert-scale items to a total maximum of 35) and was the dependent
variable (Crook et al., 1992). Verbal memory was assessed using both a list learning and story learning task i.e. the California Verbal Learning Test-Second edition (CVLT-II) immediate and delayed recall measures (Delis et al., 2000) and the Wechsler Memory Scale Logical Memory (LM; Story A only) immediate and delayed recall measures (Wechsler, 1945). Non-verbal memory was assessed via the Rey Complex Figure Test (RCFT) 3 and 30 minute delayed recall (Meyers and Meyers, 1995). The affective variables used were the Geriatric Depression Scale (GDS; Yesavage et al., 1983) and the Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1983).

**Image acquisition**

The AIBL imaging protocol (including image acquisition and analysis) has been outlined previously (Chételat et al., 2010; Rowe et al., 2010). Healthy controls (HC) who underwent PiB-PET imaging were preferentially recruited with the intent that approximately 50% should be APOEε4 carriers.

**11C-PiB PET Scanning**

The index used for measurement of amyloid burden in the brain was the standardized uptake value ratio (SUVR), which involved creating a ratio between the regional SUVs of interest (neocortical regions, i.e. the frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate regions) and the SUVs for a control region with characteristically low amyloid burden, usually considered to be the cerebellar cortex. In the current study, the SUVR index was considered as a continuous variable.

**Magnetic Resonance Imaging (MRI)**

T1- and T2-weighted MRIs were delineated into gray matter (GM), white matter (WM) and left and right hippocampal (Hi) volume for each participant (for process, see Rowe et al., 2010). These volumes were then normalized comparative to the intracranial volume.

**Statistical analyses**

Analyses were conducted using PASW Version 18.0. We wanted identify whether there were selection biases in the study by comparing responders and non-responders to the MAC-Q. We used independent t-tests and χ² tests of independence to determine if there were differences between the groups in terms of age, education level, sex, cognitive variables (list learning memory, non-verbal memory, and discourse) and affective variables (published as supplementary material online attached to the
electronic version of this paper at http://www.journals.cambridge.org/ipg). T-tests and χ² analyses were also used to identify any differences between those who responded to the MAC-Q and participated in the PiB-PET imaging sub-study and those who responded to the MAC-Q but did not receive brain scans (published as supplementary material online attached to the electronic version of this paper at http://www.journals.cambridge.org/ipg). Cronbach’s α was calculated using the MAC-Q indices in order to determine the reliability of the MAC-Q measure. Objective memory tests were factor analysed using principle components analysis with an orthogonal rotation in order to extract memory structures from the data. After the factor analysis of the objective memory variables, a multiple hierarchical regression model was used to determine the influence of all variables on the dependent variable, complaint severity (as measured by the MAC-Q total score). This model was chosen so as to be able to control for covariates such as age, group membership, years of education and whether the participant was a carrier of the APOEε4 allele. All MAC-Q respondents’ memory scores and affective scores were used to identify predictors of memory complaints. A separate multiple hierarchical regression model was analyzed post-hoc in order to determine whether different variables related to the MAC-Q in healthy controls. The MCI group had a small sample size (N = 65), and therefore a Pearson correlation was performed to determine what variables were associated with memory complaint severity. Those who also participated in the PiB-PET imaging study were analysed further to determine whether amyloid loading related to complaint severity.

**Results**

A total of 773 participants (HC = 692, MCI = 81) were available at 18-month follow-up. In the current study, we included 740 participants (HC = 674, MCI = 66), as not all participants returned their MAC-Q questionnaire. Furthermore, analyses involving the measurement of β-amyloid deposition via PiB-PET imaging data incorporated a smaller sample size (those who responded to the MAC-Q: HC = 130, MCI = 19), as funding only permitted about a quarter of all participants to be scanned at baseline and 18 months follow-up.

In healthy controls, there was no significant difference in mean age between those who did (M = 72.74 years, SD = 6.7, range = 33 years, N = 674) and did not (M = 72.74 years, SD = 8.8, N = 19) respond to the MAC-Q, t(689) = 3.63, p = ns (published as supplementary material online attached to the electronic version of this paper at http://www.journals.cambridge.org/ipg). We found no significant age difference between the MCI participants who responded to the MAC-Q (M = 77.08 years, SD = 7.5, range = 33 years, N = 66) and those who did not (M = 80.38 years, SD = 7.5, N = 17). PiB imaged healthy controls had a lower proportion of females compared to the rest of the AIBL cohort, χ²(1, N = 817) = 6.51, p < .01, and had a higher proportion of APOEε4 positive participants, χ²(1, N = 817) = 9.57, p < .01 (published
as supplementary material online attached to the electronic version of this paper at http://www.journals.cambridge.org/ipg). The mean and standard deviations of each measure for the all MAC-Q responders and the sub-group of MAC-Q responders who were imaged are shown in Error! Reference source not found.. The MCI group had a higher complaint severity ($M = 27.13$, $SD = 4.6$) compared to healthy controls ($M = 25.17$, $SD = 4.3$), $t(738) = 5.02$, $p < .0001$, Cohen’s $d = 0.63$. The MAC-Q had high internal consistency, Cronbach’s $\alpha = 0.82$. 


Table 3. Demographics, cognitive performance, affective score, and APOEε4 status for the AIBL participants who responded to the MAC-Q

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CONTROLS (N = 674)</th>
<th>MCI (N = 66)</th>
<th>T</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL MAC-Q RESPONDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC-Q total score</td>
<td>25.17 (4.3)</td>
<td>27.13 (4.6)</td>
<td>5.02</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age</td>
<td>72.73 (6.7)</td>
<td>77.08 (7.5)</td>
<td>5.00</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>GDS</td>
<td>0.96 (1.6)</td>
<td>1.80 (2.2)</td>
<td>2.99</td>
<td>.01</td>
</tr>
<tr>
<td>HADS-Depression</td>
<td>2.44 (2.1)</td>
<td>3.42 (2.6)</td>
<td>3.00</td>
<td>.01</td>
</tr>
<tr>
<td>HADS-Anxiety</td>
<td>4.00 (2.9)</td>
<td>4.67 (3.1)</td>
<td>1.77</td>
<td>ns</td>
</tr>
<tr>
<td>List-learning</td>
<td>0.15 (0.9)</td>
<td>-1.52 (0.6)</td>
<td>19.22</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-verbal memory</td>
<td>0.09 (1.0)</td>
<td>-0.76 (0.9)</td>
<td>6.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Discourse</td>
<td>0.10 (0.9)</td>
<td>-0.83 (0.9)</td>
<td>7.61</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CONTROLS (N = 130)</th>
<th>MCI (N = 19)</th>
<th>T</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>58</td>
<td>52</td>
<td>1.14</td>
<td>ns</td>
</tr>
<tr>
<td>Years of education (&lt;12 years)</td>
<td>45</td>
<td>55</td>
<td>2.80</td>
<td>ns</td>
</tr>
<tr>
<td>APOEε4 carrier (Yes)</td>
<td>26</td>
<td>37</td>
<td>2.91</td>
<td>ns</td>
</tr>
</tbody>
</table>

| IMAGED SUB-GROUP OF MAC-Q RESPONDERS | | | | |
| PiB SUVR | 1.38 (0.4) | 1.78 (0.6) | 2.95 | .01 |
| MRI | | | | |
| Gray Matter volume | 669.20 (57.0) | 632.40 (74.4) | 2.52 | .01 |
| Left Hippocampal vol | 3.19 (0.3) | 2.95 (0.5) | 2.86 | .005 |
| Right Hippocampal vol | 3.10 (0.3) | 2.74 (0.4) | 4.44 | <.0001 |
| Age | 74.08 (7.3) | 77.59 (7.1) | 2.14 | .04 |
| GDS | 0.85 (1.4) | 2.36 (2.8) | 2.51 | .02 |
| HADS-Depression | 2.60 (2.1) | 2.82 (2.2) | 0.46 | ns |
| HADS-Anxiety | 3.80 (2.7) | 4.27 (2.5) | 0.77 | ns |
| List-learning | 0.07 (0.9) | -1.37 (0.7) | 7.33 | <.0001 |
| Non-verbal memory | 0.19 (1.0) | -0.46 (1.0) | 2.78 | .006 |
| Discourse | 0.11 (1.0) | -0.89 (0.8) | 4.54 | <.0001 |

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CONTROLS (N = 130)</th>
<th>MCI (N = 19)</th>
<th>T</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>47</td>
<td>50</td>
<td>0.07</td>
<td>ns</td>
</tr>
<tr>
<td>Years of education (&lt;12 years)</td>
<td>45</td>
<td>55</td>
<td>0.18</td>
<td>ns</td>
</tr>
<tr>
<td>APOEε4 carrier (Yes)</td>
<td>39</td>
<td>41</td>
<td>0.02</td>
<td>ns</td>
</tr>
</tbody>
</table>

*a* Data reported as mean, SD  
*b* Data reported as %  
MCI = Mild Cognitive Impairment; MAC-Q = Memory Assessment Clinics Self-Rating Questionnaire; GDS = Geriatric Depression Score; HADS = Hospital Anxiety and Depression Scale, APOEε4 = apolipoprotein E ε4, SUVR = standard uptake value ratio, GM = Grey matter
Factor analysis

We performed data reduction on seven memory variables using factor analysis. We extracted three factors, which accounted for 92.9% of the variance explained: they were labelled List Learning, Non-Verbal Memory and Discourse. The List Learning memory structure involved the three CVLT-II variables, the Non-Verbal Memory structure comprised the two RCFT variables and the Discourse structure incorporated the two WMS LM variables. The loadings of these variables onto each factor can be found in Error! Reference source not found..
Table 4. *Memory structures extracted from exploratory factor analysis*

<table>
<thead>
<tr>
<th></th>
<th>List Learning</th>
<th>Non-Verbal Memory</th>
<th>Discourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT-II Immediate Recall</td>
<td><strong>0.903</strong></td>
<td>0.211</td>
<td>0.204</td>
</tr>
<tr>
<td>CVLT-II Learning</td>
<td><strong>0.876</strong></td>
<td>0.205</td>
<td>0.268</td>
</tr>
<tr>
<td>CVLT-II Delayed Recall</td>
<td><strong>0.864</strong></td>
<td>0.282</td>
<td>0.280</td>
</tr>
<tr>
<td>RCFT 3 min Delay</td>
<td>0.238</td>
<td><strong>0.937</strong></td>
<td>0.172</td>
</tr>
<tr>
<td>RCFT 30 min Delay</td>
<td>0.248</td>
<td><strong>0.935</strong></td>
<td>0.168</td>
</tr>
<tr>
<td>WMS LM Immediate Recall</td>
<td>0.262</td>
<td>0.154</td>
<td><strong>0.920</strong></td>
</tr>
<tr>
<td>WMS LM Delayed Recall</td>
<td>0.311</td>
<td>0.195</td>
<td><strong>0.893</strong></td>
</tr>
</tbody>
</table>

Note: CVLT-II = California Verbal Learning Test-Second edition; RCFT = Rey Complex Figure Test; WMS LM = Wechsler Memory Scale Logical Memory
Interactive effects of age and group membership on complaint severity

Using a one-way ANCOVA, we found a significant interaction between group membership (i.e. HC vs MCI) and age (considered as a covariate) on complaint severity, $F(1, 736) = 4.15, p = .04$. Age was also considered to have a significant main effect on complaint severity, $F(1, 736) = 12.12, p = .001$, and therefore age and the interaction term were included in the linear model.

Memory and affective relationships with complaint severity

Initial analyses of the hierarchical multiple regression indicated no violation of normality, linearity, multicollinearity or homoscedasticity. We entered covariates (age, the interaction between group membership and age, years of education and $APOE \varepsilon4$ carrier status) into the model first, which explained 4.9% of the variance in complaint severity. We did not include group membership as a main effect as it violated assumptions of multicollinearity. Cognitive factors entered the model next, but failed to make an additional contribution to the explained variance, $[F_{\text{change}}(3,721) = 1.06, ns]$. The last block involved the affective variables (GDS, HADS-D and HADS-A). These explained a further 7.7% of the variance in the total complaint severity score, $[F_{\text{change}}(3,718) = 21.15, p < .0001]$, effect size $f^2 = 0.15$. The total model accounted for 13% of the variance in complaint severity. In the final model, four measures contributed to complaint severity, the interaction variable, HADS-Depression, HADS-Anxiety and $APOE \varepsilon4$ carrier status (see Error! Reference source not found., Model 1). The HADS-Depression score recorded the highest $\beta$ value ($\beta = 0.20, p < .0001$) followed by the interaction variable ($\beta = 0.12, p = .016$), the HADS-Anxiety score ($\beta = 0.09, p = .03$), and $APOE \varepsilon4$ carrier status ($\beta = 0.07, p = .05$).

Differential relationships with complaint severity in healthy controls and MCI participants

To examine the differential relationships with complaint severity between HC and MCI participants we performed a hierarchical multiple regression analysis on the HC group. The model explained 9.6% of the overall variance in the total complaint severity score, effect size $f^2 = 0.11$. The addition of cognitive measures did not result in additional contribution to the model, $[F(3,658) = 0.96, ns]$, but the inclusion of affective variables accounted for an additional 9.3%, of the variance in complaint severity $[F(3,655) = 19.38, p < .0001]$. Two measures contributed significantly to this model, HADS-Depression ($\beta = 0.21, p < .0001$) and HADS-Anxiety ($\beta = 0.09, p = .027$) (see Error! Reference source not found., Model 2).

A Pearson correlation revealed a significant correlation between total MAC-Q score and age in the MCI group, $r (66) = 0.33, p = 0.006$. There was also a borderline significant correlation between MAC-Q score and HADS-D score, $r (66) = 0.25, p =$
0.046. There were no other significant correlations between total MAC-Q score and other variables in the MCI group (published as supplementary material online attached to the electronic version of this paper at http://www.journals.cambridge.org/ipg).

The effect of biomarkers on complaint severity in controls and MCI

We also used hierarchical multiple regression to assess how biomarkers (PiB SUVR, GM volume, right and left Hi volume and APOE ε4 status) related to total MAC-Q score in the imaged sub-group. Again, there was no violation of assumptions. The first block contained the covariates (age, the interaction between group membership and age and years of education), which explained 8% of the variance in complaint severity. The addition of AD biomarker variables did not contribute significantly to the model, \[F_{\text{change}}(4,142) = 1.121, ns\], with the overall model explaining only 10.9% of variance in complaint severity (see Error! Reference source not found., Model 3). Dichotomizing the sample into PiB positive (PiB SUVR ≥ 1.5) and negative (PiB SUVR < 1.5) (Rowe et al., 2010) subgroups did not alter the overall contribution of PiB retention to complaint severity, with the model explaining only 11.2% of variance in complaint severity.
Table 5. The coefficients and model fit indices for all three hierarchical regression models with subjective memory complaint severity representing the outcome variable

<table>
<thead>
<tr>
<th>Model 1: All MAC-Q responders (N_HC = 674, N_MCI = 66)</th>
<th>B (SE)</th>
<th>β</th>
<th>R²</th>
<th>ΔF (DF)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOCK 1</td>
<td>0.05</td>
<td></td>
<td>11.68</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BLOCK 2</td>
<td>0.05</td>
<td></td>
<td>1.19 (721)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>BLOCK 3</td>
<td>0.12</td>
<td></td>
<td>21.15 (718)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.03 (0.02)</td>
<td>0.05</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group x Age</td>
<td>0.02 (0.01)</td>
<td>0.12</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.52 (0.3)</td>
<td>0.06</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOEε4 carrier</td>
<td>0.68 (0.3)</td>
<td>0.07</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List learning</td>
<td>-0.15 (0.2)</td>
<td>-0.03</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-verbal</td>
<td>-0.03 (0.2)</td>
<td>-0.01</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discourse</td>
<td>-0.21 (0.2)</td>
<td>-0.05</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS-D</td>
<td>0.41 (0.1)</td>
<td>0.20</td>
<td>&lt;.0001</td>
<td></td>
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</tr>
<tr>
<td>HADS-A</td>
<td>0.13 (0.1)</td>
<td>0.09</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS</td>
<td>0.13 (0.1)</td>
<td>0.05</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2: HCs who responded to the MAC-Q (N_HC = 674)</th>
<th>B (SE)</th>
<th>β</th>
<th>R²</th>
<th>ΔF (DF)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOCK 1</td>
<td>0.01</td>
<td></td>
<td>2.59 (661)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>BLOCK 2</td>
<td>0.02</td>
<td></td>
<td>0.96 (658)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>BLOCK 3</td>
<td>0.96</td>
<td></td>
<td>19.38 (655)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.03 (0.01)</td>
<td>0.05</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.30 (0.3)</td>
<td>0.04</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOEε4 carrier</td>
<td>0.67 (0.4)</td>
<td>0.07</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List learning</td>
<td>-0.22 (0.2)</td>
<td>-0.05</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-verbal</td>
<td>-0.09 (0.2)</td>
<td>-0.02</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discourse</td>
<td>-0.17 (0.2)</td>
<td>-0.04</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS-D</td>
<td>0.43 (0.1)</td>
<td>0.21</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS-A</td>
<td>0.14 (0.1)</td>
<td>0.09</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS</td>
<td>0.11 (0.1)</td>
<td>0.04</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3: MAC-Q responders who were neuroimaged (N_{HC} = 130, N_{MCI} = 19)</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLOCK 1</strong></td>
<td>0.09</td>
<td>3.50 (141)</td>
<td>.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLOCK 2</strong></td>
<td>0.12</td>
<td>0.95 (137)</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.05 (0.1)</td>
<td>0.09</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group x Age</td>
<td>0.03 (0.02)</td>
<td>0.17</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.34 (0.7)</td>
<td>0.04</td>
<td><em>ns</em></td>
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<td></td>
</tr>
<tr>
<td>APOE(\varepsilon)4 carrier</td>
<td>0.59 (0.8)</td>
<td>0.07</td>
<td><em>ns</em></td>
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<td></td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>0.16 (0.9)</td>
<td>0.02</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM vol</td>
<td>-0.01 (0.01)</td>
<td>-0.11</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hi vol</td>
<td>-2.99 (2.2)</td>
<td>-0.24</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Hi vol</td>
<td>2.47 (2.2)</td>
<td>0.20</td>
<td><em>ns</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APOE\(\varepsilon\)4 = apolipoprotein E \(\varepsilon\)4, HADS = Hospital Anxiety and Depression Scale, GDS = Geriatric Depression Score; SUVR = standard uptake value ratio, GM = Grey matter, Hi vol = Hippocampal volume
Discussion

This is the first study to examine the effects of AD biomarkers, memory and affect on memory complaint severity treated as a continuous measure. As expected, MCI patients were more concerned about their memory than healthy controls, and this finding produced a moderate effect size. We argue that this stands as a validation of the MAC-Q measure because it mirrors the diagnostic criterion for MCI. It also supports similar findings in the literature (Reisberg and Gauthier, 2008). Having a memory complaint does not preclude the possibility of being a healthy control and, as an informant’s complaint can be substituted is a not a necessary criterion for a diagnosis of MCI. Gauthier and colleagues (2006) suggested that an SMC should not necessary for a diagnosis of MCI because many individuals with MCI symptomatology can present without a complaint. Our finding suggests that although both groups have potential to be concerned about their memory, memory complaints become more severe when an individual is mildly cognitively impaired. Some researchers argue that the level of awareness of cognitive deficits is variable in MCI and may impair one's ability to appraise one’s cognitive acuity accurately (Roberts et al., 2009). Our results present a counter-position and support findings of Greenop and colleagues (2011) that showed individuals with cognitive impairment but no dementia (CIND) do exhibit an awareness of cognitive decline. This group differentiation, therefore, strengthens the argument that subjective memory complaints are emanating from an insidious onset of cognitive change that individuals are noticing.

This difference in complaint severity seems to be driven by different processes. The main contributors to SMC severity were depressive symptomatology and the interaction between classification (HC versus MCI) and age. In MCI patients, the sole contributor to SMC severity was age, while in healthy controls the main contributors were anxiety and depression. Objective memory impairment was not associated with SMC severity, which aligns with previous literature.

Influence of biomarkers on subjective memory complaints

The influence of the interaction of age and diagnosis on SMC severity mirrors the same interaction effects on brain amyloid burden. Firstly, age is consistently reported as a risk factor for both a diagnosis of DAT and also for the accumulation of AD neuropathology such as beta-amyloid. Rowe and colleagues (2010) found that the prevalence of amyloid plaques increases with age regardless of diagnosis. Other studies also show that “older-old” individuals with and without dementia (> 85 years old) often are neuropathologically indistinguishable at post-mortem, in terms of both neuritic plaques and neurofibrillary tangles. Thus, as individuals increase in age, so does the risk of displaying neuropathological features such as neuritic plaques (or brain amyloid burden ante-mortem). Secondly, β-amyloid deposition can also be differentiated according to whether an individual is healthy or has an MCI or AD
diagnosis. Previous studies suggest that MCI patients have significantly higher neocortical PIB retention and decreased global grey matter volume compared to healthy controls (Chételat et al., 2010; Jack et al., 2010). This disparity in PiB retention between healthy controls and MCI patients is also significant in the current study (see Table 3). Furthermore, research from our collaboration also shows that being a carrier of the APOE ε4 allele produces a stronger correlation between age and PiB retention compared to non-carriers (Rowe et al., 2010) and is argued to induce an earlier initiation of the AD pathological cascade (Jack et al., 2010). We were able to support this relationship. Together, these findings demonstrate that an interaction between age and classification influences the AD pathophysiological process. We therefore suggest a similar pathological aetiology for memory complaints cannot be discounted as we found a significant interactive effect of age and diagnosis on SMCs. One caveat is that no direct association between neuroimaging variables and SMCs was found.

**Influence of mood on SMC severity**

Mood and anxiety symptomatology as measured by the HADS were highly significant contributors to complaint severity in healthy older adults controls. Mood often amplifies cognitive complaints in other clinical populations such as clinically depressed individuals (Plotkin, Mintz, & Jarvik, 1985). The group means for HADS-Depression and HADS-Anxiety fell below clinical levels suggesting that affective variations in our sample were sub-clinical. Reid and colleagues (2011) showed similar findings using the MAC-Q although their sample was considerably younger (66% between 35-49 years of age) and predominantly male (at least 97%). Other findings have shown that symptoms of depression and anxiety influence SMCs particularly in individuals below 75 years of age (Abdulrab and Heun, 2008; Elfgren et al., 2010). Age is a strong risk factor for AD pathology. Jonker et al. (2000) therefore argued that a complaint in the “younger” older adults was unlikely to be driven by organic brain changes. They also suggested that a complaint from an “older than old” individual should be taken more seriously due to their increased risk of dementia. The healthy older adults controls in the current study were significantly younger than the MCI patients (and had a significantly lower mean PiB SUVR) and therefore align with Jonker and colleagues’ (2000) argument.

**Strengths and limitations**

Most studies consider memory complaints as categorical, but important information can be lost when dichotomizing responses. A key strength of this study is to extend on previous literature by examining the relationship of the full spectrum of SMC severity rather than dichotomizing this complex phenomenon. This study also has the advantage of involving a large and well-characterised sample of subjects who have undergone detailed assessments (Ellis et al., 2009). It is a convenience community-based sample, which relied partly on volunteer recruitment and partly on medical
referral. This sample, therefore, is not representative of the population. This may have produced bias results as Jonker et al. (2000) have argued that negative mood correlates with SMCs predominantly in these types of samples. Another caveat may be that by the 18-month follow up, some participants may have adjusted their memory concerns according to their perceived performance at baseline. Simply participating in, and successfully completing, a neuropsychological assessment may have allayed fears and therefore reduced cognitive concerns.

