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Superior Memory Reduces 8-year Risk of Mild Cognitive Impairment and Dementia But Not Amyloid β-Associated Cognitive Decline in Older Adults

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Abstract

Objective: To prospectively examine 8-year risk of clinical disease progression to mild cognitive impairment (MCI)/dementia in older adults ≥60 with superior episodic memory (SuperAgers) compared to those cognitively normal for their age (CNFA). Additionally, to determine the extent to which SuperAgers were resilient to the negative effects of elevated amyloid-beta (Aβ+) on cognition.

Method: Participants were classified as SuperAgers based on episodic memory performance consistent with younger adults aged 30–44 and no impairment on non-memory tests (n = 179), and were matched with CNFA on age, sex, education, and follow-up time (n = 179). Subdistribution hazard models examined risk of clinical progression to MCI/dementia. Linear mixed models assessed the effect of Aβ on cognition over time.

Results: Prevalence of Aβ+ and *APOE* ε4 was equivalent between SuperAgers and CNFA. SuperAgers had 69%–73% reduced risk of clinical progression to MCI/dementia compared to CNFA (HR: 0.27–0.31, 95% CI: 0.11–0.73, $p < .001$). Aβ+ was associated with cognitive decline in verbal memory and executive function, regardless of SuperAger/CNFA classification. In the absence of Aβ+, equivalent age-related changes in cognition were observed between SuperAgers and CNFA.

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Conclusions: SuperAgers displayed resilience against clinical progression to MCI/dementia compared to CNFA despite equivalent risk for Alzheimer's disease (AD); however, SuperAgers had no greater protection from Aβ+ than CNFA. The deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability. Thus, superior cognitive performance does not reflect resistance against the neuropathological processes associated with AD, and the observed resilience for SuperAgers may instead reflect neuropsychological criteria for cognitive impairment.

Keywords: Alzheimer's disease; Dementia; Mild cognitive impairment; Elderly/geriatrics/aging

Introduction

Neuropsychological models indicate that cognitive decline is an expected consequence of increasing age beyond 60 years (Harada, Natelson Love, & Triebel, 2013; Salthouse, 2009). For example, a recent meta-analysis of international aging studies observed that cognitive aging extends across all aspects of cognition, with the magnitude ranging from −0.26 to −0.12 *SD* units per decade from 60 years (Lipnicki et al., 2017). Most studies infer cognitive aging by observing that group mean test performance declines with the increasing age of the cohorts studied. However, variability associated with these means also increases with age, indicating that individual differences in cognitive aging become greater with increasing age (Christensen, 2001; Deary et al., 2009; Mungas et al., 2010; Wilson et al., 2002). Some of the increased individual differences in cognitive aging have been explained by the uncontrolled effects of preclinical neurodegenerative disease, such as Alzheimer's disease (AD), in aging samples (Harrington et al., 2017; Hassenstab et al., 2016; Jansen et al., 2018). For example, amyloid-beta (Aβ) biomarker studies show that approximately 16%–44% of older adults classified as cognitively normal (CN) have abnormally elevated Aβ in the brain (Aβ+) that is indicative of preclinical AD (Jansen et al., 2015). Despite being clinically asymptomatic, older adults with preclinical AD show subtle, but clear, cognitive decline, particularly in episodic memory and executive function (Baker et al., 2017; Hedden, Oh, Younger, & Patel, 2013). Consequently, inclusion of these individuals in samples of CN older adults can introduce negative biases in group mean performance that increase with age and lead to increased estimates of inter-individual variability (Harrington et al., 2017; Hassenstab et al., 2016; Hohman et al., 2017; Sliwinski, Lipton, Buschke, & Stewart, 1996).

Another explanation for increasing individual differences in cognitive aging is the presence of older adults who are resilient to cognitive decline despite their increasing age. Theoretical constructs proposed to describe these individuals include successful cognitive agers (Lin et al., 2017b; Negash et al., 2011; Pudas et al., 2013), resilient-agers (Bott et al., 2017), cognitively elite (Dixon & de Frias, 2014), supernormals (Lin et al., 2017a), optimal memory performers (Dekhtyar et al., 2017), and SuperAgers (Harrison, Weintraub, Mesulam, & Rogalski, 2012). While each construct describes similar phenomena with different operational definitions, the construct of SuperAgers currently provides the clearest psychological definition with the greatest neurobiological validity to date (Rogalski et al., 2013). The SuperAger concept originates from the perspective of Mesulam (2000) that individual differences in cognitive aging reflect a stochastic combination of non-modifiable factors such as time and genetics, and modifiable factors such as the cumulative neurobiological effects of a lifetime history of injuries and exposures (e.g., systemic illnesses, stress, head trauma, etc.). In this context, age, or the passage of time, increases the probability of encountering these events but does not guarantee them. Thus, a SuperAger is an older adult who has had reduced exposure, or is resilient, to these effects and their cognitive abilities have consequently been maintained from mid-life through to late-life. SuperAging studies therefore define SuperAgers as older adults with episodic memory performance at, or above, the mean of normative samples 20–30 years younger and with normal-for-age performance (i.e., scores not below −1 *SD* compared to normative means) on other cognitive domains (e.g., Harrison et al., 2012; Sun et al., 2016).

