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DOI
10.1002/alz.13087

Publication date
2023

Document Version
Final published version

Published in
Alzheimer's and Dementia

Received: 7 January 2023 | Revised: 15 March 2023 | Accepted: 20 March 2023

DOI: 10.1002/alz.13087

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

The correlation between neuropathology levels and cognitive performance in centenarians

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Funding information
ZonMW, Grant/Award Number: 73305095007; Health~Holland, Topsector Life Sciences & Health, Grant/Award Number: LSHM20106

Abstract

INTRODUCTION: Neuropathological substrates associated with neurodegeneration occur in brains of the oldest old. How does this affect cognitive performance?

METHODS: The 100-plus Study is an ongoing longitudinal cohort study of centenarians who self-report to be cognitively healthy; *post mortem* brain donation is optional. In 85 centenarian brains, we explored the correlations between the levels of 11 neuropathological substrates with *ante mortem* performance on 12 neuropsychological tests.

RESULTS: Levels of neuropathological substrates varied: we observed levels up to Thal-amyloid beta phase 5, Braak-neurofibrillary tangle (NFT) stage V, Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-neuritic plaque score 3, Thal-cerebral amyloid angiopathy stage 3, Tar-DNA binding protein 43 (TDP-43) stage 3, hippocampal sclerosis stage 1, Braak-Lewy bodies stage 6, atherosclerosis stage 3, cerebral infarcts stage 1, and cerebral atrophy stage 2. Granulovacuolar degeneration occurred in all centenarians. Some high performers had the highest neuropathology scores.

DISCUSSION: Only Braak-NFT stage and limbic-predominant age-related TDP-43 encephalopathy (LATE) pathology associated significantly with performance across multiple cognitive domains. Of all cognitive tests, the clock-drawing test was particularly sensitive to levels of multiple neuropathologies.

1 | BACKGROUND

With increasing age, the human brain commonly accumulates various proteinopathies associated with neurodegenerative diseases that, accompanied by the concurrent loss of neuronal synapses and dendrites, is associated with the increased incidence of cognitive decline in elderly individuals.[1–6] The most common form of cognitive decline is due to Alzheimer's disease (AD), which is characterized by the accumulation of (1) amyloid beta (Aβ) plaques, (2) neuritic plaques (NPs), and (3) neurofibrillary tangles (NFTs).[7,8] Aβ plaques are extracellular deposits of aggregated Aβ peptides. NPs are Aβ plaques that contain a contracted central core of fibrillar Aβ peptide with neighboring dystrophic neurites and surrounded by reactive astrocytes and activated microglial cells.[9,10] NFTs are intracellular deposits of phosphorylated tau protein aggregated into paired helical filaments. AD patients frequently copresent, to different extents, with additional neuropathological substrates associated with aging and/or other neurodegenerative disorders such as cerebral amyloid angiopathy (CAA),[11] Lewy bodies,[12,13] atherosclerosis,[14] cerebral infarcts,[15] limbic-predominant age-related Tar-DNA binding protein 43 (TDP-43) encephalopathy (LATE) pathology (characterized by TDP-43 in combination with hippocampal sclerosis),[16,17] and other cerebrovascular disorders.[18] Copresentation of neuropathological substrates is associated with increased severity of cognitive impairment.[19]

We and others previously showed that the accumulation of these neuropathological substrates not only occur in the brains of patients with AD or other dementias but that they also accumulate with age in the brains of individuals that are cognitively healthy.[1,20–22] Many studies focusing on the oldest old population also reported the accumulation of multiple neuropathological substrates present in both demented and non-demented brains.[23–27] This leads to the question of how prevalent these different neuropathological substrates are in the oldest old and the extent to which increased levels of each substrate associate with cognitive performance.

To investigate this, we evaluated 11 different neuropathological substrates in *post mortem* brains and brain weight from well-phenotyped centenarians who participated in the 100-plus Study, an ongoing longitudinal cohort study of self-reported cognitively healthy centenarians. Previous findings in this cohort indicated that the levels of both *ante mortem* cognitive performance and *post mortem* neuropathological substrates were variable across centenarians.[20,28] These features render this cohort ideal for the evaluation of (1) the prevalence of and intercorrelation between the levels of different neuropathological substrates in the oldest old and (2) the correlations between levels of neuropathological substrates and neuropsychological performances across different cognitive domains. Together, this investigation will allow for a deeper understanding of the effect of neuropathological substrates on cognitive performance at extreme ages.

RESEARCH IN CONTEXT

1. **Systematic review**: Mixed neuropathologies are often observed in the *post mortem* brains of the elderly. However, it is currently unclear how prevalent these different neuropathological substrates are in the oldest old and to what extent they associate with cognitive performance.
2. **Interpretation**: The levels of neuropathological substrates varied widely across centenarians, and some centenarians maintained the highest levels of cognitive performance despite having accumulated neuropathological substrates to the highest levels. Only Braak-NFT stage and LATE pathology (i.e., TDP-43 and hippocampal sclerosis) associated significantly with cognitive performance across multiple domains, and performance on the clock-drawing test correlated most strongly with multiple neuropathological substrates.
3. **Future directions**: Our results emphasize NFTs and LATE pathology as prime contributors to cognitive decline in the elderly.

2 | METHODS

2.1 | Neuropsychological assessment

Trained researchers visited the centenarians at their homes annually to subject them to a comprehensive neuropsychological testing battery covering five cognitive domains: memory, verbal fluency, attention/processing speed, executive functions, and visuospatial functions. A composite *z*-score for each of the five cognitive domains was computed to allow associations with levels of neuropathological substrates. The Mini-Mental State Examination (MMSE) was administered[29] as a measure of global cognition, and scores on all cognitive domains were combined in a composite global cognition score. For this study, we used cognitive data collected at the last available study visit, which occurred a few months before death, to ensure a minimal time between neuropsychological measurements and neuropathological status at death.