Conclusion

Our study is the first to examine the continuum of SMC severity in relation to AD biomarkers, memory and affect. We found that SMCs in the cognitively healthy older adults were related to mood and, in MCI patients, were correlated with age. There was no relationship between AD neuroimaging biomarkers and memory complaint severity although the influence of APOE ε4 genotype and age provides support for a clinicopathological connection, as a similarity can be drawn with the contributors to brain amyloid burden. SMCs are inherently complex and involve a multi-faceted etiology, as evidenced by the continued debate about their antecedents, which depends primarily on both the age of the individual and their cognitive status.
Chapter 4 showed that greater complaint severity in healthy older adults was strongly affect-driven, which some would argue supports the argument that subjective memory complaints are not reflecting real memory dysfunction (Lenehan et al., 2012; A. J. Mitchell, 2008a). Alternatively, the finding could suggest that neuropsychological measures are not able to detect subtle cognitive deficits at preclinical stages (de Jager et al., 2002), or, more likely, that the MAC-Q is not measuring entirely the concept it purports to measure (M. Reid et al., 2011). SMCQs are screening tools, which means that, while they allow for ease of administration, and can be applied to large at-risk populations, they are non-interactive, non-specific, and involve a pre-set format (Herman, 2006). To reiterate a point made earlier, subjective memory complaints are highly nuanced and often counterintuitive, and so must be approached from a more idiographic perspective. To date, no study has characterised the phenomenological experience of memory function in those at risk of AD, that is, those who exhibit abnormal AD biomarkers or mild cognitive impairment. The aim of this chapter is to uncover these descriptive nuances to determine whether group-specific complaint typologies exist, and how these relate to depressive symptomatology and neuropsychological measures of new learning and retention.

5.1 Qualitative thematic procedure

Qualitative studies of other clinical populations, such as surgically-treated patients with intractable forms of temporal lobe epilepsy (TLE), developed a thematic analysis technique to uncover psychosocial outcomes post-surgery (Wilson et al., 1999; Srikanth et al., 2004). In their procedure, Wilson and colleagues (1999) created detailed transcripts from semi-structured interviews, and extracted similar clusters of meaningful phrases in the text. From these clusters, themes emerged relating to different psychosocial outcomes arising from surgical treatment. This study was the first to uncover the positive and negative factors of psychosocial post-treatment. In the current chapter, the objective is to utilise this qualitative procedure to examine the clinical semiology of complaints from a phenomenological perspective.

5.2 Aims of Chapter 5

In this chapter, the aim is to conduct a thematic analysis of subjective memory complaints that are elicited via a semi-structured interview (detailed in Chapter 3). Phenomenological experiences will be compared in putatively healthy and at-risk ageing.
Introduction

Subjective memory complaints (SMCs) are an important phenomenological occurrence as they form the bridge connecting individuals at risk for Alzheimer’s disease (AD) to clinical services (Reisberg & Gauthier, 2008). Current research practice seeks to identify and quantify SMCs in non-demented older adults via standardized questionnaires (Jessen et al., 2014). The predominant approach is to utilize questionnaire data to develop global scores with continuous metric properties to quantify the magnitude of SMCs in older adults (Amariglio et al., 2011; Hohman et al., 2011; Jorm et al., 2004). Criterion values can also be developed for metric scales and non-demented older individuals can be classified as memory complainers, if their score exceeds this value, or non-complainers (Bartley et al., 2012; Jessen et al., 2010; Lautenschlager et al., 2005). Despite the acknowledged importance of SMCs to clinical diagnoses of early AD, studies using standardised scales have not provided conclusive evidence that SMCs are indicative of an AD prodrome (Jessen et al., 2014). Equivocal findings in SMC research in early AD suggest that SMCs are not a useful marker of future progression to AD in preclinical or prodromal stages (Lenehan et al., 2012; Mitchell, 2008). An alternative view is that current methodologies used to measure SMCs might not capture the complexity of the subjective experience. For example, the use of standardized questionnaires or even single questions to gauge the presence or severity of a complaint does not capture the motivation and context surrounding any type of memory complaint. In other areas of neuropsychology it has been shown that a more reliable way to characterise the phenomenological experience of subjective experiences is through a thematic analysis of semi-structured interview. Thematic analysis involves the qualitative exploration of the context surrounding an individual’s response (Wilson et al., 1999). For instance, studies of surgically-treated patients with intractable epilepsy have developed and utilized qualitative thematic procedures to examine phenomenological experiences post-surgery (Wilson et al., 1999). What is currently missing from the literature is a thematic exploration of SMCs in non-demented older adults. Characterising the phenomenological experience in individuals at risk of progression to AD, such as those with mild cognitive impairment (MCI) or healthy individuals with elevated neocortical β-amyloid (Aβ) burden might reveal subtle variations in the types of complaints that are endorsed by different clinical populations.

Few studies have addressed the thematic elements of a memory complaint in older adults. Concerns of ‘forgetting what you are attending to’ or ‘getting lost’ in healthy older adults have been conceptualised as potential indicators of progression to AD (Amariglio et al., 2011; Tobiansky, et al., 1995), and similar complaints have been demonstrated in informant-based research (Yoon et al., 2011). By contrast, older adults who express embarrassment at forgetting things from ‘one second to the next’ have been shown to be at lower risk for progressive cognitive decline (Amariglio et al., 2011; Tobiansky et al., 1995). In addition, healthy memory complainers who cannot provide subjective examples of memory loss upon clinical assessment, are also less
likely to manifest cognitive decline over time (Flicker, Ferris, & Reisberg, 1993). Findings of complaints that are related to disparate cognitive functional outcomes raises the question of whether the subjective architecture of a memory complaint is different in older adults with mild cognitive impairment (MCI) compared with those who are cognitively normal.

In healthy older adults, studies report a relationship between neocortical Aβ burden and SMCs (Barnes et al., 2006; Chételat et al., 2010; Perrotin et al., 2012). For example, Amariglio and colleagues (2012) found that while a composite measure of memory complaints was related to global amyloid burden, groups of questions related to cognitive domains, were not. Perrotin and colleagues (2012) reported that individuals with high Aβ load (or significant levels of neocortical Aβ according to PET neuroimaging parameters; Aizenstein et al., 2008) felt less confident in their overall memory function. Other studies, however, have found no relationship between Aβ and SMC severity (Rodda et al., 2010), or only report a relationship in carriers of apolipoprotein E epsilon 4 (APOE ε4; Rowe et al., 2010). As such, it is still unclear, how subjective memory complaints are related to Aβ, and to the authors’ knowledge, no research has yet developed a characterisation of SMCs in individuals who have high Aβ load.

The aim of this study was to utilise these qualitative procedures to describe SMC themes and the level of endorsement of those themes in individuals with MCI and in healthy older adults with high Aβ load. The first hypothesis was that individuals with MCI would endorse more overall SMC themes, particularly changes related to daily function than would healthy older adults. The second hypothesis was that healthy memory complainers might complain similarly to individuals with MCI, but we weren’t sure how. The third hypothesis was that individuals with high Aβ, regardless of diagnosis, would acknowledge a subtle decrease in memory function. Depression is a well-established confounding factor with SMCs in healthy older adults (Jorm et al., 2004; Lautenschlager et al., 2005), so the influence of depressive symptomatology on complaint themes was also examined.

**Methods**

**Participants**

The Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing is a longitudinal study with follow-up assessments every 18 months (Ellis et al., 2014). The current cross-sectional study recruited a subgroup of 80 HC and 43 MCI participants from the 36-month AIBL cohort. The study size was arrived at when all MCI participants in the AIBL study had been contacted; five MCI participants declined to participate, two were unreachable, and four had progressed to a diagnosis of AD by the time of assessment for the current study. Ethics approval was obtained in Victoria
from St Vincent’s Hospital and the University of Melbourne, and from Hollywood Private Hospital in Western Australia. All participants for the current study were recruited via telephone contact and asked to participate in a semi-structured interview in their home. The interviews were recorded with permission. At the 36-month AIBL follow-up assessment, 67 of the participants in the current study (HC = 47, MCI = 15) also had positron emission tomography (PET) images of neocortical Aβ burden available for analysis.

The recruitment and diagnostic methods of the AIBL Study have been published elsewhere (Ellis et al., 2009). In brief, volunteers responded to a media appeal or were referred by their medical practitioner and were screened via telephone for basic demographic information, and the following exclusion criteria: a history of dementia other than AD, psychiatric illness (such as significant current (but not past) depression, which was determined by a Geriatric Depression Scale (GDS; Yesavage et al., 1983) score of greater than five), obstructive sleep apnoea, Parkinson’s disease, cancers within the last few years, symptomatic stroke, uncontrolled diabetes, and alcohol consumption greater than Australian recommended levels. A diagnostic review panel of neurologists, geriatricians, psychiatrists and neuropsychologists oversaw the classification into HC, MCI and AD groups according to well-established criteria (Ellis et al., 2009; Petersen et al., 1999; Winblad et al., 2004). MCI classification was made based on performance falling 1.5SD or more below age-adjusted levels in formal cognitive assessment, expressed cognitive complaint/subjective memory concern, and current preservation of activities of daily living, as described previously (Ellis et al., 2009).

*Image acquisition: 11C-PiB, 18F-flutemetamol and 18F-florbetapir PET imaging*

Aβ imaging with positron emission tomography (PET) was conducted using either 11C-Pittsburgh Compound B (PiB), 18F-florbetapir or 18F-flutemetamol. Forty-one participants (HC = 30, MCI = 11) underwent PiB-PET imaging, 22 participants (HC = 19, MCI = 3) underwent 18F-flutemetamol PET scans, and 13 participants (HC = 12, MCI = 1) had 18F-florbetapir PET imaging. PET methodology has previously been described in detail (Clark, Schneider, Bedell, & et al., 2011; Rowe et al., 2010). A 30 minute acquisition was started 40 minutes post-injection of PiB, a 20 minute acquisition was performed 50 minutes post-injection of florbetapir and 90 minutes post-injection of flutemetamol. For PiB-PET, standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV, and the resulting tissue ratio was termed SUV ratio (SUVR). As advocated by each pharmaceutical company, the whole cerebellum was the reference region for florbetapir (Clark et al., 2011), while for flutemetamol the reference region was the pons (Thurfjell, Lundqvist, Buckley, Smith, & Sherwin, 2013). In the current study, the SUVR index was considered as a dichotomous variable (Aβ+/Aβ-). Participants who underwent PiB-PET imaging were
classified Aβ+ when SUVR ≥ 1.5 (Rowe et al., 2007), florbetapir when SUVR ≥ 1.11 (Clark et al., 2011), and for flutemetamol when SUVR ≥ 0.62 (Thurfjell et al., 2013).

**Verbal and non-verbal memory measures**

The standard AIBL neuropsychological assessment involved a mean administration time of two hours (Ellis et al., 2009). The following memory test measures were collected at the 36 month time-point. The California Verbal Learning Test-Second edition (CVLT-II-II) Short Delay recall and Long Delay recall (Delis, Kramer, Kaplan, & Ober, 2000), and the Wechsler Memory Scale (WMS) Logical Memory (LM) immediate and delayed recall (Story 1 only) were administered to measure verbal learning. The Rey Complex Figure Test (RCFT) 30 minute delayed recall, and the CANTABeclipse v3.0 Paired Associate Learning (PAL) stage 6 errors adjusted score (Robbins et al., 1994), to measure nonverbal memory (participants who were unable to complete Stage 6 were allocated the error score of the lowest-performing individual attempting the stage).

**Qualitative analysis: Semi-structured interview**

The semi-structured interview was developed, using clinical experience and aligning with previous interviews constructed by the final author, MS (Wilson et al., 1999), to elicit a rich description of an individual’s subjective experience of memory changes. Administration of the interview took approximately 30 minutes. It was structured to probe circumstances in which memory lapses were likely to occur (see supplementary material for the interview). Eight scenarios were developed to probe a) the subjective frequency of memory lapses; b) whether the individual could provide details about a set of elicited scenarios; and c) how the individual recovers from acknowledged lapses in memory (see Appendix B).

**Procedure**

Our procedure followed the qualitative procedure carried out by final author, MS, on the psychosocial outcomes of individuals with surgically-treated intractable temporal lobe epilepsy (Wilson et al., 1999). The responses were recorded, with permission, and transcribed verbatim. Authors RB and MS read each interview and extracted codes, defined by Miles and Huberman (Miles & Huberman, 1994) as phrases or sentences that contain a single theme or piece of information. In the current study, codes were considered to be phrases which were meaningful to the person’s experience of their own memory function. These codes were assigned descriptive labels, for example, the phrase ‘I do things when I think of them’, was labelled as an adaptive response (or coping strategy). Discussions between the coders, RB and MS, were held until consensus was reached for each code (Srikanth et al., 2004). Meticulous notes were kept during discussions in order to keep track of the decisions surrounding each code.
Similar codes were then grouped into themes, and re-analysed and reconceptualised until a consensus was reached. Twelve unique themes emerged from the thematic analysis, and which are defined below.

**Complaint themes**

It is important for the reader to note that while we followed the thematic analysis procedure from previous studies, these themes emerged entirely from the transcripts in the current study. The themes were frequency, sense of predomination and growing concern, situational memory lapses, spatio-temporal contextualisation, coping strategies, dismissive attitude, mental control/vagueness, impact on affect, progression, over-endorsed complaint, dependency, quality of account, and affective influences on memory.

1. **Increasing frequency**

This theme reflects the participant’s perception of the frequency of memory lapses. It is important to note that this is a subjective sense or appreciation of frequency, rather than carrying any objectively quantitative implications. Verbalisations such as ‘often’, ‘always’, or ‘all the time’ is taken to signify an experience of untoward frequency, while ‘rarely’, ‘almost never’, or ‘sometimes’ are taken to signify an infrequent and less intrusive experience.

2. **Sense of predomination and growing concern**

A sense of predomination and growing concern is apparent in phrases such as ‘it happens a couple of times at day at the very least’, where the individual emphasizes the frequency of memory lapses with an embellishment of concern. The theme is also expressed through allusions of alarm, urgency, or anxiety, such as, ‘I’ve often pulled the house to pieces looking for it’. Statements of growing concern are often associated with a sense of increasing frequency, such as, ‘it certainly would have happened today’ or ‘I can’t really recall. But I suspect it wasn’t long ago!’

3. **Situational lapses**

This theme defines the memory lapses that occur in specific settings. This involves a high demand on memory, such as overseas trips, where there is an element of being “put on the spot”, or the individual is required to be constantly ‘online’. An example of this type of response is, ‘I don’t when I’m home but I drive everybody mad when I go overseas...’. An alternative situation involves low stress environments where habitual actions can lead to momentary memory lapses, for example, ‘Especially if I’m in the garage. I put things in a quick convenient place, and then forget I’ve put them there.’
4. Relative absence of spatio-temporal contextualisation

An individual’s ability to provide contextual specificities of the episode. Responses are dichotomized as detailed or poverty stricken. Good contextualisation is exemplified by accounts such as:

“I was cooking, it was on Saturday morning. I was making a trifle and I wanted to get all of the cream out of the bottom of the jar and I went to that cabinet to get the parfait spoon and I couldn’t get it. I couldn’t find it. I found it the next day, I’d put it in the drawer. I mean I didn’t worry about it, I was like, “oh”, coz I was listening to the radio and I was turning up the music – and I can’t even remember what was on the radio but I was thinking about that so I wasn’t thinking about what I was doing physically.”

Responses are considered as poverty stricken if the individual is not able to provide any detail, such as:

(When was the last time that happened to you?) Laughs. ‘Um, oh, probably uh...oh, it might have been, oh, probably today even.’ (Can you tell me more about the event?) ‘I don’t know!’ Laughs. ‘I don’t know!’

Another example of a poverty stricken response reflects instances where initial contextualisation is unidimensional (only a single dimension of detail pertaining to time, location, or mood is provided) but after further elicitation, the individual does not provide more detail. For example:

‘I lost my handbag...’ (And what happened?) ‘Because I had my keys in it!’ (How long did it take to find them?) ‘I don’t know.’ (Can you tell me anything else?) ‘No.’

5. Burdensome coping strategies

This theme is defined by the individual’s employment of a strategy to compensate for memory lapses. Coping strategies are dichotomized as being either adaptive, in that they might facilitate activities of daily living, or burdensome. An adaptive coping strategy includes phrases like, ‘Don’t put it down, put it away’, ‘I usually retrace my steps...’ or ‘I do things when I think of them’. Burdensome strategies include examples such as, ‘I leave things where I can see them’. Within the context of this strategy, the individual had piles of papers and objects all over the tables and floor of the room. Alternatively, a burdensome response involves the expression of increasing
dependency on another, such as, ‘Well, if there’s something I’ve lost, I ask (my husband) to get it’.

6. Dismissive attitude

The occurrence of dismissive responses informed this theme. A response involves defensiveness, rationalisation or justification. Defensiveness is apparent when the individual is diminishing the value of the to-be-remembered activity or goal, for instance: ‘If I can’t find it then I forget about it because I feel it’s a waste of time...’. Rationalisation or justification is evident where the individual explains away or makes light of the memory lapse. For example, ‘you get silly in your old age’ or ‘it could be that I have far too many possessions and that doesn’t help’.

7. Attentional fluctuation/vagueness

An individual’s inability to maintain attentional focus on relevant stimuli in a given situation, is given the term attentional fluctuation/vagueness. To be clear, this theme does not refer to a persistently vague clinical presentation, but a self-expressed reference to instances that suggest a loss of attentional focus or loss of mental control. The most common self-reported endorsements of this theme are during instances of multitasking, disinterest, or loss of attention, such as, ‘I think it’s because I get very busy and, um, I’m just trying to do three or four things at once, you know?’ or ‘perhaps I should pay more attention at the time...I think that things could be improved if I deliberately did that.’ The following are examples of self-expressed vagueness or absent-mindedness: ‘It’s a vague absentmindedness’, and ‘I was sort of fluffing around and I put my glasses down...’.

8. Impact on affect

Impact on affect pertains to how memory lapses impinged on an individual’s mood. It does not refer to the valence of the impact. Expressions can involve the gamut of emotional expressions, from repeatedly laughing, to expressing frustration, annoyance, stress, or depression. Examples included: ‘I get frustrated with myself...’, and ‘I stamp my foot! I get confused and upset that I can’t find it...’. Examples of repeated laughing are:

(And what is your usual strategy for finding things?) ‘I keep looking!’ Laughs. (And how long would it take you to find things?) ‘Oh, so long as the object’s available, not long.’ Laughs. ‘Sometimes you try looking for something that doesn’t exist!’ Laughs. ‘Doesn’t help.’
9. **Progression**

The theme of progression focuses on the subjective acknowledgement that memory lapses are gradually becoming worse. For example, ‘It’s probably gone on for years but it’s worse now’ and ‘more and more which was never the case’.

10. **An over-endorsed complaint**

An over-endorsed complaint is characterised by insistent, sometimes strident and over-inclusive accounts of very poor memory incorporating multi-domain failures. An example of an over-inclusive complaint is as follows (with multiple complaints underlined):

‘I forget to eat. I haven’t had breakfast because I’m not hungry and I’ve lost my sense of taste and smell so what’s the point. And I’ve forgotten how to cook a lot. My son comes round Friday nights with a meal because there’s usually not much here. I used to buy McCain’s meals. I’ve only been getting them the last couple of years really. Hardly conducive to eating well!’ (Yes but can you tell me the last time when you put something down and forgot where it was?) ‘I’d have to think...uh...oh I couldn’t find my cane this morning. I’d had my shower and I was just getting dressed and I reached to get my cane and it wasn’t where it normally is. And, uh...I just had to keep searching. It was over on the dressing table and I was in the ensuite and I was looking for it.’

11. **Dependency**

Dependency involves an expressed reliance on a significant other to fill functional lacunes left by perceived or actual memory loss, such as, ‘Usually, I get my uh...my...uh, resident – resident finder to find it for me!’

12. **Affective influences on memory**

Affective influences on memory encapsulate expressions of memory failure that are contextualised against a background of events that are troubling in their life. The salience of the memory lapse is amplified by psychosocial factors, for instance, ‘When I was stressed at that particular time, I was hopeless.’

*Statistical analysis*
The transcripts were scored according to endorsements of each theme on any of the eight questions, such that an individual could possess a maximum score of eight on each theme. Analysis of variance (ANOVA) and chi-square (χ²) tests of independence were used to determine demographic and memory differences between diagnostic categories (HC/MCI) and (HC-NMC/HC-SMC/MCI), and high or low amyloid burden (HC Aβ-/HC Aβ+/MCI Aβ-/MCI Aβ+). Non-parametric tests were used to determine the difference in endorsement of complaint themes: the Mann-Whitney U was used to compare complaint theme endorsement between diagnostic categories (HC/MCI), and the Kruskal-Wallis χ² was used to compare the three diagnostic groups (HC-NMC/HC-SMC/MCI), and the four Aβ status groups (HC Aβ-/HC Aβ+/MCI Aβ-/MCI Aβ+) on complaint themes. Separate Mann-Whitney U analyses were used for post-hoc group comparisons between the latter groups. Non-parametric Spearman rank-order (ρ) correlations were used to determine partial correlations between complaint themes and memory measures, after accounting for age and depression in the HC and MCI groups. Two themes (over-endorsed complaints and affective influences on memory) were highly skewed so we excluded them from the correlational analyses. Findings were corrected for multiple comparisons using Sidak corrections. Analyses were conducted using SPSS Version 22.0. Missing data existed for cognitive and affective measures but totalled less than 10% of the entire data set (Error! Reference source not found.).