The SuperAger construct provides a useful foundation for studying resilience to age-associated cognitive decline because of its clear and well-validated psychometric classification criteria. For example, neurobiological investigations show that SuperAgers ≥80 years of age have greater preservation of cortical thickness compared to middle-aged adults, and reduced rates of cortical atrophy compared to cognitively normal for age (CNFA) adults (Cook et al., 2017; Gefen et al., 2015; Harrison et al., 2012). SuperAgers also show lower frequency of Aβ plaques and AD-type neurofibrillary tangles than CNFA on post-mortem examination, suggesting these individuals also possess increased resilience to neurodegenerative disease (Gefen et al., 2015). Together, these observations suggest that SuperAger classification is associated with some protection against the biological changes associated with both aging and neurodegenerative disease such as AD (Rogalski et al., 2013). This is consistent with findings from two prospective studies that these individuals are protected against cognitive decline measured from baseline over 18 months (Gefen et al., 2014) and up to an average of 5 years (Harrison, Maass, Baker, & Jagust, 2018). A recent prospective study also extended prior findings by showing that individuals classified as successful agers were also resilient to decline in episodic memory associated with Aβ+ (Harrison et al., 2018). This study retrospectively

classified older adults ≥70 enrolled in the Berkeley Aging Cohort Study (BACS) as successful agers if their performance on a list learning test was within the normative range of performance of 18–32 year-old adults on the same test, and normal-for-age performance on the Trail Making Test B (i.e., SuperAgers, as per Sun et al., 2016). In their sample of 150 adults with an average age of 75 years, 26 (17.3%) were classified as successful agers. Group mean levels of Aβ and the proportion of adults with Aβ+ were equivalent between the successful agers and the typical older adults (i.e., CNFA) at baseline assessment, consistent with another study of "optimal agers" (Dekhtyar et al., 2017). Although higher Aβ levels were associated with memory decline in the typical older adult group over an average of five years, individuals classified as successful agers showed no Aβ-associated decline in episodic memory (Harrison et al., 2018). Thus, while the superior memory performance characteristic of SuperAging was not associated with reduced accumulation of Aβ, it did provide resilience to the downstream effects of Aβ on episodic memory in these individuals.

The possibility that superior memory performance in older adults reflects resilience to the deleterious effects of Aβ must be considered cautiously with respect to the limitations of the aforementioned study (Harrison et al., 2018). First, the sample of successful agers was relatively small (i.e., $n = 26$) and the sub-sample of Aβ+ successful agers even smaller ($n = 10$). Studies measuring the effect of Aβ on cognitive decline in older adults show that such decline is observed only with abnormally high levels of Aβ (i.e., AB+) (Harrington et al., 2018). Thus, it is likely that the absence of any Aβ-associated memory decline in the successful ager group was due to a small sample and, therefore, inadequate statistical power for detecting group differences and interactions in longitudinal analyses (Button et al., 2013). A related issue is that the length of time for which follow-up data is available varies substantially between participants in BACS study sample. Reduced numbers of data points at the longer follow-up intervals also reduces the statistical power of analyses comparing slopes of cognitive change between groups and may additionally inflate the influence of any sample biases (Hansen & Collins, 1994). Third, although it is important to examine cognitive change over time in individuals classified as successful agers or SuperAgers, the clinical implications of these changes are difficult to determine when considered in isolation. One more meaningful criterion by which to assess the clinical consequences of SuperAger classification is the extent to which this protects individuals against clinical disease progression to mild cognitive impairment (MCI) or dementia.

The overarching aim of this study was to investigate the extent to which individuals classified as SuperAgers displayed resilience against cognitive decline associated with age and with AD. The first aim was to compare the 8-year risk of clinical disease progression to mild cognitive impairment (MCI)/dementia in a large group of older adults with superior episodic memory at baseline (SuperAgers) compared to CNFA. The second aim was to determine the extent to which SuperAgers were resilient to the negative effects of Aβ+ on cognition. The first hypothesis was that individuals classified as SuperAgers would be at reduced risk of progression to a clinical classification of MCI/dementia over 8 years when compared to well-matched CNFA adults. The second hypothesis was that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e., Aβ+) compared to their matched CNFA counterparts. We also explored the extent to which age influenced relationships between SuperAger classification, Aβ status, and prognosis.

Method

Participants

Participants were from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The full study protocol has been previously reported (Ellis et al., 2009). Briefly, volunteers were ineligible for study entry if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hr of post-traumatic amnesia, or current regular alcohol intake of >4 standard drinks per day for men or >2 per day for women (National Health and Medical Research Council, 2001). Health status was determined from a medical assessment that included measurement of vital signs (height, weight, blood pressure, and abdominal circumference), blood tests, and self-reported medical history. Current health was reviewed for all participants at each study visit for the present study, and all included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, Hollywood Private Hospital, and Edith Cowan University, and written informed consent was collected from all participants prior to undertaking any assessment procedures.

The AIBL study currently includes 620 CN adults who satisfied the baseline inclusion criteria, were aged over 60 with MMSE>24, underwent Aβ PET neuroimaging, and who have attended at least two study visits. These participants were recruited in two waves: an inception cohort ($n = 439$) followed every 18 months for up to 8 years, and an enrichment cohort ($n = 181$)

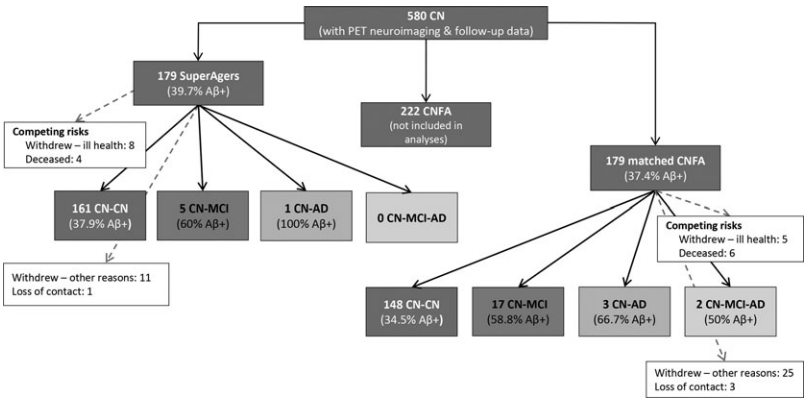

Fig. 1. Sample classification and clinical disease progression in the AIBL sample over 8 years.

followed for up to 4.5 years. Data were available for assessments spanning from November 2006 through to April 2016. The sample was further restricted to those who reported no history of stroke, transient ischemic attack (TIA), or serious head injury at baseline ($n = 599$). Participants whose clinical classification or Aβ status fluctuated during the study period were excluded ($n = 19$). This left 580 CN older adults with complete data available for analysis, 179 of whom were classified as SuperAgers.

