Published in final edited form as:

J Alzheimers Dis. 2015 September 24; 48(0 1): S151–S159. doi:10.3233/JAD-150113.

Amyloid-beta imaging in older adults presenting to a memory clinic with subjective cognitive decline

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Abstract

Background—Subjective cognitive decline (SCD) in otherwise normal aging may be identified via symptom inventories in a research setting (‘questionnaire-discovered complaints’) or via patients seeking evaluation / services in a clinical setting (‘presenting complainers’). Most studies of SCD and amyloid-beta (A β) imaging to date have used the former approach, with inconsistent results.

Objective—To test whether ‘presenting SCD’ participants in an academic memory clinic setting show increased brain A β deposition on imaging.

Methods—Fourteen patients (mean age 68.1, SD 4.0 years) diagnosed with subjective cognitive complaints with normal neuropsychological testing were recruited into a Pittsburgh compound B (PiB)-PET study. Detailed self-report inventories and additional cognitive tests were administered. Results were compared to a reference cohort of cognitively normal (CN) volunteers from an independent neuroimaging study (mean age 73.6, SD 5.8 years)

Results—57% (8/14) of SCD participants were PiB-positive by a sensitive, regionally-based definition, compared to 31% (26/84) of the CN cohort. SCD participants had significantly higher PiB retention (SUVR) than CN in three of six regions of interest: frontal cortex ($p=.02$), lateral temporal cortex ($p=.02$) and parietal cortex ($p=.04$). Findings were suggestive that deficits on verbal associative binding may be specific to A β -positive vs. A β -negative SCD.

Conclusion—Older participants with SCD presenting to a memory clinic have higher brain A β deposition compared to normal aging study volunteers unselected on complaints. Further study of presenting SCD are warranted to determine the prognostic significance of A β deposition in this context.

MeSH keywords

Memory; Cognition; Amyloid beta-protein; Positron-Emission Tomography

Subjective complaints about memory and thinking abilities are commonly reported in older adults, with large variation in prevalence estimates (ranging from 25–55% in community-based studies) [1, 2]. Evidence from longitudinal studies indicates complaints confer a degree of elevated risk for subsequent cognitive decline and/or incident dementia/Alzheimer Disease (AD) [3, 4], although there is considerable variability among studies. Reviews also emphasized that determinants of subjective memory complaints (SMCs) in aging are complex and include individual differences in mood and personality [3, 5].

Over the past decade, evidence has accumulated of AD-biomarker associations with subjective memory concerns in otherwise cognitively normal older individuals. Glucose hypometabolism [6, 7], hippocampal atrophy [8, 9], APOE*4 allele status [10, 11], CSF amyloid-beta (A β) and tau [12], and amyloid-beta (A β) imaging [13, 14] may be linked to subjective memory complaints. Other reports included associations with other neuroimaging biomarkers, such as white matter hyperintensities [15, 16]. Several functional MRI studies demonstrated altered task-related activation [17, 18] or increased [19] / decreased [20] default mode network (DMN) connectivity associated with subjective memory complaints. This line of research is relevant to the NIA-AA proposed staging categories for preclinical AD [21], particularly stage III defined by amyloidosis and early neurodegenerative markers accompanied by subtle cognitive/behavioral decline. This last stage of preclinical AD in the model putatively captures individuals approaching the border zone with clinical criteria for mild cognitive impairment (MCI). As noted in the NIA-AA recommendations on defining preclinical stages of AD [21], subjective memory complaints in otherwise healthy individuals are consistent with the construct of ‘subtle cognitive decline’ [22].

This pilot study reports initial findings on A β imaging in patients who have presented to a memory-disorders clinic with cognitive concerns but with normal objective evaluation. Previous studies of subjective memory complaints and A β imaging have been inconsistent, with several studies reporting associations [13, 14, 23] and others finding no association [24, 25]. These studies included volunteers completing symptom inventories and self-report measures in a research setting, but otherwise not complaining in a clinically significant context (‘questionnaire-discovered complaints’). The present paper focuses on individuals having sufficient concern about their memory to motivate spontaneous complaint in a clinical setting (‘presenting complainers’). This narrow selection criterion limits generalizability of study findings but is of more direct relevance to the common scenario of the “worried well” in a practice setting [26]. The longer-term study goal is to determine the clinical and prognostic significance of A β in subjective cognitive decline (SCD) presenting in this context. In addition to A β imaging with Pittsburgh compound B (PiB)-PET, we evaluated subjective cognitive symptoms, depressive symptoms, personality, and performance on more challenging / specific cognitive tasks. In this preliminary report, we hypothesized that clinically presenting SCD individuals will have higher greater A β load compared to cognitively normal (CN) older study volunteers.

