Title: Aβ-Positivity Predicts Cognitive Decline but Cognition Also Predicts Progression to Aβ-Positivity

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ABSTRACT

Introduction: Biomarker positivity predicts cognitive decline and Alzheimer's dementia. But what predicts biomarker positivity? We hypothesized that cognitive function and p-tau would predict progression from normal to abnormal levels of β-amyloid (Aβ).

Methods: Baseline cognition in 292 non-demented, Aβ-negative Alzheimer's Disease Neuroimaging Initiative (ADNI) participants was measured with two cognitive composites and compared between those that progressed to Aβ-positivity versus Aβ-stable. Follow-up analyses included continuous CSF Aβ and p-tau levels to examine subthreshold effects.

Results: Continuously measured baseline subthreshold Aβ and p-tau predicted progression to Aβ-positivity, but both baseline cognitive measures predicted progression to Aβ-positivity even after controlling for baseline biomarker levels.

Discussion: Current Aβ thresholds may be ignoring relevant subthreshold pathology. Importantly, cognitive function can be an important early predictor of future risk, even earlier than the key biomarkers as currently measured. Moreover, A-/T+ individuals may still be on the AD pathway because p-tau also predicted progression to positivity.

Keywords: biomarker trajectories, β-amyloid, cognition, Alzheimer's disease (AD), mild cognitive impairment (MCI)

1. INTRODUCTION

The amyloid cascade hypothesis has long been the predominant model of Alzheimer's disease (AD) pathophysiological progression [1, 2]. This hypothesis posits that β-amyloid (Aβ) is the initiating event that then elicits a number of downstream pathological processes including tau accumulation, neuronal dysfunction, and neurodegeneration. An influential model of biomarker trajectories was based on this hypothesis, in which levels of Aβ are the first measures to become abnormal, followed by abnormal tau, neurodegeneration, and finally, cognitive impairments [3]. A revision to the model acknowledged that this ordering may not hold when the underlying processes are below the detection threshold [4].

The more recent A/T/(N) framework classifies individuals based on whether they surpass the threshold for abnormal Aβ (A), tau (T), or neurodegeneration (N) [5]. This framework is similar to previous approaches to staging based on simply counting the number of abnormal biomarkers [6] in that both are agnostic to the sequence of biomarker ordering. The field has rapidly adopted this framework due to its clear description of the pathological features that define each group [7]. However, the groupings that result from the A/T/(N) classification system are often interpreted in the context of the amyloid cascade hypothesis. That is, individuals who have abnormal levels of amyloid (Aβ-positive) are considered to be on the AD trajectory, whereas Aβ-negative individuals who may have abnormal levels of tau or neurodegeneration are not [8, 9]. The latter has been termed "suspected non-Alzheimer pathology" (SNAP) [10]. It has become clear that, because of the long prodromal period, AD treatment should begin as early as possible [11]. Under the standard model, this would mean that individuals with evidence of abnormal tau or neurodegeneration would not be targeted for AD-related intervention if they do not also have evidence of abnormal Aβ.

It has been acknowledged that the processes leading to Aβ and tau deposition may occur independent of each other and with the potential for variable ordering [4, 12] For example, abnormal tau in the locus coeruleus may appear relatively early in life, prior to Aβ deposition

[13, 14]. Models of biomarker trajectories, by definition, describe the ordering of *measured* values of pathophysiology. Biomarker measures that exceed thresholds for abnormality may also demonstrate variable ordering. Among cognitively normal individuals with one abnormal biomarker at baseline who later progress to clinically-defined mild cognitive impairment (MCI) or AD, neurodegeneration-only was more common than amyloid-only cases [6]. A study that applied the A/T/(N) framework to individuals ages 50-95 found that, at age 65, a large proportion of individuals exhibited one abnormal biomarker, and the proportions of A only, T only, and N only were similar [9]. At age 80, the A+/T+/N+ group contained the largest proportion of people, indicating that although individuals may start at different points, they eventually converge on a more “typical” AD phenotype.