Baseline SuperAger classification required performance above the sex-adjusted normative average for 30–44 year olds on the California Verbal Learning Test – Second Edition (CVLT-II) Long Delay Free Recall trial (≥13 for women, ≥12 for men) (Delis, Kramer, Kaplan, & Ober, 2000), and above −1 *SD* using published normative data for all non-memory tests identified to be optimal for the study of cognitive aging, including the Digit Symbol Substitution Test, the Victoria Stroop Test (words trial), Digit Span, Letter Fluency (FAS), and Category Fluency (total animals and male names, and fruit and furniture) (e.g., Harrington et al., 2016). These psychometric criteria are consistent with those originally used by the Northwestern SuperAging Study (Harrison et al., 2012) and other studies (Harrison et al., 2018; Sun et al., 2016), despite the greater number of non-memory tests used for classification in the current study. SuperAgers were then case-matched with the remaining CN participants (i.e., CNFA) based on age, sex, education, and follow-up time to ensure that the study results were not driven by demographic differences. Therefore, 358 participants were included in this study (179 SuperAgers, 179 CNFA, Fig. 1).

Measures

A comprehensive neuropsychological battery was administered to all participants at each visit, the details of which are described elsewhere (Ellis et al., 2009). Four composite domain scores were derived via exploratory factor analysis, as previously reported, and were calculated for each participant visit by averaging z-scores of the respective tests for each domain (Harrington et al., 2018). Z-scores were calculated relative to the full CN AIBL sample. The verbal memory composite included CVLT-II Long Delay Free Recall, CVLT-II Immediate Recall Trials 1–5, and Logical Memory II. The executive function composite included Category Fluency (total animals and male names, and fruit and furniture), Letter Fluency (FAS), Victoria Stroop Test (words trial), and Digit Symbol Substitution Test. Working memory included two Cogstate tasks (One Back, One Card Learning). Finally, processing speed included the Cogstate Identification and Detection tasks. Education was coded as ≤12 years or >12 years. Mood symptomology was assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The Memory Complaint Questionnaire (MAC-Q) (Crook, Feher, & Larrabee, 1992) raw score was used to assess subjective memory complaint. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology (Porter et al., 2018).

Cognitive Status Assessment

An expert clinical panel made consensus classifications using standard clinical criteria for MCI (Winblad et al., 2004) and AD (McKhann et al., 1984), and was blinded to any information concerning Aβ and *APOE* ε4 status. The panel reviewed all available neuropsychological and psychiatric information for participants who performed below −1.5 *SD* on published age- and education-adjusted normative data on at least two neuropsychological tests. Participants who performed within normal limits for their age on cognitive testing were classified as CN, and those who were classified with MCI/dementia during the follow-up period were coded as progressors.

Amyloid-beta PET Neuroimaging

PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, $n = 140$), ^{18}F-NAV4694 (NAV, $n = 44$), ^{18}F-Florbetapir (FBP, $n = 87$), or ^{18}F-Flutemetamol (FLUTE, $n = 87$). PET methods and procedures have been reported previously (Rowe et al., 2010; Villemagne et al., 2014). Briefly, PET acquisitions were performed up to 90 min following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). The accepted cut-off values for significant Aβ deposition vary by radiotracer, so a linear regression transformation was applied to the FBP and FLUTE SUVR to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT; Villemagne et al., 2014). All particiants with SUVR/BeCKeT ≥ 1.40 at their most recent PET scan were classified as Aβ+, and those below the threshold were classified as Aβ−.

Statistical Methods

R version 3.4.3 (R Core Team, 2017) and SPSS 23 were used for all statistical analyses, with statistical significance set at $p < .05$. SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age and follow-up time were ±2 years and ±1 visit, respectively. Eligible matches were selected at random.

Baseline group differences in clinical characteristics. Normality of continuous variables was assessed by visual inspection of Q–Q plots. Between-group comparisons by SuperAger status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. A Kruskal–Wallis one-way ANOVA was used for non-normally distributed variables. Differences in dichotomous variables were assessed using Fisher's exact tests. No adjustments were made for multiple comparisons due to their conservative nature; rather, Cohen's *d* was used to guide interpretation of statistically significant results, such that significant comparisons with very small effect sizes ($d < 0.20$) were suspected Type I errors.

Survival analysis. Fine-Gray subdistribution hazard modeling was used instead of cause-specific Cox modeling due to its ability to account for the presence of competing risks, which were defined as death or withdrawal from the study due to illness unrelated to dementia. Progression to MCI/dementia was coded as events, and time to event was entered in months from the baseline visit. Non-progressors were right-censored at the time of their most recent study visit. Schoenfeld residuals tests were non-significant for predictors and the global value was non-significant for the entire model, indicating that the proportional hazards assumption was met. All DFBETA values were within the size-adjusted cut-score; therefore, no outliers were detected.

Survival models evaluated the first hypothesis in five stages to determine whether SuperAger classification can predict non-progression to MCI/dementia. Model 1 included only SuperAger status. Model 2 added estimated premorbid IQ. Standard demographic predictors that have been indicated as risk factors for MCI/dementia were added to Model 3: baseline age and sex. Presence of the *APOE* ε4 allele was added in Model 4. Finally, Model 5 included Aβ status (+/−). Cumulative hazard functions were plotted, and hazard ratios were calculated with 95% confidence intervals.

Influence of Aβ on cognitive change. Multiple linear mixed model (LMM) analyses with maximum likelihood estimation were conducted with each of the four cognitive domain composite scores as continuous dependent measures. Nonlinear models did not improve model fit nor the amount of variance explained, and visual examination indicated that the data most closely fit a linear pattern. Fixed factors were SuperAger status, Aβ status, time from baseline assessment in years, and their interactions. Participant was entered as a random factor with random slopes for time. Covariates were baseline age, progression status, premorbid IQ, and *APOE* ε4 status. To explore the extent to which the effects of SuperAger classification on cognitive change were influenced by age, additional LMMs were run to test interactions between SuperAger status, Aβ status, and age.

