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RESEARCH ARTICLE

Resistance and resilience to tau pathology in Alzheimer's disease: Effects of age, sex, and *APOE* alleles

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Abstract

INTRODUCTION: Neurofibrillary tangles (NFTs), a hallmark of tau pathology in Alzheimer's disease (AD), accumulate in the aging brain. However, some individuals remain cognitively intact despite high Braak (III–VI) stages, which characterize NFTs' accumulation.

METHODS: We studied resistance and resilience to tau pathology by assessing Braak stages based on apolipoprotein E (*APOE*) alleles, sex, and age in a sample of 1932 cognitively intact individuals of European ancestry from the Alzheimer's Disease Sequencing Project (ADSP).

RESULTS: Resistance, characterized by low (0–II) Braak stages, was observed in men and women younger than 85 years of age. Resilience, indicated by high (III–VI) Braak stages, increased significantly with age in both men and women for each *APOE* allele. It became more pronounced, with the proportion of high Braak stages exceeding 50% at 85 years and older in women, irrespective of the *APOE* allele.

DISCUSSION: The identification of factors underlying resistance and resilience against AD-related pathologies is essential for promoting cognitively healthy aging.

KEYWORDS
aging, tau pathology, Alzheimer's disease, *APOE* allele, Braak stages, cognitive health, neurofibrillary tangles (NFTs), resilience, resistance, sex

Highlights

- We investigated cognitive resistance and resilience to tau pathology in Alzheimer's disease (AD).
- This study included individuals who were not diagnosed with AD.
- Braak stages 0–II and III–VI were considered as a measure of resistance and resilience, respectively.
- Resistance was stronger at ages younger than 85 years in non-carriers of the apolipoprotein E (*APOE*) ε4 allele.
- Resilience increased with age for each *APOE* allele independently of sex.
- At age 85 years and older, high resilience (>50%) was observed in women regardless of the *APOE* allele.

1 | BACKGROUND

Every year, as the elderly population grows, the incidence of age-related diseases, including Alzheimer's disease (AD) and related dementias (ADRD), also increases. In aging individuals, the brain accumulates neurofibrillary tangles (NFTs) and amyloid beta (Aβ), which are neuropathological hallmarks of AD.[1] Approximately 30% of individuals with AD pathology maintain cognitive health, even in the presence of intermediate- or high-stage AD pathology.[2] Studies have revealed that among the cognitively normal older individuals, 29% exhibit Braak stage III–VI, 26% show Consortium to Establish a Registry for Alzheimer's Disease (CERAD) B or C, and 11% display Thal phase 4 or 5.[3] This wide range of AD pathologies in cognitively intact individuals may be associated with brain reserves, cognitive reserves, or a combination of both.[4–7] Recently this concept has been expanded and integrated into the framework of cognitive resilience and resistance.[8–11] Within this framework, cognitive resilience and resistance refer to maintaining normal cognitive function in the presence of related pathologies (resilience) and in the absence of such pathologies (resistance). This definition is used in this study. The mechanisms of cognitive resistance and resilience may depend on the levels of AD pathologies and their combinations, as well as their interactions with other factors. When considering tau and amyloid pathologies in AD, it is crucial to examine cognitive (brain) resistance and resilience to each pathology separately, as well as their combined effects. The identification of measured variables is a crucial step in further development and success of this approach.

The level of deposition of AD biomarkers in human brain is associated with the type of apolipoprotein (*APOE*) allele, a major genetic factor commonly associated with AD.[12,13] The *APOE* ε4 allele is linked to higher levels of Aβ and NFTs accumulation, as well as a faster rate of cognitive decline, whereas the *APOE* ε2 allele is known for its protective properties compared to the *APOE* ε3 allele. However, these effects may vary with age.[13,14] Research suggests that the detrimental association of the *APOE* ε4 allele with AD tends to diminish and may disappear at the age of 90 and older.[14,15] Conversely, although the *APOE* ε2 allele is associated with a lower risk of AD compared to the ε3 allele, it may be associated with an increased risk of AD in individuals 90 years of age and older.[16] These findings underscore the need for further analyses of the effects of the *APOE* alleles, given their high relevance to the aging process.

