Hippocampal hypometabolism in older adults with memory complaints and increased amyloid burden

ABSTRACT

Objective: To identify the functional and pathologic correlates underlying subjective memory complaints (SMCs) in cognitively normal older adults.

Methods: Two hundred fifty-one older adults underwent resting-state fluorodeoxyglucose (FDG)-PET and Pittsburg compound B-PET β-amyloid (Aβ) imaging and filled out a questionnaire regarding SMCs. Participants were classified into 2 groups based on their Aβ burden. Age-adjusted voxel-wise correlations were used to examine SMCs, amyloid status (Aβ+ vs Aβ−), and the interaction between SMCs and Aβ status as predictors of metabolism. Region-of-interest (ROI) analyses were performed to confirm the whole-brain analyses and to test for additional covariates.

Results: Greater SMCs correlated with decreased FDG metabolism in the bilateral precuneus, bilateral inferior parietal lobes, right inferior temporal lobe, right medial frontal gyrus, and right orbitofrontal gyrus. A significant interaction effect between SMCs and amyloid burden was found such that Aβ+ individuals with increased complaints had decreased FDG metabolism in the bilateral medial temporal lobes. ROI analyses confirmed the voxel-wise analyses result in that decreased precuneus metabolism was associated with greater SMCs regardless of Aβ status, age, or thickness, whereas the relationship between hippocampal metabolism and SMCs was a function of Aβ, even after adjustment for age, hippocampal volume, or depressive symptoms.

Conclusions: These data show the relevant role of posterior and anterior midline regions in SMCs in older individuals. Decreased hippocampal metabolism may be a specific marker of subclinical changes in cognition due to amyloid pathology. However, longitudinal studies are needed to determine whether our findings foreshadow clinical decline.

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer disease; CN = cognitively normal; FDG = fluorodeoxyglucose; FDR = false discovery rate; GDS = Geriatric Depression Scale; MFG = middle frontal gyrus; MGH = Massachusetts General Hospital; MTL = medial temporal lobe; PiB = Pittsburg compound B; ROI = region of interest; SMC = subjective memory complaint.

Subjective memory complaint (SMC) is defined by self-reports of memory worsening and objective memory performance in the normal adjusted range. SMCs are common in the elderly population without dementia, with an estimated prevalence range between 22% and 56%,1 and have been associated with increased risk of incident Alzheimer disease (AD).2 Despite the high prevalence of self-perceived changes in memory among older adults, relatively little is known about its functional and pathologic correlates, especially in the preclinical stages of AD. This information is crucial because SMCs alone may have insufficient sensitivity and specificity to predict the development of dementia.

With regard to SMCs and β-amyloid (Aβ; one hallmark of AD pathology most commonly used to define the preclinical stage), previous studies have found conflicting results. Whereas most studies have reported an association between SMCs and Aβ,3-6 others could not...
demonstrate this relationship. Previous studies with fluorodeoxyglucose (FDG)-PET, a biomarker supposed to reflect neuronal integrity, have demonstrated hypometabolism when comparing cognitively normal (CN) individuals with and without SMCs, but the results have been inconsistent as to which brain regions show hypometabolism, e.g., the precuneus, parietotemporal and parahippocampal gyrus, or periventricular region. These inconsistent patterns of FDG-PET hypometabolism could be due to several factors, including the use of different techniques to measure SMCs. In addition, although FDG metabolism has been studied in groups of individuals with and without SMCs, correlation between continuous measures of self-reported complaints and FDG metabolism has never been assessed. Because the degree of memory complaints varies greatly within older adults, investigating the changes in metabolic function that covary with self-appraisal of memory function may shed some additional light on the brain substrate underlying SMCs. Lastly, the contribution of Aβ pathology to the functional metabolic correlates of SMCs in CN elders also remains to be elucidated. This information would improve our ability to understand whether SMCs may have prognostic meaning.

The objective of the present study is to further our understanding of the functional and pathologic substrate underlying SMCs by investigating the relationship between self-reported measures of memory function and functional brain metabolism in a large cohort of CN older adults with known Aβ status. We hypothesized that the metabolic consequences of SMCs might depend on the presence of Aβ pathology and that the occurrence of different FDG patterns might help us better distinguish between SMCs due to decline in cognitive aging from preclinical AD.

