Neural correlates of domain-specific cognitive decline

The ARIC-NCS Study

Andrea L.C. Schneider, MD, PhD, Matthew L. Senjem, MS, Aozhou Wu, MHS, Alden Gross, PhD, MHS, David S. Knopman, MD, Jeffrey L. Gunter, PhD, Christopher G. Schwarz, PhD, Thomas H. Mosley, PhD, Rebecca F. Gottesman, MD, PhD, A. Richey Sharrett, MD, DrPH, and Clifford R. Jack, Jr., MD

Correspondence

Dr. Schneider
achris13@jhmi.edu

Neurology® 2019;92:e1051-e1063. doi:10.1212/WNL.0000000000007042

Abstract

Objective

To evaluate the association of cognitive declines in the domains of memory, language, and executive function with brain gray matter (GM) volume in old age.

Methods

This was a prospective study of 1,846 participants in the Atherosclerosis Risk in Communities (ARIC) Study who underwent 3T brain MRI scans in 2011 to 2013. Participants were categorized by cognitive domain performance trajectory over the prior 20 years (cut point to define decline: 20th percentile). Associations between GM volume and cognitive declines were assessed at the voxel level with voxel-based morphometry and at the regional level with atlas-defined GM volumes of specific regions of interest.

Results

Participants were an average age of 76 years; 60% were female; and 28% were black. Participants in the top 20th percentile for decline in the memory domain had smaller GM volumes in the medial temporal lobe (−3.3%, 95% confidence interval [CI] −4.6% to −2.1%), amygdala (−2.7%, 95% CI −4.1% to −1.3%), entorhinal cortex (−4.1%, 95% CI −6.0% to −2.2%), and hippocampus (−3.8%, 95% CI −5.2% to −2.4%) compared to participants who were in the lowest 80th percentile for decline in all domains. In contrast, among participants who were in the top 20th percentile for decline in the language or executive function domains, GM volumes were smaller in more brain regions.

Conclusions

Declines in memory function were associated with brain volume loss in the medial temporal and hippocampal formations. Declines in language and executive function were associated with decreases in brain volumes across more noncontiguous brain regions.

From the Department of Neurology (A.L.C.S., R.F.G.), Johns Hopkins University School of Medicine, Baltimore, MD; Departments of Radiology (M.L.S., J.L.G., C.G.S. C.R.J.), Information Technology (M.L.S., J.L.G.), and Neurology (D.S.K.), Mayo Clinic, Rochester, MN; Department of Epidemiology (A.W., A.G., R.F.G., A.R.S.), Johns Hopkins University Bloomberg School of Public Health; Johns Hopkins University Center on Aging and Health (A.G.), Baltimore, MD; and Department of Geriatrics (T.H.M.), University of Mississippi Medical Center, Jackson.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ARIC = Atherosclerosis Risk in Communities; **CI** = confidence interval; **DSST** = Digit Symbol Substitution Test; **DWRT** = Delayed Word Recall Test; **GM** = gray matter; **MCALT** = Mayo Clinic Adult Lifespan Template; **MMSE** = Mini-Mental State Examination; **WFT** = Word Fluency Test.

Gray matter (GM) atrophy in older adults affects all areas of the brain but is more pronounced in some areas than others.^{1–3} Prior studies have investigated the associations of current cognitive function and prevalent dementia with GM volume using voxel-based morphometry methods^{4–9}; however, the association of GM volume in old age with the trajectory of cognitive change over the years preceding the assessment of GM volume among individuals is less well studied. Associations in older populations that take into account prior cognitive change are more likely than cross-sectional associations to represent common brain pathology that develops over the age interval during which the change in cognition is assessed.¹⁰ Cross-sectional associations, in contrast, might reflect brain differences that occurred earlier such as from traumatic injuries or even inherited brain-structural differences.

