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Special Section: Are the rates of age- and amyloid β-associated cortical atrophy influenced by sustained exceptional cognitive functioning in older adults?

Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

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Abstract

Introduction: Superior cognitive performance in older adults may reflect underlying resistance to age-associated neurodegeneration. While elevated amyloid β (Aβ) deposition (Aβ+) has been associated with increased cortical atrophy, it remains unknown whether "SuperAgers" may be protected from Aβ-associated neurodegeneration.

Methods: Neuropsychologically defined SuperAgers (n = 172) and cognitively normal for age (n = 172) older adults from the Australian Imaging, Biomarkers and Lifestyle study were case matched. Rates of cortical atrophy over 8 years were examined by SuperAger classification and Aβ status.

Results: Of the case-matched SuperAgers and cognitively normal for age older adults, 40.7% and 40.1%, respectively, were Aβ+. Rates of age- and Aβ-associated atrophy did not differ between the groups on any measure. Aβ− individuals displayed the slowest rates of atrophy.

Discussion: Maintenance of superior memory in late life does not reflect resistance to age- or Aβ-associated atrophy. However, those individuals who reached old age without cognitive impairment nor elevated Aβ deposition (i.e. Aβ−) displayed reduced rates of cortical atrophy.

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1. Introduction

Although cognitive decline is considered characteristic of aging [1,2], the existence of older adults with superior cognitive ability for their age suggests that cognitive decline is not inevitable [3]. Studies describe such individuals as successful agers [4–7], optimal memory performers [8], supernormals [9–11], or SuperAgers [12,13]. Despite similar goals, each study employs different classification criteria. For example, SuperAger classification originally included individuals older than 80 years with episodic memory performance equivalent to, or above, the normative mean for adults aged 50-65 years and age-appropriate performance in other cognitive domains [12,14–16]. SuperAgers are, thus, considered to have maintained "youthful" memory performance into old age [14]. Other studies have used similar neuropsychological criteria but lowered the minimum age criterion to 70 (i.e. "successful agers") [7] and 60 years (i.e. "SuperAgers") [3,13]. While the chronological age at which SuperAging can be classified is still being determined, elucidation of the neurobiological basis of aging without cognitive decline could yield important insights into prevention of age-associated neurodegenerative diseases such as Alzheimer's disease (AD).

Cross-sectional comparisons of brain morphology between SuperAgers and elderly controls report that SuperAgers do not show typical age-associated atrophy on magnetic resonance imaging (MRI) measures of cortical thickness and volume [12]. SuperAgers also show greater left hippocampal volume and greater cortical thickness in anterior cingulate cortex and default mode and salience network regions [13,16]. Greater regional cortical thickness and hippocampal volume and lower burden of white matter lesions were observed in successful agers compared to typical older adults [7]. Given that normal aging is associated with gradual loss of brain volume [17], larger brain volumes and reduced markers of cerebral small vessel disease are inferred to reflect preservation of cortical integrity despite aging, raising the possibility that maintenance of superior memory performance in old age reflects some resistance or protection against age-associated neurodegeneration [14].

SuperAging may also reflect some protection from AD [16]. Abnormally high levels of amyloid β (Aβ+) and carriage of the *APOE* ε4 allele are AD risk factors [18]; however, prevalence of Aβ+ and *APOE* ε4 carriage are consistently similar between individuals with superior memory performance and typical older adults [3,7,8,10,16]. These individuals maintain superior cognitive ability despite Aβ+ [3,7,8] or substantial markers of AD neuropathology upon post-mortem examination [19], suggesting that any resilience to AD pathogenesis experienced by SuperAgers either ameliorates or acts independently from the risk conferred by Aβ+ and *APOE* ε4. For example, neurobiological factors associated with SuperAging may protect against Aβ-associated neurodegeneration. Although the adverse effects of Aβ+ on brain volume over time have been well described [20–25], it remains unknown whether SuperAgers may be protected from them.

