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RESEARCH ARTICLE

Longitudinal cognitive performance of Alzheimer's disease neuropathological subtypes

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Abstract

Introduction: Alzheimer's disease (AD) neuropathological subtypes (limbic predominant [lpAD], hippocampal sparing [HpSpAD], and typical [tAD]), defined by relative neurofibrillary tangle (NFT) burden in limbic and cortical regions, have not been studied in prospectively characterized epidemiological cohorts with robust cognitive assessments.

Methods: Two hundred ninety-two participants with neuropathologically confirmed AD from the Religious Orders Study and Memory and Aging Project were categorized by neuropathological subtype based on previously specified diagnostic criteria using quantitative regional NFT counts. Rates of cognitive decline were compared across subtypes using linear mixed-effects models that included subtype, time, and a subtype–time interaction as predictors and four cognitive domain factor scores (memory,

executive function, language, visuospatial) and a global score as outcomes. To assess if memory was relatively preserved in HpSpAD, non-memory factor scores were included as covariates in the mixed-effects model with memory as the outcome.

Results: There were 57 (20%) with lpAD, 22 (8%) with HpSpAD and 213 (73%) with tAD. LpAD died significantly later than the participants with tAD (2.4 years, $P = .01$) and with HpSpAD (3.8 years, $P = .03$). Compared to tAD, HpSpAD, but not lpAD, performed significantly worse in all cognitive domains at the time of initial impairment and declined significantly faster in memory, language, and globally. HpSpAD did not have relatively preserved memory performance at any time point.

Conclusion: The relative frequencies of AD neuropathological subtypes in an epidemiological sample were consistent with a previous report in a convenience sample. People with HpSpAD decline rapidly, but may not have a memory-sparing clinical syndrome. Cohort-specific differences in regional tau burden and comorbid neuropathology may explain the lack of clinicopathological correlation.

KEYWORDS

Alzheimer's disease, cognitive decline, cognitive trajectories, executive function, hippocampal sparing, language, limbic predominant, memory, Memory and Aging Project, neuropathological subtypes, Religious Orders Study, visuospatial function

1 | INTRODUCTION

Alzheimer's disease (AD) neuropathology is defined by the presence of extracellular amyloid beta (Aβ) plaques and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated paired helical filament tau (PHFtau) protein. In AD, the progressive neurofibrillary degeneration of limbic and cortical brain regions has been traditionally described by Braak staging,[1,2] where there is substantial involvement of the limbic structures, including the entorhinal cortex and hippocampus, prior to cortical involvement. More recently, it has been recognized that a subset of AD cases do not follow traditional Braak staging, instead demonstrating disproportionate involvement of the cortex with more limited involvement of the hippocampus.[3–6] Murray et al. formalized this distinction, describing three AD neuropathological subtypes based on the absolute and relative NFT burden in limbic and cortical brain regions: typical AD (tAD), limbic predominant AD (lpAD), and hippocampal-sparing AD (HpSpAD).[7] They found that HpSpAD had a younger age at onset, declined faster, and died younger, compared to tAD and lpAD. Compared to tAD and lpAD, HpSpAD more often had *ante mortem* clinical diagnoses usually associated with non-AD pathologies, including behavioral variant frontotemporal dementia, progressive non-fluent aphasia, semantic dementia, progressive supranuclear palsy, and Parkinson's disease dementia. Further, they estimated that HpSpAD and lpAD account for nearly 25% of neuropathologically confirmed AD cases.

In addition to neuropathological subtypes, atypical clinical subtypes of AD have also been described, including logopenic primary progressive aphasia (PPA), posterior cortical atrophy (PCA), corticobasal syndrome (CBS), and a dysexecutive/frontal variant.[8–11] These atypical clinical subtypes are defined based on differences in cognitive profiles compared to tAD and by definition demonstrate relatively preserved memory compared to other cognitive domains. Even among patients with tAD, there is marked variation in relative cognitive performance in non-memory domains compared to memory performance, although to a lesser extent than in atypical clinical AD phenotypes.[12] Further, there is longstanding clinicopathological and imaging evidence linking episodic memory to the hippocampus and related structures.[5,13–16] Despite this indirect evidence, there has been limited research directly linking AD neuropathological subtypes to neuropsychological trajectories. The Murray et al. study was based on analyses from a convenience sample biorepository with limited prospective clinical data (i.e., Mini-Mental State Examination [MMSE]; Clinical Dementia Rating [CDR]) and no uniform neuropsychological data.[7] Petersen et al. investigated cross-sectional neuropsychological performance near the time of death in a highly selected sample classified into AD neuropathological subtypes.[17] Further, because these studies were based on convenience samples, it is unclear if the observations generalize to the larger population of older adults. Here, we use the prospective Religious Orders Study (ROS) and the community-based prospective Rush Memory and Aging Project (MAP), both of which have robust longitudinal, prospective cognitive data and large autopsy samples, to address these questions. We used the Murray et al. criteria to identify tAD, lpAD, and HpSpAD subtypes. We also used memory, language, visuospatial, and executive function factor scores previously derived using an advanced psychometric approach.[18,19] We hypothesized that compared to the tAD, HpSpAD would have faster cognitive decline, but relatively better memory performance, and that lpAD would perform similarly to tAD.

2 | METHODS

2.1 | Participants

Participants were drawn from two different prospective clinicopathologic cohorts of aging and dementia established at the Rush University Alzheimer's Disease Center—ROS and MAP. ROS has enrolled Catholic nuns, priests, and brothers nationally ages 65 or older since 1994.[20–23] MAP has enrolled elderly individuals age 59 or older in northeastern Illinois since 1997.[23–25] Assessment procedures are the same across studies with a large common core of data, allowing the two studies to be pooled across most data points.[20,21,24] In both studies, which together will be referred to as ROSMAP, participants agreed to annual clinical assessment and cognitive testing, as well as brain donation. The autopsy rate is 86%, and participant follow-up exceeds 95% annually.[20] Detailed descriptions of ROSMAP can be found in previous publications.[20–26] Studies were approved by an Institutional Review Board of Rush University Medical Center and all participants signed documents indicating their informed consent, an Anatomical Gift Act, and a repository consent to share tissue.