Results

Demographic and cognitive differences

Individuals with MCI were older, had more APOE ε4 carriers and individuals who were Aβ+, showed exhibited a trend towards being less educated (p = 0.09), and performed significantly worse on all memory measures compared to healthy non-complainers (see Table 6). Both healthy subjective memory complainers and individuals with MCI were older and exhibited elevated levels of depressive symptomatology than healthy non-memory complainers. Healthy memory complainers did not differ from healthy non-complainers on any other demographic or memory measures.
Table 6. Demographic variables by diagnostic category (HC/MCI and HC-NMC/HC-MC/MCI)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HC (n = 80)</th>
<th>MCI (n = 43)</th>
<th>t or χ² (Cohen’s d or ϕ)</th>
<th>sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.61 (6.9)</td>
<td>79.63 (6.9)</td>
<td>-3.08</td>
<td>-0.58</td>
</tr>
<tr>
<td>Gender (% F)</td>
<td>46</td>
<td>58</td>
<td>1.58</td>
<td>0.11</td>
</tr>
<tr>
<td>Education (%&gt;12 yrs)</td>
<td>65</td>
<td>48</td>
<td>3.03</td>
<td>-0.16</td>
</tr>
<tr>
<td>APOE ε4 (% Yes)</td>
<td>24</td>
<td>50</td>
<td>7.88</td>
<td>0.26</td>
</tr>
<tr>
<td>Aβ status (% Aβ+)</td>
<td>23</td>
<td>53</td>
<td>5.09</td>
<td>0.28</td>
</tr>
<tr>
<td>Age (HC-NMC (n = 43)</td>
<td>73.77 (6.1)</td>
<td>77.76 (7.3)</td>
<td>79.6 (6.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Gender (% F) (HC-MC (n = 37))</td>
<td>56</td>
<td>35</td>
<td>58</td>
<td>0.20</td>
</tr>
<tr>
<td>Education (% &gt; 12 yrs) (MCI (n = 43))</td>
<td>65</td>
<td>49</td>
<td>49</td>
<td>0.16</td>
</tr>
<tr>
<td>APOE ε4 (% Yes)</td>
<td>23</td>
<td>25</td>
<td>50</td>
<td>0.26</td>
</tr>
<tr>
<td>Aβ status (% Aβ+)</td>
<td>25</td>
<td>21</td>
<td>53</td>
<td>0.28</td>
</tr>
<tr>
<td>PAL stage 6 err (adj)* (HC)</td>
<td>9.65 (10.1)</td>
<td>19.02 (15.4)</td>
<td>-3.57</td>
<td>-0.71</td>
</tr>
<tr>
<td>LM immediate recall† (HC-MC)</td>
<td>13.24 (3.6)</td>
<td>3.96 (3.5)</td>
<td>9.36</td>
<td>2.61</td>
</tr>
<tr>
<td>LM delayed recall‡ (HC-MC)</td>
<td>12.28 (3.7)</td>
<td>4.26 (4.0)</td>
<td>11.09</td>
<td>2.08</td>
</tr>
<tr>
<td>CVLT short delay‡ (MCI)</td>
<td>1.31 (1.1)</td>
<td>-1.26 (1.2)</td>
<td>11.70</td>
<td>2.23</td>
</tr>
<tr>
<td>CVLT long delay‡</td>
<td>1.20 (0.9)</td>
<td>-1.22 (1.3)</td>
<td>11.43</td>
<td>2.16</td>
</tr>
<tr>
<td>RCFT 30 minute‡</td>
<td>1.34 (1.6)</td>
<td>-0.46 (1.4)</td>
<td>5.96</td>
<td>1.20</td>
</tr>
<tr>
<td>Mood (n)</td>
<td>80</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS score (HC-NMC (n = 43))</td>
<td>1.08 (1.6)</td>
<td>2.35 (2.0)</td>
<td>-3.73</td>
<td>-0.70</td>
</tr>
</tbody>
</table>

Note: * = adjusted if a participant failed to complete stage 6, † = age-scaled score, ‡ = z-score. PAL = Paired Associates Learning, LM = Logical Memory, CVLT = California Verbal Learning Test, RCFT = Rey Complex Figure Test, GDS = Geriatric Depression Scale, *= variables are not significantly different (Tukey's method), b= variable is significantly different (Tukey's method)
Participants who were and were not administered amyloid scans, were tested for differences in demographic variables and cognitive performance. Healthy older adults and MCI participants were no different on any variables (see Table 7), whether they were scanned or not. In terms of high and low Aβ burden, none of the groups (HC Aβ-/HC Aβ+/MCI Aβ-/MCI Aβ+) differed on age, gender, or education level (see Table 8). Both HC and MCI Aβ+ groups were likely to carry an APOE ε4 allele, and exhibit poorer performance on prose and list-learning recall compared to either Aβ- group. The MCI Aβ+ group showed poorer nonverbal memory performance compared to the other three groups, and elevated levels of depressive symptomatology compared to the HC Aβ- group.
Table 7. Differences between those who did and did not receive an amyloid scans (all differences p > .05)

<table>
<thead>
<tr>
<th></th>
<th>HC without scan</th>
<th>HC with scan</th>
<th>MCI without scan</th>
<th>MCI with scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 52) M (SD)</td>
<td>(n = 28) M (SD)</td>
<td>(n = 28) M (SD)</td>
<td>(n = 15) M (SD)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>75.54 (6.8)</td>
<td>75.75 (7.2)</td>
<td>79.90 (7.2)</td>
<td>79.07 (6.4)</td>
</tr>
<tr>
<td>Gender (% F)</td>
<td>50</td>
<td>44</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Education (%&gt;13 yrs)</td>
<td>57</td>
<td>69</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td><strong>APOE ε4 (% Yes)</strong></td>
<td>15</td>
<td>29</td>
<td>63</td>
<td>29</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAL (n)</td>
<td>52</td>
<td>28</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>PAL stage 6 err (adj)*</td>
<td>3.37 (1.9)</td>
<td>3.46 (1.8)</td>
<td>6.93 (3.0)</td>
<td>6.14 (2.8)</td>
</tr>
<tr>
<td>LM (n)</td>
<td></td>
<td></td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>LM immediate recall†</td>
<td>13.40 (3.4)</td>
<td>12.93 (3.9)</td>
<td>6.72 (3.6)</td>
<td>7.36 (3.5)</td>
</tr>
<tr>
<td>LM delayed recall‡</td>
<td>12.71 (3.7)</td>
<td>11.50 (3.4)</td>
<td>3.97 (4.4)</td>
<td>4.86 (3.1)</td>
</tr>
<tr>
<td>CVLT-II (n)</td>
<td>51</td>
<td>28</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>CVLT-II short delay^</td>
<td>64.65 (8.4)</td>
<td>65.19 (8.4)</td>
<td>40.52 (10.1)</td>
<td>43.62 (12.5)</td>
</tr>
<tr>
<td>CVLT-II long delay‡</td>
<td>1.15 (1.0)</td>
<td>1.30 (0.8)</td>
<td>-1.30 (1.3)</td>
<td>-1.08 (1.5)</td>
</tr>
<tr>
<td>RCFT (n)</td>
<td>50</td>
<td>27</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>RCFT 30 minute‡</td>
<td>1.44 (1.6)</td>
<td>1.15 (1.7)</td>
<td>-0.67 (1.4)</td>
<td>-0.05 (1.4)</td>
</tr>
<tr>
<td>Mood (n)</td>
<td>52</td>
<td>28</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>GDS</td>
<td>1.06 (1.7)</td>
<td>1.11 (1.6)</td>
<td>2.30 (2.3)</td>
<td>2.46 (1.3)</td>
</tr>
</tbody>
</table>

Note: * = adjusted if a participant failed to complete stage 6, † = age-scaled score, ^ = T-score, ‡ = z-score. PAL = Paired Associate Learning, LM = Logical Memory, CVLT-II = California Verbal Learning Test, RCFT = Rey Complex Figure Test, GDS = Geriatric Depression Scale. a = variables are not significantly different (Tukey’s method), b = variable is significantly different (Tukey’s method)
### Table 8. Demographic and cognitive variables by Aβ status

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HC Aβ- (n = 40)</th>
<th>HC Aβ⁺ (n = 12)</th>
<th>MCI Aβ- (n = 7)</th>
<th>MCI Aβ⁺ (n = 8)</th>
<th>Effect size (ηp² or ϕ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>74.47 (6.5)</td>
<td>79.08 (6.6)</td>
<td>78.00 (6.4)</td>
<td>80.00 (6.8)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Gender (% F)</strong></td>
<td>45</td>
<td>42</td>
<td>72</td>
<td>50</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Education (%&gt;13 yrs)</strong></td>
<td>70</td>
<td>66.7</td>
<td>57.1</td>
<td>50</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>APOE ε4 (% Yes)</strong></td>
<td>20</td>
<td>58b</td>
<td>0</td>
<td>62b</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Global PiB SUVR (n)</strong></td>
<td>21</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Global PiB SUVR</strong></td>
<td>1.20 (0.1)a</td>
<td>2.00 (0.3)b</td>
<td>1.16 (0.2)a</td>
<td>2.24 (0.2)b</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAL (n)</strong></td>
<td>40</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>PAL stage 6 err (adj)†</strong></td>
<td>7.93 (8.8)</td>
<td>11.42 (10.7)</td>
<td>12.57 (17.6)</td>
<td>15.13 (15.5)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>LM (n)</strong></td>
<td>40</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>LM immediate recall†</strong></td>
<td>13.68a (3.6)</td>
<td>12.50 (2.8)a</td>
<td>7.14 (2.7)b</td>
<td>7.25 (4.1)b</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>LM delayed recall†</strong></td>
<td>12.92 (3.6)a</td>
<td>12.00 (3.7)a</td>
<td>5.43 (2.6)b</td>
<td>4.00 (3.4)b</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>CVLT-II (n)</strong></td>
<td>40</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>CVLT-II short delay‡</strong></td>
<td>1.19 (1.2)a</td>
<td>1.54 (0.9)a</td>
<td>-0.57 (1.3)b</td>
<td>-1.36 (1.1)b</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>CVLT-II long delay‡</strong></td>
<td>1.08 (1.0)a</td>
<td>1.41 (0.7)a</td>
<td>-0.50 (1.6)b</td>
<td>-1.43 (1.5)b</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>RCFT (n)</strong></td>
<td>39</td>
<td>11</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>RCFT 30 minute‡</strong></td>
<td>1.40 (1.5)a</td>
<td>1.55 (1.9)a</td>
<td>0.30 (1.4)a</td>
<td>-0.52 (1.4)b</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Mood (n)</strong></td>
<td>40</td>
<td>12</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>GDS</strong></td>
<td>1.20 (1.8)a</td>
<td>0.58 (1.2)a</td>
<td>1.83 (0.8)a</td>
<td>2.75 (1.5)b</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Note: * = adjusted if a participant failed to complete stage 6, † = age-scaled score, ‡ = z-score. PAL = Paired Associate Learning, LM = Logical Memory, CVLT-II = California Verbal Learning Test, RCFT = Rey Complex Figure Test, GDS = Geriatric Depression Scale. a = variables are not significantly different (Tukey’s method), b = variable is significantly different (Tukey’s method).
Differences in thematic complaints: HC vs MCI

Individuals with MCI endorsed themes of increasing frequency ($U = 1311.50$, $p = .03$), sense of predomination ($U = 1156.50$, $p = .002$), relative absence of contextualisation ($U = 1028.50$, $p < .001$), burdensome coping strategies ($U = 868.00$, $p < .001$), dismissive attitude ($U = 1207.00$, $p = .004$), impact on affect ($U = 1098.00$, $p = .001$), progression ($U = 1102.00$, $p < .001$), and dependency ($U = 1339.50$, $p = .01$), in comparison to the HC group. All significant differences involved moderate to strong effect sizes (see Error! Reference source not found.A).
Figure 7. (A) Magnitude of difference between HC and MCI on complaint themes (small: 0.1 < 0.3 < 0.5: large) and (B) Kruskal-Wallis mean ranking of complaint themes according to diagnostic status. Light blue = HC-NMC, purple = HC-SMC, and turquoise = MCI.
Differences in thematic complaints: HC-NMC, HC-SMC and MCI

Complaint themes that were significantly different between all three groups were increasing frequency ($\chi^2 = 16.41$, $p < .001$), sense of predomination ($\chi^2 = 18.87$, $p < .001$), relative absence of contextualisation ($\chi^2 = 17.69$, $p < .001$), burdensome coping strategies ($\chi^2 = 33.56$, $p < 0.001$), dismissive attitude ($\chi^2 = 9.00$, $p = .01$), attentional fluctuation/vagueness ($\chi^2 = 6.49$, $p = .04$), progression ($\chi^2 = 18.47$, $p < .001$), and dependency ($\chi^2 = 8.15$, $p = .02$). In comparison to the HC-SMC group, individuals with MCI were significantly elevated on themes of relative absence of contextualisation ($U = 565.00$, $p = .02$), burdensome coping strategies ($U = 439.00$, $p < .001$), and dismissive attitude ($U = 527.50$, $p = .006$). The HC-SMC group were elevated on the theme of attentional fluctuation/vagueness ($U = 573.00$, $p = 0.03$), and significantly elevated on themes of increasing frequency ($U = 462.00$, $p = .001$), sense of predomination ($U = 493.00$, $p = .002$), impact on affect ($U = 556.50$, $p = .02$), and progression ($U = 626.50$, $p = .03$) in comparison with the HC-NMC group. These differences are demonstrated in Kruskal-Wallis mean rank scores in Error! Reference source not found.B.

Differences in thematic complaints: HC Aβ-/HC Aβ+/MCI Aβ-/MCI Aβ+

Complaint themes that were significantly different between all four groups were sense of predomination ($\chi^2 = 10.21$, $p = .02$), burdensome coping strategies ($\chi^2 = 23.47$, $p < .001$), dismissive attitude ($\chi^2 = 8.84$, $p = .03$), progression ($\chi^2 = 17.97$, $p < .001$), and dependency ($\chi^2 = 14.32$, $p < .001$). Post-hoc analyses revealed the MCI Aβ+ group expressed significantly more concerns about sense of predomination ($U = 77.00$, $p = 0.02$), burdensome coping strategies ($U = 46.00$, $p = .001$), dismissive attitude ($U = 79.00$, $p = .02$), progression ($U = 64.00$, $p = .006$), and dependency ($U = 51.00$, $p = .002$), in comparison with HC Aβ- individuals. Similar comparisons were also found between HC Aβ+ and MCI Aβ+ groups (see Error! Reference source not found.). The HC Aβ+ group expressed a greater sense of progressive memory decline compared with the HC Aβ- group ($U = 174.0$, $p = .04$).
Figure 8. Kruskal-Wallis mean ranking of complaint themes according to Aβ load (+/-) and diagnosis (HC/MCI). Light blue = HC Aβ-, purple = HC Aβ+, turquoise = MCI Aβ-, and dark blue = MCI Aβ+.
Association between themes and depressive symptomatology

In healthy controls, greater levels of depressive symptomatology were associated with greater endorsement of poorer contextualisation, $r(80) = 0.44, p < .001$, burdensome coping strategies $r(80) = 0.29, p = .01$, a sense of predomination and growing concern, $r(80) = 0.29, p = .01$, and increasing frequency, $r(80) = 0.25, p = .02$. In participants with MCI, depressive symptomatology was solely associated with greater endorsement of dependency, $r(40) = 0.35, p = .03$ (see Table 9 and Table 10).

Associations between complaint themes and memory variables

In healthy controls, no memory measures contributed unique variance to complaint themes after age and depression were taken into account. In individuals with MCI, more burdensome coping strategies were related to poorer performance on CVLT long delay, $r(31) = -0.49, p = .004$, and CVLT short delay, $r(31) = -0.37, p = .03$, after partialling out the unique variance explained by age and depression. Greater acknowledgement of increasing frequency was related to poorer performance on CVLT long delay, $r(31) = -0.40, p = .02$. Increased expressions of dependency were also related to poorer performance on CVLT long delay, $r(31) = -0.36, p = .03$ (see Table 9 and Table 10).
Table 9. Correlation matrix of complaint themes against depressive symptomatology and memory variables in HC

<table>
<thead>
<tr>
<th>Complaint themes</th>
<th>GDS</th>
<th>PAL</th>
<th>CVLT SD</th>
<th>CVLT LD</th>
<th>LM SD</th>
<th>LM LD</th>
<th>RCFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing frequency</td>
<td>0.25*</td>
<td>-0.11</td>
<td>0.05</td>
<td>0.02</td>
<td>0.08</td>
<td>0.07</td>
<td>-0.04</td>
</tr>
<tr>
<td>Predomination</td>
<td>0.29**</td>
<td>-0.09</td>
<td>0.09</td>
<td>-0.004</td>
<td>0.004</td>
<td>-0.06</td>
<td>-0.04</td>
</tr>
<tr>
<td>Situational</td>
<td>-0.02</td>
<td>0.21</td>
<td>0.04</td>
<td>0.02</td>
<td>-0.03</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Contextualisation</td>
<td>0.44**</td>
<td>-0.09</td>
<td>-0.02</td>
<td>0.07</td>
<td>-0.12</td>
<td>-0.07</td>
<td>-0.10</td>
</tr>
<tr>
<td>Burdensome coping strat.</td>
<td>0.29**</td>
<td>0.19</td>
<td>0.04</td>
<td>-0.14</td>
<td>-0.03</td>
<td>-0.07</td>
<td>-0.20</td>
</tr>
<tr>
<td>Dismissive attitude</td>
<td>0.16</td>
<td>-0.23</td>
<td>-0.11</td>
<td>-0.03</td>
<td>0.21</td>
<td>0.21</td>
<td>-0.03</td>
</tr>
<tr>
<td>Attentional fluctuation</td>
<td>0.06</td>
<td>-0.16</td>
<td>0.12</td>
<td>-0.06</td>
<td>-0.07</td>
<td>-0.05</td>
<td>-0.03</td>
</tr>
<tr>
<td>Impact on affect</td>
<td>0.11</td>
<td>-0.12</td>
<td>0.15</td>
<td>-0.06</td>
<td>0.04</td>
<td>0.07</td>
<td>-0.21</td>
</tr>
<tr>
<td>Progression</td>
<td>0.18</td>
<td>-0.02</td>
<td>-0.09</td>
<td>-0.17</td>
<td>0.12</td>
<td>0.07</td>
<td>-0.08</td>
</tr>
<tr>
<td>Dependency</td>
<td>0.15</td>
<td>0.15</td>
<td>0.14</td>
<td>0.04</td>
<td>0.07</td>
<td>0.02</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

Note: ** = p < 0.01, † Partial correlations accounting for age and GDS score. GDS = Geriatric Depression Score, PAL = Paired Associates Learning stage 6 errors (adj), CVLT= California Verbal Learning Test, SD = short delay, LD = long delay, LM = Logical Memory, RCFT = Rey Complex Figure Test
Table 10. Correlation matrix of complaint themes against depressive symptomatology and memory variables in MCI

<table>
<thead>
<tr>
<th>Complaint themes</th>
<th>GDS</th>
<th>PAL†</th>
<th>CVLT SD†</th>
<th>CVLT LD†</th>
<th>LM IR†</th>
<th>LM DR†</th>
<th>RCFT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing frequency</td>
<td>0.03</td>
<td>-0.20</td>
<td>-0.03</td>
<td>-0.40*</td>
<td>0.30</td>
<td>0.19</td>
<td>0.21</td>
</tr>
<tr>
<td>Predomination</td>
<td>0.13</td>
<td>-0.13</td>
<td>-0.19</td>
<td>0.21</td>
<td>0.00</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>Situational</td>
<td>-0.05</td>
<td>-0.08</td>
<td>0.13</td>
<td>0.14</td>
<td>-0.002</td>
<td>0.05</td>
<td>0.25</td>
</tr>
<tr>
<td>Contextualisation</td>
<td>0.19</td>
<td>0.06</td>
<td>-0.09</td>
<td>-0.24</td>
<td>-0.07</td>
<td>-0.23</td>
<td>-0.16</td>
</tr>
<tr>
<td>Burdensome coping strat.</td>
<td>0.15</td>
<td>-0.02</td>
<td>-0.37*</td>
<td>-0.49**</td>
<td>-0.14</td>
<td>-0.17</td>
<td>-0.14</td>
</tr>
<tr>
<td>Dismissive attitude</td>
<td>0.01</td>
<td>0.21</td>
<td>-0.14</td>
<td>-0.11</td>
<td>-0.15</td>
<td>0.09</td>
<td>-0.01</td>
</tr>
<tr>
<td>Attentional fluctuation</td>
<td>0.11</td>
<td>-0.17</td>
<td>0.35</td>
<td>0.25</td>
<td>0.22</td>
<td>0.33</td>
<td>0.32</td>
</tr>
<tr>
<td>Impact on affect</td>
<td>-0.01</td>
<td>-0.16</td>
<td>-0.04</td>
<td>-0.04</td>
<td>0.31</td>
<td>0.18</td>
<td>-0.001</td>
</tr>
<tr>
<td>Progression</td>
<td>0.05</td>
<td>-0.12</td>
<td>0.09</td>
<td>0.05</td>
<td>0.17</td>
<td>0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Dependency</td>
<td>0.35*</td>
<td>-0.10</td>
<td>-0.10</td>
<td>-0.36*</td>
<td>0.20</td>
<td>-0.16</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

Note: * = p < 0.03, ** = p < 0.01, † Partial correlations accounting for age and GDS score. GDS = Geriatric Depression Score, PAL = Paired Associates Learning stage 6 errors (adj), CVLT = California Verbal Learning Test, SD = short delay, LD = long delay, LM = Logical Memory, RCFT = Rey Complex Figure Test
Discussion

Twelve themes emerged from the qualitative analysis of an interview-based assessment of subjective memory complaints. These were, increasing frequency, sense of predominance, situational, relative absence of spatio-temporal contextualisation, burdensome coping strategies, dismissive attitude, attentional fluctuation/vagueness, impact on affect, progression, dependency, over-endorsed complaint and affective influences on memory. As expected, endorsement of most themes was predominantly elevated in individuals with MCI, aligning with current conceptions of the MCI symptom complex (Gauthier et al., 2006; Morris, 1993; Petersen et al., 2001; Reisberg et al., 1982; Winblad et al., 2004), and supports the criterion validity of our semi-structured interview. The purpose of this study, however, was not to develop a novel diagnostic marker of subjective memory complaints, but to explore from a scientific perspective the differing subjective experiences of memory change in putative healthy and pathological aging. Individuals with MCI were much more likely to elicit comments regarding burdensome coping strategies, suggesting that functional changes arising from an increase in the implementation of maladaptive coping strategies may well signify an interim early stage outcome of accumulating memory dysfunction in MCI, as activities of daily living gradually start to decline (Amieva et al., 2008; Reisberg et al., 1982).

The healthy memory complainer group, who were identified according to their affirmative response on a single memory complaint question, displayed a similar thematic complaint profile as individuals with MCI. Unidimensional concerns assayed via a single question have been found to be indicative of future cognitive decline or progression to DAT (Crowe et al., 2006; Geerlings et al., 1999; St John & Montgomery, 2002; van Oijen et al., 2007). This type of question is the neuropsychological equivalent of, “Do you feel sick?”, which represents a sensitive question to illness but lacks aetiological specificity. The finding signifies that, while diagnostically uninformative, a simple binary response in healthy memory complainers can reveal subjective memory changes akin to those in MCI. Their complaint profiles notably diverged, however, on certain themes. Individuals with MCI elicited more burdensome coping strategies and dependency on a significant other, while healthy memory complainers endorsed more attentional fluctuations. Increasing acknowledgement of burdensome coping strategies and dependency on others may well signify an interim early stage outcome of accumulating memory dysfunction in MCI, as activities of daily living gradually start to decline (Amieva et al., 2008; Reisberg et al., 1982). Attentional fluctuations reported by healthy memory complainers, on the other hand, might represent stress or mood driven attentional dysfunctions rather than portending a primary memory problem. Subtle executive dysfunction, particularly in working memory, has been noted in non-demented older adults who subsequently progress to DAT (Albert et al., 2001; Duara et al., 2011; Schmid, Taylor, Foldi, Berres, & Monsch, 2013) and in healthy older adults memory complainers (Amariglio et al., 2012; I. P. Martins, Mares, & Stilwell, 2012; Rouch et al., 2008), suggesting the possibility of an
MCI precursor. An evaluation of the predictive utility of these themes was not an aim of this study, but the possibility that this implies an early stage prodromal marker of DAT cannot be discounted.

