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Title:

Phenomenological characterization of memory complaints in preclinical and prodromal alzheimer's disease

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Abstract

Objective: To explore the subjective experience of memory change in groups at risk of dementia (those with mild cognitive impairment MCI or high β -amyloid ($A\beta^+$) burden) to determine the existence of potential phenomenological typologies. **Method:** We recruited 123 healthy controls (HC) and individuals with MCI from the Australian Imaging, Biomarker and Lifestyle (AIBL) study. Sixty-seven (HC=47, MCI=20) had $A\beta$ scans available for analysis. Semi-structured interviews were administered, transcribed, and meaningful phrases extracted from transcripts. Twelve themes were defined and compared across diagnostic status and $A\beta$ status. **Results:** MCI endorsed more complaints of burdensome coping strategies, increasing frequency, sense of predominance, poor contextualisation, progression, dependency, impact on affect, and dismissive attitudes. $HCA\beta^+$ acknowledged a progressive memory decline compared to $HCA\beta^-$, while $MCI A\beta^+$ expressed more burdensome coping strategies, dismissive attitudes and dependency comparative to either healthy group. Depression was more likely to be related to complaint themes in HCs, while complaint themes were associated with poorer list-learning performance in individuals with MCI. **Conclusion:** Complaint themes in those with MCI align with the MCI symptom complex, particularly when accompanied with high $A\beta$ load. Healthy $A\beta^+$ individuals acknowledged progressive memory change, suggesting they are aware of memory changes not yet detectable via neuropsychological measures. Depressive symptomatology associated with HC complaints, suggesting certain themes are affect-driven, while complaints in MCI are associated with organically-driven functional impairment. Qualitative analysis of SMCs can inform the earliest clinical manifestations of Alzheimer's disease. Our findings can inform diagnostic approaches to the clinical evaluation of memory complaints in the non-demented elderly.

Keywords: Subjective memory complaints, memory, mild cognitive impairment, Alzheimer's disease, β -amyloid

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, Townsend, Grodstein, Sperling, & Rentz, 2011; Hohman, Beason-Held, Lamar, & Resnick, 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, Flicker, Vasikaran, Leedman, & Almeida, 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, Klekociuk, & Summers, 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, Saling, Lawrence, & Bladin, 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 ($A\beta$) 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 the elderly. Concerns of ‘forgetting what you are attending to’ or ‘getting lost’ in the healthy elderly have been conceptualised as potential indicators of progression to AD (Amariglio et al., 2011; Tobiansky, Blizard, Livingston, & Mann, 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 $A\beta$ burden and SMCs (Barnes, Schneider, Boyle, Bienias, & Bennett, 2006; Chételat et al., 2010; Perrotin, Mormino, Madison, Hayenga, & Jagust, 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 $A\beta$ load (or significant

levels of neocortical A β according to PET neuroimaging parameters; Aizenstein, Nebes, Saxton, & et al., 2008) felt less confident in their overall memory function. Other studies, however, have found no relationship between A β and SMC severity (Buckley et al., 2013; Rodda et al., 2010), or only report a relationship in carriers of *apolipoprotein E* epsilon 4 (*APOE* ϵ 4; (Rowe et al., 2010). As such, it is still unclear, how subjective memory complaints are related to A β , and to the authors' knowledge, no research has yet developed a characterisation of SMCs in individuals who have high A β 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 A β 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 individuals with high A β , regardless of diagnosis, would acknowledge a subtle decrease in memory function. Depression is a well-established confounding factor with SMCs in healthy older adults (Buckley et al., 2013; Jorm et al., 2004; Lautenschlager et al., 2005), so we additionally analysed the influence of depressive symptomatology on complaint themes.