The Atherosclerosis Risk in Communities (ARIC) Study is ideally poised to assess associations of GM volume in old age with cognitive declines occurring over a median of 20 years before MRI scans among community-dwelling individuals. We hypothesized that greater prior declines in the domains of memory, language, and executive function are associated with reduced GM volume in distinct brain regions compared with persons with less declines in any of the domains. Specifically, we hypothesized that prior decline in (1) memory is associated with reduced GM volume in the medial temporal lobe, posterior cingulate, olfactory campus, amygdala, entorhinal cortex, and hippocampus; (2) language is associated with reduced volume in the left inferior frontal gyrus and left superior temporal gyrus, and (3) executive function is associated with reduced volume in the prefrontal cortex, anterior cingulate, and subcortical regions.

Methods

Study participants

The ARIC Study is an ongoing community-based prospective cohort of 15,792 adults 45 to 65 years of age at study baseline (visit 1, 1987–1989) from the 4 US communities of selected suburbs of Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi.¹¹ A subsample of participants who attended the fifth visit in 2011 to 2013 was selected for brain MRI scans. Selection criteria for the MRI scan were described in detail previously¹² but briefly included absence of MRI contraindications and any of the following: prior participation in an ARIC Brain MRI Ancillary Study,^{13,14} low cognitive test scores or declines on longitudinally administered tests, or an

age-stratified random sample of participants without evidence of cognitive impairment at visit 5. Very few participants ($n = 11$, 0.6%) with significant cognitive impairment consistent with dementia (defined as low Mini-Mental State Examination [MMSE] score [<21 for whites and <19 for blacks]) were included in the brain MRI population. In total, 1,846 participants had adequate visit 5 brain MRI scans (0.6% with dementia as defined by the MMSE criteria above, 36% meeting criteria for mild cognitive impairment, and 63% classified as cognitively normal by the adjudication panel using methods described previously¹⁵).

Standard protocol approvals, registrations, and patient consents

The ARIC Study has been approved by the Institutional Review boards of all participating institutions (University of Minnesota, Johns Hopkins University, University of North Carolina, Wake Forest University, and University of Mississippi). All participants gave written informed consent at each study visit.

Neuropsychological tests and definition of cognitive decline

Cognitive function was assessed at visits 2 (1990–1992), 4 (1996–1998), and 5 (2011–2013). At visits 2 and 4, 3 standard tests were used: the Delayed Word Recall Test (DWRT),¹⁶ the Word Fluency Test (WFT),¹⁷ and the Digit Symbol Substitution Test (DSST).¹⁸ At visit 5, the test battery included the DWRT,¹⁶ Logical Memory I and II,¹⁹ Incidental Learning,¹⁸ the WFT,¹⁷ the Boston Naming Test,²⁰ the DSST,¹⁸ the Trail Making Test Parts A and B,²¹ and Digit Span Backwards.¹⁹ The tests were grouped into 3 domains (memory, language, and executive function), as previously described.²²

The memory domain comprised the DWRT, Logical Memory I and II, and Incidental Learning. The DWRT¹⁶ is a test of delayed episodic verbal memory in which participants register and then are asked to recall 10 common nouns after a 5-minute delay. Logical Memory I and II of the Wechsler Memory Scale–Revised¹⁹ are tests of immediate and delayed recall for events from 2 short stories. Incidental Learning¹⁸ is a test of delayed recall for elements of the DSST.

The language domain was made up of the WFT and the Boston Naming Test. The WFT¹⁷ is a test of language that tests the ability to spontaneously generate words beginning with a particular letter (F, A, and S) in 60 seconds. The Boston Naming Test²⁰ is a test of language in which participants name common objects from pictures.

The executive function domain was composed of the DSST, the Trail Making Test Parts A and B, and Digit Span Backwards. The DSST of the Wechsler Adult Intelligence Scale III¹⁸ is a test of executive function and processing speed in which participants are asked to translate numbers to symbols using a key. The Trail Making Test Part A²¹ is a test of processing speed in which participants are asked to connect randomly ordered numbers on a page. The Trail Making Test Part B²¹ is a test of processing speed and task-switching ability that involves alternating between numbers and letters on a page. Digit Span Backwards¹⁹ is a test of attention in which participants state a series of digits backward.

