Title: Self-reported confusion is related to global and regional β -amyloid: data from the Women's Healthy Ageing Project

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Acknowledgments

We would like to acknowledge the contribution of participants, team members, partners and their supporters who have given their time and patience for over 20 years to the university. A full list of all researchers contributing to the WHAP and membership of our Scientific Advisory Board is available at www.whap.unimelb.edu.au. Funding for the WHAP has been provided by the Australian National Health and Medical Research Council (NHMRC 1062133, 547600, 1032350), Bayer Healthcare, the Ramaciotti Foundation, the Brain Foundation, the Alzheimer's Association of Australia, the Australian Menopausal Society, the Shepherd Foundation, the Scobie and Claire Mackinnon Trust, the Collier Trust Fund, the J.O. & J.R. Wicking Trust, the Mason Foundation and the Alzheimer's Association (NIA320312). Inaugural funding was provided by VicHealth and the NHMRC.

ABSTRACT

INTRODUCTION: Disease-modifying treatments for Alzheimer's disease (AD) may require implementation during early stages of β -amyloid accumulation, well before patients have objective cognitive decline. In this study we aimed to assess the clinical value of subjective cognitive impairment (SCI) by examining the cross-sectional relationship between β -amyloid load and SCI.

METHODS: Cerebral β -amyloid and SCI was assessed in a cohort of 112 cognitively normal subjects. Subjective cognition was evaluated using specific questions on memory and cognition and the MAC-Q. Participants had cerebral β -amyloid load measured with ^{18}F -Florbetaben Positron Emission Tomography (PET).

RESULTS: No associations were found between measures of subjective memory impairment and cerebral β -amyloid. However, self-reported confusion was predictive of a higher global β -amyloid burden ($p = 0.002$), after controlling for confounders. Regional analysis revealed significant associations of confusion with β -amyloid in the prefrontal region ($p = 0.004$), posterior cingulate and precuneus cortices ($p = 0.004$) and the lateral temporal lobes ($p = 0.001$) after controlling for confounders.

DISCUSSION: An *in vivo* biomarker for AD pathology was associated with SCI by self-reported confusion on cross-sectional analysis. Whilst there has been a large body of research on SMC, our results indicate more research is needed to explore symptoms of confusion.

KEY WORDS: Alzheimer's Disease, subjective cognitive impairment, subjective memory, β -amyloid, PET imaging, confusion

1. INTRODUCTION

The pathological hallmark of Alzheimer's disease (AD), neocortical β -amyloid deposition is known to begin years before the onset of clinical disease (Jack et al. 2013). Whilst current treatments are aimed at symptomatic improvement (Massoud and Leger 2011), disease-modifying therapies may be most effective if started before objective cognitive decline is apparent. Positron emission tomography (PET) allows visualization and quantification of β -amyloid *in vivo*, using amyloid-sensitive radiotracers (Mori et al. 2012). The PET ligand ^{18}F -Florbetaben shows an affinity for β -amyloid plaques, with clinicopathological correlations demonstrating high sensitivity and specificity for the presence of AD pathology (Rowe et al. 2008). However, a proportion of cognitively healthy subjects will also show cerebral amyloid deposition on PET scanning, possibly representing individuals at the very early stages of disease (Mintun et al. 2006). Some studies suggest that cognitively healthy individuals demonstrating elevated β -amyloid accrual are at higher risk of cognitive decline (Doraiswamy et al 2014; Resnick et al. 2010; Villemagne et al. 2011), and therefore may be candidates for the trial of disease-modifying interventions. However, the invasive nature of PET neuroimaging and the low pretest probability precludes its routine use as a screening tool for identifying at risk individuals.

Subjective cognitive impairment (SCI) is a characteristic of the pre-dementia syndrome, mild cognitive impairment (MCI; Albert et al. 2011). However, some cognitively normal individuals report subjective impairment without deficits on testing of objective cognition. It is possible that these symptoms may be an early indicator of developing AD pathology (Jonker et al. 2000). Some studies report an association between SCI and β -amyloid by PET imaging (Amariglio et al. 2012; Merrill et al. 2012; Perrotin et al. 2012), whereas others have

not (Buckley et al. 2012; Chetelat et al. 2010; Pike et al. 2011). Furthermore, subjective memory is complicated by its relationship to anxiety and depression (Buckley et al. 2013; Comijs et al. 2002), which may occur coincidentally with, or separate from the prodrome of dementia. Despite the complexity overlaid by mood disorders, there is clearly a subset of people with SCI who have evidence of disease (Amariglio et al. 2012; Perrotin et al. 2012).

