Subjective Cognition and Amyloid Deposition Imaging

A Pittsburgh Compound B Positron Emission Tomography Study in Normal Elderly Individuals

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Objective: To study the relationship between subjective cognition and the neuropathological hallmark of Alzheimer disease (AD), amyloid-β (Aβ) deposition, using carbon 11–labeled Pittsburgh Compound B (PiB) positron emission tomography in normal elderly individuals.

Design: Cross-sectional analysis.

Subjects: Forty-eight cognitively normal elderly subjects (11 with high PiB uptake and 28 with low PiB uptake) were included. All underwent clinical and neuropsychological evaluations, magnetic resonance imaging, and positron emission tomography.

Setting: Berkeley Aging Cohort Study.

Main Outcome Measure: Relationship between PiB uptake and subjective cognition measures.

Results: Subjects with high PiB uptake showed significantly lower performance than those with low PiB uptake on an episodic memory measure and were less confident about their general memory abilities when required to evaluate themselves relative to other people of the same age. High and low PiB uptake groups did not differ on the accuracy of their subjective cognitive self-reports compared with objective cognitive performance. General memory self-reports from the whole group were significantly correlated with regional PiB uptake in the right medial prefrontal cortex and anterior cingulate cortex and in the right precuneus and posterior cingulate cortex. Reduced confidence about memory abilities was associated with greater PiB uptake in these brain regions. All results were independent of demographic variables and depressive affects.

Conclusions: A decrease of self-confidence about memory abilities in cognitively normal elderly subjects may be related to the neuropathological hallmark of AD measured with PiB–positron emission tomography. Subjective cognitive impairment may represent a very early clinical manifestation of AD.

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mimic those commonly observed in AD (ie, decreased gray matter volume\textsuperscript{16-21} and cerebral metabolism reduction\textsuperscript{22,23}) and increased genetic risk for AD (eg, the apo-lipoprotein E ε4 allele\textsuperscript{24,25}). Furthermore, postmortem studies have consistently observed that memory complaints in healthy older adults were associated with Aβ deposition in autopsied tissues at death.\textsuperscript{26,27} Using Aβ imaging, 2 recent studies have examined PiB retention in subjects with SCI. Rodda et al\textsuperscript{28} studied Aβ load in 5 subjects with memory complaints and observed that only 1 subject had significantly increased PiB uptake relative to control subjects. Chételat et al\textsuperscript{29} reported that the proportion of subjects classified as having positive PiB uptake in an SCI group (39%) was higher than that in a control group (29%), although this difference did not reach significance.

Subjective cognition or cognitive self-awareness is a metacognitive monitoring function enabling the evaluation of one's own cognitive system. Metacognition literature usually distinguishes off-line vs online monitoring. Off-line cognitive monitoring corresponds to self-assessment of global cognitive functioning and covers declarative knowledge about one's own cognitive abilities.\textsuperscript{30} Online monitoring involves ongoing assessment of one's performance within the context of a particular cognitive task.\textsuperscript{31} Whereas previous studies examining the relationships of SCI with AD biomarkers have used general off-line monitoring assessment, the present study addresses this association using different subcomponents of metacognitive monitoring.

In this study, we investigate whether subjective cognition in a group of cognitively normal elderly individuals is associated with the neuropathological hallmark of AD, Aβ deposition. To this end, subjective cognition was assessed with off-line monitoring measures that included self-assessment of one's daily memory abilities using a general question addressing overall memory functioning and with online monitoring measures that included self-assessment of one's performance during a specific cognitive task using a postdiction of performance procedure. Deposition of Aβ was assessed using PiB uptake with PET imaging. Based on results from postmortem studies,\textsuperscript{26,27} we hypothesized that subjective cognition would be associated with early markers of AD in the in vivo brain. Specifically, cognitively normal and non-depressed subjects with high PiB uptake would report more cognitive complaints. In terms of regional brain localization, we expected that relationships between PiB uptake and subjective cognition measures would be the highest in regions where Aβ deposition is typical (ie, greater and earlier) in the AD pathological process.

