Cognitive correlates of white matter lesion load and brain atrophy

The Northern Manhattan Study

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ABSTRACT

Objective: We investigated white matter lesion load and global and regional brain volumes in relation to domain-specific cognitive performance in the stroke-free Northern Manhattan Study (NOMAS) population.

Methods: We quantified white matter hyperintensity volume (WMHV), total cerebral volume (TCV), and total lateral ventricular (TLV) volume, as well as hippocampal and cortical gray matter (GM) lobar volumes in a subgroup. We used general linear models to examine MRI markers in relation to domain-specific cognitive performance, adjusting for key covariates.

Results: MRI and cognitive data were available for 1,163 participants (mean age 70 ± 9 years; 60% women; 66% Hispanic, 17% black, 15% white). Across the entire sample, those with greater WMHV had worse processing speed. Those with larger TLV volume did worse on episodic memory, processing speed, and semantic memory tasks, and TCV did not explain domain-specific variability in cognitive performance independent of other measures. Age was an effect modifier, and stratified analysis showed that TCV and WMHV explained variability in some domains above age 70. Smaller hippocampal volume was associated with worse performance across domains, even after adjusting for *APOE* ε4 and vascular risk factors, whereas smaller frontal lobe volumes were only associated with worse executive function.

Conclusions: In this racially/ethnically diverse, community-based sample, white matter lesion load was inversely associated with cognitive performance, independent of brain atrophy. Lateral ventricular, hippocampal, and lobar GM volumes explained domain-specific variability in cognitive performance. ***Neurology*® 2015;85:441–449**

GLOSSARY

EMEM = episodic memory; **EXEC** = executive function; **GM** = gray matter; **NC** = neurocognitive; **NOMAS** = Northern Manhattan Study; **PS** = processing speed; **SMEM** = semantic memory; **SVD** = small vessel disease; **TCV** = total cerebral volume; **TIV** = total intracranial volume; **TLV** = total lateral ventricular; **WMHV** = white matter hyperintensity volume.

With the aging of the US population,[1] there is increasing interest in cognitive aging, a complex process that includes the effects of neurodegenerative and cardiovascular processes prevalent in older adults. Data regarding region-specific brain volumes and domain-specific cognitive performance from racially/ethnically diverse studies are limited.

Measures of global brain atrophy, such as ventricular enlargement and total cerebral volume (TCV), have correlated with worse cognitive performance and an increased risk of stroke and dementia.[2–6] Lobar and hippocampal volumes have also been observed to decrease variably over the lifespan.[7] Frontal and temporal atrophy have been associated with deficits in executive function and memory, whereas hippocampal atrophy is a risk factor for cognitive decline in cognitively normal people.[6,8] Cerebral small vessel disease (SVD) is common in older adults and

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has been associated with worse cognitive performance and decline in cognitively normal individuals and a greater risk of stroke, dementia, and mortality.[9–11]

Associations of these imaging markers with domain-specific cognitive performance are not well-understood on a population-based level, especially among middle-aged and older Hispanics and blacks. We hypothesized that imaging markers of global cerebral and ventricular volumes and cerebral SVD would explain variability in cognitive performance in this diverse population-based sample. Also, because vascular damage and Alzheimer disease are the most prevalent causes of cognitive decline in older adults, we hypothesized that cerebral SVD would predominantly affect frontal lobe function, resulting in worse executive function, whereas brain atrophy would affect cognitive function more broadly.

METHODS

Participants. The Northern Manhattan Study (NOMAS) is a prospective population-based cohort study. The general recruitment, design, and demographics of NOMAS have been previously described in detail.[12] Eligible participants were stroke-free, were >40 years old, and resided >3 months in a Northern Manhattan household with a telephone. We enrolled 3,298 participants using random digit dialing between 1993 and 2001. All participants underwent a baseline evaluation of demographic characteristics, health behaviors, and health status, including comprehensive medical history, physical/neurologic examination, medical record review, and fasting blood samples. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System.

