Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals

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Abstract

Background

Subjective cognitive impairment (SCI) as an early clinical manifestation in Alzheimer disease (AD) is a central and highly debated question.

Objective

To study the relationship between subjective cognition and the neuropathological hallmark of AD, amyloid-beta (Aβ) deposition, imaged with [^{11}C]-Pittsburg compound B (PiB) - positron emission tomography (PET), 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 and MRI and PET scanning.

Results

High PiB subjects showed significantly lower performance than low PiB subjects 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 groups did not differ on the accuracy of their cognitive self-reports compare to objective cognitive performance. General memory self-reports from the whole group were significantly correlated to regional PiB uptake in the right medial prefrontal cortex (PFC)/anterior cingulate cortex (ACC) and in the right precuneus/posterior cingulate cortex (PCC). Reduced confidence about memory abilities was associated with greater PiB in these brain regions. All results are independent of demographic variables and depressive affects.

Conclusions

Our findings suggest that a decrease of self-confidence about memory abilities in cognitively normal elderly subjects is related to the neuropathological hallmark of AD measured with PiB-PET imaging. The relevance of SCI in the early stages of the AD pathological process is addressed.

MESH Keywords Aged ; Aged, 80 and over ; Aging ; physiology ; Amyloid beta-Peptides ; metabolism ; Aniline Compounds ; Biological Markers ; Cerebral Cortex ; radionuclide imaging ; Cognition ; physiology ; Cognition Disorders ; metabolism ; psychology ; radionuclide imaging ; Cohort Studies ; Female ; Humans ; Image Processing, Computer-Assisted ; Magnetic Resonance Imaging ; Male ; Memory ; physiology ; Middle Aged ; Neuropsychological Tests ; Positron-Emission Tomography ; Prefrontal Cortex ; radionuclide imaging ; Radiopharmaceuticals ; Reference Values ; Thiazoles

Author Keywords subjective cognition ; normal aging ; Alzheimer's disease (AD) ; amyloid-beta (Aβ) ; [11C]-Pittsburgh compound B (PiB) - positron emission tomography (PET)

Introduction

Subjective cognitive impairment (SCI) is an early behavioral manifestation in the course of Alzheimer disease (AD) which may precede objective mild cognitive impairment (MCI) in the continuum of disease progression[1–4]. Cognitive complaints in older adults as a predictor of future dementia[5,6]remains controversial. This disagreement is partially explained by confounding affective and personality

factors that may be unrelated to development of AD[7,8]. Thus, to test the validity of cognitive complaints as an early sign of AD, it is of interest to evaluate subjective cognition in relation to specific markers of AD pathology.

Amyloid-beta (Aβ) peptide deposition in senile plaques is a key neuropathological feature of AD[9]and may be the initiating event of the Alzheimer's pathological cascade[10,11]. Brain imaging offers the opportunity to visualize and quantify this pathology in vivo, using positron emission tomography (PET) with the [^{11} C]-PiB (Pittsburgh compound B) radiotracer which binds specifically to fibrillar Aβ plaques. Elevated PiB has been shown in AD and MCI patients[12,13], as well as in about 30% of cognitively normal older subjects[14,15]. Elevated PiB uptake in AD is typically found in the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC)[14].

The study aimed to investigate the relationship between subjective cognition in the healthy elderly population and PiB status. Although the present study did not specifically recruit SCI subjects, previous work in SCI has shown brain structural and functional abnormalities that mimic those commonly observed in AD (i.e. decreased grey matter volume[16–21], cerebral metabolism reduction[22,23]), as well as increased genetic risk for AD (such as apolipoprotein E ε4 allele[24,25]). Furthermore, postmortem studies have consistently observed that memory complaints in healthy older adults were associated with amyloid in autopsied tissues at death[26,27]. Using amyloid imaging, two recent studies have examined PiB retention in people with SCI. Rodda et al.[28]studied amyloid load in 5 subjects with memory complaints and observed that only 1 subject had significantly increased PiB uptake relative to controls. Chételat et al.[29]reported that the proportion of subjects classified as PiB positive in an SCI group (39%) was higher than 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 two forms of monitoring: off-line versus on-line monitoring. Off-line cognitive monitoring corresponds to self-assessment of global cognitive functioning, and covers declarative knowledge about one's own cognitive abilities[30]. On-line monitoring involves ongoing assessment of one's performance within the context of a particular cognitive task[31]. Whereas previous studies examining the relationships of SCI with AD biomarkers have used general offline 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. To this end, subjective cognition was assessed with off-line monitoring measures, i.e. self-assessment of one's daily memory abilities using a general question addressing overall memory functioning, as well as with on-line monitoring measures, i.e. self-assessment of one's performance during a specific cognitive task using a postdiction of performance procedure. Aβ deposition was assessed using PiB uptake with PET imaging. Based upon results from postmortem studies, we hypothesized that subjective cognition would be associated with early markers of AD in *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, it is expected that relationships between PiB uptake and subjective cognition measures would be the highest in regions where amyloid deposition is typical (i.e. greater and earlier) in the AD pathological process.