Studies investigating the relationship between neocortical Aβ burden and memory complaining in healthy older adults are gaining traction (Amariglio et al., 2012; Barnes et al., 2006; R. Buckley et al., 2013; Chételat et al., 2010; Perrotin et al., 2012; Rodda et al., 2010; Rolstad et al., 2011). The current tenor of these findings, including the existence of small effect sizes in our study, points to the existence of an attenuated relationship. Both SMCs and neocortical Aβ burden are present at the very earliest stages of AD but signify opposing ends of the clinicopathological spectrum; one reflects an upstream pathological hallmark of AD, while the other is an individual’s subjective reality of memory change. Healthy older adults with high Aβ acknowledged the presence of progressive memory decline, suggesting that memory changes are likely detectable at a broader phenomenological level but cannot be elucidated further. Considering this group is regarded as cognitively normal it is unsurprising that individuals are unable to identify more focused changes in memory function.

Depressive symptomatology has a well-established association with subjective memory complaints in healthy older adults (Bartley et al., 2012; R. Buckley et al., 2013; Jorm et al., 2004; Lautenschlager et al., 2005), prompting some researchers to question their diagnostic utility (Lenehan et al., 2012; A. J. Mitchell, 2008b). A greater influence of depressive symptomatology was found in the memory complaints of healthy older adults, which was not mirrored in MCI, consistent with the notion that memory complaints in MCI are much more likely to be contributed to by neuropathology. Memory complaints in the healthy community-dwelling older adults are largely driven by poor mood or stress (Steinberg et al., 2013; Vestrergren & Nilsson, 2011). The only complaint theme to relate to depression in MCI was increased endorsement of dependency, which may well be induced by a gradual decline of activities of daily living and reduction of independence.

Delayed recall of word lists was associated with the endorsement of burdensome coping strategies, increasing frequency and dependency in individuals with MCI, after taking into account the effects of age and depression. These findings support research that suggests an awareness of objective cognitive changes in MCI (Crowe et al., 2006; Greenop et al., 2011) that peaks during this clinical stage (for a review see Reisberg & Gauthier, 2008). By contrast, no relationship was found between memory complaint themes or measures of learning or retention in healthy controls, supporting the notion of disparate memory complaint aetiologies in the two groups.

Conclusion
This is the first examination of subjective memory complaint symptomatology using a semi-structured interview reminiscent of a clinical interview. A phenomenological characterisation of an individual’s self-appraisal of their everyday memory function was developed according to diagnosis and Aβ biomarker status. Current methods of SMC measurement reflect a binary ‘yes/no’ outcome or a cumulative score from a questionnaire, which neglect the experience that forms the crucial foundation of the complaint. These findings emphasize the notion that expressions of memory failure are feature against a backdrop of clinicopathological changes, which can be revealed by a qualitative approach.
The previous chapters have investigated the meaning of a subjective memory complaint from both a quantitative and qualitative perspective. Chapter 4 was concerned with the cognitive, affective and AD biomarker correlates of memory complaint severity, particularly in individuals with MCI. Memory complaint severity, as measured via a commonly-used questionnaire, was found to be primarily affect-driven in healthy older adults, and associated solely with age in individuals with MCI. Chapter 5 used a novel approach of measuring the qualitative experiences of memory change in those at risk of AD. Individuals with MCI acknowledged increasing functional issues in daily life, particularly with issues relating to increased dependence on others and the implementation of poor coping strategies. The implication is that initial subjective expressions of functional changes are an early interim stage marker of disease, supporting clinical staging markers of the disease (Morris, 1993; Reisberg et al., 1982). Healthy older memory complainers largely aligned with MCI in their phenomenological experiences of memory lapses, but they diverged on these themes and tended to acknowledge more attentional fluctuations and vagueness. This finding could signal an initial early-stage outcome of subtle cognitive changes in healthy older adults that are not detectable by neuropsychological measures.

One complaint theme that was elevated in both healthy memory complainers and individuals with MCI was a relative absence of contextualisation of recent memory lapses. That is, individuals struggled to produce spatiotemporal or emotional episodic details relating to recent memory lapses. An ability to recall richly detailed personal information pertaining to an event is a function of the autobiographical memory (ABM) system. This finding suggests a dysfunction of ABM, which will be investigated further in this chapter.

6.1 Autobiographical and personal semantic memory impairment

Autobiographical memory (ABM) performance has been found to be impaired in studies of individuals with MCI (Barnabe et al., 2012; Gilboa et al., 2005; Irish et al., 2011; Leyhe et al., 2009; Murphy et al., 2008). Impairment of personal semantic memory (PSM), on the other hand, is unclear, with some studies showing a PSM impairment in individuals with MCI (Irish et al., 2010; Leyhe et al., 2012), while others do not (Murphy et al., 2008). As far as the candidate is aware, no studies have measured the level of ABM and PSM in healthy individuals with a memory complaint.
An assessment of everyday personal memory function does not form a part of the mainstream diagnostic approach to MCI. A gauge of cognitive impairment is made via neuropsychological measures, with new learning and retention forming the most sensitive early indicators of DAT (Albert et al., 2001, 2011; Chen et al., 2000; Collie & Maruff, 2000; de Jager et al., 2003; Ficker et al., 1991; Lehrner et al., 2005; Mura et al., 2014; Rabin et al., 2009; Ritchie et al., 2001; Salmon et al., 2002). Impairment on measures of new learning and retention is argued to have a higher risk of conversion to DAT than impairment on tasks that tap into other cognitive domains (Gauthier, 2006), with a high sensitivity and specificity for early detection (Albert et al., 2001; Collie & Maruff, 2000; de Jager et al., 2003; Lehrner et al., 2005; Mura et al., 2014; Rabin et al., 2009; Salmon et al., 2002). As such, measures of new learning and retention will be used to compare and further understand the pattern of impairment in ABM and PSM in healthy memory complainers and individuals with MCI.

6.2 Aims of Chapter 6

The aim of this chapter is to assess everyday ABM and PSM performance in healthy memory complainers and individuals with MCI to determine if the pattern of everyday memory impairment aligns with well-established impairment in measures of new learning and retention. The following results section is presented in its published format, which was published in *Journal of Alzheimer’s Disease* (R. Buckley, Saling, Irish, Ames, Rowe, Lautenschlager, et al., 2014).
Personal memory function in mild cognitive impairment and subjective memory complaints: Results from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) Study of Ageing


Abstract

Background: Autobiographical memory (ABM) refers to the recollection of individual experiences, while personal semantic memory (PSM) refers to personally relevant, but shared, facts. Mild cognitive impairment (MCI) is routinely diagnosed with the aid of neuropsychological tests, which do not tap the ABM and PSM domains. Objective: We aimed to characterise the nature of ABM and PSM retrieval in HC memory complainers, non-memory complainers and MCI participants, and to investigate the relationship between neuropsychological tests and personal memory.

Methods: Sex and education-matched participants (HC = 80 and MCI = 43) completed the Episodic ABM Interview (EAMI) and a battery of neuropsychological tests.

Results: ABM and PSM did not differ between complainers and non-complainers, but were poorer in MCI participants, after accounting for age and depressive symptomatology. There were significant associations between personal memory and objective memory measures were found in MCI participants, but standard cognitive measures were more sensitive to MCI.

Conclusion: Personal memory was compromised in MCI, reflected by lower scores on the EAMI. Memory complaining, assessed by current approaches, did not have an impact on personal memory. Standard subjective questionnaires might not reflect the sorts of concerns that bring individuals to clinical attention. Understanding personal memory function in older adults may aid in the development of a more sensitive measure of subjective memory concerns.
Introduction

Autobiographical memory (ABM) and personal semantic memory (PSM) are forms of everyday personal memory. ABM refers to the recollection of highly contextualised individual experiences (Wheeler et al., 1997). Essential elements of ABM involve remembering the details of the event as they took place within a temporal, spatial, and emotional context, with rich accompanying visual imagery (Irish, Lawlor, O’Mara, et al., 2011). Personal semantic memory (PSM), on the other hand, refers to personally relevant knowledge or facts about the individual (Robinson & Swanson, 1990). At its core, general semantic memory implies abstracted knowledge that is shared by many (Tulving, 1985). PSM, by contrast, is shared at a community level by individuals with overlapping autobiographical experiences (Greene & Hodges, 1996; Westmacott et al., 2004).

ABM and PSM are commonly treated as distinct sub-systems of personal memory in studies of clinical populations (Robinson & Swanson, 1990; Tulving, Schacter, McLachlan, & Moscovitch, 1988; Wheeler et al., 1997), perhaps mimicking the episodic/semantic distinction in declarative memory. Studies of patients with amnesia resulting from predominantly diencephalic/limbic lesions suggest that ABM is selectively impaired with relative sparing of PSM (for a commentary, see Nadel & Moscovitch, 1997). Healthy older adults show a similar but non-pathological pattern, relative to younger individuals, producing fewer autobiographical details in personal narratives (Levine et al., 2002; Piolino, Desgranges, Benali, & Eustache, 2002). As a result, non-autobiographical details predominate, and appear to be imbued with greater subjective salience. A neural correlate of the ABM/PSM distinction has been developed from differential patterns of activation in response to autobiographical and personal semantic content (for a meta-analysis see, Svoboda et al., 2006). Specifically, autobiographical memory recruits hippocampal and posterior cingulate (Gilboa et al., 2004; Levine, 2004) activity, while personal semantic memory recruits activity in regions associated with general semantic processing such as the middle temporal gyrus (Svoboda et al., 2006).

The literature examining the effects of mild cognitive impairment (MCI) and dementia of the Alzheimer’s type (DAT) on personal memory function is relatively small but all studies support the notion that ABM is impaired (Barnabe et al., 2012; Greene et al., 1995; Irish et al., 2010; Irish, Lawlor, O’Mara, et al., 2011; Ivanoiu et al., 2006; Leyhe et al., 2009; Murphy et al., 2008). The level of impairment in PSM, as well as the rationale for its dysfunction early in AD, remains unclear. Some studies have reported a relatively spared PSM compared with ABM (Greene et al., 1995; Murphy et al., 2008). Greene, Hodges and Baddeley (1996) reported an impaired recall of details surrounding a personal event but relatively preserved recall of personal semantic detail in patients with mild DAT. Additionally, a study of individuals with MCI reported a reduction of contextual (internal) details and elevation of incidentally-
associated semantic (external) details within a personal narrative, revealing a
dissociation similar to that observed in normal older individuals (Murphy et al.,
2008). Other studies, however, report that individuals with MCI and DAT are
impaired in both ABM and PSM, particularly for recent memories (Irish, Lawlor,
O’Mara, et al., 2011; Leyhe et al., 2009). Taking the literature as a whole, the following
question emerges: how do deficits in personal forms of memory align with current
concepts of memory impairment in MCI, and its subsequent progression?

Mainstream approaches to diagnosis of MCI generally do not formally
investigate autobiographical and/or personal semantic memory dysfunction. It is
concerns of personal memory loss, however, that represent the principal driver of
presentation to a clinician. This may be due to the fact that autobiographical narratives
are inherently subjective and are difficult to verify against normative standards, and
diagnosis of MCI is supported chiefly by performance on standard neuropsychological
testing. Tests of new learning and retention, such as the learning of word lists and
short stories, have been found to be early markers of conversion to DAT, with varying
levels of sensitivity, but are poorly correlated with conventional measures of subjective
memory complaints (R. Buckley et al., 2013; Lenahan et al., 2012; Purser et al., 2006).
Indeed, memory complaints, either elicited via a single question or a longer
questionnaire, have been primarily associated with affective symptomatology (R.
Buckley et al., 2013) thus raising the question of their prognostic value. While
psychometric assessment samples the abilities on which the formation of personal
memories is mounted, it does not reflect the broad and richly articulated landscape of
personal memory.

The clinical symptomatology of MCI might align more closely with a subjective
awareness of discrepancies in personal memory function. Given the current
discrepancies in the literature, a study of patterns of personal memory loss in MCI is
essential to deepen our understanding of, and clinical access to, early memory
symptomatology in this population. Our objective was to ascertain how the MCI
symptom complex, which is principally defined by performance on standard memory
tasks, and subjective cognitive decline (SCD) impact personal memory function. Our
secondary aim was to determine the sensitivity of personal memory measures in
differentiating between diagnostic categories relative to standard cognitive measures.
Lastly, we aimed to study the relationship between standard neuropsychological tests
commonly used in the diagnosis of MCI, and personal memory dysfunction. We
hypothesized that both ABM and PSM would be compromised in individuals with MCI
but given their poor relationship with objective memory measures, that SCD would be
an unlikely contributor to personal memory dysfunction. And finally we predicted that
personal memory function would relate to measures of new learning and retention.
Methods

Participants

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing is a longitudinal study with follow-up assessments at 18-month intervals. At the third time-point (36-months post baseline), the cohort comprised participants diagnosed with dementia due to DAT (154), participants classified as MCI (58), or classified as cognitively healthy (HC: 611). A smaller sub-section of one hundred and twenty-four participants (HC = 80; MCI = 48) were recruited for this study. This study was treated as a cross-sectional study, focusing exclusively on data collected at the 36-month time-point. Human Research Ethics approval for the current study was obtained in Victoria from St Vincent’s Hospital and the University of Melbourne, and Hollywood Private Hospital in Western Australia. All participants were recruited via telephone and asked to participate in a one hour semi-structured interview in their homes. There were 70 HCs and 25 individuals with MCI in Victoria and 10 HCs and 19 MCI participants in Western Australia. The recruitment procedures and exclusion criteria for the AIBL study have been published (K. A. Ellis et al., 2009). In brief, older volunteers responded to a media appeal or a referral by their medical practitioner and were screened via telephone for basic demographic information, and the following exclusion criteria: a history of dementia other than DAT, psychiatric illness (such as significant current (but not past) depression, which was determined by a Geriatric Depression Scale (GDS: Yesavage et al., 1983) score of greater than five), Parkinson’s disease, cancers within the last few years, symptomatic stroke, uncontrolled diabetes, and alcohol consumption greater than recommended levels. Only HC and MCI participants were eligible to participate in the study reported here. In this sub-study, five participants with MCI were excluded as four MCI individuals had progressed to DAT by the time they were invited to participate in this study, and one had an elevated GDS score of eight at the 36-month time point. This gave a final sample size of 80 HCs and 43 individuals with MCI. Memory complaining was determined by a single question, “Do you have difficulties with your memory, yes or no?”. This question split the HC group further, with 43 healthy controls with no subjective cognitive decline (HC-NSD) and 37 healthy controls with subjective cognitive decline (HC-SCD).

Thirty-six month follow-up cognitive assessments were carried out prior to the commencement of the present study. The mean administration time for the standard neuropsychological protocol was two hours (for details see: K. A. Ellis et al., 2009). A diagnostic review panel of neurologists, geriatricians, psychiatrists and neuropsychologists, chaired by the fourth author (DA), oversaw the classification into HC, MCI and DAT groups according to well-established criteria (K. A. Ellis et al., 2009; Petersen et al., 1999; Winblad et al., 2004). MCI classification was made based on performance falling 1.5SD below age-adjusted levels in formal memory assessment,
expressed memory complaint/subjective memory concern, and current preservation of activities of daily living.

Cognitive measures

The following tests were administered by AIBL neuropsychologists at the 36 month time-point. To measure verbal learning, the California Verbal Learning Test—Second edition (CVLT-II) new learning, post-interference recall, delayed recall, and recognition measures (Delis et al., 2000), and the Wechsler Memory Scale—Third edition (WMS-III) Logical Memory (LM) immediate and delayed recall measures (D Wechsler, 1997) were administered. To measure non-verbal memory, the Rey Complex Figure Test (RCFT) 30 minute delayed recall and recognition (Meyers & Meyers, 1995) was administered. The Fruit and Furniture Switching (FFS) task from the D-KFES (Delis et al., 2001) and the Stroop test (Trenerry et al., 1989) were used to measure fundamental components of executive functioning. Language difficult in the form of naming was assessed using the US version of the 30-item Boston Naming Test (BNT: Mack et al., 1992). The GDS was included as the affective covariate.

Measure of personal memory

This measure was administered in the participant’s home by the first author (RB). The duration of this assessment was approximately forty minutes. Both forms of personal memory were measured using the Episodic Autobiographical Memory Interview (EAMI: Irish et al., 2008; Irish, Lawlor, O’Mara, et al., 2011). The EAMI is a semi-structured interview that involves two parts; the first assesses PSM recall by probing personal factual information that can be shared by family and friends, and the second assesses ABM event recall by probing subjective experiences that are unique to the individual and can be recalled within a specific spatiotemporal context. For the current study, a shortened version of the EAMI was used in which recall was constrained to the Recent Period (within the last 5 years).

The PSM part involved three items. The first asked the participant to recall the names of three people that they had only met in the last five years (one point for the full name and one point for their relationship to the individual). The second involved recalling the location and route to a frequented establishment in the last five years (one point each for the name of the establishment, location, what they did there and how they travelled there). The third item related to the ability to recall the exact date, month, year and location of a personally significant event within the last five years (one point for each of the four specifics remembered). This totalled to a maximum score of 14 for the PSM component. In an effort to avoid any compensatory effects that ABM may play on PSM, this section was administered first.
The ABM component involved recalling in as much detail as possible a personally significant event that occurred within the last five years. Once participants stopped spontaneously producing information pertaining to the event, the interviewer probed for further details using seven phenomenological categories taken from the Event Details Checklist of Moscovitch and colleagues (2000). These probes included event detail, temporal, spatial, sensory, implication of the event, emotion, and thought recall. Each detail was awarded a maximum score of one point, which would be summed to a maximum score of seven points. These interviews were recorded with the approval of the participant, transcribed, and scored by the interviewer and a blinded clinical neuropsychologist. Inter-rater reliability, as measured by intraclass correlation coefficient, was high for both sections (rABM = 0.92; rPSM = 0.94).

Statistical analyses

Analyses were conducted using SPSS Version 21.0. We performed a multivariate analysis of covariance (MANCOVA) to determine whether ABM or PSM would differ according to diagnostic category, HC non-memory complainer (HC-NMC), HC subjective memory complainer (HC-SMC) or MCI, while including age and depression as covariates. To determine the sensitivity and specificity of personal memory to classify diagnostic categories (HC and MCI), we conducted a discriminant function analysis (DFA). The grouping of HC and MCI was based on performance on standard cognitive tasks in conjunction with a clinical assessment. We used another DFA to determine how the neuropsychological measures would classify the groups as they were not the sole grouping determinant. Finally, we attempted a linear regression model to determine which cognitive measures best predicted personal memory performance but we found very high multicollinearity amongst the predictor variables. To counteract this problem, we correlated personal memory and neurocognitive measures of memory, language and executive functioning. Missing data existed for both cognitive and affective measures but totalled less than 10% of the entire data set (refer to Table 8).

Results

Differences between healthy controls and individuals with MCI

The demographic and cognitive information for the HC-NMC, HC-SMC and MCI groups is presented in Table 11. Individuals with MCI (M_{Age} = 79.6 years, SD = 6.9, range = 67-94 years) and healthy memory complainers were significantly older (M_{Age} = 77.8 years, SD = 7.3, range = 67-95 years) than the healthy non-complainers (M_{Age} = 73.8 years, SD = 6.1, range = 66-93 years), F(2, 120) = 8.48, p < .001, η^2 = .12. The MCI and healthy memory complaining group demonstrated more depressive symptomatology compared to the healthy non-complainers, F(2, 117) = 13.09, p < .001, η^2 = .18. There was no difference between the groups in level of education, χ^2 =
3.03, df = 2, p = ns, Φ = .16, or gender, χ² = 4.98, df = 2, p = .08, Φ = 0.20. Individuals with MCI were significantly impaired across all cognitive measures compared to both healthy control groups (all p values < .001).
Table 11. Demographic and cognitive differences between groups

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HC-NMC (n = 43)</th>
<th>M (SD)</th>
<th>HC-MC (n = 37)</th>
<th>M (SD)</th>
<th>MCI (n = 43)</th>
<th>M (SD)</th>
<th>( \eta^2 )</th>
<th>sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.77 (6.1)a</td>
<td></td>
<td>77.76 (7.3)b</td>
<td></td>
<td>79.6 (6.9)b</td>
<td></td>
<td>0.12</td>
<td>.002</td>
</tr>
<tr>
<td>Gender (% F)</td>
<td>56</td>
<td></td>
<td>35</td>
<td></td>
<td>58</td>
<td></td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Education (% &gt; 12 yrs)</td>
<td>65</td>
<td></td>
<td>65</td>
<td></td>
<td>49</td>
<td></td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Personal Memory (n)</td>
<td>40</td>
<td></td>
<td>40</td>
<td></td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABM performance*</td>
<td>5.16 (1.2)a</td>
<td></td>
<td>4.88 (1.5)a</td>
<td></td>
<td>3.53 (2.0)b</td>
<td></td>
<td>0.18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PSM performance*</td>
<td>12.91 (1.3)a</td>
<td></td>
<td>11.74 (2.5)a</td>
<td></td>
<td>9.70 (4.2)b</td>
<td></td>
<td>0.19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM (n)</td>
<td>43</td>
<td></td>
<td>37</td>
<td></td>
<td>43</td>
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<tr>
<td>Immediate recall*</td>
<td>14.00 (3.7)a</td>
<td></td>
<td>12.35 (3.2)a</td>
<td></td>
<td>6.93 (3.5)b</td>
<td></td>
<td>0.44</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delayed recall*</td>
<td>13.21 (3.6)a</td>
<td></td>
<td>11.22 (3.5)a</td>
<td></td>
<td>4.26 (4.0)b</td>
<td></td>
<td>0.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVLT (n)</td>
<td>42</td>
<td></td>
<td>36</td>
<td></td>
<td>38</td>
<td></td>
<td>0.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New Learning^</td>
<td>64.55 (8.6)a</td>
<td></td>
<td>65.17 (10.4)a</td>
<td></td>
<td>41.58 (10.9)b</td>
<td></td>
<td></td>
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<tr>
<td>Post-interference recall</td>
<td>1.20 (1.1)a</td>
<td></td>
<td>1.44 (1.1)a</td>
<td></td>
<td>-1.26 (1.2)b</td>
<td></td>
<td>0.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delayed recall Recognition</td>
<td>1.10 (0.9)a</td>
<td></td>
<td>1.36 (0.9)a</td>
<td></td>
<td>-1.22 (1.3)b</td>
<td></td>
<td>0.54</td>
<td>&lt;.001</td>
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<tr>
<td>RCFT (n)</td>
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<td>35</td>
<td></td>
<td>41</td>
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<td></td>
<td></td>
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<tr>
<td>30min delay</td>
<td>1.27 (1.6)a</td>
<td></td>
<td>1.48 (1.7)a</td>
<td></td>
<td>-0.46 (1.4)b</td>
<td></td>
<td>0.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recognition</td>
<td>0.91 (1.1)a</td>
<td></td>
<td>0.75 (1.1)a</td>
<td></td>
<td>-0.87 (1.5)b</td>
<td></td>
<td>0.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BNT (n)</td>
<td>39</td>
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<td>36</td>
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<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Cue</td>
<td>0.88 (0.5)a</td>
<td></td>
<td>0.99 (0.7) a</td>
<td></td>
<td>0.15 (0.9)b</td>
<td></td>
<td>0.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D-KFES FFS (n)</td>
<td>39</td>
<td></td>
<td>35</td>
<td></td>
<td>40</td>
<td></td>
<td>0.19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FFS#</td>
<td>11.64 (3.0)a</td>
<td></td>
<td>11.06 (3.1)a</td>
<td></td>
<td>8.13 (3.2)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop (n)</td>
<td>40</td>
<td></td>
<td>33</td>
<td></td>
<td>40</td>
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<td></td>
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</tr>
<tr>
<td>Stroop</td>
<td>-0.71 (0.6)</td>
<td></td>
<td>-0.51 (0.6)</td>
<td></td>
<td>-0.36 (0.7)</td>
<td></td>
<td>0.04</td>
<td>ns</td>
</tr>
<tr>
<td>Affect</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GDS score (n)</td>
<td>41</td>
<td></td>
<td>36</td>
<td></td>
<td>40</td>
<td></td>
<td>0.51 (0.9)a</td>
<td>1.78 (2.0)b</td>
</tr>
</tbody>
</table>

