Cognitive & Behavioral Assessment

Actual memory as a mediator of the amyloid-subjective cognitive decline relationship

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ABSTRACT

Introduction: Amyloid pathology in cognitively normal adults is associated with subjective cognitive decline, potentially reflecting awareness of Alzheimer’s-related memory deficits. To clarify the mechanism underlying this relationship, we used mediational analyses to determine the role of depression, anxiety, and actual memory performance.

Methods: To assess amyloid deposition, we imaged 85 cognitively normal adults with florbetapir positron emission tomography imaging. Subjective cognitive decline was measured using a multidimensional instrument that assessed seven subjective memory domains. Mediational measures included assessments of actual memory performance (current and retrospective longitudinal change), depression, and anxiety.

Results: The relationship between amyloid and subjective cognitive decline was mediated by poorer memory performance and greater retrospective memory decline, not depression or anxiety. The mediational roles were significant for domains associated with memory function and memory-related anxiety.

Discussion: In individuals harboring amyloid, self-reported beliefs of declining memory likely indicate early self-awareness of actual worsening function rather than depression or anxiety.

KEYWORDS: Amyloid; Subjective cognitive decline; Subjective cognitive concerns; Memory complaints; Metamemory; Preclinical AD; Retrospective decline; Longitudinal change; Anxiety; Depression; Mediation

1. Background

Growing evidence indicates that amyloid deposition in cognitively normal adults signals a prolonged asymptomatic period of subtle neuropathology, lasting a decade or more, that precedes the clinical symptoms of Alzheimer’s disease (AD) \cite{1,2}. The high prevalence of AD combined with considerable media attention to the disorder has resulted in many older adults having concerns that their declining memory is symptomatic of AD \cite{3}. The mechanism underlying this relationship between amyloid and subjective cognitive decline (SCD) is thought to be actual memory performance but is in fact poorly understood \cite{4–6}. An issue of growing importance is whether increased SCD in cognitively normal individuals with elevated amyloid reflects actual declines related to early AD pathology \cite{7,8} or perhaps results from anxiety or depression.

Among existing studies that found a relationship between amyloid and SCD (see a comprehensive summary in Appendix A), five included both measures of actual cognition and depression or anxiety but yielded inconsistent findings \cite{9–13}. To address this issue, we used mediational
analysis [14] to assess the mechanism underlying the relationship between amyloid and SCD. This approach provides stronger evidence than traditional models that correlate depression, anxiety, or actual cognition to SCD and directly investigates whether a mediational model including potential mediators (e.g., actual memory, depression, anxiety) explains the amyloid/SCD relationship.

SCD presumably reflects an individual’s belief of past memory change, so it is conceptually more closely related to retrospective memory change rather than just present performance. Thus, the present study included two measures of actual memory—current memory performance measured at the time of SCD assessment and retrospective memory change over the previous 4 years—allowing us to verify that not just level of performance, but actual decline, mediated increased SCD in people harboring amyloid. In addition, concerns of SCD are multidimensional [15], but there has been little investigation of different categories of memory complaints.

The present study clarifies these issues by (1) simultaneously assessing the mediational effects of depression, anxiety, and actual memory as mediators of the amyloid/SCD relationship, (2) including both current performance and retrospective decline as measures of actual memory, and (3) using a multidimensional SCD questionnaire, the “Metamemory in Adulthood” [16] that differentiates seven subjective memory domains, allowing us to isolate the specific features of SCD that are most sensitive to amyloid deposition.

In addition, we studied a broader age spectrum than previous research by including middle-aged adults as there is some evidence that SCD is more predictive of amyloid pathology [17] and memory decline [18] in younger-older adults compared with the oldest adults. We also included measures of other cognitive abilities, including processing speed, inductive reasoning, and vocabulary, and examined whether deficits or declines in any of these domains mediated the amyloid/SCD relationship. We expected to see a specific association between actual memory and subjective complaints in memory.