Method

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 = 20) also had positron emission tomography (PET) images of neocortical A β 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 apnea, Parkinson's disease, cancers within the last few years, symptomatic stroke, uncontrolled diabetes, and alcohol consumption greater than Australian recommended levels. Health status, measured according to the number of vascular risk factors (VRFs) for each individual, was calculated according to evidence of the following criteria; hypertension, diabetes, dyslipidaemia, body mass index, smoking, chronic kidney disease, and elevated homocysteine levels. For analytical purposes, those with more than two VRFs were collapsed into one category (Restrepo et al., 2012). A diagnostic review panel of neurologists, geriatricians, psychiatrists and neuropsychologists, chaired by the fourth author (DA), 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: ^{11}C -PiB, ^{18}F -flutemetamol and ^{18}F -florbetapir PET imaging

A β imaging with positron emission tomography (PET) was conducted using either ^{11}C -Pittsburgh Compound B (PiB), ^{18}F -florbetapir or ^{18}F -flutemetamol. Thirty-eight participants (HC = 30, MCI = 8) underwent PiB-PET imaging, 12 participants (HC = 9, MCI = 3) underwent ^{18}F -flutemetamol PET scans, and 13 participants (HC = 12, MCI = 1) had ^{18}F -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 (A β + / A β -). Participants who underwent PiB-PET imaging were classified A β + when $\text{SUVR} \geq 1.5$ (Rowe et al., 2007), florbetapir when $\text{SUVR} \geq 1.11$ (Clark et al., 2011), and for flutemetamol when $\text{SUVR} \geq 0.62$ (Thurfjell et al., 2013).

Measures

Verbal and non-verbal memory. 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).

Executive function. The Fruit and Furniture Switching (FFS) task from the D-KFES (Delis, Kaplan, & Kramer, 2001) and the Stroop test (Trenerry, Crosson, DeBoe, & Leber, 1989) were used to measure fundamental components of executive functioning.

Mood. The 15-item version of the GDS (Yesavage et al., 1983) was used to measure levels of depressive symptomatology.

Qualitative analysis

Materials and procedure. 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. Eight scenarios were developed to elicit a subjective exploration of memory lapses, such as, remembering the location of household objects, recalling an objective upon entering a room, recalling whether tasks have been completed, recalling the location of a parked car, recalling names, recalling passwords and pin numbers, and remembering the contents of newspapers or books. The interviewer probed the occurrence of memory lapses in these scenarios in terms of the following features; 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.

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 predominance 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. This is the subjective sense or appreciation of frequency, rather than carrying any objectively defined quantitative implications. Verbalisations such as 'often', 'always', or 'all the time' are 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 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 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. 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!'

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'. 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 resident finder 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'.

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. 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?' The following are examples of self-expressed vagueness or absent-mindedness: 'I was sort of vaguely fluffing around ...'.

8. Impact on affect

Impact on affect pertains to how memory lapses impinged on an individual's affect. 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 or stress. For instance, 'I get frustrated with myself'.

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. And I’ve forgotten how to cook a lot.’

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 (χ^2) tests of independence were used to determine demographic and memory differences between diagnostic categories (HC/MCI), and high or low amyloid burden ($A\beta^+/A\beta^-$). 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 χ^2 was used to compare HC $A\beta^-$ /HC $A\beta^+$ /MCI $A\beta^-$ /MCI $A\beta^+$ groups on complaint themes. Separate Mann-Whitney U analyses were used for *post-hoc* group comparisons between the latter four groups. Non-parametric Spearman rank-order (ρ) correlations were

used to determine partial correlations between complaint themes and memory and executive function measures, after accounting for age and depression. 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 totaled less than 10% of the entire data set (see Figure 1 and 2).

Results

Demographic and cognitive differences

Individuals with MCI were older, were more likely to be *APOE* $\epsilon 4$ carriers, performed significantly worse on all memory measures, and exhibited elevated levels of depressive symptomatology compared to healthy controls (see Table 1). There were no differences in number of VRFs between the groups, and only a trend towards lower levels of education in individuals with MCI. None of the $A\beta$ status groups (HC $A\beta^-$ /HC $A\beta^+$ /MCI $A\beta^-$ /MCI $A\beta^+$) differed on age, gender, or education level (see Table 2). Both HC and MCI $A\beta^+$ groups were likely to carry an *APOE* $\epsilon 4$ allele, and exhibit poorer performance on prose and list-learning recall compared to either $A\beta^-$ group. The MCI $A\beta^+$ group showed poorer nonverbal memory performance and executive functioning compared to the other three groups, and elevated levels of depressive symptomatology compared to the HC $A\beta^-$ group.