A variety of methods have been employed to determine cognitive self-assessments, from a single question to more comprehensive surveys (Abdulrab and Heun 2008). Most studies focus on questions around memory performance; tools employed include the Memory Complaint Questionnaire (MAC-Q; Crook et al. 1992) and the Memory Functioning Questionnaire (MFQ; Gilewski et al. 1990). The method used to determine subjective cognition may be an important factor in its relevance to prodromal dementia and its relationship to confounders. The significant variation in methods of defining SCI may explain, in part, the variability in findings between studies. Thus, given the poor specificity of subjective memory it would be beneficial to explore other symptoms relevant to cognitive decline and dementia.

Research on episodes of sub-syndromal delirium in hospital (e.g. symptoms of disorientation, confusion or clouded consciousness) have suggested that these symptoms lead to poor long-term cognitive and functional outcomes (Cole et al. 2003; Nelson et al. 2006). In community-dwelling elderly populations, episodes of delirium also increase the risk of developing cognitive impairment and dementia (Davis et al. 2012; De Lange et al. 2013).

Confusion is a common symptom encountered in clinical practice of medicine, especially in the elderly. It may be a feature of a variety of organic and psychiatric pathologies, including dementia, delirium and mood disorders (Bayne, 1978; Downing, Caprio, & Lyness, 2013;

Riedel-Heller, Schork, Matschinger, & Angermeyer, 2000; Thurston, 1997). However, there is a deficiency in the literature regarding a precise definition of confusion. In addition, clinicians and nurses do not appear to have a unified view on what this symptom entails (Simpson, 1984). Investigators identified early stage ‘confusional states’ described by both care-givers and patients themselves are characterised by disorientation, failure of memory (e.g. unable to place people), incompetence and anxiety around decision making and word-finding difficulties (Berry, 2014). Despite the lack of a strong definition, there is extensive research and published case-studies on this common presenting complaint.

Much research on confusion presenting in the elderly focuses on the acute confusional state of delirium, defined as a syndrome of disturbed cognition and attention (Cavagnoud, Losson, & Rossel, 2012; Han et al., 2013; Regazzoni, Aduriz, & Recondo, 2000; Rockwood, 1989). Delirium in hospitalised patients has been shown repeatedly to lead to higher rates of nursing home placement at discharge (Cole & Primeau, 1993; Dasgupta & Brymer, 2014) and greater declines in cognitive performance on long-term follow-up (Francis & Kapoor, 1992). In addition, studies have shown that those with pre-existing dementia are likely to experience an acceleration in decline after an episode of delirium (Fong et al., 2009). A study investigating the relationship between delirium, dementia and neuropathology with long-term follow-up, confirmed previous studies that delirium is a significant risk factor for deteriorating cognition (Davis et al., 2012). Induction of a delirium-like neuronal bioenvironment by administration of Lipopolysaccharide in animal models, have shown accumulation of A β 1-42 in the hippocampus and cerebral cortex of mice through the induction of γ - and β -secretases (Lee et al., 2008). These findings support the theory of inflammation as major component in amyloidogenesis (Perry, 2004), and may account for the association of delirium, often ascribed to an acute inflammatory state, with subsequent cognitive deterioration.

In this study, we investigate the cross-sectional relationship of β -amyloid and subjective cognitive impairment, determined using three different methods. We investigated the subjective state of “feeling confused”, in addition to more traditional questions on memory, involving subjects’ assessment of their memory compared to others and the MAC-Q. We hypothesized that the value of SCI for predicting β -amyloid load by ^{18}F -florbetaben PET scanning may differ for the various methods employed to probe subjective cognition.

2. METHODS

2.1 Study participants

The Women’s Healthy Ageing Project (WHAP) is a population-based longitudinal study that began in 1991 as the Melbourne Women’s Midlife Health Project. Recruitment for the study was performed using random digit dialling, resulting in a sample of 438 white women from the Melbourne metropolitan area without the influence of volunteer bias or clinic referral. Women were eligible for inclusion in the original cohort if they were ages 45-55 years and Australian born, had menstruated 3 months before recruitment, and had not taken oestrogen-containing hormone replacement therapy. A detailed description of the WHAP design is reported elsewhere (Szoek et al. 2013). The data used in this study was collected in 2012/13 and included baseline lifestyle, psychosocial data and a comprehensive neuropsychological assessment. Measures of mood used in this study include the Centre for Epidemiological Studies Depression scale (CESD) and Affectometer questionnaire (Kamman and Flett 1983).