2. Methods

2.1. Participants

This study included a total of 85 cognitively normal adults (aged 34-93 years) from the Dallas Lifespan Brain Study who completed the Metamemory in Adulthood questionnaire, and the assessment in memory, depression, and anxiety, as well as $^{18}$F fluorobetapir positron emission tomography (PET) imaging. Detailed information about participant characteristics is included in Table 1.

| Table 1 | Demographic information and characteristics of participants |
|---------|----------------------------------------------------------|
| Variable | Total (N = 85) | Liberal threshold SUVR = 1.09 | Conservative threshold SUVR = 1.12 |
|         | | Negative (N = 53) | Positive (N = 32) | P | Negative (N = 61) | Positive (N = 24) | P |
| Age (SD) | 66.97 (15.11) | 61.25 (14.86) | **76.46 (9.96)** | <.001* | 62.80 (14.82) | **77.59 (9.85)** | <.001* |
| Female, n (%) | 56 (65.9) | 32 (60.4) | 24 (75.0) | .155 | 39 (63.9) | 17 (70.8) | .548 |
| APOE e3/e4 or e4/e4 (%) | 17 (20) | 8 (15.1) | 9 (28.1) | .155 | 10 (16.4) | 7 (29.2) | .228 |
| Amyloid, SUVR (SD) | 1.13 (0.19) | 1.02 (0.36) | **1.30 (0.21)** | <.001* | 1.03 (0.42) | **1.37 (0.20)** | <.001* |
| Years of education (SD) | 15.99 (2.34) | 15.76 (2.24) | 16.38 (2.47) | .238 | 15.89 (2.30) | 16.25 (2.45) | .520 |
| MMSE (SD) | 29.12 (1.19) | 28.66 (1.23) | **29.41 (1.07)** | .005* | 29.41 (1.07) | 28.38 (1.17) | <.001* |
| CES-D (SD) | 4.62 (4.94) | 4.48 (5.16) | 4.83 (4.65) | .760 | 4.70 (5.01) | 4.41 (4.87) | .819 |
| NIHTB fear survey (SD) | 9.04 (2.68) | **9.44 (3.04)** | 8.35 (1.76) | .042* | 9.22 (2.76) | 8.57 (1.90) | .324 |
| Wave 1 and wave 2 interval | 3.99 (0.23) | 4.02 (0.25) | 3.95 (0.17) | .155 | 4.00 (0.24) | 3.97 (0.18) | .533 |

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression; MMSE, Mini-Mental State Examination; NIHTB, NIH Toolbox Emotion Battery; SUVR, standard uptake value ratio; VRM, Verbal Recognition Memory.

NOTE. Results are presented as means (SDs) or percents. Values in bold indicate a significant higher group mean compared with the other group.

*Indicates significance level of $P < .05$. 

2.2. Behavioral measures

SCD was measured using the Metamemory in Adulthood questionnaire, an instrument that assesses specific domains of subjective memory, including participants’ perception of memory capacity, stability, control, anxiety of poor memory performance, memory strategy use, knowledge about memory processes, and importance of memory achievements. Each domain is assessed with 10-18 statements (Appendix B). Participants rated how much they agree with each statement on a five-point Likert scale with lower scores reflecting greater complaints, except for memory-related anxiety where a high value reflects greater complaints.

To measure actual memory, eight measures from four episodic memory tasks were standardized and then averaged to form a single composite that represents the level of participants’ current performance. The eight measures included immediate and delayed scores from the WMS Logical Memory [19]; immediate and delayed scores from the Woodcock-Johnson Memory for Names Test [20]; immediate free-recall, delayed free-recall, and delayed recognition scores from the Hopkins Verbal Learning Test [21]; and immediate free-recall from the CANTAB Verbal Recognition Memory [22]. This composite score of current performance had a very high internal consistency, Cronbach’s $\alpha = .915$. In addition, we obtained a retrospective memory score from data collected from the same participants 4 years earlier, using five episodic memory measures (immediate free-recall, delayed free-recall, and delayed recognition from the Hopkins Verbal Learning Test and immediate free-recall and delayed recognition from the CANTAB Verbal Recognition Memory). Four of the measures were assessed at both waves of testing, and the retrospective composite score also yielded a high internal consistency, Cronbach’s $\alpha = .809$. Retrospective decline was computed as the difference score between the current score and the retrospective score 4 years prior (wave 2 – wave 1).

