Cognitive Trajectories and Alzheimer Disease Biomarkers: From Successful Cognitive Aging to Clinical Impairment

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Objective: Cross-sectional definitions of successful cognitive aging have been widely utilized, but longitudinal measurements can identify people who do not decline. We performed this study to contrast maintenance with declining trajectories, including clinical conversion.
Methods: We included baseline cognitively unimpaired Alzheimer's Disease Neuroimaging Initiative participants with 3 or more cognitive testing sessions (n = 539, follow-up 6.1 ± 3.5 years) and calculated slopes of an episodic memory composite (MEM) to classify them into two groups: maintainers (slope ≥ 0) and decliners (slope < 0). Within decliners, we examined a subgroup of individuals who became clinically impaired during follow-up. These groups were compared on baseline characteristics and cognitive performance, as well as both cross-sectional and longitudinal Alzheimer disease (AD) biomarker measures (beta-amyloid [Aβ], tau, and hippocampal volume).
Results: Forty-one percent (n = 221) of the cohort were MEM maintainers, and 33% (n = 105) of decliners converted to clinical impairment during follow-up. Compared to those with superior baseline scores, maintainers had lower education and were more likely to be male. Maintainers and decliners did not differ on baseline MEM scores, but maintainers did have higher non-MEM cognitive scores. Maintainers had lower baseline global Aβ, lower tau pathology, and larger hippocampal volumes than decliners, even after removing converters. There were no differences in rates of change of any AD biomarkers between any cognitive trajectory groups except for a higher rate of hippocampal atrophy in clinical converters compared to maintainers.
Interpretation: Using longitudinal data to define cognitive trajectory groups reduces education and sex bias and reveals the prognostic importance of early onset of accumulation of AD pathology.

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Cognitive trajectories in aging are heterogeneous, and some individuals show no evidence of cognitive decline even into the 9th and 10th decades of life.[1,2] Many terms have been used to describe these individuals, including successful agers, SuperAgers, exceptional agers, and optimal agers. Successful aging has been primarily explored using definitions based on cross-sectional cognitive data, which generally categorize individuals with superior cognitive performance as successful agers given the assumption that superior performance at a single time

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point likely indicates similar performance (no decline) in the preceding decades. We propose, however, that successful aging should be defined as the lack of cognitive decline, or cognitive maintenance, over time. This definition includes people whose cognitive performance may be average but remains stable over the course of longitudinal follow-up. Although such individuals are successful agers because their cognition is not declining as they age, they may have fewer characteristics associated with superior cognitive performance such as high socioeconomic status and more education.[3,4] We predict, therefore, that a cognitive maintenance definition of successful aging will be more inclusive of people with diverse backgrounds. We further predict that cognitive maintenance is clinically relevant and related to risk of conversion to mild cognitive impairment (MCI) or Alzheimer disease (AD).

Using cross-sectional definitions, successful aging has been previously associated with greater brain volumes in the hippocampus and cortex, especially in the middle/anterior cingulate and medial prefrontal cortex.[2,5–7] There is also evidence that successful aging is related to slower rates of atrophy.[8] Successful aging defined by superior cross-sectional performance is not related to lower beta-amyloid (Aβ) burden,[5,6,9] but there is some evidence that superior performers have decreased risk of conversion to MCI or AD.[9] In contrast to the findings with Aβ pathology, a recent study found that superior performers had lower tau pathology in the medial temporal lobe.[10] Together, these studies suggest a robust neural signature of superior cognitive performance.

In this study, we compared baseline-normal cognitive maintainers to those who decline and, within that group, to those who develop clinical impairment to better understand the characteristics of each trajectory. Our design studying successful aging (no decline), normal aging (some decline but no clinical impairment), and pathological aging (decline and clinical impairment) in the same cohort allows us to capture the factors that underlie these important specific trajectories. Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ideal dataset to explore these concepts, because the lengthy longitudinal cognitive and clinical follow-up allows for categorization of individuals based on their cognitive trajectory despite the complexity of these data.[11,12] We explored an episodic memory composite (MEM) as our primary measure of interest as well as an executive function composite (EF) and a multidomain composite score (Preclinical Alzheimer Cognitive Composite [PACC]). For each cognitive measure, we compared baseline cognition between cognitive maintainers, decliners, and clinical converters. We predicted that baseline cognition would not be predictive of future cognitive trajectory but that AD biomarkers would predict cognitive trajectory group and degree of decline (slope) within the decliner and converter groups.

Subjects and Methods

Participants

Our cohort selection approach is detailed in Figure S1. All ADNI participants with at least one positron emission tomography (PET) scan as of March 2023, cognitively normal diagnosis at their baseline cognitive assessment, and at least 2 additional cognitive assessments (3 or more total) were included. A subset of these participants underwent Aβ- and tau-PET scanning, with a further subset undergoing follow-up scanning. We examined concurrent magnetic resonance imaging (MRI) data for participants with Aβ- and tau-PET scans. Baseline neuroimaging sessions did not necessarily align in time with baseline cognitive assessment.

ADNI has been approved by the local institutional review boards at each site, and all participants signed an informed consent form.

Neuropsychological Assessment

ADNI participants undergo annual cognitive testing and clinical assessments. The domain composites scores MEM and EF were previously developed and validated in ADNI using confirmatory factor analysis.[13,14] In the current study, we used these composite scores along with the PACC, which is a composite score that includes cross-domain measures in episodic memory, timed executive function, and global cognition.[15] Diagnosis conversion to MCI or AD was determined according to established methods.[16] In the present study, all available cognitive time points were included for each participant.

Classification of Cognitive Maintainers and Decliners

We calculated slopes for 3 cognitive composite measures: MEM, EF, and PACC. Specifically, we used simple linear regression with time predicting cognitive score and extracted the slope of this regression for each participant. For all cognitive slopes, we defined participants as cognitive maintainers if their slope ≥ 0 and as decliners if their slope < 0. Our primary analyses focused on cognitive maintainers and decliners based on MEM slope. We explored EF (nonmemory, single domain) and PACC (multidomain composite) slope-based definitions of cognitive maintainers and decliners as sensitivity analyses. All study participants were cognitively normal at baseline, but a subset of the decliners converted to a clinical diagnosis of MCI or AD during follow-up.

