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FEATURED ARTICLE

Resilience and resistance to the accumulation of amyloid plaques and neurofibrillary tangles in centenarians: An age-continuous perspective

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Abstract

Introduction: With increasing age, neuropathological substrates associated with Alzheimer's disease (AD) accumulate in brains of cognitively healthy individuals—are they resilient, or resistant to AD-associated neuropathologies?

Methods: In 85 centenarian brains, we correlated NIA (amyloid) stages, Braak (neurofibrillary tangle) stages, and CERAD (neuritic plaque) scores with cognitive performance close to death as determined by Mini-Mental State Examination (MMSE) scores. We assessed centenarian brains against 2131 brains from AD patients, non-AD demented, and non-demented individuals in an age continuum ranging from 16 to 100+ years.

Results: With age, brains from non-demented individuals reached the NIA and Braak stages observed in AD patients, while CERAD scores remained lower. In centenarians, NIA stages varied (22.4% were the highest stage 3), Braak stages rarely exceeded stage IV (5.9% were V), and CERAD scores rarely exceeded 2 (4.7% were 3); within these distributions, we observed no correlation with the MMSE (NIA: $P = 0.60$; Braak: $P = 0.08$; CERAD: $P = 0.16$).

Discussion: Cognitive health can be maintained despite the accumulation of high levels of AD-related neuropathological substrates.

KEYWORDS
aging, Alzheimer's disease, centenarian, neuropathology, resilience, resistance

Highlights

- Cognitively healthy elderly have AD neuropathology levels similar to AD patients.
- AD neuropathology loads do not correlate with cognitive performance in centenarians.
- Some centenarians are resilient to the highest levels of AD neuropathology.

1 | BACKGROUND

Cognitive decline due to Alzheimer's disease (AD) is associated with the loss of neuronal synapses and dendrites, which coincides with the extracellular accumulation of amyloid beta (Aβ) plaques and the intracellular aggregation of phosphorylated tau protein into neurofibrillary tangles (NFTs).[1] Whether the accumulation of these neuropathological hallmarks of AD is causative for the loss of neuronal synapses and dendrites is a matter of strong debate,[2] especially since in vivo clearance of plaques and tangles by immunotherapies does not, at present, attenuate the progression of cognitive decline as hoped for.[3–5] Furthermore, levels of these neuropathological substrates increase with age in the postmortem brains of cognitively healthy individuals.[6–9] In fact, a large autopsy study found that 30% to 40% of the brains from 79-year-olds harbor significant AD-associated neuropathological changes, while only 15% of these elderly were clinically diagnosed with AD.[10,11] In line with this, we and others previously observed that the levels of these neuropathological substrates are highly variable in nonagenarians and centenarians with diverse cognitive performance.[8,12–16] This variability in the levels of cognitive performance and neuropathological substrates represents a window of opportunity to investigate whether maintaining cognitive performance during aging depends on being tolerant to the effects of accumulated AD-associated neuropathological substrates (resilience), or whether it depends on avoiding the build-up of those neuropathological substrates (resistance).

Here, we correlated the levels of neuropathological substrates observed in the brains of 85 centenarians with cognitive performance determined close to death by the Mini-Mental State Examination (MMSE). Next, we compared these levels of AD-associated neuropathological substrates with those observed in the brains of 2131 individuals, representing an age continuum from 16 to 100+ years (851 AD cases, 654 non-demented [ND] controls, and 626 non-AD demented individuals). This allowed us to determine (1) to what extent the levels of neuropathological substrates change with age; (2) the effect of age on the potential of each AD-associated pathological substrate to distinguish between AD and cognitive health; and (3) how the intercorrelation between the levels of different pathological substrates changes with increasing age.

2 | METHODS

2.1 | 100-plus Study cohort

We included brains donated by 85 centenarians (ages at death: 100 to 111) who died between 2013 and 2021 and self-reported to be cognitively healthy at inclusion in the 100-plus Study cohort,[17] confirmed by a proxy. For each participant, cognitive performance was assessed during a baseline visit and yearly follow-up visits. In this study, the MMSE score, an 11-item cognitive screen test with a maximum score of 30 points, from the last available visit was used to indicate the cognitive performance of each donor before death.[12,17] Scores were imputed for missing values when <6 of the 30 points could not be scored due to sensory deficits such as hearing and vision impairment and/or general fatigue;[12] otherwise the MMSE score was set to "missing."

2.2 | Netherlands Brain Bank (NBB) cohort

Neuropathology data were obtained from 2131 individuals, comprising the three groups of AD cases, ND individuals, and non-AD demented individuals, who agreed to brain donation to the Netherlands Brain Bank (NBB, www.brainbank.nl) between 1979 and 2018. These brains formed an age continuum from 16 to 103 years of age. The diagnosis of AD was based on a combination of clinical criteria of probable AD[18,19] and histopathological confirmation by autopsy.

