

RESEARCH ARTICLE

Late-life cognitive decline is associated with hippocampal volume, above and beyond its associations with traditional neuropathologic indices

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Abstract

Introduction: Reduced hippocampal volume is associated with late-life cognitive decline, but prior studies have not determined whether this association persists after accounting for Alzheimer's disease (AD) and other neuropathologies.

Methods: Participants were 531 deceased older adults from community-based cohort studies of aging who had undergone annual cognitive evaluations. At death, brain tissue underwent neuropathologic examination and magnetic resonance imaging (MRI). Linear mixed models examined whether hippocampal volume measured via MRI accounted for variation in decline rate of global cognition and five cognitive domains, above and beyond neuropathologic indices.

Results: Demographics and indices of AD, cerebrovascular disease, Lewy body disease, hippocampal sclerosis, TDP-43, and atherosclerosis accounted for 42.6% of the variation in global cognitive decline. Hippocampal volume accounted for an additional 5.4% of this variation and made similar contributions in four of the five cognitive domains.

Discussion: Hippocampal volume is associated with late-life cognitive decline, above and beyond contributions from common neuropathologic indices.

KEYWORDS

Alzheimer's disease, atrophy, hippocampal sclerosis, older adults, TDP-43

1 | INTRODUCTION

Cognitive decline is a common, costly, and feared consequence of aging.^{1,2} However, individuals deteriorate at markedly different rates, with some declining precipitously, others remaining relatively stable until death, and many falling somewhere between those extremes.^{3,4} Although much of this variation can be accounted for by histopathologic indices of the known drivers of dementia including Alzheimer's disease (AD), cerebrovascular disease, and Lewy body disease (LBD), about half remains unexplained by common neuropathologic indices.³ Identifying other neurobiologic factors that contribute to this unexplained variation in the rate of cognitive decline is crucial to the development of additional interventional strategies that may

effectively delay the onset of late-life cognitive decline or slow its progression.

Brain volumetric measures represent one such avenue for investigation beyond neuropathologic indices derived via histopathology.⁴ Because they are readily available via MRI, these measures provide a potentially important *in vivo* window to the neuropathology that led to brain atrophy. Atrophy is a common correlate of several forms of dementia,⁵⁻⁷ suggesting that it reflects non-specific neuronal loss resulting from a variety of upstream causes, including AD and other known neuropathologies,⁸⁻¹⁰ but also perhaps from other pathologies that have yet to be identified or well quantified. Hippocampal volume in particular has been tied to decline in multiple cognitive domains including episodic, semantic, working memory, and visuospatial

ability.¹¹⁻¹³ These associations between hippocampal volume and cognitive decline are often attributed to underlying AD pathology, particularly neurofibrillary tangles.¹⁴ However, clinical-pathologic data are needed to clarify these relationships; prior studies have not determined whether hippocampal volume's association with cognitive decline persists after accounting for AD and other commonly quantified pathologies.

We approached this question by analyzing postmortem MRI and histopathologic data from 531 participants in two clinicopathologic studies of aging. Participants underwent detailed annual cognitive evaluations over many years before death, providing an estimate of their longitudinal decline trajectory. Via a series of linear mixed models, we quantified the degree to which hippocampal volume derived from MRI accounted for variation in the decline rate of global cognition and five individual cognitive domains, beyond the contributions of common neurodegenerative and vascular pathologic indices as well as total cerebral volume.

2 | METHODS

2.1 | Participants

Participants were drawn from two clinicopathologic studies of aging, the Rush Memory and Aging Project (MAP) and the Religious Orders Study (ROS).¹⁵ MAP and ROS enrollees provided written informed consent to annual interviews, including detailed cognitive evaluations, and organ donation at death, in accordance with protocols approved by the Rush University Institutional Review Board. These procedures have been harmonized between MAP and ROS to allow pooling of their data in analyses. To be included in this study, participants were required to have at least two annual cognitive evaluations, autopsy data, and post-mortem brain MRI. At the time of our analyses in November of 2018, a total of 3485 participants had completed baseline testing (2037 in MAP and 1448 in ROS). Since the inception of postmortem MRI in MAP and ROS in October 2006, 1212 participants died and 87% (1054) of those cases came to autopsy, 671 of which underwent postmortem brain MRI. Quality control and post-processing had been performed on the first 552 of these, and we further excluded 21 participants who had only undergone one cognitive exam prior, leaving a sample of 531.