Memory was evaluated using the immediate and delayed story recall subtest of the Rivermead Behavioral Memory Test (RBMT) and the Visual Association Test A (VAT-A).[30,31] Verbal fluency was measured using the Controlled Oral Word Association Test D-A-T (letter fluency, LF) and animal fluency (AF).[32,33] Attention/processing speed were evaluated with the digit span forward (DSF) subtest of the Wechsler Adult Intelligence Scale (WAIS-III) and the Trail Making Test (TMT) part A (scores were reversed, such that higher scores indicate better performance).[34,35] Executive functions were evaluated using the TMT part B (scores were also reversed), key search (KS) subtest of

the Behavioral Assessment of the Dysexecutive Syndrome Test Battery, and the digit span backward (DSB) subtest of the WAIS-III.[34–36] Visuospatial functions were evaluated with the number location (NL) subtest of the Visual Object and Space Perception Battery (VOSP) and the clock-drawing test (CDT).[37,38] Methods of test administration and implemented adaptations were described previously.[28]

2.2 | Neuropathological assessment

Autopsies were performed in collaboration with the Netherlands Brain Bank (NBB).[20] For each brain, we evaluated the level or distribution of 11 neuropathological substrates: (1) amyloid plaques (Thal-Aβ phase), (2) neurofibrillary tangles (Braak-NFT stage), (3) neuritic plaques (CERAD-NP score), (4) granulovacuolar degeneration (Thal-GVD stage), (5) cerebral amyloid angiopathy (Thal-CAA stage), (6) phosphorylated transactive response DNA-binding protein 43 (TDP-43 stage), (7) hippocampal sclerosis, (8) atherosclerosis, (9) cerebral infarcts, (10) Lewy bodies (Braak-LB stage), and (11) cerebral atrophy, as well as (12) brain weight. Methods for pathology assessments and scoring strategies are described in detail in the Supplementary Material, and an overview of primary antibodies used for immunohistochemical assessments is given in Table S1. All centenarian brains were investigated by the same neuropathologist, keeping interrater variability to a minimum.

2.3 | Quality control and missing data imputation

Of the 395 centenarians that had been included in the 100-plus Study at the start of this analysis, 85 centenarians agreed to brain donation, allowing *post mortem* neuropathological assessment (Figure 1). Few neuropathology staging levels were missing (Table S2); to make full use of the data, these were imputed across all 85 centenarians using MICE (version 3.13.0[39]) using all neuropathological substrates, sex, age at death, apolipoprotein E (*APOE*) genotype, and brain weight as variables (Supplementary Material).

At the last study visit, a few months before death, fatigue, hearing, and vision problems were common, which in some cases contributed to an inability to complete the cognitive testing battery[40] (Table S3). Missing data occurred across cognitive tests and across items within tests, and missingness became more prevalent as study visits occurred closer to the death of the centenarian. To make optimal use of available data, we used MICE to impute (1) missing MMSE items and (2) test scores across the cognitive testing battery. MMSE scores were imputed when ≤5 of the 30 points were missing as previously described[20]; otherwise, MMSE was set to "missing." Missing data for the 12 neuropsychological tests were imputed across data collected at the last available visit from the 322 centenarians in the 100-plus Study cohort for whom at least half of the neuropsychological tests were available (excluding MMSE; Figure 1 and Supplementary Material). As variables for the imputation, we included all neuropsychological test scores, imputed MMSE score, and education level (International Standard Classification of Education [ISCED]). After imputation, full autopsy and full neuropsychology assessments were available for 69 centenarians, allowing the investigation of the association between neuropathology and neuropsychology (Figure 1).

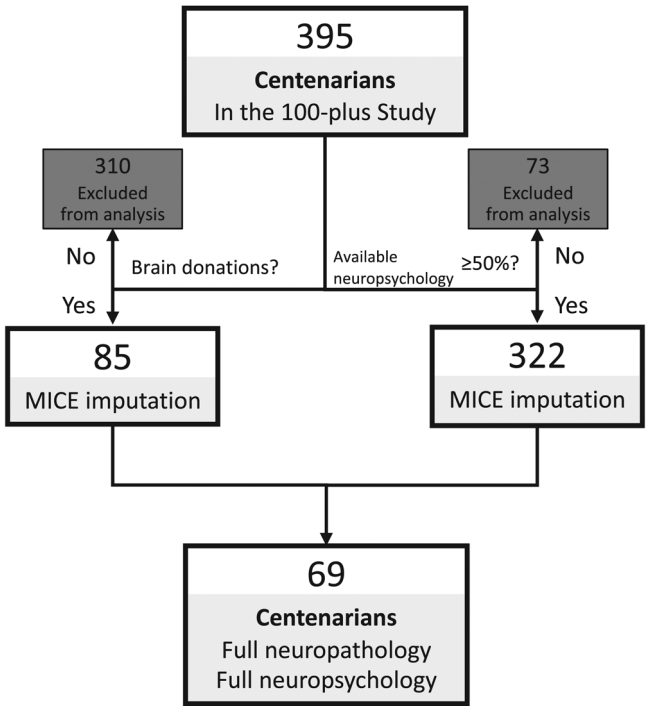

FIGURE 1 Flowchart of quality control and missing data imputation. A total of 395 centenarians had been included in the 100-plus Study at the start of this analysis. Of these, 85 centenarians donated their brain for autopsy. The prevalence of different neuropathologies and the hidden structure was investigated in all 85 brain donors. Missing values for neuropathology were imputed across all 85 centenarian brains using MICE. Across the 322 centenarians for whom scores of at least half of the neuropsychological tests were collected at the last study visit (available neuropsychology ≥50%), missing scores were imputed with MICE. This resulted in 69 centenarians for whom all (imputed) neuropathology levels and all (imputed) neuropsychology test scores were available; these were included in the correlation analysis between neuropathology and neuropsychology.

2.4 | Statistical analyses

2.4.1 | Pairwise correlation between neuropathological substrates

The correlation between each pair of neuropathological levels, as measured in all 85 centenarian brains, was determined by calculating the Pearson correlation coefficient. Associated *p* values were corrected for false discovery rate (FDR) using the Benjamini-Hochberg method.