Standard protocol approvals, registrations, and patient consents. All participants signed informed consent and the institutional review boards of Columbia University and the University of Miami approved the study.

Neurologic testing and cognitive domain scores. From 2003 to 2008, 1,290 stroke-free participants eligible for MRI (including 199 newly enrolled NOMAS household members meeting above entry criteria) completed a neurocognitive (NC) battery in English or Spanish based on language spoken at home. To assign cognitive domain labels, we explored interrelationships among individual NC test scores with factor analysis and used a Scree plot of eigenvalues to determine the number of constructs (domains). We computed composite scores for each domain by averaging individual *z* scores transformed from raw test scores, as previously described[13–15]: episodic memory (EMEM): subscores from a 12-word 5-trial list-learning task (total, delayed recall, and delayed recognition); executive function (EXEC): time to complete Color Trails 2 minus Color Trails 1 and the sum of Odd-Man-Out subtests 2 and 4; processing speed (PS): nondominant hand Grooved Pegboard times, Color Trails 1 time, and Visual-Motor Integration test scores[16]; semantic memory (SMEM): picture naming (modified Boston Naming), category fluency (Animal Naming), and phonemic fluency (C, F, L in English speakers and F, A, S in Spanish speakers).

Brain MRI measurements. During the initial MRI study, we focused on cerebral volumes and did not include infratentorial structures or brainstem. Brain MRI scans were obtained from 2003 to 2008 on the same day as the NC battery. We used a 1.5T Philips Intera scanner (Philips, Best, the Netherlands) at Columbia University Medical Center. Images were transferred electronically to University of California, Davis for morphometric analysis of TCV, total lateral ventricular (TLV) volume, and white matter hyperintensity volume (WMHV) using T1 and fluid- attenuated inversion recovery sequences, as previously described.[16–18] Briefly, nonbrain elements were manually removed from the image by operator-guided tracing of dura mater within the cranium, including the middle cranial fossa but excluding the posterior fossa and brainstem. The resulting measure was defined as total intracranial volume (TIV). TCV was computed as the sum of whole brain volume voxels from the T1 segmentation process. After segmentation into brain matter and CSF, voxels belonging to the CSF class within the region of interest were summed to quantify TLV volume. WMHV was calculated as the sum of voxels ≥3.5 SDs above the mean image intensity multiplied by pixel dimensions and section thickness. We expressed TCV, TLV volume, and WMHV as proportions of TIV to correct for individual differences in head size. For consistency with prior publications we do not use Standards for Reporting Vascular Changes on Neuroimaging, as previously described.[e1]

Volumetric segmentation of lobar gray matter (GM) volumes and hippocampal volumes was performed with high-quality data sets using the publicly available FreeSurfer image analysis suite (Version 5.1) (http://surfer.nmr.mgh.harvard.edu/).[19,20] All T1-weighted MRIs underwent motion correction, skull stripping, and transformations into Talaraich space before segmentation, identification of gray/white matter boundaries, automated topology correction, and surface deformation.[21,22] Through 3-dimensional segmentation methods, neuroanatomic labels for regional white matter and cortical GM parcellations were assigned to each voxel using a probabilistic atlas and Bayesian classification rule.[19] FreeSurfer provides an estimate of hippocampal volume, and 68 cortical GM parcellations were summed to estimate frontal, temporal, occipital, and parietal lobe GM volumes using recommended methods.[20,23] All regional GM volumes were expressed as ratios of TCV to account for relative differences in brain size (rather than head size, as was done for the global measures) in order to examine the relative importance of regional GM volumes.

***APOE* genotyping.** DNA samples were extracted from peripheral blood white cells using *Hha*I digestion and amplified by PCR, as previously described.[24] *APOE* ε4 carriers were identified as individuals with a genotype of *APOE* ε4/ε2, *APOE* ε4/ε4, and *APOE* ε4/ε3.