2.2 | Cognitive evaluation and clinical diagnosis

Trained study staff administered a battery of cognitive tests at annual study visits in MAP and ROS. The Mini-Mental State Exam (MMSE) was used for descriptive purposes only. As described previously, a composite score of global cognition was computed based on z-scores from 17 other tests that are common to both studies.¹⁶ Scores representing performance in five cognitive domains were computed based on subsets of the 17 tests defined in previous work.¹⁶ Clinical classification

RESEARCH IN CONTEXT

1. Systematic review: The authors searched for studies on the relation between human hippocampal volume and late-life cognition using PubMed and Google Scholar. Although associations between hippocampal volume and cognition are well established, fewer studies investigated longitudinal trajectories of decline, and very few controlled for neuropathology.
2. Interpretation: Our findings show that the association of hippocampal volume with late-life decline in global cognition and multiple cognitive domains persists after controlling for a broad range of neurodegenerative and vascular brain pathologies, including Alzheimer's disease (AD) pathology. Decline is more strongly associated with hippocampal volume than cerebral hemisphere volume.
3. Future directions: Because hippocampal volume accounts for variation in cognitive decline rate beyond traditional neuropathologic indices, future work should investigate the additional factors that influence cognitive abilities by way of a reduction to hippocampal volume. Candidate factors include additional neuropathologies not accounted for here and person-to-person differences in the rates hippocampal neurogenesis throughout life.

of dementia and cognitive impairment was carried out via a three-step process implemented at the inception of MAP and ROS. In the first step, computerized scoring of 11 of the cognitive tests generated impairment ratings in five cognitive domains.^{15,17} Next, a neuropsychologist reviewed these computer-generated ratings and rendered a judgment on impairment in light of cognitive data, education, sensorimotor function, and motivation, but blinded to all other data. In the final step, an experienced clinician reviewed the cognitive data, neuropsychologist's impairment ratings, medical history, and results of neurologic examination, and rendered a decision on whether dementia was present and its likely cause. Clinical diagnosis of Alzheimer's dementia was based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).^{17,18} These criteria are consistent with our previous work as well as with most other research on the clinical syndrome of Alzheimer's dementia. They include a history of cognitive decline with impairment in memory and at least one other cognitive domain. Cases of cognitive impairment not meeting the criteria for dementia were classified as mild cognitive impairment (MCI).^{15,18} At death, all available clinical data were reviewed by a board-certified neurologist who rendered a summary diagnostic opinion of the most likely clinical diagnosis at the time of death.¹⁹

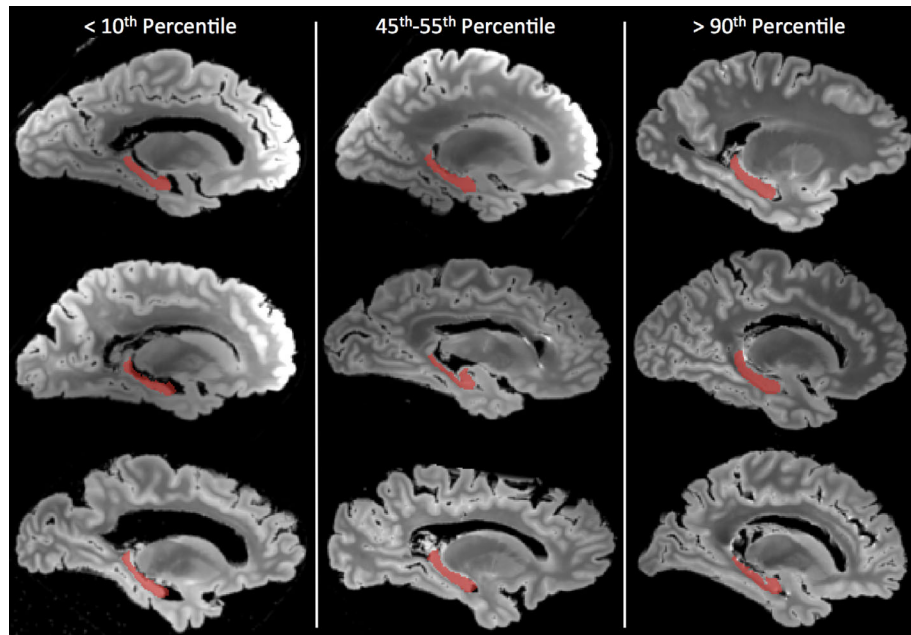


FIGURE 1 Representative hippocampal segmentations (red) overlaid on sagittal slices of the shortest echo time image from a fast spin-echo MRI pulse sequence carried out postmortem. Three ranges are represented: hippocampi with volume below the 10th percentile are shown in the left column, those between the 45th and 55th percentile in the middle column, and those above the 90th percentile in the right column. For each range, three cases were randomly selected for display

2.3 | Postmortem brain MRI and volumetric measures

Upon death of a participant, the brain was removed and hemisected during rapid autopsy using previously described techniques. One cerebral hemisphere was immersed in 4% paraformaldehyde solution and refrigerated at 4°C in preparation for imaging and neuropathologic evaluation.¹⁵ The other hemisphere was frozen in preparation for alternative processing, including genomic and proteomic techniques. At ≈ 30 days postmortem, this specimen was warmed to room temperature and imaged in a 3-Tesla MRI scanner using techniques and pulse sequences described previously.^{20,21}