Results

Sample Characteristics

Over the 8-year period, 28 participants progressed to clinically-classified MCI/dementia (22 CNFA, 6 SuperAgers), 10 died, 13 withdrew due to ill health, 36 formally withdrew from the study for reasons unrelated to health, and 4 could not be

Table 1. Baseline group differences

Measure	Total sample	CNFA	SuperAgers	*p*-value	*d*
n	358	179	179		
Aβ+, %	38.50	37.40	39.70	.75	
APOE ε4 carrier, %	27.90	27.40	28.50	.91	
Age at baseline, years	68.48, 68.00 (9)	68.53, 68.00 (8)	68.43, 68.00 (9)	.89	
Female, %	53.60	53.60	53.60	1	
Premorbid IQ	112.24, 114.00 (8)	111.28, 114.00 (8)	113.25, 114.00 (5)	**.002**	0.31
Education >12 years, %	65.40	65.40	65.40	1	
HADS A	4.40, 4.00 (5)	4.45, 4.00 (5)	4.34, 4.00 (5)	.43	
HADS D	2.66, 2.00 (3)	2.50, 2.00 (3)	2.82, 2.00 (3)	.39	
MAC-Q	25.25, 25.00 (6)	24.89, 25.00 (6.75)	25.61, 25.00 (6)	.86	
Progressors, %	7.80	12.30	3.40	**.003**	0.77
Withdrawn due to ill health/deceased, %	6.40	6.10	6.70	1	
Subsequent stroke/TIA, %	5.00	5.00	5.00	1	
Hypertension, %	50.60	54.20	46.90	.21	
Diabetes, %	8.90	11.70	6.10	.09	
People followed up at all assessment time points (6 over 90 months), %	62.80	63.70	62.00	.83	
Length of follow up (months)	75.75, 90.00 (20)	77.38, 90.00 (19)	74.04, 90.00 (35)	.33	
Verbal memory composite score	0.26, 0.30 (1.08)	−0.08, −0.12 (1.06)	0.63, 0.63 (0.79)	**<.0005**	1.13
Executive function composite score	0.12, 0.19 (0.91)	−0.10, −0.12 (1.02)	0.36, 0.35 (0.71)	**<.0005**	0.74
Working memory composite score	0.00, 0.006 (0.85)	−0.03, −0.04 (0.81)	0.03, 0.04 (0.84)	.16	
Processing speed composite score	0.21, 0.27 (1.03)	0.14, 0.25 (1.09)	0.27, 0.28 (0.96)	.16	

All descriptive statistics for continuous variables reported as mean, median (interquartile range); categorical variables reported as percentages. *p*-values shown for comparisons between SuperAger and CNFA groups; Cohen's *d* shown for comparisons with $p < .05$

Note: Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage; CNFA = cognitively normal for age; HADS A = Hospital Anxiety and Depression Scale – Anxiety; HADS D = Hospital Anxiety and Depression Scale – Depression; MAC-Q = Memory Complaint Questionnaire; TIA = Transient ischemic attack.

contacted for follow-up (Fig. 1). Median follow up time for the full sample was 90 months (interquartile range: 20) and 62.8% of all participants were followed throughout the entire study period. Participants were 68.5 years of age on average (range: 60–83), and most were educated beyond 12 years (65.4%). See Table 1 for demographic and clinical characteristics.

Baseline Group Differences

As expected, no group differences (SuperAgers vs. CNFA) were observed in baseline age, sex, education, or follow-up time (Table 1). The groups also did not differ on any clinical factors. SuperAgers had higher estimated premorbid IQ (two points) compared to matched CNFA. The proportion of *APOE* ε4 carriers and participants with Aβ+ was similar between both groups. These findings were also observed between groups in the full sample before case-matching. Consistent with the classification criteria, SuperAgers had significantly higher mean verbal memory and executive function performance at baseline; however, the differences in working memory and processing speed were not significant. No differences were observed between SuperAgers and CNFA on subjective memory assessment.

Prognostic Utility of SuperAging Criteria

Fisher's exact test showed that SuperAgers were less likely to progress to MCI/dementia than CNFA (OR: 0.248, 95% CI: 0.098–0.626; $p = .003$). Survival analyses results are shown in Table 2. SuperAger status decreased risk of progression to MCI/dementia in all models by 69%–73% compared to CNFA (Fig. 2). In Model 2, premorbid IQ did not influence risk of progression. Females had 68% less risk than males in Model 3, and premorbid IQ reduced risk by 8% for each point increase with the addition of sex in the model. In Model 4, *APOE* ε4 carriage increased risk by 227%. Aβ status conferred no additional risk in Model 5, but reduced the risk conferred by *APOE* ε4 status to 188%. The effect of age was significant and remained consistent across Models 3–5, which showed 8%–9% increased risk of progression to MCI/dementia per additional year of age at baseline, although this risk was not influenced by SuperAger classification or Aβ status.

Table 2. Survival analyses

MODEL 1	*p*-value	HR	95% confidence interval	
SuperAger status	**.004**	**0.27**	**0.11**	**0.65**
MODEL 2	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.73**
Estimated premorbid IQ	.082	0.96	0.91	1.01
MODEL 3	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.74**
Estimated premorbid IQ	**.007**	**0.92**	**0.86**	**0.98**
Baseline age	**.013**	**1.08**	**1.02**	**1.15**
Sex	**.011**	**0.32**	**0.13**	**0.76**
MODEL 4	*p*-value	HR	95% confidence interval	
SuperAger status	**.007**	**0.30**	**0.13**	**0.72**
Estimated premorbid IQ	**.015**	**0.93**	**0.87**	**0.99**
Baseline age	**.005**	**1.09**	**1.03**	**1.16**
Sex	**.017**	**0.33**	**0.13**	**0.82**
APOE ε4 carrier	**.003**	**3.27**	**1.52**	**7.05**
MODEL 5	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.74**
Estimated premorbid IQ	**.013**	**0.92**	**0.87**	**0.98**
Baseline age	**.013**	**1.08**	**1.02**	**1.15**
Sex	**.015**	**0.31**	**0.12**	**0.80**
APOE ε4 carrier	**.005**	**2.88**	**1.39**	**5.97**
Aβ+	.180	1.69	0.78	3.63

Note: HR = hazard ratio; Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage.