Differences in thematic complaints: HC and MCI

Compared with HC cases irrespective of amyloid burden, individuals with MCI endorsed themes of increasing frequency ($U = 1311.50, p = 0.03$), sense of predomination ($U = 1156.50, p = 0.002$), relative absence of contextualisation ($U = 1028.50, p < 0.001$),

burdensome coping strategies ($U = 868.00, p < 0.001$), dismissive attitude ($U = 1207.00, p = .004$), impact on affect ($U = 1098.00, p = 0.001$), progression ($U = 1102.00, p < 0.001$), and dependency ($U = 1339.50, p = 0.01$). All significant differences involved moderate to strong effect sizes (see Figure 1).

As individuals with MCI exhibited a trend towards being less educated, we conducted an analysis to determine whether education level (less or greater than 12 years of education) within each diagnostic category influenced memory complaint endorsement. We those with higher education reported more issues of attentional fluctuation/vagueness, $\chi^2 = 5.54, p = 0.02$, but no effect of education on the other themes (increased frequency, $\chi^2 = 0.17, p = 0.68$; sense of predomination, $\chi^2 = 0.06, p = 0.81$; situational, $\chi^2 = 0.24, p = 0.62$; contextualisation, $\chi^2 = 0.26, p = 0.61$; burdensome strategies, $\chi^2 = 0.54, p = 0.46$; dismissive attitude, $\chi^2 = 0.15, p = 0.09$; impact on affect, $\chi^2 = 0.13, p = 0.71$; progression, $\chi^2 = 0.72, p = 0.40$, and dependency, $\chi^2 = 2.10, p = 0.15$), and no interaction effects.

Differences in thematic complaints: HC A β ⁻/HC A β ⁺/MCI A β ⁻/MCI A β ⁺

Complaint themes that were significantly different between all four groups were sense of predomination ($\chi^2 = 10.21, p = 0.02$), burdensome coping strategies ($\chi^2 = 23.47, p < 0.001$), dismissive attitude ($\chi^2 = 8.84, p = 0.03$), progression ($\chi^2 = 17.97, p < 0.001$), and dependency ($\chi^2 = 14.32, p < 0.001$). Post-hoc analyses revealed the MCI A β ⁺ group expressed significantly more concerns about sense of predomination ($U = 77.00, p = 0.02$), burdensome coping strategies ($U = 46.00, p = 0.001$), dismissive attitude ($U = 79.00, p = 0.02$), progression ($U = 64.00, p = 0.006$), and dependency ($U = 51.00, p = 0.002$), in comparison with HC A β ⁻ individuals. Similar comparisons were also found between the HC and MCI A β ⁺ groups (see Figure 2). The HC A β ⁺ group expressed a greater sense of progressive memory decline compared with the HC A β ⁻ group ($U = 174.0, p = 0.04$). After

conducting a post-hoc rank analysis of covariance (Quade, 1967) to determine the influence of age or depressive symptomatology as covariates, we found no change in our results.

Association between themes and depressive symptomatology

In healthy controls, greater levels of depressive symptomatology were associated with greater endorsement of poorer contextualisation, $\rho(80) = 0.44, p < 0.001$, burdensome coping strategies $\rho(80) = 0.29, p = 0.01$, a sense of predomination and growing concern, $\rho(80) = 0.29, p = 0.01$, and increasing frequency, $\rho(80) = 0.25, p = 0.02$. In participants with MCI, depressive symptomatology was associated only with greater endorsement of dependency, $\rho(40) = 0.35, p = 0.03$. Tables 3 and 4 display the associations between the complaint themes, depressive symptomatology and memory performance in HC and MCI, respectively.

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-II long delay, $\rho(31) = -0.49, p = 0.004$, and CVLT-II short delay, $\rho(31) = -0.37, p = 0.03$, after partialling out unique variance explained by age and depression. Greater acknowledgement of increasing frequency was related to poorer performance on CVLT-II long delay, $\rho(31) = -0.40, p = 0.02$. Increased expressions of dependency were also related to poorer performance on CVLT-II long delay, $\rho(31) = -0.36, p = 0.03$. When executive function measures were correlated with complaint themes, there was no significant relationship in either diagnostic group after accounting for age and depression.