2.3 | Neuropathological assessment

Autopsies and neuropathological assessments for the NBB and the 100-plus Study cohorts were performed by the NBB, as described in the Supplementary material. We evaluated all donated brains

according to the following criteria: (1) Aβ plaque level using the National Institute on Aging [NIA] amyloid stages;[1] (2) NFT level using Braak stages;[20-22] (3) the level of neuritic plaques [NPs], a subtype of plaque surrounded by dystrophic neurites, using the Consortium to Establish a Registry for Alzheimer's Disease [CERAD] scores;[23] and (4) the brain weight, corrected for sex.[24] Regarding the rationale for using the NIA amyloid stages, see the Supplementary material (in the online Supporting Information). The centenarian brains and the majority of brains in the NBB age continuum were evaluated by a single neuropathologist, so that interrater variability would be kept to a minimum.

2.4 | AD versus ND comparison across the age continuum

To assess the age-related changes in the levels of AD-associated neuropathological substrates, we applied a dynamic 25-point sliding window across the ages of AD cases and ND individuals from the NBB cohort separately. Neuropathology levels in the AD and ND brains were sorted according to age at death. For each neuropathological substrate, the mean level of each 25-point window was calculated. Each window encompassed a set of 12 cases with ages lower and 12 cases with ages higher than the age of the central case. Across each window-set, we calculated a confidence interval (CI) with 5% increments to indicate the distribution of pathology levels (i.e., 5%, 10%, … 90%, 95% CI). Next, for each sliding window position, we calculated the difference in the average neuropathological levels between AD cases and ND individuals. The CI of the difference with 5% increments was determined by bootstrapping ($n = 1000$).

2.5 | Distribution of neuropathology levels by age interval

The distributions of the level of each neuropathological substrate in AD cases, ND controls, and non-AD individuals were estimated separately for each age interval (i.e., <60, 60 to 69, 70 to 79, 80 to 89, ≥90) and visualized by generating density plots using a Gaussian kernel. Next, the overall distribution of the level of each neuropathological substrate in the NBB cohort for each age interval was estimated by summing the densities.

2.6 | Pairwise correlation between different neuropathology levels

To evaluate the pairwise correlations between (1) NIA amyloid stage and Braak NFT stage, (2) NIA amyloid stage and CERAD NP score, and (3) Braak NFT stage and CERAD NP score with age, we merged the AD cases, ND controls, and non-AD demented individuals as one cohort. We used a 51-point sliding window, which was constructed in the same way as the 25-point window, but using 25 cases with ages lower and 25 cases with ages higher than the age of the central brain sample. For each neuropathology pair and sliding window position, we calculated the Pearson correlation coefficient and corresponding CIs (5% increments).

RESEARCH IN CONTEXT

1. **Systematic review**: Previous studies indicated that levels of Alzheimer's disease (AD)-associated neuropathological substrates increase with age in brains of cognitively healthy individuals. However, to what extent the elderly are resilient or resistant to the build-up of AD-associated neuropathological substrates is still unclear.
2. **Interpretation**: This study showed that with age, brains from non-demented individuals reached the NIA amyloid stages and Braak NFT stages observed in AD patients, while CERAD NP scores remained lower. Furthermore, we showed it is possible to maintain cognitive health with extreme ages despite accumulating the highest levels of NIA amyloid stages (up to 3), Braak NFT stages (up to V), and CERAD NP scores (up to 3), suggesting that these individuals employ unique mechanisms of resilience against these neuropathological substrates.
3. **Future directions**: Further elucidation of molecular mechanisms underlying resilience and resistance may contribute to the development of new strategies allowing the maintenance of cognitive health during aging.

2.7 | Statistical analyses

We applied a linear regression model to test the association between each neuropathological substrate and MMSE score in the centenarian cohort. All regressions were corrected for sex, education, and time between last acquired MMSE and death. All calculations were performed using R (version 3.6.3). Pearson correlations and linear regression were performed using the "stats" R package.[25]

3 | RESULTS

3.1 | Sample characteristics

For the 85 centenarian brain donors (74% female), the distributions of age, sex, educational attainment, cognitive performance, *APOE* genotype, and neuropathological assessments are shown in Table 1. At the last available study visit, a median of 9 months (interquartile range [IQR]: 4 to 13) before brain donation, the median MMSE score across all centenarians was 25 (IQR: 22 to 27). Of the 83 centenarians with *APOE* genotype available, seven carried one copy of the *APOE* ε4 allele, which did not correlate with the levels of neuropathological