This study presents the results on resistance and resilience to tau pathology as in AD defined by Braak staging,[17,18] which is also related to primary age-related tauopathy (PART).[19] Specifically, we examined and compared the age-dependent proportions of high (III–VI) versus low (0–II) Braak stages in carriers of different *APOE* alleles who were not diagnosed with AD, with both males and females considered separately and combined. The findings of this study contribute to the identification of groups of people exhibiting more pronounced resilience and resistance to tau pathology.

Recent studies shed light on cognitive resistance and resilience to tau pathology in AD.[20,21] These studies assessed scores of cognitive functions, such as, for example, the Mini-Mental State Examination (MMSE), as outcomes. They explored resistance and resilience by examining changes in cognitive functions among individuals already diagnosed with the disease, where resistance and resilience were insufficient to prevent significant cognitive decline leading to diagnosis. Our study complements these findings by focusing on individuals not diagnosed with AD, but who could develop AD at later ages. In this case, deterioration of their cognitive functions and AD-related pathologies could be below the threshold used for the AD diagnosis. This means that those individuals could demonstrate either resistance or resilience to cognitive decline preventing them from developing AD. This approach offers a logical rationale and provides a notable advantage of our research.

RESEARCH IN CONTEXT

1. **Systematic review**: Cognitive resistance and resilience to pathologies in Alzheimer's disease (AD) represent two distinct mechanisms that maintain healthy cognitive functions in the presence and absence of related pathologies. Previous publications have offered limited evidence regarding the impact of age, sex, and apolipoprotein E (*APOE*) allele on resistance and resilience due to a lack of measurable variables and considering individuals diagnosed with AD.
2. **Interpretation**: A higher proportion of low (0–II) and high (III–VI) Braak stages can serve as a measurable variable, characterizing resistance and resilience to tau pathology in AD. Our results support the hypothesis that the aging human brain can adapt to tau pathology to maintain cognitive function.
3. **Future directions**: The proposed approach can expedite the discovery of basic biological mechanisms underlying the deterioration of cognitive functions in AD and differentiating mechanisms of resistance, maintenance, and resilience. Ultimately, it can contribute to the development of interventions to mitigate the consequences of such deteriorations, thereby promoting cognitively healthy aging.

2 | METHODS

2.1 | Accession numbers

This study was approved by the review board of Duke University (Durham, NC, USA). This research has been conducted using data from the Alzheimer's Disease Sequencing Project (ADSP) data set, which was obtained through the National Institute on Aging Genetics of Alzheimer's Diseasett Data Storage Site (NIAGADS) at the University of Pennsylvania.

TABLE 1 Basic demographic characteristics of the ADSP cohort, which included cognitively healthy individuals, that is, individuals who were not diagnosed with Alzheimer's disease.

			APOE allele			
Age	BRAAK level	*N*	ε2	ε3	ε4	ε4–
ALL						
70 = [65; 74]	LOW	77	12	49	16	61
	HIGH	7	1	3	3	4
	%	8.33	7.69	5.77	15.79	6.15
80 = [75; 84]	LOW	466	106	306	54	412
	HIGH	143	20	94	29	114
	%	23.48	15.87	23.50	34.94	21.67
90 = 85+	LOW	669	115	480	74	595
	HIGH	570	91	395	84	486
	%	46.01	44.17	45.14	53.16	44.96
ALL	LOW	1,212	233	835	144	1068
	HIGH	720	112	492	116	604
	%	37.27	32.46	37.08	44.62	36.12
95+	LOW	22	6	13	2	20
	HIGH	55	4	47	4	51
	%	71.43	40.00	78.33	66.67	71.83
Males						
70 = [65; 74]	LOW	46	7	31	8	38
	HIGH	1	0	0	1	0
	%	2.13	0	0	11.11	0
80 = [75; 84]	LOW	233	48	163	22	211
	HIGH	63	8	44	11	52
	%	21.28	14.29	21.26	33.33	19.77
90 = 85+	LOW	298	55	211	32	266
	HIGH	196	27	133	36	160
	%	39.68	32.93	38.66	52.94	37.56
ALL	LOW	577	110	405	62	515
	HIGH	260	35	177	48	212
	%	31.06	24.14	30.41	43.64	29.16
95+	LOW	6	3	3	0	6
	HIGH	17	1	13	3	14
	%	73.91	25.00	81.25	100.0	70.00
Females						
70 = [65; 74]	LOW	31	5	18	8	23
	HIGH	6	1	3	2	4
	%	16.22	16.67	14.29	20.00	14.81
80 = [75; 84]	LOW	233	58	143	32	201
	HIGH	80	12	50	18	62
	%	25.56	17.14	25.91	36.00	23.57
90 = 85+	LOW	371	60	269	42	329
	HIGH	374	64	262	48	326
	%	50.20	51.61	49.34	53.33	49.77
ALL	LOW	635	123	430	82	553
	HIGH	460	77	315	68	392
	%	42.01	38.50	42.28	45.33	41.48
95+	LOW	16	3	10	2	14
	HIGH	38	3	34	1	37
	%	70.37	50.00	77.27	33.33	72.55