Large prospective studies are necessary to disentangle the effects of baseline brain structural characteristics, age, and neuropathological markers in SuperAgers; however, results of studies to date are mixed. One group reported slower whole-brain cortical atrophy for 24 SuperAgers compared to cognitively average elderly adults over 18 months, although this study did not take into account Aβ levels [15]. While significant baseline differences were found between 19 successful agers and 70 typical older adults in another study, rates of whole-brain cortical thinning and hippocampal atrophy over an average of 5 years were equivalent between groups [7]; however, this study also reported no association between Aβ deposition and loss of brain volume within the total sample, which is inconsistent with previous research [20–25] and may be a consequence of the small sample studied. Despite consistent cross-sectional reports that individuals with superior memory performance display relatively preserved brain morphology compared to older adults who are cognitively normal for their age (CNFA) despite varying minimum age criteria, divergent findings in prospective studies highlight the need for larger samples and longer follow-up times to examine age- and Aβ-associated brain morphological changes in SuperAging.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study is a large prospective cohort in which multiple studies have described Aβ-associated loss of brain volume [21,22,26]. This study is well-positioned to examine whether SuperAgers are resistant to age- and Aβ-associated neurodegeneration compared to CNFA older adults. The first hypothesis was that greater rate of volume loss in white matter (WM), gray matter (GM), and hippocampus would be associated with Aβ+ in CNFA older adults. The second hypothesis was that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA older adults. Finally, to examine the influence of SuperAger classification on cerebrovascular disease markers, this study also explored differences between SuperAgers and CNFA in white matter hyperintensity (WMH) volume and accumulation over time, and whether this was mediated by Aβ.

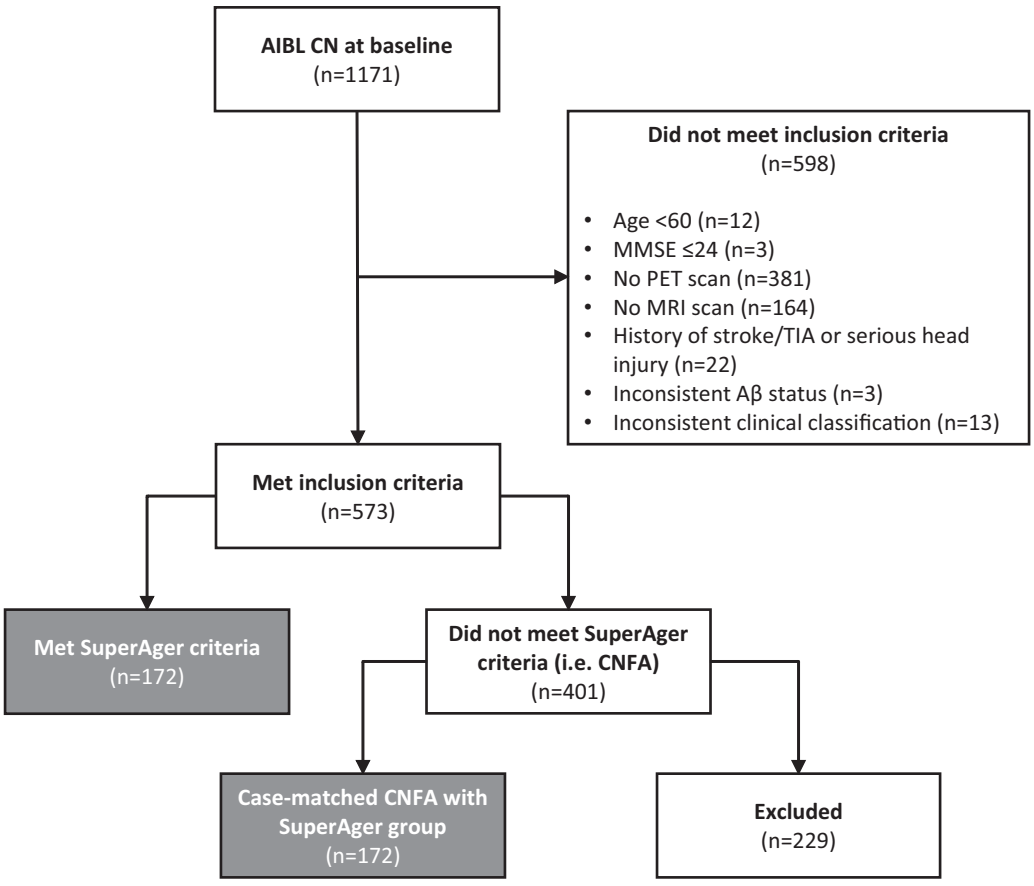

Fig. 1. Sample selection. Abbreviations: AIBL, Australian Imaging, Biomarkers and Lifestyle; CN, cognitively normal; CNFA, cognitively normal for age; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

2. Method

2.1. Participants

The AIBL study protocol has been reported previously [27]. Volunteers were ineligible for enrollment 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 hour of posttraumatic amnesia, or current regular alcohol intake beyond recommended limits [28]. 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, and Edith Cowan University, and all participants provided written informed consent at each visit.