TABLE 1 Characteristics of the centenarians in the 100-plus Study cohort

	100-plus Study cohort	
	n	**minimum, median (IQR), maximum**
Clinical demographics		
Age (y)	85	100.4, 103.2 (102.3–104.6), 111.8
Female/male	63/22	–
APOE genotype	83	E2/E2: 2, E2/E3: 15, E2/E4: 2, E3/E3: 59, E3/E4: 5
Education	85	0, 3 (1–4), 6
MMSE	85	9.4, 25 (22–27), 30
Neuropathological substrates		
NIA amyloid stage	85	2 (1–2); 0: 9.4%, 1: 35.3%, 2: 32.9%, 3: 22.4%
Braak NFT stage	85	3 (3–4); I: 2.4%, II: 14.1%, III: 42.4%, IV: 35.3%, V: 5.9%
CERAD NP score	85	1 (0–2); 0: 43.5%, 1: 29.4%, 2: 22.4%, 3: 4.7%
Brain weight (g)	F: 63; M: 22	F: 820, 1067 (1005–1125), 1255
		M: 990, 1165 (1091–1220), 1290
		Sex-corrected: 820, 1068 (1005–1125), 1255

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; IQR, interquartile range; MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NP, neuritic plaque.

substrates (Figure 1C,G,K, Table S1). Education correlated significantly with MMSE (Table S2). The levels of each neuropathological substrate did not correlate with age at death, corrected for sex and education (Table S3). Based on clinical data provided upon autopsy and on observed postmortem neuropathology, the 2131 NBB brain donors (56% female) were diagnosed as 851 AD cases (aged 37 to 102), 654 ND controls (aged 16 to 103), and 626 non-AD individuals with dementia (aged 16 to 103) (Table 2). Patients with non-AD dementia died with or from diverse dementia subtypes and age-related pathology: frontotemporal dementia (35.3%), NFT-predominant dementia (26.0%), Parkinson's disease (18.4%), vascular dementia (15.2%), or other (5.1%) (see Table S4).

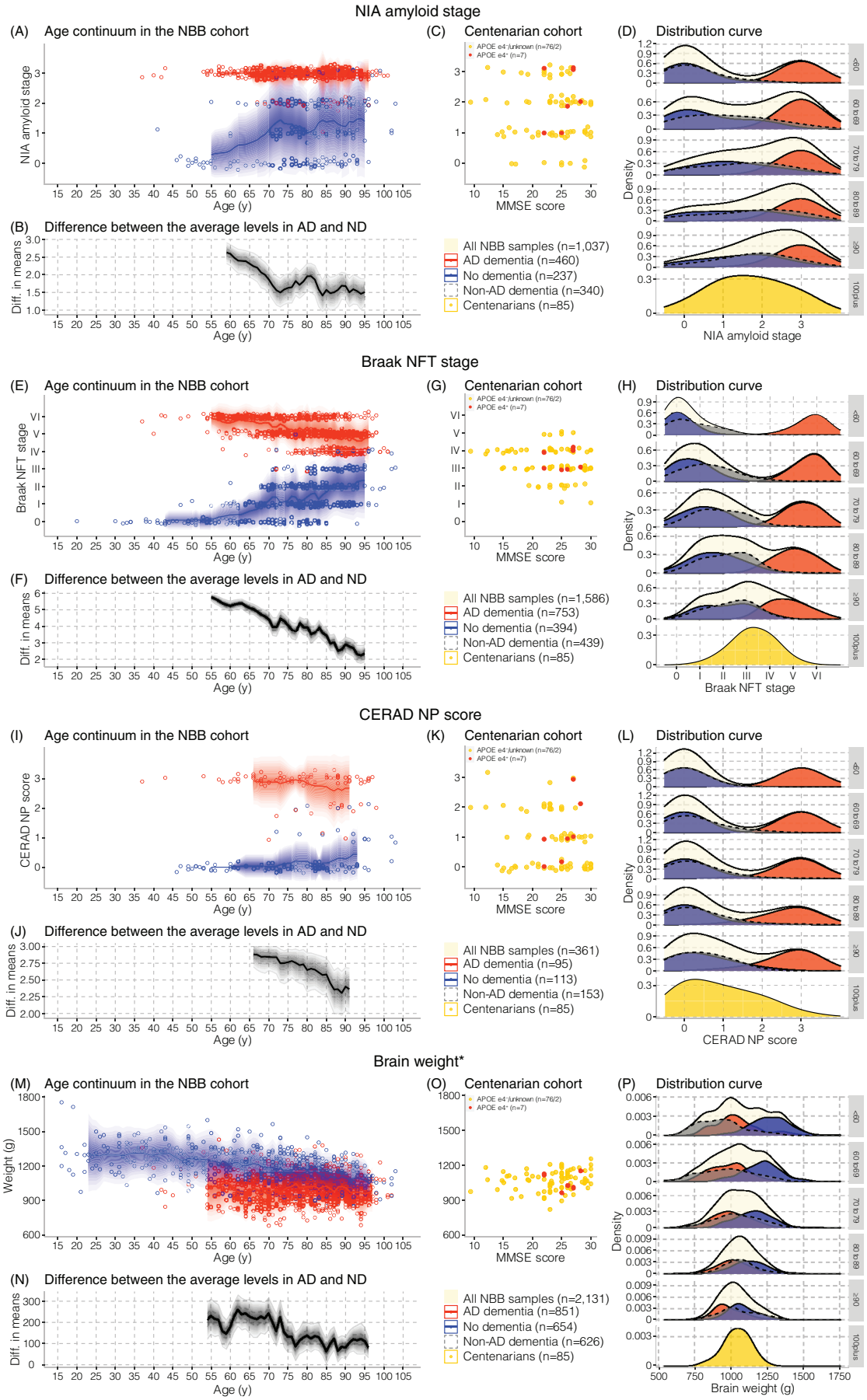
First, we investigated the extent of change with increasing age in the levels of each neuropathological substrate and brain weight for cognitively healthy (ND) individuals and those diagnosed with AD (Figure 1A,E,I,M). The differences between the mean levels for the AD and ND groups are shown in Figure 1B,F,J,N. Then, we investigated the neuropathology levels observed in centenarians as a function of the MMSE (Figure 1C,G,K,O). Last, we investigated the potential of each neuropathological substrate to discriminate between AD and cognitively normal performance as a function of age. For this, we compared the distribution of neuropathological substrate levels and brain weight for each NBB cohort group across the different age intervals (<60, 60 to 69, 70 to 79, 80 to 89, ≥90), and against the data for the centenarian cohort (Figure 1D,H,L,P). For this analysis, we were cognizant that postmortem diagnosis of AD is based not only on cognitive decline, but also on having high levels of AD-associated neuropathology, leading to a possible overestimation of the potential for each neuropathological substrate to discriminate between overall decline and cognitively normal performance. To avoid this possible bias, we accordingly included in the investigation of the NBB cohort the distribution of neuropathology levels in brains of the non-AD dementia group. The centenarian cohort includes all individuals with diverse cognitive performance at last study visit, regardless of levels of AD neuropathology. Thus, inclusion of the non-AD dementia group in the NBB cohort age-continua allowed us to examine to what extent neuropathology levels in centenarians were as expected according to their age.