Note: Age groups were defined by decades, that is, the age group "70" includes individuals with lifespan between 65 and 74 years inclusively, and so on. Age groups of "90" and "95+" includes individuals who lived 85 years or longer and 95 years or longer, respectively.

Three groups of individuals carrying the apolipoprotein E (*APOE*) ε2 (ε2/ε2 or ε2/ε3 genotype), ε3 (ε3/ε3 genotype), and ε4 (ε4/ε4 or ε3/ε4 genotype) alleles were defined. The *APOE* ε4– group includes individuals of the *APOE* ε2 and ε3 groups.

"%" means proportion of individuals with high Braak stage in a group stratified by age and/or *APOE* allele status.

2.2 | Study cohorts

The study cohort (Table 1) included 1932 individuals of European ancestry (1095 women and 837 men) who were not diagnosed with AD and for whom information on *APOE* genotype, lifespan (defined as age at death), and tau pathology (Braak staging of NFTs)[18] was available from the ADSP data set.[22] Data on individuals who were 65 years of age or older were considered in the analyses. The inclusion criteria for considering individuals who were not diagnosed with AD are based on the assumption that the deterioration of their cognitive functions and AD-related pathologies was below the diagnostic threshold. This means that from the point of view of AD diagnostics, the selected individuals can be considered cognitively intact, although some may exhibit lower cognitive scores due to other cognitive conditions. Finally, this indicates that the selected individuals demonstrated either resistance or resilience to the cognitive decline associated with AD.

This study is neither cross-sectional nor longitudinal because it includes individuals born in the first half of twentieth century, and because measurements were obtained at the end of individual's life, spanning two decades of twenty-first century.

2.3 | *APOE* genotypes and alleles

Three groups of individuals carrying the *APOE* ε2 (ε2/ε2 or ε2/ε3 genotype), ε3 (ε3/ε3 genotype), and ε4 (ε4/ε4 or ε3/ε4 genotype) alleles were defined. Individuals with the *APOE* ε2/ε4 genotype are often excluded from the analysis because the effects of the ε2 and ε4 alleles cannot be delineated explicitly for them. We considered a combined group of ε4/ε4 or ε3/ε4 genotypes because of the small number (11 individuals) of homozygous carriers of the *APOE* ε4 allele (see Table S1).

2.4 | Phenotypes

Information on lifespan (age at death), AD status, and Braak stage of NFTs was provided by the ADSP project. We included in the analysis only individuals who were not diagnosed with AD and for whom autopsy results for Braak staging (stages 0–VI) were available. In this study, the Braak staging variable was dichotomized as low (Braak stage 0–II) and high (Braak stage III–VI) level. The Braak stages III–IV and V–VI were considered as one group because corresponding regions of the brain are related to short and long memory, respectively. Three age groups of 70 (65 to 74 years), 80 (75 to 84 years), and 90 (85 years and older) years were examined. In addition, we considered groups of individuals 95 years of age and older in order to demonstrate the observed trend at extreme ages.