Factor scores for memory, language, and executive functioning were generated for each visit using latent variable methods previously described.^{22–25} Briefly, we estimated a confirmatory factor analysis of the ARIC cognitive test battery at ARIC visit 5. The model was extended to ARIC visits 2 and 4 by fixing item parameters to be equal across visits for the tests common to all visits. This method provides an unbiased estimate of each participant's level of cognitive performance at each study visit that are on a common metric regardless of the test battery used at any particular visit.^{22–24} Hence, this method provides a valid approach for measuring within-person cognitive decline, which we then used to classify persons into the worst quintile of cognitive decline.

Linear mixed-effects models with random intercepts and random slopes (unstructured correlation matrices and robust variance estimates) adjusted for age (continuous) and race (white, black) were used to obtain the slope of cognitive change over ≈ 20 years (from visit 2 to 5) for each domain for each participant. Prior cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈ 20 years). Participants were then grouped into 8 groups: least 80% decline in all domains (reference) ($n = 1,122$); greatest 20% decline in memory only ($n = 164$); greatest 20% decline in language only ($n = 136$); greatest 20% decline in executive function only ($n = 140$); greatest 20% decline in memory and language ($n = 56$); greatest 20% decline in memory and executive function ($n = 55$); greatest 20% decline in language and executive function ($n = 85$); and greatest 20% decline in all domains ($n = 88$). Our main analyses focused on the first 4 groups with either the least 80% decline (reference) in all domains or the greatest 20% decline in only 1 domain.

Brain MRI and voxel-based morphometry

Brain MRI scans at ARIC visit 5 were performed with four 3T scanners (Maryland: Siemens Verio; North Carolina: Siemens Skyra; Minnesota: Siemens Trio; Mississippi: Siemens Skyra; Siemens Medical Solutions, Malvern, Pennsylvania). Each participant's T1-weighted MRI scan was segmented into GM, white matter, and CSF probability map images using SPM12 unified segmentation²⁶ with the Mayo Clinic Adult Lifespan Template (MCALT; nitrc.org/projects/mcalt/) tissue priors²⁷

and population-optimized segmentation settings.²⁸ For voxel-based morphometry analyses, the GM images were spatially normalized to the MCALT space, modulated, and smoothed with an 8-mm full width at half-maximum gaussian kernel. The smoothed, modulated, normalized GM images were then used in the SPM12 general linear model framework to estimate models of associations between the cognitive decline groups and GM volume on a voxel-wise basis. For the region of interest-level analyses, an atlas consisting of 122 region-of-interest labels, derived from the automated anatomic labeling atlas,²⁹ was propagated from the MCALT space to each participant's MRI native space using Advanced Normalization Tools software.³⁰ The participant space atlas labels were then used to parcellate each participant's GM images into regions of interest, and the GM volume for each region of interest was computed by summing the GM probabilities within each region of interest and multiplying by the voxel volume. To obtain total intracranial volume, the GM, white matter, and CSF probabilities were summed and thresholded. Hole filling and morphologic operations were performed to remove any spurious disconnected regions.

We hypothesized a priori that GM volumes would be associated with cognitive domain decline groups in regions of interest known to be associated with current performance in their respective domains: memory (medial temporal lobe, hippocampus, amygdala, posterior cingulate, and olfactory cortex), language (left inferior frontal gyrus and left superior temporal gyrus), and executive function (prefrontal cortex, anterior cingulate, and subcortical regions). Several other regions of interest were also explored including: angular gyrus, calcarine fissure, cerebellum, basal ganglia, fusiform gyrus, Heschl gyrus, insula, lingual, cuneus, precentral gyrus, precuneus, postcentral gyrus, rolandic fissure, supplementary motor cortex, supramarginal gyrus, and thalamus.