Statistical analyses. To evaluate the association of brain volumetric measures with domain-specific cognitive performance, we built a series of models to adjust for potential confounders: age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other), education, body mass index, waist-to-hip ratio, smoking (never, former, and current), reported moderate alcohol intake (1 drink per week to ≤ 2 drinks per day vs other), reported moderate leisure-time physical activity (vs inactive),[25] antihypertensive medication use, antidiabetic medication use, lipid-lowering medication use, systolic and diastolic blood pressure, glucose, low-density lipoprotein, high-density lipoprotein, and triglycerides. The

primary analysis used general linear models and adjusted for age, sex, race/ethnicity, education, and TIV (or TCV for regional analyses) for the association between each brain volumetric measure and performance in a domain. As secondary analyses, additional adjustments were made for *APOE* genotype and for all MRI variables simultaneously to ensure that any effect of one brain measure was independent of the others. In sensitivity analysis, regional volume associations were also evaluated using the proportion of TIV (instead of TCV). Finally, joint effects of brain morphologic parameters and potential interactions with other covariates were assessed with models that included multiple significant morphologic predictors and their interaction terms. We did stratified analyses for interactions with p values <0.1. We used SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS Participant characteristics are summarized in table 1. Half the sample was above age 70, with an average of 10 years of education. The majority of participants were women, were of Hispanic/Latino origin, reported taking blood pressure medication, and reported moderate to heavy leisure-time physical activity. Total cerebral and regional brain volumes are summarized in table 2. Global cognition was high (mean Mini-Mental State Examination score = 26.7 ± 3.3), in keeping with our prior estimate of <5% cognitive impairment at baseline.[26]

Examining the whole sample, larger TCV was not significantly associated with variability in cognitive performance in any domain after adjusting for age, sex, race/ethnicity, and education. This remained true after adjusting further for lifestyle and vascular factors, *APOE* genotype, and other brain measures (table 3). In contrast, those with larger TLV volume and WMHV had worse EMEM, PS, and SMEM performance after adjusting for age, other sociodemographic and vascular risk factors, *APOE* ε4 allele status, and TCV. Those with larger WMHV showed worse EXEC performance after adjusting for sociodemographic, lifestyle, and vascular risk factors, but this attenuated slightly after adjusting for *APOE* ε4 status and did not reach significance after adjusting for other brain measures ($p = 0.09$, table 3). Both TCV and WMHV interacted with age in relation to EMEM and SMEM performance, and there was a weaker interaction between TCV and age in relation to PS (table 4), whereas TLV volume did not interact with age. We therefore stratified at median age and found that smaller TCV was associated with worse memory and PS, whereas greater WMHV was associated with worse performance in EMEM and SMEM, in those older than age 70 after adjusting for vascular factors, *APOE* ε4 status, and other brain measures (table 4).

Regional GM volumes explained some variability in domain-specific cognitive performance among 813 participants with available data (tables 2 and 5). Those with smaller hippocampal volumes showed worse performance across cognitive domains, especially EMEM, after adjusting for sociodemographic and vascular risk factors and *APOE* genotype (table 5). Those with smaller frontal GM volumes performed significantly worse in the EXEC domain. Participants with smaller temporal lobe and parietal lobe GM volumes performed worse in EMEM and EXEC domains with a trend for worse performance in the SMEM domain, and smaller temporal lobe GM volumes contributed to worse performance in the PS domain. Occipital lobe GM volumes did not explain variability in domain-specific cognitive performance (table 5).