2.5 | Statistical analyses

The analysis was focused on testing whether the difference of proportions of high and low Braak levels between the two groups was statistically significant. This involved testing differences between adjacent age groups for the same *APOE* allele or between pairs of the *APOE* alleles for the same age group. Fisher's exact test[23] was applied to the relevant 2 × 2 contingency tables for this analysis. The difference between proportions was deemed significant if the *p*-value from Fisher's exact test was less than 0.05.

3 | RESULTS

3.1 | Study overview

This study aimed to test the difference in the proportions of Braak stages of NFTs—high (Braak stages III–VI) versus low (Braak stages 0–II)—in groups of cognitively healthy individuals (i.e., with no diagnosis of AD) stratified by lifespan and by *APOE* allele status. The analysis was conducted in a sample of 1932 individuals of European ancestry (56.6% women), which was drawn from the ADSP project (see **Methods** and Table 1).

Fisher's exact test was used for comparing the proportions of Braak stages (high vs low) in pairs of different groups of individuals. Each group included individuals with similar lifespan (age groups 70, 80, and 90) who carried one of the three *APOE* alleles (ε2, ε3, or ε4) (see **Methods**). There were nine such groups for each sex and nine groups in the combined sample (Table 1). Two types of tests were performed. First, we performed 18 tests ($18 = 2 \times 3 \times 3$) for the difference in Braak stage proportions between groups of adjacent ages (70 vs 80 and 80 vs 90) for each *APOE* allele in men and women separately and combined. Second, we performed 27 tests ($27 = 3 \times 3 \times 3$) for the difference in Braak stage proportions between groups of carriers of different *APOE* alleles (ε4 vs ε3, ε4 vs ε2, and ε3 vs ε2) in each of the three age groups (70, 80, and 90) in men and women separately and combined. In total, 45 tests were performed. Therefore, Braak stage proportions were compared among carriers of different *APOE* alleles within the same age groups and between different age groups within carriers of the same *APOE* allele, without mixing different age and *APOE* groups in the analysis. In our opinion, this design minimizes the effects of survival bias associated with different *APOE* alleles, which could arise from the case–control design of the ADSP cohort from which the sample of this study was drawn.

TABLE 2 *p*-values from Fisher's exact test for proportions of high (III–VI) and low (0–II) Braak stages at different ages in carriers of different *APOE* alleles separately.

Age	*APOE ε2*	*APOE ε3*	*APOE ε4*	*APOE ε4–*
ALL				
70 vs 80	6.91E-01	1.99E-03	1.69E-01	1.66E-03
80 vs 90	5.70E-08	6.63E-14	9.66E-03	2.32E-20
Males				
70 vs 80	5.81E-01	2.023E-03	2.47E-01	8.31E-04
80 vs 90	1.66E-02	2.10E-05	8.87E-02	7.37E-07
Females				
70 vs 80	1.00E+00	2.97E-01	4.71E-01	4.69E-01
80 vs 90	1.66E-06	1.11E-08	5.41E-02	1.54E-13

Note: Age groups were defined by decades, that is, the age group "70" includes individuals with lifespan between 65 and 74 years inclusively, and so on. Age group of "90" includes individuals who lived 85 years or longer. Three groups of individuals carrying the apolipoprotein E (*APOE*) ε2 (ε2/ε2 or ε2/ε3 genotype), ε3 (ε3/ε3 genotype), and ε4 (ε4/ε4 or ε3/ε4 genotype) alleles were defined. The *APOE* ε4– group includes individuals of the *APOE* ε2 and ε3 groups.

3.2 | Proportion of high Braak stages increases with age

Table 1 displays the sample sizes of groups categorized by low (Braak stages 0–II) and high (Braak stages III–VI) Braak stages and stratified by age and the *APOE* alleles, in men and women combined and separately. Figure 1 illustrates the proportion of high Braak stages (III–VI) within each of these groups. Table 2 provides the results of Fisher's exact tests, evaluating differences in proportions of low and high Braak stages between adjacent age groups for men and women (combined and separately) carrying different *APOE* alleles.