Methods

Participants

14 individuals who sought evaluation at the University of Pittsburgh Alzheimer Disease Research Center (ADRC) were included. Specific inclusion criteria were 1) age 60 and older; 2) subjective concern regarding memory or thinking was a reason for seeking evaluation; 3) normal neuropsychological test performance; 4) English language fluency. Exclusion criteria were 1) significant neurologic conditions known to affect CNS function (e.g., tumor, seizure disorder); 2) active major psychiatric disorder (e.g., major mood disorder, psychotic disorder); and 3) contraindications for MRI or PET imaging. The ADRC diagnostic neuropsychological (NP) test battery consisted of tests of a) *memory* (Word List Learning from the Consortium to Establish a Registry in Alzheimer's Disease battery [27], Logical Memory Story A from the Wechsler Memory Scale – Revised [28], modified Rey Osterrieth [R-O] figure recalls [29]); b) *visuospatial construction* (modified block design subtest from the Wechsler Adult Intelligence Scale – Revised [WAIS-R] [30], copy of the R-O figure); c) *language* (semantic and letter fluency [31], Boston Naming Test [32]); d) *attention and executive functions* (Trail Making Test A & B [33], Digit Symbol and Digit Span forward and backward from the WAIS-R [28], Stroop color-word interference test [34], clock drawing [35], and abstract reasoning subtest from the Mattis Dementia Rating Scale [36]). Cognitive diagnostic adjudication was determined via multi-disciplinary consensus conference [37], in which NP testing, medical and social history, daily functioning, reported cognitive symptoms, and structural MRI findings were reviewed. Criteria for normal NP were: 1) no more than 1 test score lower than expected within a cognitive domain; no more than 2 scores lower than expected across domains. The threshold for 'lower than expected' performance corresponded to –1 SD below age-adjusted control means.

APOE genotyping was completed as part of the ADRC evaluation for non-diagnostic research purposes.

Participants were approached and recruited for the present pilot study after their ADRC visit and consensus adjudication as SCD. All study procedures approved by the University of Pittsburgh Institutional Review Board; all participants completed written informed consent.

Self-report inventories

Participants completed subjective cognition scales, including the 64-item Memory Functioning Questionnaire (MFQ) [38]; the 25-item Cognitive Failures Questionnaire (CFQ) [39]; and a 24-item subjective cognitive complaints scale (SCCS) [40]. Depressive symptoms were measured with the 30-item Geriatric Depression Scale (GDS) [41]. Personality traits were assessed with the NEO Five-Factor Inventory (NEO FFI-3), a 60 item questionnaire measuring the domains neuroticism, consciousness, extraversion, agreeableness, and openness-to-experience [42]. Raw NEO-FFI scores were converted to standardized T-scores (mean 50, SD 10) according to test manual norms and procedures.

Of note, self-report scales were not used in study inclusion criteria or to classify participants as SCD, but were administered after recruitment into the SCD study and within 3 months of PiB-PET imaging.

Memory Capacity Test (MCT; [43])

The MCT is a verbal memory paradigm with controlled learning (via semantic encoding) that measures associative binding. First, a 16-item word list is presented visually (4 words at a time) and the participant is asked to identify and name the word associated with a unique category cue (e.g., “Which word is a country?” “Which word is an occupation?”). The learning trial is followed by a category-cued recall trial (“Which was the country?” “Which was the occupation?”). Next, a second 16-item list is presented, composed of different exemplars from the same 16 categories as the first list. A semantically supported learning trial is administered as with the first list, followed by category-cued recall of the 2nd list (“From the 2nd list only, which was the country?” “Which was the occupation?”). In a free recall trial, participants recall all words from both lists, without cues. This test has shown specific associations in CN older study volunteers between A β deposition and lower performance on list 2 recall, consistent with poorer associative binding and heightened semantic interference [44].