2.4.2 | Factor analysis

To identify which neuropathological substrates were coregulated at extreme ages, we performed a generalized weighted least squares (GLS) factor analysis using the "oblimin" rotation method,[41] with scoring based on the "tenBerge" scheme (psych R package, version 2.1.9). The optimal number of factors was determined using the parallel analysis[42] ("nScree" function in the nFactors R package, version 2.4.1) on neuropathological measures of all 85 centenarian brains. Paired correlations between the scores from the latent factors and brain weight were investigated using the Pearson correlation coefficient.

2.4.3 | Regression analysis between neuropathology and neuropsychology

We applied linear regression models to investigate the correlation between neuropathological variables (explanatory variables) and neuropsychological variables (response variables). Models were corrected for age at death, sex, and level of education (ISCED). *APOE* genotype does not associate with neuropathology levels or cognitive performance at these extreme ages[22] and was not corrected for. The regression coefficient was used to indicate the strength of the correlation, and the corresponding p value was used to indicate the significance. All response variables and explanatory variables were standardized (z-scores) to ensure the regression coefficients were comparable.

To avoid any outlier bias, we bootstrapped all the aforementioned analysis procedures ($n = 1{,}000$). Pearson correlation coefficients, factor loadings and scores, and regression coefficients were calculated using the average values across bootstraps. We did not perform bootstrapping on p values: the p values for each analysis were determined based on the original tests, including all available centenarians. All calculations were performed using R (version 3.6.3). Pearson correlation coefficient and linear regression were performed using the stats R package.

3 | RESULTS

3.1 | Sample characteristics

The age at death of the 85 centenarian brain donors ranged between 100 and 111 years, and 75% were female. The last available study visit during which cognitive tests were administered occurred at a median of 9 months prior to brain donation (interquartile range [IQR]: 4–13). The median MMSE score at this last available study visit was 25 (IQR: 22–27). Of the 83 centenarians with *APOE* genotype available, seven carried one copy of the *APOE* ε4 allele, and *APOE* genotype did not associate with cognitive performance (Figure 2, Table S4). Within this group, we observed no association between carrying the *APOE* ε4 allele and the level of neuropathological substrates (Table S4). The characteristics of the 69 centenarians with full autopsy and full neuropsychology assessments are available in Table 1.

TABLE 1 Characteristics of 69 centenarians in this analysis.

	Median (Q1–Q3)
Clinical demographics	
Age (years)	103.3 (102.4–104.6)
Female/male	52/17
Education level (ISCED, 0–7)	3 (1–4)
MMSE (range: 0–30)	25 (22–26)
APOE genotype (percentage with *APOE* ε4 allele)	8.7% (6/69) with one *APOE* ε4 allele, 0% (0/69) with two *APOE* ε4 alleles
Neuropathological substrates, range of neuropathology scoring	
Thal-Aβ phase (range: 0–5)	3 (1–3)
Braak-NFT stage (range: 0–VI)	3 (3–4)
CERAD-NP score (range: 0–3)	1 (0–1)
Thal-CAA stage (range: 0–3)	1 (1–1)
TDP-43 stage (range: 0–3)	0 (0–2)
Hippocampal sclerosis (range: 0/1)	0 (0–0)
Thal-GVD stage (range: 0–5)	5 (4–5)
Atherosclerosis (range: 0–3)	2 (1–3)
Cerebral infarcts (range: 0/1)	1 (0–1)
Braak-LB stage (range: 0–6)	0 (0–0)
Cerebral atrophy (range: 0–3)	1 (0–1)
Brain weight (g)	F: 1062 (1005–1125); M: 1175 (1150–1250)
Neuropsychological assessments, abbreviation, range of test performance	
RBMT immediate recall test, IR (range: 0–42)	7.0 (5.0–12.0)
RBMT delayed recall test, DR (range: 0–42)	4.0 (2.0–7.5)
Visual Association Test A, VAT-A (range: 0–12)	7.4 (5.0–10.0)
Letter fluency D-A-T, LF (total word count)	25.0 (18.0–32.0)
Animal fluency, AF (total word count)	10.0 (7.0–14.0)
Trail Making Test part A, TMT-A (time to finish)	87.0 (49.0–147.2.0) (not reversed)
Trail Making Test part B, TMT-B (time to finish)	232.5 (192.9–301.6) (not reversed)
Digit span forward, DSF (range: 0–16)	7.0 (6.0–9.0)
Digit span backward, DSB (range: 0–8)	5.0 (4.0–5.0)
Clock-drawing test, CDT (range: 0–5)	3.0 (2.7–5.0)
Number location test, NL (range: 0–10)	8.9 (7.0–9.0)
Key search test, KST (range: 0–16)	5.7 (4.0–10.0)

Abbreviation: ISCED, International Standard Classification of Education.