Figure 1 shows that the proportion of high Braak stage (III–VI) increases with age for each *APOE* allele in men and women combined and separately. Table 2 reveals that the difference in proportions of Braak stages between the 80 and 90 age groups was statistically significant for each *APOE* allele in the combined samples of men and women. Within each sex, this difference was statistically significant for the *APOE* ε2 and ε3 alleles, with only marginal significance in groups with the *APOE* ε4 allele. In groups with younger individuals, the difference in proportions of high Braak stages was significant between 70 and 80 age groups for carriers of the *APOE* ε3 allele and non-carriers of the *APOE* ε4 allele in men and in the combined samples of men and women.

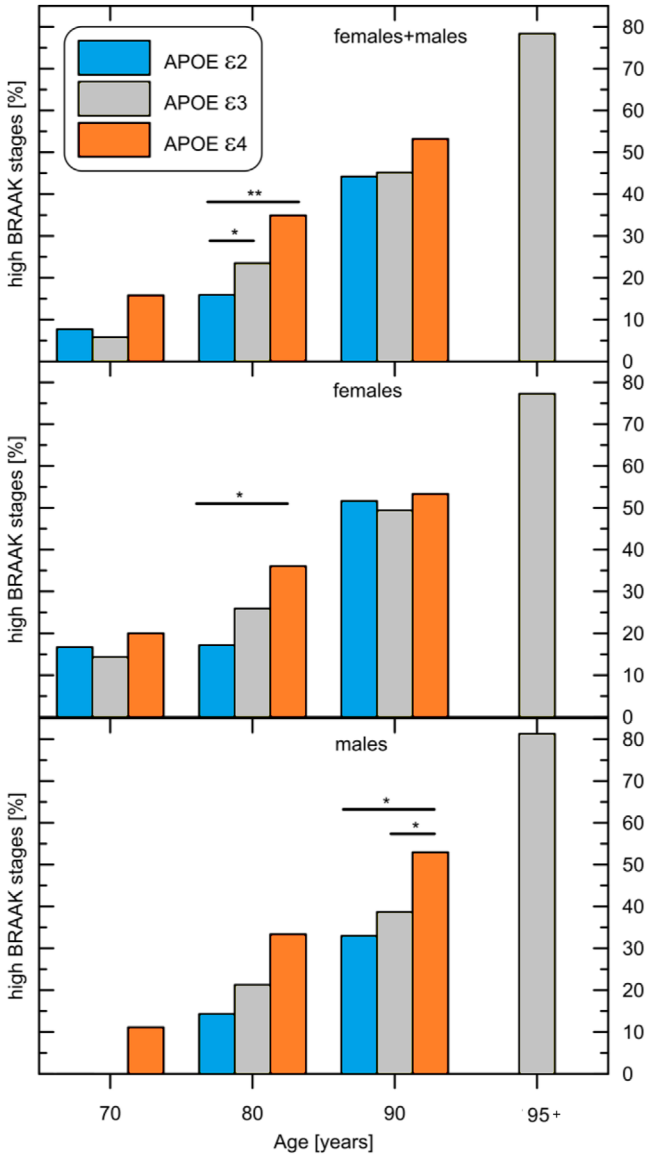

FIGURE 1 Age dependence of proportion of high Braak stage (III–VI) of neurofibrillary tangles in carriers of different *APOE* alleles. * (5E-4 < *p*-value < 0.05) and ** (*p*-value < 5E-4) mean significant difference in proportions between carriers of different *APOE* alleles. The significance is shown for the differences in proportions between the *APOE* alleles in the same age groups. Numerical estimates for these and other differences are given in Tables 2 and 3.

3.3 | Proportions of high Braak stages in carriers of different *APOE* alleles

Figure 1 illustrates that the proportions of high Braak states (III–VI) were highest in carriers of the *APOE* ε4 allele in each age group, for men and women combined and separately. In addition, it was higher in carriers of the *APOE* ε3 allele compared to the *APOE* ε2 allele in the 80 and 90 age groups for men, in the combined samples of men and women, and in the 80 age group for women. Table 3 and Figure 1 show that in the 80 age group, the proportion of high Braak stages in carriers of the *APOE* ε4 allele was significantly higher compared to each of the other *APOE* alleles, that is, versus ε2 and versus ε3, in the combined samples of men and women (ε4 vs ε2: $p = 2.44E-03$; ε4 vs ε3: $p = 3.97E-02$) as well as vs the *APOE* ε2 allele in women (ε4 vs ε2: $p = 3.14E-02$), and marginally significantly in men (ε4 vs ε2: $p = 5.88E-02$).