Statistical analyses

Visit 5 participant characteristics are shown with means and SD used for continuous variables and percentages for categorical variables. Characteristics were compared across cognitive decline groups with t tests for continuous variables and χ^2 tests for categorical variables.

Linear regression models adjusted for age (continuous; years), sex (male, female), race (white, black), education (less than high school; high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous; centimeters cubed) were used to evaluate associations of prior cognitive decline with regional GM volumes. For each region of interest, the strength of the association (regression coefficients) was expressed as percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains). A negative value indicates a smaller region of interest compared with the reference group. Interactions with age, sex, and race were tested.

Figure Voxel-based morphometry maps showing comparisons between those in the greatest 20% decline and those in the least 80% decline in (A and B) memory, (C and D), language, and (E and F) executive function (n = 1,846)

Models adjusted for age (continuous), sex (male, female), race (white, black), and education (less than high school; high school, GED, or vocational school; college, graduate or professional school). Correction was applied for multiple comparisons using false discovery rate with $p < 0.05$. Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈ 20 years). For each panel, the right and left hemispheres of the brain are depicted on the corresponding side of the figure.

Table 1 Participant characteristics at ARIC visit 5 (2011–2013) (n = 1,846)

	Least 80% decline in all domains (n = 1,122)	Greatest 20% decline in memory only (n = 164)	Greatest 20% decline in language only (n = 136)	Greatest 20% decline in executive function only (n = 140)	Greatest 20% decline in memory and language (n = 56)	Greatest 20% decline in memory and executive function (n = 55)	Greatest 20% decline in language and executive function (n = 85)	Greatest 20% decline in all domains (n = 88)
Age, mean (SD), y	75.4 (5.1)	77.7 (5.4)	76.8 (5.4)	76.3 (5.4)	77.8 (4.8)	79.1 (5.4)	77.0 (5.4)	79.7 (4.9)
Female, %	61.2	43.9	67.7	54.3	57.1	65.5	74.1	59.1
Race, %								
White	82.9	87.1	59.6	40.7	64.3	54.6	24.7	34.1
Black	17.0	12.8	40.4	59.3	35.7	45.5	75.3	65.9
Education, %								
Less than high school, high school, GED, or vocational school	43.6	53.1	76.5	67.1	78.6	74.6	85.9	87.5
College, graduate or professional school	56.4	46.9	23.5	32.9	21.4	25.5	14.1	12.5
Cigarette smoking, %								
Current	4.6	4.9	2.9	8.6	7.1	5.5	8.2	5.7
Former	48.5	48.8	49.3	48.6	48.2	49.1	31.8	44.3
Never	41.5	42.7	40.4	36.4	37.5	40.0	50.6	36.4
Missing	5.4	3.7	7.4	6.4	7.1	5.5	9.4	13.6
Hypertension, %	70.6	66.5	80.9	83.6	78.6	85.5	90.6	87.5
Diabetes mellitus, %	29.8	34.2	38.2	42.9	39.3	45.5	42.4	43.2
Coronary heart disease, %	8.7	9.8	8.8	12.1	3.6	13.6	14.1	17.1
Mild cognitive impairment, %	20.5	73.8	53.7	40.0	80.4	70.9	45.9	72.7
Cognition, mean (SD)								
MMSE score	28.3 (1.7)	26.9 (2.3)	26.4 (2.3)	26.2 (2.2)	25.5 (2.9)	25.7 (2.2)	24.6 (2.9)	23.8 (2.9)
Memory factor decline score	−3.6 (1.4)	−6.7 (0.6)	−4.6 (0.9)	−4.5 (1.0)	−6.8 (0.6)	−6.8 (0.7)	−4.7 (0.8)	−7.0 (0.6)
Language factor decline score	0.1 (0.7)	−0.3 (0.6)	−1.6 (0.3)	−0.5 (0.4)	−1.6 (0.4)	−0.6 (0.5)	−1.8 (0.4)	−1.9 (0.4)
Executive function factor decline score	−0.6 (0.6)	−0.9 (0.4)	−1.1 (0.4)	−1.9 (0.2)	−1.2 (0.3)	−1.9 (0.2)	−1.9 (0.2)	−2.0 (0.2)
Brain regions of interest, mean (SD), cm³								
Medial temporal lobe	14.7 (1.5)	14.4 (1.8)	14.2 (1.6)	14.1 (1.6)	14.0 (1.7)	13.6 (1.7)	13.6 (1.8)	13.4 (1.8)
Posterior cingulate	1.8 (0.4)	1.8 (0.4)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.6 (0.3)	1.7 (0.4)	1.6 (0.4)