2.1.1. Sample selection

The AIBL study currently includes 611 CN adults who satisfied the aforementioned baseline inclusion criteria, were aged over 60 with mini-mental status examination >24, and underwent both Aβ positron emission tomography (PET) and MRI neuroimaging. These participants were recruited in two waves: an inception cohort (n = 400) followed up every 18 months for up to 8 years, and an enrichment cohort (n = 211) followed up for up to 4.5 years. The sample was further restricted to those who reported no history of stroke, transient ischemic attack, or serious head injury at baseline (n = 589). Participants who were classified with mild cognitive impairment or dementia by a clinical panel during the follow-up period were coded as progressors; those whose clinical classification or Aβ status were inconsistent across the study period were excluded to ensure reliability of classification (n = 16). Following these exclusions, 172 of the eligible participants were classified as SuperAgers (see criteria below). SuperAgers were then case matched with the remaining CN participants (i.e. CNFA) based on age, sex, education, follow-up time, and number of serial MRI scans. The final analyses included 344 participants (172 SuperAgers, 172 CNFA; Fig. 1).

2.1.2. SuperAger classification

Individuals were classified as SuperAgers at baseline using neuropsychological criteria adapted from the Northwestern SuperAging Study criteria as described previously [3]. A greater number of nonmemory tests were included

in the classification criteria for this study compared to that used in the Northwestern SuperAging Study [12] to increase classification specificity. Classification required performance above the normative average for adults aged 30-44 years on the California Verbal Learning Test–Second Edition Long Delay Free Recall trial [29] (≥13 for women, ≥12 for men), and performance above −1 SD for their age on all nonmemory tests identified to be suitable for the study of cognitive aging: Digit Symbol Substitution Test, Victoria Stroop Test (words trial), Digit Span, Letter Fluency (FAS), and Category Fluency (total animals and male names, and fruit and furniture) [30]. CN participants who were not classified as SuperAgers were classified as CNFA.

2.1.3. Assessment

A comprehensive neuropsychological battery was administered at each study visit. Medical assessments included anthropometric measures, blood tests, and self-reported medical history (e.g. hypertension) [27]. Education was coded as ≤12 years or >12 years. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology, and participants were classified as *APOE* ε4 carriers or noncarriers [31].

2.2. Neuroimaging

2.2.1. MRI neuroimaging

Participants underwent a 3D T1-weighted magnetization-prepared rapid gradient-echo sequence using the following acquisition parameters: in-plane resolution 1 × 1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI) = 2300/2.98/900, flip angle 9°, and field of view (FOV) 240 × 256. Magnetization-prepared rapid gradient-echo images for all participants were segmented into WM, GM, and cerebrospinal fluid using an implementation of the expectation maximization algorithm [32]. Hippocampal extraction was performed using a multiatlas approach based on the Harmonized Hippocampus Protocol [33]. Some participants also underwent a 3D fluid attenuation inversion recovery (FLAIR) sequence (133 SuperAgers, 131 CNFA); therefore, exploratory analyses of WMH were conducted within this sample. Three different sets of FLAIR acquisition parameters were used: (1) in-plane resolution 0.98 × 0.98 mm, slice thickness 0.9 mm, TR/TE/TI = 6000/420/2100, flip angle 120°, FOV 240 × 256, and 176 slices; (2) in-plane resolution 0.5 × 0.5 mm, slice thickness 1.0 mm, TR/TE/TI = 5000/355/1800, flip angle 120°, FOV 512 × 512, and 160 slices; (3) in-plane resolution 1.0 × 1.0 mm, slice thickness 1.0 mm, TR/TE/TI = 5000/391/1800, flip angle 120°, FOV 256 × 256, and 192 slices. WMH were automatically segmented using the HyperIntensity Segmentation Tool based on an ensemble of pretrained neural network classifiers [34,35] and quantified from the segmented lesion masks in the common Montreal Neurological Institute space. All measures were corrected for scanner and total intracranial volume.

2.2.2. Amyloid-β PET neuroimaging

PET neuroimaging was conducted using one of the four Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n = 137), ^{18}F-NAV4694 (NAV, n = 38), ^{18}F-Florbetapir (FBP, n = 88), or ^{18}F-Flutemetamol (FLUTE, n = 81). Detailed PET methods and procedures are described elsewhere [36,37]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region to generate a SUV ratio (SUVR). Image analysis was performed using the MR-less method, CapAIBL [38]. A linear regression transformation was applied to the NAV, FBP, and FLUTE SUVRs to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation so that SUVRs across the different radiotracers were expressed on the same scale [37]. All participants with SUVR/Before the Centiloid Kernel Transformation≥1.40 at their most recent PET scan were classified as Aβ+ and those below the threshold were classified as Aβ−.