All participants were offered neuroimaging in 2012/13, which included structural 3-T Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) imaging

using the radio ligand ^{18}F -Florbetaben for quantification of β -amyloid *in vivo*. A total of 126 participants had PET scanning performed in 2012/13.

The evaluations of subjects with abnormal findings on neuropsychological testing at any stage were reviewed by a panel consisting of behavioural neurologists, neuropsychologists and study nurses. Subjects were diagnosed as either cognitively normal, MCI or AD by consensus based on clinical assessment, informant reports and the results of neuropsychological assessment (Szoek et al. 2013).

2.2 Protocols and ethics

Standard protocol approvals, registration and patient consent were gained. All study protocols were approved by the Human Research Ethics Committee at the University of Melbourne (approval number 1034765.3). All subjects provided signed informed consent to participate in the study and in the imaging protocols.

2.3 Subjective cognitive impairment

The assessment of subjective memory and cognition was performed using three methods in 2012/13. Firstly the MAC-Q (Crook et al. 1992), a set of 6 questions (MCQ1–MCQ6) with scaled responses were used. The MAC-Q targets age-related changes by asking the subject to rate current abilities compared to the subject's own abilities during their early 20s. Responses were dichotomized into those with subjective cognitive impairment (SCI), i.e. those that responded 'much poorer now' or 'somewhat poorer now', and those with no subjective cognitive impairment (NSCI), i.e. those that responded 'about the same' and 'somewhat better now', for each question. A sum of the responses generates a score ranging from 7 (no concern) to 35 (highest concern) that quantifies the degree of memory complaint. A question

on confusion from the Affectometer (Kamman and Flett 1983) was also assessed, ‘How often in the last 7 days have you felt confused?’ (confused). Responses were dichotomized into SCI, i.e. those that answered ‘sometimes’, and NSCI, i.e. those that answered ‘hardly ever’. A single question from the Geriatric Depression Scale (GDS) was examined (GDSq10), ‘Do you feel you have more problems with memory than most?’ with SCI being those that responded ‘yes’ and NSCI those that responded ‘no’.

2.4 ^{18}F -Florbetaben PET imaging

Amyloid imaging was performed by ^{18}F -florbetaben PET scanning, conducted at the Austin Health Centre for PET. Subjects were given 250 MBq of ^{18}F -florbetaben intravenously, with 20 minute acquisition commencing 90 minutes after injection. Details of the PET acquisition protocol are previously described elsewhere (Rowe et al. 2008). PET images were co-registered with each individual’s MRI and regions of interest (ROI) were drawn on. In cases where MRI was not obtained ROI were drawn directly onto the PET images by an operator blind to the subjective cognitive status of the individual. Standardized uptake values (SUV) were calculated for all brain regions examined and the SUV ratios (SUVR) generated by normalizing regional SUV by that of the cerebellar cortex at the approximate radiotracer steady-state. Regions of interest examined in this study include the ventrolateral prefrontal (prefrontal), the lateral temporal (temporal) region and the posterior cingulate and precuneus collectively (PCP). Neocortical SUVR, a global measure of β -amyloid burden, is expressed as the average SUVR of the area-weighted mean of the frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate regions.

2.5 Genotyping

Participants had apolipoprotein E (*APOE*) genotype determined by direct sequencing and dichotomized as an *APOE* $\epsilon 4$ carrier (*APOE* $\epsilon 2/\epsilon 4$, *APOE* $\epsilon 3/\epsilon 4$ and *APOE* $\epsilon 4/\epsilon 4$) or a non-carrier.

2.5 Statistical analysis

Of the 126 participants that had PET imaging performed, 124 had data available at the time of data collection, 7 participants were excluded from the analysis due to diagnoses of MCI or AD, leaving 117. A further 5 participants had incomplete data for the item ‘confused’ and were therefore removed from the analysis, leaving 112 participants. A total of 6 subjects had incomplete data for various MAC-Q items, leaving 109 subjects in these analyses. For GDSq10, 5 subjects were removed owing to incomplete data, leaving 112 for analysis.