Several lobar GM volumes and hippocampal volumes interacted with age in relation to domain-specific cognitive performance (table 4). Age was an

Table 1 Sample characteristics (N = 1,163)

Characteristic	N (%)
APOE ε4 noncarrier	878 (76)
Race/ethnicity	
White	173 (15)
Black	193 (17)
Hispanic	770 (66)
Other	27 (2)
Smoking	
Never	560 (48)
Former	501 (43)
Current	102 (9)
Physical activity	658 (57)
Moderate alcohol drinker	390 (34)
Blood pressure medication	705 (61)
Diabetes medication	234 (20)
Lipid-lowering medication	357 (31)
Characteristic	**Mean (SD)**
Age, y	70 (9)
Education, y	10 (5)
Mini-Mental State Examination score	26.7 (3.3)
BMI, kg/m^2	29 (5)
Height, cm	161 (10)
WHR	0.9 (0.1)
BS, mg/dL	100 (33)
LDL, mg/dL	115 (35)
HDL, mg/dL	53 (17)
TG, mg/dL	124 (73)
SBP, mm Hg	137 (18)
DBP, mm Hg	78 (10)

Abbreviations: BMI = body mass index; BS = blood sugar; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TG = triglycerides; WHR = waist-to-hip ratio.

Table 2 Summary of total cerebral, cortical lobar, and hippocampal volumes

Global cerebral volume measurements (N = 1,163)	Measure in cm^3	Measure in % TIV
TIV, mean ± SD	1,154.6 ± 123.2	—
TCV, mean ± SD	837.0 ± 100.0	72.5 ± 4.2
Total lateral ventricular volume, mean ± SD	37.7 ± 19.3	3.2 ± 1.6
White matter hyperintensity volume, mean ± SD	7.5 ± 9.4	0.7 ± 0.8
Regional brain measurements (N = 813)	**Measure in cm^3**	**Measure in % TCV**
Hippocampal volume, mean ± SD	7.3 ± 1.0	0.9 ± 0.1
Lobar volumes, mean ± SD		
Frontal	144.8 ± 16.9	17.4 ± 1.4
Temporal	82.4 ± 10.4	9.9 ± 1.0
Occipital	41.8 ± 5.8	5.0 ± 0.5
Parietal	108.3 ± 13.1	12.8 ± 1.1

Abbreviations: TCV = total cerebral volume; TIV = total intracranial volume.

effect modifier such that those with smaller hippocampal volumes showed worse EMEM performance across the age range, especially among older participants. In addition, older, but not younger, participants with smaller hippocampal volumes performed worse in the EXEC and SMEM domains. Finally, smaller frontal lobe, temporal lobe, and parietal lobe GM volumes were associated with worse performance in the EXEC domain only among those younger than 70. Neither race/ethnicity nor sex acted as effect modifiers of associations between MRI markers and cognitive performance. We did not find significant interactions for any other covariates.

DISCUSSION In this community-based sample of older adults free of clinical stroke, we observed that participants with a greater burden of white matter lesions and those with larger lateral ventricles exhibited worse performance across several domains. We found region-specific differences in a subset of participants, as hippocampal volumes were a strong indicator of performance across all cognitive domains, especially episodic memory, and smaller frontal lobe volumes were associated with worse executive function. Our findings did not vary significantly by race/ethnicity, suggesting consistency across this urban sample. We did find interactions with age such that variability in cognitive performance explained by the MRI markers was evident mostly in those 70 years or older. However, smaller hippocampal volumes were associated with

Table 3 Association of white matter hyperintensity volume and total brain volumetric measure ratios[a] with cognitive performance by domain (N = 1,163)