2.3. Statistical analyses

R version 3.4.3 [39] and SPSS 23 were used for all statistical analyses, with statistical significance set at $P < .05$. No adjustments were made for multiple comparisons due to their conservative nature; the early and important stage of this research highlights the importance of encouraging future studies in this area. Therefore, estimates of effect size were computed for all comparisons to guide interpretation of the results (i.e. $d < 0.20$ may be due to type I error). SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age, follow-up time, and number of serial MRI scans were ±2 years, ±1 visit, and ±1 scan, respectively. Eligible matches were selected randomly.

2.3.1. Baseline group differences

Between-group comparisons by SuperAger classification and Aβ status were conducted using one-way analyses of variance and Kruskal-Wallis one-way analyses of variance for continuous variables and Fisher's exact tests for categorical variables. Linear regressions examined baseline differences between groups for each neuroimaging measure with age as a covariate, both before and after case-matching SuperAgers with CNFA.

2.3.2. Assessment of Aβ status and SuperAger classification on longitudinal neuroimaging measures

Separate linear mixed models (LMMs) were run with each of the neuroimaging measures as dependent measures. Fixed factors were SuperAger classification, Aβ status, time (years from baseline scan), and their interactions. Random intercepts and slopes were calculated for each participant. Covariates were baseline age and progression status; *APOE* ε4 status and number of serial MRI scans did not

Table 1
Baseline group characteristics

	Total sample	CNFA Aβ−	CNFA Aβ+	SuperAger Aβ−	SuperAger Aβ+	Sig. factors
n	344	103	69	102	70	
Aβ PET SUVR	1.51, 1.32 (0.49)	1.21, 1.22 (0.14)	1.97, 1.81 (0.84)	1.21, 1.20 (0.14)	1.92, 1.87 (0.74)	A***
APOE ε4 carrier (%)	27.30	14.60	43.50	17.60	44.30	
Age at baseline	71.75, 71.00 (9)	71.30, 71.00 (7)	73.67, 73.00 (12)	70.57, 70.00 (9)	72.26, 72.00 (7)	A***
Female (%)	55.80	61.20	47.80	57.80	52.90	
Education >12 years (%)	65.10	62.10	69.60	64.70	65.70	
Hypertension (%)	50.30	15.41	12.21	13.08	9.59	
Progressors (%)	8.40	10.70	18.80	2.00	4.30	S***
Number of MRIs	2.47, 2.00 (2.25)	2.49, 2.00 (3)	2.67, 2.00 (2.50)	2.34, 2.00 (3)	2.46, 2.00 (2)	
Length of follow-up (months)	71.98, 89.00 (37)	77.97, 90.00 (19)	71.30, 89.00 (37)	70.85, 89.00 (40)	65.46, 89.00 (55)	
Baseline white matter volume (cm^3)	394.24, 394.52 (33.44)	394.40, 394.44 (32.33)	396.48, 397.26 (39.10)	390.49, 392.62 (26.55)	397.28, 398.22 (34.95)	
Baseline gray matter volume (cm^3)	461.10, 461.86 (23.28)	459.83, 461.04 (25.55)	457.97, 457.76 (25.99)	463.45, 465.32 (25.81)	462.61, 462.98 (19.88)	S* †
Baseline hippocampal volume (cm^3)	2.96, 2.96 (0.34)	2.96, 2.95 (0.35)	2.93, 2.91 (0.40)	2.96, 2.94 (0.34)	2.99, 3.00 (0.31)	
Baseline white matter hyperintensity volume (cm^3)	14.15, 11.43 (5.41)	13.48, 12.01 (11.86)	17.28, 12.74 (11.68)	13.40, 10.99 (4.21)	13.01, 11.80 (4.79)	

NOTE. *$P < .05$, ***$P < .001$; continuous variables are expressed as mean, median (IQR); categorical variables are expressed as percentages.

Abbreviations: Aβ, amyloid β, *APOE* ε4, apolipoprotein E epsilon 4 allele, CNFA, cognitively normal for their age; IQR, interquartile range; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio; A, significant effect of Aβ status; S, significant effect of SuperAger classification.

†This difference becomes nonsignificant when adjusted for age.

significantly contribute to the models and were therefore removed.