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 lapses, 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 elevated in individuals with MCI, aligning with current conceptions of the MCI symptom complex (Petersen et al., 1999; Reisberg, Ferris, de Leon, & Crook, 1982; Winblad et al., 2004), and supporting the criterion validity of the semi-structured interview. The purpose of this study, however, was not to develop a novel diagnostic marker of subjective memory complaints, but to explore the subjective experience of memory change in healthy and pathological aging. Individuals with MCI were more likely to provide comments reflecting burdensome coping strategies, suggesting that functional changes arising from an increase in maladaptive coping strategies may well signify an 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). We found that individuals with more than 12 years of education, regardless of diagnostic status, tended to endorse issues of attentional fluctuation and vagueness more frequently. Attaining a higher level of education is recognised as a factor in subjective memory complaining (Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007), but this is not consistently reported (Jessen et al., 2010; St John & Montgomery, 2002). Our finding supports the notion that level of education, a robust demographic marker of general intelligence (Deary, Strand, Smith, & Fernandes, 2007), is associated with some areas of memory self-appraisal.

Amyloidopathies, in the form of cerebral amyloid angiopathy, have long been associated with cerebrovascular disease (Jeerakathil et al., 2004; Premkumar, Cohen, Hedera, Friedland, & Kalaria, 1996). In the case of $A\beta_{40-42}$ there is the possibility that increased deposition and vascular burden may have a synergic effect on cognition (Lee et al., 2014). In our study, the healthy control and MCI groups differed in $A\beta$ deposition in the absence of any significant group differences in vascular burden, suggesting a more primary neuronal effect of $A\beta$. Our data don't address the question as to whether cerebrovascular disease induce β -amyloid deposition (Garcia-Alloza et al., 2011). It's worth noting that patients with a history of stroke were not included in the MCI group of the current study (Ellis et al., 2009). Nevertheless, vascular risk can exert a decompensatory effect on cognition in non-demented older adults (Debette et al., 2011), and so investigating the role of vascular burden alongside that of amyloid deposition on thematic memory concerns is worthy in its own right.

Studies investigating the relationship between neocortical $A\beta$ burden and SMCs in healthy older adults are gaining traction (Amariglio et al., 2012; Barnes et al., 2006; Buckley et al., 2013; Chételat et al., 2010; Perrotin et al., 2012; Rodda et al., 2010; Rowe et al., 2010). We found that healthy older adults with high $A\beta$ load noticed a progressive memory change, which adds a new perspective to the value of $A\beta$ as a clinical marker. Considering these individuals are cognitively healthy, it is possible that they are becoming increasingly aware of subtle changes that neuropsychological tasks are currently unable to detect (de Jager, Milwain, & Budge, 2002). The healthy control group were not differentiated by their $A\beta$ status on any other memory complaint themes, which aligns with the clinical reality that concerns of progressive memory decline are more likely to be elicited as a predominant complaint (Begum et al., 2012; de Boer et al., 2007). The small effect sizes observed in our study reflects a chain of causation over multiple levels of a complex hierarchy extending from extracellular pathology to subjective experiences of an early stage condition. Taking

this into account, isolation of a pathologically relevant subjective memory signal against this background is striking. A broader implication is that healthy older adults with a sense of progressive memory decline should be candidates for more detailed clinical investigation, provided a sense of progression is also established in the mind of the interviewer. In the MCI group, as might be expected, memory complaints were greater in MCI individuals with a higher A β load relative to those with a low A β load, supporting the ‘higher risk’ prodromal AD profile that includes evidence of elevated AD biomarkers (Albert et al., 2011).

Depressive symptomatology has a well-established association with SMCs in healthy older adults (Bartley et al., 2012; Buckley et al., 2013; Jorm et al., 2004; Lautenschlager et al., 2005), prompting some researchers to question the extent to which SMCs have utility for the recognition of early AD (Lenehan et al., 2012; Mitchell, 2008). While the current study observed that depressive symptomatology was related to SMCs in healthy controls, the relationship was not mirrored in MCI. This divergence raises the notion of an insidious transition in the primary drivers of memory complaints. In preclinical individuals, where the rates of AD biomarker accumulation are gradual (Villemagne et al., 2013), affective factors are relatively unconstrained determiners of cognitive discomfort. As pathology progresses to a clinically detectable level, neurobiological causation becomes more potent, constraining affective factors to a more peripheral contributory role (see, Buckley et al., 2013; Clément, Belleville, & Gauthier, 2008; Cook & Marsiske, 2006; Crowe et al., 2006; Foley, 2007). The only complaint theme to relate to depression in MCI was increased endorsement of dependency. In the context of dementia care, greater levels of depression tend to be associated with higher levels of dependency (Dawson, Powers, Krestar, Yarry, & Judge, 2013; Gauthier et al., 2006; Taylor & Lynch, 2004).