3.2 | NIA amyloid stage

The average NIA amyloid stage was high across the AD group's age continuum, while it increased with age in the ND controls (Figure 1A). We found an age-related decrease in the difference between the average NIA amyloid stages of AD cases and ND individuals, from 2.5 at age 60 to 1.5 at age ~95 (Figure 1B). Of all centenarians, 9.4% had NIA amyloid stage 0, 35.3% had stage 1, 32.9% had stage 2, and 22.4% had stage 3 (Figure 1C, Table 1), and we found no evidence for an association between NIA amyloid stage and MMSE scores ($\beta = -0.30$, $P = .60$; Table 3), nor between Thal Aβ phase and the MMSE ($\beta = -0.21$, $P = .57$; Table S2). We observed an age-related convergence from a bimodal distribution of amyloid stages at younger ages to a unimodal distribution at older ages in the NBB cohort, which was extended in the centenarian cohort (Figure 1D).

3.3 | Braak NFT stage

Braak NFT stages ranged between 0 and VI across the age continuum. Braak stages increased with age in ND individuals and decreased with age in AD patients (Figure 1E). Accordingly, the average difference



between Braak NFT stages observed in AD cases and ND individuals decreased from ~6 at age 55 to ~2 at age 95 (Figure 1F). Braak NFT stages in centenarians ranged between I and V (Figure 1G): none had Braak stage 0; 2.4% had stage I; 14.1% had stage II; 42.4% had stage III; 35.3% had stage IV; and 5.9% had stage V (Table 1). Braak stages did not significantly associate with MMSE scores in centenarians ($\beta = -1.03$, $P = .08$; Table 3); however, centenarians with a Braak stage between I and III had significantly higher MMSE scores than centenarians with a Braak stage of IV or V (Wilcoxon-rank-sum test: $P = .04$, $W = 1102$). Braak stages converged from a bimodal distribution at younger ages to a unimodal distribution in the centenarians (Figure 1H).