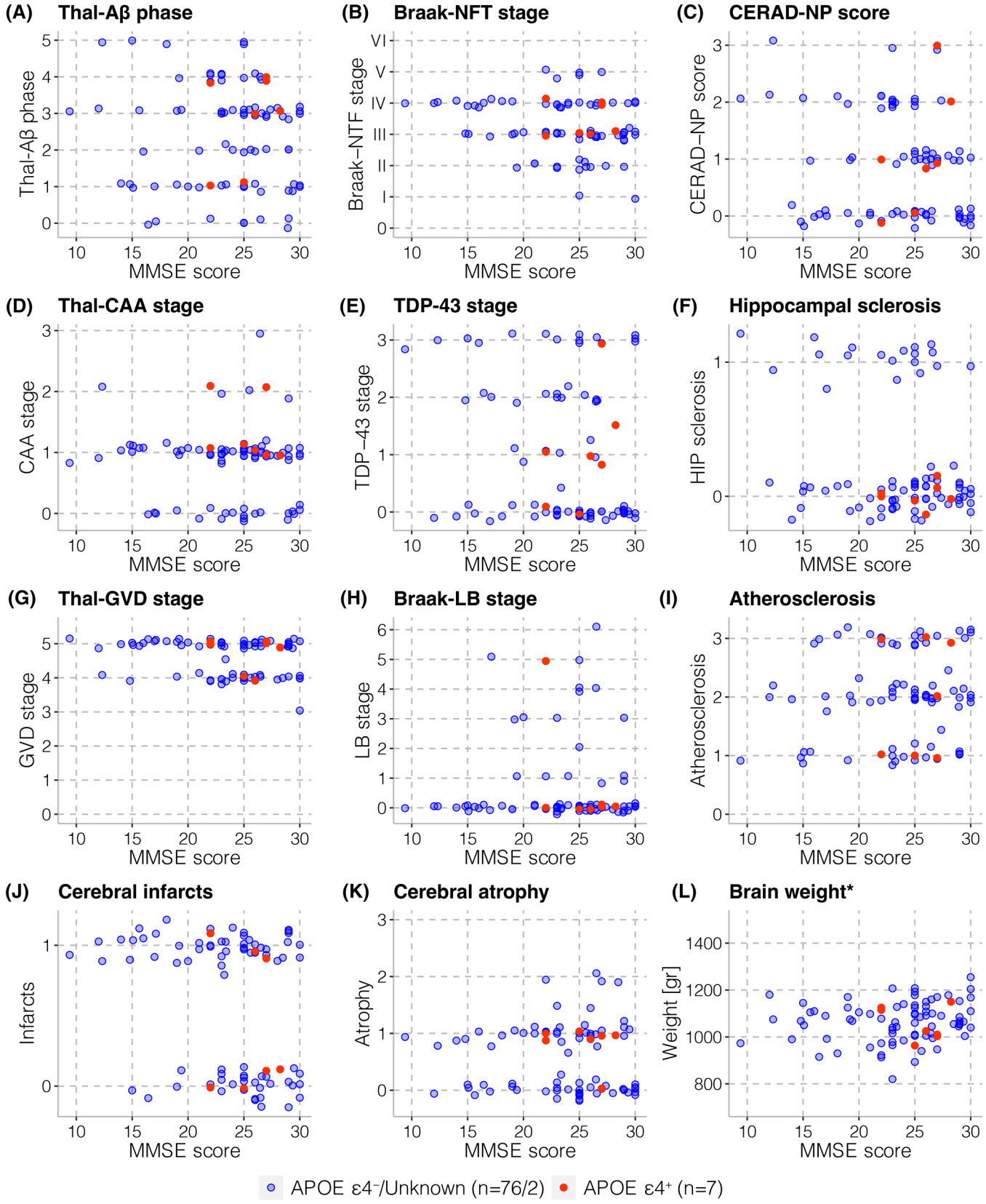

FIGURE 2 The levels of neuropathological substrates across MMSE score in 85 *post mortem* brains. Red dots: centenarians with one copy of *APOE ε4* allele; blue dots: centenarians with no copy of *APOE ε4* allele or unknown *APOE* genotype. Staging scores have been given a random component to be able to distinguish the samples. *Brain weight was corrected for sex.

3.2 | The prevalence of different neuropathologies in centenarians

The levels of neuropathological substrates varied widely across the 85 centenarians: none of the centenarians remained free of neuropathology, while three centenarians accumulated at least one level of all 11 neuropathological substrates. Centenarian brains had variable levels of TDP-43 stages and atherosclerosis and high Thal-GVD stages. Further, we observed that some centenarians accumulated a high/highest level of, for example, Thal-Aβ phase up to 5 (5.9%), Braak-NFT stages up to stage V (5.9%), CERAD-NP scores up to level 3 (4.7%), Thal-CAA stages up to stage 3 (1.2%), Braak-LB stages up to stage 6 (n = 1.2%), and cerebral atrophy up to stage 2 (4.7%). In addition, cerebral infarcts were common in the centenarian brains (58.8%), and some had hippocampal sclerosis (22.3%). However, for the large majority of centenarians, the burden of accumulated neuropathology substrates remained with a certain limit: Braak-NFT stage ≤IV (94.1%), CERAD-NP score ≤2 (95.3%), Thal-CAA stage ≤1 (91.8%), Braak-LB stage ≤1 (85.9%), and cerebral atrophy stage ≤1 (92.9%). Intriguingly, when presenting the levels of each neuropathological substrate across MMSE scores (Figure 2), we see that some of the centenarians with the highest neuropathology scores were among the best cognitive performers, suggesting that these individuals are resilient to the accumulation of these pathologies.

3.3 | Factor analysis identifies five neuropathology factors in centenarian brains

To explore the hidden structure of neuropathology in centenarian brains, we first evaluated the pairwise correlation between neuropathological substrates (Figure 3A, Table S5, see Methods). We observed that CERAD-NP score correlated significantly with Thal-Aβ phase ($r = 0.78$, FDR < 0.001), Braak-NFT stage ($r = 0.42$, FDR < 0.001), and Thal-CAA stage ($r = 0.46$, FDR < 0.001). Moreover, Thal-CAA stage correlated significantly with Thal-Aβ phase ($r = 0.61$, FDR < 0.001) and cerebral atrophy ($r = 0.33$, FDR = 0.02), but not with Braak-NFT stage ($r = 0.13$, FDR = 0.58). Hippocampal sclerosis correlated significantly with TDP-43 stage ($r = 0.68$, FDR < 0.001), and Thal-GVD stage correlated significantly with Braak-NFT stage ($r = 0.37$, FDR = 0.005). Last, brain atrophy negatively correlated with brain weight ($r = -0.35$, FDR = 0.01).

Next, an Elbow and factor analysis revealed that the 11 different neuropathological substrates (i.e., excluding brain weight, as this varies between healthy individuals irrespective of age-related changes) loaded on five neuropathological factors, which we labeled as follows: (1) an amyloid factor on which the Thal-Aβ phase, CERAD-NP score, and Thal-CAA stage loaded; (2) a LATE factor on which the TDP-43 stage and hippocampal sclerosis loaded[17]; (3) a tau factor on which Braak-NFT stage, Thal-GVD stage, and Braak-LB stage loaded; (4) a cerebral atrophy factor on which predominantly brain atrophy and, to a lesser extent, Thal-CAA stage loaded; and (5) a vascular factor onto which mainly atherosclerosis and, to a lesser extent, cerebral infarcts loaded (Figure 3B, Figure S1). Upon correlation of the latent factors, we observed a significant correlation between the amyloid and tau pathology factors ($r = 0.24$, $p = 0.01$), followed by the correlation between LATE and tau pathology factors ($r = 0.15$, $p = 0.03$). Brain weight negatively correlated with the atrophy factor ($r = -0.27$, $p = 0.02$) (Figure 3C, Table S6).