Included in the present study are ROSMAP brain donors examined through October 2016 with pathological evidence of AD (i.e., National Institute on Aging [NIA] Reagan intermediate or high) and Braak NFT stage of V or VI, but without hippocampal sclerosis. The neuropathological inclusion criteria were chosen because they matched inclusion criteria from Murray et al.[7] Figure 1 shows an inclusion flowchart. Of the 3149 total ROSMAP participants at the time of these analyses, 1595 had died, 898 had neuropathologically confirmed AD, and 292 met the neuropathological inclusion criteria and had non-missing data. As shown in Figure 1, many of the people who had neuropathologically confirmed AD, but were not included, had a Braak stage of IV or less, to match the Murray et al. inclusion criteria.

2.2 | Neuropathological evaluation

Assessment procedures were uniform and included a structured assessment of common pathologies of aging. Brain tissue of deceased ROSMAP participants were autopsied at Rush University and other predetermined sites, and subsequently examined by neuropathologists at Rush. Brains were analyzed according to standard protocols aligned with accepted guidelines and reported previously.[21,22,24,25,27] NFTs were labeled with AT8, an antibody specific for PHFtau. Additionally, NFTs were quantified using unbiased stereological mapping generating a continuous count (per mm^2) in CA1/subiculum of the hippocampus, midfrontal cortex, inferior temporal cortex, and the inferior parietal lobule.[28,29] Hippocampal sclerosis was determined to be present or absent based on gliosis in CA1 and/or subiculum, and severe neuronal loss in the region.[30] Participants with hippocampal sclerosis were excluded from these analyses to mirror Murray et al. criteria.[7] See the supporting information for additional details of the neuropathologic examination.

HIGHLIGHTS

- Alzheimer's disease (AD) neuropathological subtypes were studied in epidemiological cohorts.
- Hippocampal-sparing AD (HpSpAD) performed worse in all cognitive domains at initial impairment.
- HpSpAD declined faster in global cognition, memory, and language.
- There is no evidence for relative sparing of memory performance in HpSpAD.

RESEARCH IN CONTEXT

1. Systematic review: A PubMed review showed that Alzheimer's disease (AD) neuropathological subtypes, defined by regional neurofibrillary tangle burden, had been examined in convenience samples with limited prospective cognitive measures, but not in epidemiological cohorts.
2. Interpretation: In two longitudinal clinicopathological cohorts, there were 57 (20%) with limbic predominant AD (lpAD), 22 (8%) with hippocampal-sparing AD (HpSpAD), and 213 (73%) with typical AD (tAD). Compared to tAD, HpSpAD, but not lpAD, performed worse in all cognitive domains at the time of initial impairment and declined faster in memory, language, and globally. HpSpAD did not have relatively preserved memory performance. Cohort-specific differences in regional tau burden and comorbid neuropathology may explain the lack of clinicopathological correlation.
3. Future directions: Development of cohort-independent definitions of AD neuropathological subtypes and more robust quantification of tau and other pathologies across additional brain regions may allow for better harmonization of clinical and neuropathological AD subtypes.

2.3 | Derivation of neuropathological subtypes

Criteria for three neuropathological subtypes of AD (i.e., HpSpAD, lpAD, and tAD) were adapted from Murray et al.[7] with minor changes due to differing study protocols as outlined below. To classify participants, we considered the ratio of the hippocampal quantitative NFT counts to that of the cortex to identify participants with relative sparing of either region. In ROSMAP, NFT counts were based on AT8 immunostaining rather than thioflavin-S fluorescence microscopy used by Murray et al.[7] In ROSMAP, the subiculum and CA1 of the hippocampus were considered together as a single region rather than being

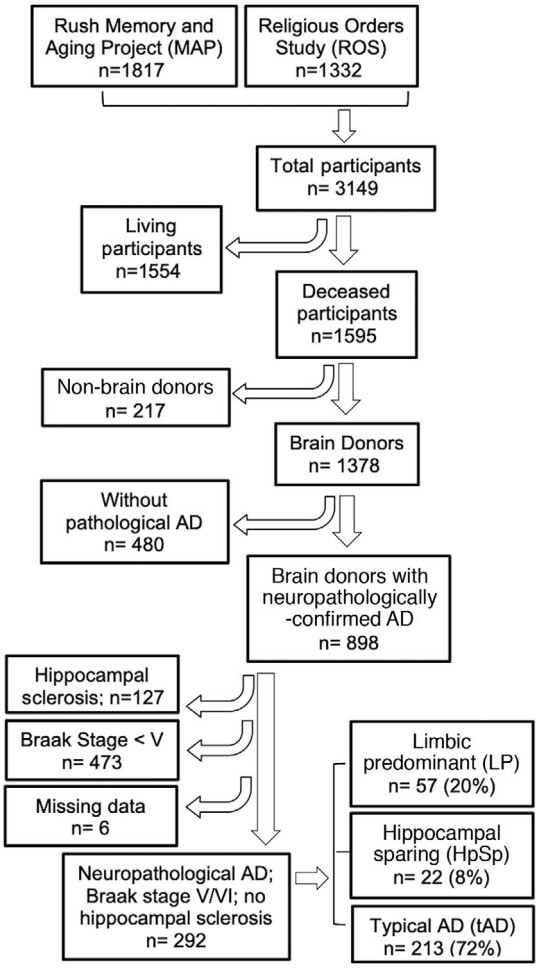

FIGURE 1 Inclusion/exclusion flowchart of participants. Individual patient data from two prospective studies of aging (Religious Orders Study and Rush Memory and Aging Project) were pooled. Inclusion/exclusion criteria were based on Murray et al.[7] Curved arrows indicate excluded participants. Brain donors with neuropathologically-confirmed Alzheimer's disease (National Institutes of Health-Reagan criteria) and Braak stage V or VI were included. Donors with hippocampal sclerosis were excluded

considered separately and averaged. Four cortical regions with NFT counts were considered in both studies: temporal cortex (superior temporal region for Murray et al.; inferior temporal gyrus for ROSMAP), inferior parietal lobule, middle frontal cortex, and the average of the three regions.[7]

2.3.1 | Hippocampal-sparing AD (HpSpAD)

Cases needed to meet the following three criteria: (1) The ratio of the hippocampal NFT counts to the average cortical NFT counts had to be less than the 25th percentile of all AD cases in the sample. (2) The hippocampal NFT counts had to be less than the median value. (3) At least three of the cortical NFT count measures had to be greater than or equal to the median values.[7]

2.3.2 | Limbic predominant AD (lpAD)

Cases needed to meet the following three criteria: (1) The ratio of the hippocampal NFT counts to the average cortical NFT counts had to be greater than the 75th percentile of all AD cases in the sample. (2) The hippocampal NFT counts had to be greater than the median value. (3) At least three of the cortical NFT counts measures had to be less than or equal to the median values.[7]

2.3.3 | Typical AD (tAD)

These were cases that met criteria for AD, but did not meet neuropathological criteria for either HpSpAD or lpAD.[7]

2.4 | Clinical evaluation

Participants underwent yearly visits from baseline until death to assess cognitive status.[20,21] The MMSE and a battery of tests of cognition[31] were administered annually. Diagnoses of no cognitive impairment, mild cognitive impairment (MCI), AD dementia, AD with other dementias, and non-AD dementia were made annually using algorithmic approaches shown to conform to standard approaches.[32] A final diagnosis of the clinical status prior to death was determined based on a review of all available data.