Despite the importance of age in driving cognitive trajectories, we chose not to adjust our cognitive slopes for age, but rather to adjust for age in our statistical models so that we could assess the effect of age in these models separately from the cognitive slopes themselves. For visualization, we compared our slopes to age-adjusted (using mean age over cognitive follow-up)

slopes and found this had a minimal effect on the slope estimates ($R^2 = 0.96$; Fig S2).

Imaging Acquisition and Preprocessing

PET data were acquired according to the standard ADNI protocols (https://adni.loni.usc.edu) for florbetapir (FBP) or florbetaben (FBB) for Aβ and flortaucipir (FTP) for tau, and were preprocessed with smoothing to a spatial resolution of 8mm^3. Next, these preprocessed PET scans were coregistered to the T1-weighted structural MRI that was acquired closest in time to the acquisition date of the PET session. All structural MRIs were processed using FreeSurfer v7.1.0 including regional segmentation and parcellation according to the Desikan–Killiany atlas.[17] The resulting regions of interest (ROIs) were used to measure structural volumes and calculate regional standardized uptake value ratio (SUVR) for each PET tracer. For FBP and FBB, we focused on the cortical summary region normalized by whole cerebellum to determine Aβ burden and positive/negative status. Cortical summary SUVRs were converted to centiloids to combine FBP and FBB data.[18,19] For FTP, we focused on entorhinal cortex (ERC) and a temporal lobe meta-ROI normalized by the inferior cerebellar gray matter, as these ROIs capture early tau burden in aging and preclinical AD. For longitudinal FTP measures, we used an eroded white matter reference region as described previously.[20] For structural MRI data, we focused on hippocampal volume derived from FreeSurfer, which we adjusted for intracranial volume using a residual adjustment strategy.[21] The relationship between hippocampal volume (HV) and intracranial volume (ICV) for a cohort of 283 ADNI Aβ-negative healthy subjects was used to generate the equation used for all participants in the current study: $HV_{adj} = HV - (2.2207e^{-3}[ICV - 1{,}491{,}698.02mm^3])$.

For PET imaging, we used true baseline scans for each tracer type (Aβ and tau) so that we could maximize the data available and calculate linear slopes for longitudinal change using all available data for the individuals who had follow-up PET data. For the structural data, we used the MRI closest to baseline Aβ-PET as baseline and all subsequent follow-up MRIs to calculate concurrent structural change as linear slope.

Statistical Analysis

Welch *t*-tests or chi-squared tests were used to compare continuous and binary variables between MEM cognitive maintainers and decliners. When appropriate, we ran multiple regression models adjusting for variables that differed between groups to ensure that our findings were not driven by confounders. When adjusting for age, we used average age over the cognitive follow-up period to adjust not only for baseline age differences but also for the length of time each participant was followed (number of cognitive sessions was also included as a separate covariate). When examining converters separately, we used analyses of variance to test for differences across 3 groups: maintainers, decliners who did not convert, and converters. Subsequently, we conducted pairwise Welch *t*-tests to identify specific group differences. Linear regression was used to examine associations between cognitive slope and baseline cognition as well as all neuroimaging variables. We limited these analyses to cognitive decliners where the variability in slope was much greater and clinically meaningful.

Logistic regressions including the following variables were used to predict (1) cognitive maintainers versus decliners in the whole cohort and (2) decliners versus converters: average age over cognitive follow-up, sex, years of education, number of cognitive sessions, baseline MEM score, baseline EF score, adjusted cross-sectional hippocampal volume, baseline Aβ burden *or* status, and baseline tau pathology in ERC *or* temporal meta region of interest (MetaROI).

As sensitivity analyses, statistical tests and models were repeated using cognitive maintainer and decliner groups defined by EF slope (single domain, nonmemory composite) and PACC slope (multidomain composite).

Results

In this section, we present the full results of our analyses using the longitudinal MEM slopes to define cognitive maintainers and decliners. Following this, we include two subheadings to describe the similarities and differences in our results when using (1) the EF or (2) the PACC measure to define cognitive maintainers and decliners.

Participants

ADNI participants' cognitive and neuroimaging session information is summarized in Table 1. Compared to cognitive decliners, cognitive maintainers were significantly younger, more likely to be female, had more education, and had fewer cognitive testing sessions. A total of 481 (89%) participants had at least one Aβ-PET scan and structural MRI available and 298 (55%) had at least one tau-PET scan. Of the 481 participants with neuroimaging data, 385 participants had their baseline Aβ-PET scan within 1 year of baseline cognitive assessment, with a mean interval of 1.1 ± 2.2 years. Baseline tau PET scans were on average 3.8 ± 3.8 years after baseline cognitive assessment.

Rates of Cognitive Maintainers and Decliners and Risk of Conversion

Of 539 ADNI subjects who met our inclusion criteria, 41% (n = 221) were cognitive maintainers whose cognitive slope was ≥0 (shown in green in Fig 1). In contrast, 59% (n = 318) were cognitive decliners with a cognitive slope < 0 (shown in orange in Fig 1A). Of the 318 cognitive decliners, 33% (n = 105; shown in red in Fig 1B) converted to MCI or AD during the course of cognitive follow-up.[16] We excluded n = 14 individuals whose cognitive slopes were ≥0 but who were given a diagnosis of clinical impairment during follow-up. This group represented the borderline between normal cognition and MCI, so we decided to remove them from analyses,

TABLE 1. MEM Groups

Characteristic	Total, n = 539	Maintainer, n = 221	Decliner, n = 318	*p*
Age, yr	75.9 (±6.2)	74.1 (±6.2)	77.1 (±5.9)	<0.001
Sex, % F	55%	60%	51%	0.026
Education, yr	16.5 (±2.6)	16.8 (±2.4)	16.2 (±2.7)	0.015
Cognitive testing sessions, n	6.1 (±3.0)	5.0 (±2.4)	6.8 (±3.1)	<0.001
APOE ε4, % carriers	31% [2 NA]	31% [1 NA]	31% [1 NA]	0.937
Amyloid PET scans				
FBP, n	413	154	259	—
FBB, n	68	45	22	—
Aβ status, % +	35% [58 NA]	25% [22 NA]	43% [36 NA]	<0.001
Tau PET scans, FTP, n	298	140	158	—

Values represent mean (standard deviation) for continuous variables and percentage for dichotomous variables. Differences between groups were investigated using independent sample *t*-test and chi-squared test for continuous and categorical variables, respectively. Participants with <3 longitudinal MEM scores were excluded.