Methods

Subjects

Forty-eight cognitively normal elderly subjects were tested in the present study. There were 31 women and 17 men ranging in age from 61–88 years (mean age=73.48 ±5.91 years), with a mean education level of 17.29 years (±1.90) and a mean Mini-Mental State Examination (MMSE) score of 29 (±1.11). These subjects come from the Berkeley Aging Cohort Study (BACS), a pool of community-dwelling healthy volunteers over 60 years old residing in the San Francisco Bay Area. BACS subjects 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 medical history, underwent a neuropsychological test battery, and interviews about functional ability and lifestyle. Eligibility criteria include independent daily living, absence of any medical, psychiatric or neurologic condition that might affect brain structure and functioning, including depression (e.g. Geriatric Depression Scale (GDS) in 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 185 BACS subjects, 48 met inclusion criteria and agreed to both MRI and PiB PET scanning for this study. The mean time between behavioral testing and PET imaging was about 6 months (mean time=182 ±160 days).

Behavioral data

Cognitive measures

All subjects underwent a detailed neuropsychological testing battery which included episodic memory assessment with the California Verbal Learning Test-Second Edition[32](CVLT-II) and the Visual Reproduction subtest of the Wechsler Memory Scale-Revised[33] (WMS-R), executive abilities measurement with the Stroop Color Word Test[34], the Digit Span forward and backward subtests of the

Wechsler Adult Intelligence Scale-Revised[35](WAIS-R), the Listening Span test[36], and fluency measures with the Letter Fluency test of the Controlled Word Association Test[37](COWAT) and the Category Fluency test[37].

Subjective cognition measures

Off-line memory monitoring. General memory self-reports were measured by asking subjects to respond to two global questions about their general daily memory functioning; one relative to other people of the same age, the other relative to 20 years ago. For each question the participant gave her/his reply using a 4-point ordinal scale: "1-*Better*", "2-*About the same*", "3-*A bit worse*", "4-*Much worse*". On-line cognitive monitoring. Global postdictions of performance were solicited after the completion of each of the 7 cognitive tasks reported above. The participant was asked to estimate performance on the test (i.e. postdiction) relative to other people of the same age, sex and similar education. The participant rated her/his own performance relative to normative data on a percentile response scale (from "*worse*" to "*better than other people*"). Based upon high correlation amongst the 7 postdiction scores, a single postdiction composite score was computed for each subject by averaging their 7 postdiction scores (see eMethods).

Brain imaging

MRI

All subjects underwent high resolution MRI scans on a 1.5-T Magnetom Avanto system (Siemens Inc., Iselin, NJ) at the Lawrence Berkeley National Laboratory (LBNL) with a 12 channel head coil run in triple mode. Three high-resolution structural T1-weighted volumetric magnetization prepared rapid acquisition gradient echo (MP-RAGE) scans were collected axially for each subject (TR/TE/TI= 2110/3.58/1100 ms, flip angle=15°, with 1.00x1.00 mm^2 in-plane resolution and 1.00 mm slice thickness).