2.5 | Derivation of cognitive scores

Descriptions of cognitive score derivations have been published.[12,33] Briefly, among all participants with an AD dementia diagnosis, we used granular ("item-level") neuropsychological data from the first visit at which a dementia diagnosis was made. Each trial administered to a participant was deemed an "item." A panel of experts including two neuropsychologists and a behavioral neurologist (JM, ET, AJS) considered each item individually and designated it as primarily a measure of memory, executive functioning, language, visuospatial functioning, or none of these. We used modern psychometric methods to obtain scores for each of the four cognitive domains. Modern psychometric approaches have proven to have incrementally better validity data than scores derived from standard approaches.[12,18,19] We used Mplus 7.4[34] to fit confirmatory factor analysis bifactor models for each domain separately. We considered several approaches for specifying the bifactor model for each domain (see the supplemental materials of our previous work[33]) and chose the model with the best model fit. All scores were scaled to have a mean of 0 and a standard deviation (SD) of 1. The parameter specifications used to derive the scores at the time of dementia diagnosis were then used to obtain a factor score for each cognitive domain for each participant at all visits. Table S1 in supporting information shows items assigned to and the secondary structure for each cognitive domain.

2.6 | Statistical analyses

Unadjusted comparisons of demographic, clinical, and neuropathological characteristics between neuropathological subtypes were conducted using a Fisher's exact test for nominal variables and analysis of variance for continuous variables. When appropriate, post hoc tests were performed using Scheffe's method to control for multiple comparisons of continuous variables and Bonferroni correction for categorical variables.

We hypothesized that HpSpAD would demonstrate faster cognitive decline and built models to determine the relative rate of cognitive decline between subtypes. In five separate mixed-effects models with random slopes and intercepts, we tested the association of neuropathological subtype, time, and the subtype–time interaction with each of the four cognitive scores and their average (termed global cognition). In each model, tAD was considered the reference group. Time = 0 was specified as the time at which a diagnosis of any cognitive impairment (MCI+; i.e., either MCI or dementia) was first made (e.g., a visit 10 years prior to MCI+ was assigned a time of −10; a visit 10 years after MCI+ was assigned a time of +10). We chose this time schema to affix time to a clinical diagnosis. For this time schema to work, we excluded individuals who were never diagnosed with MCI+ (n = 13). Additional covariates in the models included age at MCI+, sex, education, and apolipoprotein E (*APOE*) genotype, defined as ≥ 1 ε4 alleles versus 0 ε4 alleles. We did not consider race because nearly all participants were White. In sensitivity analyses, we re-ran the models using LOESS (locally estimated scatterplot smoothing) regression to visually assess linearity because the rate of cognitive decline may not be constant over time. In additional sensitivity analyses, we considered other neuropathological measures (presence of limbic/neocortical Lewy bodies, moderate or severe transactive response DNA-binding protein of 43 kDa [TDP-43], moderate or severe arteriolosclerosis, moderate or severe atherosclerosis, moderate or severe cerebral amyloid angiopathy [CAA], presence of gross infarcts, and presence of microinfarcts) as covariates in our mixed effects models to test whether the relationship between AD subtype and cognitive trajectories were independent of comorbid pathology.

Next, we hypothesized that that HpSpAD would have more preserved memory performance relative to other cognitive domains compared to the other subtypes. We added the language, visuospatial, and executive function scores as covariates in the mixed-effects model with memory score as the outcome. This model allowed us to generate a predicted "relative" memory score and to test whether memory declined faster than the other domains across subtypes. A positive predicted "relative" memory score represents better memory performance than would be expected based on language, visuospatial, and executive function performance. Again, in sensitivity analyses, we repeated the LOESS regression to assess for linearity and considered the additional neuropathological measures as covariates in the mixed effects model. All models were run in Stata 16.[35]

3 | RESULTS

Table 1 outlines the demographic and diagnostic characteristics of the 292 included participants. Two hundred fifteen (74%) participants were women, mean age at first visit was 81.3 years (SD = 5.8), mean age at last visit was 88.3 years (SD = 5.8), and mean age at death was 89.9 years (SD = 5.6). The final diagnosis prior to death was dementia for 211 (72%) participants, MCI for 54 (18%) participants, and not cognitively impaired for 27 (9%) participants. The overall sample included 125 (43%) people with ≥ 1 *APOE* ε4 allele. Table S2 in supporting information shows demographic and clinical features of included and excluded neuropathologically confirmed AD cases in ROSMAP. Excluded participants were older at the time of MCI+ and dementia diagnoses, were less clinically impaired, and more frequently did not have an *APOE* ε4 allele. Table S3 in supporting information shows the median, interquartile range (IQR), and range of NFT counts across each region by AD neuropathologic subtype. It also shows the average cortical counts and the ratio of hippocampal to average cortical.

tAD was identified in 213 (73%) participants, lpAD was identified in 57 (20%) participants, and HpSpAD was identified in 22 (8%) participants. Although the omnibus test identified significant sex differences by subtype, post hoc subtype comparisons were non-significant after correction for multiple testing. Participants with lpAD died significantly later than the participants with tAD (2.4 years, $P = .01$) and with HpSpAD (3.8 years, $P = .03$). The frequency of clinical diagnosis (i.e., no cognitive impairment, MCI, AD dementia, AD with other dementias, and non-AD dementia) at the last visit did not significantly differ by subtype. There were no participants with HpSpAD with a final diagnosis of normal cognition, but that difference was not statistically different due to the small sample size (n = 22). The frequency of *APOE* ε4 allele carriers did not significantly differ by subtype.

Comorbid pathologies[36,37] were common with 73 (25%) participants with limbic/neocortical Lewy bodies, 120 (41%) participants with moderate to severe TDP-43, 103 (35%) participants with moderate to severe arteriolosclerosis, 100 (34%) participants with moderate to severe atherosclerosis, 169 (58%) participants with moderate to severe CAA, 94 (32%) participants with gross infarcts, and 83 (28%) participants with microinfarcts. The frequency of these pathologies did not significantly differ across subtypes (Table 2).