There was no APOE genotype data for one maintainer and one decliner.

— = not applicable; AB = beta-amyloid; APOE = apolipoprotein E; F = female; FBB = florbetaben; FBP = florbetapir; FTP = flortaucipir; MEM = episodic memory; NA = not acquired or available; PET = positron emission tomography.

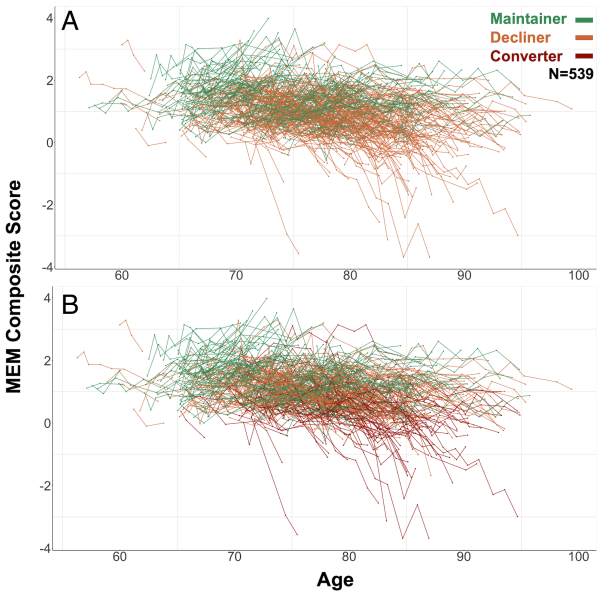

FIGURE 1: Episodic memory (MEM) score longitudinal trajectories in older adults are heterogeneous. Spaghetti plots show raw MEM composite scores over time, plotted as participant age at cognitive assessment. In the present study, we compare maintainers and decliners, shown in green and orange, respectively, in panel A. In additional analyses, we also separately consider a subgroup of decliners called converters, shown in red in panel B. Converters are cognitive decliners who converted to a diagnosis of clinical impairment during follow-up.

because we could not be confident that they were cognitively normal at baseline despite their stable cognition over time. Still, these data demonstrate a remarkable increased risk of clinical conversion in the decliner group (33%) compared to all maintainers (14/235 = 6%; $p < 0.001$).

Baseline Cognitive Scores by Cognitive Trajectory Group

Cognitive maintainers and decliners did not differ on baseline MEM scores ($p = 0.095$; Fig 2). Cognitive maintainers did, however, have better baseline EF and PACC ($p < 0.001$) performance compared to decliners. These findings were consistent when adjusting for potential confounding variables that differed across groups (see Table 1): average age, sex, education, and number of cognitive testing sessions. When considering clinical converters as a separate subgroup, we found that the converters had lower MEM, EF, and PACC scores compared to maintainers and to decliners who did not convert. Decliners who did not convert also had lower EF and PACC scores compared to maintainers.

To explore the characteristics of successful agers defined by cognitive maintenance versus exceptional performance, we identified the top 20% of MEM performers at baseline (cutoff MEM score = 1.517; shown as red

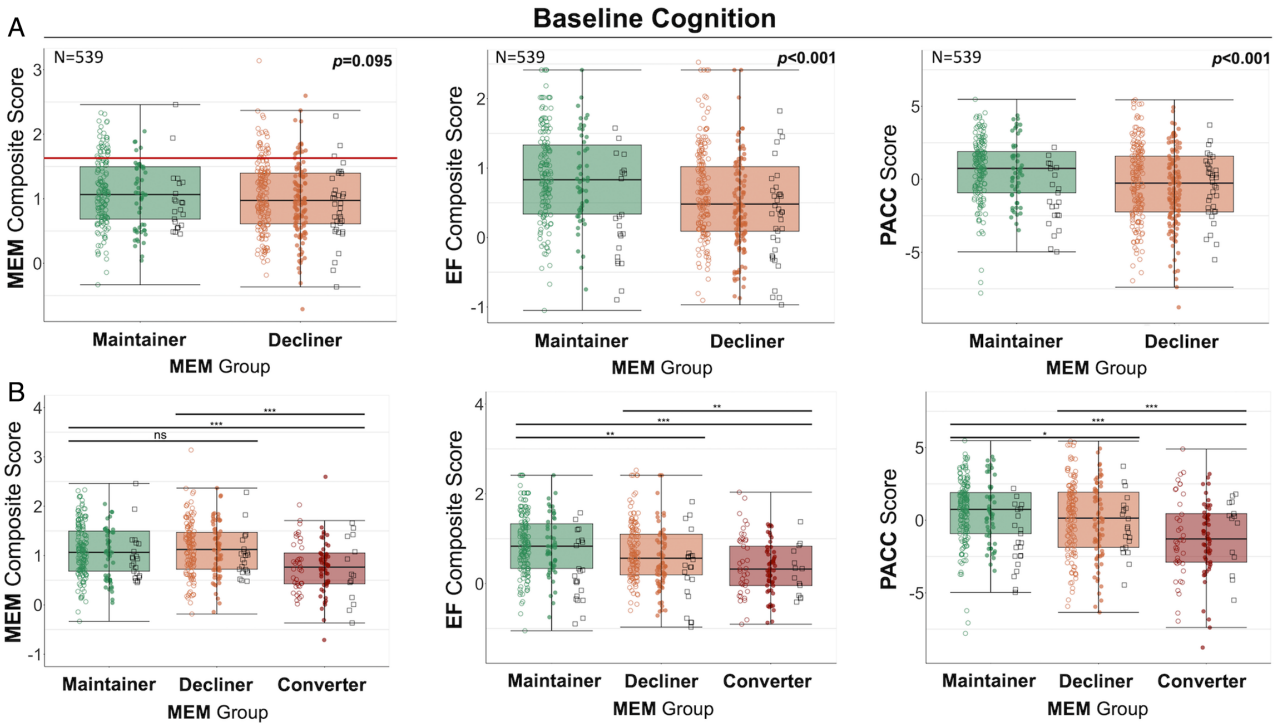

FIGURE 2: Baseline cognition did not predict longitudinal cognitive trajectories. (A) Boxplots of baseline cognitive scores by cognitive trajectory group: MEM maintainers and decliners. (B) Boxplots of baseline cognitive scores by cognitive trajectory group: episodic memory (MEM) maintainers, decliners who did not convert, and converters. Empty circles are Aβ− individuals, and filled circles are Aβ+ individuals. Empty black squares are individuals who had no beta-amyloid positron emission tomography data. Welsh *t*-tests were used to compare cognitive trajectory groups: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. EF = executive function; ns = not significant; PACC = Preclinical Alzheimer Cognitive Composite.

horizontal line Fig 2A). Of these n = 108 individuals, 52 (48%) were cognitive maintainers and 56 (52%) were cognitive decliners. This rate of 48% maintainers was only slightly higher than the rate of maintainers in the whole cohort (41%), and this difference was not significant ($p = 0.21$). Compared to these exceptional performers, cognitive maintainers who were not exceptional performers at baseline had fewer years of education ($p = 0.006$) and were less likely to be female ($p = 0.014$; Table S1). Importantly, these groups did not differ on age or any AD biomarker measure except cross-sectional hippocampal volume, where maintainers who were not exceptional performers had larger hippocampal volumes ($p = 0.044$; Table S1).