TABLE 3 *p*-values from Fisher's exact test for proportions of high (III–VI) and low (0–II) Braak stages in carriers of different APOE alleles in each age group separately.

Age	*APOE* ε2 vs ε3	*APOE* ε4 vs ε3	*APOE* ε4 vs ε2	*APOE* ε4+ vs ε4−
ALL				
70 = [65;74]	1.00E+00	3.32E-01	6.29E-01	1.88E-01
80 = [75;84]	8.23E-02	3.97E-02	2.44E-03	1.17E-02
90 = 85+	8.16E-01	6.88E-02	9.18E-02	6.00E-02
Males				
70 = [65;74]	1.00E+00	2.25E-01	1.00E+00	1.91E-01
80 = [75;84]	3.44 E-01	1.79E-01	5.88E-02	1.11E-01
90 = 85+	3.75E-01	3.14E-02	1.97E-02	2.27 E-02
Females				
70 = [65;74]	1.00E+00	1.00E+00	1.00E+00	6.53E-01
80 = [75;84]	1.88E-01	1.62E-01	3.14E-02	7.70E-02
90 = 85+	6.90E-01	4.96E-01	8.90E-01	5.75E-01

Note: Age groups were defined by decades, that is, the age group "70" includes individuals with lifespan between 65 and 74 years inclusively, and so on. Age group of "90" includes individuals who lived 85 years or longer. Three groups of individuals carrying the apolipoprotein E (*APOE*) ε2 (ε2/ε2 or ε2/ε3 genotype), ε3 (ε3/ε3 genotype), and ε4 (ε4/ε4 or ε3/ε4 genotype) alleles were defined. The *APOE* ε4− group includes individuals of the *APOE* ε2 and ε3 groups.

In the 90 age group, the proportion of high Braak stages in carriers of the *APOE* ε4 allele was significantly higher compared to each of the other *APOE* alleles, that is, versus ε2 and versus ε3, in men (ε4 vs ε2: $p = 1.97E-02$; ε4 vs ε3: $p = 3.14E-02$). However, in women, the proportions of high Braak stages were nearly the same for each *APOE* allele, and it was only marginally significant in the combined sample of men and women (Figure 1 and Table 3). Moreover, in this age group, the proportion of high Braak stages was ≈50% for each allele (Figure 1). In addition, we observed that the proportion of high Braak stages increased further beyond the level of 75% in samples of the *APOE* ε3 allele carriers with a lifespan of 95 years and older (see Table 1 and Figure 1).

Similar dependencies were observed when three *APOE* genotypes (ε3/ε2, ε3/ε3, and ε3/ε4) were considered separately in groups of individuals with Braak stages 0–II and III–IV (see Figure S1 in supplementary materials). Despite the small samples of carriers of the ε4/ε4 and ε2/ε2 genotypes having Braak stages V–VI, the numbers in Table S1 indicate that the *APOE* ε44 carriers (especially women) with high Braak stages V and VI can live longer than 90 years while remaining cognitively intact, that is, not diagnosed with AD.

4 | DISCUSSION

In this study, we investigated changes in the level of Braak stages (related to NFTs, i.e., tau pathology) in the brain with age for carriers of the *APOE* ε2, ε3, and ε4 alleles in a sample of 1932 cognitively normal individuals of European ancestry with available autopsy information from the ADSP cohort, who were not diagnosed with AD.

Our results demonstrate that the proportion of individuals with high Braak states (III–VI) increases with age in carriers of each of three *APOE* alleles, men and women combined and separately. These findings align with previous results that reported increased accumulation of NFTs (tau pathology) with age[1–3] reflected in an elevation of the average Braak stage and the proportion of high Braak stages with age in cognitively intact individuals. Our results demonstrate that these changes occur independently of the *APOE* allele status. Furthermore, in individuals older than 85 years, the proportions of high Braak stages reach ≈50% in women, regardless of the *APOE* allele, and in men carrying the ε4 allele. However, these proportions were smaller, ≈30%–35%, in men who did not carry the *APOE* ε4 allele (Table 1 and Figure 1). In addition, our results demonstrated that the proportions of high Braak stages exceeded 75% in the *APOE* ε3 allele carriers, in men and women combined and separately, 95 years of age or older (Table 1 and Figure 1). Further research is needed to clarify trends in the *APOE* ε2 and ε3 allele carriers 95 years of age or older because the currently available samples were not sufficient.