In the current study, we used images derived from a multi-spin echo sequence to compute the transverse relaxation rate constant (R_2 , the multiplicative inverse of T_2) for each voxel, as described previously.²² Images from the shortest echo time were spatially registered to a previously developed postmortem cerebral hemisphere template, using affine followed by nonlinear transformations obtained with the “flirt” tool²³ of the FMRIB Software Library and the Automated Registration Toolbox,²⁴ respectively.²¹ We produced a three-dimensional hippocampus mask based on this template by manually outlining the hippocampal formation in consecutive sagittal slices of the template, while referencing the axial and coronal planes to confirm key landmark positions, similar to our previously described techniques.²⁵ In the same manner, we produced three-dimensional masks of the amygdala, thalamus, caudate, putamen, globus pallidus, and nucleus accumbens.²⁶ We also produced a whole-hemisphere mask, which included any voxel containing a non-zero intensity in the template. These masks were back-transformed from template space into the original space of each individual brain

image by applying the inverted forms of the affine and nonlinear transformations for each hemisphere, which were concatenated into a single transformation. We eliminated non-tissue-containing voxels and calculated the resultant volume of each back-transformed mask (Figure 1). We did not normalize any of the regional volumes by total hemisphere volume because the latter is influenced to an unknown degree by generalized atrophy and could, therefore, interfere with the study’s goal of exploring the relationship between hippocampal volume and cognitive decline, beyond the effects stemming from generalized atrophy. Total intracranial volumes may be more appropriate for regional volume normalization, but these were not available from postmortem MRI.

2.4 | Neuropathologic indices

Following postmortem MRI, the cerebral hemisphere was sliced coronally into 1-cm thick slabs, which underwent further sectioning and staining to facilitate collection of common age-related pathologic indices. Global AD pathology burden was quantified by averaging the scaled counts of neuritic and diffuse plaques and neurofibrillary tangles derived from a 1-mm² area of greatest density on silver-stained 6- μ m sections from the hippocampus and four cortical regions.¹⁵ Visually identified chronic gross infarcts on any of the slabs were noted and coded as present upon histologic confirmation.^{27,28} Similarly, chronic microinfarcts were coded as present if they were identified on hematoxylin and eosin (H&E)-stained 6- μ m sections from at least nine regions including hippocampus, five cortical regions, basal ganglia, thalamus, or midbrain.²⁷ Lewy bodies were coded as present if they

were identified using antibodies to α -synuclein on 6- μ m sections from the hippocampus or any of six cortical regions.²⁹ Hippocampal sclerosis marked by severe neuronal loss and gliosis identified on H&E-stained sections in CA1 or the subiculum was graded as present or absent.³⁰ TDP-43 pathology was semi-quantitatively graded based on immunostaining of six 6- μ m sections using antibodies to a phosphorylated monoclonal TAR5P-1D3 (pS409/410; 1:100, Ascenion, Munich, Germany), with four stages corresponding to absent (stage 0), restricted to amygdala only (stage 1), extending also to the CA1 or dentate of the hippocampus or entorhinal cortex (stage 2), or further extending to midfrontal or midtemporal neocortical regions (stage 3).^{30,31} Cerebral atherosclerosis was graded on a semi-quantitative scale (none, mild, moderate, and severe) based on the number of vessels in the circle of Willis that were affected and the severity of their occlusion.³² Arteriolosclerosis was graded on a similar four-level scale based on histologic changes in arterioles of the anterior basal ganglia.³³ Cerebral amyloid angiopathy (CAA) was also scored semi-quantitatively on a four-level scale based on β -amyloid deposition in meningeal and parenchymal vessels as observed in sections from four neocortical regions immunostained using 4G8 (1:9000; Covance Labs, Madison, WI), 6F/3D (1:50; Dako North America Inc., Carpinteria, CA), or 10D5 (1:600; Elan Pharmaceuticals, San Francisco, CA).³⁴ A board-certified neuropathologist reviewed all pathology findings.

2.5 | Statistical analyses

We first employed a linear mixed model to quantify the heterogeneity among study participants in terms of the total variation in rates of global cognitive decline. All data points from every participant were analyzed simultaneously such that the sample-wide average rate of decline was estimated, with person-specific factors capturing individual's deviations above or below this typical rate, as described previously.²² We then expanded the model sequentially to include terms for demographics (age, sex, education), nine neuropathologic indices, hippocampal volume, total hemisphere volume, and each of six other brain region volumes from postmortem MRI. Accompanying terms for each factor's interaction with the time variable were also included. After each stepwise addition of terms to the model, we again assessed the total variation in rate of global cognitive decline, quantifying the reduction relative to previous models as a percentage. Using this procedure, we inferred the contribution of each variable or set of variables to variation in cognitive decline, beyond that attributable to terms in the previous models. We repeated this procedure for each of five cognitive domains.