3.4 | CERAD score

From age ~75 onwards, the average CERAD score increased with age in ND individuals and decreased in AD patients. But the changes were limited, such that the average CERAD scores stayed low in older ND individuals and high in older AD patients (Figure 1I). In line with Figure 1I, the difference in the average CERAD scores between the AD and ND groups remained high (>2) until ages ≥90 (Figure 1J). In the centenarian cohort, 43.5% had a CERAD score of 0, 29.4% had a score of 1, 22.4% had a score of 2, and 4.7% ($n = 4$) had a score of 3 (Figure 1K, Table 1). CERAD scores did not significantly associate with MMSE scores ($\beta = -0.78$, $P = .16$; Table 3). We observed a stable bimodal distribution of CERAD scores across the age continuum for the NBB cohort as a whole, and a unimodal distribution was only observed in the centenarian cohort, with the majority having low CERAD scores (Figure 1L).

3.5 | Brain weight

The brain weight of AD patients was relatively stable across the age continuum, with the median brain weight at 1003 g (IQR: 930 to 1079) for females and 1170 g (IQR: 1086 to 1261) for males, and included samples of both sexes that weighed <750 g. The mean sex-corrected brain weight of ND individuals at middle age was 200 g higher than that of AD cases, but decreased by 0.27% and 0.28% per year for males and females, respectively (Figure 1M), until at ≥90 years the difference in average brain weight was 100 g (Table 2, Figure 1N). None of the ND or centenarian brains had the extremely low brain weights (<750 g) observed in some young demented patients (Figure 1O). A regression model indicated that brain weight was not associated with the last available MMSE score in centenarians ($\beta = 0.00$, $P = .54$; Table 3). While the brain weights of non-AD dementia patients were lower than those of AD patients at ages < 60, they converged with the brain weights of AD patients and ND controls at higher ages (Figure 1P).

3.6 | Correlations between AD-associated pathological scores decrease with age

Next, we merged all AD, non-AD, and ND individuals from the NBB cohort into one dataset and assessed the changes in pairwise correlations between the three pathology scores across the age continuum (Figure 2). All pathologies were highly correlated at the youngest ages (r close to 1.0). Correlations decreased with age, in particular for the NIA amyloid stage versus Braak NFT stage, which reached $r = 0.6$ at >90 years. For the NIA amyloid stage versus CERAD NP score and the Braak NFT stage versus CERAD NP score, the correlation coefficients remained relatively high, at r-values of ~0.85 at >90 years. In the centenarian cohort, the correlation coefficients for the NIA amyloid stage versus CERAD NP score remained at ~0.75, while the NIA amyloid stage versus Braak NFT stage r-values dropped to ~0.45. Likewise, the Braak NFT stage versus CERAD NP score correlation dropped to an r-value of ~0.55.

4 | DISCUSSION

In this study we observed that, with increasing age, the levels of NIA amyloid stage and Braak NFT stage gradually increased in ND individuals. In those who reach ages of ≥100 years, NIA amyloid stages, Braak NFT stages, and CERAD NP scores varied greatly to the extent that none of these neuropathological substrates correlated with cognitive performance as measured by the MMSE. Brain weights of centenarians were according to expectations with respect to age, and showed no correlation with cognitive performance. Our findings are in agreement with previous reports that accumulation of amyloid plaques and NFTs is a common aspect of aging.[6,7,11,26] However, here we show that at extreme ages, some individuals can maintain the highest levels of

FIGURE 1 AD-associated neuropathological substrates (NIA amyloid stage, Braak NFT stage, and CERAD NP score) and brain weight in the NBB and 100-plus Study (centenarian) cohorts. (A,E,I,M) The mean levels ± 95% CIs of each neuropathological substrate and brain weight in the NBB cohort age continuum for the AD and ND groups (red and blue, respectively). (B,F,J,N) The difference in the average levels of each neuropathological substrate and brain weight between AD cases and ND controls in the NBB cohort age-continuum ± 95% CI. (C,G,K,O) The levels of each neuropathological substrate and brain weight across MMSE scores in the centenarian cohort. The red points are centenarian carriers of one *APOE*-ε4 allele; yellow points are those with no *APOE*-ε4 allele. (D,H,L,P) Distributions of the levels of each neuropathological substrate and brain weight for separate age intervals (<60, 60 to 69, 70 to 79, 80 to 89, ≥90) in the NBB cohort for the AD (red), non-AD dementia (light grey), and ND (blue) groups, and in the centenarian cohort (yellow). The beige portions represent the total distributions for each age interval of the NBB cohort. *Brain weight data were corrected for sex. AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; MMSE, Mini-Mental State Examination; NBB, Netherlands Brain Bank; ND, non-demented; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NP, neuritic plaque