In addition to memory, we also had measures of processing speed, inductive reasoning, and vocabulary (see Appendix C for details of the assessments used). We constructed current performance measures and retrospective change measures for each cognitive domain, using the same method described previously for actual memory.

To measure depression, participants completed the Center for Epidemiologic Studies–Depression (CES-D) Scale [23]. Anxiety was measured by the Fear-Affect Survey, taken from the NIH Toolbox Emotion Battery [24].

2.3. Magnetic resonance imaging protocol

Participants were scanned using a 3T Philips Achieva scanner with an eight-channel head coil. High-resolution anatomical images were collected with a T1-weighted magnetization-prepared rapid gradient-echo sequence with 160 sagittal slices (field of view: $204 \times 256 \times 160$ mm; voxel size: $1 \times 1 \times 1$ mm$^3$; time to repetition: 8.1 milliseconds; echo time: 3.7 milliseconds; flip angle: $12^\circ$).

Anatomical images were processed using FreeSurfer 5.3 (FreeSurfer, http://surfer.nmr.mgh.harvard.edu/) with thorough manual editing, as described previously [25]. Specifically, the imaging data for each individual were visually inspected, edited for inaccuracies (with rechecking and reediting, as needed). Particular attention was paid to accurate skull stripping, white matter segmentation, gray and white matter boundaries, and surface reconstruction. FreeSurfer volumetric segmentation was used to obtain cortical parcellations according to the Desikan-Killiany atlas [26].

2.4. PET protocol

Participants were injected with a 370-MBq (10 mCi) bolus of AV45-florbetapir. Fifty minutes after the injection, a 2-frame by 5-minute each dynamic emission acquisition was started using an ECAT HR PET scanner (Siemens Healthineers). The PET scan was coregistered to the magnetic resonance imaging using FMRI’s Linear Image Registration Tool (FLIRT, https://fsl.fmrib.ox.ac.uk/fsl) with a mutual-information cost function.

We used a continuous measure of the mean cortical standard uptake value ratio (SUVR) in all analyses. It was computed from seven bilateral FreeSurfer-derived regions of interest (dorsolateral prefrontal, orbitofrontal, lateral parietal, lateral temporal, precuneus, isthmus cingulate, and rostral anterior cingulate cortices), using the whole cerebellum as a reference region [24]. For descriptive purposes, we reported sample characteristics based on their amyloid positivity, using two SUVR thresholds, a liberal one of 1.09 and a conservative one of 1.12, separately set two or three SDs above the mean SUVR for a young reference group in the Dallas Lifespan Brain Study sample at baseline [8]. We had 37.6% participants ($N = 32$) categorized as amyloid-positive based on the liberal threshold and 28.2% amyloid-positive participants ($N = 24$) based on the conservative one, similar to the ratio in other samples [2,27]. Fig. 1A presents the distribution of amyloid burden across age in our sample.

2.5. Statistical analyses

First, we assessed whether there was a relationship between amyloid and SCD in different domains (perceived capacity, perceived stability, perceived control, memory-related anxiety, memory strategy use, knowledge about memory processes, and importance of memory achievements). We used multiple regression to model the effects of age, amyloid, and age $\times$ amyloid interaction on each of the seven SCD domains, controlling for sex and education. Both age and amyloid were treated as continuous
variables. The significance of effects was estimated using a bootstrap procedure with the bias-corrected and accelerated 95% confidence interval (BCa 95% CI) with 5000 iterations. A false discovery rate procedure was used to adjust $P$ values within models exploring the same family of hypotheses \[28\], correcting for multiple comparisons. Nonsignificant interactions were removed to conserve power.

Next, we investigated the relationship between the proposed mediators (current performance, retrospective decline, depression, anxiety) and measures of SCD. We conducted a series of multiple regressions that examined the individual and joint effects of potential mediators on each domain of SCD, while controlling for age, sex, and education. When examining the effect of retrospective decline, we also controlled for the baseline memory 4 years earlier.