Standard models of AD progression posit that abnormal biomarkers precede clinical symptom onset by years or even decades, and there is plenty of evidence to support this [15-17]. However, there is also evidence suggesting that cognition may be affected earlier than is typically appreciated. For example, prior work that jointly modeled multiple measures found that delayed memory became dynamic (i.e., demonstrated change) prior to other biomarker and clinical measures [18, 19]. Thus, just as tau and neurodegeneration may develop independently of (and sometimes earlier than) Aβ, cognitive declines may also precede biomarker positivity.

Examinations of biomarkers primarily focus on biomarkers as predictors of MCI or dementia, but here our focus was on biomarker positivity as an outcome. Diagnosing biomarker positive, preclinical AD provides for early identification of at-risk individuals, but predicting who is likely to become biomarker positive would provide even earlier identification. According to the amyloid cascade or the A/T/(N) models of AD progression, Aβ should predict later decline in cognition, but not vice versa. Here, we tested that assumption by examining whether baseline cognition among Aβ- individuals could predict later progression to AB-positivity. Previous work has shown that cognition or other biomarkers begin to show accelerated change across individuals with a range of baseline Aβ values, including those that do not meet the threshold for Aβ-positivity [20,

21]. Conversely, we were interested in whether Aβ levels are beginning to change across individuals with a range of baseline cognitive scores. Also, increasing evidence from autopsy studies indicates that abnormal tau appears in the brainstem prior to cortical Aβ, and tau in the absence of Aβ is associated with poorer memory performance [22]. However, individuals classified as A-/T+ are typically not considered to be on the AD continuum. Therefore, we also examined whether individuals classified as A-/T+ at baseline would be more likely than A-/T- to progress to Aβ-positivity in the future, which would indicate that they may indeed be in a preclinical state of AD.

2. METHODS

2.1. Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Participants from the ADNI-1, ADNI-GO, and ADNI-2 cohorts (mean age: 71.6) were included in this study if they 1) had valid cognitive data at baseline, 2) had two or more timepoints of amyloid data (either CSF or amyloid-PET), 3) were considered Aβ-negative at baseline, and 4) did not have a diagnosis of Alzheimer's dementia at baseline. Individuals were then classified as Aβ-stable if they showed no evidence of abnormal amyloid at any follow-up, or as Aβ-converter if they showed evidence of abnormal Aβ at a follow-up assessment. Individuals who were Aβ-positive at multiple assessments followed by a subsequent reversion to normal Aβ status on only a single timepoint were included as Aβ-converters. In contrast, individuals who

were only Aβ-positive at one assessment followed by reversion to normal, Aβ-negative status were excluded. Individuals diagnosed as MCI in ADNI using the Petersen criteria were included if they were Aβ-negative at baseline because the focus of this analysis was to determine whether poorer cognition may precede amyloid positivity and if Aβ- MCI can be MCI that is on the AD continuum. Excluding these individuals would truncate the distribution of cognitive performance, which was our predictor of primary interest. A total of 292 individuals were included (251 Aβ-stable, 41 Aβ-converters).

2.2. Cerebrospinal fluid and amyloid imaging measures

CSF samples were collected and processed as previously described [23]. Levels of CSF $A\beta_{42}$ and phosphorylated tau (p-tau) were measured with the fully automated Elecsys immunoassay (Roche Diagnostics) by the ADNI biomarker core (University of Pennsylvania). Previously established cutoffs designed to maximize sensitivity in the ADNI study population were used to classify amyloid and p-tau positivity [Aβ+: Aβ42 < 977 pg/mL; p-tau+: p-tau > 21.8 pg/mL] [http://adni.loni.usc.edu/methods/; 24].