METHODS Subjects. The study included 251 English-speaking individuals (table 1) enrolled in the Harvard Aging Brain Study at the Massachusetts General Hospital (MGH) and the Brigham and Women’s Hospital. Inclusion criteria were a Mini-Mental State Examination15 score of 27 to 30 (inclusive with educational adjustment), a global Clinical Dementia Rating16 score of 0, and a Geriatric Depression Scale (GDS, short form)14 score of <6. Exclusion criteria were a history of neurologic or major psychiatric disorder, history of head trauma with loss of consciousness, contraindications for MRI scanning, use of medications that affect cognitive function, severe cardiovascular disease, alcohol or substance abuse, or known cerebrovascular disease (as determined by a Hachinski Ischemia Score15 >4 or presence of cortical infarct, multiple lacunar strokes, or extensive white matter hyperintensities on structural MRI).

Standard protocol approvals, registrations, and patient consents. This study was approved by and conducted under the auspices of the Partners Human Research Committee at the Brigham and Women’s Hospital and MGH (Boston, MA). Informed written consent was obtained from every participant before the experimental procedures.

Subjective memory measures. SMCs were measured with the 18 first questions in the General Frequency of Forgetting Subscale of the Memory Functioning Questionnaire. In this subscale, the person is asked, “How often does remembering or doing the following things present a problem for you?” On each item, the person rates his/her subjective experience on a Likert scale ranging from 1 (always) to 7 (never). The scale was then transformed to numbers ranging from 0 to 6, and the raw scores were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of the whole sample and by groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>No.</td>
<td>251</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.3 (6.2)</td>
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<tr>
<td>Female, %</td>
<td>59</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.7 (3.1)</td>
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<tr>
<td>MMSE score</td>
<td>28.9 (1.1)</td>
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<tr>
<td>Amyloid</td>
<td>1.17 (0.2)</td>
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<tr>
<td>APOE+ , %*</td>
<td>29.7</td>
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<tr>
<td>GDS adjusted</td>
<td>1.1 (1.1)</td>
</tr>
<tr>
<td>Objective memory</td>
<td>13.6 (3.4)</td>
</tr>
<tr>
<td>Subjective memory</td>
<td>5.2 (0.9)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ = β-amyloid; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination. All values (except sex and APOE +4) represent mean ± SD. *Missing data for 11 APOE+ and 4 APOE- individuals.
converted to z scores for each participant with the use of the mean and SD from the whole group. Finally, z scores were then reversed by multiplying each value by −1 so that a higher score indicates increased complaints.

**Aβ Pittsburgh compound B-PET processing.** Pittsburgh compound B (PiB)-PET data were processed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK) using a protocol similar to that described in our previous publication.17 PiB images were realigned, and the first 8 minutes of data were averaged and used to normalize data to the Montreal Neurologic Institute 18F-fluorodeoxyglucose template. Distribution volume ratio images were created with Logan plotting (40- to 60-minute interval, gray matter cerebellum reference region). An aggregate of cortical regions that typically have elevated PiB burden in patients with AD, including frontal, lateral temporal and parietal, and retroplenial cortices, was used to extract a mean PiB value for each participant. A gaussian mixture model approach, as described previously,18 was used to classify individuals as having high or low Aβ burden. The model estimated a cutoff of PiB distribution volume ratio >1.2 for the high-Aβ group.

**FDG-PET acquisition and processing.** FDG was acquired at the MGH PET department (Boston, MA) according to previously published guidelines.19 FDG was acquired from 45 to 75 minutes after a 5- to 10-mCi bolus injection 6 times in 5-minute frames. To evaluate the anatomy of PET binding, each individual PET data set was rigidly coregistered to the participant’s MRI data with SPM8. Additional preprocessing steps included spatial normalization to the Montreal Neurologic Institute space (resampled voxel size 2 × 2 × 2 mm) with the parameters estimated from the corresponding T1-weighted MRI and quantitative scaling with the cerebellum gray matter as reference to obtain standardized uptake volume ratio images. The resulting images were used in the correlation analyses with the SMC score.

**Structural data: Acquisition.** T1-weighted structural images were acquired with a multiecho magnetization-prepared rapid gradient echo sagittal-oriented with the following parameters: repetition time = 2,200 milliseconds; inversion time = 1,100 milliseconds; echo time = 1.54, 3.36, 5.18, and 7 milliseconds; flip angle = 7°; field of view = 230 × 230 mm; matrix size = 192 × 192; number of excitations = 1; and 1.2 × 1.2 × 1.2-mm voxels.