Note: a = variables are not significantly different, b = variable is significantly different, * = t-scores, ^ = age-scaled score. * = ABM/PSM are presented as raw scores. Differences in groups were determined using independent-sample t-tests and chi-square (\( \chi^2 \)) tests of independence. LM = Logical Memory, CVLT = California Verbal Learning Test, RCFT = Rey Complex Figure Test, BNT = Boston Naming Test, FFS = Fruit and Furniture Switching, GDS = Geriatric Depression Scale.
Effect of classification, age and depression on ABM and PSM

Classification (HC-NMC/HC-SMC/MCI) was related to both forms of personal memory, Pillai’s Trace = 0.15, $F(4, 228) = 4.70$, $p = .01$, partial eta squared ($\eta^2$) = 0.08. Both ABM performance, $F(2, 114) = 7.79$, $p = .001$, $\eta^2 = 0.12$, and PSM performance were affected, $F(2, 114) = 6.02$, $p = .003$, $\eta^2 = 0.10$, indicating a medium effect sizes (see Figure 9). There was no significant influence of age or depression on personal forms of memory. Post-hoc comparisons using Tukey’s HSD revealed that MCI participants were significantly impaired in ABM and PSM comparison to both HC groups (see Figure 9) but there was no difference between healthy memory complainers or non-complainers. For this analysis, homogeneity of covariance was violated, Box’s $M = 61.05$, $p < .001$, suggesting a poor fit of the model but the similarity of the logarithms of determinants of the different covariance matrices were within acceptable limits. Homogeneity of variance was violated for ABM and PSM recall but there was no violation of linearity or multicollinearity.
Figure 9. The estimated marginal mean performances (error bars are SD) for (A) PSM and (B) ABM for healthy non-memory complainers (HC-NMC) and memory complainers (HC-SMC) and MCI participants, adjusting for covariates age (mean = 76.97 years) and GDS score (mean = 1.51). * = p value < .01
Discriminant function analyses

Two discriminant function analyses were performed to determine whether personal memory measures were as sensitive and specific as standard cognitive measures to differentiating between HC and MCI. The first model used PSM and ABM variables as predictors of membership in each group. Of the original 123 cases, one was dropped from the analysis due to missing data. Box's test of equality of covariances was violated, Box's $M = 36.42, p < .001$, but the logarithms of determinants were within acceptable limits. The function accounted for 22.2% of the total relationship between predictors and groups. The structure matrix of correlations between predictors and discriminant functions suggested both ABM and PSM were good predictors. The model correctly classified 70.5% of original grouped cases (see Table 12). The cross-validation procedure indicated 67.2% of cases were classified correctly suggesting a high degree of consistency in the classification scheme. The sensitivity and specificity of this model was 56% and 79%, respectively, suggesting that true negatives were easier to classify. The model had a positive predictive power of 59% and negative predictive power of 77%, suggesting the model was better at predicting cases as HC which turned out to be observed as HC.

The second model included all neuropsychological variables as predictors of membership in each group. Of the original 123 cases, 14 were dropped from the analysis due to missing data. Box's test of equality of covariances was violated, Box's $M = 164.86, p < .001$, but the logarithms of determinants were within acceptable limits. The function accounted for 74.0% of the total relationship between predictors and groups. The structure matrix of correlations between predictors and discriminant functions suggested that the best predictors were BNT score, RCFT recognition and CVLT post-interference recall. It is important to note that all variables had a loading of less than .50, indicating a low level of contribution to the model overall. The model correctly classified 94.5% of original grouped cases (see Table 12), and the cross-validation procedure indicated 91.7% of cases were classified correctly. The sensitivity and specificity for the model was 97% and 89%, respectively, with a positive predictive power of 87% and negative predictive power of 99%.
Table 12. Discriminant analyses of cognitive variables

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Canonical correlations</th>
<th>Univariate Model 1</th>
<th>F (1, 120)</th>
<th>ABM</th>
<th>0.60</th>
<th>23.74</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSM</td>
<td>0.60</td>
<td>23.84</td>
</tr>
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</table>

Classification Table

Model 1

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Observed</th>
<th>HC</th>
<th>MCI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>62 (79%)</td>
<td>17 (22%)</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>MCI</td>
<td>19 (44%)</td>
<td>24 (56%)</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Model 2

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Canonical correlations</th>
<th>Univariate Model 2</th>
<th>F (1, 107)</th>
<th>BNT</th>
<th>0.37</th>
<th>28.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT PIR</td>
<td>0.31</td>
<td>132.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCFT recog</td>
<td>0.31</td>
<td>59.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM DR</td>
<td>0.27</td>
<td>102.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT DR</td>
<td>0.23</td>
<td>126.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT NL</td>
<td>0.19</td>
<td>157.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFS</td>
<td>0.17</td>
<td>24.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM IR</td>
<td>0.16</td>
<td>77.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCFT delay</td>
<td>-0.15</td>
<td>32.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT recog</td>
<td>0.09</td>
<td>32.26</td>
<td></td>
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<tr>
<td>Stroop</td>
<td>0.06</td>
<td>2.07</td>
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</tbody>
</table>

Classification Table

Model 2

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Observed</th>
<th>HC</th>
<th>MCI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>66 (93%)</td>
<td>5 (7%)</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>MCI</td>
<td>1 (3%)</td>
<td>34 (97%)</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

Note: ABM = autobiographical memory, PSM = personal semantic memory, BNT = Boston Naming Test, CVLT = California Verbal Learning Test, PIR = post-interference recall, LM = Logical Memory, DR = delayed recall, NL = new learning, RCFT = Rey Complex Figure Test
Relationship between personal memory and standard cognitive tests

In all healthy controls, ABM and PSM were weakly correlated, \( r(79) = 0.23, p = .04 \), with healthy non-complainers showing a significant positive correlation and healthy memory complainers showing no correlation (see Error! Reference source not found.). ABM was found to correlate significantly with Logical Memory immediate recall, \( r(79) = 0.27, p = .05 \), and Logical Memory delayed recall, \( r(78) = 0.22, p = .05 \). No other correlations were found in the healthy control group.

Figure 10. Scatterplot of ABM and PSM performance by group, with regression lines and correlations
In MCI participants, Pearson correlation analyses revealed a significant relationship between both forms of personal memory, \( r (43) = 0.50, p = .001 \). A scatterplot summarizes the correlation in both diagnostic categories (see Figure 10). The correlations between personal memory and cognitive variables in MCI participants are presented in Table 13. There were significant correlations between ABM and the new learning measure, \( r (43) = 0.41, p = .01 \), and delayed recall measure of the CVLT, \( r (43) = 0.34, p = .04 \), and between ABM retrieval and the recognition measure of the RCFT, \( r (43) = 0.32, p = .04 \). There were significant correlations between PSM and all sub-scales of the CVLT, (with correlations ranging from 0.38 to 0.46, \( p < .05 \)), except the recognition of list words, and also PSM and the delayed recall variables of Logical Memory, \( r (43) = 0.45, p = .002 \), and the RCFT, \( r (43) = 0.47, p = .002 \). No significant associations were found between personal memory and executive function or language.
Table 13. Inter-correlation matrix of memory variables and personal forms of memory in individuals with MCI

<table>
<thead>
<tr>
<th>Memory Type</th>
<th>Autobiographical memory</th>
<th>Personal semantic memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM immediate recall</td>
<td>0.11</td>
<td>0.19</td>
</tr>
<tr>
<td>LM delayed recall</td>
<td>0.17</td>
<td>0.45**</td>
</tr>
<tr>
<td>CVLT new learning</td>
<td>0.41**</td>
<td>0.46**</td>
</tr>
<tr>
<td>CVLT post-interference recall</td>
<td>0.31</td>
<td>0.38*</td>
</tr>
<tr>
<td>CVLT delayed recall</td>
<td>0.34*</td>
<td>0.46**</td>
</tr>
<tr>
<td>CVLT recognition</td>
<td>0.31</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Non-verbal memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCFT 30 min delay</td>
<td>0.21</td>
<td>0.47**</td>
</tr>
<tr>
<td>RCFT recognition</td>
<td>0.32*</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT no cue</td>
<td>-0.07</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KFES FFS</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroop</td>
<td>0.16</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Note: *p < .05, **p < .01, p < .001. LM = Logical Memory, CVLT = California Verbal Learning Test, RCFT = Rey Complex Figure Test, BNT = Boston Naming Test, FFS = Fruit and Furniture Switching.
Discussion

In support of our hypothesis, our findings suggest that personal forms of memory, whether semantic or episodic in nature, are compromised in individuals with MCI. This observation is consistent with previous studies of personal memory in MCI and DAT (Barnabe et al., 2012; Greene et al., 1995; Irish et al., 2010; Irish, Lawlor, O'Mara, et al., 2011; Ivanoiu et al., 2006; Leyhe et al., 2009; Murphy et al., 2008). Consideration of the relative effect sizes suggests that both ABM and PSM are affected to comparable extents. Healthy older individuals with memory complaints did not display poorer personal memory performance compared to non-complainers, raising the question as to whether current complaint measures are sensitive to the subjective experience of memory decline. We found a larger magnitude of effect of MCI on measures of new learning and retention that formed the basis of the diagnosis (see Table 8), and this was an unsurprising finding. Personal memory measures possessed an acceptable level of specificity, or the ability to correctly identify healthy controls. Our aim, however, was to describe personal memory impairment in individuals with subjective memory complaints and MCI and not to define novel diagnostic markers.

PSM bridges the gap between autobiographical and non-personal semantic memory, deriving its ‘semantic-like’ quality as a result of repetition over time, and across multiple contexts (Kazui et al., 2003; Nadel & Moscovitch, 1997), by members of the individual’s social network. Functional neuroimaging (Svoboda et al., 2006) and lesion studies (Kitchener & Hodges, 1999; Yasuda, Watanabe, & Ono, 1997) suggest that semanticised personal memories are maintained by lateral temporal neocortex. Autobiographical memories are impaired in individuals with stable amnestic disorders in which the lesion involves limbic and diencephalic structures, and are generally non-responsive to cueing (Tulving et al., 1988). While personal semantic memory is also affected, it is responsive to priming (Cermak & O’Connor, 1983; Kitchener & Hodges, 1999; Tulving et al., 1988), consistent with its dependence on neocortical systems (Westmacott et al., 2004). By contrast, MCI has been related to incipient medial temporal and posterior cingulate pathology (Chételat et al., 2003; Whitwell et al., 2007), as well as temporal neocortical involvement (Chételat et al., 2003; Jack et al., 2008; C. C. Rowe et al., 2007). The involvement of lateral temporal regions in MCI is in line with our finding of compromised PSM retrieval in this group. One could also hypothesize that personal semantic memory in MCI is becoming increasingly unresponsive to cueing, an avenue that we suggest is worthy of further investigation. One limitation of the current study was the omission of a general semantic memory measure to address this issue.

Unlike the well-documented impairment of ABM in MCI, PSM impairment is unclear. Murphy and colleagues’ (Troyer et al., 2008) finding of an increase in semantic detail in an autobiographical narrative reflects the greater salience and accessibility of semantic details in the face of ABM impairment, and replicates a
complimentary relationship between PSM and ABM previously demonstrated in other populations (Levine et al., 2002; Piolino et al., 2002; Tulving et al., 1988). Differing methodological approaches could account for the disparity between our findings. While these studies elicited a narrative in which both ABM and PSM elements were counted, the EAMI directly prompted participants for personal factual information. The critical question at this juncture, is how PSM differs from ABM. One perspective is that ABM is characterised by one-time ‘autonoetic’ experiences of events that are entirely unique to the individual, while PSM involves ‘noetic’ personal information that is repeated over time and across multiple contexts (Tulving, 1985; Wheeler et al., 1997). The EAMI attempts to highlight these differences by probing highly contextualised ‘one-off’ details, such as sensory/emotion/thought details, in the ABM section and personal factual information, such as the name and location of a frequented establishment, in the PSM section. Within a free-flowing narrative, personal semantic information will likely increase in the face of ABM impairment as a compensatory mechanism but when directly challenged, a paucity of PSM detail exists. While the current study focused on recent memories, previous evidence using the EAMI showed a negative temporal gradient in PSM recall in MCI participants (Irish et al., 2010), and personal semantic memories across all epochs impaired compared to healthy older controls. This finding supports the notion that PSM function, even when learning was relatively normal, is impacted and not just the initial consolidation of the recent memory.

At a conceptual level, one could postulate an overlap between autobiographical and personal semantic memory (Conway & Pleydell-Pearce, 2000; Kazui et al., 2003; Robinson & Swanson, 1990). Conway & Pleydell-Pearce (2000) unite both forms of memory within a single self-referential memory system. The personal memory domain is comprised of interrelated autobiographical and personal semantic memory systems, the former dealing with retention and recall of uniquely personal and contextualised events, while the latter deals with semanticised memories shared by a community that has participated in the same events. Both of these memory systems link to a third system, which injects sensory-perceptual detail into the memory. Conway (1996) argued that this system, what he termed event-specific knowledge, lends richness to autobiographical narratives. The three systems interact dynamically to construct a personal memory (Conway & Pleydell-Pearce, 2000). In terms of this model, ABM impairment will inevitably be associated with some degree of PSM dysfunction, but from a neurocognitive perspective, retrievability will be contingent on the extent to which temporal neocortex is preserved.

Although the EAMI was not originally used to sort the HC and MCI groups, performance on this measure correctly classified a good majority of cases, with HCs having a greater chance of being correctly classified. Healthy older controls completed the task without difficulty, supporting the notion that personal memory is not an ‘ability-driven’ phenomenon and has the potential to be a clinical marker of abnormality. The advantage of a personal memory measure is that it involves a degree
of ecological validity, that is, it can give an indication of real-world memory performance which is not captured by standard neuropsychological tests (Chaytor & Schmitter-Edgecombe, 2003). The best neuropsychological classifiers of the diagnostic groups were two measures of new learning and retention and a marker of language difficulty, which aligns with previous research (J. Mitchell et al., 2009). Individuals with MCI were diagnosed using these cognitive tests, which may have accounted for the high specificity and sensitivity in the model, although relatively similar numbers are reported for clinical diagnosis using NINCDS-ADRDA criteria (Dubois et al., 2007), or similar tests of new learning and retention (de Jager et al., 2003).

Personal memory dysfunction in MCI was found to correlate with objective measures of new learning routinely used in diagnosis of this syndrome. Personal memory showed no association with measures of language and executive functioning, although a definitive conclusion cannot be drawn until a more comprehensive assessment of these cognitive domains is conducted. No convincing relationship was found in healthy older individuals; perhaps in healthy older adults these memory systems are semi-autonomous, and with the probability of disease, multiple levels of memory systems will be driven down. Given the relationship personal memory has with objective memory measures, it was unsurprising that no relationship existed between personal memories and memory complaints. Measuring the presence or severity of a complaint is not a substitute for probing individuals’ subjective recollection of personal events. From a clinical perspective, it is difficult to ascertain from a questionnaire whether or not an individual is expressing a memory concern. The experience of memory loss is a form of ABM, and like other personal memories, has a semanticised component, reflected in the descriptions given by significant others in clinical settings. Given our finding of a relationship between personal memory, canvassed via a semi-structured interview (Irish, Lawlor, O'Mara, et al., 2011), and standard neuropsychological measures of new learning and retention, a focus on subjectively appreciated content is an important step towards a clinically relevant understanding of subjective memory complaints. An interview approach differs from questionnaire measures of memory complaints, which typically do not relate to standard diagnostic procedures (R. Buckley et al., 2013; Lenehan et al., 2012; Purser et al., 2006). We therefore argue for the importance of incorporating assessments of subjective and personally experienced memories as an integral part of characterising the MCI symptom complex.

In conclusion, personal memory impairment is detectable in individuals with MCI but not in healthy older individuals with subjective cognitive decline. Both forms of personal memory, autobiographical events and personal semantic facts, are related to standard neuropsychological measures of new learning and retention, which are commonly used in the diagnosis of MCI. Personal memory, as measured by the EAMI, has an acceptable level of specificity indicating an ability to correctly classify healthy controls. Further investigation of personal memory breakdown in MCI is likely to lead
to a more profound understanding of the clinical syndrome, particularly its subjectively experienced aspects. We suggest that an enhanced knowledge of personal memory impairment in MCI is crucial to develop a more sensitive measure of subjective changes early in the disease process, and look to characterising the content of a complaint, not just its mere presence or severity.
CHAPTER SEVEN: AUTOBIOGRAPHICAL NARRATIVES RELATE TO ALZHEIMER’S DISEASE BIOMARKERS IN OLDER ADULTS

In Chapter 6, both forms of personal memory, that is, ABM and PSM were found to be impaired in individuals with MCI. The finding of an ABM impairment supports a large body of literature that shows impairment in ABM in MCI participants (Barnabe et al., 2012; Greene et al., 1995; Irish et al., 2010; Irish, Lawlor, O’Mara, et al., 2011; Ivanoiu et al., 2006; Levine et al., 2002; Leyhe et al., 2009; Murphy et al., 2008; Piolino et al., 2003), with recent ABMs particularly vulnerable (Greene et al., 1995; Irish et al., 2010; Kopelman & Bright, 2012; Leyhe et al., 2009; Piolino et al., 2003; Tramoni et al., 2012). A finding of impairment in PSM provided support to a smaller body of literature that suggests PSM is impaired to a similar extent in MCI cases (Irish et al., 2010; Leyhe et al., 2009; Tramoni et al., 2012).

7.1 Neural correlates of ABM, PSM and autonoetic consciousness

MRI studies show a relationship between brain volume reduction and poorer ABM performance in individuals with MCI (Matura et al., 2012; Philippi et al., 2012). Voxel-based morphometry (VBM) studies suggest that poorer ABM performance is related to overall grey matter volume (Matura et al., 2012; Philippi et al., 2012), and particularly in medial temporal regions (Matura et al., 2012; Philippi et al., 2012) and also prefrontal, anterior cingulate, and retrosplenial cortical regions (Philippi et al., 2012). These findings are also supported by functional neuroimaging (fMRI) studies of ABM performance in healthy adults (Svoboda et al., 2006: for a review). The most consistent finding across all fMRI studies, was the recruitment of a BOLD signal in bilateral regions of the hippocampus during ABM tasks (Cabeza & St Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). The autonoetic re-experiencing of ABMs involves the ability to cast one’s mind forward into the future and back to the past, and inserting oneself into the memory (Wheeler, Stuss & Tulving, 1997). This ability is conceptually argued to be a frontal process (Conway, 2005; Conway & Pleydell-Pearce, 2000; J. R. Hodges & Patterson, 1995; Tulving et al., 1994). Self-referential processing, a significant component of autonoetic consciousness, has been found in fMRI studies of healthy adults to be related to activation in the prefrontal cortices and posterior cingulate cortex (Svoboda et al., 2006; Cabeza & St Jacques, 2007; Matura et al., 2012).

fMRI studies of healthy adults have suggested that PSM is predominantly related to lateral temporal activation (Addis, Moscovitch, et al., 2004; Svoboda et al., 2006). In cases of semantic dementia, which typically involve atrophy in the lateral temporal lobes (Chan et al., 2001), studies have found that there is a deficit in personal semantic memory, in conjunction with a well-established impairment in general
semantic memory. While fewer studies have looked at neural correlates of PSM, studies converge on a lateral temporal localisation for this function.

7.2 Early topographical distribution of Aβ burden and brain atrophy

What is yet to be elucidated is the effect of differing pathological mechanisms, namely neocortical Aβ burden and brain atrophy on the different components on ABM and PSM. At the earliest stages of the pathological process, Aβ burden is found predominantly in neocortical regions (Braak & Braak, 1991). Neuroimaging PiB-PET studies demonstrate that cortical PiB binding in individuals with MCI is apparent particularly in the middle frontal (Li et al., 2008), orbitofrontal, prefrontal, parietal, posterior cingulate, and lateral temporal regions (Jack et al., 2008; Rowe et al., 2010). Structural MRI studies of brain atrophy, on the other hand, align with the topographical staging of neurofibrillary tangles (Du et al., 2001; Pennanen et al., 2004; Schroeter et al., 2009; Whitwell et al., 2007). Whitwell and colleagues (2007) found that the earliest stages of the disease were characterised by smaller medial temporal lobe volume, particularly the entorhinal cortex. This finding has been supported by studies showing that entorhinal, and to a lesser extent hippocampal volume, are the best predictors of progression to DAT in individuals with MCI (Du et al., 2001; Pennanen et al., 2004; Schroeter et al., 2009). Together, these findings indicate early stages of the disease involve brain atrophy that is apparent in basal midline regions of the brain, while Aβ burden is concurrently evident in lateral neocortical regions.

7.3 Aims of Chapter 7

The aim of this chapter is to investigate the relationship between AD biomarkers on ABM, PSM and autonoetic consciousness at the earliest stages of the disease. Considering their disparate functional networks, it is hypothesized that ABM and PSM will be impacted by separate underlying mechanisms of disease. This paper was accepted at *International Psychogeriatrics* on May 22nd, 2014 (R. Buckley, Saling, Irish, Ames, Rowe, Villemagne, et al., 2014).
Autobiographical narratives relate to Alzheimer’s disease biomarkers in older adults

Abstract

Background: Autobiographical memory (ABM), personal semantic memory (PSM), and autonoetic consciousness are affected in individuals with mild cognitive impairment (MCI) but their relationship with Alzheimer’s disease (AD) biomarkers are unclear.

Methods: Forty-five participants (healthy controls (HC) = 31, MCI=14) completed the Episodic ABM Interview and a battery of memory tests. Thirty-one (HC=22, MCI=9) underwent β-amyloid positron emission tomography (PET) and magnetic resonance (MR) imaging. Fourteen participants (HC=9, MCI=5) underwent one imaging modality.

Results: Unlike PSM, ABM differentiated between diagnostic categories but did not relate to AD biomarkers. PSM was related to neocortical β-amyloid burden after adjusting for age and APOE ε4. Autonoetic consciousness was not associated with AD biomarkers, and was not impaired in MCI.

Conclusion: ABM was impaired in MCI participants but was not related to neocortical amyloid burden, suggesting that personal memory systems are impacted by differing disease mechanisms, rather than being uniformly underpinned by β-amyloid. Episodic and semantic ABM impairment represent an important AD prodrome.