3 | RESULTS

3.1 | Descriptive data

As shown in Table 1, about two-thirds of the 531-person sample were MAP participants (62.7%), with the remainder coming from ROS. Most

TABLE 1 Demographic, cognitive, and pathologic characteristics of participants

Variable	Mean (SD) or N (%)
Total participants	531
MAP	333 (62.7%)
ROS	198 (37.3%)
Demographic	
Age at baseline (years)	80.4 (6.7)
Age at death (years)	90.4 (6.0)
Female	378 (71.2%)
Education (years)	15.8 (3.6)
White, non-Hispanic	522 (98.3%)
Clinical diagnosis	
Cognitive impairment at baseline	
Mild cognitive impairment	141 (26.6%)
Alzheimer's dementia	31 (5.8%)
Cognitive impairment at death	
Mild cognitive impairment	138 (26.0%)
Alzheimer's dementia	223 (42.0%)
Cognitive	
Number of annual cognitive evaluations	9.3 (4.7)
MMSE, baseline (score of 30)	27.7 (2.8)
MMSE, proximate to death	20.3 (9.3)
Global cognition, baseline (composite of 17 z-scores)	-0.1 (0.6)
Global cognition, proximate to death	-1.0 (1.2)
Global cognition, estimated linear rate of change (per year)	-0.099 (0.004)
Pathologic	
Postmortem interval (hours)	8.8 (5.8)
AD pathology (composite of scaled counts)	0.78 (0.61)
Gross infarcts (present)	180 (33.9%)
Microscopic infarcts (present)	166 (31.3%)
Lewy bodies (present)	128 (24.1%)
Hippocampal sclerosis (present)	63 (11.9%)
TDP-43 (Stage 2-3)	289 (35.6%)
Cerebral amyloid angiopathy (moderate to severe)	122 (23.0%)
Atherosclerosis (moderate to severe)	142 (26.7%)
Arteriolosclerosis (moderate to severe)	138 (26.0%)

were female (71.2%) and white (98.3%). The average participant had 15.8 years of education (SD = 3.6, range = 3-30) and died at age 90.4 (SD = 6.0, range = 65.9-108.3). At baseline, 26.6% of participants had MCI, while only 5.8% met the criteria for Alzheimer's dementia, owing to the fact that MAP and ROS enroll individuals who are free of known dementia. Their corresponding average MMSE scores and composite scores of global cognition at baseline were 27.7 (of 30) and -0.1 normalized unit, respectively. On average, participants completed more than nine annual cognitive evaluations (range = 2-22), declining

TABLE 2 Rates of cognitive decline by domain

Domain	Mean decline rate (units/year)	SE	P	10th Percentile	90th Percentile
Global cognition	−0.099	0.004	<0.0001	−0.22	−0.011
Episodic memory	−0.098	0.005	<0.0001	−0.24	−0.011
Semantic memory	−0.091	0.005	<0.0001	−0.21	−0.012
Working memory	−0.085	0.004	<0.0001	−0.16	−0.023
Perceptual speed	−0.127	0.005	<0.0001	−0.24	−0.039
Visuospatial ability	−0.059	0.004	<0.0001	−0.12	−0.011

TABLE 3 Contributions to variance in the rate of global cognitive decline from demographics, neuropathologic indices, and brain volumetric measures

Variables	Model identifiers			
	Ref.	1	2	3
Time	−0.100 (0.004) ^e	−0.108 (0.005) ^e	0.002 (0.009)	−0.018 (0.009) ^a
Age		0.001 (0.001)	0.002 (0.001) ^d	0.003 (0.001) ^e
Sex		0.024 (0.010)^b	0.009 (0.008)	−0.006 (0.008)
Education		0.003 (0.001)^c	0.002 (0.001) ^b	0.002 (0.001) ^b
AD pathology			−0.068 (0.006)^e	−0.058 (0.006) ^e
Gross infarcts			−0.029 (0.008)^d	−0.027 (0.008) ^d
Lewy bodies			−0.026 (0.009)^c	−0.025 (0.008) ^c
Hippocampal sclerosis			−0.058 (0.012)^e	−0.040 (0.012) ^d
TDP-43			−0.009 (0.004)^c	−0.006 (0.004) ^a
Arteriolosclerosis			−0.019 (0.005)^e	−0.015 (0.005) ^d
Hippocampal volume				0.061 (0.010)^e
% of variance accounted for by all effects	−	3.4%	42.6%	48.0%
% of variance accounted for by effects in boldface only	−	3.4%	39.2%	5.4%
Model for comparison	−	Ref.	1	2

^a $P < 0.1$, ^b $P < 0.05$, ^c $P < 0.01$, ^d $P < 0.001$, ^e $P < 0.0001$.

during that time to an average MMSE of 20.3 and global cognition score of −1.0 at their last evaluation. At death, 42.0% met the criteria for Alzheimer's dementia, while the frequency of MCI remained similar to baseline at 26.0%, and the remaining 32.0% were without cognitive impairment. Neuropathologic evaluation revealed substantial AD pathology, gross and microscopic infarcts, and Lewy bodies, but also the presence of hippocampal sclerosis, TDP-43, and moderate to severe CAA, atherosclerosis, and arteriolosclerosis, as detailed in Table 1.