**Region-of-interest analysis.** Structural images were processed with Freesurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu) to identify gray, white, and pial surfaces to permit region-of-interest (ROI) parcellation based on the Desikan-Killiany atlas. Manual quality control of the automated segmentation was performed on all participants. Three participants, 2 Aβ− and 1 Aβ+, were excluded from ROI analyses because of insufficient MRI quality. The cortical ribbon and subcortical ROIs defined by MRI were transformed into the FDG-PET native space to obtain FDG standardized uptake volume ratio values in the Freesurfer-defined ROI. Data were averaged within each right-left hemisphere ROI pair. ROIs were selected according to the voxel-wise results to control for additional covariates, including structural data.

**Statistics.** Differences in demographic and neuropsychological measures between Aβ− and Aβ+ individuals were examined with independent-sample t tests or χ² tests (sex and APOE e4) using SPSS 23 (SPSS Inc, Chicago, IL). The general linear model, univariate analysis, was used to examine SMCs (continuous variable), amyloid status (Aβ+ vs Aβ−), and the interaction between SMCs and Aβ status as predictors of cerebral metabolic rate for glucose consumption measures. Age was controlled for in all analyses. Exploratory SPM8 t maps were conducted with a threshold of p < 0.05, corrected for multiple comparisons with a voxel-level false discovery rate (FDR) method. Analyses were done with SPM8 implemented in Matlab R2014b (Mathworks, Natick, MA). Confirmatory ROI analyses, investigating the impact of additional covariates (age thickness, GDS, and amyloid) on the associations between FDG and SMCs, were conducted in selected ROIs following the voxel-wise results. ROI analyses were done offline with general linear model univariate analyses in SPSS version 23 (SPSS Inc, Chicago, IL).

**RESULTS** Participants. There were no significant differences between the Aβ− and Aβ+ individuals on most demographic variables (table 1). Because the Aβ− individuals were slightly younger than the Aβ+ individuals, age was included as covariates in all analyses. In addition, a significant difference between Aβ− status and SMCs was found such that individuals with increased amyloid burden had greater SMCs.

SMCs are related to decreased FDG metabolism in associative neocortical regions. Whole-brain voxel-wise correlations (pFDR <0.05 corrected, equal to an uncorrected p = 0.0003, r = 3.45) with SMCs (continuous variable) used as a predictor of cerebral metabolic rate for glucose consumption measures (controlling for age) demonstrated significant correlations in the bilateral precuneus, bilateral inferior parietal lobes, right inferior temporal lobe, and right middle and inferior frontal gyrus, which extended into orbitofrontal gyrus (figure 1A). Coordinate details are presented in table e-1 at Neurology.org. After GDS was added, the model did not survive correction for multiple comparisons, indicating that part of the effect may be due to depressive symptoms. Post hoc univariate analyses in the left precuneus and right middle frontal gyrus (MFG; see white circles in figure 1A) demonstrated that more complaints (increased z score) were related to decreased FDG metabolism across all participants (figure 2, A and B; left precuneus [F1,246 = 18.4, p < 0.001]; right MFG [F1,246 = 10.7, p = 0.001]). A nonsignificant interaction effect was found between amyloid and SMCs (left precuneus [F1,246 = 0.6, p = 0.45]; right MFG [F1,246 = 1.7, p = 0.2]). No significant regional hypermetabolism associated with SMCs was found.

SMCs are related to decreased FDG metabolism in hippocampal and limbic regions in CN Aβ+ individuals. SMCs by amyloid status interactions were found bilaterally in the medial temporal lobe (MTL), including parahippocampal gyrus, hippocampus, and entorhinal cortex, and other limbic areas, including the mid cingulum (figure 1B), with the use of a pFDR <0.05 corrected, equal to an uncorrected p value = 0.00002, F = 8.1. Coordinate details...
presented in table e-2. Post hoc univariate analyses in the right hippocampus and left mid cingulum (see green circles in figure 1B) showed a significant interaction effect between amyloid and SMCs (right hippocampus $F_{1,246} = 23.1, p < 0.001$; left mid cingulum $F_{1,246} = 16.0, p < 0.001$; figure 2, C and D). In these regions, the $\mathrm{A\beta}^+$ individuals demonstrated a significant correlation between SMCs and FDG metabolism such that more complaints were related to decreased FDG metabolism (right hippocampus $F_{1,58} = 8.3, p = 0.006$; left mid cingulum $F_{1,58} = 5.9, p < 0.001$). In contrast, $\mathrm{A\beta}^-$ individuals demonstrated a significant relationship between complaints and FDG metabolism (right hippocampus $F_{1,246} = 23.1, p < 0.001$; left mid cingulum $F_{1,246} = 16.0, p < 0.001$; figure 2, C and D).
Figure 2  FDG metabolism plots

