Featured Article

Amyloid-associated increases in longitudinal report of subjective cognitive complaints

Rebecca E. Amariglio[a,b,*], Rachel F. Buckley[b,c,d], Elizabeth C. Mormino[b,e], Gad A. Marshall[a,b], Keith A. Johnson[a,b,f], Dorene M. Rentz[a,b], Reisa A. Sperling[a,b]

[a]Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[c]Florey Institute, University of Melbourne, Parkville, Victoria, Australia
[d]Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria, Australia
[e]Department of Neurology, Stanford Medical School, Palo Alto, CA, USA
[f]Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Introduction: To investigate whether baseline subjective cognitive complaints (SCCs) predict longitudinal decline on neuropsychological testing and whether SCC increases longitudinally, in the setting of high levels of amyloid burden.

Methods: Two hundred seventy-nine clinically normal older participants (mean age = 73.7 ± 6.1 years) from the Harvard Aging Brain Study, a cohort of community-dwelling individuals, were followed longitudinally (4.27 ± 1.35 years) with annual subjective memory questionnaires and neuropsychological assessment. ^{11}C Pittsburgh compound-B positron emission tomography was used to measure cortical amyloid and to classify status (Aβ+/Aβ−) at baseline.

Results: Higher baseline SCC predicted more rapid cognitive decline on neuropsychological measures among those with elevated amyloid (t = -2.18, $P < .0001$). In addition, longitudinal report of SCC significantly increased over time, with SCC progression most pronounced among Aβ+ individuals (t = 2.24, $P = .0005$).

Discussion: SCC may inform risk for future cognitive decline and track progression of self-perceived decline, particularly in those along the AD trajectory, providing potentially important indicators of clinical meaningfulness in AD prevention trials.

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Keywords: Preclinical Alzheimer's disease; Subjective cognitive decline; Amyloid; PET imaging

1. Introduction

Experiencing persistent subjective cognitive complaints (SCCs) in the absence of clinical impairment may represent one of the earliest manifestations of Alzheimer's disease (AD) [1,2]. SCCs offer complementary information to standard neuropsychological assessment in that they reflect the person's own perspective, an important component in tracking early disease progression. Several cross-sectional studies have shown that greater SCCs, in older individuals who are otherwise clinically normal, are associated with AD biomarkers, including increased beta-amyloid (Aβ) and neurodegeneration [3–7] and greater entorhinal cortical tau burden [8]. Longitudinal studies using baseline SCC to predict cognitive and clinical outcomes have been mixed [9–14], but a few recent studies have suggested that SCC in the context of elevated AD biomarkers predict worse cognitive and clinical outcomes than SCC alone [15–17].

The longitudinal trajectory of SCC, particularly in individuals with elevated AD biomarkers, is not known. While it has been shown that cognitive performance on

*Corresponding author. Tel.: +(617) 732-8085. Fax: (617) 738-9122.
E-mail address: ramariglio@mgh.harvard.edu

neuropsychological assessment declines more steeply in individuals with preclinical AD [18–20], it has yet to be determined whether individuals with preclinical AD show an increase in SCC longitudinally. If a longitudinal increase in SCC was observed in individuals on the AD continuum, this would provide further support for the concept of SCC as valuable marker of AD, in that individuals perceive increasing cognitive difficulties as the disease progresses.

In the present study, we sought to examine the role of SCC in predicting and tracking disease progression in clinically normal individuals with abnormal Aβ levels measured by Pittsburgh compound B positron emission tomography (PIB-PET). First, we hypothesized that greater baseline SCC would predict steeper decline on objective neuropsychological measures particularly in the context of elevated Aβ compared to those with lower levels. Second, we predicted that SCC would increase more rapidly in individuals with abnormal Aβ compared to those with lower levels.

2. Methods

2.1. Participants

To be enrolled in HABS at baseline, participants were clinically normal, defined as a global score of 0 on the Clinical Dementia Rating Scale [21], greater than 25 on the Mini–Mental State Examination [22], less than 11 on the 30-item Geriatric Depression Scale [23], and normal performance within validated education-adjusted norms on Logical Memory II delayed recall [24]. A detailed review of medical history and functional performance as well as physical and neurologic examinations confirmed their status as clinically normal. None of the participants had a history of alcoholism, drug abuse, head trauma, or current serious medical or psychiatric illness. All study staff who assessed subjects clinically were blinded to the biomarker status of the subjects. This study included 279 HABS participants at baseline.