3.2 | Heterogeneity in rates of cognitive decline

The average rate of decline in global cognition estimated via linear mixed models was −0.099 unit per year ($SE = 0.004$, $P < 0.0001$). Consistent with previous work, there was considerable heterogeneity among participants, with individuals at the 90th percentile declining much more slowly (−0.011 unit/year) than those at the 10th percentile (−0.22 unit/year). We observed similar heterogeneity in decline rates for episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability (Table 2).

3.3 | Variance in rates of cognitive decline accounted for by neuropathology

According to linear mixed models that included factors for age, sex, and education, these demographic variables accounted for 3.4% of the variation in global cognitive decline rate (Table 3, Figure 2) and between 2.6% and 5.9% of the variation in the decline rates of the five cognitive domains (Figure 2). To each of these six core models, we added nine pathologic indices. We found that microinfarcts, arteriolosclerosis, and CAA were not significantly associated with decline in global cognition or in any domain in this dataset, so we removed them from all subsequent analysis. The other six indices (AD, gross infarcts, LBD, hippocampal sclerosis, TDP-43, and atherosclerosis) were each associated with the rates of decline in global cognition and one or more cognitive domains. Together, they accounted for 39.2% of the variation in the rate of decline of global cognition beyond that accounted for by demographics (Table 3, Figure 2), and between 26.5% (perceptual speed) and 40.0% (episodic memory) of the variation in decline in the cognitive domains (Figure 2).

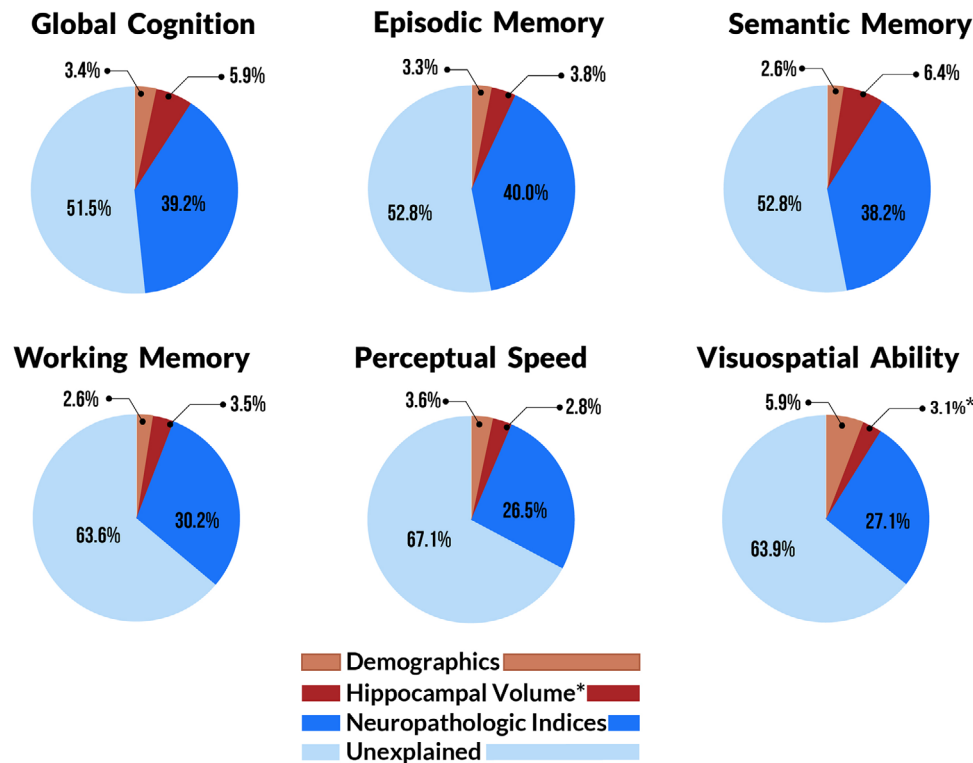


FIGURE 2 Variation in the rates of cognitive decline that is either unexplained or accounted for by each of three different factors for global cognition and each of five domains. In all domains, >50% of the variation was unexplained, while neuropathologic indices accounted for 26.5% to 40.0%, and hippocampal volume accounted for up to 6.4% in the semantic memory domain. Of the brain region volumes investigated in this work, hippocampal volume accounted for the greatest portion of variation in decline for all domains except visuospatial ability, where it accounted for 0.8% of variation. *Thus, for the visuospatial domain only, the contribution of globus pallidus volume (3.1%) rather than hippocampal volume is depicted