PET Aβ was measured with the tracers ^{11}C-Pittsburgh compound B (PiB) and ^{18}F-florbetapir, and PET data were processed according to previously published methods [http://adni.loni.usc.edu/methods/; 25, 26]. Mean standardized uptake value ratios (SUVR) were taken from a set of regions including frontal, temporal, parietal and cingulate cortices using the cerebellum as a reference region. Previously established cutoffs to determine Aβ+ were used for PiB-PET (SUVR > 1.4) and florbetapir-PET (SUVR > 1.11) [25].

2.3. Cognitive measures

We used two composite measures of baseline cognition available from the ADNI database. The ADNI_MEM measure is a composite score based on a factor model of learning, and immediate and delayed recall trials from four episodic memory tests: Rey Auditory Verbal Learning Test (RAVLT), Alzheimer's Disease Assessment Schedule – Cognition (ADAS-Cog)

word list and recognition, Mini-Mental State Examination (MMSE) word recall, and Logical Memory immediate and delayed recall [27]. The Preclinical Alzheimer Cognitive Composite [PACC; 28, 29] is a composite designed to detect amyloid-related cognitive decline and is based on the Delayed Recall portion of the ADAS-Cog, Logical Memory Delayed Recall, MMSE total score, and Trail Making Test, Part B time. The ADNI_MEM and PACC scores were converted to z-scores and reverse coded such that higher scores reflect poorer performance.

2.4. Covariates

Age and *APOE*-ε4 carrier status (ε4+ vs. ε4-) were included because of their association with increased amyloid prevalence [30]. P-tau status (p-tau+ vs. p-tau-) was included to account for differences in cognition due to other AD-related pathology. Length of follow-up was included to account for the possibility that Aβ-stable individuals were followed for a shorter amount of time, and would have been more likely to exhibit abnormal Aβ levels had they been followed for the same amount of time as Aβ-converters. Education was included to account for long-standing differences in cognitive ability or cognitive reserve that may influence the relationship between amyloid and cognition. In a set of follow-up analyses continuously measured CSF $A\beta_{42}$ and p-tau were included as covariates to determine whether subthreshold levels of pathology predict later progression to Aβ-positivity. These measures were converted to z-scores and values of CSF $A\beta_{42}$ were reverse coded such that higher values of both measures indicated abnormality.

2.5. Statistical analysis

We tested Aβ-stable and Aβ-converter groups for differences in the covariates using χ^2 and t-tests. Logistic regression models were used to test whether baseline cognition in Aβ-negative individuals was associated with increased odds of future progression to Aβ-positivity. Two models with group (Aβ-stable or Aβ-converter) as the outcome were tested: one using the ADNI_MEM score as the predictor of interest, and one using the PACC score. These models both included age, *APOE*-ε4 carrier status (ε4+ vs. ε4-), education, length of follow-up, and p-

tau status (normal vs. abnormal) as covariates. A follow-up analysis was conducted to determine whether lower cognition at baseline was due to sub-threshold levels of amyloid or tau pathology. Two models (using ADNI_MEM and PACC) were again run with group as the outcome, but with levels of CSF $A\beta_{42}$ and p-tau as continuous predictors. These models additionally controlled for age, *APOE*-ε4 carrier status, education, and length of follow-up. All analyses were conducted with R version 3.4.4 [31].

3. RESULTS

3.1. Descriptive statistics

Descriptive statistics are presented in **Table 1.** There were no significant differences between groups for age (*P* = 0.94), gender (*P* = 0.18), or proportion of individuals with MCI (*P* = 0.47). Aβ-converters were somewhat more likely to be *APOE*-ε4+, but this difference was not significant (*P*=0.08). The Aβ-converter group had a higher average education (17.3 vs. 16.2 years; *t* = 2.78, *P* = 0.007). The length of follow-up from baseline was significantly longer for the Aβ-converter group (4.22 vs. 3.23 years; *t* = 2.50, *P* = 0.02). The mean time between baseline cognitive testing and the assessment at which Aβ-converters first demonstrated progression to Aβ-positivity was 2.8 years (interquartile range: 1.98 – 4.01 years). Of the 138 individuals who were Aβ-negative and had MCI at baseline, 22 (16%) progressed to Aβ-positivity.