TABLE 2 Characteristics of the NBB donors according to age at death

Characteristic	<60 y	60–69 y	70–79 y	80–89 y	≥90 y	Total
Female/male (*N*)	103/168	158/202	268/284	450/231	210/57	1189/942
Neuropathological diagnosis						
	N, median (IQR)	*N*, median (IQR)	*N*, median (IQR)	*N*, median (IQR)	*N*, median (IQR)	*N*, median (IQR)
Alzheimer's disease (*N*)	**42**	**132**	**204**	**323**	**150**	**851**
NIA amyloid stage	29, 3 (3–3)	75, 3 (3–3)	120, 3 (3–3)	159, 3 (3–3)	77, 3 (3–3)	460, 3 (3–3)
Braak NFT stage	36, VI (VI–VI)	110, VI (V–VI)	178, V (V–VI)	292, V (V–VI)	137, V (IV–V)	753, V (V–VI)
CERAD NP score	5, 3 (3–3)	16, 3 (3–3)	29, 3 (3–3)	28, 3 (2–3)	17, 3 (2–3)	95, 3 (3–3)
Brain weight (g)	42, 1017 (950–1103)	132, 985 (890–1065)	204, 995 (913–1088)	323, 1010 (941–1084)	150, 959 (917–1052)	851, 998 (920–1078)
Non-dementia (*N*)	**180**	**90**	**161**	**158**	**65**	**654**
NIA amyloid stage	18, 0 (0–0)	17, 0 (0–1)	65, 1 (1–2)	90, 1 (0–2)	47, 2 (1–2)	237, 1 (0–2)
Braak NFT stage	52, 0 (0–0)	45, I (0–I)	113, I (I–II)	129, II (I–II)	55, II (I–III)	394, I (0–II)
CERAD NP score	16, 0 (0–0)	11, 0 (0–0)	27, 0 (0–0)	36, 0 (0–0)	23, 0 (0–1)	113, 0 (0–0)
Brain weight (g)	180, 1267 (1190–1360)	90, 1225 (1130–1274)	161, 1160 (1077–1232)	158, 1124 (1050–1199)	65, 1060 (1025–1116)	654, 1179 (1080–1265)
Non-AD dementia (*N*)	**49**	**138**	**187**	**200**	**52**	**626**
NIA amyloid stage	14, 0 (0–0)	58, 1 (0–2)	116, 2 (1–2)	117, 2 (1–3)	35, 2 (1–2)	340, 2 (1–2)
Braak NFT stage	15, 0 (0–I)	66, I (I–II)	145, II (I–III)	165, II (I–III)	48, III (II–III)	439, II (I–III)
CERAD NP score	13, 0 (0–0)	35, 0 (0–0)	56, 0 (0–0)	37, 0 (0–1)	12, 0 (0–1)	153, 0 (0–0)
Brain weight (g)	49, 926 (812–1012)	138, 978 (837–1100)	187, 1036 (946–1147)	200, 1059 (983–1121)	52, 1029 (977–1144)	626, 1029 (935–1125)
Total (*N*)	**271**	**360**	**552**	**681**	**267**	**2131**

Abbreviations: AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; IQR, interquartile range; NBB, Netherlands Brain Bank; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NP, neuritic plaque.