Mean number of visits was 7.7 (SD 4.1) for a total of 2235 annual visits. Table 3 shows mean MMSE, global cognition, and domain scores at first and last visits, and at time of MCI, MCI+, and dementia diagnoses across the three subtypes. In linear mixed-effects models adjusted for age at death, sex, education, and *APOE* ε4 status, HpSpAD performed significantly worse in global cognition, memory, visuospatial function, executive function, and language compared to tAD at the time of MCI+ diagnosis (Table 4). On average, performance was 0.88, 1.22, 0.52, 0.57, and 1.16 standardized units lower, respectively, for HpSpAD compared with tAD at the time of MCI+ diagnosis. lpAD and tAD did not significantly differ in global cognition, memory, visuospatial function, executive function, or language at the time of MCI+ diagnosis. Overall,

TABLE 1 Demographic and clinical features across subtypes, mean (SD, range) or n (%)

Characteristic	Limbic predominant (lpAD) n = 57 (20%)	Hippocampal-sparing (HpSpAD) n= 22 (8%)	Typical (tAD) n = 213 (73%)	Overall n = 292	P[d]
Female, n (%)	38 (67%)	12 (55%)	165 (77%)	215 (74%)	.03[e]
Age, mean (SD)					
At first visit	83.0 (5.1) (69.2–92.7)	82.4 (4.7) (73.3–92.2)	80.7 (6.0) (63.0–96.8)	81.3 (5.8) (63.0–96.8)	.02[f]
At first MCI diagnosis (n = 223[a])	85.0 (5.0) (70.1–92.9)	84.2 (4.3) (79.7–93.7)	82.8 (6.0) (66.0–98.2)	83.3 (5.8) (66.0–98.2)	.06
At first MCI+ diagnosis[b] (n = 279)	85.5 (5.4) (70.1–96.6)	83.8 (4.9) (73.3–93.7)	82.6 (6.0) (63.0–98.2)	83.2 (5.9) (63.0–98.2)	.005[f]
At dementia diagnosis (n = 212)	88.1 (5.7) (77.3–99.4)	84.7 (5.5) (73.3–94.6)	84.8 (6.2) (63.0–97.2)	85.4 (6.2) (63.0–99.4)	.006[f]
At last visit[c]	90.9 (5.2) (79.3–100.4)	87.5 (4.7) (80.5–97.0)	88.6 (5.9) (70.6–102.6)	88.9 (5.7) (70.6–102.6)	.01[f]
At death	92.0 (4.8) (80.3–101.2)	88.2 (4.8) (80.5–96.8)	89.6 (5.8) (70.6–102.6)	89.9 (5.6) (70.6–102.6)	.004[g]
Race, n (%)					1.0[h]
White	56 (98%)	22 (100%)	207 (97%)	285 (98%)	
Black	1 (2%)	0 (0%)	5 (2%)	6 (2%)	
Asian	0 (0%)	0 (0%)	1 (< 1%)	1 (< 1%)	
Years of education, mean (SD)	16.3 (3.9) (10–30)	15.6 (3.4) (12–23)	16.2 (3.6) (3–25)	16.1 (3.6) (3–30)	.77
First clinical diagnosis					.047
No impairment	32 (56%)	7 (32%)	94 (44%)	133 (46%)	
MCI	19 (33%)	6 (27%)	80 (38%)	105 (36%)	
AD dementia	6 (11%)	7 (32%)	37 (17%)	50 (17%)	
AD w/other dementia	0 (0%)	1 (5%)	1 (< 1%)	2 (1%)	
Non-AD dementia	0 (0%)	1 (5%)	1 (< 1%)	2 (1%)	
Last clinical diagnosis					.49
No impairment	6 (11%)	0 (0%)	21 (10%)	27 (9%)	
MCI	10 (18%)	6 (27%)	38 (18%)	54 (18%)	
AD dementia	35 (61%)	13 (60%)	138 (65%)	186 (64%)	
AD w/other dementia	5 (9%)	2 (9%)	14 (7%)	21 (7%)	
Non-AD dementia	1 (2%)	1 (5%)	2 (1%)	4 (1%)	
≥ 1 *APOE ε4* allele	23 (40%)	13 (59%)	89 (42%)	125 (43%)	.31

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.

[a]Participants who went from cognitively normal to dementia, skipping MCI, are not included in the mean age of MCI onset.

[b]MCI+ refers to either MCI or dementia.

[c]Last visit was first visit for n = 18.

[d]Analysis of variance or Fisher's exact test.

[e]Post hoc pairwise tests were non-significant after correction for multiple testing.

[f]Post hoc pairwise tests were significant for the lpAD–tAD comparison.

[g]Post hoc pairwise tests were significant for the lpAD–tAD and lpAD–HpSpAD comparisons.

[h]White versus any other race.

TABLE 2 Neuropathological features across subtypes, mean (SD) or n (%)

Characteristic	Limbic predominant	Hippocampal-sparing	Typical	Overall	P[b]
Brain weight (g), mean (SD)	1147 (121) (916–1444)	1140 (159) (891–1450)	1124 (131) (860–1547)	1130 (131) (860–1547)	.47
Limbic/neocortical Lewy bodies	19 (33%)	5 (23%)	49 (23%)	73 (25%)	.28
TDP-43[a]	19 (36%)	12 (67%)	89 (49%)	120 (48%)	.23
Braak VI	0 (0%)	1 (5%)	13 (6%)	14 (5%)	.15
Arteriolosclerosis[a]	23 (40%)	10 (45%)	70 (33%)	103 (35%)	.33
Atherosclerosis[a]	20 (35%)	11 (50%)	69 (32%)	100 (34%)	.27
CAA[a]	29 (51%)	16 (73%)	124 (58%)	169 (58%)	.22
Gross infarcts	18 (32%)	9 (41%)	67 (31%)	94 (32%)	.65
Microinfarcts	19 (33%)	7 (32%)	57 (27%)	83 (28%)	.53

Abbreviations: CAA, cerebral amyloid angiopathy; SD, standard deviation; TDP-43, transactive response DNA-binding protein of 43 kDa.
[a]Moderate or severe.
[b]Analysis of variance or Fisher exact test.

participants significantly declined in every cognitive domain as well as in global cognition over time (Figure 2). HpSpAD declined on average 0.11, 0.16, and 0.24 standardized units faster per year in global cognition, memory, and language, respectively, compared to tAD (Figure 2). There were no significant differences between lpAD and tAD for rate of decline in global cognition or any of the cognitive domains. Results remained similar in sensitivity analyses adjusted for seven pathological comorbidities (presence of limbic/neocortical Lewy bodies, moderate or severe TDP-43, moderate or severe arteriolosclerosis, moderate or severe atherosclerosis, moderate or severe CAA, presence of gross infarcts, and presence of microinfarcts; data not shown). In sensitivity analyses using LOESS regression, models appeared linear by visual assessment, and tests for three-way interactions among time, MCI+ status, and subtype were nonsignificant (data not shown).