Baseline AD Biomarkers by Cognitive Trajectory Group

Compared to decliners, cognitive maintainers had less Aβ pathology in a cortical summary region ($p < 0.001$), lower tau pathology in both the ERC ($p < 0.001$) and the temporal MetaROI ($p < 0.001$), and higher hippocampal volumes ($p < 0.001$; Fig 3A). The differences in AD biomarkers were not driven by the clinical converters; post hoc *t*-tests revealed significant differences remain between cognitive maintainers and decliners who did not convert, although these differences were small (see Fig 3B). For all analyses, group differences remained statistically significant after adjusting for average age, sex, education, and number of cognitive sessions.

Longitudinal AD Biomarker Slopes by Cognitive Trajectory Group

There were no significant differences between cognitive maintainers and decliners in the rate of change for any AD pathology biomarkers (Fig 4A). The subset of decliners who converted to clinical impairment also did not have higher rates of AD pathology accumulation compared to maintainers or decliners who did not undergo conversion, but converters did have a faster rate of hippocampal atrophy compared to maintainers (see Fig 4B). Group differences remained significant after adjusting for average age, sex, education, and the number of cognitive sessions.

Slope Variability in Decliners, Baseline Cognition, and AD Pathology

In addition to describing cognitive trajectory group differences, we also explored predictors of continuous

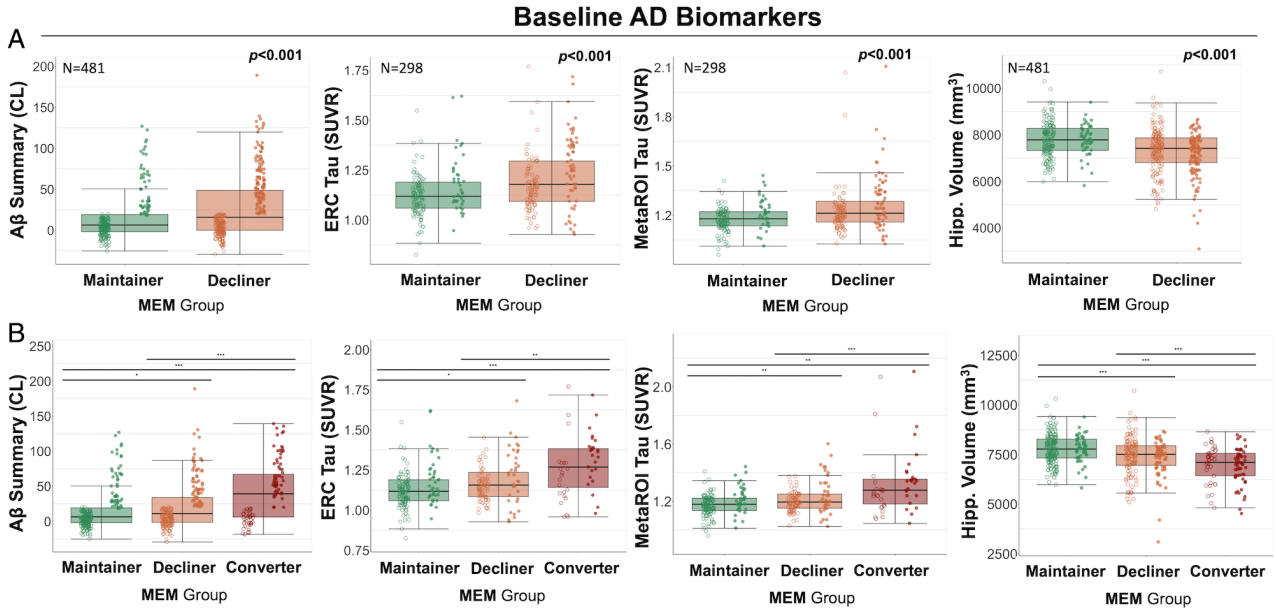

FIGURE 3: Maintainers had less Alzheimer disease (AD) pathology and higher hippocampal volumes. (A) Boxplots of baseline beta-amyloid (Aβ), tau, and hippocampal volume measures by cognitive trajectory group: episodic memory (MEM) maintainers and decliners. (B) Boxplots of baseline Aβ, tau, and hippocampal volume measures by cognitive trajectory group: MEM maintainers, decliners who did not convert, and converters. Empty circles are Aβ− individuals, and filled circles are Aβ+ individuals. Welsh *t*-tests were used to compare cognitive trajectory groups: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. CL = centiloids; ERC = entorhinal cortex; Hipp. = hippocampal; MetaROI = temporal meta region of interest; SUVR = standardized uptake value ratio.