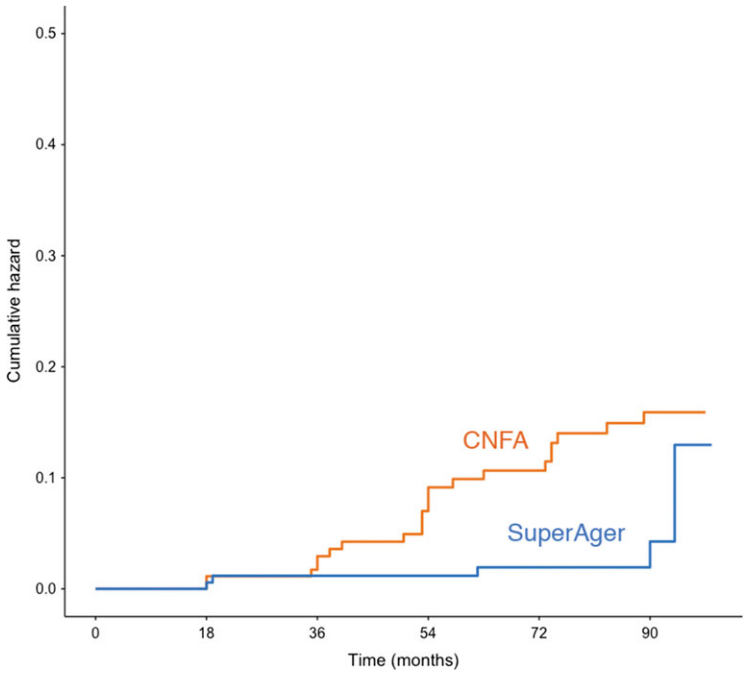

Fig. 2. Cumulative hazard functions between SuperAgers and CNFA (cognitively normal for their age).

Effect of Aβ Status on Longitudinal Cognitive Performance in SuperAgers

The LMM parameters are shown in Table 3, and the annualized group mean slopes for performance over time in each cognitive domain for the Aβ+ and Aβ− SuperAger and CNFA groups are summarized in Table 4. Table 4 shows that mean slopes for verbal memory performance over time in the Aβ− CNFA and SuperAger groups were both positive, showing improvement over time. In comparison, group mean slopes in the Aβ+ CNFA and SuperAger groups were both negative,

showing decline over time. These relationships are shown graphically in Fig. 3. This same pattern of outcomes was evident for performance over time on the executive function composite. However, for working memory, the slopes of performance over time remained close to zero for the SuperAger and CNFA groups irrespective of Aβ status, and all groups showed a decline over time for processing speed (Table 4). The LMMs identified no significant interaction between SuperAger status and time, or SuperAger status and Aβ for any composite (Table 3). For verbal memory, SuperAger status, time, age, progression status, and premorbid IQ were significant main effects, and there was a significant Aβ status by time interaction. For executive function, SuperAger status, Aβ status, time, *APOE* ε4 status, age, progression status, and premorbid IQ were all significant main effects, and the interaction between Aβ status and time was also significant. No significant main effects or interactions were observed for working memory. For processing speed, significant main effects were observed for time, age and premorbid IQ with no significant interactions. These overall findings were unchanged when premorbid IQ was removed from the LMMs. Age did not significantly interact with SuperAger status or Aβ status on any cognitive domain.

Discussion

The first hypothesis, that SuperAger classification would be associated with reduced risk of progression to a clinical diagnosis of MCI or dementia, was supported. In the total AIBL CN cohort, 30.9% met the SuperAger criteria (i.e., $n = 179$ with 71 Aβ+) and a CNFA group of the same size was matched to the SuperAger group on age, sex, education, and follow up time. The relatively high proportion of individuals classified as SuperAgers in the AIBL CN cohort most likely reflects the rigorous inclusion/exclusion criteria for AIBL as well as selection and survivor biases. Although SuperAger and CNFA groups were not matched a priori on general health or known AD risk factors, all clinical measures as well as the prevalence of the AD risk factors, Aβ+ and *APOE* ε4 carriage, were equivalent between groups (Table 1). This equivalence was also observed prior to case-matching, consistent with reports from previous studies (Dekhtyar et al., 2017; Harrison et al., 2018), and *APOE* ε4 carriage remained similar between SuperAger and CNFA groups when the imaging inclusion criterion was lifted despite the AIBL imaging sub-sample being enriched for *APOE* ε4 carriers. Similarity between the groups in physical health characteristics most likely reflects the well-documented homogeneity of the AIBL sample due to its rigorous exclusion

Table 3. Linear mixed model parameters

	Verbal memory			Executive function			Working memory			Processing speed		
	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value
Intercept	−0.94	0.64	.14	−0.73	0.62	.24	−0.32	0.54	.56	0.32	0.71	.66
SuperAger classification	0.57	0.08	**<.0005**	0.36	0.07	**<.0005**	0.13	0.07	.07	0.02	0.10	.86
Aβ status (+/−)	0.02	0.10	.83	0.18	0.09	**.04**	0.11	0.08	.19	−0.06	0.12	.60
Time (years)	0.04	0.01	**.002**	−0.01	0.01	.31	0.00	0.01	.86	−0.09	0.01	**<.0005**
APOE ε4 carrier status (+/−)	0.05	0.07	.45	−0.21	0.07	**.002**	0.02	0.06	.74	−0.13	0.08	.10
Baseline age	−0.03	0.01	**<.0005**	−0.04	0.01	**<.0005**	0.00	0.00	.29	−0.02	0.01	**<.0005**
Progression	−0.74	0.11	**<.0005**	−0.34	0.11	**.003**	−0.05	0.10	.64	−0.18	0.13	.17
Premorbid IQ	0.02	0.005	**<.0005**	0.03	0.00	**<.0005**	0.00	0.00	.85	0.01	0.01	**.01**
SuperAger * Aβ status	−0.10	0.13	.43	−0.07	0.12	.55	−0.19	0.11	.10	0.22	0.16	.18
SuperAger * Time	−0.03	0.02	.12	−0.02	0.01	.09	−0.01	0.01	.59	0.02	0.02	.19
Aβ status * Time	−0.06	0.02	**.001**	−0.03	0.01	**.04**	−0.03	0.02	.13	−0.01	0.02	.71
SuperAger * Aβ status * Time	0.03	0.03	.30	0.01	0.02	.69	0.04	0.02	.10	−0.02	0.03	.57

Note: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage.