The relative memory score is a measure of predicted memory performance relative to the other cognitive domains. It is derived by regressing the memory factor score on the other cognitive domain factor scores (i.e., visuospatial, executive functioning, and language) in a mixed effects model that also includes AD subtype, time, and the subtype–time interaction. Across all participants, memory performance declined significantly faster than would be predicted by the decline in the other cognitive domains. On average, memory declined 0.05 standardized units faster per year than predicted by the other cognitive domains. The relative memory score did not significantly differ between subtypes at the time of MCI+ diagnosis, and rates of decline of the relative memory score also did not differ between subtypes.

4 | DISCUSSION

In a community-based sample of 292 deceased brain donors with AD pathology from the ROS and MAP cohorts, the relative frequency of AD neuropathological subtypes (HpSpAD, lpAD, tAD) was consistent with a previous report in a convenience sample, with HpSpAD and lpAD making up nearly 30% of neuropathologically confirmed AD cases. Congruous with Murray et al.,[7] HpSpAD, in comparison to lpAD and tAD, was less frequent; had a younger age at death on average; and had a higher male-to-female ratio, though this difference was nonsignificant after correction for multiple testing. Contrary to previous findings, subtype differences in comorbid neuropathologies and *APOE* ε4 alleles were not identified.

This study also confirms and expands on previous studies that assessed longitudinal performance of AD neuropathological subtypes. Murray et al. showed that among 88 brain donors who had at least two MMSE scores, the difference between the first and last scores was larger for HpSpAD compared to tAD and lpAD. These data were only available in a small subset of the full study group in Murray et al.'s analyses (n = 889) and there was not uniform neuropsychological assessment to more comprehensively assess cognitive trajectories. Risacher et al. grouped living amyloid-positive Alzheimer's Disease Neuroimaging Initiative participants into analogous subtypes based on baseline hippocampal volume to cortical volume ratio measured on structural magnetic resonance imaging.[38] They found that among 100 participants with 2-year longitudinal data, people with HpSpAD declined faster than people with lpAD on the Alzheimer's Disease Assessment Scale, 13-Item Subscale (ADAS-Cog13), MMSE, and Functional Assessment Questionnaire and declined faster than tAD on the MMSE and CDR Sum of Boxes. Memory and executive scores did not significantly decline and neuropathology data were not available.[33,38] The current study expands on these studies by assessing cognitive domain–specific trajectories over a mean of 8 years in a larger sample of participants with neuropathologically defined AD subtypes. On average, over time, the full cohort demonstrated significant declines in memory, visuospatial, executive functioning, and language domains, as well as in global cognition. Compared to those having tAD, people with HpSpAD declined faster in memory, language, and global cognition and were more impaired at the time of MCI+ diagnosis in memory, language, executive function, visuospatial, and global cognition. Average rates of

TABLE 3 Cognitive scores across subtypes at various timepoints, mean (SD, range)

Cognitive scores over time	Limbic predominant (lpAD) n = 57 (20%)	Hippocampal-sparing (HpSpAD) n = 22 (8%)	Typical (tAD) n = 213 (73%)	Overall n = 292	P[a]
MMSE					
At first visit	27.0 (3.2) (14–30)	20.6 (9.7) (3–30)	26.3 (4.3) (0–30)	26.0 (5.0) (0–30)	<.001[b,c]
At MCI diagnosis (n = 223)	26.6 (2.3) (20–30)	25.3 (3.6) (17–30)	26.8 (2.6) (7–30)	26.7 (2.6) (7–30)	.15
At MCI+ diagnosis (n = 279)	25.5 (3.7) (12–30)	19.0 (9.2) (3–30)	25.6 (4.3) (0–30)	25.1 (5.0) (0–30)	<.001[b,c]
At dementia diagnosis (n = 212)	20.8 (4.7) (9–30)	15.7 (8.1) (3–30)	21.5 (5.3) (0–30)	20.8 (5.7) (0–30)	<.001[b,c]
At last visit	18.2 (8.5) (1–30)	11.7 (9.5) (0–26)	16.2 (9.1) (0–30)	16.3 (9.2) (0–30)	.02[b]
Global					
At first visit	1.4 (1.0) (−1.8–3.5)	0.2 (1.6) (−2.5–2.4)	1.2 (1.0) (−2.7–4.0)	1.1 (1.1) (−2.7–4.0)	<.001[b,c]
At MCI diagnosis (n = 223)	1.2 (0.6) (−0.1–2.4)	0.7 (0.4) (−0.1–1.4)	1.1 (0.7) (−2.1–2.7)	1.1 (0.7) (−2.1–2.7)	.10
At MCI+ diagnosis (n = 279)	0.9 (0.9) (−1.8–2.4)	−0.2 (1.3) (−2.5–1.4)	0.8 (0.8) (−2.7–2.7)	0.8 (0.9) (−2.7–2.7)	<.001[b,c]
At dementia diagnosis (n = 212)	0.0 (0.8) (−2.1–1.5)	−0.8 (1.1) (−2.5–1.0)	0.1 (0.8) (−2.7–1.9)	0.0 (0.8) (−2.7–1.9)	<.001[b,c]
At last visit	−0.3 (1.4) (−2.9–2.8)	−1.4 (1.1) (−2.8–0.4)	−0.6 (1.4) (−3.4–2.6)	−0.6 (1.4) (−3.4–2.8)	.007 [b,c]
Memory					
At first visit	1.5 (1.3) (−2.8–4.1)	0.0 (2.5) (−4.8–4.1)	1.4 (1.6) (−4.5–5.2)	1.3 (1.7) (−4.8–5.2)	<.001[b,c]
At MCI diagnosis (n = 223)	1.1 (1.1) (−1.3–3.5)	0.8 (1.0) (−1.2–2.4)	1.3 (1.2) (−3.8–4.5)	1.2 (1.2) (−3.8–4.5)	.40
At MCI+ diagnosis (n = 279)	0.9 (1.2) (−2.8–3.5)	−0.6 (2.2) (−4.8–2.4)	0.9 (1.4) (−4.5–4.5)	0.8 (1.5) (−4.8–4.5)	<.001[b,c]
At dementia diagnosis (n = 212)	−0.3 (1.0) (−2.8–1.4)	−1.3 (1.9) (−4.8–1.2)	−0.3 (1.2) (−4.5–2.5)	−0.4 (1.2) (−4.8–2.5)	.003[b,c]
At last visit	−1.1 (2.1) (−5.2–3.9)	−2.5 (2.1) (−4.9–0.8)	−1.4 (2.3) (−5.5–3.6)	−1.4 (2.2) (−5.5–3.9)	.04[b]
Visuospatial					
At first visit	1.1 (1.1) (−1.7–3.2)	0.5 (0.9) (−1.0–2.6)	1.0 (1.0) (−2.8–3.2)	1.0 (1.0) (−2.8–3.2)	.07
At MCI diagnosis (n = 223)	1.2 (1.0) (−0.3–3.2)	0.7 (0.7) (−0.1–1.9)	1.0 (1.0) (−2.9–3.2)	1.0 (1.0) (−2.9–3.2)	.17
At MCI+ diagnosis (n = 279)	1.0 (1.1) (−1.7–3.2)	0.4 (0.8) (−1.0–1.9)	0.8 (1.1) (−2.9–3.2)	0.8 (1.1) (−2.9–3.2)	.09
At dementia diagnosis (n = 212)	0.4 (1.1) (−3.2–2.8)	−0.1 (0.7) (−1.0–1.9)	0.2 (1.1) (−3.3–2.8)	0.2 (1.1) (−3.3–2.8)	.25
At last visit	0.7 (1.1) (−3.2–3.2)	0.1 (0.8) (−2.2–0.7)	0.5 (1.0) (−3.2–3.2)	0.5 (1.1) (−3.2–3.2)	.05
Executive functioning					
At first visit	1.3 (1.0) (−1.3–3.1)	0.5 (1.1) (−1.3–2.7)	1.3 (0.9) (−1.5–3.8)	1.2 (1.0) (−1.5–3.8)	<.001[b,c]
At MCI diagnosis (n = 223)	1.2 (0.7) (−0.6–2.9)	0.8 (0.5) (0.0–1.3)	1.0 (0.8) (−1.7–3.6)	1.0 (0.8) (−1.7–3.6)	.17