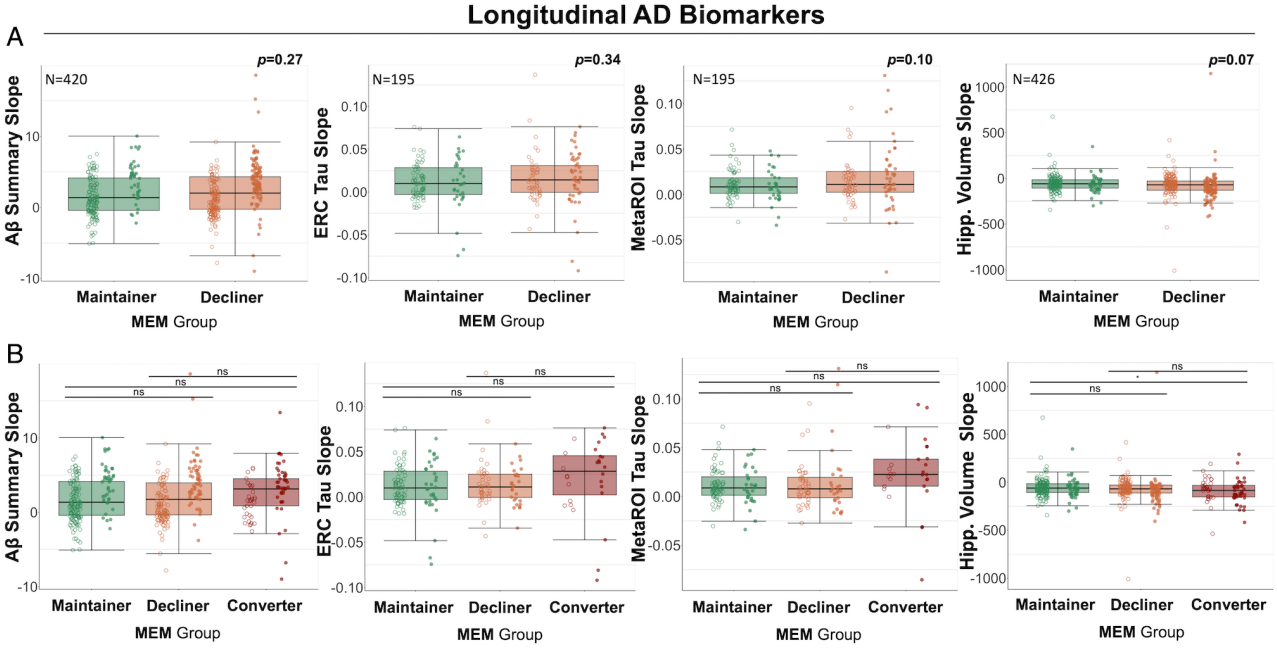

FIGURE 4: There were no differences in Alzheimer disease (AD) pathology accumulation rate between cognitive trajectory groups. (A) Boxplots of beta-amyloid (Aβ), tau, and hippocampal volume slope (change over time) measures by cognitive trajectory group: episodic memory (MEM) maintainers and decliners. (B) Boxplots of Aβ, tau, and hippocampal volume slope (change over time) measures by cognitive trajectory group: MEM maintainers, decliners who did not convert, and converters. Empty circles are Aβ− individuals, and filled circles are Aβ+ individuals. Welsh *t*-tests were used to compare cognitive trajectory groups: *$p < 0.05$. ERC = entorhinal cortex; Hipp. = hippocampal; MetaROI = temporal meta region of interest; ns = not significant.

MEM slope. We focused on decliners where there was greater variability in slopes (see Fig 1). Among all decliners, baseline MEM and PACC scores were not related to MEM slope, but lower baseline EF score was associated with steeper MEM decline ($p = 0.046$; Fig S3A). The relationships between baseline cognition

and MEM slopes were not significant in decliners and converters separately, except for a negative association between baseline MEM and MEM slope in decliners who did not convert ($p < 0.001$; Fig S3A). MEM slopes in decliners were negatively related to cross-sectional AD pathology biomarkers of Aβ and tau, but these relationships were driven by converters and were not significant in decliners who did not convert (Fig S3B). MEM slope was positively related to hippocampal volume in all decliners, but this association was not statistically significant in either group separately (Fig S3B).

Logistic Regressions Predicting Cognitive Trajectory Group

In logistic regressions predicting cognitive maintainers versus decliners (n = 298; Table 2), years of education, the total number of cognitive testing sessions, baseline EF score, and tau burden (either ERC or metaROI) were each significant predictors. We then ran logistic regressions predicting decliners who did not convert versus converters and found that number of cognitive sessions, tau burden (either ERC or MetaROI), and continuous Aβ were significant in all models, and baseline MEM score was also significant in models with ERC tau (n = 158; see Table 2).

TABLE 2. Logistic Regressions Predicting Cognitive Trajectory Groups (MEM)

	Maintainers vs Decliners			Converters vs Unimpaired Decliners		
Parameter	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
ERC model						
Intercept	−0.446	2.907	0.878	−5.871	4.472	0.189
Age, yr	−0.011	0.026	0.669	0.032	0.043	0.459
Sex, F	0.275	0.300	0.359	0.371	0.479	0.438
Education, yr	0.171	0.061	0.005	−0.065	0.089	0.466
Cognitive testing sessions, n	−0.233	0.055	*<0.001*	0.220	0.074	0.003
BL MEM score	−0.103	0.303	0.733	−1.099	0.489	0.025
BL EF score	0.603	0.222	0.007	−0.055	0.366	0.880
Adj. hippocampal vol.	<0.000	<0.000	0.071	<0.000	<0.000	0.544
Tau-PET (ERC SUVR)	−2.624	1.088	0.016	2.937	1.398	0.036
Aβ-PET (global CL)	−0.006	0.005	0.199	0.013	0.006	0.040
MetaROI model						
Intercept	1.632	3.197	0.610	−6.571	4.484	0.143
Age, yr	−0.013	0.026	0.614	0.033	0.044	0.451
Sex, F	0.314	0.302	0.298	0.287	0.484	0.553
Education, yr	0.177	0.061	0.004	−0.080	0.090	0.374
Cognitive testing sessions, n	−0.227	0.055	*<0.001*	0.228	0.074	0.002
BL MEM score	−0.221	0.311	0.477	−0.969	0.498	0.052
BL EF score	0.599	0.222	0.007	−0.054	0.368	0.883
Adj. hippocampal vol.	<0.000	<0.000	0.086	<0.000	<0.000	0.468
Tau-PET (MetaROI SUVR)	−4.067	1.490	0.006	3.562	1.445	0.014
Aβ-PET (global CL)	−0.006	0.005	0.217	0.013	0.006	0.040

AB = beta-amyloid; Adj. = adjusted; BL = baseline; CL = centiloids; EF = executive function; ERC = entorhinal cortex; F = female; MEM = episodic memory; PET = positron emission tomography; ROI = region of interest; MetaROI = temporal meta region of interest; SE = standard error; SUVR = standardized uptake value ratio; vol. = volume.