PET imaging

Radiochemical synthesis, image acquisition and processing

Radiosynthesis of [^{11} C]-PiB was completed at the LBNL Facility using a previously published protocol[38]. PET scans were performed using a Siemens ECAT EXACT HR PET scanner at LBNL in 3D acquisition mode. [^{11} C]-PiB was injected into an antecubital vein, and a 90-min dynamic acquisition as well as a 10-min transmission scan for attenuation correction were collected. PiB PET image processing was implemented using the Statistical Parametric Mapping software (SPM2; Welcome Department of Cognitive Neurology, University College, London, UK). PiB frames were realigned and the mean image was coregistered to the individual's MRI scan. PiB PET distribution volume ratio (DVR) images were created using Logan graphical analysis (with frames corresponding to 35–90 min post-injection[39,40]and a cerebellum reference region[41]). PiB DVR images were partial volume correction (PVC)[42]. Further details about image acquisition and processing are available in the eMethods.

ROI analysis

An MRI-based automated 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.[43]and in eMethods. In brief, subcortical and cortical ROIs spanning the entire brain were defined in each subject's native space[44,45]. Global PiB uptake index was produced by combining multiple cortical ROIs which are known to be associated with amyloid deposition early in AD[14]. In addition, regional PiB indices were derived from five a priori ROIs: medial PFC/ACC, lateral PFC, precuneus/PCC/ICC, medial temporal lobe and lateral temporal lobe.

PiB group classification

Subjects of the sample were classified as high or low PiB on the basis of their global PiB uptake level using a cut off approach described by Aizenstein et al.[46]. Subjects within 2.5% above or below the cutoff value were excluded from analysis.

Statistical analyses

The relationships between PiB uptake and subjective cognition were analyzed in two ways using rank-order non-parametric statistical methods. In a first step, the dichotomous PiB measure (high versus low PiB) was used to evaluate group differences on variables of interest. For this, two-sample Mann-Whitney U tests were used for all measures except for the bi-categorical variable (i.e. gender) that was analyzed with a chi-squared 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's rank correlations. Demographic variables (age, gender and education) 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., Tulsa, OK), with an alpha level of 0.05 for statistical significance.

Results

PiB group differences

The Aizenstein method revealed a cut off of 1.460, classifying 11 subjects as high and 28 as low PIB (9 subjects within 2.5% of this value were excluded). PiB group differences on demographic variables, cognitive and metacognitive measures are presented in the Table 1.

Demographic measures

No significant differences were observed between high and low PiB groups on the demographic variables.

Cognitive measures

High PiB subjects performed worse than low PIB subjects on a single episodic memory measure–the immediate recall of the CVLT, and this effect remained significant after controlling for demographics ($F(1, 33)=7.101$, $MS=1068.195$, $p=0.012$).

Metacognitive measures

High and low PiB subjects differed on an off-line monitoring measure –the general memory self-reports relative to other people, and this effect remained significant after controlling for demographics and GDS, using an ANCOVA for ordinal multinomial distributions (Wald $(1)=4.351$, $SE=0.243$, $p=0.037$). Specifically, subjects with high PiB uptake felt less confident about their memory than low PiB subjects (see Figure 1). More specifically, 44% of the low PiB subjects felt that they had better memory than most people while 9% of the high PiB subjects made this assessment. A two-proportion z-test indicated that this difference is significant ($p=0.039$). 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 on-line monitoring measures.

Correlations between subjective and objective cognition

To explore how subjective cognition relates to actual performance, relationships between metacognitive judgments and objective scores within each PiB group was examined (see eResults, eFigure 1). No significant differences in the strength of these within group correlations were identified across metacognitive measures (i.e. there was no effect of PIB status on the relationship between subjective and objective performance).

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 2 summarizes the correlations between PiB and general memory self-reports relative to other people for the five examined ROIs, controlling for age, gender, education and GDS. Significant positive correlations were noted in the R medial PFC/ACC as well as in the R precuneus/PCC/ICC. Thus, this ROI approach suggests the pattern of PiB uptake in the R medial anterior and posterior cortices is related to reduced general memory ability confidence relative to other people of the same age.

Discussion

The present study highlights that subjective cognition may be associated with the neuropathological hallmark of AD, i.e. Aβ deposition, as measured with PiB PET imaging. Our findings show that community-dwelling cognitively normal older subjects with high amyloid load tend to be less confident than those with lower amyloid load about their general memory abilities when they compare their abilities to those of other people of the same age. Nevertheless, our high PiB subjects 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 low PiB peers 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 education. However, this feeling could reflect the experience of subtle memory limitations, which may indeed correspond to an objective memory weakness since subjects with high PiB uptake have lower performance than low PiB subjects on an episodic memory measure.