The relationships between subjective cognition and ^{18}F -Florbetaben (^{18}F -FBB) uptake were analysed using rank-order, nonparametric statistical methods. In the first step, participants were grouped based on response to subjective cognition questions in each instance as SCI and NSCI and the dichotomized measures were used to evaluate group difference on variables of interest. Characteristics of SCI and NSCI individuals were compared using χ^2 test statistics for categorical variables or independent t tests for continuous variables. A nonparametric test, 2-sample Mann-Whitney, was employed for global and regional PET measures as normality assumptions were violated. The groups were compared for age, years of education, *APOE* $\epsilon 4$ carrier status, CESD and MMSE scores, PET positive classification (using the cut-off ≥ 1.4 for global amyloid; Darby et al. 2011) and global and regional mean PET SUVR. Differences in ^{18}F -FBB uptake were also explored by categorising the cohort into tertiles (lowest, middle or highest third) for global PET SUVR.

In the second step, the significant group differences were analysed further to assess the relationship between subjective cognition and global and regional ^{18}F -FBB uptake using multiple linear regression, controlling for demographic variables (*APOE* $\epsilon 4$ status, CESD score and age). One outlier with high ^{18}F -FBB retention was removed from the data to preserve the integrity of the regression models. All analyses were repeated including the outlier and statistical significance was preserved. Histograms and Q-Q plots were inspected for distribution of values. Levene's test was used to check for homogeneity of variance. Multicollinearity was tested using a correlation matrix with the upper threshold set at 0.7. Residual plots were used to inspect linearity, homoscedasticity and independences of residuals. The significance level was set to $p < 0.05$. All data analyses were performed using the IBM Statistical Package for Social Sciences v20 software for Windows.

3. RESULTS

3.1 *Comparison of those with and without β -amyloid imaging*

At the time of analyses, data was collated for 236 participants in 2012/13 phase of the project. Of those, 124 had PET scans performed at the time of data collection. There was no difference ($p = 0.56$) in mean age between those that did ($m = 69.3$ years, $SD = 2.8$) and those that did not ($m = 70.0$ years, $SD = 2.6$) undergo PET scanning. Nor was there a significant difference ($p = 0.31$) in proportion of *APOE* $\epsilon 4$ positive subjects between those that did ($n = 41$, 33%) and those that did not ($n = 26$, 27%). Of note, there was a significant difference ($p < 0.05$) in years of education between those with imaging ($m = 12.8$ years, $SD = 3.6$) and those without ($m = 11.8$ years, $SD = 3.2$). Characteristics of the 117 cognitively healthy participants that underwent PET scanning in 2012 are presented in Table 1.

3.2 Relationship of ^{18}F -FBB uptake with *APOE* $\epsilon 4$, age, years of education and mood

The effect of *APOE* $\epsilon 4$ carrier status on ^{18}F -FBB PET binding levels was assessed using linear regression modelling with *APOE* $\epsilon 4$ carriage found to be a significant predictor of global SUVR, $F(1,116) = 10.7, p = 0.001$. In addition, *APOE* $\epsilon 4$ carriage could predict lateral temporal SUVR, $F(1,115) = 14.3, p < 0.001$, PCP SUVR, $F(1,115) = 7.3, p < 0.05$, and prefrontal SUVR, $F(1,115) = 10.3, p < 0.05$. Linear regression analyses could not be used to examine age, years of education and mood as the data violated the assumptions of independence of errors and homoscedasticity. Spearman correlations found that age was not associated with global ^{18}F -FBB uptake, $r_s = 0.02$ ($p = 0.84$), nor lateral temporal, $r_s = 0.11$ ($p = 0.24$), PCP, $r_s = 0.07$ ($p = 0.45$) or prefrontal, $r_s < 0.01$ ($p = 1.00$). Spearman correlations between ^{18}F -FBB uptake and years of education found that the latter was not related to global amyloid, $r_s = -0.07$ ($p = 0.47$), nor with lateral temporal, $r_s = -0.06$ ($p = 0.51$), PCP, $r_s = -0.08$ ($p = 0.39$) or prefrontal SUVR, $r_s = -0.05$ ($p = 0.62$). The effect of mood on ^{18}F -FBB binding levels was assessed using the 20-item CESD score. Spearman rank correlation found that mood was not predictive of global ^{18}F -PET SUVR, $r_s(112) = 0.07, p = 0.47$, neither was it associated with lateral temporal $r_s(112) = 0.10, p = 0.30$, PCP, $r_s(112) = 0.07, p = 0.49$, nor prefrontal uptake, $r_s(112) = 0.08, p = 0.40$. A summary of these analyses is presented in Table 2.