Results Using EF Composite Score to Define Cognitive Trajectory Groups

Using EF slopes to define cognitive maintainers and decliners, 167 met our criteria for cognitive maintainers and 359 were cognitive decliners (Table S2). Of the 359 decliners, 92 converted to clinical impairment during follow-up. Like MEM maintainers, EF maintainers were younger and had fewer cognitive testing sessions compared to EF decliners. Unlike MEM maintainers, EF maintainers and decliners did not significantly differ on sex or years of education. EF maintainers included 95 MEM maintainers and 72 individuals who were MEM decliners (Fig S4).

Compared to EF decliners, EF maintainers had significantly higher baseline MEM scores ($p = 0.04$) and lower baseline EF scores ($p = 0.01$), and there were no differences in baseline PACC scores ($p = 0.50$). When considering converters as a separate group, converters had lower baseline cognition scores compared to the other groups in each domain (pairwise t-tests, all $p < 0.03$), and EF decliners who did not convert still showed higher baseline EF scores compared to EF maintainers (pairwise t-test, $p < 0.001$).

EF maintainers had significantly lower Aβ ($p = 0.003$) and tau burden (ERC, $p = 0.02$; MetaROI, $p = 0.03$) compared to decliners (Fig 5A). EF maintainers also had significantly higher hippocampal volumes ($p = 0.001$). Converters had higher Aβ and tau pathology markers and lower hippocampal volume compared to EF maintainers and EF decliners who did not convert (see Fig 5B; all $p < 0.01$), whereas no biomarker differences remained between EF maintainers and decliners who did not convert.

There were no differences in AD pathology biomarker rates of change between EF maintainers and all decliners (Aβ, ERC tau, MetaROI tau, hippocampal atrophy), nor when converters were considered separately.

Results Using PACC Score to Define Cognitive Trajectory Groups

Using PACC slopes to define cognitive maintainers and decliners, 202 met our criteria for cognitive maintainers and 338 were cognitive decliners (Table S3). Of the 338 decliners, 107 converted to clinical impairment during follow-up. Like MEM maintainers, PACC maintainers were younger and had fewer cognitive testing sessions compared to EF decliners. Unlike MEM maintainers, PACC maintainers and decliners did not significantly differ on sex or years of education. PACC maintainers included 145 MEM maintainers and 56 individuals who were MEM decliners (Fig S4).

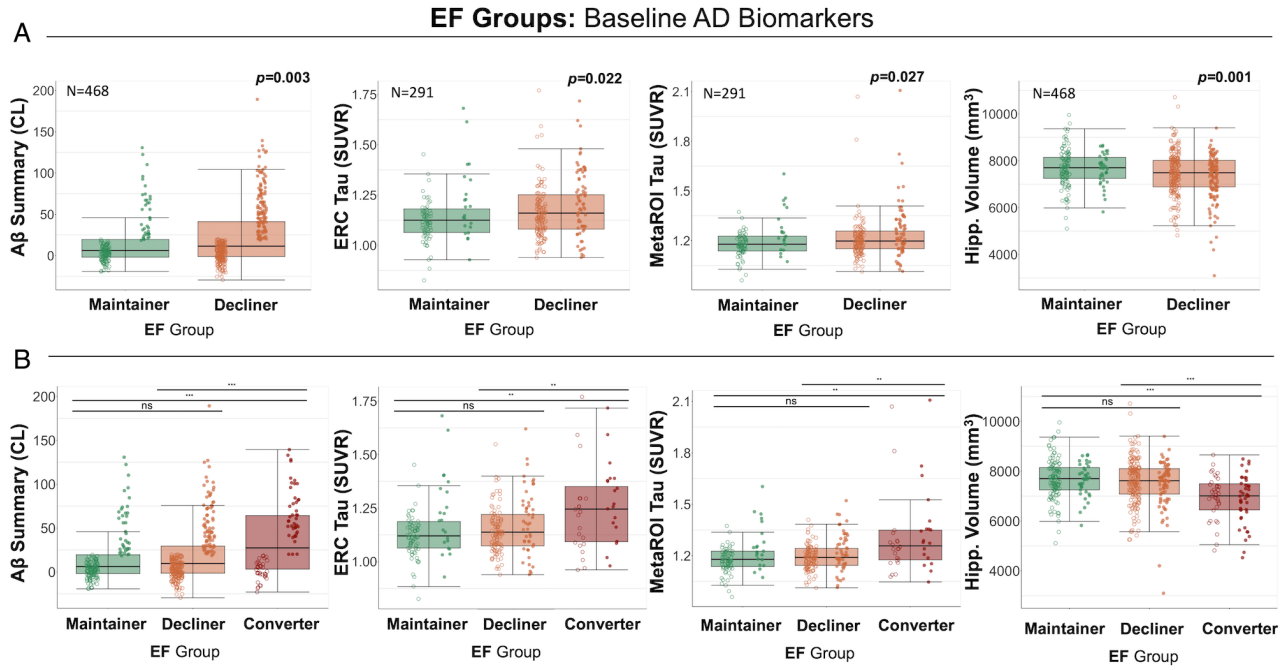

FIGURE 5: Executive function (EF)-defined cognitive trajectory groups. (A) Boxplots of baseline beta-amyloid (Aβ), tau, and hippocampal volume measures by cognitive trajectory group: EF maintainers and decliners. (B) Boxplots of Aβ, tau, and hippocampal volume measures by cognitive trajectory group: EF maintainers, decliners who did not convert, and converters. Empty circles are Aβ− individuals, and filled circles are Aβ+ individuals. Welsh t-tests were used to compare cognitive trajectory groups: ** $p < 0.01$, *** $p < 0.001$. AD = Alzheimer disease; CL = centiloids; ERC = entorhinal cortex; Hipp. = hippocampal; MetaROI = temporal meta region of interest; ns = not significant; SUVR = standardized uptake value ratio.

PACC maintainers had significantly higher baseline MEM and EF scores ($p < 0.001$) but did not differ from decliners on baseline PACC scores ($p = 0.15$). When considering converters as a separate group, converters had lower baseline cognition scores in each domain (pairwise t-tests, all $p < 0.02$), and PACC decliners who did not convert also had significantly lower scores compared to maintainers in MEM and EF (pairwise t-tests, $p < 0.02$).