Table 4. Annualized group mean slopes for cognitive performance for Aβ− and Aβ+ SuperAgers and CNFA

	CNFA		SuperAgers	
	Aβ−	Aβ+	Aβ−	Aβ+
Verbal memory	0.04 (0.12)	−0.02 (0.12)	0.01 (0.12)	−0.02 (0.13)
Executive function	−0.01 (0.08)	−0.03 (0.08)	−0.03 (0.08)	−0.05 (0.09)
Working memory	−0.002 (0.1)	−0.03 (0.11)	−0.01 (0.11)	0.005 (0.11)
Processing speed	−0.092 (0.13)	−0.1 (0.14)	−0.07 (0.13)	−0.09 (0.13)

Presented as mean slopes (SD). Abbreviations used: Aβ− = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for their age; SD = standard deviation.

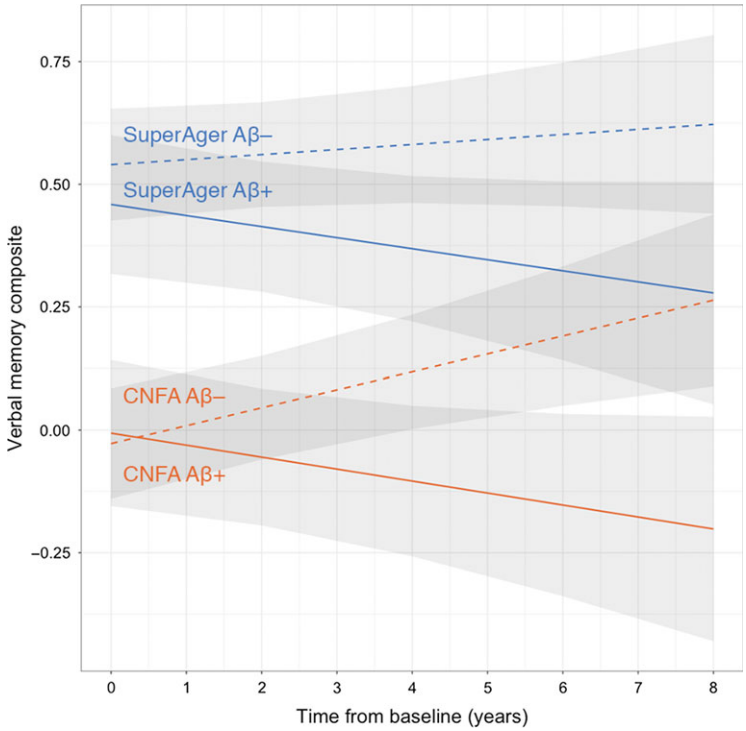

Fig. 3. Verbal memory performance over time by SuperAger and Aβ status. Abbreviations used: Aβ− = cerebral amyloid-beta within normal range (PET SUVR < 1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for their age.

criteria (Ellis et al., 2009). In this context, the similar prevalence of AD risk factors indicates that SuperAger classification, reflective of superior baseline cognitive performance, did not reflect resistance against neuropathological processes central to the development of AD (Jack et al., 2013; Selkoe & Hardy, 2016). Despite the equivalent risk for AD, only 3.4% of the SuperAger group progressed to a clinical classification of MCI/dementia over the 8-year follow-up interval compared to 12.3% of the CNFA group. When examined in survival models, this difference reflected a 69%–73% reduction in risk of progression to MCI/dementia for SuperAgers compared to CNFA. Furthermore, the reduced risk of clinical progression in SuperAgers was not modified by *APOE* ε4 carriage, Aβ+ or age (Table 2). The continued resilience of SuperAgers to clinical progression despite similar levels of AD risk suggests that, while SuperAgers are not resistant to the accumulation of Aβ, they may have some resilience to the effects of elevated Aβ on cognitive change. Although clinical disease outcomes associated with SuperAging have not been explored previously, it has been reported that individuals classified as SuperAgers display less Aβ-associated memory decline compared to CNFA despite equivalent levels of Aβ burden (Harrison et al., 2018).

The second hypothesis, that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e., Aβ+), was not supported. While, by definition, SuperAgers had superior verbal memory compared to CNFA adults at baseline, cognitive change over the following 8 years was equivalent between the Aβ+ SuperAgers and Aβ+ CNFA adults in both nature and magnitude (Fig. 3), consistent with that reported in other prospective studies of cognitive change associated with Aβ+ (Baker et al., 2017; Hedden et al., 2013). In the absence of preclinical AD (i.e., Aβ−), both the SuperAger and CNFA groups showed no decline in verbal memory or executive function and equivalent rates of decline in processing speed and working memory (Fig. 2). Thus, individuals classified as SuperAgers showed no unique resilience to Aβ-associated cognitive decline in this study. These findings are inconsistent with two recent studies of SuperAging, which suggest that SuperAger classification reflects increased resilience against the effects of AD-associated pathological change (Harrison et al., 2018; Rogalski et al., 2018). A post-mortem study found maintenance of superior episodic memory in 7/10 of the studied SuperAgers despite moderate or frequent neuritic plaques and neurofibrillary tangles in more than half of them (Rogalski et al., 2018). Furthermore, a study of the BACS cohort reported that successful agers displayed no episodic memory decline compared to CNFA over an average of 5 years. Although levels of Aβ burden were equivalent between groups, the successful agers were resilient to Aβ-associated memory decline whereas the CNFA older adults were not (Harrison et al., 2018). The discrepancy in findings may reflect methodical differences between these studies. First, the present study had a much larger sample of SuperAgers ($n = 179$ with 71 Aβ+) than the BACS sample of successful agers ($n = 25$ with longitudinal follow-up, of whom 10 were Aβ+). Second, the