To test the first hypothesis, the interaction of Aβ status × time was examined only in the CNFA group. To test the second hypothesis, interactions between SuperAger classification, Aβ status, and time were examined for the full study sample. Having controlled for baseline age in the analyses, interactions with time were interpreted to reflect changes associated with aging. For each comparison, the magnitude of effect was expressed using Cohen's *d*.

Associations of Aβ+ and SuperAger classification with WMH volume were explored using a gamma generalized LMM fitted with a log link function. The same fixed and random factors from the LMMs were included in the generalized LMM. Covariates were baseline age, *APOE* ε4 status, and self-reported hypertension.

3. Results

Across the 344 SuperAgers and CNFA included in this study, average age was 71 years (range 60-93). The majority had >12 years education (65.1%) and 55.8% were female. Participants were followed up for a median of 89 months (interquartile range: 37) with an average of 2 MRI scans each (maximum 6). As expected due to the case-matching parameters, no differences in demographics or follow-up time were observed between the SuperAger and CNFA groups, and prevalence of both Aβ+ and *APOE* ε4 carriage were nearly equivalent (Table 1). Compared to the Aβ− group, the Aβ+ group had higher prevalence of *APOE* ε4 carriage (odds ratio: 4.08, 95% confidence interval [CI]: 2.47-6.73; $P < .0005$) and were 2 years older on average [$F(1,343) = 10.84$, $P = .001$; $d = 0.36$)]. As previously reported for this sample, SuperAgers were less likely to progress to mild cognitive impairment/dementia compared to CNFA (24 CNFA and 5 SuperAgers; odds ratio: 0.19, 95% CI: 0.07-0.50; $P < .0005$) [3].

3.1. Baseline brain morphological differences

Before case-matching, significantly greater WM, GM, and hippocampal volumes were observed in SuperAgers compared to CNFA. These differences were no longer significant after adding age as a covariate. After case-matching, a significant group difference was found only for GM volume; however, the effect size was small ($d = 0.22$), and this became nonsignificant after adjusting for age. No Aβ group differences were observed on any MRI measure.

3.2. Influence of Aβ on brain morphological changes in CNFA older adults

Annualized rate of volume loss within CNFA was 1.37 cm^3 (0.35%) for WM, 1.80 cm^3 (0.39%) for GM, and 0.015 cm^3 (0.52%) for hippocampus. Significant Aβ status × time interactions were observed for all MRI measures. Mean slopes for both Aβ+ and Aβ− CNFA

Table 2
Annualized group mean slopes and Cohen's *d* for Aβ-associated neurodegeneration in CNFA

Measure	Aβ−	Aβ+	Cohen's *d*	Lower 95% CI	Upper 95% CI
White matter volume	−1.4 (2.16)	−2.27 (2.05)	0.42	0.11	0.72
Gray matter volume	−1.81 (3.00)	−2.74 (2.85)	0.32	0.01	0.62
Hippocampal volume	0.04 (0.57)	−0.03 (0.03)	0.17	−0.14	0.47

NOTE. Values are presented as mean slopes (SD).

Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; CI, confidence interval; CNFA, cognitively normal for their age; SD, standard deviation.

showed that Aβ+ was associated with faster loss of WM, GM, and hippocampal volume over time (Table 2). This translates to greater volume loss of 0.88 cm^3 in WM, 0.93 cm^3 in GM, and 0.07 cm^3 in hippocampus per year for Aβ+ compared to Aβ− CNFA. Progressors had lower GM and hippocampal volume across all time points. Both older age at baseline and longer time in study were associated with smaller WM, GM, and hippocampal volumes.

3.3. Influence of SuperAger classification and Aβ on brain morphological changes

The LMM results for WM, GM, and hippocampal volume for the full study sample are summarized in Table 3. Mean slopes for each of the morphological measures are shown graphically in Fig. 2. The Aβ status × time interaction remained significant for all MRI measures after accounting for SuperAger classification. However, the SuperAger status × Aβ status × time interaction was not statistically significant for any MRI measure. Slopes were not significantly different between SuperAgers and CNFA within the Aβ− and Aβ+ groups nor were they different between Aβ groups within the SuperAger and CNFA groups. Fig. 3 shows that Aβ+ was associated with greater volume loss over time in both SuperAger and CNFA groups for each MRI measure but there was substantial overlap in the 95% CIs for each effect size. The two-way interaction of SuperAger classification × time was not significant for any morphological measure with data collapsed across Aβ groups. Although there was a significant main effect of baseline age on all measures, no interactions with age were observed. Analyses restricted to participants over age 80 were not conducted due to small cell sizes.