3.4 | Individual neuropathological substrates versus individual neuropsychological tests

When correlating the levels of the 11 neuropathological substrates and brain weight with the performance on individual neuropsychological tests (Methods), we found that of all neuropsychological tests, the CDT showed the strongest correlation with levels of multiple neuropathological substrates (Figure 4, Table S7). Braak-NFT stage significantly correlated with immediate recall ($\beta = -0.32$, $p = 0.008$), delayed recall ($\beta = -0.34$, $p = 0.004$), VAT-A ($\beta = -0.34$, $p = 0.005$), TMT part A ($\beta = -0.27$, $p = 0.03$) and B ($\beta = -0.26$, $p = 0.03$), KS ($\beta = -0.26$, $p = 0.02$), and CDT ($\beta = -0.35$, $p = 0.003$); TDP-43 stage and hippocampal sclerosis correlated with AF ($\beta = -0.27$, $p = 0.02$; $\beta = -0.27$, $p = 0.02$) and CDT ($\beta = -0.40$, $p = 0.001$; $\beta = -0.25$, $p = 0.04$). Lastly, LB stage significantly correlated with CDT ($\beta = -0.30$, $p = 0.03$). Mentioned p values here and in what follows were not adjusted for multiple testing because the tests were not independent.

3.5 | Individual neuropathological substrates versus predefined cognitive domains

Investigation of the correlations between neuropathology and cognitive domains yielded a similar result (Figure 4, Table S7). Braak-NFT stage significantly correlated with memory ($\beta = -0.37$, $p = 0.001$), executive function ($\beta = -0.31$, $p = 0.004$), and visuospatial function ($\beta = -0.30$, $p = 0.01$) domains. TDP-43 stage correlated with executive function ($\beta = -0.23$, $p = 0.03$) and visuospatial function ($\beta = -0.27$, $p = 0.03$) domains. Hippocampal sclerosis correlated with fluency ($\beta = -0.26$, $p = 0.02$). Braak-LB stage and cerebral atrophy both significantly correlated with visuospatial function ($\beta = -0.27$, $p = 0.04$; $\beta = -0.25$, $p = 0.05$).

3.6 | Neuropathology latent factors versus individual cognitive tests and cognitive domains

We investigated the effect of each neuropathological factor on cognitive performance on the individual test level and domain level (Figure 4, Table S7). We observed that the LATE factor correlated significantly with AF and the CDT test scores (respectively $\beta = -0.29$, $p = 0.01$, and $\beta = -0.37$, $p = 0.001$), and also with the corresponding fluency and visuospatial function domains (respectively $\beta = -0.25$, $p = 0.03$ and $\beta = -0.23$, $p = 0.05$). The tau factor correlated with CDT and TMT part A (respectively $\beta = -0.29$, $p = 0.005$ and $\beta = -0.29$, $p = 0.03$) and the