METHODS

SUBJECTS

Forty-eight cognitively normal elderly subjects underwent testing in the present study. They included 31 women and 17 men ranging in age from 61 to 88 (mean [SD] age, 73.5 [5.9]) years, with a mean educational level of 17.3 (1.9) years and a mean Mini-Mental State Examination score of 29.1 (1.1). These subjects come from the Berkeley Aging Cohort Study, a pool of community-dwelling healthy volunteers older than 60 years residing in the San Francisco Bay Area of California. Subjects in the Berkeley Aging Cohort Study were recruited through advertisements in senior centers and local newspapers requesting participation in a research project investigating aging and changes in cognitive function. The study was approved by the local ethics committee, and subjects gave written informed consent. All subjects provided data on their medical history and underwent a neuropsychological test battery and interviews about functional ability and lifestyle. Eligibility criteria included independent daily living; the absence of any medical, psychiatric, or neurologic condition that might affect brain structure and functioning, including depression (eg, Geriatric Depression Scale [GDS] score in the normal range); normal performance on cognitive tests; absence of psychoactive medication use; and absence of sensory impairment that might interfere with the cognitive testing. From the sample of 183 subjects in the Berkeley Aging Cohort Study, 48 met the inclusion criteria and agreed to undergo magnetic resonance imaging (MRI) and PiB PET scanning for this study. The mean (SD) time between behavioral testing and PET imaging was 182 (160) days (about 6 months).

BEHAVIORAL DATA

Cognitive Measures

All subjects underwent a detailed neuropsychological testing battery. Episodic memory was assessed with the California Verbal Learning Test, second edition,\textsuperscript{32} and the Visual Reproduction Subtest of the Wechsler Memory Scale–Revised.\textsuperscript{17} Executive abilities were measured with the Stroop Color Word Test,\textsuperscript{33} the Digit Span Forward and Backward Subtests of the Wechsler Adult Intelligence Scale–Revised,\textsuperscript{34} and the Listening Span Test.\textsuperscript{35} Fluency measures included the Letter Fluency Subtest of the Controlled Word Association Test\textsuperscript{37} and the Category Fluency Test.\textsuperscript{37}

Subjective Cognition Measures

For off-line memory monitoring, general memory self-reports were measured by asking subjects to respond to 2 global questions about their general daily memory functioning, one relative to other people of the same age and the other relative to themselves 20 years ago. For each question the participant gave her or his reply using a 4-point ordinal scale in which 1 indicates better; 2, about the same; 3, a bit worse; and 4, much worse. For online cognitive monitoring, global self-assessments of performance were solicited after the completion of each of the 7 cognitive tasks reported in the previous paragraph. The participant was asked to estimate performance on the test (ie, postdiction) relative to other people of the same age, the same sex, and similar educational level. The participant rated her or his own performance relative to normative data on a percentile response scale (from worse to better than other people). Based on high correlation among the 7 postdiction scores, a single postdiction composite score was computed for each subject by averaging the 7 postdiction scores (see eMethods; http://jagustlab.neuro.berkeley.edu/suppdata.html).

BRAIN IMAGING

All subjects underwent high-resolution MRI on a 1.5-T system (Magnetom Avanto; Siemens Corp) at the Lawrence Berkeley National Laboratory with a 12-channel head coil run in triple mode. Three high-resolution structural T1-weighted volumetric magnetization-prepared rapid-acquisition gradient-echo scans.
PET IMAGING

Radiochemical Synthesis, Image Acquisition, and Processing

Radiochemistry of $^{[11C]}$PiB was completed at the Lawrence Berkeley National Laboratory using a previously published protocol. Positron emission tomography was performed using a scanner (ECAT EXACT HR; Siemens Corp) at Lawrence Berkeley National Laboratory in 3-dimensional acquisition mode. The $^{[11C]}$PiB was injected into an antecubital vein, and a 90-minute dynamic acquisition and 10-minute transmission scan for attenuation correction were collected. The PiB PET image processing was implemented using the Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, University College, London). The PiB frames were realigned and the mean image was coregistered to the individual's MRI. The PiB PET distribution volume ratio images were created using Logan graphical analysis (with frames corresponding to 35 to 90 minutes after injection and a cerebellum reference region). The PiB distribution volume ratio images underwent partial volume correction. Further details about image acquisition and processing are available in the eMethods.