3.2. Baseline cognition predicts future progression to Aβ+

Individuals with poorer memory performance on both cognitive composites at baseline showed higher odds of progressing to Aβ-positivity at follow-up (ADNI_MEM: OR = 1.71, *P* = 0.008; PACC: OR = 1.72, *P* = 0.006). Aβ-converters were more likely to be an *APOE*-ε4 carrier, have a higher education, and have a longer duration of follow-up. Age and p-tau status were not significantly associated with progression to Aβ-positivity in either model. Full results of the regression models are presented in **Table 2**.

3.3. Levels of baseline p-tau and subthreshold Aβ predict future progression to Aβ-positivity

We also conducted follow-up analyses with continuous values of baseline CSF Aβ and p-tau included as covariates. More abnormal levels of baseline CSF Aβ and p-tau were associated with increased odds of progression to Aβ-positivity (CSF Aβ: OR = 2.55, $P < 0.001$; CSF p-tau: OR = 1.47, $P = 0.042$), although in the case of CSF Aβ, we note that these values were all in the normal range according to standard cut-offs. In these models, both the ADNI_MEM composite and PACC score remained significant predictors of progression to Aβ-positivity (ADNI_MEM: OR = 1.70, $P = 0.015$; PACC: OR = 1.56, $P = 0.042$). Full results of the regression models including CSF Aβ and P-tau are presented in **Table 3**.

4. DISCUSSION

In this study of individuals who were Aβ-negative at baseline, we found that individuals with lower cognitive performance were more likely to progress to Aβ-positivity at follow-up. These results indicate that cognition can itself be a strong early risk indicator. They suggest that cognition may be affected much earlier in the disease process than is typically recognized. Alternatively, individuals with lower cognitive ability may be at greater risk of Aβ accumulation, perhaps due to shared genetic factors or the cumulative effects of differential brain activity over the lifespan [32]. This is consistent with prior work on predicting progression to Alzheimer's dementia that finds cognition, primarily memory, may begin to change or demonstrate accelerated decline in individuals who are still below the threshold of abnormal Aβ, prior to other biomarkers [18-21]. Given that cognition arises from the brain, we do not suggest that changes in cognition are preceding pathology or neurofunctional alterations to the brain. However, it does appear that there is overlap in the ordering of cognitive and biomarker measures.

A number of analyses that predict progression from MCI to AD find that cognitive measures provide the strongest predictive utility [33-36]. As noted by Sperling, Aisen [37], it is important to keep in mind that behavioral markers may still hold great promise for early identification. It is

perhaps not surprising that cognitive measures would be the best predictor of future cognition, but our results underscore the potential for cognitive tests to provide useful information regarding disease risk quite early in its progression. Moreover, they indicate that cognitive tests can even be sensitive enough to signal that pathological processes may be underway before they can be detected by currently available biomarker measurements.

In a follow-up analysis, we found that subthreshold levels of Aβ predicted later progression to Aβ-positivity, consistent with previous findings [38]. However, cognition still predicted future progression to Aβ-positivity even after controlling for subthreshold Aβ. On the other hand, controlling for subthreshold Aβ did attenuate the effect, which lends support to the idea that levels of Aβ on the lower end of current detection limits are at least partially contributing to lower cognitive performance. This fits with growing evidence that subthreshold levels of Aβ are clinically relevant. The trajectory of cognition and other biomarkers has been found to begin changing among individuals with subthreshold levels of Aβ [21]. It has been argued that Aβ thresholds may be too high, and that making them less conservative may improve sensitivity without a substantial sacrifice of specificity [39]. An alternative to altering current thresholds is to examine the accumulation of Aβ over time. Several studies have examined individuals who do not meet the criteria for abnormal Aβ, but do demonstrate evidence of change in Aβ [40-44]. These studies find that a change in levels of Aβ is associated with atrophy and cognitive decline. Regardless of the approach taken, our results support the idea that subthreshold levels of Aβ may provide clinically relevant information, but also that cognitive performance can predict progression to Aβ-positivity.