3.4. Exploratory analyses of SuperAger classification and Aβ on WMH

No baseline differences were observed between SuperAger or Aβ groups. WMH accumulation increased at an average rate of 7% per year for all participants. Older age at baseline and longer time in study were associated with increased WMH volume (Table 3). No main effect of Aβ status nor SuperAger classification were observed, and no interactions with time were observed.

4. Discussion

The first hypothesis, that Aβ+ was associated with greater loss of volume in WM, GM, and hippocampal structures in older adults classified as CNFA, was supported. These data are consistent with previous findings from the AIBL cohort and others that Aβ+ is associated with GM volume loss and hippocampal atrophy in CN individuals [20–25]. The second hypothesis that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA older adults was not supported: no differences between SuperAgers and CNFA older adults were observed for rates of Aβ-associated atrophy (Figs. 2 and 3). Furthermore, no differences were observed for age-associated brain volume loss between SuperAgers and CNFA older adults despite controlling for Aβ. Exploratory analyses of WMH also showed no differences between SuperAgers and CNFA older adults in baseline WMH volume nor rate of accumulation, and neither were influenced by Aβ status. Taken together, the results indicate that SuperAger classification based entirely on neuropsychological criteria does not reflect any unique protection from age- or Aβ-associated neurodegeneration or cerebral small vessel disease.

The SuperAging construct was developed to describe a phenotype of preserved cognitive function in older age that may reflect unique neurobiological characteristics such as protection from neurodegeneration and consequent cognitive decline in aging. This notion was supported by early cross-sectional studies conducted in small samples of SuperAgers [12,13,16,40,41]. Consistent with past reports, the present study observed significantly greater WM, GM, and hippocampal volumes in SuperAgers at baseline prior to case-matching with CNFA, but these differences were not maintained after adjusting for age. SuperAging studies have not adjusted for age for cross-sectional analyses, although only one morphological study of successful agers did so for longitudinal analyses [7]; therefore, it is possible that the reported findings may be confounded by demographic characteristics rather than reflecting true group differences. Furthermore, prospective findings have been mixed, potentially because of limited power to conduct longitudinal analyses due to small sample sizes [7,15]. The finding that individuals classified as SuperAgers were not any more protected against age- or Aβ-associated atrophy than CNFA, regardless of baseline age, does not support the conclusion that maintenance of cognitive abilities from midlife to late-life reflects preservation of brain structure in aging [7,12–16]. These early studies provide important and provocative foundations for models of SuperAging; however, the use of small samples and lack of adjustment for age may limit the generalizability of their conclusions

Table 3
Mixed model parameters

	White matter volume*			Gray matter volume*			Hippocampal volume*			WMH volume†		
Fixed effects	Estimate	Std. error	*P*	Estimate	Std. error	*P*	Estimate	Std. error	*P*	Estimate	Std. error	*P*
Intercept	500.96	15.34	<.001	570.81	11.40	<.001	4.03	0.18	<.001	0.59	0.53	.27
SuperAger classification	−5.62	3.14	.07	1.72	2.29	.45	−0.02	0.04	.59	0.19	0.13	.13
Aβ status (−/+)	5.79	3.52	.10	3.32	2.57	.20	0.02	0.04	.60	0.28	0.14	.05
Time	−1.40	0.21	**<.001**	−1.81	0.30	**<.001**	−0.02	0.00	**<.001**	0.07	0.02	**<.001**
Baseline age	−1.49	0.21	**<.001**	−1.54	0.16	**<.001**	−0.01	0.00	**<.001**	0.02	0.01	**.002**
Progression	−6.04	4.34	.16	−11.18	3.25	**<.001**	−0.13	0.05	**.01**	0.20	0.15	.17
APOE ε4 carrier status (−/+)	-	-	-	-	-	-	-	-	-	0.11	0.10	.25
Hypertension (−/+)	-	-	-	-	-	-	-	-	-	0.07	0.08	.37
SuperAger × Aβ status	3.73	4.91	.45	−0.94	3.58	.79	0.04	0.06	.49	−0.32	0.20	.10
SuperAger × time	−0.52	0.32	.11	0.11	0.45	.81	0.00	0.00	.38	−0.03	0.03	.29
Aβ status × time	−0.88	0.33	**.01**	−0.93	0.45	**.04**	−0.01	0.00	**.004**	−0.02	0.03	.45
SuperAger × Aβ status × time	0.65	0.49	.19	0.09	0.69	.90	0.01	0.01	.31	0.02	0.04	.70

Bolded values are significant at $P < .05$.
Abbreviations: Aβ, amyloid β; *APOE* ε4, apolipoprotein E epsilon 4 allele.
*+Analyzed using a linear mixed model, total n = 344.
†Analyzed using a gamma generalized linear mixed model fitted with a log link function, total n = 264.