Participants were followed for an average of 4.27 ± 1.35 years (range: 2–6 years) with annual cognitive testing. Participants underwent *APOE* genotyping. Demographics at baseline can be found in Table 1. Study protocols were approved by the Partners Institutional Review Board, and all participants provided informed consent before undergoing any study procedures.

2.2. Test battery and timeline

HABS participants were administered a set of seven yes or no questions annually, adapted from the Structured Telephone Interview for Dementia Assessment (STIDA) used in a large epidemiological study of nurses for assessing cognitive change in older individuals [25,26]. Answers on these questions (0 = no, 1 = yes) were added together to create a summary score that was used in statistical analyses. Subsequently, a z-score, using the baseline average, was

Table 1
Demographics table at baseline

	All	Aβ+	Aβ−
N	279	70	209
Age (years)	73.4 (6.1)	75.0 (5.7)	72.9 (6.0)
Sex (% female)	59	61	59
Years of education	15.8 (3.0)	16.3 (3.0)	15.7 (3.1)
APOE ε4 status (% carriers)	29	61	18
Logical Memory delayed recall	13.7 (3.3)	14.0 (2.1)	13.6 (3.3)
MMSE	29.0 (1.1)	28.8 (1.0)	29.1 (1.1)
Free and Cued Selective Reminding Test (/96)	80.9 (5.9)	80.7 (6.0)	81.0 (5.9)
Digit Symbol Coding Test	47.23 (10.7)	46.9 (10.0)	47.3 (11)
Sum of STIDA (/7)	1.14 (1.2)	1.4 (1.3)	1.03 (1.2)

Abbreviations: MMSE, Mini–Mental State Examination; STIDA, Structured Telephone Interview of Dementia Assessment.
NOTE. Values represent mean (standard deviation) except for sex and amyloid status in which values represent percentages.

calculated for each year of the study that was used in analyses. Higher scores on the STIDA z-score indicate greater subjective cognitive concerns.

Objective cognitive performance was examined using the Preclinical Alzheimer Cognitive Composite (PACC) [20,27], a cognitive composite that has previously been shown to be sensitive to amyloid-related decline. The PACC comprised the following neuropsychological tests: (1) Logical Memory delayed recall [24] (2) Free and Cued Selective Reminding Test free and total cued recall score [28], (3) number completed on the digit-symbol test [29], and (4) Mini–Mental State Examination total score [22]. Measures were z-transformed based on the mean and standard deviation from the larger HABS baseline sample and averaged. Lower scores on the PACC z-score indicate lower cognitive performance. Participants were administered measures from the PACC annually.

2.3. PiB-PET imaging

[11]C Pittsburgh compound-B PET data were collected at baseline, as previously been described in detail [30]. PiB-PET cerebellar gray matter was used as the reference region from the Freesurfer aseg atlas as previously described [31,32], and a summary distribution volume ratio was used. A composite PiB distribution volume ratio measure of cortical amyloid burden that comprised frontal, lateral, and retrosplenial regions [33] was calculated for each participant. Baseline amyloid status (Aβ+/Aβ−) was classified using a previously reported Gaussian mixture modeling approach with a cutoff of 1.19 [34].

2.4. Statistical analyses

Two sets of longitudinal analyses were conducted. First, linear mixed models in which baseline STIDA score was used to predict longitudinal PACC performance were assessed with covariates that included age, education, and

sex. Second, linear mixed models in which baseline Aβ status was used to predict longitudinal STIDA scores were assessed with covariates that included age, education, and sex. We also ran secondary models with GDS and *APOE* ε4 carrier status in separate models.

In the first series of models, baseline STIDA score and covariates were used to predict PACC score (PACC ∼ STIDA*time + age*time + sex*time + education*time). Subsequent models included an interaction term between baseline Aβ status and STIDA score to predict PACC decline with covariates (PACC ∼ Aβ$_{status}$*STIDA*time + age*time + sex*time + education*time).

In addition, we examined the STIDA as a longitudinal outcome to determine whether there was an increase in report of symptoms over time, controlling for covariates (STIDA ∼ time + age*time + sex*time + education*time) and whether differences could be observed by Aβ group (STIDA ∼ Aβ$_{status}$*time + age*time + sex*time + education*time). All analyses using Aβ status were repeated using amyloid as continuous variable. We used the statistical package R version 3.3.2 for all statistical analyses.