3.4 | Variance in rates of cognitive decline accounted for by hippocampal and total hemisphere volume

Retaining demographics and the six significant neuropathologic indices in the linear mixed models, we next added terms for hippocampal volume derived from postmortem MRI. Hippocampal volume was associated with decline in global cognition and accounted for 5.4% of its variance, beyond that attributable to demographics and indices of pathology ($P < 0.001$) (Table 3, Figure 2). Hippocampal volume was also associated with decline in all five individual cognitive domains examined in this work (visuospatial: $P = 0.007$; all others: $P < 0.001$). It accounted for the most variance in the decline rate for semantic memory (6.4%), which was approximately twice that of episodic memory (3.8%), working memory (3.4%), and perceptual speed (2.8%) (Table 4, Figure 2). Hippocampal volume accounted for the least variance in the decline rate for visuospatial ability (0.8%, not shown in Figure 2). The total variation in decline rate accounted for by the combination of demographics, neuropathologic indices, and hippocampal volume was 47.8% for global cognition and between 32.9% (perceptual speed) and 47.2% (episodic memory) for each of five cognitive domains (Figure 2).

Because the associations of hippocampal volume with cognitive decline could be driven by generalized brain atrophy, we repeated the previous models while further controlling for whole hemisphere

volume, which was moderately correlated with hippocampal volume (Pearson $r = 0.57$, $P < 0.0001$). We did not observe significant associations between hemisphere volume and cognitive decline. Of particular note, the associations between hippocampal volume and decline were essentially unchanged by the addition of whole hemisphere volume to the models.

3.5 | Variance in rates of cognitive decline accounted for by other brain region volumes

We next examined the associations between cognitive decline and six other deep brain regions (amygdala, thalamus, caudate, putamen, globus pallidus, and nucleus accumbens), which exhibited mild to moderate correlations with hippocampal volume ($P < 0.0001$ for all six volumes, Pearson r ranging from 0.44 for the nucleus accumbens to 0.77 for the amygdala). We entered terms for each of these regional volumes, one at a time, in the models for global cognition and each cognitive domain. There were two instances in which these additional volumes were significantly associated with the rate of decline after controlling for hippocampal volume. The volume of the amygdala was associated with the rate of decline in global cognition, although it accounted for <1% of the variance in decline rate and was quite weakly

TABLE 4 Contributions to variance in the rate of cognitive decline in five domains from the hippocampal volumetric measure

Variables	Model outcome (cognitive domain)									
	Episodic memory		Semantic memory		Working memory		Perceptual speed		Visuospatial ability	
Time	0.024 (0.011) ^b	0.004 (0.011)	0.008 (0.010)	-0.018 (0.011)	-0.015 (0.009) ^a	-0.030 (0.010) ^c	-0.048 (0.011) ^e	-0.065 (0.011) ^e	-0.008 (0.009)	-0.017 (0.009) ^a
Age	0.002 (0.001) ^b	0.002 (0.001) ^c	0.002 (0.001) ^c	0.003 (0.001) ^e	0.002 (0.001) ^c	0.002 (0.001) ^d	0.002 (0.001) ^c	0.003 (0.001) ^d	0.002 (0.001) ^b	0.002 (0.001) ^c
Sex	0.005 (0.009)	-0.012 (0.010)	0.013 (0.009)	-0.003 (0.010)	0.002 (0.008)	-0.008 (0.009)	0.015 (0.010)	-0.001 (0.010)	0.018 (0.007) ^b	0.011 (0.008)
Education	0.003 (0.001) ^c	0.003 (0.001)	0.001 (0.001)	0.000 (0.001)	0.002 (0.001) ^b	0.002 (0.001) ^b	0.002 (0.001)	0.002 (0.001)	0.000 (0.001)	0.000 (0.001)
AD pathology	-0.078 (0.007) ^e	-0.069 (0.008) ^e	-0.085 (0.007) ^e	-0.072 (0.007) ^e	-0.045 (0.005) ^e	-0.039 (0.006) ^e	-0.052 (0.007) ^e	-0.043 (0.008) ^e	-0.040 (0.006) ^e	-0.036 (0.006) ^e
Gross infarcts	-0.035 (0.009) ^d	-0.034 (0.009) ^d	-0.022 (0.009) ^b	-0.019 (0.009) ^b	-0.032 (0.008) ^e	-0.031 (0.008) ^e	-0.018 (0.009) ^a	0.018 (0.009) ^a	-0.005 (0.007)	-0.004 (0.007)
Lewy bodies	-0.010 (0.010)	-0.009 (0.010)	-0.018 (0.010) ^a	-0.017 (0.010) ^a	-0.022 (0.009) ^c	-0.022 (0.008) ^b	0.047 (0.010) ^e	-0.047 (0.010) ^e	-0.021 (0.008) ^b	-0.020 (0.008) ^b
Hippocampal sclerosis	-0.075 (0.014) ^e	-0.058 (0.014) ^e	-0.073 (0.014) ^e	-0.050 (0.014) ^d	-0.026 (0.012) ^b	-0.014 (0.012)	-0.045 (0.014) ^c	-0.029 (0.015) ^a	-0.023 (0.012) ^b	-0.015 (0.012)
TDP-43	-0.016 (0.004) ^d	-0.013 (0.004) ^c	-0.006 (0.004)	-0.003 (0.004)	-0.002 (0.004)	-0.001 (0.004)	-0.004 (0.004)	-0.001 (0.004)	-0.004 (0.004)	-0.002 (0.004)
Arteriosclerosis	-0.022 (0.005) ^e	-0.019 (0.005) ^d	-0.009 (0.005) ^a	-0.005 (0.005)	-0.014 (0.005) ^c	-0.011 (0.005) ^b	-0.017 (0.006) ^c	-0.014 (0.005) ^c	-0.013 (0.004) ^c	-0.012 (0.004) ^c
Hippocampal volume		0.067 (0.015) ^e		0.071 (0.015) ^e		0.044 (0.013) ^d		0.060 (0.016) ^e		0.029 (0.013) ^b
% of variance accounted for by all effects	43.3%	47.1%	40.8%	47.2%	32.8%	36.4%	30.1%	32.9%	33.1%	33.8%
% of variance accounted for by hippocampal volume	-	3.8%	-	6.4%	-	3.5%	-	2.8%	-	0.8%