Key words: Autobiographical memory, β-amyloid, hippocampal volume, mild cognitive impairment
Introduction

Subjective experiences of memory dysfunction are of growing importance in research on pathological aging (Sperling et al., 2010), particularly because they hold promise for very early preclinical detection of dementia of the Alzheimer’s type (DAT). At present, mild cognitive impairment (MCI) is commonly classified on the basis of neuropsychological assessment with an emphasis on episodic memory dysfunction (Petersen et al., 1999). Clinical criteria for MCI also require the presence of a subjective memory complaint, or, in some cases, an observation of change from an informant. This is usually described in general terms and is elicited within the context of a routine clinical history (Petersen et al., 1999; Winblad et al., 2004). Importantly, there is no definitive framework to guide clinicians’ exploration of subjective memory symptomatology. There is, however, an emerging interest in developing and refining the clinical evaluation of memory symptoms on presentation (Jessen et al., 2014).

There is no global consensus on the measurement of subjective memory complaints in MCI. Studies investigating subjective memory complaints predominantly rely on questionnaires that probe responses to itemized lists of circumstances where memory lapses can occur, such as the Memory Assessment Clinics Questionnaire, or MAC-Q (Buckley et al., 2013). Direct evaluation of memory personally relevant episodic or semantic knowledge, arguably the archetypical expression of subjective memory, is not typically included in the mainstream diagnostic approach to MCI, perhaps due to the difficulty in verifying the response. Personal memory encompasses autobiographical memory (ABM), personal semantic memory (PSM), and autonoetic consciousness. ABM refers to the recollection of highly contextualised individual experiences (Wheeler et al., 1997), involving remembering the details of the event as they took place within a spatiotemporal and emotional context (Irish, Lawlor, Coen, et al., 2011; Irish, Lawlor, O’Mara, et al., 2011). Autonoetic consciousness represents the rich accompanying re-experiencing of the event, and the mental capacity to travel forwards and backwards in time (Wheeler et al., 1997). Personal semantic memory (PSM), on the other hand, refers to personally relevant knowledge or facts about the individual (Robinson & Swanson, 1990). For instance, an individual’s recall of a birthday party will be characterised by the rich spatiotemporal and emotional ABM detail, and perhaps intensified by the autonoetic re-experiencing or reliving of the event in the mind’s eye. In addition, personal semantic knowledge will be accessible to the individual, for example, of their birth date or the names of the individuals who attended. The ABM-PSM system as a cognitive entity is underpinned by a neural network involving medial and lateral temporal, prefrontal, and posterior parietal cortices (for a review see Svoboda et al. 2006). There is also growing evidence for a loss of ABM-PSM function in individuals with MCI and DAT (Fraser, O’Carroll, & Ebmeier, 2008; Hou et al., 2005; Irish et al., 2010; Irish, Lawlor, O’Mara, et al., 2011; Leyhe et al., 2009). In our view, this provides a promising foundation on which to investigate the nature of subjective memory at a preclinical stage.
In individuals with DAT, poor ABM performance is associated with bilateral medial temporal atrophy and anterolateral temporal neocortex. PSM, on the other hand, is associated with atrophy in the temporal neocortex, often bilaterally (Gilboa et al., 2005). Measures of new learning and retention are associated with decrements in entorhinal and hippocampal volume in healthy older individuals and in MCI (Mormino et al., 2009). Despite extensive work on new learning (Kantarci et al., 2012; Lim, Ellis, Ames, et al., 2013; Lim, Ellis, Harrington, et al., 2013; Mormino et al., 2009; Pike et al., 2011; Rentz et al., 2011) no studies have investigated the relationship between ABM, PSM and autonoetic consciousness, and AD biomarkers such as neocortical β-amyloid burden, brain atrophy and apolipoprotein E ε4 (APOE ε4), to the best of our knowledge. While this study will primarily focus on ABM and PSM, measures of new learning will also be included because they play a major role in the current diagnosis of MCI. Neuroimaging studies of healthy older adults also suggest that a relationship exists between poorer performance on new learning tasks and increased brain β-amyloid load both cross-sectionally (Kantarci et al., 2012; Rentz et al., 2011) and longitudinally (Lim, Ellis, Harrington, et al., 2013). This relationship is complex; some studies report a low to moderate effect size (Kantarci et al., 2012; Mormino et al., 2009), and others report no relationship (Pike et al., 2011). Carrying the APOE ε4 allele might also play a mediating role in this relationship (Kantarci et al., 2012; Lim, Ellis, Ames, et al., 2013; Pike et al., 2011).

The first aim of this study was to determine the extent to which neocortical β-amyloid, brain atrophy and APOE ε4, influences ABM, PSM, and autonoetic consciousness. The second aim was to determine which memory variables (new learning, ABM and PSM) would explain variations in β-amyloid burden. As PSM is affected by primarily neocortical pathology, and because β-amyloid accumulation first appears in neocortical tissue, we hypothesized that PSM would be a stronger predictor of β-amyloid burden in individuals with MCI than will ABM, which is more dependent on medial temporal regions.

Methods

Participants

The Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing is a longitudinal study with follow-up assessments every 18 months. This is a study of healthy controls and individuals with MCI 36 months after the larger AIBL baseline assessment. By the 36-month time-point, the cohort comprised 154 AD participants, 58 MCI participants and 611 healthy controls (HC). Funding permitted approximately one quarter of these subjects to undergo imaging at baseline.

Recruitment of the AIBL cohort
Human research approval for the current study was obtained in Victoria from St Vincent’s Hospital and the University of Melbourne, and Hollywood Private Hospital in Western Australia. The methods of recruitment and exclusion criteria for the AIBL Study have been published elsewhere (Ellis et al., 2009). In brief, older volunteers were screened for the following exclusion criteria: a history of dementia other than DAT, psychiatric illness, Parkinson’s disease, cancers within the last few years, symptomatic stroke, uncontrolled diabetes, diagnosed sleep apnoea and alcohol consumption greater than recommended levels. A diagnostic review panel of neurologists, geriatricians, psychiatrists and neuropsychologists, chaired by the fourth author (DA), oversaw the classification into HC, MCI and DAT groups according to well-established criteria (Ellis et al., 2009; Petersen et al., 1999). MCI classification was made based on cognitive performance falling at least 1.5 SD below appropriate normative levels on one or more neuropsychological tests (or two or more if initially recruited as a healthy control), expressed subjective memory complaint, and current preservation of activities of daily living. We recruited MCI participants who were still diagnosable with MCI three years after baseline AIBL diagnosis, or those with a new diagnosis of MCI by the 36-month AIBL assessment.

Recruitment for this study

This is a cross-sectional sub-study that recruited AIBL participants at the 36 month follow-up time-point of the larger AIBL study, who had specifically undergone positron emission tomography (PET) and magnetic resonance (MR) imaging at the 36-month follow-up AIBL assessment (Ellis et al., 2014). Only HC and MCI participants were eligible to participate, and 45 (HC = 31; MCI = 14) consented to participate in this study. All participants were recruited via telephone and asked to participate in a one hour semi-structured interview and the CANTAB Paired Associate Learning (PAL) task in their homes.

Personal memory measure

The Episodic Autobiographical Memory Interview (EAMI) was administered in the participant’s home by the first author (RB). This interview has been described in detail elsewhere (Irish et al., 2010; Irish, Lawlor, O’Mara, et al., 2011). The EAMI is a semi-structured interview that involves three parts; the first assesses PSM recall by probing personal factual information that can be shared by family and friends, and the second assesses ABM event recall by probing subjective experiences that are unique to the individual and can be recalled within a specific spatiotemporal context. The final part probed an individual’s ability to re-experience the event. For the current study, a shortened version of the EAMI was used, taking approximately 40 minutes, in which recall was constrained to the Recent Period (within the last 5 years).
The PSM part involved three items. The first asked the participant to recall the names of three people that they had only met in the last five years (one point for the full name and one point for their relationship to the individual). The second involved recalling the location and route to a frequented establishment in the last five years (one point each for the name of the establishment, location, what they did there and how they travelled there). The third item related to the ability to recall the exact date, month, year and location of a personally significant event within the last five years (one point for each of the four specifics remembered). This totaled to a maximum score of 14 for the PSM component.

The ABM component required the participant to recall, in as much detail as possible, a personally significant event that occurred within the last five years. Once participants stopped spontaneously producing information pertaining to the event, the interviewer probed for further details using seven phenomenological categories taken from the Event Details Checklist of Moscovitch and colleagues (2000). These probes included event detail, temporal, spatial, sensory, implication of the event, emotion, and thought recall. Each detail was awarded a maximum score of one point, which would be summed to a maximum score of seven points. The autonoetic consciousness section was attached to the ABM component, and asked the individual to describe each of the following aspects within the autonoetic experience: perspective, continuity, image quality, emotional connection and recollective experience.

These interviews were recorded with the approval of the participant, transcribed, and scored by the interviewer and a blinded clinical neuropsychologist. Inter-rater reliability, as measured by intraclass correlation coefficient, was high for all three sections ($r_{\text{ABM}} = 0.92; r_{\text{PSM}} = 0.94, r_{\text{AUTOCON}} = 0.92$), aligning with reported values for the longer version of the EAMI (Irish, Lawlor, Coen, et al., 2011). In an effort to avoid any compensatory effects of ABM, the PSM section was administered first. Interviews were recorded with the approval of the participant, transcribed, and scored by the interviewer and a blinded clinical neuropsychologist. Both ABM and PSM recall were treated as continuous measures, while the autonoetic consciousness variables were dichotomous, i.e. an individual displayed ease or difficulty with the variable.

**Measures of new learning and retention**

The standard neuropsychological assessment involved a mean administration time of two hours (for details and references see Ellis et al., 2009). The following tests were administered by AIBL neuropsychologists at the 36 month time-point. The California Verbal Learning Test-Second edition (CVLT-II) short delay free recall and long delay free recall, and the Wechsler Memory Scale (WMS) Logical Memory (LM) immediate and delayed recall measures (Story 1 only) were administered to measure verbal learning, and the Rey Complex Figure Test (RCFT) 30 minute delayed recall and the CANTABeclipse v3.0 PAL stage 6 errors adjusted score, to measure nonverbal memory
(participants who were unable to complete Stage 6 were allocated the error score of the lowest-performing individual attempting the stage).

**Image acquisition**

Participants in the current study had already undergone imaging in the larger AIBL study at the 36-month time-point, which we accessed. In total, 42 individuals (HC = 31, MCI = 11) underwent PiB-PET or MR imaging, and 30 of these participants (HC = 22, MCI = 8) underwent both PiB-PET imaging and MR. There were no demographic differences between those who underwent one or both scans so we treated these participants as the same in statistical analyses. We will now discuss the larger AIBL study imaging protocol.

**¹¹C-PiB-PET imaging**

Amyloid imaging with PET was conducted using ¹¹C-Pittsburgh Compound B (PiB). PET methodology has previously been described in detail (Rowe et al., 2010). Standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV, and the resulting tissue ratio is termed SUV ratio (SUVR). In the current study, the PiB SUVR index was considered as a continuous measure. Thirty-eight participants (HC = 30, MCI = 8) underwent PiB-PET imaging.

**Magnetic Resonance Imaging (MRI)**

T1-weighted MRIs were segmented into cerebrospinal fluid, grey and white matter. Estimates of grey matter as well as for left and right hippocampal volumes for each participant were calculated (for detailed methods, see Rowe et al., 2010). All volumes were normalized to intracranial volume. Thirty-four participants (HC = 23, MCI = 11) underwent MR imaging.

**Statistical analyses**

Analyses were conducted using SPSS Version 22.0. In order to reduce the potential for multicollinearity, PCA was performed to reduce left and right hippocampal volume into one factor. The distribution of β-amyloid deposition values was skewed in HC, so a bootstrapping technique available in SPSS was used to determine a robust estimate of the mean difference between HC and MCI. Differences in AD imaging biomarkers were ascertained using t-tests and analysis of covariance (ANCOVA) analyses. T-tests (and chi-square analyses for the dichotomous autonoetic consciousness variables) were used to determine the difference between HC and MCI on all personal memory variables, namely, ABM, PSM, and autonoetic consciousness. Logistic regression (for autonoetic consciousness variables) and hierarchical regression (for PSM, ABM and
the measures of new learning and retention) models were used to determine how AD imaging biomarkers relate to both personal and measures of new learning and retention, taking into account the variance explained by age and APOE ε4 carrier status. Missing data existed for both memory and affective measures but totaled less than 10% of the entire data set (refer to Table 13).

**Results**

*Demographic characteristics*

No significant differences between the HC and MCI groups were evident for age, sex and APOE ε4 carrier status. As expected, there was an elevated percentage of non-carriers in the HC group (71% compared with 54%). Healthy controls showed a trend towards having a higher percentage of individuals who attained more than 12 years of education (74% compared with 46%) although this did not reach statistical significance (see Table 14).
Table 14. Demographic, AD biomarker and memory differences between HC and MCI

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 31)</th>
<th>MCI (n = 11)</th>
<th>t or χ² value</th>
<th>sig</th>
<th>Cohen’s d or φ</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Age (M, SD)</td>
<td>77.23 (7.2)</td>
<td>79.09 (7.3)</td>
<td>-0.74</td>
<td>.47</td>
<td>-0.26</td>
</tr>
<tr>
<td>Sex (% F)</td>
<td>48</td>
<td>46</td>
<td>0.03</td>
<td>.87</td>
<td>-0.03</td>
</tr>
<tr>
<td>Education (% &gt;12 years)</td>
<td>74</td>
<td>46</td>
<td>3.02</td>
<td>.08</td>
<td>-0.27</td>
</tr>
<tr>
<td>APOE ε4 carrier status (% Carrier)</td>
<td>29</td>
<td>40</td>
<td>0.42</td>
<td>.52</td>
<td>0.10</td>
</tr>
<tr>
<td>PiB-PET SUVR (n)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Global SUVR</td>
<td>1.44 (0.4)</td>
<td>1.68 (0.6)</td>
<td>-0.24</td>
<td>.19</td>
<td>-0.47</td>
</tr>
<tr>
<td>Brain volume (n)</td>
<td>23</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grey matter vol.</td>
<td>437.35 (21.5)</td>
<td>427.91 (21.2)</td>
<td>1.26</td>
<td>.25</td>
<td>0.45</td>
</tr>
<tr>
<td>R hipp. vol.</td>
<td>2.00 (0.2)</td>
<td>1.89 (0.2)</td>
<td>1.27</td>
<td>.17</td>
<td>0.55</td>
</tr>
<tr>
<td>L hipp. vol.</td>
<td>2.07 (0.2)</td>
<td>1.95 (0.2)</td>
<td>1.28</td>
<td>.14</td>
<td>0.60</td>
</tr>
<tr>
<td>Hippocampal factor</td>
<td>0.16 (1.0)</td>
<td>-0.39 (0.9)</td>
<td>1.33</td>
<td>.14</td>
<td>0.58</td>
</tr>
<tr>
<td>Personal memory</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AC Perspective (%)</td>
<td>17</td>
<td>18</td>
<td>0.01</td>
<td>.91</td>
<td>0.01</td>
</tr>
<tr>
<td>AC Continuity (%)</td>
<td>16</td>
<td>27</td>
<td>0.65</td>
<td>.42</td>
<td>0.13</td>
</tr>
<tr>
<td>AC Image quality (%)</td>
<td>23</td>
<td>27</td>
<td>0.10</td>
<td>.75</td>
<td>0.05</td>
</tr>
<tr>
<td>AC Emotional connection (%)</td>
<td>13</td>
<td>0</td>
<td>1.71</td>
<td>.21</td>
<td>-0.19</td>
</tr>
<tr>
<td>AC Overall Recollection (%)</td>
<td>33</td>
<td>55</td>
<td>1.52</td>
<td>.22</td>
<td>0.19</td>
</tr>
<tr>
<td>ABM (M, SD)</td>
<td>-0.01 (1.0)</td>
<td>-1.00 (0.9)</td>
<td>2.81</td>
<td>.007</td>
<td>1.04</td>
</tr>
<tr>
<td>PSM (M, SD)</td>
<td>0.03 (0.8)</td>
<td>-0.60 (1.1)</td>
<td>1.95</td>
<td>.06</td>
<td>0.64</td>
</tr>
<tr>
<td>Objective memory (M, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAL stage 6 errors*</td>
<td>7.61 (7.6)</td>
<td>15.73 (12.5)</td>
<td>-2.56</td>
<td>.01</td>
<td>-0.78</td>
</tr>
<tr>
<td>LM immediate recall†</td>
<td>13.35 (4.0)</td>
<td>6.55 (3.5)</td>
<td>5.04</td>
<td>&lt;.001</td>
<td>1.87</td>
</tr>
<tr>
<td>LM delayed recall†</td>
<td>12.57 (4.1)</td>
<td>5.64 (3.4)</td>
<td>5.03</td>
<td>&lt;.001</td>
<td>1.92</td>
</tr>
<tr>
<td>CVLT post-interference recall</td>
<td>1.45 (0.9)</td>
<td>-0.67 (1.3)</td>
<td>5.48</td>
<td>&lt;.001</td>
<td>1.79</td>
</tr>
<tr>
<td>CVLT delayed recall‡</td>
<td>1.35 (0.7)</td>
<td>-0.78 (1.5)</td>
<td>6.08</td>
<td>.003</td>
<td>1.71</td>
</tr>
<tr>
<td>RCFT 30 min delay‡</td>
<td>1.45 (1.8)</td>
<td>0.12 (1.6)</td>
<td>2.19</td>
<td>.04</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Note: † = bootstrapping was calculated using SPSS-specified method, ‡ = adjusted score (if a participant failed stage 6), * = age-scaled score, ‡ = z-score, SUVR = standard uptake value ratio, vol. = volume, R hipp. = right hippocampus, L hipp = left hippocampus, AC = autonoetic consciousness, ABM = autobiographical memory, PSM = personal semantic memory, PAL = paired associate learning, LM = logical memory, CVLT = California Verbal Learning Test, RCFT = Rey Complex Figure Test
Factor analysis of left and right hippocampal volumes

Left and right hippocampal volume were significantly correlated, $r(35) = 0.86$, $p < .0001$. These data were reduced in a PCA to produce one hippocampal volume factor. The loadings of both right and left hippocampal volume on the factor were 0.96, and this factor accounted for 92.7% of the total variance explained.

Hippocampal and grey matter volume

There were no differences between HC and individuals with MCI in terms of right and left hippocampal volume or the hippocampal volume factor (Table 14). When age was included as a covariate, it had no influence on hippocampal volume, $F(1, 31) = 1.56$, $p = .21$, $\eta^2 = 0.05$.

There was also no significant difference in overall grey matter volume between HC and MCI. Age had a significant main effect on grey matter volume, $F(1, 31) = 11.43$, $p = .002$, $\eta^2 = 0.27$, supporting previous findings of age-associated grey matter atrophy (Giorgio et al., 2010; C. D. Good et al., 2002). APOE $\epsilon 4$ carrier status did not influence any brain volume measures.

Global and regional PiB SUVR

There were no differences between HC and individuals with MCI in terms of global and regional PiB SUVR deposition (see Table 14 and a scatterplot of the individual SUVRs for each group in Figure 11). PiB retention was moderately variable in the two groups, and as expected, most healthy controls clustered below the PiB positive cut-off. While our healthy control group showed equivalent global PiB retention rates as reported by Rowe et al., (2010) in the 18-month follow-up, our global SUVR mean was slightly elevated in comparison with the mean PiB SUVR of 1.38 reported at 36-month follow-up (Villemagne et al., 2013). The average global PiB retention in our MCI group was below the PiB SUVR of 1.96 reported at both 18-month and 36-month time-points (Rowe et al., 2010; Villemagne et al., 2013). Global SUVR was highly correlated with regional SUVR values, so global PiB retention was used to represent PiB retention in individuals.

Age was significantly correlated with global SUVR in HC, $r(30) = 0.45$, $p = .02$, but not in individuals with MCI, $r(8) = 0.01$, $p = .98$. Having an APOE $\epsilon 4$ allele positively correlated with global SUVR in individuals with MCI, $\rho(8) = 0.76$, $p = .03$, but this relationship was only a positive trend in HC, $\rho(30) = 0.32$, $p = .08$. 
Compared to HCs, MCI participants performed worse on ABM recall but not on any other personal memory variables (perspective, continuity, image quality, emotional connection, overall recollection and PSM recall). Although individuals with MCI did not perform significantly poorer on PSM recall, a moderate effect size existed, suggesting an impact to some degree. As expected, MCI participants performed worse on all measures of new learning and retention (PAL 6 stage errors, Logical Memory immediate and delayed recall, CVLT short and long delayed recall, RCFT 30 minute delay). Table 14 shows the scores for each group and their respective effect sizes.