PiB-PET Neuroimaging

[11C]PiB was produced as previously described [45]. Prior to PiB-PET, an MPRAGE sequence was obtained on a 3T Siemens Trio TIM scanner for each subject for co-registration and region-of-interest (ROI) definition [45]. PET imaging was conducted using a Siemens/CTI ECAT HR + (3D mode, 15.2 cm field-of-view, 63 planes, reconstructed image resolution ~ 6 mm FWHM). The participant's head was immobilized to minimize head motion. PiB was injected intravenously (12–15 mCi, over 20 s, specific activity ~ 1–2 Ci/ μ mol) and PET scanning was performed at least 50–70 min post injection. Analysis of the PiB PET data utilized standardized uptake value ratio (SUVR) (determined 50–70 min post-injection). To calculate SUVR, SUV was first determined by normalizing regional tissue radioactivity concentration to injected dose and body mass, and then each regional SUV was divided by the cerebellar reference SUV that was representative of free and nonspecific radiotracer retention. Because of the relatively young age of the participants, SUVR values were not atrophy corrected. PiB retention was quantified in six regions of interest: precuneus, anterior cingulate, frontal, parietal, lateral temporal and the striatum. Overall PiB status (negative vs. positive) was defined in this study as PiB-positivity in at least one of these 6 ROIs, based on regional cutoffs derived from sparse-k-means cluster analysis [46].

CN comparison group

Data from n=84 participants enrolled in an independent study on normal aging were used in these analyses and presented here as a reference group [47, 48]. Participants 65 years and older were recruited via advertisements in local newspapers, senior centers and research registries. Exclusion criteria included history of major psychiatric or CNS disease, use of psychoactive medications, GDS > 15, or neuropsychological test performance inconsistent with normal cognition. The NP test battery was identical to the ADRC / SCD test battery. Participants completed the same MR and PiB-PET imaging protocols as the SCD study.

Subsets of the NC group completed the same self-report (subjective cognition, depression and personality) scales as the SCD study (n=48), as well as the Memory Capacity Test (n=68).

Analysis

As the SCD sample size is small (n=14) in this preliminary report, we limited inferential statistical analysis to the primary hypothesis of increased A β deposition in SCD compared to NC. We used ANCOVA covarying for age on mean SUVR in each of the 6 PiB-PET ROIs (see above). Other data are presented in case series format, with other summary measures presented as descriptive.

Results

Participant characteristics and PiB status

Characteristics of fourteen SCD study participants are shown in Table 1, with reference to the NC comparison group. Of note, they were slightly younger [mean age 68.1 (SD 4.0)] than the NC comparison group, and they were highly educated [mean 17.5 years (SD 2.1)]. APOE*4 allele was present in 4 /13 (30.8%, compared to 19.2% NC), and PiB status was positive for 8/14 (57.1%, compared to 31.0% NC). Table 1 also presented selected NP test scores, which were almost entirely within 1 SD of the NC group means. This was as expected since these NP tests were used in the diagnostic classification of 'normal test performance' at ADRC clinical case conference.

PiB-PET SUVR

SCD participants had higher mean SUVR in *frontal cortex* [1.60 (SD 0.45)] compared to NC [1.38 (SD 0.29); $F(1,95) = 5.32, p = .02$] (Figure 1). This was also observed in *lateral temporal cortex* [SCD 1.49 (SD 0.29) vs. NC 1.31 (SD 0.26); $F(1,95) = 5.69, p = .02$] (Figure 1), and in *parietal cortex* [SCD 1.55 (SD 0.40) vs. NC 1.39 (SD 0.27); $F(1,95) = 4.3, p = .04$]. There were no significant group differences in *precuneus* [SCD 1.57 (SD 0.29) vs. NC 1.40 (SD 0.34); $F(1,95) = 3.23, p = .08$]; *anterior cingulate* [SCD 1.57 (SD 0.45) vs. NC 1.37 (SD 0.35); $F(1,95) = 3.43, p = .07$]; or *anterior ventral striatum* [SCD 1.47 (SD 0.33) vs. NC 1.35 (SD 0.29); $F(1,95) = 2.49, p = .12$].

Self-report inventories

Table 2 presents scores on subjective cognition, depression and neuroticism self-report scales. In contrast to normal performance on NP diagnostic tests, the SCD participants as a group characteristically scored outside the 1 SD range around NC means in the direction of worse cognition across the 3 measures. This was a similar general trend for higher number of depressive symptoms and higher trait neuroticism. There was no obvious pattern of association with PiB-positivity.

Memory Capacity Test

Table 3 presents selected MCT scores. Immediate cued recall of the 1st list is an easy condition as can be seen by scores near ceiling. Cued recall of the 2nd list is affected by

proactive semantic interference. Free recall (of words from both lists, but with scores broken out by list) reflects associative binding. While the association with PiB status was not formally tested, notably all four participants with scores falling below the -1 SD normative threshold were PiB-positive. Each had lower scores on at least one list 2 measure - either cued or free recall. Conversely, 4 PiB-positive SCD participants had normal range MCT performance.