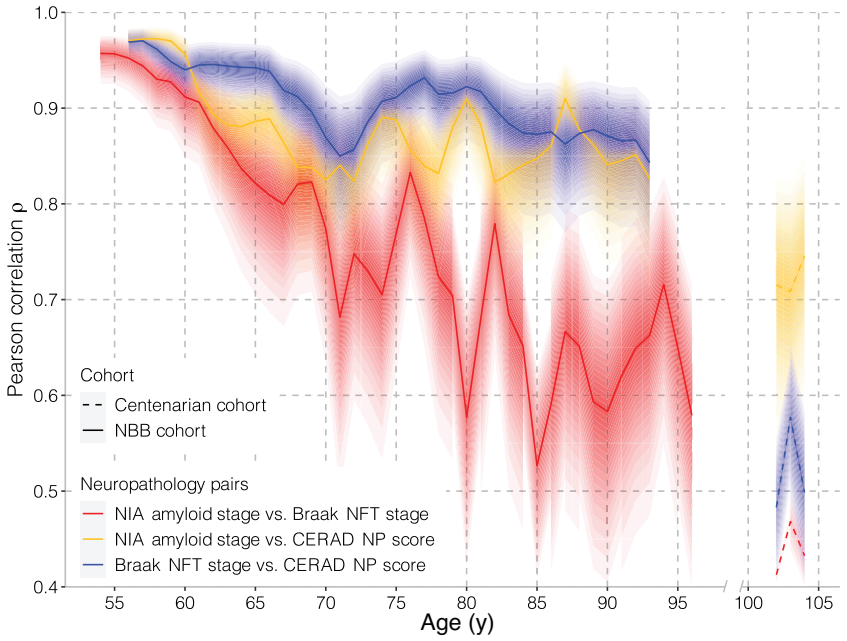


FIGURE 2 Pairwise Pearson correlation coefficients ± 95% confidence interval CIs between AD-associated neuropathological substrates across the age continuum in the NBB, and the centenarian cohorts, shown separately. The NBB age continuum includes AD patients, non-demented individuals, and non-AD demented individuals in a merged sample. The centenarian age continuum includes all centenarians. AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; NBB, Netherlands Brain Bank; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NP, neuritic plaque

TABLE 3 Associations between neuropathological substrates and MMSE scores in the NBB cohort

Neuropathology	Estimate β (95% CI)	*P*-value
NIA amyloid stage	−0.30 (−1.40, 0.81)	0.60
Braak NFT stage	−1.03 (−2.21, 0.14)	0.08
CERAD NP score	−0.78 (−1.87, 0.32)	0.16
Brain weight (g)	0.00 (−0.01, 0.02)	0.54

Note: Using linear regression, we tested the association between the levels of each neuropathological substrate and MMSE score. The β reflects the change in MMSE score associated with one unit increase in the level of neuropathology. The associations for AD-associated neuropathological substrates and brain weight were corrected for sex, education, and time between the last available MMSE and death. Detailed statistics of each regression model are provided in Table S2. Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; MMSE, Mini-Mental State Examination; NBB, Netherlands Brain Bank; NFT, neurofibrillary tangle; NIA, National Institute on Aging; NP, neuritic plaque.

cognitive performance despite accumulating levels of neuropathological substrates equivalent to AD patients.

When focusing on amyloid plaques, we rarely observed amyloid pathology in brains <65 years, while some of the brains older than 95 years reached amyloid plaque levels similar to AD patients. Of all the centenarians in this study, 9.4% resisted amyloid accumulation and had an NIA amyloid stage of 0; cognitive performance varied widely in this group. In contrast, 22.4% of the centenarians had the highest NIA amyloid stage of 3, of whom 26% had maintained high levels of cognitive performance (MMSE scores of ≥26).[27] This is in agreement with reports showing that the correlation between amyloid plaque burden and neuronal and synaptic loss is limited.[28,29] A first explanation for this is that a considerable fraction of Aβ deposits in the oldest old may be "diffuse plaques" (DPs),[11,12] depositions of aggregated non-fibrillar Aβ peptides with no organized internal architecture.[30,31] This subtype of plaque is considered less toxic than NPs,[11] which contain a contracted central core of fibrillar Aβ peptide with neighboring dystrophic neurites and surrounded by reactive astrocytes and activated microglial cells.[31-34] In contrast to DPs, NPs are associated with the degeneration observed at the synaptic junction, that is, the morphology of dendrites and axons with NPs was frequently abnormal.[32,34,35] Nevertheless, we observed that CERAD NP scores also increased in brains of ND individuals across the age continuum, but the increase remained within limits. CERAD NP scores in centenarians were mainly within the 0 to 2 range, indicating that most centenarians were resistant to accumulating the highest level of NPs. Within this range, CERAD NP scores did not correlate with MMSE scores. In fact, four centenarians (4.7%) had the highest CERAD NP score of 3, of whom two scored ≥26 points on the MMSE prior to death, suggesting that it is apparently possible to be resilient to the highest NP scores.[36]

For NFTs, Braak stages increased with age in ND individuals, which is in agreement with previous reports.[6,7,11] However, we found that Braak NFT stages decreased with age in AD cases, which suggests that at high ages, death can occur before the highest Braak NFT stage is reached, presumably due to the competing risk of comorbidity and the effects of other copathologies that accumulate with age, for example, TDP-43, α-synuclein, and vascular impairments.[3,15–17] Most centenarians had accumulated NFTs consistent with Braak stages II to IV; only two centenarians (2.4%) resisted accumulation of NFTs beyond Braak stage I, with variable cognitive performance. In contrast, five centenarians (5.9%) had Braak stage V, of whom three scored ≥25 points on the last available MMSE, indicating that resilience to high levels of accumulated tau is possible. While the association between Braak NFT stages and the MMSE did not reach significance in a regression model, centenarians with Braak stages I to III had significantly higher

MMSE scores than those with Braak stages IV and V. This is in line with the observation that clinical symptoms of AD often start when the Braak stage reaches IV,[37] and with the common assumption that of all AD neuropathological hallmarks, the Braak NFT stage associates most strongly with cognitive performance.[11,38]