	Episodic memory		Executive function		Processing speed		Semantic memory	
Parameters	β ± SE	*p*	β ± SE	*p*	β ± SE	*p*	β ± SE	*p*
TCV, per 1 SD increase								
Model A	0.029 ± 0.029	0.33	0.000 ± 0.029	0.97	0.063 ± 0.029	0.03	0.025 ± 0.029	0.41
Model B	0.029 ± 0.029	0.34	−0.063 ± 0.029	0.82	0.042 ± 0.029	0.15	0.038 ± 0.029	0.19
Model C	0.034 ± 0.029	0.31	−0.050 ± 0.029	0.86	0.046 ± 0.029	0.13	0.038 ± 0.029	0.19
Model D	−0.008 ± 0.034	0.79	−0.008 ± 0.034	0.76	0.021 ± 0.034	0.52	0.017 ± 0.029	0.63
TLV volume per 1 SD increase								
Model A	−0.139 ± 0.030	<0.001	−0.034 ± 0.027	0.21	−0.122 ± 0.029	<0.001	−0.090 ± 0.027	0.001
Model B	−0.142 ± 0.030	<0.001	−0.027 ± 0.027	0.32	−0.110 ± 0.029	<0.001	−0.093 ± 0.027	<0.001
Model C	−0.142 ± 0.030	<0.001	−0.027 ± 0.027	0.32	−0.110 ± 0.029	<0.001	−0.093 ± 0.027	<0.001
Model D	−0.122 ± 0.034	<0.001	−0.016 ± 0.030	0.59	−0.078 ± 0.032	0.02	−0.070 ± 0.030	0.02
WMHV per 1 SD increase								
Model A	−0.119 ± 0.027	<0.001	−0.060 ± 0.024	0.01	−0.134 ± 0.026	<0.001	−0.090 ± 0.025	<0.001
Model B	−0.114 ± 0.027	<0.001	−0.051 ± 0.024	0.03	−0.113 ± 0.026	<0.001	−0.077 ± 0.025	0.002
Model C	−0.109 ± 0.027	<0.001	−0.046 ± 0.024	0.05	−0.109 ± 0.026	<0.001	−0.075 ± 0.025	0.003
Model D	−0.078 ± 0.029	0.01	−0.042 ± 0.025	0.09	−0.090 ± 0.027	<0.001	−0.058 ± 0.026	0.03

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TIV = total intracranial volume; TLV = total lateral ventricular; WMHV = white matter hyperintensity volume.
Model A: adjusted for age, sex, race/ethnicity, and education; model B: model A adjusted further for smoking, moderate alcohol use, leisure-time physical activity, body mass index, waist-to-hip ratio, systolic and diastolic blood pressure, use of antihypertensive medications, fasting glucose, use of diabetes medications, LDL-C, HDL-C, triglycerides, and use of lipid-lowering medications; model C: model B additionally adjusted for *APOE* genotype; model D: model C additionally adjusted for other brain measures.
[a] All volumes expressed as a percentage of TIV.

Table 4 Interactions between age and brain volumetric measures on cognitive performance

Group	Cognitive domain	Brain volumetric measure	Interaction with age		Age <70 y (N = 570)		Age ≥70 y (N = 593)		p Value for age <70 y vs age ≥70 y
			β ± SE	p	β ± SE	p	β ± SE	p	
Total[a]	Episodic memory	TCV	0.008 ± 0.003	0.009	−0.046 ± 0.046	0.32	0.109 ± 0.046	0.014	<0.0001[b]
		WMHV	−0.007 ± 0.004	0.038	−0.048 ± 0.060	0.423	−0.116 ± 0.032	0.0003	
	Semantic memory	TCV	0.007 ± 0.001	0.012	−0.007 ± 0.042	0.663	0.080 ± 0.042	0.055	0.4344[b]
		WMHV	−0.007 ± 0.003	0.042	−0.003 ± 0.054	0.956	−0.066 ± 0.030	0.025	
	Processing speed	TCV	0.005 ± 0.003	0.077	0.034 ± 0.046	0.448	0.109 ± 0.042	0.011	<0.0001
Subset[c]	Episodic memory	HC	0.008 ± 0.003	0.017	0.146 ± 0.046	0.001	0.290 ± 0.041	<0.0001	<0.0001
		FL	−0.008 ± 0.004	0.028	0.130 ± 0.043	0.003	−0.020 ± 0.046	0.676	<0.0001
	Executive function	HC	0.005 ± 0.003	0.099	0.064 ± 0.040	0.109	0.139 ± 0.036	0.0001	0.4021
		FL	−0.007 ± 0.003	0.007	0.113 ± 0.038	0.004	0.015 ± 0.039	0.695	0.1653
		TL	−0.005 ± 0.003	0.085	0.114 ± 0.039	0.004	0.052 ± 0.038	0.17	0.2227
		OL	−0.007 ± 0.003	0.011	0.061 ± 0.035	0.08	−0.002 ± 0.036	0.957	0.1994
		PL	−0.007 ± 0.003	0.014	0.120 ± 0.037	0.002	0.023 ± 0.040	0.549	0.2444
	Semantic memory	HC	0.005 ± 0.003	0.091	0.018 ± 0.041	0.657	0.097 ± 0.037	0.009	0.5613