While the metacognition literature has repeatedly confirmed the multidimensional nature of monitoring processes[47–49], 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, when participants have 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 in comparison to memory monitoring based on the present. For the on-line monitoring measure, subjects could be less prone to experience subtle cognitive limitations when they have to assess their ongoing performance in unfamiliar laboratory tasks.

Additionally, we found that regional PiB 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 amyloid load is typically the highest and the earliest, which

confirms the consistency of the association of subjective cognition with the neuropathological signs of AD. Interestingly, these regions and their right hemispheric location are also commonly associated with the self and metacognitive processes[50–52]. Nevertheless, the presence of amyloid in medial PFC/ACC and precuneus/PCC/ICC regions does not have detrimental effects on subjects' insight about their cognition. Related to this, the impact of the regional amyloid 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 people were related to genetic risks[25]and brain structural and functional features of AD[18,22]. In reference to the biomarker cascade model of AD proposed by Jack et al.[11]Aβ deposition measure in cognitively intact older subjects may be the most appropriate measure to detect the earliest manifestation of AD. While the two previous PiB studies involving SCI subjects were not conclusive about the association of PiB with SCI[28,29], our results are consistent with findings from postmortem investigations showing a relationship between memory complaints and AD pathology (including amyloid) in older people without dementia[26,27].

Our study provides new evidence that cognitively normal and non depressed 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[1–4]. Interestingly, a recent study[29]enriches the cascade model of AD proposed by Jack et al.[11]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 amyloid accumulates and subtle neurodegeration 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[53]. Then, amyloid deposition may reach a plateau, atrophy rates may accelerate and MCI may appear[11].

With regard to the interpretation of SCI in aging (SCI is often associated with affective or personality traits rather than dementia[54]), our results suggest that lower confidence about one's memory in older subjects with intact cognition may not be a benign symptom and should be evaluated carefully since it may reflect an underlying degenerative process. These conclusions should be considered cautiously for several reasons. The present study is amongst the first to test the relationship between subjective cognition and an AD neuropathological hallmark, thus, replication studies are warranted. Whereas our high PiB subjects are less confident about their memory than low PiB subjects, they cannot be identified as "complainers", and it is unclear whether similar results would be identified in SCI subjects. 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 considering these limitations and with longitudinal follow-up of participants.

Acknowledgements:

The authors thank all the participants from the study. This work was supported by a grant from the National Institute on Aging (AG027859), the Alzheimer's Association (ZEN-08-87090), the Lavoisier grant from the French Ministry of Foreign and European Affairs, the France-Berkeley Fund, the Therese et Rene Planiol foundation, and the Societe de Neuropsychologie de Langue Francaise association.

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Figure 1

Proportion of self-reports to the general question about one's memory abilities relative to other people of the same age, according to the PiB group.

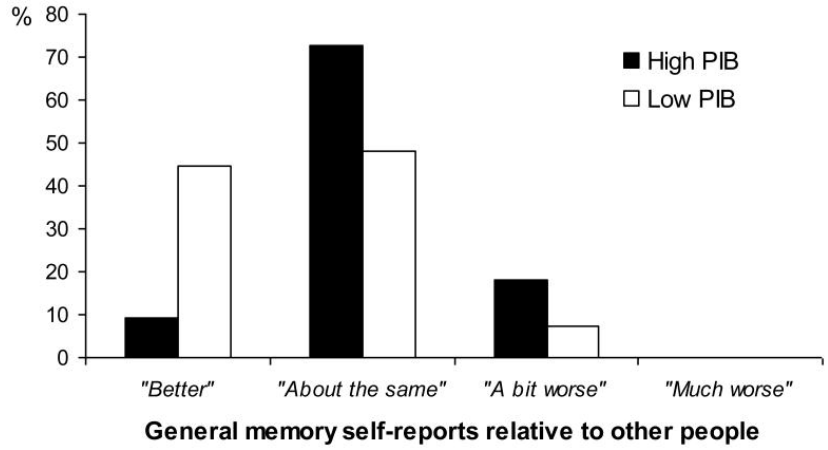

Table 1

PiB group differences on demographic variables, cognitive and metacognitive measures.