(Continues)

TABLE 3 (Continued)

Cognitive scores over time	Limbic predominant (lpAD) n = 57 (20%)	Hippocampal-sparing (HpSpAD) n = 22 (8%)	Typical (tAD) n = 213 (73%)	Overall n = 292	P[a]
At MCI+ diagnosis (n = 279)	1.0 (1.0) (−1.9–2.9)	0.3 (0.9) (−1.3–1.8)	0.9 (0.9) (−1.5–3.6)	0.9 (0.9) (−1.9–3.6)	.002[b,c]
At dementia diagnosis (n = 212)	0.5 (1.2) (−1.9–2.4)	−0.1 (0.9) (−1.3–1.8)	0.8 (1.0) (−1.7–3.1)	0.7 (1.1) (−1.9–3.1)	.004[c]
At last visit	0.1 (1.1) (−1.9–2.5)	−0.4 (0.9) (−1.4–2.1)	−0.1 (1.0) (−2.4–2.7)	−0.1 (1.0) (−2.4–2.7)	.20
Language					
At first visit	1.4 (1.6) (−2.5–4.8)	−0.1 (2.5) (−4.7–4.0)	1.1 (1.6) (−5.3–4.8)	1.1 (1.7) (−5.3–4.8)	.001[b,c]
At MCI diagnosis (n = 223)	1.1 (1.2) (−1.6–3.5)	0.5 (0.9) (−0.5–2.7)	1.1 (1.2) (−3.6–4.8)	1.1 (1.2) (−3.6–4.8)	.27
At MCI+ diagnosis (n = 279)	0.8 (1.4) (−2.5–3.6)	−1.0 (2.0) (−4.7–2.7)	0.8 (1.4) (−5.3–4.8)	0.6 (1.5) (−5.3–4.8)	<.001[b,c]
At dementia diagnosis (n = 212)	−0.7 (0.9) (−2.5–0.7)	−1.6 (1.7) (−4.7–0.9)	−0.4 (1.2) (−5.3–1.5)	−0.6 (1.2) (−5.3–1.5)	<.001[b,c]
At last visit	−1.0 (2.3) (−5.7–3.4)	−2.8 (2.1) (−6.1–1.0)	−1.5 (2.3) (−6.5–3.5)	−1.5 (2.3) (−6.5–3.5)	.007[b,c]

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
Notes: MCI+ refers to either MCI or dementia.
Participants who went from cognitively normal to dementia, skipping MCI, are not included in scores at MCI diagnosis, but they are included in scores for MCI+ diagnosis.
[a]Based on analysis of variance.
[b]Post hoc pairwise tests were significant for the lpAD–HpSpAD comparisons.
[c]Post hoc pairwise tests were significant for the tAD–HpSpAD comparisons.

TABLE 4 Estimated cognitive scores[a] and time[b] (95% confidence interval), compared to typical AD, mixed effects models[c,d]

Term	Global	Memory	Visuospatial	Executive functioning	Language	Relative memory[e]
Limbic predominant	0.06 (−0.19, 0.31)	−0.02 (−0.39, 0.42)	0.08 (−0.15, 0.32)	0.03 (−0.18, 0.25)	0.08 (−0.32, 0.49)	−0.04 (−0.28, 0.19)
Hippocampal-sparing	−0.88 (−1.26,−0.50)	−1.22 (−1.82,−0.62)	−0.52 (−0.88–0.16)	−0.57 (−0.89,−0.24)	−1.16 (−1.77,−0.56)	−0.06 (−0.41, 0.30)
Time	−0.29 (−0.31,−0.26)	−0.45 (−0.49,−0.41)	−0.07 (−0.09, −0.05)	−0.19 (−0.21,−0.17)	−0.39 (−0.43,−0.35)	−0.04 (−0.06,−0.02)
Limbic predominant x time	0.02 (−0.03, 0.07)	0.05 (−0.04, 0.13)	0.00 (−0.03, 0.03)	0.00 (−0.04, 0.04)	0.04 (−0.05, 0.13)	0.01 (−0.04, 0.05)
Hippocampal-sparing x time	−0.11 (−0.20,−0.02)	−0.16 (−0.29,−0.02)	−0.05 (−0.12, 0.02)	−0.03 (−0.10, 0.04)	−0.24 (−0.39,- −0.09)	0.01 (−0.07, 0.08)

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; MCI, mild cognitive impairment.
[a]Scores are in standard units.
[b]Time is years from MCI+ diagnosis, with positive values occurring after MCI+ diagnosis.
[c]Adjusted for age at death, sex, years of education, and presence of an *APOE* ε4 allele.
[d]N = 277 for these models rather than 279 because *APOE* genotype was missing for two participants.
[e]Derived by adding visuospatial, executive functioning, and language scores as covariates to the model with memory score as the outcome.

decline for people with lpAD and people with tAD were similar across cognitive domains and globally and these subtypes did not significantly differ in any of the cognitive domains at the time of MCI+ diagnosis.