Region of Interest Analysis

An MRI-based automated region of interest (ROI) technique was used to extract regional PiB data using the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/). These FreeSurfer processing steps are detailed in Mormino et al and in the eMethods section. In brief, subcortical and cortical ROIs spanning the entire brain were defined in each subject’s native space. A global PiB uptake index was produced by combining multiple cortical ROIs, which are known to be associated with $\lambda$ deposition early in AD. In addition, regional PiB indices were derived from the following 5 a priori ROIs: the medial PFC and ACC; the lateral PFC; the precuneus, PCC, and isthmus cingulate cortex (ICC); the medial temporal lobe; and the lateral temporal lobe.

PiB Group Classification

Subjects were classified as having high or low PiB uptake using a cutoff approach described by Aizenstein et al. Subjects within 2.5% above or below the cutoff value were excluded from analysis.

STATISTICAL ANALYSIS

The relationships between PiB uptake and subjective cognition were analyzed using rank-order nonparametric statistical methods. In a first step, the dichotomous PiB measure (high vs low PiB uptake) was used to evaluate group differences on variables of interest. For this evaluation, 2-sample Mann-Whitney tests were used for all measures except for the bicategorical variable (ie, sex), which was analyzed with a $\chi^2$ test. In a second step, continuous PiB measures were used to evaluate the relationship between regional values of PiB uptake and subjective cognition measures using Spearman rank correlations. Demographic variables (age, sex, and educational level) were controlled for in each analysis, as well as a measure of depression (GDS) in analyses involving metacognitive measures. All statistical analyses were conducted using computerized statistical software (Statistica 8.0; StatSoft, Inc), with an $\alpha$ level of .05 for statistical significance.

RESULTS

PiB GROUP DIFFERENCES

The method used by Aizenstein et al revealed a cutoff of 1.460, classifying 11 subjects with high intake and 28 with low PiB intake (9 subjects within 2.5% of this value were excluded). The PiB group differences on demographic variables and cognitive and metacognitive measures are presented in Table 1 and Table 2. No significant differences were observed between the high and low PiB uptake groups on the demographic variables.

Cognitive Measures

Subjects with high PiB uptake performed worse than those with low PiB uptake on a single episodic memory measure (the immediate recall measure of the California Verbal Learning Test). This effect remained significant after controlling for demographics ($F_{1,35} = 7.10$; mean square = 1068.19; $P = .01$).

Metacognitive Measures

Subjects with high and low PiB uptake differed on the off-line self-reports of the general memory monitoring measure relative to other people. This effect remained significant after controlling for demographics and GDS, using an analysis of covariance for ordinal multinomial distributions ($Wald_1 = 4.35$; $SE = 0.24$; $P = .04$). Specifically, subjects with high PiB uptake felt less confident about their memory than those with low PiB uptake (Figure). More specifically, 44% of the subjects with low PiB uptake (12 of 27) believed that they had better memory than most people, whereas 9% of the subjects with high PiB uptake (1 of 11) made this assessment. A 2-proportion $z$ test indicated that this difference was significant ($P = .04$). No significant PiB group effect was observed on the off-line monitoring measure that assessed memory relative to their abilities 20 years before or on the online monitoring measures.

CORRELATIONS BETWEEN SUBJECTIVE AND OBJECTIVE COGNITION

To explore how subjective cognition relates to actual performance, we examined relationships between metacognitive judgments and objective scores within each PiB group (see eResults and eFigure). No significant differences in the strength of these within-group correlations were identified across metacognitive measures (ie, there was no effect of PiB status on the relationship between subjective and objective performance).
### Table 1. PiB Group Differences on Demographic Variables and Cognitive Measures