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. Our findings support research suggesting an awareness of objective cognitive changes in MCI (Crowe et al., 2006; Greenop et al., 2011), that peaks during this clinical stage (Reisberg et al., 1982). 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 between the two groups. The absence of a relationship with executive tasks might possibly raise the notion of a secondary influence of executive function on subjective memory complaints, but there is no evidence in our study of a direct link. Overall, our findings lend support to a thematic approach to memory complaining, and speak to what may well signify better specificity of this approach to investigating this inherently subjective phenomenon.

Limitations and Conclusion

This sample is convenience-based, and healthy controls were recruited by the larger AIBL study via volunteer methods from the community. This has the possibility of recruiting more individuals who are naturally inclined to be more concerned of their memory. Initial AIBL publications suggest that healthy memory complainer and non-complainer sample sizes (as measured according to a single question, ‘do you have difficulties with your memory, yes or no?’) were relatively comparable on cognitive, affective and other demographic information (Ellis et al., 2009). For present inquiry, healthy participants were randomly sampled from both groups to avoid a potential recruitment bias.

This is the first examination of subjective memory complaint symptomatology using a semi-structured interview reminiscent of a clinical interview. We have developed a phenomenological characterisation of an individual’s self-appraisal of their everyday memory function according to diagnosis and A β 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 foundation of the complaint. Our findings emphasize the notion that expressions of memory failure feature against a backdrop of clinicopathological changes, which can be revealed by a qualitative approach.

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Competing Interests

None.

Description of authors' roles

Rachel Buckley developed and administered the semi-structured interview, carried out the statistical analyses and wrote the paper. Michael Saling developed the semi-structured interview, aided in the coding of the data, and oversaw the analyses. David Ames, Alan Rembach, Stephanie Rainey-Smith and Kathryn Ellis oversee and coordinate the AIBL study at the Melbourne site. David Ames also chairs the AIBL diagnostic panel, on which Nicola Lautenschlager, Greg Savage, Cassandra Szoek and Kathryn Ellis also serve. Nicola Lautenschlager, Paul Maruff and Greg Savage serve on the leadership group of the Clinical and Cognitive Stream of the AIBL study. David Ames, Lance Macaulay, Ralph Martins, Chris Rowe and Colin Masters oversee the AIBL study, sit on the management committee. Ralph Martins and Stephanie Rainey-Smith lead and coordinate the Perth arm of the AIBL study. Chris Rowe leads the AIBL imaging arm, and Victor Villemagne also oversaw the

imaging component. Cassandra Szoeki represented CSIRO at management committee meetings from 2009-2011. All authors critically reviewed drafts of this manuscript.

Table 1.

Demographic and cognitive variables by diagnostic category

	HC (n = 80) M (SD)	MCI (n = 43) M (SD)	<i>t</i> or χ^2 score	Effect size (Cohen's <i>d</i> or ϕ)	<i>sig</i>
Demographics					
Age	75.61 (6.9)	79.63 (6.9)	-3.08	-0.58	0.003
Gender (% female)	46	58	1.58	0.11	0.25
Education (%>13 yrs)	65	48	3.03	-0.16	0.09
APOE ϵ 4 (% carrier)	24	50	7.88	0.26	0.005
A β status (% A β^+)	23	53	5.09	0.28	0.02
VRF status (%)	0 VRF: 18 1 VRF: 38 2+ VRF: 44	0 VRF: 14 1 VRF: 43 2+ VRF: 43	0.18	0.05	0.92
Memory					
PAL (n)	80	42			
PAL stage 6 err (adj) [*]	9.65 (10.1)	19.02 (15.4)	-3.57	-0.71	0.001
LM (n)	79	43			
LM immediate recall [†]	13.24 (3.6)	3.96 (3.5)	9.36	2.61	<0.001
LM delayed recall [†]	12.28 (3.7)	4.26 (4.0)	11.09	2.08	<0.001
CVLT-II (n)	78	38			
CVLT-II short delay [‡]	1.31 (1.1)	-1.26 (1.2)	11.70	2.23	<0.001
CVLT-II long delay [‡]	1.20 (0.9)	-1.22 (1.3)	11.43	2.16	<0.001
RCFT (n)	77	41			
RCFT 30 minute [‡]	1.34 (1.6)	-0.46 (1.4)	5.96	1.20	<0.001
Executive function					
Fruit/furniture switching [†]	11.21 (3.1)	8.13 (3.2)	5.06	0.98	<0.001