^a $P < 0.1$, ^b $P < 0.05$, ^c $P < 0.01$, ^d $P < 0.001$, ^e $P < 0.0001$.

associated in comparison to hippocampal volume ($P = 0.037$ for amygdala volume vs $P = 0.001$ for hippocampal volume). The volume of the globus pallidus, however, was not related to decline in global cognition but was more strongly associated than hippocampal volume with the rate of decline in visuospatial ability ($P = 0.007$ for globus pallidus volume vs $P = 0.13$ for hippocampal volume), and accounted for 3.1% of the variance in decline, as reflected in Figure 2.

4 | DISCUSSION

In a group of >500 older adults, we examined the associations between hippocampal volume derived from postmortem MRI and the rate of late-life cognitive decline estimated from up to 22 annual cognitive evaluations, after controlling for common neurodegenerative and vascular brain pathologies and generalized brain atrophy. Hippocampal volume was associated with the rate of decline in global cognition and five cognitive domains, after controlling for the effects of nine common age-related pathologies, including AD, as well as total cerebral volume. In particular, hippocampal volume accounted for 5.4% of the variation in the decline rate of global cognition and up to 6.4% in individual cognitive domains, beyond the percentages attributed to available neuropathologic indices. These findings suggest that in addition

to the known neuropathologic indices that were accounted for in this study, late-life cognitive abilities are also influenced by other factors that are associated with hippocampal volume loss but were either not included in this study or have not yet been identified. Future studies based on this work that incorporate volumetric measures from other brain regions and additional imaging-based indicators of brain integrity might provide valuable clues for identifying targetable determinants of cognitive decline. Such studies are highly warranted in light of the looming public health crisis created by the combination of the high incidence of cognitive impairment among older persons and the rapid growth of our older population.

The current study makes a unique contribution to our understanding of the relationship between hippocampal volume and late-life cognitive decline by clarifying the degree to which this association persists after accounting for currently known and quantified neuropathologic drivers of cognitive impairment. Numerous studies investigated the link between hippocampal volume and cognition,^{35,36} several others explored the neuropathologic correlates of hippocampal atrophy,^{14,37} and our own past work elucidated the association between hippocampal volume and level of cognition proximate to death, after accounting for neuropathology.³⁸ However, the key finding of the current study has not been reported previously. Namely, the association of hippocampal volume with late-life cognitive decline rate persists even

after adjustment for a broad range of neurodegenerative and vascular neuropathologic indices, including AD. This finding differs partly from that of a recent study that did not find cognitive decline attributable to reduced hippocampal volume beyond brain amyloidosis, a marker of AD pathology.³⁹ Results of the current work instead suggest that the association between hippocampal volume and cognitive decline is indeed partly influenced by factors other than AD and other known neuropathologic drivers of cognitive decline. This has important implications for charting the course of development of therapeutic strategies to combat late-life cognitive decline. For example, our findings provide evidence that in Alzheimer's dementia clinical trials employing hippocampal volume either as part of an enrichment strategy or as an outcome measure, the apparent effectiveness of a therapy against Alzheimer's-related hippocampal atrophy and the associated cognitive decline could be influenced by the presence of non-targeted pathologies or factors.⁴⁰