Continued

Table 1 Participant characteristics at ARIC visit 5 (2011–2013) (n = 1,846) (continued)

	Least 80% decline in all domains (n = 1,122)	Greatest 20% decline in memory only (n = 164)	Greatest 20% decline in language only (n = 136)	Greatest 20% decline in executive function only (n = 140)	Greatest 20% decline in memory and language (n = 56)	Greatest 20% decline in memory and executive function (n = 55)	Greatest 20% decline in language and executive function (n = 85)	Greatest 20% decline in all domains (n = 88)
Olfactory	1.7 (0.3)	1.8 (0.3)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)
Amygdala	2.2 (0.2)	2.2 (0.3)	2.2 (0.3)	2.2 (0.3)	2.1 (0.3)	2.1 (0.2)	2.1 (0.3)	2.1 (0.3)
Entorhinal cortex	3.8 (0.6)	3.8 (0.7)	3.6 (0.6)	3.6 (0.6)	3.5 (0.6)	3.5 (0.7)	3.4 (0.5)	3.4 (0.6)
Hippocampus	7.1 (0.8)	6.9 (0.9)	6.9 (0.9)	6.8 (0.8)	6.8 (0.8)	6.5 (0.8)	6.6 (0.9)	6.4 (0.9)
Left inferior frontal gyrus	7.1 (1.2)	7.0 (1.2)	6.6 (1.2)	6.6 (1.1)	7.2 (1.5)	6.5 (1.4)	6.2 (1.1)	6.4 (1.1)
Left superior temporal gyrus	12.7 (1.6)	12.8 (1.6)	12.2 (1.6)	12.1 (1.6)	12.3 (1.8)	12.0 (1.6)	11.8 (1.9)	12.0 (1.5)
Prefrontal cortex	35.1 (4.1)	35.2 (4.1)	33.4 (4.1)	33.1 (4.3)	34.1 (5.1)	33.2 (5.1)	32.0 (5.0)	32.5 (4.5)
Anterior cingulate	7.0 (1.2)	7.1 (1.4)	6.8 (1.2)	6.6 (1.2)	6.8 (1.5)	6.3 (1.3)	6.3 (1.4)	6.3 (1.0)
Subcortical	32.7 (3.1)	33.0 (3.2)	31.6 (3.2)	31.5 (3.3)	32.1 (3.2)	30.5 (3.8)	31.0 (3.6)	30.7 (3.3)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; MMSE = Mini-Mental State Examination.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

In sensitivity analyses, models for the language domain were repeated restricted to right-handed participants (n = 1,725). In 3 other sensitivity analyses, we repeated all analyses (1) excluding 213 participants scoring <5th percentile on any baseline (visit 2, 1990–1992) cognitive test (n = 1,633), (2) excluding 11 participants with low MMSE score (<19 for blacks and <21 for whites, n = 1,835) to exclude possible prevalent cases of mild dementia at baseline, and (3) excluding 567 participants with prior infarct(s) and individuals with the greatest 10% white matter hyperintensity burden (n = 1,279).