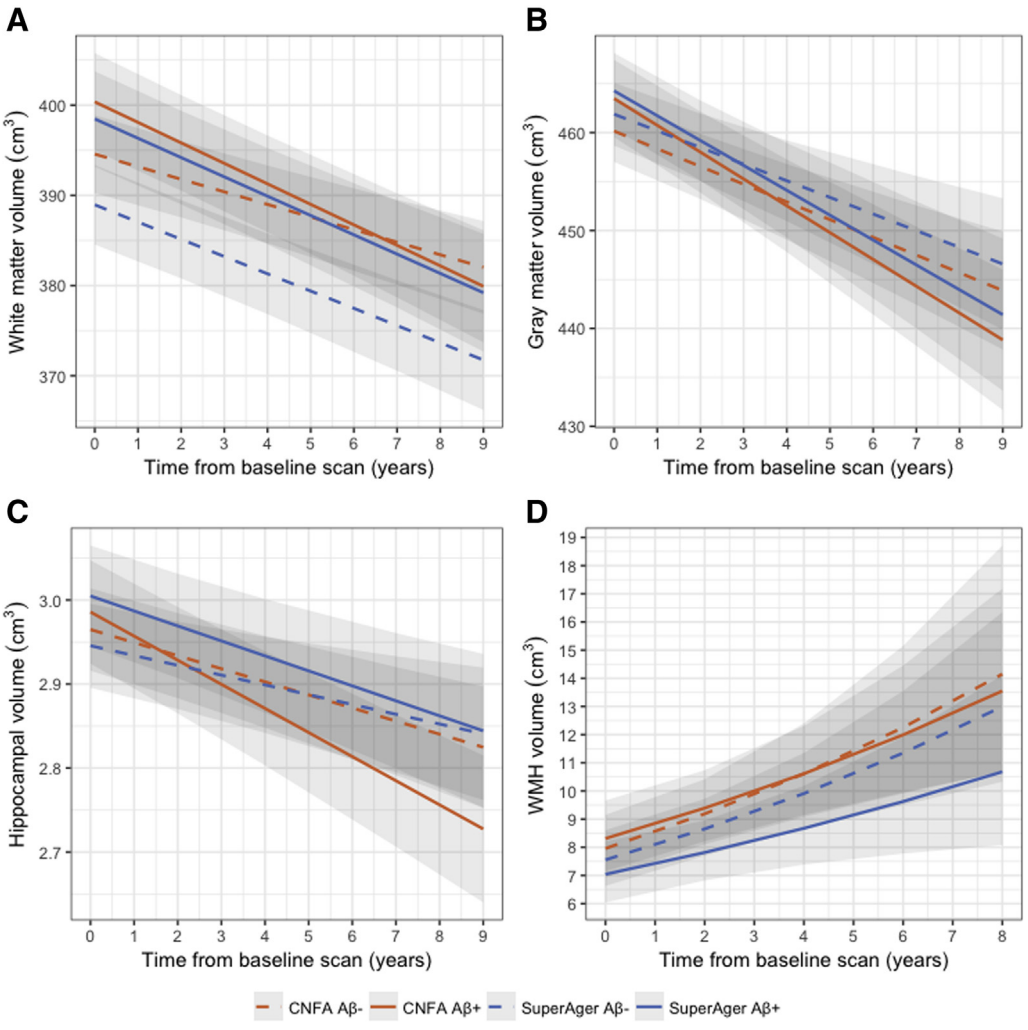

Fig. 2. Morphological changes over time by SuperAger and Aβ status; slopes for Aβ+ (solid lines) were significantly steeper than slopes for Aβ− (dashed lines) for white matter, gray matter, and hippocampal volumes (panels A-C) but no difference was observed for white matter hyperintensities (panel D). No difference in slopes between CNFA (orange lines) and SuperAgers (blue lines) was observed for any measure. Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; CNFA, cognitively normal for their age; WMH, white matter hyperintensity.