length of follow-up in the BACS sample varies between participants and it is unknown how many successful agers were assessed at the longest follow-up interval. In contrast, 62.8% of the present study sample provided complete data over the full 8-year period of available AIBL data (i.e., 111 SuperAgers), providing the current design with greater statistical power. Therefore, the BACS finding that individuals classified as successful agers displayed no memory decline associated with Aβ+ was likely due to the small sample sizes studied resulting in lack of statistical power to detect these effects. Finally, differences between studies with regard to specific neuropsychological and age criteria for SuperAger classification can limit comparisons from one study to another. The BACS sample included individuals over 70 years old and classified successful agers using the CVLT-II normative mean for 18–32 year olds that was not adjusted for sex (Harrison et al., 2018). In the present study, the criteria for SuperAger classification included adults over age 60 whose memory performance was defined using the sex-adjusted CVLT-II normative mean for 30–44 year olds. Although the gap between participants' age and the reference age varies between studies, these differences should be negligible if SuperAgers do indeed maintain their "youthful" cognitive ability into late-life; however, older age was associated with lower cognitive performance for verbal memory, executive function and psychomotor speed across all participants with no differential effects between SuperAgers and CNFA. Despite these methodological differences, the current finding that a substantial sample of CN older individuals classified as SuperAgers using careful psychometric and rigorous inclusion/exclusion criteria have no greater protection from the negative effects of Aβ+ than do well-matched CNFA indicates that the deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability.

Results of the current study are consistent with the proposition that the increasing individual differences in cognition, which become greater with age, are likely to reflect the presence of at least two distinct subgroups of older adults. First, individuals with occult neurodegenerative disease such as preclinical AD cannot be considered to be aging normally; therefore, their inadvertent inclusion in aging study samples will negatively bias estimated effects of cognitive aging (Harrington et al. 2018). A second subgroup of older adults who exhibit baseline cognition superior to other CN adults of the same age can also be present in aging samples. Previous SuperAging studies have used different minimum age criteria for SuperAger classification (i.e., 60–80; Harrison et al., 2018, 2012; Sun et al., 2016), but only one has examined how age influences the cognitive and neurobiological outcomes of psychometrically-defined SuperAgers. They report a negative relationship between age and Aβ deposition in SuperAgers; however, this relationship became non-significant following removal of outlier data (Harrison et al., 2018). Although the present study found that increasing age was associated with greater risk of clinical disease progression to MCI/dementia and lower cognitive performance, the effect of age on cognition was consistent across all individuals regardless of SuperAger classification or Aβ status. This suggests that cognitive decline in preclinical AD is due to neuropathological changes beyond the effect of age, itself, and that individuals classified as SuperAgers are no more resilient to changes in cognition associated with age or with preclinical AD than are CNFA.

In contrast, studies of cognitive reserve report that the relationship between Aβ and cognitive decline is modified by greater years of education and higher premorbid IQ (Rentz et al., 2010; Yaffe et al., 2011). It has additionally been reported that greater participation in cognitively stimulating activities is associated with lower Aβ deposition (Landau et al., 2012). It is possible that the SuperAger and cognitive reserve constructs overlap; however, they are not the same. Individuals with high cognitive reserve are typically identified using proxy measures such as education, premorbid IQ and cognitive activity, and may display greater cognitive performance with equivalent levels of AD neuropathological markers compared to individuals with low cognitive reserve (Stern, 2012). Classification criteria for SuperAgers are psychometrically-based; therefore, while the superior cognitive performance observed in SuperAging samples may be reflective of higher cognitive reserve, this study specifically matched SuperAgers and CNFA on education. Additionally, previous studies report no difference in premorbid IQ between SuperAgers and their CNFA controls (Cook et al., 2017; Sun et al., 2016). While SuperAgers in the current study did show slightly better premorbid IQ than the CNFA group, the magnitude of this benefit was trivial when considered clinically (i.e., two points). Because individuals classified as SuperAgers exhibited better cognitive ability than CNFA at all time points despite similar levels of Aβ deposition, cross-sectional examinations may support the notion that SuperAgers represent a population with high cognitive reserve; however, this does not bear out in the longitudinal examination conducted in this study given that Aβ+ older adults, regardless of classification, showed clear Aβ-associated cognitive decline compared to Aβ− participants. According to these findings, SuperAgers are not resilient to Aβ-associated cognitive decline as suggested by the construct of cognitive reserve (e.g., Stern, 2012), although one small study examining Aβ-associated cognitive change in successful agers did find evidence of such resilience (Harrison et al., 2018). Finally, studies of cognitive reserve indicate that individuals with high cognitive reserve experience more rapid cognitive decline than those with low cognitive reserve, which was not observed in this study as rates of cognitive change were equivalent between SuperAgers and CNFA. Together, these observations suggest the possibility that the SuperAger and cognitive reserve constructs are different, a point that was also noted by the group who pioneered the SuperAger construct (Rogalski et al., 2013).

The SuperAger construct is based on the observation that some adults progress from middle-age to old-age without showing any decline in their cognitive abilities (Gefen et al., 2015). Because it is rare to possess neuropsychological data across