Thematic analysis of subjective memory complaints

Stroop Score [‡]	-0.61 (0.6)	-0.36 (0.7)	-1.93	-0.38	0.05
Mood (n)	80	40			
GDS	1.08 (1.6)	2.35 (2.0)	-3.73	-0.70	0.001

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-Second edition, RCFT = Rey Complex Figure Test, GDS = Geriatric Depression Scale

Table 2.

Demographic and cognitive variables by A β status

	HC A β - (n = 40) M (SD)	HC A β + (n = 12) M (SD)	MCI A β - (n = 7) M (SD)	MCI A β + (n = 8) M (SD)	Effect size (ηp^2 or ϕ)
Demographics					
Age	74.47 (6.5)	79.08 (6.6)	78.00 (6.4)	80.00 (6.8)	0.12
Gender (% F)	45	42	72	50	0.17
Education (%>13 yrs)	70	66.7	57.1	50	0.15
APOE ϵ 4 (% Yes)	20	58	0	62	0.45
Global PiB SUVR (n)	21	9	4	5	
Global PiB SUVR	1.20 (0.1)	2.00 (0.3)	1.16 (0.2)	2.24 (0.2)	0.85
Memory					
PAL (n)	40	12	7	8	
PAL stage 6 err (adj)*	7.93 (8.8)	11.42 (10.7)	12.57 (17.6)	15.13 (15.5)	0.05
LM (n)	40	12	7	8	
LM immediate recall [†]	13.68 (3.6)	12.50 (2.8)	7.14 (2.7)	7.25 (4.1)	0.38
LM delayed recall [†]	12.92 (3.6)	12.00 (3.7)	5.43 (2.6)	4.00 (3.4)	0.49
CVLT-II (n)	40	11	7	7	
CVLT-II short delay [‡]	1.19 (1.2)	1.54 (0.9)	-0.57 (1.3)	-1.36 (1.1)	0.41
CVLT-II long delay [‡]	1.08 (1.0)	1.41 (0.7)	-0.50 (1.6)	-1.43 (1.5)	0.42
RCFT (n)	39	11	7	8	
RCFT 30 minute [‡]	1.40 (1.5)	1.55 (1.9)	0.30 (1.4)	-0.52 (1.4)	0.17
Mood (n)	40	12	6	8	
GDS	1.20 (1.8)	0.58 (1.2)	1.83 (0.8)	2.75 (1.5)	0.14

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. Bolded scores are significant using Sidak *post-hoc* analyses

Table 3.

Spearman rank-order correlations between complaint themes against depressive symptomatology and memory variables in HC

Complaint themes	GDS	PAL [†]	CVLT-II SD [‡]	CVLT-II LD [‡]	LM SD [†]	LM LD [†]	RCFT [‡]	FFS [†]	Stroop [‡]
Increasing frequency	0.25*	-0.11	0.05	0.02	0.08	0.07	-0.04	-0.17	0.09
Predomination	0.29**	-0.09	0.09	-0.004	0.004	-0.06	-0.04	-0.03	-0.01
Situational	-0.02	0.21	0.04	0.02	-0.03	-0.01	0.05	-0.09	0.03
Context.	0.44**	-0.09	-0.02	0.07	-0.12	-0.07	-0.10	-0.23	0.09
Burden. coping strat.	0.29**	0.19	0.04	-0.14	-0.03	-0.07	-0.20	-0.03	0.08
Dismissive attitude	0.16	-0.23	-0.11	-0.03	0.21	0.21	-0.03	0.14	-0.17
Attent. fluctuation	0.06	-0.16	0.12	-0.06	-0.07	-0.05	-0.03	-0.06	-0.06
Impact on affect	0.11	-0.12	0.15	-0.06	0.04	0.07	-0.21	-0.07	0.12
Progression	0.18	-0.02	-0.09	-0.17	0.12	0.07	-0.08	0.02	-0.20
Dependency	0.15	0.15	0.14	0.04	0.07	0.02	-0.12	-0.19	0.19