3. Results

In the first set of longitudinal models, baseline STIDA score did not predict longitudinal PACC performance across participants (t = −1.3, P = .19). However, when we examined the impact of baseline Aβ status on the relationship between STIDA and PACC decline, the interaction term was significant (t = −2.18, P < .0001) such that higher STIDA score was more strongly associated with longitudinal PACC decline in Aβ+ individuals compared to Aβ− individuals (Fig. 1). Findings were also significant for all models when Aβ was used as a continuous measure (t = −3.13, P = .0018). GDS was not a significant independent predictor in the model and did not impact overall findings of SCC by Aβ to predict PACC. Similarly, adding *APOE* ε4 carrier sta-

tus as an independent predictor in the model was not significant and did not impact overall findings of SCC to predict PACC.

In the second set of models, we examined the longitudinal trajectory of the STIDA over the course of the study, controlling for covariates. Overall, STIDA score significantly increased over time (t = 2.24, P = .025) (Fig. 2). The time by Aβ group interaction was significant (t = 3.52, P = .0005), such that Aβ+ individuals demonstrated a greater increase in STIDA score over time compared to Aβ− individuals (Fig. 3). Taken in a different way, there was an annual increase in STIDA score of 0.03 in Aβ− individuals compared to 0.14 in Aβ+ individuals. When using amyloid as a continuous measure, the results were consistent with analyses using Aβ group, such that the interaction term with amyloid and time significantly predicted an increase in STIDA score (t = 2.52, P = .017). When GDS was added as an independent predictor, it did not significantly predict longitudinal SCC. When *APOE* ε4 carrier status was included in the model, *APOE* ε4 carrier status was not a significant predictor, but Aβ positivity remained a significant predictor of increasing SCC.

4. Discussion

In the present study, we found that higher self-report of cognitive complaints (i.e., STIDA) at baseline was associated with longitudinal cognitive decline on a neuropsychological composite sensitive to change in preclinical AD (i.e., PACC) in the setting of elevated Aβ. In addition, we found that SCC showed an overall increase during the study and that this increase was most evident in individuals who were Aβ+ at baseline.

Only a few previous studies have investigated the role of SCC in predicting longitudinal outcomes in the context of AD biomarker positivity. One previous study [15] demonstrated that in clinically normal individuals who were Aβ+, greater SCC predicted greater rates of clinical progression to mild cognitive impairment or dementia, although
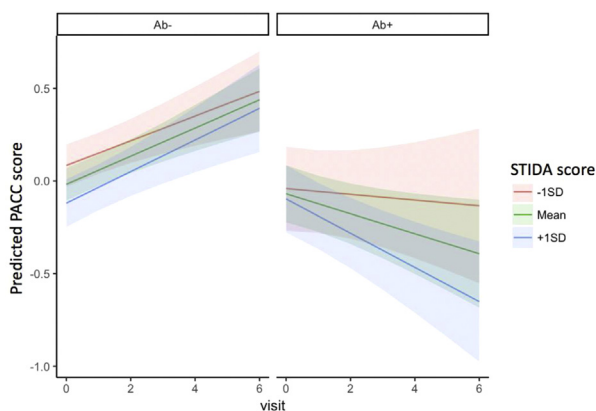

Fig. 1. STIDA predicting PACC decline separated by Aβ group. Visit occurs on an annual basis. Abbreviations: PACC, Preclinical Alzheimer Cognitive Composite; SD, standard deviation; STIDA, Structured Telephone Interview for Dementia Assessment.
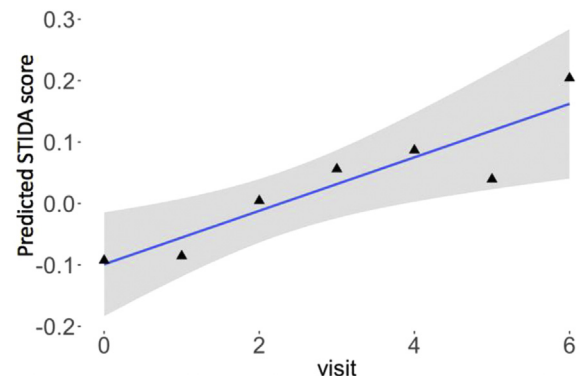