Extracted FDG metabolism in (A) left precuneus and (B) right middle frontal gyrus (see white circles from figure 1A) showing the main effect of SMCs. In these regions, decreased glucose metabolism relates to increased SMCs regardless of amyloid status. Extracted FDG metabolism in (C) right hippocampus and (D) left mid cingulum (see green circles in figure 1B) demonstrating the SMCs by amyloid interaction. In Aβ+ individuals (triangles/solid line), having more complaints is related to decreased glucose metabolism. Aβ = β-amyloid; FDG = fluorodeoxyglucose; SMC = subjective memory complaint; SUVR = standardized uptake volume ratio.

hippocampus \(F_{1,187} = 17.9, p < 0.001\) and left mid cingulum \(F_{1,187} = 10.6, p = 0.001\) such that more complaints were related to increased FDG metabolism. The results remained the same when GDS was added to the model. Age was controlled for in all analyses.

ROI analysis: Precuneus. ROI analysis in the bilateral precuneus confirmed a significant main effect of SMCs \(F_{1,246} = 6.38, p = 0.012\) such that more complaints were related to decreased FDG metabolism. The results became marginally significant when age, precuneus thickness, and GDS were added to the model \(F_{1,243} = 3.12, p = 0.08\). A nonsignificant interaction effect was found between amyloid and SMCs \(F_{1,241} = 0.35, p = 0.56\), with age, precuneus thickness, and GDS as covariates in the model.

ROI analysis: Hippocampus. A nonsignificant main effect of SMCs \(F_{1,247} = 1.61, p = 0.21\) on bilateral hippocampal metabolism was observed. The results became marginally significant when age, hippocampal volume, and GDS were added to the model \(F_{1,244} = 3.74, p = 0.054\). ROI analysis confirmed a significant interaction effect between amyloid and SMCs in bilateral hippocampus \(F_{1,243} = 4.51, p = 0.035\), with age, hippocampal volume, and GDS as covariates in the model.
DISCUSSION The present study investigated the functional and pathologic correlates underlying SMCs by combining measures of regional brain metabolism (as measured with FDG-PET) and Aβ burden (as measured with PiB-PET). Our results demonstrate that SMCs in CN older adults are related to reduced metabolism in cortical midline regions, which are brain structures known to play a role in self-referential processing. The MTL, a region known to be involved in memory performance, related to SMCs only in the participants who had high Aβ, a pattern that suggests that SMCs have different functional correlates according to Aβ status. Specifically, decreased MTL metabolism may be a specific marker of subclinical changes in cognition in preclinical AD.

Consistent with our expectation and prior published results, we found that Aβ+ individuals had more SMCs than Aβ− individuals. No difference was found between the groups in regard to sex, education, global cognition, or depression, although the Aβ+ individuals were slightly older than the Aβ− individuals. The current data reinforce the notion that SMCs may be a useful marker to identify individuals who might be in the preclinical stages of AD. In line with this, we recently reported that when multiple biomarkers were combined, those CN older individuals who exhibited either increased Aβ burden or neurodegeneration (smaller hippocampal volume or decreased FDG metabolism in a set of AD-vulnerable regions) had a statistically significant higher report of SMCs when compared to biomarker-negative CN individuals. In our previous study, we operationalized Aβ and neurodegeneration groups by using cutoffs of predefined regions. In the current study, we went one step further by trying to characterize the brain substrate underlying SMCs. Specifically, to unveil the brain metabolic correlates of SMCs, we used an exploratory approach by entering the individual SMCs scores and performed a whole-brain voxel-wise correlation in individual FDG-PET maps.

Our findings demonstrate that self-appraisal of memory function, more specifically, increased SMCs, was associated with decreased glucose metabolism in the posterior (precuneus) and anterior (MFG) midline regions, as well as the bilateral inferior parietal lobes and the right inferior temporal lobe. Interestingly, with regard to the midline regions, evidence from several lines of research has converged on the same set of brain regions (including the ventromedial prefrontal, medial parietal, and posterior cingulate cortex and the inferior parietal lobule) implicated in self-referential processing.