PACC maintainers had significantly lower Aβ ($p < 0.001$) and tau burden (ERC, $p = 0.002$; MetaROI, $p < 0.001$) compared to PACC decliners (Fig 6A). PACC maintainers had significantly higher hippocampal volumes ($p = 0.004$) compared to decliners. Converters had higher Aβ and tau pathology markers and lower hippocampal volume compared to PACC maintainers and PACC decliners who did not convert (see Fig 6B; all $p < 0.002$). Compared to PACC maintainers, decliners who did not convert had borderline higher cortical Aβ burden ($p = 0.049$), but there were no other AD biomarker differences between these groups.

Unlike the MEM and EF trajectory groups, PACC maintainers had a lower rate of tau accumulation (ERC, $p = 0.04$; MetaROI, $p = 0.04$) and hippocampal atrophy rate ($p = 0.01$) compared to PACC decliners. There was no difference in cortical summary Aβ accumulation rate between PACC maintainers and decliners ($p = 0.70$). When converters were considered separately, there were no group differences in rate of accumulation for Aβ or tau measures. For hippocampal atrophy, PACC maintainers had slower atrophy rates compared to decliners who did not convert and to converters (pairwise t-tests, all $p < 0.04$).

Discussion

Here, we show that successful aging defined by maintenance of episodic memory performance, like successful aging definitions based on cross-sectional exceptional performance, is characterized by lower AD pathology burden and higher hippocampal volume. Successful aging defined by cognitive maintenance is also more common and more inclusive than definitions based on exceptional performance, as well as more clinically relevant given the emphasis on longitudinal cognitive trajectories in clinical trials. Predictably, cognitive maintainers are much less likely to convert to a clinical diagnosis, which considers more than just cognitive performance, than those whose cognition is declining over time. Although maintenance of episodic memory was our primary focus, we found the maintenance of executive function or PACC score was also associated with lower Aβ burden and greater hippocampal volume. In contrast, we found that the EF

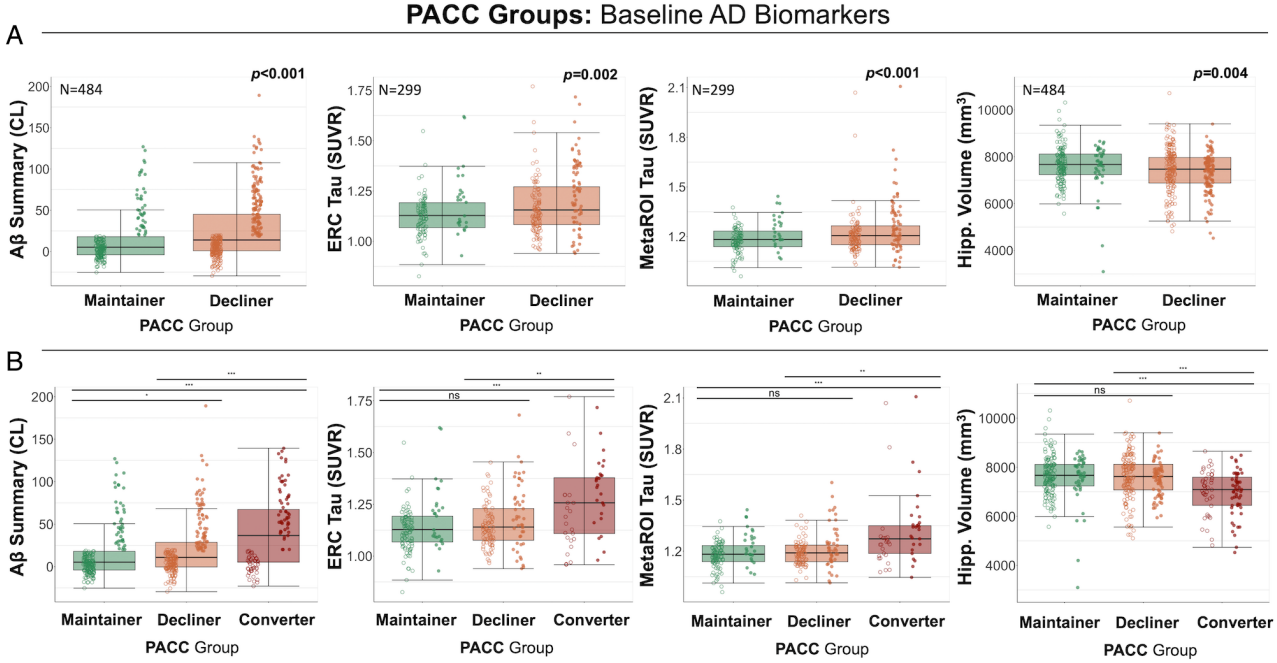

FIGURE 6: Preclinical Alzheimer Cognitive Composite (PACC)-defined cognitive trajectory groups. (A) Boxplots of baseline Aβ, tau and hippocampal volume measures by cognitive trajectory group: PACC maintainers and decliners. (B) Boxplots of beta-amyloid (Aβ), tau, and hippocampal volume measures by cognitive trajectory group: PACC maintainers, decliners who did not convert, and converters. Empty circles are Aβ− individuals, and filled circles are Aβ+ individuals. Welsh t-tests were used to compare cognitive trajectory groups: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. AD = Alzheimer disease; CL = centiloids; ERC = entorhinal cortex; Hipp. = hippocampal; MetaROI = temporal meta region of interest; ns = not significant; SUVR = standardized uptake value ratio.

maintainer group did not have lower tau burden, suggesting that lower tau is not a factor supporting EF maintenance like it appears to be for memory. Finally, PACC maintainers had slower rates of tau accumulation compared to PACC decliners, but this difference was not observed for MEM or EF groups.