Note: * = $p < 0.03$, ** = $p < 0.01$, [†] Partial correlations with age and GDS as covariates. GDS = Geriatric Depression Score,

PAL = Paired Associate Learning stage 6 errors (adj), CVLT-II= California Verbal Learning Test, SD = short delay, LD = long delay, LM = Logical Memory, RCFT = Rey Complex Figure Test; FFS = Fruit and Furniture Switching

Table 4.

Spearman rank-order correlations between complaint themes against depressive symptomatology and memory variables in MCI

Complaint themes	GDS	PAL [†]	CVLT-II SD [‡]	CVLT-II LD [‡]	LM SD [†]	LM LD [†]	RCFT [‡]	FFS [†]	Stroop [‡]
Increasing frequency	0.03	-0.20	-0.03	-0.40*	0.30	0.19	0.21	0.14	-0.01
Predominant	0.13	-0.13	-0.19	0.21	0.00	0.13	0.12	0.19	0.17
Situational	-0.05	-0.08	0.13	0.14	-0.002	0.05	0.25	0.02	0.14
Context.	0.19	0.06	-0.09	-0.24	-0.07	-0.23	-0.16	-0.15	0.15
Burden. coping strat.	0.15	-0.02	-0.37*	-0.49**	-0.14	-0.17	-0.14	-0.16	0.15
Dismissive attitude	0.01	0.21	-0.14	-0.11	-0.15	-0.09	-0.01	0.05	0.08
Attent.fluctuation	0.11	-0.17	0.35	0.25	0.22	0.33	0.32	0.29	0.16
Impact on affect	-0.01	-0.16	-0.04	-0.04	0.31	0.18	-0.001	0.04	0.26
Progression	0.05	-0.12	0.09	0.05	0.17	0.17	0.001	0.05	0.13

Thematic analysis of subjective memory complaints

Dependency	0.35*	-0.10	-0.10	-0.36*	0.20	-0.16	-0.09	-0.10	0.18
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Note: * = $p < 0.03$, ** = $p < 0.01$, [†] Partial correlations accounting for age and GDS score. GDS = Geriatric

Depression Score, PAL = Paired Associate Learning stage 6 errors (adj), CVLT-II= California Verbal Learning Test,

SD = short delay, LD = long delay, LM = Logical Memory, RCFT = Rey Complex Figure Test; FFS = Fruit and