This finding suggests the involvement of biological mechanisms that aid in adaptation of the aging brain to tau pathology, with cognitive reserves playing a secondary role in this adaptation. If cognitive reserves were the primary factor, we would expect the highest proportion of high Braak stages to occur at an earlier age rather than at the oldest ages. In addition, our results suggest that women start adapting to tau pathology earlier than men. This is supported by smaller proportion of individuals with high Braak stages observed in men in the 70 age groups compared to women of the same age groups, and by achieving the 50% level of high Braak stages first in women then in men (see Figure 1).

The proportion of high Braak stages was consistently larger in carriers of the *APOE* ε4 allele compared to non-carriers at any age below 85 years. In women 85 years of age or older, this proportion exceeded 50% (and this proportion reached 75% in women 95 years of age or older). In addition, in women, the difference in this proportion became non-significant between carriers of different *APOE* alleles. This suggests that at age 85 years or older, at least 50% of women would have a high Braak stage of tau pathology (related to NFTs) and yet remain without signs of significant cognitive deteriorations. In men, the difference in the proportion remains significant between carriers and non-carriers of the *APOE* ε4 allele at an age of 85 years or older.

Our findings corroborate previous results[14] that the difference in proportions of high and low Braak stages in cognitively intact women who carry different *APOE* alleles becomes trivial and non-significant at ages of 85 years or older. The difference between carriers and non-carriers of the *APOE* ε4 allele remains significant in men. Further analysis is required to determine whether this difference in the proportion of high Braak stages in men effectively vanishes at oldest ages, that is, in men who lived longer than 95 years.

In addition (see Table 1, men and women combined), it should be noted that the change in the proportion of high Braak stages is 2.08 times higher in the 90 age group compared to the 80 age group in non-carriers of the *APOE* ε4 allele, whereas it is only 1.52 times higher between the same age groups in carriers of the *APOE* ε4 allele. This result suggests that either adaptation to brain changes related to tau pathology starts earlier in carriers of the *APOE* ε4 allele or the adaptation is faster in non-carriers of the *APOE* ε4 allele.

A speculative explanation for the sex-dependent results in our study could be better adaptive biological mechanisms developed during human evolution in females, likely related to their reproductive functions. The *APOE*-independent results observed in individuals 85 years of age or older might be due to adaptation of the human body following hormone-related changes at or after 65 years of age. If this is the case, such adaptation likely occurs through the *APOE*-independent mechanisms, which warrants further investigation.

4.1 | Resistance versus resilience to tau pathology in AD

Our results can be interpreted in terms of resistance and resilience to tau pathology in AD. They provide further insight into how resistance and resilience contribute to tau pathology in AD. Specifically, resistance in this context refers to mechanisms that guard the human brain against the initiation of tau pathology related to AD and maintain individuals as cognitively healthy. Resilience here refers to mechanisms that keep individuals cognitively intact in the presence of tau pathology related to AD. Our results suggest that resistance to tau pathology in AD is more crucial at ages younger than 85 years (as demonstrated by the low proportions of high vs low Braak stages; see Figure 1 and Table 1). However, resilience to tau pathology is the major driving factor for cognitively healthy life at an older age (85+), as indicated by about 50% of high Braak stages, with one exception: male non-carriers of the *APOE* ε4 allele (see Figure 1 and Table 1). Moreover, our results suggest that resilience to tau pathology in AD at 85 years of age or older is driven predominantly by *APOE*-independent mechanisms.