Abbreviations: FL = frontal lobe; HC = hippocampus; OL = occipital lobe; PL = parietal lobe; TCV = total cerebral volume; TL = temporal lobe; TLV = total lateral ventricular; WMHV = white matter hyperintensity volume.

[a] Covariates were those in model D in table 3 plus the interactions between age and brain volumetric measures.

[b] For the total sample, the p value represents effect of age adjusted for TCV, WMHV, and TLV volume, the 3 interactions between age and these brain volumetric measures, and all covariates in model D.

[c] Subset of participants who had available regional brain volume data. Covariates were those in model C in table 5 plus the interaction between age and the specific lobar brain volume.

worse memory across the full age range, and frontal lobe GM volume was a marker of executive function in younger participants.

Other studies, some of which were population-based, have reported relationships between total brain or cerebral volumes and cognitive performance.[3,6] Unlike these other studies, TCV was not associated with overall cognitive performance in this diverse sample until we examined older participants separately. This is perhaps unsurprising since cerebral volume is less important than other factors such as efficiency of network connections and synaptic complexities that we are unable to assess using structural imaging. These differences could be due to methodologic differences across studies, as some studies used different measures of cerebral volume losses, such as visual rating scales, instead of quantitative measures of TCV. Also, some studies excluded those with dementia, thereby selecting older participants with more normal cognition, and others included participants from memory clinics, thereby selecting participants with greater cognitive disability.[6] Because we excluded participants with clinical stroke but not those with cognitive disorders or dementia and the average age was 70, it is likely that we included both younger people at low risk of neurocognitive disorders and older people in whom these processes may have been active. The prevalence of cognitive impairment is estimated to be less than 5% in our cohort at the time of these assessments. Thus, TCV may not have been as strongly related to cognitive performance in our overall sample because of this heterogeneity, explaining why TCV was associated with memory and processing speed in older participants after stratifying at median age. Our data suggest that larger cerebral volumes could be protective in older age, and some prospective data support this idea.[6]

In this study and others, MRI-defined SVD was associated with worse cognition across domains.[2,9,27] Small vessel damage caused by exposure to potentially modifiable vascular risk factors such as hypertension can cause arteriolosclerosis and cerebral hypoperfusion, resulting in demyelination or complete necrosis of white matter, which can, in turn, globally compromise cognition.[28] In addition, we found that those 70 years or older with greater WMHV performed worse in episodic and semantic memory domains. This finding may be driven by the cumulative effects of cardiovascular risk factors or subclinical Alzheimer pathology on cerebrovascular integrity in this mixed sample, both of which may synergize with age in relation to cognitive performance. Cerebral amyloid angiopathy may underlie some white matter lesions[29] in older participants and has been associated with Alzheimer disease in autopsy studies.[30]

Table 5 Association of lobar brain volume measure ratios[a] with cognitive performance by domain (N = 813)