We had hypothesized that HpSpAD would have preserved memory performance relative to other cognitive domains compared to the other subtypes. We assessed this by regressing memory performance on each of the other cognitive domain scores and using the predicted "relative" memory score as a measure of how much better or worse memory performance was relative to the other cognitive domains. On average, across the cohort, memory declined faster than the other

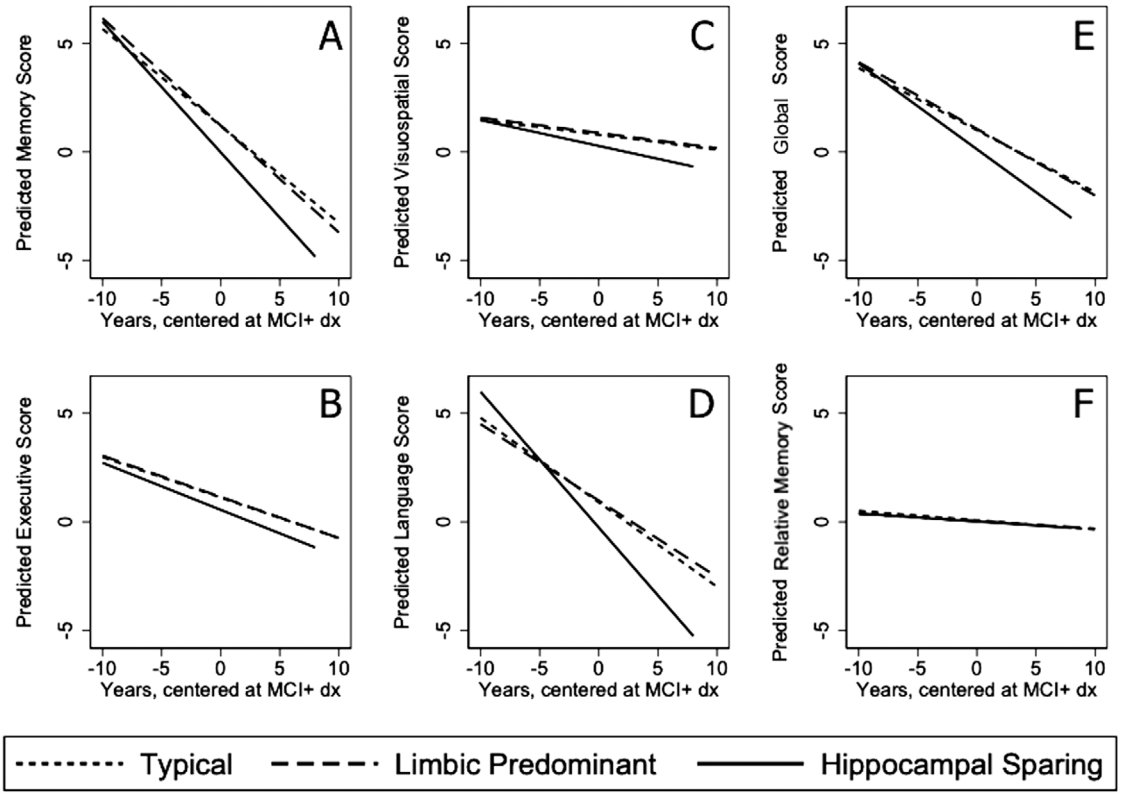

FIGURE 2 Predicted cognitive scores over time of Alzheimer's disease neuropathological subtypes. Predicted scores were obtained from five mixed-effects models with neuropathological subtype, time in years (with t = 0 at time of mild cognitive impairment [MCI+] diagnosis), and the subtype–time interaction as predictors and the four cognitive scores (A-D) and their average (global cognition) (E) as outcomes; Typical Alzheimer's disease (tAD) was the reference group. Overall, participants significantly declined in each cognitive domain and globally over time. Limbic predominant (lpAD) and tAD subtypes did not significantly differ at the time of MCI+ diagnosis or in the rate of decline in each of the cognitive domains or globally. Hippocampal-sparing AD (HpSpAD) was significantly more impaired at the time of MCI+ diagnosis than tAD in memory (A), executive function (B), visuospatial function (C), language (D), and globally (E). HpSpAD declined significantly faster than tAD in memory (A), language (D), and globally (E), but not in executive function (B) or visuospatial function (C). An additional mixed-effects model (F) added language, visuospatial, and executive function scores as covariates to the model with memory as the outcome (relative memory model). Across all subtypes, memory performance declined significantly faster than would be predicted by the decline in the other domains. No significant differences were observed in the relative memory score between subtypes at the time of MCI+ diagnosis or over time

cognitive domains. Contrary to our hypothesis, across subtypes, the relative memory score did not differ at the time of MCI+ diagnosis and the rate of decline of the relative memory score did not differ. Together, these results imply that, on average, over the course of the study, there was not a time when participants with HpSpAD had disproportionate sparing of memory performance relative to performance in other domains. Our hypothesis was based on longstanding clinicopathological and imaging evidence linking episodic memory to the hippocampus.[14,16,39] There is also substantial evidence showing correlations between clinical subtypes of atypical AD and different anatomic distributions of PHFtau pathology in the brain both from neuropathological assessment and from tau positron emission tomography scans.[5,17,38–40] For instance, PHFtau pathology is disproportionately found in inferior parietal and superior temporal cortices in logopenic PPA and disproportionately found in the posterior parietal and occipital cortices in PCA.[8] Compared to the current study, most of these past studies were conducted in clinic-based samples composed of younger individuals with atypical presentations at the phenotypic extremes. In contrast, ROSMAP participants are older and sampled from the community.