All reported tests were 2 sided, and a value of $p < 0.05$ was considered significant. In voxel-based analyses, correction for multiple comparisons was performed using a false discovery rate with $p < 0.05$. Analyses were performed with Stata SE version 15 (StataCorp, College Station, TX) and SPM12 (<http://www.ucl.ac.uk/spm/software/spm12>).

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Characteristics of the study population at visit 5 (2011–2013) are shown by pattern of cognitive decline in table 1.

Participants were an average of 76 years of age; 60% of the participants were female; and 28% were black. Compared to participants with the least 80% decline in all domains, those with the greatest 20% decline in ≥1 domains were older (78 vs 75 years, $p < 0.001$); of similar sex (58% vs 61% female, $p = 0.2$); more likely to be black (45% vs 17%, $p < 0.001$); less likely to have a college, graduate, or professional school education (28% vs 56%, $p < 0.001$); and more likely to have hypertension (81% vs 71%, $p < 0.001$) and diabetes mellitus (40% vs 30%, $p < 0.001$).

Table 2 shows the adjusted associations of decline groups with region of interest GM volumes. Participants with the greatest 20% decline in the memory domain only (i.e., whatever declines they had in other domains did not put them into the category of greatest 20%) had smaller GM volumes in the medial temporal lobe (−3.3%, 95% confidence interval [CI] −4.6% to −2.1%), amygdala (−2.7%, 95% CI −4.1% to −1.3%), entorhinal cortex (−4.1%, 95% CI −6.0% to −2.2%), and hippocampus (−3.8%, 95% CI −5.2% to −2.4%) compared to participants with the least 80% decline in all domains. Participants with the greatest 20% decline in the language domain had smaller GM volume in the left inferior frontal gyrus (−3.3%, 95% CI −4.4% to −0.5%) and the left superior temporal gyrus (−2.6%, 95% CI −4.6% to −0.7%) compared to participants with the least 80% decline in all domains, as hypothesized, but also in the prefrontal cortex (−2.6%, 95% CI −4.4% to −0.9%) and subcortical areas (−1.5%, 95% CI

Table 2 Adjusted^a associations of decline groups with region of interest GM volumes^b (n = 1,846)