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>High PiB Uptake</th>
<th>Low PiB Uptake</th>
<th>Difference Statistic b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11 75.73 (6.05)</td>
<td>28 71.89 (5.45)</td>
<td>.12</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>11 16.82 (1.89)</td>
<td>28 17.61 (2.92)</td>
<td>.17</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 13</td>
<td></td>
<td>.10 c</td>
</tr>
<tr>
<td>Female</td>
<td>9 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS score</td>
<td>11 4.45 (2.73)</td>
<td>28 3.86 (3.04)</td>
<td>.47</td>
</tr>
<tr>
<td>MMSE score</td>
<td>11 29.18 (0.98)</td>
<td>28 28.96 (1.23)</td>
<td>.76</td>
</tr>
<tr>
<td>Cognitive measure d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-II Immediate Free Recall</td>
<td>10 40.20 (8.08)</td>
<td>28 50.46 (10.55)</td>
<td>.07</td>
</tr>
<tr>
<td>CVLT-II Short-Delay Free Recall</td>
<td>10 8.00 (4.52)</td>
<td>28 10.75 (2.86)</td>
<td>.10</td>
</tr>
<tr>
<td>CVLT-II Short-Delay Cued Recall</td>
<td>10 10.90 (2.81)</td>
<td>28 12.14 (2.73)</td>
<td>.21</td>
</tr>
<tr>
<td>CVLT-II Long-Delay Free Recall</td>
<td>10 9.40 (4.03)</td>
<td>28 11.39 (3.27)</td>
<td>.15</td>
</tr>
<tr>
<td>CVLT-II Long-Delay Cued Recall</td>
<td>10 10.20 (3.58)</td>
<td>28 11.86 (2.65)</td>
<td>.20</td>
</tr>
<tr>
<td>CVLT-II Recognition Hits</td>
<td>10 13.80 (3.52)</td>
<td>28 14.21 (1.73)</td>
<td>.86</td>
</tr>
<tr>
<td>z CVLT-II Delayed performance e</td>
<td>10 −0.29 (1.02)</td>
<td>28 0.13 (0.78)</td>
<td>.28</td>
</tr>
<tr>
<td>VR-I Immediate Recall total</td>
<td>11 76.82 (13.67)</td>
<td>28 81.46 (13.18)</td>
<td>.31</td>
</tr>
<tr>
<td>VR-II Delayed Recall total</td>
<td>11 53.64 (24.76)</td>
<td>28 67.39 (19.52)</td>
<td>.07</td>
</tr>
<tr>
<td>VR Recognition total</td>
<td>11 42.64 (4.48)</td>
<td>28 45.21 (2.33)</td>
<td>.07</td>
</tr>
<tr>
<td>z VR Delayed Performance f</td>
<td>11 −0.16 (1.11)</td>
<td>28 0.50 (0.69)</td>
<td>.06</td>
</tr>
<tr>
<td>Stroop Color Word Test, No. correct in 60 s</td>
<td>11 48.73 (13.95)</td>
<td>28 50.11 (12.50)</td>
<td>.77</td>
</tr>
<tr>
<td>Digit Span total score</td>
<td>11 17.09 (3.86)</td>
<td>28 16.50 (3.97)</td>
<td>.49</td>
</tr>
<tr>
<td>Listening Span Test, total No. recalled</td>
<td>11 41.73 (6.90)</td>
<td>27 47.04 (8.28)</td>
<td>.07</td>
</tr>
<tr>
<td>Letter Fluency Subtest, total score</td>
<td>11 48.64 (11.36)</td>
<td>27 47.74 (9.62)</td>
<td>.86</td>
</tr>
<tr>
<td>Category Fluency Test, total score</td>
<td>11 33.09 (12.09)</td>
<td>27 37.19 (8.51)</td>
<td>.31</td>
</tr>
</tbody>
</table>

**Abbreviations:** CVLT-II, California Verbal Learning Test, second edition; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; PiB, Pittsburgh Compound B; VR, Visual Reproduction Subtest.

a PiB group classification is described in the “PET imaging” subsection of the “Methods” section.
b Unless otherwise indicated, differences are calculated as P values using the Mann-Whitney test.
c Calculated using the chi-squared test.
d Measures are described in the “Behavioral Data” subsection of the “Methods” section.
e A CVLT-II delayed composite score was calculated by averaging the z scores for the CVLT-II Long-Delay Free Recall, Long-Delay Cued Recall, and Recognition (see eResults).
f A Visual Reproduction delayed composite score was calculated by averaging the z scores for the Visual Reproduction delayed recall and recognition (see eResults).