Discussion

These pilot study results show that by selecting for study older adults presenting to a memory clinic with concerns about their cognition, but testing within normal limits on objective evaluation, one observes 1) measurable deviations on standardized scales of subjective cognition and negative affect; and 2) increased A β deposition on PiB-PET imaging. Self-ratings of subjective cognition, depressive symptoms and trait neuroticism were not obviously associated with PiB status in this small case series. There were suggestive preliminary data that specific deficits on the Memory Capacity Test, a measure of associative binding and susceptibility to semantic interference, may be specific for A β -positive SCD (though not sensitive). Further study with a larger sample is needed to evaluate and confirm these observations more formally.

The distinction between ‘questionnaire-discovered complainers’ and ‘clinically presenting complainers’ has been discussed [5, 22] but not systematically investigated with regard to SCD characteristics and outcomes. Not surprisingly, the questionnaire approach dominates in the literature as it is more feasibly employed in aging studies and arguably more relevant to questions of public health and screening. Several A β imaging studies have used the questionnaire approach. In a small study by Perrotin et al. of cognitively normal volunteers [13], a meta-cognition rating (“rate your general memory compared to others of the same age”) significantly differed between PiB-positive ($n=11$) and PiB-negative ($n=28$) individuals. Amariglio et al. [14] reported a significant association between a subjective memory complaint composite score and A β deposition in the Harvard Aging Brain Study of CN study participants ($n=131$). Snitz et al. [23] observed an association between PiB retention and one (of three) subjective cognition measures in CN older study volunteers ($n=92$). In contrast, subjective memory complaints (SMCs) among healthy control volunteers were *not* associated AD-biomarkers, including A β imaging, in the large AIBL cohorts [24, 25].

Studying clinically presenting complainers may be the likelier selection approach to yield significant associations with preclinical AD [49]. It also more closely captures a very real clinical scenario: the older patient, motivated enough by subjective memory concerns to show up in the clinic, but an otherwise normal exam. Worry motivates health service-seeking behavior, although other factors are also influential [50, 51]. Worry may also have prognostic significance: Jessen et al. [52] reported that SMCs accompanied by worry significantly increased the odds of incident dementia over four years follow-up, compared to SMCs without worry, in a large cohort of German primary care patients.

An important limitation, however, to studying presenting complainers is the constraint on generalizability and external validity. In general, this approach has little relevance to efforts to develop SMC screening measures for otherwise unselected populations. The participants in this study were highly selected, with regard to the academic specialty center setting, the exclusion criteria, as well as the nature of self-referral. They were highly educated, relatively young, and healthy - thereby increasing the odds that AD-related pathology, rather than other disease processes, underlies subjective cognitive decline. Further, high education may contribute to ceiling effects and lowered sensitivity in diagnostic neuropsychological assessment [53].

Recommended guidelines for appropriate use of Amyloid PET imaging were published in 2013, based on consensus of experts convened by the Society for Nuclear Medicine and Molecular Imaging and the Alzheimer's Association [54]. An appropriate indication is for "persistent or progressive unexplained MCI", in individuals for whom clinical management may altered and who would likely benefit from greater certainty in underlying etiology. This recommendation is based on empirical evidence review of prognostic value of Amyloid PET for predicting future outcomes in MCI. Inappropriate indications include asymptomatic individuals, as well as "patients with a cognitive complaint which is unconfirmed on clinical exam." For both scenarios, the taskforce concluded that evidence is too incomplete to date regarding prognostic information of a positive (or negative) scan. However, the taskforce stated that appropriate use guidelines will require periodic reassessment, as both dementia research and care and Amyloid PET technology are in active development. Studies of 'presenting SCD' with longitudinal follow-up are needed to assess the prognostic value of a positive Amyloid PET scan in this clinical context.

In sum, we report evidence of increased A β deposition in older adults presenting at a memory clinic with subjective concerns but normal NP performance. Further follow-up will determine whether A β positivity on neuroimaging in clinically presenting SCD increases risk for cognitive decline.

Acknowledgments

This study was funded by grants from the NIH-NIA: K23 AG038479; R37 AG025516; P50 AG005133.

We gratefully acknowledge the generous time and effort of the study participants, the University of Pittsburgh ADRC and PET Research Center staff, and especially Ms. Claire McConaha.