the entire adult lifespan for individuals, studies of SuperAging approximate "youthful" cognition (Rogalski et al., 2013) in their samples by comparing neuropsychological performance of their older adults to normative data derived from individuals 20–30 years younger (Harrison et al., 2012). While the results of the current study confirm the validity of the SuperAgers construct, they raise the question of what is actually reflected by the superior cognition observed in SuperAgers. This study matched the SuperAger and CNFA groups on age, sex, education and follow-up time, and found similar physical health and AD risk profiles between groups (Table 1). However, as individual differences in cognitive aging reflect complex interactions between time, genetics and a stochastic combination of events (Mesulam, 2000), it is not feasible to experimentally or statistically control all possible differences. For example, higher occupational complexity has been associated with greater white matter integrity and cognitive function in later life (Kaup et al., 2017), and increased physical activity has been linked to better cognition and attenuated age-associated brain atrophy (Gomez-Pinilla & Hillman, 2013). The inconsistency between risk factors for MCI/dementia, defined psychometrically (i.e., SuperAger classification, which reflects superior baseline cognitive performance) and biologically (i.e., Aβ and *APOE* ε4) in the current study, indicates that other neuroimaging biomarkers are necessary to understand how SuperAging can influence cognitive aging. For example, future studies in large cohorts, like AIBL, should seek to examine volumetric and functional differences between SuperAgers and CNFA in brain regions associated with verbal memory and executive function by Aβ status. Previous studies have reported cross-sectional differences in regional volumes and cortical thickness, albeit without consideration to Aβ status (Harrison et al., 2012; Sun et al., 2016). Although one study did examine longitudinal morphological changes in successful agers with respect to Aβ burden, reporting no differences between successful agers and typical older adults and no Aβ-associated differences, the sample size was limited ($n = 19$ successful agers) (Harrison et al., 2018). If these differences are observed in a larger sample and persist even in preclinical AD, such a finding would indicate that SuperAgers' resilience to progression is a consequence of greater neuronal integrity (Harrison et al., 2012). Furthermore, although imaging and pathological studies consistently show that SuperAgers have superior brain and neuronal structure to CNFA adults, an observation that would be consistent with SuperAgers having lower levels of tau even in the presence of Aβ+ (Desikan et al., 2011; Jack et al., 2013), no study of SuperAging has yet measured levels of cortical tau.

Given that SuperAgers progressed to MCI/dementia at a lower rate than did CNFA despite being equally affected by cognitive aging and Aβ+, consideration must be given to the clinical classification process. Classification of clinical disease progression in AIBL is guided by considering the level of performance on neuropsychological tests at each visit with reference to published normative data for those tests. Consequently, because of their superior test performance, SuperAgers who are Aβ+ and have exhibited the cognitive decline pathognomonic of preclinical AD continue to have their test performance classified as unimpaired relative to the normative data. This can be interpreted in two ways. First, superior cognitive performance in SuperAgers allows them to tolerate AD neuropathological changes for longer than CNFA. Alternatively, reliance on static published normative data to guide clinical classification is unsatisfactory. More accurate identification of MCI/dementia in SuperAgers may occur if classification decisions took into consideration cognitive change over time; however, this is limited by the lack of available normative data for longitudinal change (Fuchs et al., 2013; Stein et al., 2012). It is, therefore, possible that SuperAger classification may not prevent, but rather delays, clinical classification of MCI/dementia due to the greater

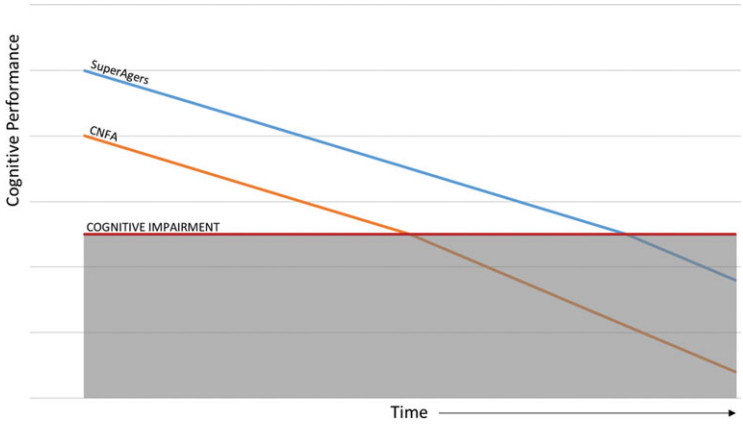

Fig. 4. Theoretical trajectory to cognitive impairment for CNFA and SuperAgers. The same rate of change in cognition was observed between SuperAgers and case-matched cognitively normal for age (CNFA) participants on all cognitive domains. Because cognitive impairment is determined by neuropsychological test performance in reference to normative data and SuperAgers exhibit superior cognitive performance at baseline, SuperAgers may take longer to reach the threshold for cognitive impairment.

amount of time needed for high baseline test performance to decline past the threshold for defined cognitive impairment, as illustrated in Fig. 4.

The generalizability of the present findings must be considered in the context of the following caveats. AIBL is a convenience sample of relatively healthy, well-educated and ethnically homogeneous individuals with strict inclusion criteria; therefore, the characteristics of SuperAgers and CNFA in this study may differ from the general population. Nearly one-third of the CN AIBL sample were classified as SuperAgers, which may be greater than that expected in the general population; however, the prevalence of SuperAgers has not been reported in previous SuperAging studies. Furthermore, participants of the AIBL study have completed the neuropsychological battery up to six times over 8 years and display considerable practice effects, particularly in the memory tests. While it has been observed in AIBL and in other prospective studies that CN Aβ+ individuals do not necessarily display decline in cognition over time, but rather a loss of practice effects (Duff, Foster, & Hoffman, 2014; Hassenstab et al., 2015; Lim et al., 2016; Mormino et al., 2014), this study did observe that CN Aβ+ individuals declined on verbal memory over time. Despite these caveats, the present study has a number of strengths. First, no other study of SuperAgers has case-matched CNFA based on age, sex, education, and follow-up time. Second, this is the first study to examine longitudinal cognitive performance in SuperAgers with consideration to Aβ status in this large a sample over a relatively long time interval. Finally, there is great potential to further study the SuperAger construct in AIBL, particularly with reference to the effects of Aβ on brain volumetric measures over time to determine whether SuperAger classification offers any protection against neurodegeneration or tau accumulation downstream of elevated Aβ deposition.

The process of aging is complex, in which considerable inter-individual variability is inherent, and this is partially reflected by different individual levels of Aβ deposition and neurodegenerative disease markers. Therefore, the present findings indicate that the study of normal cognitive aging necessitates examination of individuals without evidence of clinically significant pathologic change or neurodegenerative disease, regardless of baseline cognitive performance, as these individuals have clearly displayed resistance to the accumulation of these neuropathological markers in aging.

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Conflict of Interest

None declared.

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