Standard models of biomarker trajectories based on the amyloid cascade hypothesis state that measures of amyloid become abnormal before tau with the caveat that this may not hold at lower levels [3, 4]. Tau-PET studies find that tau seems to be confined to the medial temporal lobe and only spreads to the rest of the isocortex once Aβ is present [45-48]. While our results showed that being classified as p-tau positive was not associated with significantly higher odds

of future conversion to Aβ-positivity, the continuous measures of CSF tau significantly predicted later conversion. Although the A/T/(N) classification system is itself agnostic to the ordering of these 3 biomarkers [5], A-/T+ individuals are not considered to be on the AD spectrum, consistent with serial models of biomarker trajectories. Our results suggest that A-/T+ individuals may, in fact, have preclinical AD and will in time develop a more typical A+/T+ AD-like profile. We would argue that, at best, it is inconclusive as to whether individuals classified as A-/T+ are on the AD spectrum, but that elevated levels of p-tau can reflect heightened risk. Our results further suggest that continuous and binary A/T/(N) measures may lead to different inferences about biomarker sequencing.

Although we found that cognition at baseline predicted later progression to Aβ-positivity, some previous studies did not [38, 49]. However, the sample size of the current study is considerably larger than either of the previous studies (292 in the current study versus 207 and 35 in the previous studies). Thus, the discrepancy may be due to a difference in power. Furthermore, we examined two cognitive composites: one was a factor score representing memory [27] and the other was designed specifically to detect amyloid-related decline, although it includes memory measures as well [28, 29]. It seems likely that weighted combinations of multiple tests provide more sensitivity to subtle differences in cognition during early disease states.

It is worth noting that some individuals were diagnosed as MCI at baseline despite normal levels of Aβ. There is evidence that individuals who progress to MCI in the absence of Aβ exhibit different biomarkers and cognitive profiles, and therefore are on a non-AD trajectory [50]. This may be the case for those MCI subjects who remained Aβ-stable. However, 16% of MCI participants did progress to Aβ-positivity, indicating that they are likely to be on the AD continuum, albeit with a non-typical progression. This lends further evidence that the ordering of detectable biomarker abnormality and cognitive decline can be heterogenous. It also has implications for studies that include only Aβ biomarker-confirmed MCI cases. Biomarker

confirmation will reduce the number of false positive MCI diagnoses, and will provide more certainty that cognitive deficits arise from AD pathology. This is desirable in scenarios such as clinical trials of anti-Aβ drugs. However, it will result in a substantial number of "false negatives," i.e., individuals with normal levels of Aβ and MCI who may in fact be on the AD pathway as reflected by later progression to Aβ-positivity. If the goal of a study is to examine the factors involved at the earliest stages of AD, it may be important to capture these individuals who demonstrate putative atypical disease progression.

Although there is much evidence for the standard model of biomarker and cognitive trajectories, the current results demonstrate that not all cases adhere to an invariant sequence. Differences in cognition that predict future progression to Aβ-positivity may be driven by subthreshold pathology, which would suggest a need to reconsider current biomarker thresholds or to consider approaches that measure Aβ accumulation. Additionally, higher levels of tau are associated with increased risk of becoming Aβ-positive, so individuals with elevated levels of tau should not be ignored when identifying those at risk for developing AD. Individuals with MCI but normal levels of Aβ may similarly be on the AD pathway as indicated by later progression to Aβ-positivity. Importantly, the results strongly suggest that cognition should not simply be viewed as a late-stage endpoint of AD, but can provide a sensitive, low-cost, non-invasive predictor of risk that can signal the onset of earliest stages of disease pathogenesis, potentially before current thresholds for Aβ-positivity are reached.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

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TABLES AND FIGURES

Table 1. Sample characteristics. Descriptive statistics of Aβ-stable and Aβ-converter participants at baseline. Mean (SD) presented for continuous variables, count (%) presented for categorical variables. An asterisk indicates a significant ($p < 0.05$) difference between the two groups.