	Episodic memory		Executive function		Processing speed		Semantic memory	
Parameters	β ± SE	*p*	β ± SE	*p*	β ± SE	*p*	β ± SE	*p*
Hippocampal volume per 1 SD increase								
Model A	0.208 ± 0.032	<0.001	0.088 ± 0.029	0.003	0.088 ± 0.032	0.006	0.066 ± 0.030	0.03
Model B	0.201 ± 0.032	<0.001	0.091 ± 0.029	0.002	0.094 ± 0.031	0.003	0.062 ± 0.030	0.04
Model C	0.199 ± 0.032	<0.001	0.089 ± 0.029	0.002	0.091 ± 0.031	0.004	0.062 ± 0.030	0.04
Frontal lobe GM volume per 1 SD increase								
Model A	0.059 ± 0.032	0.07	0.069 ± 0.028	0.01	0.048 ± 0.031	0.12	0.031 ± 0.028	0.28
Model B	0.056 ± 0.032	0.09	0.063 ± 0.028	0.03	0.042 ± 0.029	0.16	0.021 ± 0.028	0.45
Model C	0.049 ± 0.032	0.13	0.057 ± 0.028	0.04	0.034 ± 0.031	0.26	0.020 ± 0.029	0.48
Temporal lobe GM volume per 1 SD increase								
Model A	0.110 ± 0.032	<0.001	0.089 ± 0.028	0.002	0.089 ± 0.031	0.003	0.061 ± 0.029	0.04
Model B	0.107 ± 0.033	0.001	0.076 ± 0.028	0.007	0.077 ± 0.031	0.01	0.056 ± 0.029	0.05
Model C	0.104 ± 0.033	0.002	0.073 ± 0.028	0.01	0.073 ± 0.031	0.02	0.055 ± 0.029	0.06
Occipital lobe GM volume per 1 SD increase								
Model A	0.017 ± 0.029	0.56	0.031 ± 0.026	0.24	−0.027 ± 0.028	0.33	0.006 ± 0.027	0.82
Model B	0.016 ± 0.029	0.59	0.028 ± 0.026	0.27	−0.029 ± 0.028	0.29	0.002 ± 0.026	0.95
Model C	0.015 ± 0.029	0.62	0.027 ± 0.026	0.29	−0.031 ± 0.028	0.25	0.001 ± 0.026	0.97
Parietal lobe GM volume per 1 SD increase								
Model A	0.084 ± 0.032	0.009	0.081 ± 0.028	0.004	0.058 ± 0.031	0.06	0.062 ± 0.029	0.03
Model B	0.078 ± 0.033	0.02	0.072 ± 0.028	0.01	0.051 ± 0.030	0.09	0.052 ± 0.029	0.07
Model C	0.072 ± 0.033	0.03	0.067 ± 0.029	0.02	0.043 ± 0.030	0.16	0.052 ± 0.029	0.07

Abbreviations: GM = gray matter; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TCV = total cerebral volume. Model A: adjusted for age, sex, race/ethnicity, education, and TCV; model B: model A additionally adjusted for smoking, moderate alcohol drinking, leisure-time physical activity, body mass index, waist-to-hip ratio, systolic and diastolic blood pressure, use of antihypertensive medications, plasma glucose, use of diabetes medications, LDL-C, HDL-C, triglycerides, and use of lipid-lowering medications; model C: model B additionally adjusted for *APOE* genotype.
[a] All volumes expressed as a percentage of TCV.

We found 2 population-based studies reporting ventricular enlargement to be associated with worse executive function and processing speed, but they did not include Hispanic/Latino participants.[2,31] TLV volume was more strongly associated with episodic and semantic memory than executive function in our cohort. TLV volume is a measure of central atrophy, and greater TLV volume may be a more sensitive marker of damage that affects cognition than TCV[4] in this sample. Because TLV volume did not interact with age in relation to cognitive performance, TLV volume may serve as a marker of processes less dependent on aging itself. This finding is consistent with longitudinal studies showing that ventricular enlargement is a marker of dementia progression and may implicate neurodegenerative processes.[4]

Hippocampal volume has been associated with memory,[32] but some, though not all, cross-sectional data have also shown that greater hippocampal volumes can correlate with better executive function.[6,33] In this community-based sample unselected for cognitive status, smaller hippocampal volumes served as a marker of worse performance across all cognitive domains, reflecting the importance of the hippocampus in successful aging.[34] That hippocampal volumes interacted with age in relation to memory function in both younger and older age groups suggests that hippocampus volumes are a general indicator of memory ability in late middle age as well as old age. Hippocampal volume also interacted with age in relation to executive function and semantic memory performance, and those 70 years or older with smaller hippocampal volumes had worse performance. This is most likely due to the later involvement of these cognitive domains as cognitive disorders advance.