Furniture Switching

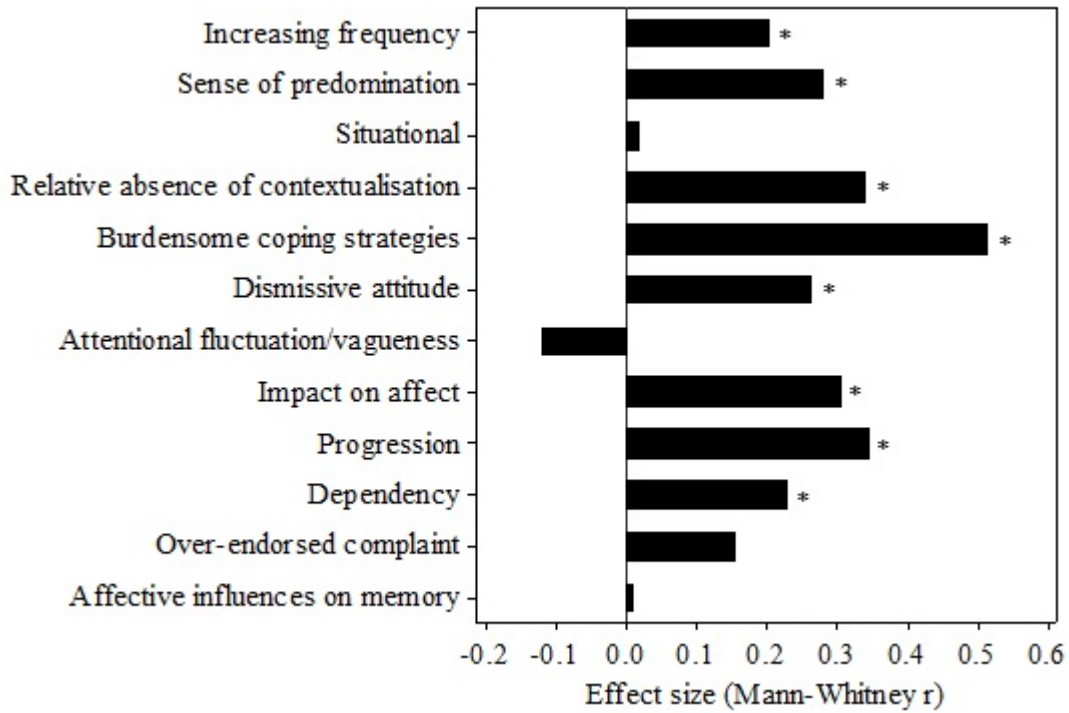


Figure 1. Mean differences on complaint themes between HC and MCI, represented as effect size r (small $0.1 < 0.3 < 0.5$ large) * = significant difference

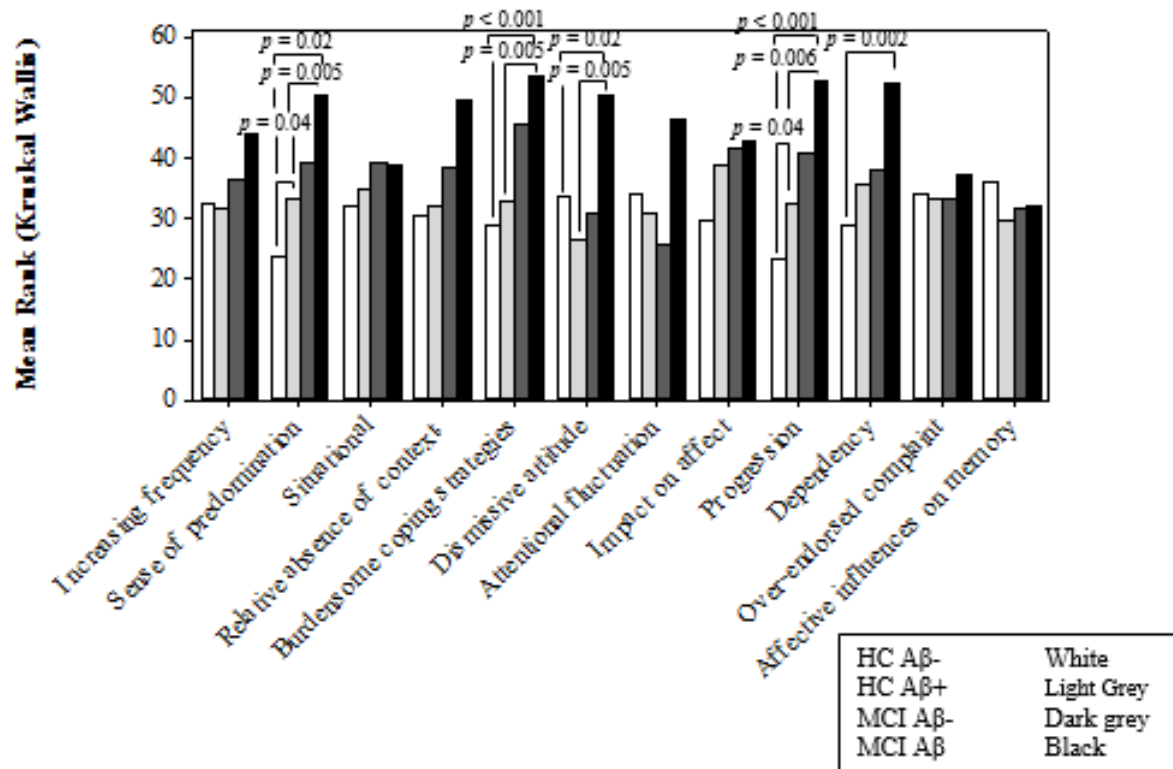


Figure 2. Kruskal-Wallis mean ranking of complaint themes according to Aβ load (+/-) and diagnosis (HC/MCI)

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