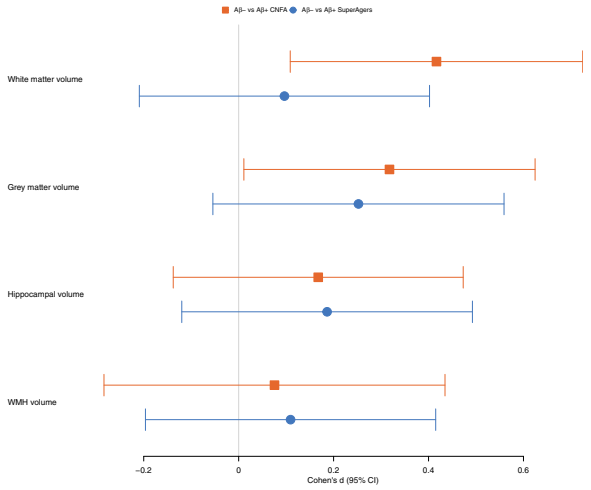

Fig. 3. Comparison of effect sizes for rates of Aβ-associated atrophy; substantial overlap in the 95% CIs for each effect size reflects no difference in the slopes of Aβ-associated volume loss between the SuperAger and CNFA groups. Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; WMH, white matter hyperintensity.

due to low statistical power, potential for sampling bias, and type I error.

In contrast to a previous report of successful agers [7], the present study observed similar levels of WMH between SuperAgers and CNFA older adults both cross-sectionally and longitudinally that was not modified by Aβ status. This may reflect a larger sample with strict exclusion of high vascular risk factors. In addition, the previous study measured WM hypointensities using T1-weighted images, which can result in lower volume estimates compared to the 3D FLAIR sequences used here to measure WMH [42]. The lack of association between Aβ status and WMH observed in the present study is, however, consistent with reports that Aβ and WMH accumulation reflect independent processes whose deleterious effects on cognition are additive [43–45].

Limitations to the generalizability of these results are related to the experimental nature of the AIBL cohort; due to rigorous inclusion criteria, AIBL participants are healthier and more educated than the general population [46]. Not enough information is available to ascertain the prevalence of SuperAgers in the general population although experimental cohorts have reported rates of 17.3-42.5% in their respective samples [7,13]. Taking into account sample and survivor biases, it may not be unexpected that 30% of the CN AIBL cohort were classified as SuperAgers despite differences in age criteria and using more stringent neuropsychological criteria compared to other studies [7,12,13]. Unfortunately, operational definitions of successful aging lack consistency between studies [47], which is also the case in studies of youthful memory performance or "SuperAging". Comparisons between studies may thus be limited despite similar goals; however, a strength of the present study was case-matching SuperAgers with CNFA older adults to ensure that the results adequately captured differences due to neuropsychological classification. Whole-brain and hippocampal volumetric measures were most appropriate for the aims of this study due to the increased likelihood of widespread cortical Aβ deposition in Aβ+ individuals [48]. Future studies should conduct region of interest and surface-based analyses of longitudinal morphological change due to Aβ in SuperAgers to determine whether cortical regions reported to be relatively preserved (e.g. anterior cingulate) are protected from Aβ-associated neurodegeneration [7,11,13,16]. Furthermore, although previous studies have suggested that Aβ-associated neurodegeneration occurs only in the presence of elevated tau [49] or that neurodegeneration is more strongly associated with tau than with Aβ [50], this study did not include measures of tau, which future studies should endeavor to do.

5. Conclusions

Despite significant differences in baseline cognitive ability, individuals in the AIBL CN cohort classified as SuperAgers displayed similar levels of AD neuropathological markers such as Aβ+ compared to CNFA older adults. While this may be suggestive of some resilience to the effects of Aβ, SuperAgers and CNFA older adults displayed similar rates of cognitive and morphological change due to both age and Aβ over 8 years [3]. Therefore, defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from the effects of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

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RESEARCH IN CONTEXT

1 Systematic review: Inconsistent terms are used to describe samples of older adults with "youthful" or superior memory performance; therefore, PubMed was searched for "SuperAging" and "successful agers," and author publication lists and references were perused to identify all relevant papers. PubMed was also searched for "(amyloid or beta-amyloid) and (atrophy or brain volume loss or neurodegeneration)."

2 Interpretation: Defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from brain atrophy because of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

3 Future directions: Longitudinal analyses with larger, population-based samples with Alzheimer's disease biomarkers and statistical age corrections are necessary to further examine protection from cognitive decline and brain atrophy associated with age or Aβ in SuperAgers.

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