We then subjected those SCD domains that showed significant relationships with amyloid to a mediational analysis using PROCESS \[14\]. Although traditionally mediation requires a significant association between the mediator and the dependent variable, the most recent studies suggest that it is more appropriate to consider all \textit{a priori} potential mediators, even if they do not have a significant individual effect \[29,30\]. We simultaneously assessed the role of actual memory, depression, and anxiety in explaining the amyloid/SCD relationship, while controlling for age, sex, and education. We then also considered age as a moderator of the mediation.

Finally, we conducted supplementary analyses that examined (1) reverse causality \[31\] by modeling possible mediation of SCD in the relationship between amyloid and actual memory, (2) possible influences of hippocampal and entorhinal volume measures (based on the volumetric measures from FreeSurfer segmentation), race, and $APOE$ status in any observed mediation effects, and (3) whether the mediation was limited to memory or would also be found with measures in other cognitive domains. All analyses were performed in SPSS v25.

3. Results

3.1. Relationship between amyloid and different domains of SCD

The first set of regression assessed the relationship between amyloid and SCD. Amyloid burden was associated with four of the seven domains (Fig. 1B; Appendix D): higher amyloid was related to lower perceived capacity ($\beta = -.256$, $P = .010$, $P_{adj} = .023$), lower perceived stability ($\beta = -.614$, $P = .001$, $P_{adj} = .007$), lower perceived control ($\beta = -.588$, $P = .006$, $P_{adj} = .049$), and greater memory-related anxiety ($\beta = .273$, $P = .027$, $P = .027$, $P = .027$. $P = .027$, $P = .027$.
Although there was no age effect, we found a significant age × amyloid integration for perceived stability \( (P = .025) \) and control \( (P = .027) \). Both occurred because higher amyloid burden was related to greater SCD at younger ages \(^1\) (Appendix E). The other three SCD domains that involved attributes of memory rather than actual function—use of memory strategy, knowledge about memory processes, and importance of memory achievement—were not related to amyloid \( (P < .1; \text{Appendix D}) \).

### 3.2. Relationship between different domains of SCD and actual memory, depression, and anxiety

The next set of analyses address the relationships between potential mediators (current performance/retrospective decline, depression, and anxiety) and SCD. Using multiple regression, we found that current memory performance was related to lower perceived capacity \( (\beta = .431, P = .006, P_{adj} = .021) \), lower perceived control \( (\beta = .346, P = .022, P_{adj} = .051) \), and memory-related anxiety \( (\beta = -.380, P = .006, P_{adj} = .021) \) and marginally related to lower perceived stability \( (\beta = .240, P = .067, P_{adj} = .117; \text{Fig. 2A; Appendix D}) \). Depression was associated with lower perceived stability \( (\beta = -.303, P = .021, P_{adj} = .081) \) and memory-related anxiety \( (\beta = .334, P = .023, P_{adj} = .081) \) and marginally with lower perceived capacity \( (\beta = .334, P = .073, P_{adj} = .128) \). Anxiety, however, was not related to any SCD domains \((P's > .1)\). Models for the other three SCD domains were not significant \((P's > .1; \text{Appendix D})\).

Similarly, regressions with retrospective decline, depression, and anxiety showed that greater retrospective decline was significantly associated with lower perceived capacity \( (\beta = .293, P = .042, P_{adj} = .098) \), lower perceived control \( (\beta = .363, P = .009, P_{adj} = .060) \), and greater memory-related anxiety \( (\beta = -.310, P = .060) \) and marginally associated with lower perceived stability \( (\beta = .209, P = .088, P_{adj} = .154; \text{Fig. 2B}) \). Depression was related to lower perceived stability \( (\beta = -.297, P = .028, P_{adj} = .098) \) and greater memory-related anxiety \( (\beta = .330, P = .028, P_{adj} = .098) \) and marginally related to lower perceived capacity \( (\beta = -.218, P = .058, P_{adj} = .135) \). Anxiety did not show any significant relationships \((P's > .1)\). None of the effects of potential mediators for the other three SCD domains were significant \((P's > .1; \text{Appendix D})\).