	High PiB			Low PiB			Difference test (a)
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**p**
Demographics							
Age	11	75.73	6.05	28	71.89	5.45	0.115
Education, years	11	16.82	1.89	28	17.61	2.02	0.170
Gender, n	9F/2M			15F/13M			0.103 (b)
GDS	11	4.45	2.73	28	3.86	3.04	0.473
MMSE	11	29.18	0.98	28	28.96	1.23	0.755
Cognitive measures							
CVLT Immediate Free Recall	10	40.20	9.08	28	50.46	10.55	**0.007**
CVLT Short-Delay Free Recall	10	8.00	4.52	28	10.75	2.86	0.097
CVLT Short-Delay Cued Recall	10	10.90	2.81	28	12.14	2.73	0.208
CVLT Long-Delay Free Recall	10	9.40	4.03	28	11.39	3.27	0.154
CVLT Long-Delay Cued Recall	10	10.20	3.58	28	11.86	2.65	0.196
CVLT Recognition Hits	10	13.80	3.52	28	14.21	1.73	0.855
z CVLT delayed performance	10	−0.29	1.02	28	0.13	0.78	0.281
VR-I Immediate Recall Total	11	76.82	13.67	28	81.46	13.18	0.310
VR-II Delayed Recall Total	11	53.64	24.76	28	67.39	19.52	0.073
VR Recognition Total	11	42.64	4.48	28	45.21	2.33	0.073
z VR delayed performance	11	−0.16	1.11	28	0.50	0.69	0.063
Stroop Correct in 60 s	11	48.73	13.95	28	50.11	12.50	0.767
Digit Span Total	11	17.09	3.86	28	16.50	3.97	0.492
Listening Span Total Recalled	11	41.73	6.90	27	47.04	8.28	0.071
Letter Fluency Total	11	48.64	11.36	27	47.74	9.62	0.859
Category Fluency Total	11	33.09	12.09	27	37.19	8.51	0.311
Metacognitive measures							
Off-line monitoring							
SR relative to other people	11	2.09	0.54	27	1.63	0.63	**0.039** (c)
SR relative to 20 years ago	11	2.82	0.75	27	2.93	0.55	0.872 (c)
On-line monitoring							
SR CVLT Post-delay	10	47.70	20.48	28	55.50	21.63	0.426
SR VR Post-delay	11	66.00	21.34	28	70.29	19.34	0.574
SR Stroop	11	53.18	27.55	28	60.25	20.22	0.483
SR Digit Span	11	54.36	23.29	28	57.25	23.12	0.651
SR Listening Span	11	33.55	25.16	27	36.89	18.61	0.499
SR Letter Fluency	11	57.36	22.67	27	53.07	21.73	0.520
SR Category Fluency	11	55.45	19.29	27	57.63	17.39	0.872
Composite on-line SR (d)	11	53.05	18.19	28	56.14	15.04	0.391

Notes. (a)= Mann-Whitney U Test; (b)= Chi-square difference test; (c)= Mann-Whitney U Test (Z statistic adjusted for ties); (d)= Given missing data for 2 subjects, their composite on-line SR score was calculated on the basis on four and six on-line SR measures, respectively, rather than on the seven on-line SR measures. GDS= Geriatric Depression Scale; MMSE= Mini Mental State Examination; CVLT: California Verbal Learning Test; VR= Visual Reproduction test; SR= Self-reports.

Table 2

Correlations between PiB and general memory self-reports relative to other people of the same age, for the five key ROIs (effects of age, gender, education and GDS were removed).

ROIs		**PiB * Memory self-reports relative to other people (N=47)**	
		r	**p**
Medial PFC/ACC	L	.16	.302
	R	**.31**	.044
Lateral PFC	L	.19	.217
	R	.19	.213
Precuneus/PCC/ICC	L	.18	.259
	R	**.33**	.031
Medial TL	L	.15	.355
	R	.14	.380
Lateral TL	L	.15	.333
	R	.18	.250

Notes. L= left hemisphere; R= right hemisphere; PFC= prefrontal cortex; ACC= anterior cingulate cortex; PCC= posterior cingulate cortex; ICC= isthmus cingulate cortex; TL= temporal lobe.