Fig. 2. Greater endorsement on STIDA over the course of the study. Visit occurs on an annual basis. Abbreviation: STIDA, Structured Telephone Interview for Dementia Assessment.
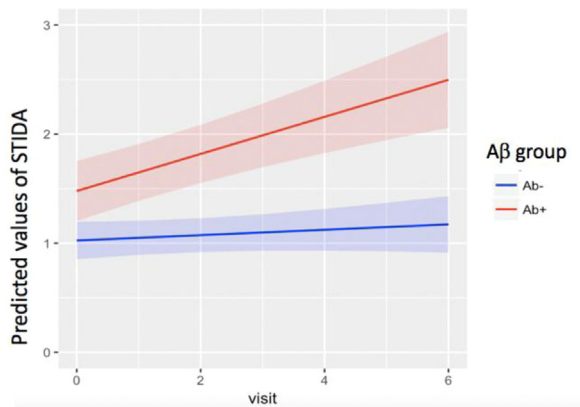
Fig. 3. Longitudinal STIDA by baseline Aβ group. Visit occurs on an annual basis. Abbreviations: STIDA, Structured Telephone Interview for Dementia Assessment; Aβ group, amyloid group.

they did not find evidence of higher rates of cognitive decline in this relatively small sample. In studies examining memory clinic patients who had memory concerns but were cognitively unimpaired on testing, one found that reduced glucose metabolism in the right precuneus at baseline predicted memory decline [16] and another found steeper cognitive decline was related to evidence of preclinical AD based on cerebrospinal fluid biomarkers [17]. Our results in the present study are in keeping with these findings, but unique in that our sample includes individuals recruited from the community who were not selected on the basis of SCC or from clinics where patients were evaluated for cognitive concerns.

Very limited studies have investigated the trajectory of SCC with longitudinal subjective report. The few studies that have compared longitudinal SCC with longitudinal cognitive performance found alignment between these measures in cognitively unimpaired individuals [35,36]. Not surprisingly, however, longitudinal self-report trajectories and neuropsychological performance were shown to diverge as individuals reached dementia, when anosognosia becomes quite common [37]. In the present study, we had the advantage of examining the natural course of SCC progression in individuals thought to be in the preclinical stages of AD based on Aβ biomarker evidence. Our findings are in support of the notion that SCC does in fact reflect progression of AD, as an increase in SCC was observed in Aβ+ individuals, even after controlling for the impact of age and other covariates.

A few limitations to the present study are worth highlighting. The SCC measure used in the present study was brief; however, we were nonetheless able to observe change over time on this measure. Furthermore, its brevity makes it more appropriate for clinical settings as in lengthy AD prevention trials. In addition, our sample was community based and participants were not required to have baseline SCC to participate in the study. While we, nonetheless, observed a longitudinal increase in SCC symptoms in our sample, it will be important to evaluate if this effect is even stronger in individuals who report high levels of SCC, such as from a memory clinic setting [38].

In the context of elevated amyloid, we provide evidence for the potential added value of SCC assessment to predict and track cognitive decline, as well as to understand disease progression from the person's own perspective that may impact everyday functioning. Longitudinal monitoring of SCC has the potential to offer insight into clinically meaningful therapeutic effects of interventions being tested in clinical trials that cannot be fully realized by objective cognitive test measures alone. Importantly, our findings suggest that longitudinal assessment of SCC in the setting of preclinical AD biomarkers may be particularly valuable for tracking progression of the earliest symptomatic changes of AD.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. While there is growing consensus that subjective cognitive complaints (SCCs) is a useful marker within the context of preclinical Alzheimer's disease (AD), no studies have examined longitudinal SCC report in clinically normal older individuals with elevated amyloid.

2. Interpretation: We demonstrate that SCC report increases longitudinally in individuals with elevated amyloid. Our findings suggest that longitudinal assessment of SCCs in the setting of preclinical AD biomarkers may be particularly valuable for tracking progression of the earliest symptomatic changes of AD.

3. Future directions: Secondary AD prevention trials are in search of sensitive tools to track clinically meaningful treatment effects in response to interventions. This article provides support for using SCC questionnaires as an outcome measure in prevention trials.

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