3.3 Relationship of global ^{18}F -FBB uptake with subjective cognition

The relationship between subjective memory impairment determined by the MAC-Q with amyloid load was analysed using simple linear regression. The total MAC-Q score was not a significant predictor of global SUVR, $F(1,108) = 0.9, p = 0.34$. In addition, no associations were found to global β -amyloid when examining the individual components of the MAC-Q (data not shown). Those reporting SCI by the item GDSq10 did not have a significantly

higher global amyloid compared with those denying memory problems, 1.11 (SD = 0.2) for SCI and 1.20 (SD = 0.2) for NSCI ($p = 0.06$).

Subjective impairment defined as feeling confused was found to be a predictor of global ^{18}F -FBB uptake, $F(1,111) = 8.9$, $p < 0.01$. In addition, when participants were grouped by global ^{18}F -FBB SUVR tertile (lowest, middle or highest third) and whether they had felt confused in the last 7 days, those feeling confused ‘sometimes’ had a higher portion in the upper tertile than those confused ‘hardly ever’, and this difference was statistically significant, $\chi^2(2) = 10.01$, $p < 0.01$. A summary of these analyses are presented in Figure 1.

3.4 Relationship of global and regional ^{18}F -FBB uptake with reported confusion

To further assess self-reported episodes of confusion and its predictive value for neocortical β -amyloid, multivariable linear regressions for global and regional ^{18}F -FBB uptake were performed controlling for age, mood and *APOE* $\epsilon 4$ status. Although rank-order correlations found that CESD scores were not associated with global β -amyloid load, regression analysis of the mood score for predicting confusion was significant, $\chi^2(4) = 6.85$, $p < 0.01$, accounting for 10% (Nagelkerke R^2) of variation and therefore was included in these analyses.

Despite age not being a significant predictor of β -amyloid in our data set, given substantial prior evidence for a relationship between these two variables, it was also included in these analyses. Years of education was not a significant predictor for global or regional amyloid load, nor for SCI and therefore was not included in the models. A summary of the results of multivariable regression analyses, presented in Table 3, show that reported confusion was correlated with ^{18}F -FBB uptake globally and in all regions analysed ($p < 0.005$).

To further explore the effect of mood on reports of SCI, a logistic regression was performed including CESD score and ^{18}F -FBB uptake. The logistic regression model was statistically significant, $X^2(2) = 14.76$, $p = 0.001$, and both variables were significant predictors for reporting confusion. When the mood score was removed from the model, β -amyloid load remained a significant predictor, suggesting that both these variables may independently contribute to the symptom of confusion.

4. DISCUSSION

This study examined the relationship between amyloid accrual and self-reported measures of memory and cognition in a cohort of community-dwelling, cognitively normal elderly. The key finding that self-reports of confusion was related to β -amyloid accrual measured by ^{18}F -Florbetaben PET suggests that subjective cognitive symptomatology may be related to AD-pathology. Correlations of self-reported confusion were found with global β -amyloid, in addition to regional accrual in the lateral temporal, ventrolateral prefrontal, posterior cingulate and precuneus cortices. These findings are consistent with a recent publication by Perrotin et al. (2012), who identified a relationship between general memory complaints and β -amyloid using Pittsburgh compound B uptake in the prefrontal and PCP cortices in cognitively-normal individuals. In our cohort, the strongest association was seen for the temporal neocortex. This area of the brain is one of the first sites to demonstrate β -amyloid plaque formation at histology (Thal et al. 2002), and the findings of our regional analyses support the notion that subjective confusion may be an indicator of early disease.

In our study, there was no association seen between other measures of subjective cognition related to memory and β -amyloid burden. It may be that more traditional indicators of SCI,

“memory performance compared to peers” and the MAC-Q, probe aspects of cognition that are highly influenced by personality and mood (Comijs et al. 2002). For example, Buckley et al. (2013) found a significant association between perceived severity of SCI (MAC-Q scores) with mood and anxiety scores, but not β -amyloid, which is also consistent with our findings reported here.