Thus, this study further emphasizes the need for investigations aimed at uncovering additional factors that contribute to late-life cognitive decline. It also provides a potentially valuable clue that some of these factors exert vital influence on cognition via their effects on hippocampal volume. There are several possible mechanisms by which this could occur. For example, additional age-related neuropathologies that have not yet been identified or quantified may lead to hippocampal atrophy and cognitive impairments. Another possibility is that hippocampal neurogenesis, the subject of recent controversy as to whether it actually occurs in late life,^{41,42} affects the total number of neurons, and thus, the volume of the structure in old age, with an accompanying effect on cognition. There is also evidence that development and continued health of the hippocampi are negatively affected by chronic psychological distress due to, for example, stress hormones such as cortisol^{43,44} or decreased density of dendrites and dendritic spines.⁴⁵ It is, therefore, possible that stressful experiences throughout life erode a potential store of cognitive resilience that might otherwise have been imparted in the form of well-developed and maintained hippocampi. Because some of these factors will be more readily targetable than others, it is necessary to elucidate their relative contributions to variation in hippocampal volume and cognition in order to judiciously allocate resources to the development of different interventions.

Although the major findings of this study are based on analyses in which global cognition was the outcome, we also report results from domain-specific analyses. Of particular interest, hippocampal volume accounted for approximately twice as much variation in decline of semantic memory (6.4%) than that of episodic memory (3.5%). This was somewhat surprising, because although both forms of memory are served by the hippocampus,⁴⁶ most evidence suggests that episodic memory is more tightly linked to hippocampal function,⁴⁷ with semantic memory relying to a greater degree on surrounding medial temporal regions.^{48,49} This apparent discrepancy can be partly explained by the fact that demographics and neuropathologic indices accounted for slightly more variation in decline of episodic memory (43.3%) than that of semantic memory (40.8%) (Figure 2), some of which might otherwise have been attributed to hippocampal volume.

Our analyses also demonstrated that total hemisphere volume makes no appreciable contribution to the variation in decline when considered in the same models alongside hippocampal volume. Because any form of cognition involves communication among multiple regions of the brain, we assumed that generalized brain atrophy would complement hippocampal volume in accounting for variation in cognitive decline rates. This was not the case in our analyses of global cognition or in any of five cognitive domains, as the effect of total hemisphere volume was not significant, and the explained percentage of variation in decline rates remained essentially unchanged regardless of whether hemisphere volume was included in the models with hippocampal volume.

In addition, we considered the associations between the volumes of six other deep brain regions and cognitive decline. The volume of the globus pallidus was associated with the rate of decline in visuospatial ability, accounting for 3.1% of its variance and resulting in a weakening of the association between hippocampal volume and decline in that domain to a non-significant level. This appears to be a unique finding in the literature and may warrant further investigation. However, this domain-specific finding reflects the only instance in which any of the six volumes exhibited an association with decline that was stronger than hippocampal volume's association. These results reaffirm the role of hippocampal volume as a particularly consistent determinant of late-life decline in multiple cognitive domains.

More than half of the total variation in rates of decline remained unexplained (Figure 2) after accounting for demographics, neuropathologic indices, and volumes of multiple deep brain regions derived from MRI. A number of factors could be responsible for this phenomenon, and we offer three possibilities. First, our current quantification of age-related neuropathology is incomplete; this is in part because there are likely additional, as yet unidentified pathologies that contribute to decline and also because some of our pathologies are measured via binary measures (present vs absent) such that we do not capture the full burden of disease. Second, resilience factors that buffer against cognitive decline even in the face of accumulating pathology may also play a role. Third, because the same cognitive tests are administered annually, practice effects may differentially influence scores among individuals. Additional work is needed to further understand the basis of the unexplained decline.

The availability of both volumetric and neuropathologic data in the same study is rare because MRI is usually carried out during life, whereas most types of neuropathologic data are available only upon postmortem examination of tissue. A major strength of this work was the circumvention of this difficulty by employing postmortem brain MRI in ongoing clinicopathologic studies of aging in which cognition was assessed annually and all participants agree to brain donation as a condition of enrollment. This approach facilitated the relatively rapid accumulation of cases with all three types of data required for our analyses. Although antemortem MRI is also underway in the MAP and ROS cohorts, the respective sample sizes at the time of our analyses still favored the use of postmortem MRI.

Limitations of the study are also noted. First, hippocampal volume was assessed at only one timepoint at the end of life. This measure is

sensitive to hippocampal atrophy, but might also partly reflect maximum hippocampal volume attained earlier in life. We also cannot establish the timing of hippocampal atrophy relative to the onset of cognitive decline. The accuracy of the volumetry technique itself may also be considered a limitation, as we relied on a manual tracing on a single template that was then propagated to all individual images. Work is underway to develop a more accurate multi-atlas approach tailored for use with postmortem brain images. Neuropathologic indices were derived from only one cerebral hemisphere for each individual, a limitation in that certain pathologies such as hippocampal sclerosis may exhibit considerable asymmetry. Finally, we note that our sample consisted of very old adults who had voluntarily participated in aging research. Generalizability to broader populations will need to be explored in future studies.

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