### Table 2. PiB Group Differences on Metacognitive Measures

<table>
<thead>
<tr>
<th>Off-line monitoring</th>
<th>High PiB Uptake</th>
<th>Low PiB Uptake</th>
<th>Difference Statistic b</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR relative to other people</td>
<td>11 2.09 (0.54)</td>
<td>27 1.63 (0.63)</td>
<td>.04 c</td>
</tr>
<tr>
<td>SR relative to 20 y ago</td>
<td>11 2.82 (0.75)</td>
<td>27 2.93 (0.55)</td>
<td>.87 c</td>
</tr>
<tr>
<td>Online monitoring d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR CVLT-II Post-Delay</td>
<td>10 47.70 (20.48)</td>
<td>28 55.50 (21.63)</td>
<td>.43</td>
</tr>
<tr>
<td>SR VR Post-Delay</td>
<td>11 66.00 (21.34)</td>
<td>28 70.29 (19.34)</td>
<td>.57</td>
</tr>
<tr>
<td>SR Stroop Color Word Test</td>
<td>11 53.18 (27.55)</td>
<td>28 60.29 (20.22)</td>
<td>.48</td>
</tr>
<tr>
<td>SR Digit Span Subtest</td>
<td>11 54.36 (23.29)</td>
<td>28 57.25 (23.12)</td>
<td>.65</td>
</tr>
<tr>
<td>SR Listening Span Test</td>
<td>11 33.55 (25.16)</td>
<td>27 36.89 (18.61)</td>
<td>.50</td>
</tr>
<tr>
<td>SR Letter Fluency Subtest</td>
<td>11 57.36 (22.67)</td>
<td>27 53.07 (21.73)</td>
<td>.52</td>
</tr>
<tr>
<td>SR Category Fluency Test</td>
<td>11 55.45 (19.29)</td>
<td>27 57.63 (17.39)</td>
<td>.87</td>
</tr>
<tr>
<td>Composite online SR</td>
<td>11 53.05 (18.19)</td>
<td>28 56.14 (15.04)</td>
<td>.39</td>
</tr>
</tbody>
</table>


a PiB group classification is described in the “PET imaging” subsection of the “Methods” section.
b Unless otherwise indicated, differences are calculated as P values using the Mann-Whitney test.
c Calculated using the Mann-Whitney test (z statistic adjusted for ties).
d Measures are described in the “Behavioral Data” subsection of the “Methods” section.
e Given missing data for 2 subjects, their composite online SR score was calculated on the basis of 4 and 6 online SR measures, respectively, rather than on the 7 online SR measures.
CORRELATIONS BETWEEN REGIONAL PiB UPTAKE AND SUBJECTIVE COGNITION

We explored the relationship between the subjective cognition measure that was related to PiB status (the general memory self-reports relative to other people) and regional PiB uptake as a continuous variable in specific ROIs. Table 3 summarizes the correlations between PiB uptake and general memory self-reports relative to other people for the 5 examined ROIs, controlling for age, sex, educational level, and GDS. Significant positive correlations were noted in the right medial PFC/ACC and in the right precuneus/PCC/ICC. Thus, this ROI approach suggests that the pattern of PiB uptake in the right medial anterior and posterior cortices is related to reduced general memory ability confidence relative to other people of the same age.

COMMENT

The present study highlights that subjective cognition may be associated with Aβ deposition, the neuropathological hallmark of AD, as measured with [11C]PiB PET imaging. Our findings show that community-dwelling cognitively normal older subjects with a high Aβ load tend to be less confident than those with a lower Aβ load about their general memory abilities when they compare their abilities with those of other people of the same age. Nevertheless, our subjects with high PiB uptake cannot be simply classified as “complainers” because they did not report that they were significantly worse than other people, but they are clearly dissimilar to their peers with low PiB uptake on their degree of self-confidence about memory abilities. Our results show that this more cautious self-report is not related to depressive affect or higher educational levels. However, this feeling could reflect the experience of subtle memory limitations, which may indeed correspond to an objective memory weakness because subjects with high PiB uptake have a poorer performance than those with low PiB uptake on an episodic memory measure.