The method used to determine SCI is an important factor in its clinical utility. Amariglio et al. (2012) found a relationship between regional β -amyloid in those reporting subjective memory impairment compared to their peers but not compared to their younger selves (20 years prior). Examining further, the same study assessed cerebral β -amyloid and subjective memory in healthy subjects using a battery of subjective memory questionnaires. While a composite subjective memory score was related to β -amyloid burden, few associations were found with individual SCI tools, with the exception of subscales relating to frequency of forgetting and executive functioning, which were also significant (Amariglio et al. 2012).

We have identified that reporting confusion is related to AD-pathology in cognitively-normal individuals, whereas other markers of SCI were not. It may be that self-reported confusion is more specific for amyloid pathology than other markers of subjective *memory* impairment. Whilst highly subjective, it is likely that individuals reporting confusion are, in truth, reporting a ‘symptom’ of disease, rather than self-assessments of memory performance, which may be greatly influenced by factors unrelated to dementia pathology. Self-reported confusion may represent early impairment in domains of higher-order thinking, comprehension or certain aspects of memory. To fully explore the relationship between episodes of confusion and disease risk, examination of objective cognitive measures and long term follow-up are required.

Pietrzak et al. (2014) reported that anxiety symptoms were strongly related to decreased executive functioning, irrespective of other risk factors including a high β -amyloid load. In our cohort, mood was found to be a significant predictor for reporting confusion. Although CESD score was not associated with β -amyloid burden, both CESD score and global ^{18}F -FBB uptake were significantly associated with reporting confusion when included together in a logistic regression (see Appendix A). This suggests that self-reported confusion may relate to either early AD or presence of mood disorder. As previously discussed, the association between SCI and mood is well documented (Pietrzak et al. 2014; Rowe et al. 2010), and it may be that delineation of the presence of a mood disorder is necessary to isolate those with developing Alzheimer's pathology.

This study has some limitations. The sample size is small, although this number is respectable for a community cohort in a longitudinal study with amyloid imaging (Rowe et al. 2010). It should also be emphasized also that the analyses presented here are exploratory in nature and are not corrected for the number of comparisons performed. As such, validation of these findings in larger cohorts with broader sociodemographic makeup is vital. Although the cohort reflected a random community sample at baseline (1990), there has been subsequent cohort attrition which may contribute to bias. Further, participants that took part in neuroimaging were of higher educational attainment than those who declined. In our study cohort, participants answered a dichotomous question on experiencing episodes of confusion. However, the lack of agreed definition of confusion and varying participant interpretation of the term, may influence how the question is answered. Probing what is understood as confusion, and elucidation of a specific question or aspect of this symptom, may assist in developing a more specific, early indicator of Alzheimer's Disease. Finally, this study was

performed in an entirely female sample, meaning that further studies on mixed-gender cohorts are required to extend the applicability of findings to the general population. The usefulness of SCI and the symptom of confusion may be different in an age-matched male population, considering previous findings that a given amount of AD-pathology may have differing clinical expression according to gender (Barnes et al. 2005). However, there is evidence that SCI, particularly in females, indicates an increased risk of developing dementia (Peres et al. 2011), and these remain important findings. Our findings support the growing body of evidence that confusion is an important symptom in the elderly that should not be dismissed, and may be an indicator of developing neurodegenerative disease.

The design of simple and accurate measures for identifying subjects at risk of developing AD is essential for trials of disease-modifying interventions. Our results contribute to the growing collection of evidence that subjective cognitive impairment may herald Alzheimer's Disease pathology in cognitively-normal people. Employing the appropriate question to probe subjective cognition is an important consideration as it may affect the clinical utility of this symptom. Memory is highly subjective, whereas asking specifically about confusion may yield greater value as a marker of amyloid pathology. It will be important to further examine the nature and context of confusion as reported by participants, and to examine the relationship of reported confusion with objective performance across different domains of cognition. Long-term functional and cognitive follow-up of subjects is required to assess the predictive value of SCI for the development of clinical disease. Additional amyloid imaging at follow-up will also provide means for assessing SCI as an indicator for progression of AD pathology.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1