Financial disclosures: Drs. Klunk and Mathis are co-inventors of PiB, a technology described in this manuscript. As such, they have a financial interest in the license agreement, which GE Healthcare holds with the University of Pittsburgh. GE Healthcare provided no grant support for this study and had no role in the design or interpretation of results or preparation of this manuscript Dr. Lopez has consulted for Lilly, Baxter, Lundbeck & Grifols.

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Figure 1.

PiB retention (SUV-R) in frontal and lateral temporal cortical regions of interest, in n=84 cognitively normal (CN) older participants and n=14 participants with subjective cognitive decline (SCD). Horizontal line indicates median; cross indicates mean.

Table 1

Demographics, selected NP test performance, APOE*E4 and PiB status of 14 presenting SCD participants, with reference to the NC comparison group (n=84)

Case #	Age (years)	Sex	Education (years)	APOE	MMSE	CERAD WLL DR (max=10)	mR-O Copy (max=24)	Animal Fluency	Trails B (sec)	PIB status
1	70	M	20	33	30	6	23	17	40	+
2	66	F	20	33	29	10	23	30	78	+
3	65	F	18	34	30	8	21	23	57	+
4	69	F	20	33	30	8	24	25	45	-
5	74	F	16	33	29	9	23	30	68	-
6	67	F	16	34	29	6	23	28	64	-
7	65	F	17	34	28	7	22	19	58	+
8	70	M	20	34	30	8	24	22	60	+
9	63	M	16	33	27	8	24	21	64	-
10	76	F	16	---	29	*	19	15	80	-
11	69	F	13	33	28	8	24	24	62	+
12	69	M	18	33	29	7	22	17	68	-
13	69	F	18	33	30	7	23	34	89	+
14	61	M	18	23	30	8	24	17	69	+
<hr/>										
NC comparison group (n=84) 73.6 (5.8) 54 F (64%) 15.1 (2.6) 14/73 E4 carriers (19.2%) 28.6 (1.3) 7.0 (1.3) 20.4 (2.0) 20.0 (4.7) 75.7 (33.1) 26/84 PIB(+) (31.0%)										

Notes. MMSE = Mini Mental State Exam; CERAD = Consortium to Establish a Registry in Alzheimer's Disease; WLL = Word List Learning; DR =delayed recall; mR-O = modified Rey-Osterrieth Figure;

* California Verbal Learning Test score = 10 / 16 words; Z-score by CVLT manual norms (ref) =0.0

Shaded cells signify NP test values below -1 SD below the mean of the NC comparison group

Table 2

Scores on subjective cognition, depression and neuroticism self-report scales

Case #	MFQ (higher=better)	CFQ (higher=worse)	SCCS (higher=worse)	GDS	Neuroticism (T-score)	PIB status
1	257	52	6	16	57	+
2	228	50	9	---	50	+
3	262	51	10	11	55	+
4	230	37	9	9	58	-
5	265	50	15	15	71	-
6	269	48	8	2	50	-
7	229	51	16	8	59	+
8	219	54	15	10	46	+
9	277	44	11	7	44	-
10	242	40	8	11	46	-
11	249	64	10	26	75	+
12	299	34	6	3	39	-
13	193	59	12	6	50	+
14	243	62	12	5	39	+

NC comparison group (n = 48), mean (SD) 299.2 (38.2) 34.6 (9.6) 4.3 (3.6) 3.8 (3.8) 41.7 (7.6)

Note. MFQ=Memory Functioning Questionnaire; CFQ=Cognitive Failures Questionnaire; SCCS=Subjective Cognitive Complaint Scale; GDS=Geriatric Depression Scale

Shaded cells signify values greater than 1 SD distance from the mean of the NC comparison group, in the pathologic direction (worse subjective cognition / higher symptoms / higher neuroticism)

Table 3

Memory Capacity Test (MCT) performance and PiB status

Case #	Immediate cued recall 1 st list (max=16)	Immediate cued recall 2 nd list (max=16)	Immediate free recall 1 st list (max=16)	Immediate free recall 2 nd list (max=16)	PiB status
1	16	12	11	8	+
2	16	16	11	12	+
3	16	16	10	0	+
4	16	16	11	12	-
5	16	15	11	13	-
6	16	13	10	7	-
7	15	13	3	6	+
8	15	8	5	6	+
9	16	16	10	10	-
10	16	16	8	9	-
11	16	12	9	7	+
12	16	14	8	9	-
13	16	10	9	7	+
14	16	16	11	10	+
NC comparison group (n=68), mean (SD)					9.6 (2.8)

Notes. Shaded cells signify values below -1 SD below the mean of the NC comparison group