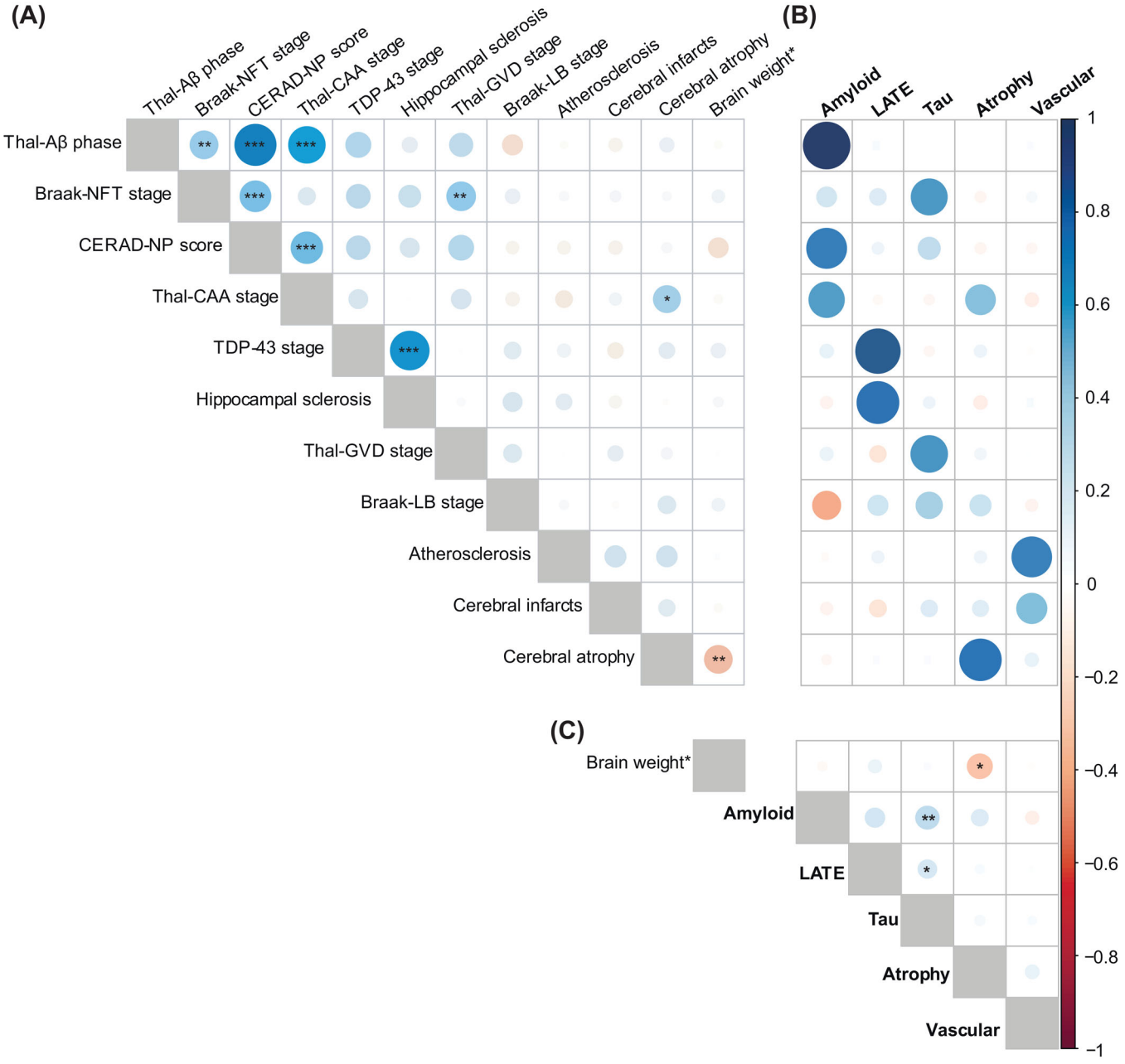

FIGURE 3 The correlation and factor analysis of neuropathological substrates. (A) Pairwise correlation between neuropathological substrates and brain weight. The correlation coefficients and the *p* values were calculated using Pearson correlation. All *p* values were corrected for false discovery rates (FDRs) using the Benjamini-Hochberg method. The asterisks indicate the significance of the correlation with FDR (* ≤0.05, ** ≤0.01, and *** ≤0.001). (B) An exploratory factor analysis (EFA) was performed for the 11 neuropathological substrates, and the five latent factors were determined using the Elbow method (see Methods). Bold text: factor names. Color and size of circles indicate loading of each neuropathological substrate on each factor, where blue indicates positive loads, red negative loads. (C) Pairwise Pearson correlation correlations between the neuropathological latent factors and brain weight. Asterisks indicate the significance of the correlation with *p* value (* ≤0.05, ** ≤0.01, and *** ≤0.001). Color and size of circles indicate strength of Pearson correlation coefficient, where blue indicates positive correlation and red indicates negative correlation. *Brain weight was corrected for sex.

visuospatial function domain ($\beta = -0.24$, $p = 0.03$). LATE and tau factor significantly correlated with composite global cognition ($\beta = -0.22$, $p = 0.03$; $\beta = -0.23$, $p = 0.02$). The vascular factor correlated with the NL test ($\beta = -0.21$, $p = 0.04$) and with the MMSE score ($\beta = -0.12$, $p = 0.05$), and the atrophy factor also significantly correlated with the visuospatial function domain ($\beta = -0.27$, $p = 0.03$).

3.7 | Individual neuropathological substrates versus global cognition

A significant correlation was observed between the Braak-NFT stage and the composite global cognition score ($\beta = -0.33$, $p = 0.001$), which was in line with expectations given that Braak-NFT stage significantly