	Least 80% decline in all domains (n = 1,122)	Greatest 20% decline in memory only (n = 164)	Greatest 20% decline in language only (n = 136)	Greatest 20% decline in executive function only (n = 140)	Greatest 20% decline in memory and language (n = 56)	Greatest 20% decline in memory and executive function (n = 55)	Greatest 20% decline in language and executive function (n = 85)	Greatest 20% decline in all domains (n = 88)
Regions hypothesized to be associated with memory								
Medial temporal lobe	0 (Reference)	-3.3 (-4.6 to -2.1)	-0.7 (-2.1 to 0.7)	-0.8 (-2.3 to 0.6)	-2.9 (-4.9 to -0.8)	-2.5 (-4.6 to -0.4)	-2.5 (-4.4 to -0.7)	-4.0 (-5.8 to -2.2)
Posterior cingulate	0 (Reference)	-1.2 (-4.0 to 1.7)	-2.0 (-5.2 to 1.1)	-0.5 (-3.7 to 2.7)	-0.9 (-5.6 to 3.8)	-5.6 (-10.4 to -0.9)	-0.7 (-4.8 to 3.4)	-4.5 (-8.6 to -0.5)
Olfactory	0 (Reference)	-0.6 (-2.5 to 1.3)	-0.7 (-2.8 to 1.4)	-0.2 (-2.4 to 1.9)	0.1 (-3.0 to 3.3)	-0.2 (-3.4 to 3.0)	-2.0 (-4.8 to 0.7)	-1.1 (-3.8 to 1.6)
Amygdala	0 (Reference)	-2.7 (-4.1 to -1.3)	-0.9 (-2.4 to 0.7)	-1.2 (-2.7 to 0.3)	-3.5 (-5.7 to -1.2)	-2.5 (-4.8 to -0.2)	-2.2 (-4.1 to -0.2)	-3.7 (-5.6 to -1.7)
Entorhinal cortex	0 (Reference)	-4.1 (-6.0 to -2.2)	-1.3 (-3.4 to 0.8)	-0.3 (-2.5 to 1.8)	-4.6 (-7.7 to -1.5)	-1.0 (-4.1 to 2.2)	-2.0 (-4.7 to 0.7)	-4.2 (-6.9 to -1.5)
Hippocampus	0 (Reference)	-3.8 (-5.2 to -2.4)	0.0 (-1.6 to 1.5)	-1.3 (-2.9 to 0.2)	-2.3 (-4.6 to 0.0)	-3.8 (-6.1 to -1.4)	-3.0 (-5.0 to -1.0)	-4.6 (-6.5 to -2.6)
Regions hypothesized to be associated with language								
Left inferior frontal gyrus	0 (Reference)	-1.5 (-4.1 to 1.0)	-3.3 (-6.1 to -0.5)	-3.5 (-6.4 to -0.7)	4.1 (0.0 to 8.3)	-2.3 (-6.6 to 1.9)	-7.5 (-11.1 to -3.8)	-3.3 (-6.9 to 0.3)
Left superior temporal gyrus	0 (Reference)	-1.2 (-2.9 to 0.6)	-2.6 (-4.6 to -0.7)	-3.1 (-5.1 to -1.2)	-2.2 (-5.1 to 0.7)	-1.6 (-4.5 to 1.4)	-4.5 (-7.0 to -2.0)	-2.2 (-4.7 to 0.3)
Regions hypothesized to be associated with executive function								
Prefrontal cortex	0 (Reference)	-0.8 (-2.4 to 0.8)	-2.6 (-4.4 to -0.9)	-3.1 (-4.9 to 1.4)	-1.2 (-3.8 to 1.4)	-0.8 (-3.5 to 1.9)	-5.1 (-7.4 to -2.8)	-2.9 (-5.1 to -0.6)
Anterior cingulate	0 (Reference)	0.3 (-2.2 to 2.8)	-0.5 (-3.3 to 2.3)	-1.8 (-4.6 to 1.1)	-0.2 (-4.3 to 4.0)	-4.4 (-8.6 to -0.2)	-5.5 (-9.1 to -1.9)	-4.8 (-8.4 to -1.3)
Subcortical	0 (Reference)	-0.3 (-1.5 to 0.9)	-1.5 (-2.8 to -0.2)	-2.0 (-3.3 to -0.7)	-0.6 (-2.6 to 1.3)	-3.0 (-5.0 to -1.0)	-2.5 (-4.2 to -0.8)	-3.0 (-4.7 to -1.3)

Abbreviation: GM = gray matter.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

^a Adjusted for age (continuous), sex (male, female), race (white, black), education (less than high school; high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous).^b Regression coefficients represent percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains).

Table 3 Adjusted^a associations of decline groups with language region of interest GM volumes^b (sensitivity analyses looking at language and handedness; n = 1,725)

Sensitivity analysis: restricted to right-handed participants (n = 1,721)	Least 80% decline in all domains (n = 1,051)	Greatest 20% decline in memory only (n = 148)	Greatest 20% decline in language only (n = 127)	Greatest 20% decline in executive function only (n = 133)	Greatest 20% decline in memory and language (n = 51)	Greatest 20% decline in memory and executive function (n = 53)	Greatest 20% decline in language and executive function (n = 79)	Greatest 20% decline in all domains (n = 83)
Left inferior frontal gyrus	0 (Reference)	-1.8 (-4.5 to 0.8)	-4.0 (-6.9 to -1.0)	-3.0 (-6.0 to -0.1)	4.5 (0.1 to 8.9)	-2.0 (-6.3 to 2.4)	-7.2 (-11.0 to -3.4)	-2.8 (-6.6 to 0.9)
Left superior temporal gyrus	0 (Reference)	-1.6 (-3.4 to 0.2)	-3.0 (-5.0 to -1.0)	-3.4 (-5.4 to -1.4)	-3.4 (-6.5 to -0.4)	-1.5 (-4.5 to 1.5)	-4.9 (-7.5 to -2.3)	-2.7 (-5.3 to -0.2)

Abbreviation: GM = gray matter.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

^a Adjusted for age (continuous), sex (male, female), race (white, black), education (less than high school, high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous).^b Regression coefficients represent percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains).