Compared to these other studies, the older age of ROSMAP participants may have had several implications. Both HpSpAD and atypical clinical AD subtypes tend to have a younger age at onset than the other corresponding neuropathological and clinical subtypes.[41–43] Similarly, NFT density in the neocortex and the NFT distribution in association cortices relative to hippocampal structures tend to be greater among people who develop AD at younger ages.[44] Consistently, in our sample, compared to Murray et al., there were fewer participants with HpSpAD (8% vs. 11%) and more with lpAD (20% vs. 14%). Additionally, because the algorithm to derive neuropathological subtypes is a function of the regional NFT counts median and IQR of the sample being studied, the absolute and relative regional density required to meet criteria for a given subtype may vary by study. Indeed, we observed markedly more NFTs in the hippocampus compared to Murray et al., but counts in the cortical regions were similar across studies. The additional pathology in the hippocampus may be responsible for memory not being relatively

preserved in HpSpAD. This limitation of the criteria also complicates cross-cohort comparisons and the generalizability of findings beyond any given cohort studied.

The older age of ROSMAP compared to other studies of AD neuropathological subtypes also likely led to higher proportions of comorbid pathology. It is possible that their high rates of comorbid pathology confounded the regional effects of the PHFtau pathology on cognitive performance. For instance, HpSpAD had a higher proportion (albeit non-significant) of concomitant moderate to severe TDP-43 pathology (67%) compared to tAD (49%) and HpSpAD (36%). TDP-43 pathology distributes around limbic regions and is associated with memory impairment.[45] Among participants with HpSpAD, those with TDP-43 had more impaired memory (albeit non-significant) compared to those without TDP-43 (Table S3). This may explain the prominent memory deficits in the HpSpAD group. Similarly, lpAD had a higher frequency (albeit non-significant) of comorbid Lewy body disease (LBD; 33%) compared to tAD (23%) and HpSpAD (23%). LBD is associated with visuospatial and executive impairment[46,47] and may have similarly confounded group differences in cognition. Although we did adjust for comorbid pathologies in our mixed effects models, the measures of comorbid pathologies were global rather than regional.

An alternative explanation for the lack of clinicopathologic correlation in the neuropathological subtypes may relate to insufficient attention to regional cortical burden. Although the relative burden of PHFtau pathology in the hippocampus versus the cortex is considered in the definition, the distribution of pathology across the cortex is not considered. Including regional cortical burden in neuropathological subtyping may improve clinicopathological correlation with respect to relative cognitive domain performance. Indeed, the non-memory cognitive domain most disproportionately affected in HpSpAD (language) can be localized to two (inferior temporal, inferior parietal) of the three cortical regions used in the algorithm to derive subtypes. Interestingly, Petersen et al. recently proposed an alternative hierarchical clustering approach to neuropathological AD subtyping and showed in their clinic-based sample enriched for atypical subtypes, the alternative approach correlated better with clinical indicators than the Murray et al. approach.[7,17] Both approaches only use three cortical regions; sampling of more cortical regions may improve correlation with cognitive performance.

Another explanation for the lack of clinicopathologic correlation in the neuropathological subtypes may relate to the test items that contribute to the cognitive factor score. Although these items were assigned to the memory domain by expert clinicians and were subsequently shown to better correlate with each other than with items in other domains, the memory domain items nonetheless assess multiple types of memory, including verbal episodic encoding, retrieval, and recognition. Considering these memory subtypes separately may result in better clinicopathological correlation. A similar rationale could be made for subtypes of the other cognitive domains.

The study has several strengths. To our knowledge, this is the first time cases of neuropathologically confirmed AD from a community-based study were neuropathologically subtyped using rich quantitative measures of PHFtau pathology across multiple brain regions. Brain donors were administered a full, prospective, neuropsychological battery, the items from which were used to derive psychometrically sound domain-specific scores. A limitation of the study was the sample size, at least relative to Murray et al., in which AD neuropathological subtypes were first described. Although 1378 ROSMAP participants had come to autopsy, only 292 met inclusion criteria as proposed in Murray et al. With the intent of replicating the subtyping procedures of Murray et al., we limited inclusion to NIA Reagan intermediate or high probability of AD, a Braak stage of V or VI, and no evidence of hippocampal sclerosis. Although these inclusion/exclusion criteria were necessary for replicating the Murray et al. approach, we nonetheless excluded 67.5% of participants who met NIA Reagan criteria for AD and 100% who had co-occurring AD and hippocampal sclerosis. Not surprisingly, these excluded participants with lower Braak scores who were less cognitively impaired. For improved generalizability, subtyping would not exclude these participants. Additionally, due to the sample size, we were unable to limit analyses to participants with incident cognitive impairment. For instance, there were only seven participants with HpSpAD with incident impairment. Differences in the frequencies of incident and prevalent cases across subtypes may have contributed to the consistently lower cognitive scores in HpSpAD, as well as other observed differences. An additional limitation is the minor differences in neuropathological assessment compared to Murray et al. By combining CA1 and subiculum into a single region in our study, the criteria for HpSpAD and LpAD became marginally more permissive. This may explain the marginally smaller frequency of tAD seen in our study compared to Murray et al (73% vs. 75%). Additionally, tau burden in the subiculum has been more clearly linked with an amnestic syndrome than in CA1[17] and combining the regions may have diluted the measured relationships with memory function. The use of AT8 immunostaining compared to thioflavin-S in Murray et al. may have also introduced differences in NFT tangle quantification. Thioflavin-S detects mostly mature tangles and ghost tangles, while AT8 primarily detects earlier NFT maturity levels.[48] Additionally, ROSMAP does not code diagnoses of atypical AD syndromes including logopenic PPA, PCA, CBS, or a dysexecutive/frontal variant so we could not report the frequencies of these diagnoses in the sample.

5 | CONCLUSION

In this community-based study of neuropathologically confirmed cases of AD, we identified similar frequencies of AD neuropathological subtypes (lpAD, tAD, HpSpAD) as described previously in a large convenience sample. People with HpSpAD declined faster across multiple cognitive domains and globally than people with tAD or lpAD. However, no differences in relative memory performance were identified across subtypes. Cohort-specific differences in regional tau burden and comorbid neuropathology may explain the lack of clinicopathological correlation. Effectively defining and characterizing AD subtypes may aid in prognosis, enrollment in clinical trials, and ultimately the development of a personalized medicine approach to AD.

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CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to report.

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SUPPORTING INFORMATION

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