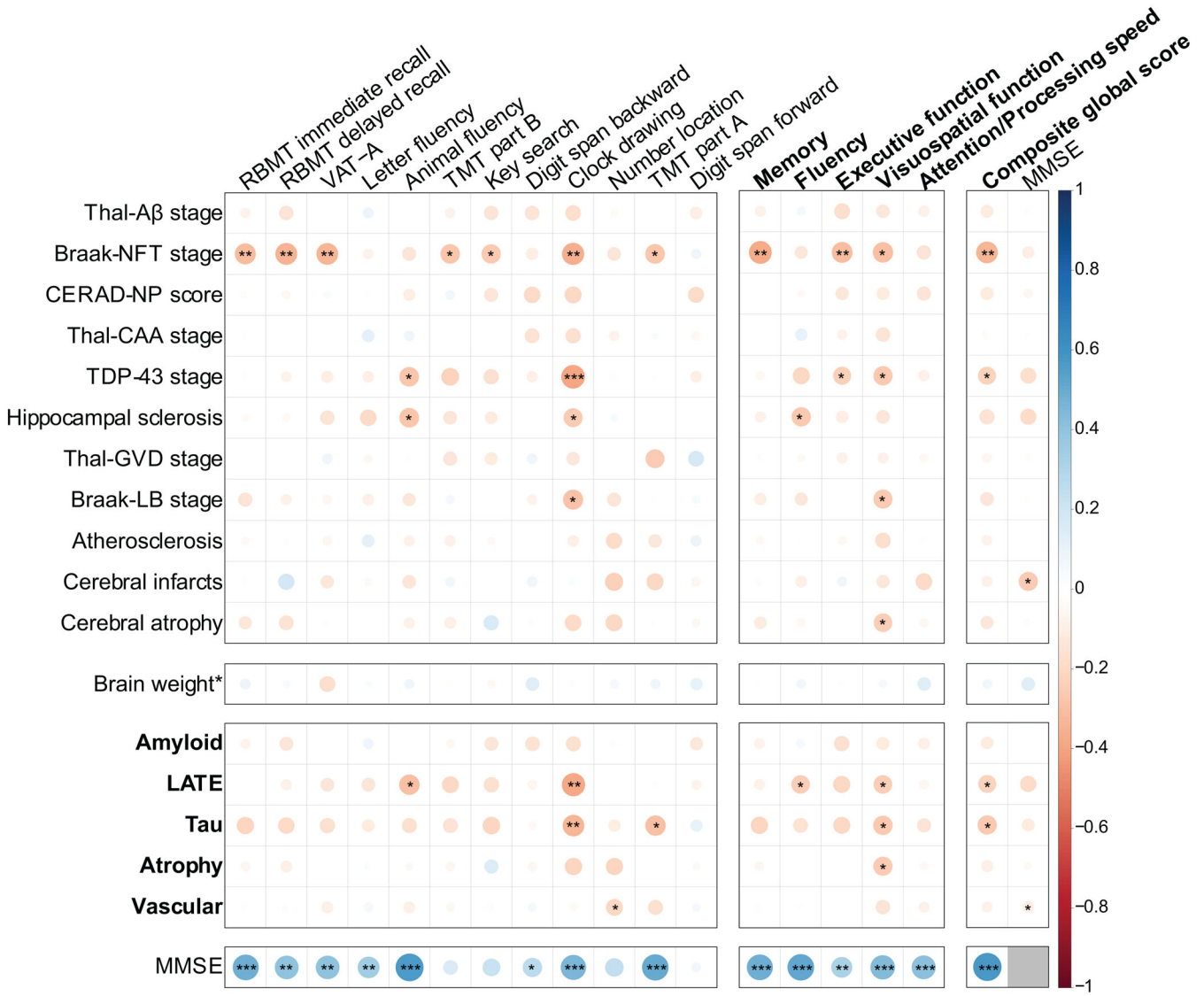

FIGURE 4 Regression analysis between neuropathology and neuropsychology (see Methods). Rows: levels of individual neuropathological substrates, brain weight, neuropathological factors, and MMSE. Columns: performance of individual neuropsychological tests, cognitive domains, composite global cognition, and MMSE. Color and size of circles indicate strength of regression coefficient, where blue indicates positive correlation, red negative correlation. Asterisks indicate significance of correlation with *p* value (* ≤0.05, ** ≤0.01, and *** ≤0.001, uncorrected). The name of cognitive domains, composite global cognition, and neuropathology latent factors were indicated in bold text. *Brain weight was corrected for sex.

correlated with almost all neuropsychological tests (Figure 4, Table S7). TDP-43 stage also correlated with composite global cognition score ($\beta = -0.23$, $p = 0.04$). While the MMSE score significantly correlated with all cognitive domains as well as the composite global cognition score, neither Braak-NFT stage nor TDP-43 stage correlated with the MMSE score. MMSE, but none of the cognitive domains or composite global cognition scores, significantly correlated with cerebral infarcts ($\beta = -0.26$, $p = 0.02$).

4 | DISCUSSION

The levels of neuropathological substrates in centenarians varied, with Braak-NFT stages and LATE pathology correlating most strongly with cognitive performance. Other substrates such as Thal-Aβ, Thal-GVD, and atherosclerosis had little to no correlation. Despite the high burdens of substrates, some centenarians maintained cognitive health, suggesting resiliency. Interestingly, performance on the CDT correlated most strongly with levels of neuropathological substrates, even more strongly than the MMSE.

Overall, positive correlations were observed between Thal-Aβ phase, Braak-NFT stage, CERAD-NP score, Thal-CAA stage, TDP-43 stage, hippocampal sclerosis, and Thal-GVD stages, suggesting functional connections. Vascular changes such as atherosclerosis, cerebral infarcts, and CAA mostly occur independently of each other. CAA significantly associated with cerebral atrophy in centenarians, supporting reports that CAA could independently contribute to cortical atrophy.[43]

Our analysis identified an amyloid and a tau factor. The amyloid factor supports the established association between levels of Aβ plaques, NPs, and CAA.[44] Despite being strongly correlated with CERAD-NP score, Braak-NFT stage loaded on the tau factors with Braak-LB stage (rare in centenarians) and Thal-GVD stage (high in all centenarians). Higher levels of intracellular NFTs and α-synuclein may associate with the formation of granulovacuolar bodies, neuronal lysosomal structures in which endocytic and specific cytosolic cargo accumulates.[45,46] While cerebrovascular disease and amyloid accumulation frequently co-occur in AD,[47] the amyloid or tau factors did not associate with the vascular factor, suggesting that they need not be mechanistically related. While amyloid-dependent vascular factors such as CAA are prevalent in the aging human brain, amyloid-independent factors such as cerebral atherosclerosis, cerebral small vessel disease, and microvascular degeneration also contribute to cerebral vascular disease.

Similar to younger individuals, Braak-NFT stage correlated most strongly with cognitive performance in the centenarians.[48,49] In contrast, Thal-Aβ phase varied widely across centenarians and did not associate with neuropsychological test performance, despite a significant association with Braak-NFT stage. Indeed, some centenarians showed the presence of NFTs in the absence of Aβ plaques: we observed eight cases with definitive and 30 with possible primary age-related tauopathy (PART),[50] which did not associate with MMSE. Our data suggest that the deposition of Aβ plaques may be a natural consequence of aging and not directly causative of functional decline in centenarians.[21,22,49]

A considerable fraction of Aβ deposits observed in elderly, including the centenarians investigated in this study (data not shown), are diffuse plaques (DPs),[20] consisting of a less toxic form of Aβ[49]. In contrast, NPs, as measured by CERAD-NP, include dendrites and axons with abnormal morphology, suggestive of degeneration at the synaptic junction.[10,51,52] Although the CERAD-NP score increases with age in cognitively healthy individuals, most centenarians resisted CERAD-NP scores beyond 2,[22] which may explain the lack of association with cognitive performance. Similarly, Thal-CAA stage rarely exceeds level 2 and also did not correlate with cognitive performance, also suggesting that these centenarians resisted building up higher levels. Furthermore, GVD bodies accumulated to the highest levels in centenarian brains, but GVD levels did not correlate with any neuropsychological test. This suggests that the formation of GVD bodies may not be specifically toxic.[53]

TDP-43, in the context of LATE, is a neuropathological substrate that contributes to changes in cognitive performance. TDP-43 stage correlated strongly with hippocampal sclerosis, and these both loaded onto the LATE factor. While LATE pathology is commonly observed in brains of patients with frontotemporal lobar degeneration and AD, its role in cognitive decline is unclear[17]. We found that TDP-43 correlated significantly with AF, which supports the notion that verbal fluency is affected in TDP-43-positive patients and less affected in individuals with AD pathology.[48,54] TDP-43 stage also associates with a lower performance on the CDT. We cannot infer any causality for this association or that the observed effects of TDP-43 and LATE pathology on cognitive performance should be replicated in larger studies.