Although the metacognition literature has repeatedly confirmed the multidimensional nature of monitoring processes, an unexpected result is that PiB uptake was not significantly related to the other subjective cognition measures. In particular, it is surprising that subjects responded rather differently to the other off-line monitoring measure in which participants had to assess their memory abilities relative to 20 years ago. It is possible that the insidious and gradual occurrence of subtle cognitive problems may make an accurate monitoring of one’s abilities over time difficult compared with memory monitoring based on the present. For the online monitoring measure, subjects could be less prone to experience subtle cognitive limitations when they have to assess their ongoing performance in unfamiliar laboratory tasks.

In addition, we found that regional PiB uptake in the right medial PFC/ACC and precuneus/PCC/ICC was significantly related to general memory self-reports. These regions correspond precisely to those where the Aβ load is typically the highest and the earliest, which confirms the consistency of the association of subjective cognition with the neuropathological signs of AD. These regions and their right hemispheric location are also commonly associated with the self and metacognitive processes. Nevertheless, the presence of Aβ in the medial PFC/ACC and precuneus/PCC/ICC regions does not have detrimental effects on subjects’ insight about their cognition. In relation to this finding, the effect of the regional Aβ load on local regional function is unclear in the literature.

The significant relationship observed between PiB uptake and subjective cognition measured with general memory self-reports relative to age-equivalent peers echoes previous studies showing that memory complaints in healthy subjects were related to genetic risks and the structural and functional features of AD in the
brain. In reference to the biomarker cascade model of AD proposed by Jack et al., Aβ deposition levels in cognitively intact older subjects may be the most appropriate measure to detect the earliest manifestation of AD. Although the 2 previous PiB studies involving subjects with SCI were not conclusive about the association of PiB uptake with SCI, our results are consistent with findings from postmortem investigations showing a relationship between memory complaints and AD pathologic processes (including Aβ deposition) in older people without dementia.

Our study provides new evidence that cognitively normal, nondepressed older subjects with less confidence about their memory abilities may have neuropathological signs of AD. By extension, this observation is consistent with the idea that SCI may represent a very early clinical manifestation of incipient dementia, which supports the predictive validity of memory complaints for AD and the claim that SCI may constitute a pre-MCI stage. A recent study enriches the cascade model of AD proposed by Jack et al. by showing that elevated PiB uptake was strongly related to brain atrophy in SCI but not in MCI or in AD. Therefore, at the initial stage of AD development when Aβ accumulates and subtle neurodegeneration begins, cognitive changes may be functionally compensated for and remain undetectable, whereas subjective complaints may be present (i.e., the SCI stage). A probable duration of 15 years for the SCI stage has been proposed. At that point, Aβ deposition may reach a plateau, atrophy rates may accelerate, and MCI may appear.

With regard to the interpretation of SCI in aging (SCI is often associated with affective or personality traits rather than dementia), our results suggest that, in older subjects with intact cognition, lower confidence about their memory may not be a benign symptom and should be evaluated carefully because it may reflect an underlying degenerative process. These conclusions should be considered cautiously for several reasons. The present study is among the first to test the relationship between subjective cognition and an AD neuropathological hallmark; thus, replication studies are warranted. Although our subjects with high PiB uptake were less confident about their memory than those with low PiB uptake, they could not be identified as complainers, and it is unclear whether similar results would be found in subjects with SCI. Furthermore, we did not assess the influence of personality features on metacognition, which may weight these relationships. Overall, relationships between subjective cognition and AD development should be clarified with consideration of these limitations and longitudinal follow-up of participants.

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Online-Only Material: The eMethods, eResults, and eFigure cited in the text are available on the authors’ website at http://jagustlab.neuro.berkeley.edu suppdata.html.

Additional Contributions: We thank all the participants from the study.

REFERENCES