In addition, to better interpret the effects of retrospective decline, we examined the effects of testing wave on memory scores to verify the direction of longitudinal change. We used a mixed-design analysis of variance including wave, age, and amyloid as factors and found that dichotomizing amyloid leads to similar but weaker effects and that slightly elevated, but below-threshold, amyloid deposition has a predictive value for SCD.
declined from wave 1 to wave 2. We also found a significant interaction between amyloid and wave indicating that the overall decline was driven by the individuals with greater amyloid (Appendix F).

### 3.3. Mediatational mechanism underlying the relationship between amyloid and SCD

We first simultaneously examined whether current performance, depression, and/or anxiety mediated the amyloid/SCD relationship, while controlling for age, sex, and education. We found that only current performance, not depression or anxiety, had significant mediatational effects: the significant mediation models (perceived capacity, perceived control, memory-related anxiety) are shown in Fig. 3. In each model, the total effect refers to the initial relationship of amyloid on SCD, excluding the mediator. The direct effect represents the direct amyloid effect that is independent of the mediator. The indirect effect represents the magnitude of the effect accounted for by the mediator, implying a possible causal relationship of amyloid on SCD through the mediator [32]. Models A, B, and C show that the effect of amyloid on perceived capacity, perceived control, and memory-related anxiety is greatly reduced when current memory performance is included as a mediator (Fig. 3; Appendix G). Depression or anxiety did not show significant mediation for any SCD domain (Appendix G).

Then, using the same approach, we examined the mediational effects of retrospective decline, depression, and anxiety, controlling for age, sex, education, and baseline memory. For the same SCD domains previously noted, the retrospective memory decline, but not depression or anxiety, mediated the relationships (Fig. 4; Appendix G), suggesting a consistent finding that SCD in individuals harboring amyloid reflects actual memory deficits that are related to early amyloid pathology, rather than depressive or anxious symptoms (Appendix G). Excluding anxiety did not change the results (Appendix H).

We also tested whether the mediation differed as a function of age. For perceived capacity, we found a significant moderated mediation of current performance (Table 2), such that poorer memory mediated the amyloid/SCD relationship at the middle (age = 53) and younger-old age (age = 68), but not the oldest age (age = 83). Despite that both amyloid/SCD relationship and amyloid/memory relationship were significant at all ages.

**Fig. 3.** Mediation of current memory performance for the relationship between amyloid and SCD on perceived capacity (A), perceived control (B), and memory-related anxiety (C). Depression and anxiety were simultaneously estimated as potential mediators but did not show any significant mediation. Age, sex, and education were controlled. Age × amyloid interaction was also controlled for perceived control. Abbreviations: CI, confidence interval; SCD, subjective cognitive decline.
ages, poorer memory did not mediate SCD at the oldest age, suggesting that younger individuals’ SCD of perceived capacity more accurately reflected their current memory difficulties related to amyloid, compared with the oldest individuals. We did not find any age-related differences in any other mediational effect.

Finally, we conducted a series of supplementary analyses to verify the significant mediations. First, to confirm the directionality of the mediation, we considered reverse causality and examined whether SCD may mediate the relationship between amyloid and actual performance. We did not find any significant effect of SCD as a mediator (Appendix I), confirming the legitimacy of the mediation models and the directionality of the relationship. Then, we considered possible influences of hippocampal and entorhinal volume differences, race, and APOE status (ε4 carrier or non-carrier) and repeated the mediation analyses including them as additional covariates. All observed effects remained significant or marginally significant (Appendix J). Finally, we examined whether the mediation of actual performance was limited to memory function, or declines in other cognitive domains may also be mediating the amyloid/SCD relationship. Measures of current performance and retrospective decline in three additional cognitive domains (processing speed, inductive reasoning, and vocabulary) were examined as mediators individually. We found no evidence of mediation for any SCD domain (Appendix K).

4. Discussion

The goal of the present study was to examine the mechanism underlying the increased SCD related to amyloid deposition in cognitively normal individuals. The recent NIA-AA framework of AD recognized SCD as one of the earliest behavioral markers that precede the clinical symptoms of AD.
Understanding this marker is of critical importance because there is increasing evidence that effective interventions to slow or prevent AD will need to be administered before individuals are clinically impaired [34]. Our results show that poorer memory performance and greater decline accounted for a significant proportion of the amyloid/SCD relationships for the complaints on perceived capacity, perceived control, and memory-related anxiety, suggesting that individuals with greater amyloid burden report more SCD probably because they actually experience greater memory difficulties due to their amyloid pathology.