Braak-NFT stage and TDP-43 stage significantly correlated with composite global cognition but not with MMSE, which may lack sensitivity.[55] Braak-NFT stage, TDP-43 stage, hippocampus sclerosis, and Braak-LB stage all significantly associated with performance on the CDT, which provides the first objective preliminary evidence that the CDT may be sensitive to critical levels of neuropathological changes. Previous reports indicated that the CDT had a high sensitivity and specificity for the diagnosis of early AD in younger individuals.[56] As a measure of global cognitive function,[57] the CDT assesses many cognitive skills, including short-term memory, understanding verbal instructions, spatial orientation, abstract thinking, planning, concentration, and executive and visuospatial skills.[58] Our data suggest that the CDT is sensitive for the detection of the early effects of accumulated neuropathology on cognition.[59] The MMSE was sensitive to detecting cerebral infarcts. The sensitivity of CDT and MMSE for neuropathology and cerebral infarcts will have to be replicated in other studies.[60]

Other studies of neuropathology in the oldest old also reported that levels of neuropathological substrates varied and that AD-related pathologies, including NFTs, NPs, and LATE pathology, correlated most strongly with cognitive performance.[24–27,61–65] Some studies also reported that some individuals were "resilient" to high levels of these pathologies,[24,26] and others observed a correlation between cerebral atrophy, cerebral infarcts, and/or LBs with cognitive performance.[25,61] In our sample, the effect of cerebral atrophy and NPs on cognitive performance is limited, likely because the centenarians in our study had lower levels of these neuropathologies following the inclusion criteria of self-reported cognitive health.

The availability of neuropsychological test performance measured shortly before brain donation[22] is unique for the 100-plus Study cohort, and this greatly contributes to the reliability of correlations between neuropathology burden. While a sample of 85 centenarian brains is large, it is relatively small for the identification of robust correlations. The sample is still growing, and follow-up analyses may allow some of the observed weaker associations to reach significance. A larger sample might also enable the detection of possible confounding and/or mediation effects.

The weak correlation between neuropathology and neuropsychology at extreme ages may have several underlying biological reasons. (1) With increasing age, AD-associated neuropathologies, such as Aβ deposits, NFTs, and NPs, may appear across brain regions, independently of disease-related processes. We speculate that the spread of age-related accumulation of neuropathologies across brain regions may be similar to the disease-related spread observed in AD patients, but the neuropathology loads per brain region may be lower in centenarians than in AD patients. To further investigate this, our future studies will focus on regional burdens of neuropathological substrates and their correlation with neuropsychological performance. (2) Coexisting neuropathological changes may lower the required burden of one neuropathological substrate to cause cognitive decline.[1,66] (3) Centenarians may recruit compensatory mechanisms translating to a resilience to the adverse effect of neuropathological substrates on the

survival of synapses and dendrites during the aging process.[67] (4) The accumulation of non-pathogenic neuropathological substrates might explain the observed "resilience" to presumed toxic neuropathologies in our study subjects. Indeed, the field is currently exploring potential pathogenicity differences within the diverse subtypes of neuropathological substrates.[49,50] We hypothesize that based on neuropathological substrate, a unique combination of these possible explanations will clarify the observed weakened correlation between neuropathology and neuropsychology at extreme ages.

We acknowledge that the inclusion criterion of self-reported cognitive health selects a unique subgroup of centenarians.[68] Approximately 75% of the centenarian population is demented,[68] and the cognitive performance of the remaining 25% ranges between non-demented to high performers. We estimate that at inclusion, the cognitive performance of the centenarians in our cohort is representative of the 10%–20% highest performers in the Dutch centenarian population. Nevertheless, during follow-up, some centenarians develop dementia-related symptoms (17.4% have MMSE < 20 at the last visit), making this group ideal for correlating cognition with observed pathological substrates. We previously found that, relative to middle-aged individuals, this group is enriched with genetic factors that associate with increased longevity[69] and depleted with genetic risk factors for AD, including the *APOE ε4* allele[70]. Therefore, we caution that correlations observed in this group may not be representative of the entire population.

5 | CONCLUSION

Within the highly variable levels of neuropathological substrates in centenarian brains, Braak-NFT stages and LATE pathology significantly correlated with cognitive performance as measured shortly before brain donation. We presented preliminary evidence that the performance on the CDT may be representative of higher burdens of these neuropathological substrates. To increase our understanding of the association between neuropathological burden and cognitive performance, we propose that future studies address the loads and subtypes, rather than distribution, of neuropathological substrates.

AUTHOR CONTRIBUTIONS

Andrea B. Ganz, Annemieke J. M. Rozemuller, Susan Rohde, and the Netherlands Brain Bank collected and performed the neuropathological characterization of the brain tissues donated to the 100-plus Study. Meng Zhang, Andrea B. Ganz, and Marc Hulsman performed data analysis. Meng Zhang, Andrea B. Ganz, Susan Rohde, Sietske A.M. Sikkes, Marc Hulsman, Jeroen J.M. Hoozemans, and Henne Holstege wrote the manuscript. Jeroen J.M. Hoozemans and Henne Holstege supervised the research. Philip Scheltens, Sietske A.M. Sikkes, 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.

ACKNOWLEDGMENTS

The authors thank and acknowledge all participating centenarians and their family members and the team who visited the centenarians over the years: Chandeny, Debbie, Elizabeth, Esther, Ilse, Karlijn, Kimberley, Kimja, Linda, Linette, Marieke, Nina, Sanne, Sterre, and Tjitske for collecting the neuropsychological data. Finally, this work would not have been possible without the great collaboration we have enjoyed with the wonderful staff of the Netherlands Brain Bank. This work was supported by BrightFocus A2021031S and Stichting VUmc Fonds. H.H. and M.J.T.R. are recipients of ABOARD, a public-private partnership receiving funding from ZonMW (73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; LSHM20106). H.H. was supported by the Hans und Ilse Breuer Stiftung (2020) and the HorstingStuit Foundation (2018).

CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC. Informed consent was obtained from all participants. Brain donors consented to brain donation. The study was conducted in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

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

How to cite this article: Zhang M, Ganz AB, Rohde S, et al. The correlation between neuropathology levels and cognitive performance in centenarians. *Alzheimer's Dement*. 2023;19:5036–5047. https://doi.org/10.1002/alz.13087