The rate of successful aging based on cognitive maintenance in the present study ranged from 32% to 41% depending on the cognitive measure used to estimate cognitive trajectory. Often cross-sectional definitions of successful aging are based on relatively arbitrary cutoffs to select exceptional performers (e.g., top 20% of performers on a chosen task or composite score).[5,10] Alternatively, other definitions of successful aging require older adults perform at the normative level of younger adults.[2,6,7,22] We show here that these approaches are missing individuals whose performance is not exceptional but who do not decline over time. The proportion of individuals who are not showing cognitive decline is important to estimate, as these individuals are less likely to convert to clinical impairment. By (1) accurately categorizing lower performing cognitive maintainers as successful agers rather than including these individuals in "typical" aging groups and (2) by excluding exceptional performers whose performance is declining, we suggest we are decreasing noise in the definition of successful aging, which may be the reason that we see significant differences in Aβ burden when no Aβ effect was reported in several studies using exceptional performance definitions of successful aging.[5,6,9]

Defining successful aging based on cognitive maintenance has several advantages, including reducing sex biases in successful aging research. Due to their susceptibility to early age- and AD-related decline, verbal memory tests are often used to define successful agers in cross-sectional studies. This results in successful ager groups with significantly more women than men because women consistently have higher scores in tests of verbal memory.[23,24] In the current study, there are still significantly more women in the maintainer group compared to decliners, but this bias is much reduced compared to cross-sectional definitions using exceptional verbal memory performance.[6,7] Using the cognitive maintenance approach, we include many more men who are successfully aging, despite their scores not being in the exceptional range (Table S1). The utility of our approach is also highlighted by the finding that cross-sectional, baseline MEM performance is not predictive of prospective change in MEM scores and does not differentiate future cognitive maintainers and decliners. In other words, future cognitive maintenance or decline cannot be reliably predicted with cross-sectional data. Finally, another advantage of a successful aging definition based on within-subject change in performance (slope) rather than cross-sectional exceptional performance is that it is more inclusive. Factors related to exceptional performance are likely to include early life advantages like higher socioeconomic status and longer duration of formal education.[25,26] We observed a statistically significant higher level of education in individuals with exceptional performance at baseline compared to nonexceptional performers who maintained their cognition (Table S1). In this ADNI sample that currently has limited enrollment of individuals from minoritized racial and ethnic groups, we did not observe any differences in rate of individuals from minoritized groups in the exceptional agers compared to maintainers. There is, however, evidence from the literature that suggests minoritized racial and ethnic groups would be underrepresented in successful aging definitions based on exceptional performance. For example, Black individuals score worse on memory tests compared to White individuals, but this difference is accounted for by reading level.[27] In another large cohort study, years of education mediated a substantial proportion of racial differences in baseline cognitive score and AD risk.[28] Based on this evidence, we hypothesize that cognitive maintenance definitions of successful aging would be more inclusive of minoritized groups in more diverse cohorts.

A large body of evidence suggests that greater AD pathology is related to worse cognition even in cognitively normal older adults.[29,30] Our findings support the strong relationship between biomarkers of Aβ, tau, and neurodegeneration and cognitive outcomes. We found that those who maintain their cognition, across each of the cognitive composite scores we examined (MEM, EF, PACC), had less AD pathology and greater hippocampal volume. This naturally leads to the question: are cognitive maintainers avoiding AD pathology (resistance) or are they accumulating pathology at a slower rate? Despite consistent cross-sectional biomarker differences, we found limited evidence that biomarker rates of change were differed by cognitive trajectory. The exception was PACC maintainers, where tau accumulation rates were lower and hippocampal atrophy rate was borderline slower compared to decliners. Because the PACC is a multidomain cognitive composite, it is less noisy over time. It may be that this reduction in noise allows for a better estimate of true cognitive maintainers versus decliners, which then reveals important differences in AD biomarker changes over time. If so, it is important to also note that the number of cognitive maintainers using the PACC slopes or the MEM slopes was very similar, but these individuals only partially overlap (Fig S4).

All participants in the current study were cognitively normal at baseline, but ~22% of them converted to

clinical impairment during follow-up. Nearly all clinical converters were cognitive decliners, but there were some converters in each of the maintainer groups we examined (14 for MEM, 27 for EF, and 12 for PACC; Fig S1). These individuals had stable cognition at a borderline level where individual clinician assessment may result in different determinations about clinical status. We decided to exclude cognitive maintainers who received a clinical diagnosis, because we felt we could not be sure these individuals were cognitively normal at baseline. When we considered declining clinical converters separately, we found that this group drove some of the differences between cognitive maintainers and decliners. Within decliners as a whole, greater Aβ, tau, and hippocampal atrophy were associated with lower/worse cognitive slopes, but the Aβ and tau associations were significant only in clinical converters when we considered converters and decliners who did not convert as separate groups (Fig S3). Logistic regressions predicting converters versus decliners who did not convert highlighted baseline Aβ and tau burden as key predictors. In contrast, tau (not Aβ), baseline EF score and years of education were significant in logistic regressions predicting maintainers versus all decliners. Taken together, these data further support the relationship between AD biomarkers, especially tau, and risk for cognitive decline and, as decline worsens, a clinical diagnosis.

This study has several notable strengths. First, we used the unique, extensive longitudinal cognitive data available in ADNI and combined it with both cross-sectional and longitudinal measures of AD biomarkers as well as clinical assessments to define impairment status. We used straightforward methodology to estimate cognitive slopes that can be easily replicated by other groups with access to longitudinal cognitive data. There are also some limitations to our approach. First, we recognize that in many cases only cross-sectional data are available. We suggest that studies using cross-sectional data to define successful aging should acknowledge the limitations of such definitions, as noted above. Second, when using cognitive slopes as a primary measure, the influence of practice effects must be considered. Because we are using true baseline and all cognitive sessions following this baseline for all individuals, practice effects should not introduce any bias in the current study. By choosing to use all available cognitive data for each participant, the imaging data collection does not occur at the same time as cognitive data follow-up across participants. Finally, these analyses need to be replicated in cohorts with greater heterogeneity, especially in race and ethnicity, to further support our assertion that cognitive maintenance is a more inclusive definition of successful aging.

Conclusions

There are many ways to age successfully, but successful *cognitive* aging should be defined by the maintenance of within-individual cognitive abilities over time. Here we show individuals with varying levels of baseline performance avoid cognitive decline for up to 15 years. Even with our more inclusive approach, we show that cognitive maintainers have lower Aβ and tau burden and also have greater hippocampal volumes, a finding that has been associated with successful cognitive aging across different definitions. Future work in a more diverse sample will explore the ways in which different definitions of successful cognitive aging affect inclusion of individuals from minoritized racial and ethnic groups.

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Author Contributions

T.M.H. and W.J.J. contributed to the conception and design of the study. T.M.H., T.C., S.P., and J.L. contributed to the acquisition and analysis of data. T.M.H. and T.C. contributed to drafting the manuscript

or preparing the figures. All authors contributed to editing the manuscript.

Potential Conflicts of Interest

Nothing to report.

Data Availability

All data used in this article are available to the public at the ADNI data repository at the Laboratory of Neuroimaging (adni.loni.usc.edu). Derived data are available from the authors upon request.

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