Relating AD imaging biomarkers to personal memory variables

AD imaging biomarkers, age and APOE ε4 were not associated with autonoetic consciousness variables (i.e. perspective, continuity, image quality, emotional connection and overall recollection, refer to Table 15 for details). The data for emotional connection were highly skewed so this variable was excluded from analyses. At a univariate level, ABM recall showed a trend towards being related to global SUVR ($\beta = -0.39$, $p = 0.06$) and had a significant relationship with $APOE$ ε4 ($\beta = 0.43$, $p = 0.04$), but the overall model was not significant ($p = .25$). A trend between poorer ABM
recall and smaller hippocampal volume in MCI participants showed a moderate effect size, this was not significant. PSM recall was significantly related to global PiB retention ($\beta = -0.62$, $p = .001$) after taking into account the variance explained by age, APOE $\epsilon 4$ carrier status, grey matter and hippocampal volume (see Table 16). Figure 12 shows the strong relationship between poorer PSM recall and larger global PiB retention in both the HC and MCI groups, although the relationship was not significant in individuals with MCI.
Table 15. Logistic regression models predicting autonoetic consciousness variables

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>Wald</th>
<th>Odds ratio</th>
<th>OR: 95% CI</th>
<th>p value</th>
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<tr>
<td><strong>Model 1: Perspective</strong></td>
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<tr>
<td>Block</td>
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<tr>
<td></td>
<td>$\chi^2$(df)=7.54 (4)</td>
<td></td>
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<tr>
<td>Age</td>
<td>-0.09 (0.1)</td>
<td>0.50</td>
<td>0.48</td>
<td>0.70, 1.18</td>
<td>.26</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>-3.73 (3.3)</td>
<td>1.28</td>
<td>0.02</td>
<td>0.00, 15.6</td>
<td>.23</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td>-0.05 (0.04)</td>
<td>1.42</td>
<td>0.95</td>
<td>0.87, 1.04</td>
<td>.71</td>
</tr>
<tr>
<td>Hi vol</td>
<td>-0.33 (0.9)</td>
<td>0.14</td>
<td>0.71</td>
<td>0.13, 4.01</td>
<td>.17</td>
</tr>
<tr>
<td><strong>Model 2: Continuity</strong></td>
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<td>Block</td>
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<tr>
<td></td>
<td>$\chi^2$(df)=3.39 (4)</td>
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<tr>
<td>Age</td>
<td>-0.01 (0.1)</td>
<td>0.01</td>
<td>1.01</td>
<td>0.86, 1.18</td>
<td>.93</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>-0.30 (1.2)</td>
<td>0.06</td>
<td>0.74</td>
<td>0.07, 7.53</td>
<td>.80</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td>0.05 (0.04)</td>
<td>1.85</td>
<td>1.05</td>
<td>0.98, 1.13</td>
<td>.17</td>
</tr>
<tr>
<td>Hi vol</td>
<td>-0.67 (0.5)</td>
<td>1.70</td>
<td>0.51</td>
<td>0.19, 1.40</td>
<td>.19</td>
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<tr>
<td><strong>Model 3: Image quality</strong></td>
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<td>Block</td>
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<tr>
<td></td>
<td>$\chi^2$(df)=1.81 (4)</td>
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<td>.77</td>
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<tr>
<td>Age</td>
<td>-0.07 (0.08)</td>
<td>0.78</td>
<td>0.93</td>
<td>0.79, 1.09</td>
<td>.38</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>0.79 (0.9)</td>
<td>0.73</td>
<td>2.20</td>
<td>0.36, 13.42</td>
<td>.39</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td>-0.02 (0.02)</td>
<td>0.86</td>
<td>0.98</td>
<td>0.93, 1.03</td>
<td>.35</td>
</tr>
<tr>
<td>Hi vol</td>
<td>0.0 (0.5)</td>
<td>0.00</td>
<td>1.01</td>
<td>0.41, 2.46</td>
<td>.96</td>
</tr>
<tr>
<td><strong>Model 4: Overall recollection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\chi^2$(df)=6.50 (4)</td>
<td></td>
<td></td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.1)</td>
<td>1.21</td>
<td>1.09</td>
<td>0.93, 1.28</td>
<td>.27</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>0.71 (0.9)</td>
<td>0.62</td>
<td>2.03</td>
<td>0.35, 11.84</td>
<td>.43</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td>-0.03 (0.5)</td>
<td>1.04</td>
<td>0.97</td>
<td>0.92, 1.03</td>
<td>.31</td>
</tr>
<tr>
<td>Hi vol</td>
<td>0.72 (0.5)</td>
<td>1.89</td>
<td>2.06</td>
<td>0.74, 5.78</td>
<td>.17</td>
</tr>
</tbody>
</table>

Note: AC Emotional connection is excluded due to very significant skew. Hi = hippocampal. SUVR = Standard uptake value ratio, Hi vol = hippocampal volume.
Table 16. Hierarchical linear regression models predicting personal measures

<table>
<thead>
<tr>
<th>Model 1: ABM recall (dependent variable)</th>
<th>B (SE)</th>
<th>β</th>
<th>R²</th>
<th>ΔF (df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td>0.08</td>
<td></td>
<td>1.11 (27)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td>0.14</td>
<td></td>
<td>1.48 (24)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>0.02</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>0.93 (0.4)</td>
<td>0.43</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>-0.82 (0.4)</td>
<td>-0.39</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td>-0.01</td>
<td>-0.18</td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Hi vol</td>
<td>-0.05 (0.2)</td>
<td>-0.05</td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2: PSM recall (dependent variable)</th>
<th>B (SE)</th>
<th>β</th>
<th>R²</th>
<th>ΔF (df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td>0.09</td>
<td></td>
<td>1.34 (27)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td>0.35</td>
<td></td>
<td>5.11 (24)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>-0.17</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>0.48 (0.3)</td>
<td>0.26</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>PiB SUVR</td>
<td>-1.10 (0.3)</td>
<td>-0.62</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Grey matter vol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi vol</td>
<td>-0.19 (0.1)</td>
<td>-0.23</td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3: Global PiB SUVR (dependent variable)</th>
<th>B (SE)</th>
<th>β</th>
<th>R²</th>
<th>ΔF (df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td>PSM recall and APOE ε4 carrier</td>
<td>0.26</td>
<td>8.68 (25)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td>APOE ε4 carrier</td>
<td>0.14</td>
<td>5.42 (24)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>PSM recall</td>
<td>APOE ε4 carrier</td>
<td>-0.36 (0.1)</td>
<td>-0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td></td>
<td>0.39 (0.2)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*These measures were reduced to produce two factors using PCA orthogonal rotation.
^ PAL stage 6 error score, CVLT short and long delayed recall, and RCFT 30 min delay were not related to global SUVR, hippocampal or grey matter volume, age or APOE ε4 carrier status in a separate regression analysis. Logical Memory immediate and delayed recall were related to age (β = -0.54, p = .002 and β = -0.47, p = .01, respectively), but no other variables.
ABM = autobiographical memory, PSM = personal semantic memory, vol = volume, PAL = Paired Associates Learning, CVLT = California Verbal Learning Test, LM = Logical Memory, RCFT = Rey Complex Figure Test.
Figure 12. Scatterplot of global PiB SUVR by ABM and PSM recall (as represented by z-scores) in healthy controls and individuals with MCI (Note: the x-value cut-off indicates a PiB SUVR = 1.5)

ABM recall
\( r_{HC} (22) = -0.21, p = .36 \)
\( r_{MCI} (8) = 0.07, p = .87 \)

PSM recall
\( r_{HC} (22) = -0.51, p = .016^* \)
\( r_{MCI} (8) = -0.61, p = .11 \)
In order to reduce the number of variables in a post-hoc regression analysis, PCA with varimax rotation was run on the measures of new learning and retention (PAL stage 6 errors, Logical Memory immediate and delayed recall, and CVLT short and long delayed recall). RCFT 30 minute delayed recall was excluded from the analysis as it produced a Hayward case (or a loading greater than 1). Two memory factors with Bartlett factor scores were produced, accounting for 83% of the variance explained; the first factor incorporated the CVLT-II and PAL measures, and the second factor included the Logical Memory measures.

A post-hoc step-wise regression model was conducted to find the best statistical predictor (out of ABM, PSM, the two memory factors, age and APOE ε4) of global PiB retention in HC and those with MCI (see Table 16, Model 3). The best predictor was PSM recall ($\beta = -0.59, p = 0.001$), followed by APOEε4 ($\beta = 0.41, p = 0.02$). This overall model accounted for 40% of the variance explained in global PiB retention.

**Discussion**

Autobiographical memory recall was impaired in individuals with MCI, supporting previous research (Hou et al., 2005; Irish et al., 2010; Irish, Lawlor, O’Mara, et al., 2011; Leyhe et al., 2009). Performance in PSM recall did not differentiate the diagnostic groups, but the moderate effect size is commensurate with that shown in our previous study (Buckley et al., 2014). Participants with MCI did not differ from controls on the overall autonoetic re-experiencing of a memory, consistent with a previous investigation using the same measure (Irish et al., 2010). Unlike Irish and colleagues (Irish et al., 2010), we did not find differences between the groups in emotional connection, continuity of the imagery, viewer perspective and vividness, most likely reflecting different in patient samples and study methodology. Aligning with the established profile for amnestic MCI (Winblad et al., 2004), participants with MCI were impaired on all measures of new learning and retention, namely Logical Memory, CVLT-II, RCFT and the PAL task. Inclusion in the MCI group was dependent on performance at least 1.5SD below the normative mean on any one of the first three measures (or other AIBL measures not reported here). While this introduces some potential for circularity, the PAL task, which played no role in defining the groups, also differentiated HC from MCI.

There were no differences in global neocortical amyloid burden or grey matter volumes between healthy controls and those with MCI. The healthy control group showed global PiB retention comparable to that observed in previous AIBL studies, but the average PiB retention for our MCI participants was lower than the larger AIBL cohort, at 1.7 compared with 1.9 (Rowe et al., 2010; Villemagne et al., 2013). The present cohort is derived from the Villemagne et al. (2013) study, in the context of the
longitudinal AIBL study. Individuals with a longer history of cognitive decline, who had since converted to diagnosable dementia, who in their majority presented with high PiB retention, did not meet selection criteria for the present study, yielding a cohort with low PiB retention. We also found a large dispersion of grey matter volumes in both diagnostic groups, similar to that seen in the larger AIBL cohort (Rowe et al., 2010; Villemagne et al., 2013).

Personal memory, specifically, PSM, ABM and autonoetic consciousness, was not related to overall grey matter or hippocampal volumes. There was a trend towards a relationship between smaller hippocampal volume and lower ABM performance in individuals with MCI, but this did not reach statistical significance. In functional imaging studies of healthy adults, ABM is associated with a ‘core’ functional network, featuring the hippocampus (for a review, see Maguire, 2001; Svoboda et al., 2006). Hippocampal atrophy did not have a relationship with ABM in either diagnostic category, raising the notion that different samples and imaging methodologies might play a role in the divergent finding. It is also possible that through the course of a 36-month longitudinal study, our sample contained a higher percentage of individuals with non-progressive MCI, which might explain the lack of an expected finding. An alternative explanation is that this might be a slightly more resilient group, and the data might be considered in this light.

Global neocortical amyloid burden had a significant impact on PSM recall in healthy controls. A correlation of moderate size was also evident in the MCI group, but fell short of significance due to small sample size. Our findings align with studies showing verbal memory dysfunction in amyloid positive non-demented older adults (Lim, Ellis, Harrington, et al., 2013; Pike et al., 2007; Rentz et al., 2011). This relationship between PSM and neocortical amyloid deposition was not changed by controlling for age, grey matter volume, and APOE ε4 carrier status, suggesting a slight divergence from some studies showing a moderating effect of APOE ε4 (Kantarci et al., 2012; Lim, Ellis, Ames, et al., 2013). PSM performance was the sole personal memory variable associated with brain neocortical amyloid burden in the final model, contributing unique variance to PiB retention, even when measures of new learning and retention were included. Interestingly, PSM did not differentiate HC from MCI. Unlike PSM, ABM recall did differentiate between the diagnostic categories but did not demonstrate a convincing relationship with neocortical amyloid burden. This pattern raises the possibility that ABM difficulties are underpinned by an alternative neuropathological mechanism, such as tauopathy. The autonoetic re-experiencing of personal memories, which is fundamental to ABM function (Conway & Pleydell-Pearce 2000; Wheeler et al., 1997), was also not associated with neocortical amyloid deposition.

Conclusion
While the samples in this study are smaller than desirable, these findings do open up what we consider to be an important new direction in Alzheimer’s research. To the best of our knowledge, this study provides the first insight into the impact of early AD-related neuropathological changes on personal memory function in non-demented older adults. Our findings show that ABM and PSM were differentially affected by diagnostic category. Neocortical amyloid deposition affected both systems disparately by influencing PSM but not ABM. These findings suggest that separate neuropathological mechanisms are mediating ABM and PSM. ABM and PSM are largely dependent on different, but overlapping and interacting, neurofunctional components of the temporal system (Gilboa et al., 2004; Maguire 2001; Svoboda et al., 2006). Our findings show that PSM is influenced by neocortical Aβ burden, while other underlying neurodegenerative processes that initially impinge on the hippocampal formation, such as tauopathy, might exert a greater effect on the essentially episodic aspects of autobiographical narratives.
CHAPTER EIGHT: GENERAL DISCUSSION

This thesis sought to clarify a number of issues surrounding perceived memory change in non-demented older adults, that is, the clinical semiology of subjective memory complaining and the pattern of personal memory impairment and their relationship with cognitive, affective and AD biomarker factors. To date, the current trend in ageing research has largely been concerned with the quantification of the experience of memory decline, in the form of SMC questionnaires, and conceptualised within a predictive framework by investigating monotonic associations with objective measures of memory dysfunction (Blackford & La Rue, 1989; Derouesné et al., 1989; McGlone et al., 1990; Sunderland et al., 1986). Apparent failure of questionnaires to predict performance on memory measures was then interpreted as a validity failure of methodologies (Derouesné et al., 1994; McGlone et al., 1990; A. J. Mitchell, 2008a; M. Reid et al., 2011), and subsequently the SMC concept as a whole (Jorm et al., 1994; Lenehan et al., 2012; A. J. Mitchell, 2008b; Purser et al., 2006; Riedel-Heller et al., 1999). At the same time, research showed a strong relationship between memory complaints and affective state, which was more strongly predictive of a score on an SMCQ than measures of new learning and retention (Derouesné et al., 1989; Grut et al., 1993; Jorm et al., 1994; McGlone et al., 1990; O'Connor et al., 1990). Questioning of SMC validity was based on the expectation that memory complaints would translate into a simple, straightforward proxy for objective measures (Crook et al., 1986; Larrabee & Crook, 1994; M. Reid et al., 2011; Riedel-Heller et al., 1999). The problem underlying this assumption was a failure to understand the complex, and sometimes counter-intuitive (Reisberg et al., 1982), nature of memory complaining and the myriad ways concerns of memory loss can be expressed. The treatment of memory complaining as a unidimensional entity does not recognise the possibility that the phenomenology of the complaint contains important clinical information (Leder, 1990; Wulff, 1999).

The medical profession has long recognised the significance of an individual’s expression of their maladies in the diagnostic process (B. J. Good & Good, 1981; Leder, 1990; Wulff, 1999), regardless of the presence of objective health issues (Sørensen, 1988; Sullivan, 2003). As Erikson (1964) quoted, “…the patient’s complaint is more extensive than his symptom, and the state of sickness more comprehensive than localised pain or dysfunction” (p. 51). The experience and subsequent expression of subjective appreciation of an illness sits within a framework of sociocultural factors, such that a more severe memory complaint could arise from stressors beyond the individual’s mindfulness of memory lapses (for instance, a family member’s Alzheimer’s diagnosis, external stress related to work, reports of dementia in the media: Commissaris et al., 1993; Kessler et al., 2012; Laforce Jr & McLean, 2005). As such, subjective memory complaints involve complexities beyond the notion of a unidimensional self-appraisal of memory lapses, supporting the argument that subjective experiences do not lend themselves well to a simplistic monotonic
relationship with neuropsychological measures of memory. It is only through clinical evaluation of the individual and their complaint, that complexities like these can be teased out and investigated within an experienced clinical framework of potential diagnostic outcomes. The aim of the present inquiry was to highlight the subjective experience of memory change in individuals with MCI, examine how this experience relates to objective memory, affect, and AD biomarkers, and to help to inform future approaches to the clinical evaluation of older individuals with subjective memory complaints prior to diagnosis.

8.1  **Summary of findings**

In Chapter 4, memory complaint severity, as measured via a commonly-used memory complaint questionnaire, the MAC-Q, was solely related to affect in healthy older adults, and age-associated in those with MCI. Neither cognitive nor AD biomarkers were found to be related to memory complaint severity in either diagnostic category. Previous research has questioned the prognostic utility of memory complaints, due to their prevailing relationship with depressive symptomatology, particularly in healthy older adults (Lenehan et al., 2012; Mitchell, 2008; Purser et al., 2006). The literature has consistently reported on the large role that affective factors play in subjective memory complaining, particularly in the absence of evidence of memory impairment (Abdulrab & Heun, 2008; Collins & Abeles, 1996; Derouesné et al., 1989; Derouesné et al., 1999; Gallassi et al., 2008; Grut et al., 1993; Jonker et al., 2000; Jorm et al., 2004; Jorm et al., 1994; Kahn et al., 1975). Findings from the current study using the MAC-Q align with this contention, that depression may well be the major influence of SMCs in the absence of, or only subtle evidence of, an organic driver, such as first-ever lacunar syndrome (Anderson et al., 2008), concussional head injury (Kinsella et al., 1996), and first-ever stroke patients (van Rijsbergen et al., 2014). Importantly, these findings suggest a phase of transition in which affective factors are the primary driver of subjective memory complaints in cognitively normal older adults, but as organic factors emerge, biological factors like age become a significant driver.

The next study (Chapter 5) characterised the clinical semiology of memory complaining in different AD risk populations, such as healthy memory complainers, healthy individuals with high Aβ load, and individuals with MCI. Healthy individuals with evidence of high neocortical Aβ burden noticed a progressive memory decline compared to those with low Aβ, although this was a small effect. This supports accruing evidence for a relationship between Aβ burden and memory complaining, and raises the notion that the subjective experience of memory change at such an early stage in the disease process is difficult to elucidate. Healthy memory complainers (identified via a single question), were more closely aligned to complaint themes endorsed by individuals with MCI than their healthy non-complaining counterparts. These findings support the notion that subjective concerns, as elicited via a single question, are able to isolate healthy older adults who subjectively experience a similar
form of memory loss as those with clinically diagnosed cognitive impairment. Complaint themes diverged when only individuals with MCI acknowledged issues with daily functioning, while healthy memory complainers were inclined to endorse issues with attentional fluctuation. It is possible that complaints relating to changing activities of daily living are markers of an early stage interim outcome of prodromal AD. It is important to remember that these changes of functional impairment do not fulfil the criteria of dementia, but they are evidently salient to the MCI group. This finding was recently supported by a study of psychological well-being in MCI that found cognitive complaints were related to increasing functional impairment (Gates, Valenzuela, Sachdev, & Singh, 2014). Memory complaint themes in healthy older adults were more likely to be related to greater depressive symptomatology, while complaints in individuals with MCI were more likely to relate to measures of new learning and retention. These differing correlates imply that diagnostic categories are expressing divergent clinical semiology; one that is affect-driven, and the other that is of organic origin.

Both healthy memory complainers and individuals with MCI endorsed more complaints of poorer spatiotemporal and emotional contextualisation of memories in comparison with healthy non-complainers. This finding could be interpreted as subjective evidence of a gradual decrease in autobiographical memory function. The most likely source for gauging one’s memory function, such as one’s ability to recall spatiotemporal contextual details, is via an experiential survey of your personal memories. Chapter 6 contained an examination of the pattern of impairment of personal memories, namely ABM and PSM, in healthy memory complainers and individuals with MCI. The findings from this study support a body of literature showing an impairment of ABM in MCI (Barnabe et al., 2012; Gilboa et al., 2005; Irish, Lawlor, O’Mara, et al., 2011; Leyhe et al., 2009; Murphy et al., 2008), but also support some studies that suggest an impairment in PSM in MCI (Irish et al., 2010; Leyhe et al., 2012). This dual impairment of ABM and PSM lends support to the conceptual theories that suggest an overlap between these two systems (Conway, 1990, 1996; Conway & Pleydell-Pearce, 2000). In contrast to MCI, healthy memory complainers did not show impairment of ABM or PSM, unlike individuals with MCI. Our finding supports the notion that the concern expressed by healthy older adults may be nominally different from the experience in individuals with MCI, who exhibit a demonstrable memory impairment in conjunction with the concern itself.

Finally, in Chapter 7, AD biomarkers were examined in relation to the episodic, autonoetic and personal semantic components of personal memory. PSM was negatively associated with neocortical Aβ burden, consistent with its dependence on lateral temporal neocortex. This relationship was found in healthy older adults, supporting the notion that Aβ neuropathology has an effect on memory early in the disease process (Lim, Ellis, Ames, et al., 2013), most likely due to its early, rapid accumulation (Jack et al., 2013; Villemagne et al., 2013). ABM was not influenced by neocortical Aβ burden, but was the only form of personal memory to exhibit a clear
impairment in MCI, suggesting a differing neuropathological driver, such as tauopathy. The results showed a moderate but sub-threshold association between hippocampal volume and ABM in individuals with MCI, supporting findings showing the influence of hippocampal activation on ABM function (Addis, Moscovitch, et al., 2004; Cabeza & St Jacques, 2007; Denkova & Manning, 2014; Gilboa et al., 2005; Hirshhorn, Newman, & Moscovitch, 2011; Maguire & Frith, 2003; Philippi et al., 2012; Svoboda et al., 2006).

8.2 New perspective on SMCs

Current measures of subjective memory complaints

One issue with using SMCQs is that they measure the presence or the severity of the complaint, which strips the complaint of its qualitative meaning, and reduces the amount of information that can be extracted. A total severity score is problematic if one is interested in determining the underlying genesis of a memory complaint, as it is not a particularly informative outcome measure from a clinical perspective. For instance, if an individual is solely concerned with their poor ability to remember initial introductions, their score will be relatively low and thus will be considered a non-complainer according to an SMC severity measure. From a clinical perspective, however, the nature and form of this acknowledgement has the potential to be indicative of something more important.

Another issue concerns the prognostic value of subjective memory complaints in relation to memory complaint total scores. Theoretically, for this relationship to exist, each item of an SMC questionnaire should target memory concerns that are indicative of AD-related neuropsychological dysfunction. For instance, an item pertaining to an individual’s self-appraisal of their ability to learn novel face-name pairings could be considered as an ecologically valid measure of arbitrary associative learning. This does not necessarily translate into reality. For instance, the MAC-Q questionnaire includes the item, “I have trouble remembering names that are introduced to me”. The issue with this item is it does not simply probe an individual’s arbitrary associative learning ability, because new introductions involve stressful situations where an individual is required to be constantly ‘online’. When answering this item, an individual might also self-appraise their ability to keep track of a conversation while pairing a name with a face (a task for which they might already feel a heightened sense of stress), their ability to remember learn names at once, and their ability to navigate an environment (i.e. a party) where multiple complex stimuli are occurring. Thus, a question in this form is not measuring AAL in isolation, and may well include factors of stress and anxiety that are intrinsically related to new introductions. This is one potential rationale for a prevailing relationship with depression in questionnaires (Jonker et al., 2000). The advantage of a semi-structured interview is that, while the same question might be used, the inherent flexibility in
methodology can uncover motivations behind the concern (Frank et al., 2010; Mol et al., 2007).

Effect of depressive symptomatology

In the current study, the MAC-Q questionnaire was largely related to affect, particularly in healthy older adults, which supports the findings of a large body of literature (Aarts et al., 2010; Abdulrab & Heun, 2008; Blazer et al., 1997; Chin et al., 2014; Clarnette et al., 2001; Jonker et al., 2000; Jorm et al., 2004; Jungwirth et al., 2004; Kahn et al., 1975; Lenehan et al., 2012; McGlone et al., 1990; Minett et al., 2005; O'Connor et al., 1990; Schmand et al., 1997; Smith et al., 1996; Zandi, 2004; Zlatar et al., 2014). In the qualitative analysis, some complaint themes were found to be related to depressive symptomatology in healthy older adults, particularly a sense of predomination, relative absence of contextualisation, and burdensome coping strategies. The implication is that while some complaint endorsements are more indicative of negative mood, a qualitative investigation has the ability to elicit complaint themes that are driven by other factors. For instance, the endorsement of progressive memory loss in healthy older adults with high Aβ burden was not related to depressive symptomatology. This raises the possibility of certain phenomenological aspects of memory complaints in healthy older adults that are driven by factors other than affect.

In individuals with MCI, endorsing an increased dependency on significant others or family members was related to greater depressive symptomatology. Frank and colleagues (Frank et al., 2010) conducted a qualitative analysis of the psychosocial impact of cognitive impairment on individuals with MCI, and found the issue of increasing burden and changing family dynamics to be particularly salient. Specifically, a strong sense of fear was related to becoming increasingly more dependent on family friends and co-workers. Joosten-Weyn and colleagues (2008) found that MCI individuals would report a loss of confidence in their ability to complete daily activities, acknowledged abandoning leisure activities out of frustration and anger. Complaints related to dependency were also uniquely related to impairment on the delayed recall of word lists. It seems that the endorsement of increasing dependency is associated both with the likely causal factor (cognitive impairment) and a clinical outcome (depression).

Unlike healthy older adults, a number of themes related to measures of new learning and retention over and above the effects of depression and age in MCI. Themes of increasing frequency and burdensome coping strategies in individuals with MCI were also uniquely related to poor verbal memory performance, suggesting that memory complaints are more closely aligned to the MCI symptom complex than is argued by some researchers (Lenehan et al., 2012; Mitchell, 2008; Purser et al., 2006). Verbal memory performance was related to complaints regarding functional
impairment, which is unsurprising given that changes in functional impairment are driven by gradual cognitive decline (Farias, Harrell, Neumann, & Houtz, 2003; Joosten-Weyn Banningh, Vernooij-Dassen, Rikkert, & Teunisse, 2008; Luck et al., 2010). These findings support the notion of a gradual change in the clinical semiology of subjective memory concerns across the earliest stages of the disease trajectory.