With regard to the pathophysiology of AD, mounting evidence has demonstrated the vulnerability of the same cortical midline brain regions to AD-like changes, including early Aβ deposition decreased glucose metabolism, structural changes and functional disruption. The convergence of these effects was further pointed out by Buckner et al., who proposed that these cortical brain regions, including the MTL, may be part of a network, the disruption of which contributes to memory impairment. Although the relationships between the hippocampus and the cortical midline regions are not yet fully elucidated, the parahippocampal gyrus could play a critical role in linking these regions together.

With regard to FDG metabolism, previous studies showed that hippocampal metabolism is closely related to memory performance. That is, previous studies have shown that hippocampal metabolism is preserved in preclinical AD but decreased in prodromal AD. In contrast and concurrent with the present results, precuneus metabolism has been shown to decrease in the preclinical AD stage, before the onset of cognitive impairment. However, the specificity of precuneus FDG in AD dementia has been criticized because it has been shown that Aβ+ individuals with mild cognitive impairment also exhibit hypometabolism in this region. Interestingly, our main effect of SMCs in the midline regions did not survive when we added depression (GDS) to the model, suggesting that some of the observed changes in the posterior midline regions might be due to depressive symptoms. Indeed, previous findings from our group have indicated a relationship between higher GDS score and FDG hypometabolism in AD-vulnerable regions, including the precuneus in CN older adults. In contrast, we found that the interaction effect between SMCs and Aβ pathology remained significant after controlling for age, GDS, and hippocampal volume in the model, supporting the idea that the observed decreased MTL metabolism may be a specific marker of subclinical changes in cognition due to amyloid pathology, above and beyond depressive symptoms. Noteworthy is the finding that the relationship between SMCs and metabolism was affected by amyloid burden in the hippocampus, an area with relatively little amyloid deposition, but not in the precuneus, an area with high amyloid deposition. These findings complement previous functional neuroimaging studies in patients with mild cognitive impairment demonstrating functional abnormalities in the MTL during memory task performance (for review, see reference 35), indicating that this region is a site of very early pathology in AD, e.g., neurofibrillary tangles. Thus, the observed finding of hypometabolism in the MTL is consistent with the expected effects of progressive AD pathology, resulting in increased neurodegenerative processes, e.g., neurofibrillary tangles. The recent advent of tau-PET...
imaging in conjunction with PiB-PET will enable future studies to provide regionally specific information about the underlying distribution of AD pathology to shed further light on this issue.

The current results are also in concordance with a previous study by Mosconi et al., demonstrating FDG hypometabolism in the parahippocampus in CN older individuals with an APOE ε4 allele and SMCs, further supporting the idea that alterations in the MTL may be a specific marker of subclinical changes in cognition in preclinical AD. Although we were not able to unravel the relationships among genotype, amyloid, SMCs, and metabolism in the current study, we did find, in line with the findings of Mosconi et al., a significantly increased percentage of APOE ε4 carriers in the Aβ+ group (61.4%).

We acknowledge that there are several limitations to this study. First, to date, there is no consensus on how to assess SMCs. Previous studies have used methods ranging from nonstandardized clinical interviews to well-validated scales, as well as having the complaints corroborated by an informant. In this study, we used the Memory Functioning Questionnaire to create a subjective memory score. Although this test does not include an informant version, future studies will use other subjective memory questionnaires to investigate potential discrepancies between the participant’s self-report and the report of the informant to gain insight into the self-awareness of these memory problems in our participants and how that is related to Aβ and FDG metabolism. Second, we are aware that self-reports on cognitive decline could be influenced by confounding factors, for instance, substance use, medication, or other neurologic and medical conditions. In the current study, a history of neurologic or major psychiatric disorder, the use of medications that affect cognitive function, and alcohol and substance abuse were used as exclusion criteria. In addition, none of the participants met the criteria for depression. However, other factors that could have influenced the results such as personality traits, anxiety, and hypochondria were not considered in this study.

These findings add to existing literature by demonstrating the importance of obtaining measures of biomarkers in addition to subjective report of memory complaints because they may help distinguish between SMGs due to decline in cognitive aging from preclinical AD dementia.

AUTHOR CONTRIBUTIONS

P. Vannini and B. Hanseusen: study concept and design, analysis and interpretation of the data, preparation of the manuscript. C. Munro: analysis and interpretation of the data, review and approval of the manuscript. A. Pascual-Leone: study concept and design, interpretation of the data, review and approval of the manuscript. K. Johnson: interpretation of the data, review and approval of the manuscript. R. Sperling: study concept and design, interpretation of the data, review and approval of the manuscript.

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