Descriptive characteristics of the cognitively normal subjects of the Women's Health Ageing Project that underwent PET scanning during the period 2012/13

Characteristic	Mean (SD) / Frequency (%)
Age	69.2 years (2.5)
Years of education	13.0 years (3.6)
Education > 12 years	67 (57%)
<i>APOE</i> ε4 carriers	37 (32%)
CESD score	7.9 (6.9)
MMSE score	28.6 (1.3)
¹⁸F-FBB PET imaging	
PET SUVR mean	1.13 (0.19)
PET SUVR > 1.4	12 (10%)
Subjective cognitive impairment	
Confused	18 (15%)
More memory problems than most (GDSq10)	9 (8%)
MAC-Q score	25.5 (4.2)

Abbreviations: SD, standard deviation; CESD, Centre for Epidemiological Studies

Depression scale; MMSE, Mini-mental State Exam; FBB, florbetaben; PET, positron emission tomography; SUVR, standardized uptake value ratio

Table 2

Summary of Spearman-rank correlations and univariate linear regression models for ^{18}F -Florbetaben uptake

Characteristic	Global	Temporal	PCP	Prefrontal
Age	$r_s = 0.02$	$r_s = 0.11$	$r_s = 0.07$	$r_s = 0.00$
<i>APOE</i> $\epsilon 4$ positive	$F(1,116) = 10.7^{**}$	$F(1,115) = 14.3^{**}$	$F(1,115) = 7.3^*$	$F(1,115) = 10.3^*$
Years of education	$r_s = -0.07$	$r_s = -0.06$	$r_s = -0.08$	$r_s = -0.05$
CESD score	$r_s = 0.07$	$r_s = 0.10$	$r_s = 0.07$	$r_s = 0.08$

Abbreviations: PCP, posterior cingulate and precuneus; CESD, Centre for Epidemiological Studies Depression scale

$^{**}p = 0.001$; $^*p < 0.05$

Table 3

Correlations between subjective cognitive impairment by feeling confused and ^{18}F -Florbetaben uptake in the global neocortex and 3 key ROIs

Cortical region	Correlation	
	Standardised β coefficient	<i>P</i> value
Global	0.303	0.002
Lateral temporal	0.321	0.001
Posterior cingulate and precuneus	0.281	0.004
Ventrolateral prefrontal	0.279	0.004

Abbreviations: ROIs, regions of interest

Effects of age, *APOE* $\epsilon 4$ carrier status and CESD score were included in the models

APPENDIX

Table 1. Logistic regression model for reporting confusion including variables CESD score and global ^{18}F -FBB uptake

Predictor	β	$SE\ \beta$	Wald's χ^2	df	p	e^β (odds ratio)
Constant	-7.771	2.018	14.829	1	0.000	NA
CESD Score	0.087	0.036	6.023	1	0.014	1.091
^{18}F -FBB SUVR	4.704	1.689	7.760	1	0.005	110.394
Test			χ^2	df	p	R^2
Model evaluation						
Test of model coefficients			14.762	2	0.001	
Cox & Snell						0.125
Nagelkerke						0.212

Abbreviations: CESD, Centre for Epidemiological Studies Depression scale; FBB, Florbetaben; SUVR, standardized uptake value ratio

Table 2. Logistic regression model for reporting confusion including the variable global ^{18}F -FBB uptake

Predictor	β	$SE\ \beta$	Wald's χ^2	df	p	e^β (odds ratio)
Constant	-2.437	0.437	31.038	1	0.000	0.002
^{18}F -FBB SUVR	4.083	1.537	7.061	1	0.008	59.339
Test			χ^2	df	p	R^2
Model evaluation						
Test of model coefficients			6.922	1	0.009	
Cox & Snell						0.059
Nagelkerke						0.102

Abbreviations: FBB, Florbetaben; SUVR, standardized uptake value ratio

Fig. 1. (A) Trendline for MAC-Q scores versus global β -amyloid by ^{18}F -FBB uptake shows no significant association; (B) Box and whisker plots of global ^{18}F -FBB uptake by response to the item GDSq10 ('Do you feel you have more problems with memory than most?'); (C) Proportion of subjects within each ^{18}F -FBB SUVR tertile for those feeling confused 'hardly ever' (NSCI) and those feeling confused 'sometimes' (SCI) in the last 7 days.

Figure 1

G.E. McCluskey