4.2 | Sex specific resilience to tau pathology

The results of this study suggest that women in the age group 85+ demonstrated higher resilience to tau pathology than men who did not carry the *APOE* ε4 allele (50% vs 35%), but not in carriers of the *APOE* ε4 allele (see Figure 1 and Table 1). This finding supports the hypothesis about sex-specific mechanisms of resilience to tau pathology in AD.[24] Moreover, our results show that women who carry the *APOE* ε2 and ε3 alleles demonstrate faster adaptation to tau pathology than men. These results suggest that male carriers of the *APOE* ε2 and ε3 allele demonstrate stronger contribution of resistance to tau pathology than women to survive over 85 years.

5 | CONCLUSIONS

Resistance and resilience are two groups of mechanisms that contribute to healthy life. Herein we reported the results on resistance and resilience to tau pathology, which is one of the hallmarks of AD. Resilience and resistance to AD refer to maintaining normal cognitive function in the presence of related pathologies (resilience) and in the absence of such pathologies (resistance). For this purpose, we compared the proportion of high (III–VI) Braak stages at autopsy in carriers of different *APOE* alleles, who lived longer than 65 years, and changes of the proportions with age in men and women combined and separately. Our findings show that the proportion of high (vs low) Braak stages in cognitively healthy individuals increases with age in carriers of each *APOE* allele. This proportion achieved 50% in women 85+ years of age independently of the *APOE* allele status and in the ε4-positive men. These findings show the increasing importance of resilience to tau pathology in AD at older ages in these groups. However, the ε4-negative men 85+ years of age seem to have higher resistance. Our findings suggest three implications. First, additional mechanisms of cognitive resilience exist, enabling the aging brain to adapt to AD-related tau pathology. Further investigations are needed to identify the genetic and non-genetic factors underlying these mechanisms. Second, resilience and adaptation, along with their respective mechanisms, extend beyond those related to the *APOE* gene. Third, the mechanisms of resilience, adaptation, and resistance may be sex specific, warranting further clarification. Finally, the results of this study, along with previous research, suggest a new direction in AD research, focusing on resilience to AD-related pathologies, identification of respective adaptation mechanisms, and understanding resistance to those pathologies with consideration of age- and sex-dependent effects. This new direction on resilience to AD-related pathologies can substantiate concepts of cognitive and brain reserve and related approaches. Within the current framework of cognitive and brain reserve concepts, it is challenging to separate the effects of resistance, resilience, and maintenance and to identify respective measurable variables of age- and disease-related changes. Therefore, it is difficult to pinpoint related biological mechanisms. Our approach offers a potential solution by uncovering measurable variables, particularly, in the dimension of tau pathology. Furthermore, these or similar variables can be utilized to identify new or alternative mechanisms employed by or developed in the aging brain (and possibly the entire human body) to mitigate or ameliorate the consequences and effects of brain deterioration on cognitive function. Ultimately, this approach allows differentiation of mechanisms related to resistance, maintenance, and resilience.

5.1 | LIMITATIONS

We acknowledge the study limitations. First, it did not account for the age difference between the last assessment of cognitive function and death, and it did not consider the mild cognitive impairment status of the included individuals. Second, the use of information from ADSP designed as a case–control study limits the ability to detect potential survival bias. Third, the case–control ADSP design and the small sample size of homozygous carriers of the *APOE* ε2 (18 individuals) and ε4 (11 individuals) alleles prevented us from assessing age-related changes in Braak-stage proportions in these groups separately and comparing them to other *APOE* genotypes in the considered age groups. Fourth is the mixed design of this study, which is neither cross-sectional nor longitudinal. Fifth, these findings require replication as we did not consider correction of multiple testing.

AUTHOR CONTRIBUTIONS

Alexander M. Kulminski conceived this study. Yury Loika and Alexander M. Kulminski designed the study. Yury Loika, Stephanie Webster, and Elena Loiko prepared data. Yury Loika and Stephanie Webster performed statistical analyses. Elena Loiko performed bioinformatic and biological analysis. Yury Loika, Stephanie Webster, Elena Loiko, and Alexander M. Kulminski discussed the results and wrote the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest. Author disclosures are available in the Supporting information

CONSENT STATEMENT

This study includes secondary analysis of data obtained from the Alzheimer's Disease Sequencing Project (ADSP) and does not involve gathering data from human subjects directly. Informed consent was obtained from all subjects by primary ADSP investigators who gathered data.

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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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