**Relationship with neocortical Aβ burden**

This is the first study to open a window onto the clinical semiology of memory complaining in individuals with high neocortical Aβ burden. Complaint severity as measured by the MAC-Q did not show a relationship with neocortical Aβ load (β = 0.02, p = ns), and this is most likely due to the fact that a relationship between these two variables is subtle (Amariglio et al., 2012; Barnes et al., 2006; Perrotin et al., 2012). This argument was supported by the data presented in Chapter 5 where qualitative differences in the experience of memory changes between high and low Aβ were attenuated. It is also possible that the hypothetical sigmoidal curve for biomarkers outlined by Jack and colleagues (2013) make an assumption of a linear relationship difficult. Future studies with larger sample sizes should investigate a possible non-linear relationship between these two factors. Relating back to the preceding argument, a severity measure is unlikely to accurately detect such subtle levels of concern. Healthy older adults with high Aβ burden noticed a progressive memory change, but considering these individuals are classified as cognitively healthy, it is unlikely that changes in new learning are driving the complaint. It is possible that these individuals are becoming aware of subtle changes that neuropsychological tasks are unable to detect (de Jager et al., 2002).

### 8.3 Everyday personal memory impairment in MCI

**Alignment with theoretical models of memory consolidation**

ABM and PSM were impaired in individuals with MCI, with the magnitude of effect of ABM impairment much more apparent than PSM. This dual impact on both autobiographical and personal memory systems implies that both of these memory systems are inter-related. This idea is well-represented in the theoretical models that speculate a dynamic connection between ABM and PSM (Conway, 1990, 1996, 2005; Conway & Pleydell-Pearce, 2000; Moscovitch et al., 2005; Robinson & Swanson, 1990). The hippocampus plays an enduring role in the retrieval of everyday personal memories (Svoboda et al., 2006), even though they might become increasingly semanticised over time (Linton, 1982). For instance, the multiple trace theory (MTT Nadel & Moscovitch, 1997; Shimamura, Squire, & Shacter, 2002), states that more semanticised memory traces become increasingly consolidated in the neocortex, although traces represented in the medial temporal lobe (MTL) are not entirely lost (Moscovitch, 2008; Moscovitch et al., 2005). Studies of patients with semantic
dementia, a condition that characteristically involves semantic memory dysfunction, show an overlap between ABM and general semantic memory (Graham, Lambon, & Hodges, 1997; Snowden, Griffiths, & Neary, 1994; Westmacott et al., 2004; Westmacott & Moscovitch, 2003). As a consequence of this relationship, an ABM is likely to scaffold memories of that construct (Westmacott et al., 2004; Westmacott & Moscovitch, 2003). Thus, a dual impairment of ABM and PSM is unsurprising, when taking into account theoretical considerations of autobiographical narratives. Other findings that suggest PSM is preserved in non-demented older adults (Levine et al., 2002; Murphy et al., 2008), is most likely arising from a methodological divergence from the current study. The paradigms used in Murphy and colleagues’ (2008) and Levine and colleagues’ (2002) studies were more likely to encourage greater PSMs as they elicited whole personal narratives and counted the frequency of ABM and PSM occurrences while the EAMI probes each form of memory separately. The current finding might show a particularly salient impact of the MCI diagnosis on PSM given that recent memories were measured, and so that personal semantic knowledge would be more likely to have an attached ABM component.

Relationship with AD biomarkers

Although ABM and PSM are conceptually considered as dynamically interactive memory systems (Conway, 1990; 1995; 1996; Conway & Pleydell-Pearce, 2000; Robinson & Swanson, 1990), the findings of Chapter 7 demonstrate evidence for differing disease-driven effects. PSM was strongly related to Aβ burden, particularly in healthy older adults and a trend in individuals with MCI. Unlike PSM, ABM was able to differentiate clearly between healthy older adults and individuals with MCI, but was not related to AD biomarkers. There was a trend for a relationship between ABM performance and hippocampal volume in individuals with MCI that did not survive correction for multiple comparison. For a relationship to show such small effect sizes, the implication is that hippocampal volume has not changed significantly enough to produce a statistical effect. Previous research suggests that hippocampal volume is not a significant predictor of AD at the earliest stages of the disease (Dickerson et al., 2001; Du et al., 2001; Gómez-Isla et al., 1996; Jessen et al., 2006; Killiany et al., 2002; Pennanen et al., 2004; Whitwell et al., 2007). Thus, hippocampal volume might not have such a profound impact on ABM function at this early stage.

8.4 Limitations, implications and future directions

Subjective memory complaint questionnaires have been appealing to clinicians because of their ease of administration (Folstein et al., 1975), their ability to be used on large at-risk populations, and because they do not require specialised clinical training for their administration or scoring (J. M. G. Wilson & Jungner, 1968). As such, these questionnaires possess similar properties to a screening tool, such as the MMSE, the HADS, and the GDS (Reisberg, 2007; Reisberg et al., 1982; Snaith & Zigmond,
in that they can provide evidence for the existence of a concern, and perhaps the level of severity of the concern (Folstein et al., 1975; Goldberg, 1985; Williams, Tarnopolsky, & Hand, 1980). They also allow for cutting scores that in turn make group discrimination against a variety of external criteria, for instance diagnostic parameters (Snaith & Zigmond, 1983). Beyond this level, however, screening tools are unable to provide further diagnostic information (Folstein et al., 1975; Snaith & Zigmond, 1983). For instance, Folstein (1975) stated:

“it is an elementary but important point that as with any examination of cognitive performance, the MMSE cannot be expected to replace a complete clinical appraisal in reaching a final diagnosis of an individual patient. Cognitive difficulties arise in a number of different clinical conditions.” (p. 195)

A requirement for further clinical evaluation beyond the outcome of a screening tool is due, in part, to low levels of interaction that a questionnaire-based method imposes between an individual and the clinician. That is, an SMC questionnaire does not permit room for further elucidation on a pre-set question. Screening tools are also non-specific (Herman, 2006), and they are designed for self-report use or non-expert administration.

The current literature on subjective memory complaints is founded on the assumption of a direct monotonic relationship with objective measures of memory performance. That this is not always the case is well illustrated by the examples provided in the introductory chapter of the case of H.M., who suffered from profound amnesia after gross bilateral resection of temporal lobe structures, and did not show memory concerns commensurate with the severity of the memory dysfunction (Ogden, 2005). Patients with DAT are much the same (Reisberg & Gauthier, 2008), characteristically giving a muted memory complaint despite more alarmed concerns raised by family and friends (Martin, 1975). The responses from these clinical populations sit in opposition to some of the more strident memory complaints in patients with subtle cognitive impairment manifesting from conditions such as first-ever lacunar syndrome (Anderson et al., 2008), temporal lobe epilepsy (O’Shea, 1996), and major depressive disorder (Beck, 1967; Kahn et al., 1975). In this sense, counter-intuitive aspects can occur in subjective experience of memory loss, raising the notion that subjective memory complaints have a diagnostically relevant *internal logic* that can only be discovered via an interactive and purposeful interview with the patient.

Semi-structured interviews allow for a truly interactive and idiographic approach to the patient. This issue surfaces even in conditions with somatic and concrete symptomatology (Cone, 1986; desRosiers, 1992; Greeno, Marcus, & Wing, 1995; Lipton, Stewart, & Solomon, 1992; Selby & Lance, 1960; S. J. Wilson et al., 1999). Black and colleagues (1996) argue that phenomenological experience of binge-eating is
difficult to measure via questionnaires because of imprecise clinical definitions of binge-eating, and a community-based misconception of eating to excess.

Some researchers argue that subjective experiences of memory dysfunction should not be included in the diagnostic criteria of MCI (Lenehan et al., 2012; Mitchell et al., 2012). This argument rests on the assumption that clinical evaluation of subjective aspects of a condition should be discounted if they don’t relate in a simple or straightforward way to a measureable cognitive outcome. The psychometric view of neuropsychological assessment adheres to the concept of dependability, or the stability of a diagnostic decision across multiple situations and contexts, driven predominantly by performance on all-inclusive neuropsychological test batteries (Russell, Russell, & Hill, 2005). From this perspective, that a clinical analysis could rely to some degree, on qualitative, and therefore difficult to validate, phenomena looms large as a confound for ‘objective’ clinical decision-making. Examples exist in the clinical realm of conditions which feature cognitive and behavioural symptomatology that do not translate into objective cognitive dysfunction on neurocognitive testing. The behavioural variant of frontotemporal dementia (FTD), for instance, which is a dementia defined by initial changes to personality. In particular, core features of the condition involve impaired interpersonal conduct, lowered personal inhibitions, emotional blunting and limited insight, in the face of retained episodic memory and visuospatial function (Piguet & Hodges, 2013). On this condition, Neary and Snowden (1991) wrote:

“A third reason for the lack of clinical recognition of non-Alzheimer forms of cerebral atrophy is the nature the neuropsychological examination itself. Neuropsychological assessment has in the past relied almost entirely on standardised test batteries, which yield quantitative measures of performance at the expense of analytic and qualitative evaluations directed to the characterisation of distinct neuropsychological syndromes.” (p. 305)

In this condition, the clinical presentation of the earliest stages of this disease is largely subjective, with the diagnostic process underpinned by detailed history taking from family members and through clinical observation (Piguet & Hodges). Despite these changes in social and emotional conduct, the individual will usually perform well upon neuropsychological testing, with no clear cognitive profile apparent early in the disease (Mioshi et al., 2007), making this condition difficult to isolate according to the psychometric perspective. This is not the case, however, with case identification grounded in careful medical history taking, information from family members, and a reliance on clinical investigation (B. J. Good & Good, 1981). The importance of the subjective presentation of conditions cannot be overlooked,
particularly in situations where the diagnosis is formed by exclusion, such as the behavioural variant of FTD and even mild cognitive impairment.

From a broader perspective, the experience of subjective dysfunction is a component of the individual’s presentation, and is often the antecedent for medical help-seeking. It follows axiomatically that it is an important and worthy object of clinical investigation. The current inquiry opens a window onto the difference in phenomenological experiences of memory change in pathological and non-pathological ageing. That is, perceived changes in memory within the context of pathology possesses qualitatively different *qualia* to that expressed by those who are putatively pathological healthy. This knowledge can be harnessed to better inform diagnostic approaches to preclinical AD. Future studies should address the question of whether phenomenological expression of perceived memory loss differs in those who have attended a memory clinic for their concern. While it is understood that their complaint severity is increased (Abdulrab et al., 2008; Jonker et al., 2000; Kessler et al., 2014), and there is a suggestion that their risk of AD is greater (Jessen et al., 2014), no study has yet conducted a qualitative investigation into their subjective experiences.

**Limitations**

An inherent limitation is the necessarily cross-sectional nature of the experimental design, and it is obvious that a longitudinal perspective developed in future research is essential, however, the establishment of association in this study lays the groundwork for investment for future longitudinal studies. The present study gives much needed impetus to the issue of SMCs as a marker of very early-stage dementia. The effect sizes in models explaining the variance in subjective memory complaining are known to be small, and there are many other findings showing similar effect sizes (Amariglio et al., 2011; Amariglio et al., 2012; Geerlings et al., 1999; Perrotin et al., 2012). This explains why such large sample sizes are required in order to maintain adequate statistical power. It is not logical to expect to see large variances explained in these models, particularly considering the variables that are being analysed. Subjective memory complaining is a subjective entity, being explained by AD biomarkers which are an underlying pathological mechanism; as such, the causal distance between these two concepts is large and there could be myriad variables potentially influencing this relationship. The existence of a finding across a range of past research, however subtle, supports the notion that subjective memory complaints are driven in some way by underlying neurobiological factors. Future research questions will likely focus on determining *how* this occurs. Finally, recent findings from the larger AIBL study demonstrate that the combination of *APOE ε4* and *BDNF Met* polymorphisms appear to be the most detrimental clinically and pathologically. This is still a somewhat controversial finding as it involves only a small sample size (n = 8), and requires further validation. The current study did not include an analysis of *APOE ε4* and *BDNF*
in combination, although future studies should investigate the potential influence of other neurogenetic markers on subjective memory complaints.

8.5 Avoidance of the subjective

To reiterate a point made earlier, subjective memory complaints form the bridge that connects an individual to clinical attention. In the field of memory research, the descriptive exploration of the subjective experiences of memory dysfunction has been avoided in favour of an unfounded unidimensional and predictive view of memory complaints. This attitude is beginning to change (Abdulrab & Heun, 2008; Jessen et al., 2014), with researchers calling for “a characterisation of at-risk states” and a “refinement of knowledge about the characteristics of subjective decline” (Jessen et al., 2014) (p. 2 and 3) at prodromal stages of AD where subtle cognitive impairment is hard to detect with standard neuropsychological tests. Subjective memory complaint research in AD is still at the stage of standardising research settings, defining participant populations, and methods of measurement (Jessen et al., 2014), and is yet to focus on the phenomenological aspects of the field. The current thesis is that there are unanticipated complexities, but nevertheless rich diagnostic information, in the way that people describe their concerns about their memory function, and the content about the description. First-person experiential accounts have long evoked scepticism, particularly with regard to the lack of empirical evidence for their validity, and subsequently questioning their trustworthiness (Windt, 2013). Windt (2013) argues, in relation to self-reporting of dreams, the trustworthiness of subjective self-report is plagued by the misguided assumption that experiential accounts should map isomorphically onto empirical correlates of an underlying dysfunction. It is argued here that an anti-sceptical approach (Windt, 2013), which encourages scientific investigation of experiential accounts under ideal reporting conditions. In the context of the present inquiry, the ideal condition involves expert clinical investigation, as opposed to counting instances. This sentiment has been expressed before: “Not everything that can be counted counts. Not everything that counts can be counted.” (coincidentally misattributed to Albert Einstein; Cameron, 1963).
REFERENCES


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10.1086/302710

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10.1017/S1355617705050812


DEM2003016002078 [pii]


10.1016/j.biopsych.2007.05.030


10.1016/j.archger.2009.04.018


## APPENDIX A: List of acronyms used in this thesis

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAL</td>
<td>Arbitrary associative learning</td>
</tr>
<tr>
<td>ABM</td>
<td>Autobiographical memory</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APOE</td>
<td>Apolipoprotein</td>
</tr>
<tr>
<td>AÎ²</td>
<td>Beta-amyloid</td>
</tr>
<tr>
<td>BNT</td>
<td>Boston Naming Test</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Cambridge neuropsychological testing automated battery</td>
</tr>
<tr>
<td>CVLT</td>
<td>California Verbal Learning Test</td>
</tr>
<tr>
<td>DAT</td>
<td>Dementia of the Alzheimer’s type</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional MRI</td>
</tr>
<tr>
<td>GDS</td>
<td>Geriatric depression scale</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HC</td>
<td>Healthy control</td>
</tr>
<tr>
<td>LM</td>
<td>Logical Memory</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTL</td>
<td>Medial temporal lobe</td>
</tr>
<tr>
<td>PAL</td>
<td>Paired associates learning</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal components analysis</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PiB</td>
<td>Pittsburgh compound B</td>
</tr>
<tr>
<td>PSM</td>
<td>Personal semantic memory</td>
</tr>
<tr>
<td>RCFT</td>
<td>Rey Complex Figure Test</td>
</tr>
<tr>
<td>SMC</td>
<td>Subjective memory complaint</td>
</tr>
<tr>
<td>SMCQ</td>
<td>Subjective memory complaint questionnaire</td>
</tr>
<tr>
<td>SUVR</td>
<td>Standard uptake value ratio</td>
</tr>
</tbody>
</table>
APPENDIX B: MAC-Q (Crook, Feher & Larrabee, 1992)

Memory Complaint Questionnaire (MAC-Q)
As compared to when you were in high school or college, how would you describe your ability to perform the following tasks involving your memory?

<table>
<thead>
<tr>
<th>Task</th>
<th>Much better now (1)</th>
<th>Somewhat better now (2)</th>
<th>About the same (3)</th>
<th>Somewhat poorer now (4)</th>
<th>Much poorer now (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Remembering the name of a person just introduced to you</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Recalling telephone numbers or zip codes that you use on a daily or weekly basis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Recalling where you have put objects (such as keys) in your home or office</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Remembering specific facts from a newspaper or magazine article you have just finished reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Remembering the item(s) you intended to buy when you arrive at the grocery store or pharmacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. In general, how would you describe your memory as compared to when you were in high school?</td>
<td>(2)</td>
<td>(4)</td>
<td>(6)</td>
<td>(8)</td>
<td>(10)</td>
</tr>
</tbody>
</table>

Total Score ________________
APPENDIX C: Memory complaint semi-structured interview

1. Do you ever put things down and forget where they are? For instance, do you ever put your keys down and forget where you left them a little while later?

(i) Yes/No

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ii) How often would you say that happens?</td>
<td>Almost Always/Frequently/Sometimes/Very rarely</td>
</tr>
<tr>
<td>(iii) When is the last time you believe that happened?</td>
<td></td>
</tr>
<tr>
<td>Can you tell me more about that event?</td>
<td></td>
</tr>
<tr>
<td>(iv) How did you find that object again?</td>
<td></td>
</tr>
</tbody>
</table>

2. Do you often enter a room and forget what you intended to do there?

(i) Yes/No

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ii) How often would you say that happens?</td>
<td>Almost Always/Frequently/Sometimes/Very rarely</td>
</tr>
<tr>
<td>(iii) Can you recall the last time when that happened?</td>
<td></td>
</tr>
<tr>
<td>Can you tell me more about that event?</td>
<td></td>
</tr>
<tr>
<td>(iv) How long does it take to realise your intention?</td>
<td></td>
</tr>
</tbody>
</table>
3. *Do you often check and recheck whether you completed a task moments after doing it for instance, turning off the oven, locking your car or house, etc?*

(i) Yes/No  

<table>
<thead>
<tr>
<th>Response</th>
</tr>
</thead>
</table>
| (ii) How often would you say that happens? | Almost Always/Frequently/Sometimes/Very rarely  
| (iii) When is the last time you believe that happened? |  
| Can you tell me more about that event? |  

4. *Do you ever forget where you park your car, for instance, when you go to the supermarket or the shopping centre, etc?*

(i) Yes/No  

<table>
<thead>
<tr>
<th>Response</th>
</tr>
</thead>
</table>
| (ii) How often would you say that happens? | Almost Always/Frequently/Sometimes/Very rarely  
| (iii) When is the last time you believe that happened? |  
| Can you tell me more about that event? |  
| (iv) What happens next? i.e. how do you recover? |  

5. *Do you have trouble remembering people’s names?*

(i) Yes/No

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(v) Does that happen frequently?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>(vi) Does that cause you significant embarrassment?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>(iv) What do you do in that situation—does that name come back?</td>
<td></td>
</tr>
</tbody>
</table>

6. *Do you ever forget your pin number at an ATM or at the supermarket checkout?*

(i) Yes/No

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ii) How often would you say that happens?</td>
<td>Almost Always/Frequently/Sometimes/Very rarely</td>
</tr>
<tr>
<td>(iii) When is the last time you believe that happened?</td>
<td></td>
</tr>
<tr>
<td>Can you tell me more about that event?</td>
<td></td>
</tr>
<tr>
<td>(iv) How did you recover from that situation?</td>
<td></td>
</tr>
</tbody>
</table>
7. Do you get easily distracted, for instance, do you leave pots to burn on the stove, appliances running, tasks half done, etc?

(i) Yes/No

<table>
<thead>
<tr>
<th>(ii) How often would you say that happens?</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Almost Always/Frequently/Sometimes/Very rarely</td>
</tr>
</tbody>
</table>

(iii) When is the last time you believe that happened?  
Can you tell me more about that event?

8. When you read the newspaper or a book, do you believe you’ve remembered what you have read?

(i) Yes/No

<table>
<thead>
<tr>
<th>(vii) Do you think you read less now because you believe you can’t remember the details?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No: Prompt: Can you tell me a bit more about this?</td>
</tr>
</tbody>
</table>

(viii) Supplementary: Do you enjoy reading less?

(ix) Supplementary: Do you find yourself re-reading paragraphs?

<table>
<thead>
<tr>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
</tr>
</tbody>
</table>
APPENDIX D: The Episodic Autobiographical Memory Interview (Irish et al., 2008)

Personal Semantic Memory Section

1. *Can you give the full names of three people from among your acquaintances at this period? For example, the name of a friend, neighbour, doctor, priest, teacher or colleague? If possible, try to restrict your answers to people you have only known during the period in question.*

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
</table>
| (i) Name of person  
Profession/Relationship |     |
| (ii) Name of person  
Profession/Relationship |     |
| (iii) Name of person  
Profession/Relationship |     |
| Total Score |     |

2. *Can you give me the name of a social club or establishment that you have frequented in the last five years? How did you get there?*

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of club/establishment</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Nature of activity</td>
<td></td>
</tr>
<tr>
<td>Travel to location</td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
</tr>
</tbody>
</table>
3. Can you recall an important date in this time period such as a birth, death, ceremony? Please give the event, the complete date (month and year) and the location.

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>Month</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
</tbody>
</table>

**Autobiographical Memory Section**

“I would like you to describe out loud and with as much detail as possible, an event that occurred during this time period that stands out for you.”

Description/Free Recall:

<table>
<thead>
<tr>
<th>Prompts</th>
<th>Notes</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Event Detail</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What happened?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Who was present?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Their relationship to you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What was the weather like?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What were you wearing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What food/music/transport?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was this a once-off event?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Temporal Specificity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What year?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What season?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 192 | What month?  
What date?  
What day of the week?  
What time of day? |
|---|---|
| 3. Sensory/Perceptual Detail | What can you picture/visualise now when you think about this event?  
What textures/physical sensations?  
What movements did you make?  
What sounds/smells/tastes?  
Is this memory vivid or vague? |
| 4. Spatial Specificity | Where did this event occur?  
What country/city/street?  
What building/floor/room?  
Where were you within that scene? |
| 5. Emotion | What did you feel at the time in terms of emotion? |
| 6. Implication | What happened beforehand?  
What happened afterwards? |
| 7. Thoughts | What were you thinking at the time? |

| Total Score |   |
Autonoetic Consciousness Section

1. *Perspective*
   (i) When you replay this event in your mind’s eye, are you looking at the scene through your:
   Own eyes ___  Third person’s perspective ___  Neither ___  No image ___

2. *Continuity*
   (i) Do the images follow in sequence with no gaps in between?
   (ii) How would you describe the event as it appears in your mind’s eye?
       Plays from start to finish with no gaps in between? ___
       A series of moving images but there some details are missing in between? ___
       One moving image? ___
       A series of static, non-moving, images, like photographs in sequence? ___
       One overall static, non-moving image? ___
   Would you describe it as something else?
       ____________________________________________________________________________

3. *Emotional Connection*
   (i) When you remember this event, do you re-experience the same emotions as you felt at the time?
       Not Re-experiencing Partially Re-experiencing it Fully Re-experiencing it
       0% 25% 50% 75% 100%

4. *Recollective Experience*
   (i) Would you say you are *reliving* what happened? Or are you more like an observer watching the event unfold?
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