4.1. Actual performance mediates the Amyloid/SCD relationship

The main finding was that the relationship between amyloid pathology and greater complaints was mediated by actual memory function, both at the time of test and the magnitude of decline over the past 4 years. This highlights the validity of SCD as an indicator of pathological and cognitive changes in the very early stage of AD. We found little evidence that depression and anxiety contributed to the amyloid-related SCD. The use of mediational analyses provides convincing evidence that actual deficits and declines are important basis for SCD in individuals harboring amyloid, suggesting an early and accurate awareness of worsening cognition related to pathology.

The correspondence between subjective and objective memory in cognitively normal individuals has been controversial [35–37], and most studies have only focused on the cross-sectional associations (for a meta-analysis, see [38]). Thus, particularly notable was the finding that the longitudinal measure of memory decline mediates the amyloid/complaint relationship, validating the sensitivity of SCD in reflecting actual retrospective declines, likely resulted from AD pathology, which may be too subtle to detect with clinical testing in cognitively normal adults.

We also note that depression is also related to SCD and may be an important predictor of SCD in individuals low in amyloid, but amyloid-related SCD, which is more predictive of future declining [9,39], is more likely due to actual deficits and declines. This also suggests the complexity of SCD and the importance of considering the reliability of SCD in identifying individuals at risk for AD pathology, which may be too subtle to detect with clinical testing in cognitively normal adults.

In conclusion, the present study indicates that concerns about lower perceived capacity, perceived control, and memory-related anxiety in individuals with higher amyloid burden were due to current memory difficulties and greater retrospective declines, rather than depression or anxiety. Moreover, SCD is multidimensional, and specific concerns are more reflective of amyloid pathology and objective declines. We argue that, with considerable media attention to the disorder, individuals’ perceived memory self-efficacy reflects valid concerns of their declining functioning and may be useful to identify individuals at risk for AD.

5. Conclusion

In conclusion, the present study indicates that concerns about lower perceived capacity, perceived control, and memory-related anxiety in individuals with higher amyloid burden were due to current memory difficulties and greater retrospective declines, rather than depression or anxiety. Moreover, SCD is multidimensional, and specific concerns are more reflective of amyloid pathology and objective declines. We argue that, with considerable media attention to the disorder, individuals’ perceived memory self-efficacy reflects valid concerns of their declining functioning and may be useful to identify individuals at risk for AD.

Acknowledgment

This study was supported by funding from the National Institute on Aging 5R37AG-006265 (D.C.P.) and RC1AG036199 (D.C.P.), as well as the Alzheimer’s Association. The tracer was provided at no cost by Avid Radiopharmaceuticals.
a wholly owned subsidiary of Eli Lilly, Inc. Avid also provided financial support for PET imaging costs. The authors thank Neil Savalia, BS, and Micaela Chan, PhD, for FreeSurfer data processing and quality control. Finally, the authors thank Melissa Rundle for administrative and scientific management of the Dallas Lifespan Brain Study.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2018.12.007.

RESEARCH IN CONTEXT

1. Systematic review: A thorough literature search was performed using “subjective cognitive decline/subjective memory complaints + amyloid/preclinical AD” in Google Scholar. Authors went through articles and identified 31 studies examining the amyloid-SCD relationship in cognitively normal individuals. The systematic review (Table A) showed discrepancy across studies and a lack of understanding on the mechanism underlying SCD related to amyloid pathology.

2. Interpretation: Our findings that the amyloid-SCD relationship is mediated by poorer memory performance and greater decline, not depression/anxiety, suggest that actual deficits related to amyloid pathology, although subtle, are likely the basis of increased SCD in individuals harboring amyloid. We also considered the multidimensionality of SCD and identified that SCD domains on memory functioning have the potential utility as markers of AD pathology.

3. Future directions: Future study with longitudinal measures of SCD and AD biomarkers is needed to further validate its reliability and use in identifying individuals at higher risk for AD.

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