	Aβ-stable	**Aβ-converter**
n	251	41
Age	71.62 (7.21)	71.71 (6.62)
Gender	127 (50.6%)	26 (63.4)
APOE-ε4+	41 (16.3%)	12 (29.3%)
P-tau+	66 (26.3%)	17 (41.5%)
MCI Diagnosis	116 (46.2%)	22 (53.7%)
Education*	16.20 (2.55)	17.27 (2.24)
Length of follow-up (years)*	3.23 (1.58)	4.22 (2.46)

Table 2. Predictors of future conversion to Aβ-positivity in individuals that are Aβ-negative at baseline. Results of two logistic regression models are presented. Measures are all taken from baseline and predict future progression to Aβ-positivity. The table on the left includes the ADNI_MEM composite score, and the table on the right includes the PACC score. Cognitive scores were converted to z-scores and reverse coded such that higher scores indicate poorer performance. Significant p-values are in bold.

Predictor (units)	*Odds Ratios*	*CI*	*p*
Intercept	0	0.00 – 0.10	**0.005**
ADNI_MEM	1.71	1.16 – 2.57	**0.008**
P-tau+	1.76	0.83 – 3.66	0.133
APOE-ε4+	2.91	1.18 – 7.08	**0.019**
Age (years)	0.99	0.94 – 1.05	0.828
Education (years)	1.26	1.08 – 1.48	**0.004**
Length of follow-up (years)	1.42	1.18 – 1.73	**<0.001**

Predictor (units)	*Odds Ratios*	*CI*	*p*
Intercept	0	0.00 – 0.05	**0.002**
PACC	1.72	1.17 – 2.55	**0.006**
P-tau+	1.83	0.87 – 3.83	0.108
APOE-ε4+	3.09	1.25 – 7.61	**0.014**
Age (years)	1	0.95 – 1.05	0.962
Education (years)	1.29	1.10 – 1.52	**0.002**
Length of follow-up (years)	1.44	1.20 – 1.75	**<0.001**

Table 3. Predictors of future conversion to Aβ-positivity including continuous measures of Aβ and p-tau. Results of two logistic regression models are presented. Measures are all taken from baseline and predict future progression to Aβ-positivity. The table on the left includes the ADNI_MEM composite score, and the table on the right includes the PACC score. Cognitive scores were converted to z-scores and reverse coded such that higher scores indicate poorer performance. CSF Aβ and P-tau were both z-scored and CSF Aβ was reverse coded such that higher values on both indicates abnormality. Significant p-values are in bold.

Predictor (units)	*Odds Ratios*	*CI*	*p*
Intercept	0.01	0.00 – 1.32	0.068
ADNI_MEM (sd)	1.7	1.12 – 2.63	**0.015**
CSF Aβ (sd)	2.55	1.75 – 3.84	**<0.001**
CSF P-tau (sd)	1.47	1.02 – 2.15	**0.042**
APOE-ε4+	1.99	0.74 – 5.24	0.166
Age (years)	0.97	0.92 – 1.03	0.368
Education (years)	1.23	1.04 – 1.46	**0.016**
Length of follow-up (years)	1.4	1.16 – 1.72	**0.001**

Predictor (units)	*Odds Ratios*	*CI*	*p*
Intercept	0	0.00 – 0.72	**0.041**
PACC (sd)	1.56	1.02 – 2.41	**0.042**
CSF Aβ (sd)	2.48	1.70 – 3.74	**<0.001**
CSF P-tau (sd)	1.47	1.03 – 2.14	**0.039**
APOE-ε4+	2.1	0.78 – 5.52	0.135
Age (years)	0.98	0.92 – 1.04	0.489
Education (years)	1.24	1.05 – 1.48	**0.013**
Length of follow-up (years)	1.41	1.17 – 1.72	**<0.001**