Temporal and parietal lobe GM volumes were associated with performance in multiple domains, including memory and executive function. Perhaps

unsurprisingly, frontal lobe GM volume was only associated with executive function. Other community-based studies with more homogeneous samples found that smaller frontal and temporal lobe volumes were associated with worse general cognitive performance.[33] However, we were unable to find community-based studies that explicitly analyzed the relationship between parietal lobe volumes and cognition. Nonetheless, other studies have shown that executive performance is affected by processing speed and age-related memory performance.[35] Also, free recall of noncontextual verbal information (list learning), which dominated our memory testing, requires some executive control.[36] Some lobar volumes were associated with performance in several cognitive domains, but domain-specific constructs are somewhat artificial and the cognitive processes they represent are distributed. However, it is of interest that our stratified analysis showed that lobar GM volumes were markers of executive performance among those <70 years, whereas smaller TCV was associated with worse performance only in older participants. Since the TCV measure represents both gray and white matter structures in both hemispheres, it is likely to be a marker of a wider array of insults, whereas GM volume variability is more likely to be a marker of aging and neurodegeneration.

Strengths of the present study include our large ethnically and racially diverse population-based cohort that represents an urban US community. Longitudinal studies have reported that greater WMHV and smaller hippocampal volumes are related to greater risk of dementia or stroke, but few samples have been in clinically stroke-free or ethnically and racially diverse cohorts.[3,5,10,34] One cross-sectional study investigated differences in brain morphology between Hispanics/Latinos, African Americans, and Caucasians but did not evaluate associations with cognitive performance.[37] Another study that included Hispanics/Latinos examined the relationship of white matter lesions and cognition in the context of cognitive reserve,[38] but we did not find studies examining regional GM volumes and domain-specific cognitive performance. Many studies with diverse cohorts had small samples or relatively young participants.[11,39] Another strength of this study is our use of volumetric measures of SVD that are more reliable than visual rating scales.[40]

We cannot determine causality between brain morphology and cognitive performance because this study is cross-sectional. Residual confounding is likely in studies of this type. Also, since we did not identify cognitive disorders, we cannot tie our findings to specific causes. In addition, some of our analyses may have been underpowered, especially our interaction and regional brain volume analyses. Also, there may have been ceiling effects since half our sample is younger than 70 and both brain atrophy and cognitive dysfunction are less prevalent in this age group. Finally, the sample under study here survived and remained stroke-free until evaluation and is therefore healthier than the original cohort, but this should underestimate any associations between imaging markers and cognition compared with the whole sample.

In this urban community-based US population, central atrophy and SVD contributed to variability in cognitive performance, and smaller lobar GM volumes were related to worse cognitive performance in late middle age. Markers of brain atrophy and cerebral SVD may provide important information about underlying processes that affect cognition in older adults, and this requires further study.

AUTHOR CONTRIBUTIONS

As principal investigator, Dr. Wright had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Chuanhui Dong: study concept and design, statistical analysis, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Nooshin Nabizadeh: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Michelle Caunca: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Ying Kuen Cheung: critical revision of the manuscript for important intellectual content. Tatjana Rundek: critical revision of the manuscript for important intellectual content, obtaining funding. Mitchell Elkind: acquisition of data, critical revision of the manuscript for important intellectual content, obtaining funding. Charles DeCarli: acquisition of data, critical revision of the manuscript for important intellectual content. Ralph Sacco: acquisition of data, critical revision of the manuscript for important intellectual content, obtaining funding. Yaakov Stern: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtaining funding. Clinton Wright: study concept and design, study supervision, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

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