Notably, we observed strong correlations between NIA amyloid stage, Braak NFT stage, and CERAD NP score, which suggests a dependency between mechanisms supporting the accumulation of these substrates.[39] However, with age, the correlation between NIA amyloid stage and Braak NFT stage decreased to ~0.5, indicating that the disease processes that lead to the buildup of these substrates in the elderly might be partly independent and with different etiology than at younger ages.[38,40] For example, primary age-related tauopathy is commonly observed in aged individuals, in which NFTs occur independently of amyloid plaques.[41]

Brain weight loss starts from ~40 years onwards, and amounts to 0.28% per year, which is likely due to the loss of white matter.[42] White-matter loss is associated with a decrease in processing speed, and this is characteristic for cognitive performance in the centenarian cohort.[43] The brain weight of centenarians was in keeping with their age, and showed no correlation with cognitive performance. This indicates that maintaining a high brain weight is not a prerequisite for maintaining cognitive health as measured by the MMSE.

That some centenarians were able to maintain high levels of cognitive health despite accumulating high levels of neuropathological substrates may be explained by their intrinsic resilience, that is, a genetically defined lower vulnerability to the adverse effects of these pathologies. We previously found that, relative to a middle-aged population, the genomes of the centenarians are depleted with respect to AD risk-alleles (including the strongly risk-increasing *APOE* ε4 allele) and enriched in terms of protective genetic variants.[44] Such a favorable genetic constellation is progressively selected for during the aging process of cognitively healthy individuals.[44,45] This advantageous genetic constellation concerns specifically genetic variants associated with the immune response, autophagy, and the endolysosomal system, mechanisms involved in the processing of many neuropathological substrates. Therefore, the resistance and resilience to accumulation of high levels of amyloid and tau may also extend to resilience to, for example, TDP-43, α-synuclein, and other neuropathological hallmarks of neurodegenerative diseases.[46] Lastly, we previously showed that the centenarians in this cohort have a relatively high educational attainment,[17,47] which may contribute to cognitive reserve: more efficient use of existing neuron networks (i.e., neural reserve), or the ability to recruit alternate networks in response to network disruptions (i.e., neural compensation).[48–50]

One of the unique aspects of this study is that the antemortem cognitive performance of the presented centenarian brains was tested only a few months prior to brain donation, such that correlations between neuropathology and brain function are exceptionally accurate. At study inclusion, centenarian participants self-reported to be cognitively healthy, and brain donation occurred 0 to 6 years later. Therefore, we acknowledge that this brain cohort represents the neuropathological changes associated with the transition from cognitive health to cognitive decline, while changes associated with late-stage dementia remain unaddressed. As a measure of cognitive performance, we used the MMSE, which was the first test in our testing battery, hence despite the fatigue commonly observed at last study visit, the measure was available for almost all centenarians. However, we acknowledge that the MMSE precludes the evaluation of neuropathological changes associated with different cognitive domains.[47] Likewise, we acknowledge that other neuropathological substrates may influence the observed resistance and resilience against the accumulation of amyloid and tau neuropathology. These aspects should be the focus for evaluation in future studies.

Concluding, we show that some individuals reach extreme ages with preserved cognitive health, despite accumulating levels of neuropathology similar to those observed in AD. While in vivo positron emission tomography amyloid and tau imaging and cerebrospinal fluid/plasma-based amyloid and tau levels are being implemented as biomarkers that aid clinical diagnosis of AD in memory clinics worldwide, the results of our work lead us to caution that the value of these pathologies may change with increasing age. Lastly, our results advocate for in-depth studies of these resilient brain samples to obtain a deeper understanding of the molecular mechanisms supporting the preservation of cognitive functioning until extreme ages.

AUTHOR CONTRIBUTIONS

Andrea B. Ganz, Annemieke J. M. Rozemuller, Susan Rohde, and Netherlands Brain Bank collected and performed the neuropathological characterization of the brain tissues donated to the 100-plus Study. Netherlands Brain Bank and Annemieke J. M. Rozemuller collected and provided additional data from the Netherlands Brain Bank cohort. Meng Zhang, Andrea B. Ganz, and Marc Hulsman performed the data analysis. Meng Zhang, Andrea B. Ganz, Susan Rohde, Marc Hulsman, Jeroen J.M. Hoozemans, and Henne Holstege wrote the manuscript. Jeroen J.M. Hoozemans and Henne Holstege supervised the research. Philip Scheltens, Marcel J.T. Reinders, Marc Hulsman, Jeroen J.M. Hoozemans, and Henne Holstege were involved in designing the study. Meng Zhang, Andrea B. Ganz, Susan Rohde, and Henne Holstege verified the underlying data. All authors read and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interest. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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