-2.8% to -0.2%). In language domain sensitivity analyses restricted to right-handed participants, associations with the left inferior frontal and left superior temporal gyri were similar but slightly stronger compared to our main results (table 3). Participants with the greatest 20% decline in the executive function domain had smaller GM volumes in the prefrontal cortex (-3.1%, 95% CI -4.9% to -1.4%) and subcortical (-2.0%, 95% CI -3.3% to -0.7%) areas compared to participants with the least 80% decline in all domains, as hypothesized a priori, and in the left inferior frontal gyrus (-3.5%, 95% CI -6.4% to -0.7%) and in the left superior temporal gyrus (-3.1%, 95% CI -5.1% to -1.2%). In general, smaller GM volumes were seen in more regions among participants with the greatest 20% decline in multiple domains (table 2). There was no evidence for interaction by age in any of these associations (all *p* for interaction > 0.05); however, there was evidence for 2 interactions by sex in associations of decline groups with olfactory (*p* for interaction = 0.009) and amygdala (*p* for interaction < 0.001) volumes, with stronger associations of memory with smaller olfactory volumes among men and smaller amygdala volumes among women. There was also evidence for interactions by race in associations of decline groups with olfactory volumes (*p* for interaction = 0.01) volumes, with stronger associations of memory with smaller volumes in this region among blacks. Sensitivity analyses yielded conclusions similar to our main results when 213 participants scoring below the fifth percentile on any baseline (visit 2, 1990–1992) cognitive test were excluded (table 4), when 11 participants with low MMSE scores (<19 for blacks and <21 for whites) were excluded (table 5), and when 567 participants with prior infarct(s) and individuals with the greatest 10% white matter hyperintensity burden were excluded (table 6).

Voxel-based morphometry group difference comparisons of GM between those in the greatest 20% decline and those in the least 80% decline in memory, language, and executive function are shown in the figure. The voxel-based morphometry maps show sharply limited areas of smaller volume in the medial temporal lobes and hippocampus in association with prior memory decline and show more broadly distributed areas in association with prior declines in language and executive function. Adjusted associations of decline groups with 16 regions of interest GM volumes not hypothesized a priori to be associated with cognitive decline domains are shown in table e-1 (available from Dryad, doi.org/10.5061/dryad.nr0kj16). In these exploratory analyses, prior declines in language and executive function were associated with smaller GM volumes in multiple regions of interest, whereas prior decline in memory was associated only with smaller GM volume in the precuneus (-2.1%, 95% CI -3.9% to -0.4%).

Discussion

In this community-based population, prior decline in the memory domain was associated with lower GM volumes in

Table 4 Adjusted^a associations of decline groups with regions of interest GM volumes^b excluding individuals scoring below the fifth percentile on any baseline (visit 2) cognitive test (n = 1,633)

	Least 80% decline in all domains (n = 1,065)	Greatest 20% decline in memory only (n = 149)	Greatest 20% decline in language only (n = 114)	Greatest 20% decline in executive function only (n = 119)	Greatest 20% decline in memory and language (n = 44)	Greatest 20% decline in memory and executive function (n = 46)	Greatest 20% decline in language and executive function (n = 49)	Greatest 20% decline in all domains (n = 47)
Regions hypothesized to be associated with memory								
Medial temporal lobe	0 (Reference)	-3.3 (-4.6 to -2.0)	-0.6 (-2.1 to 0.9)	-0.6 (-2.2 to 0.9)	-3.5 (-5.8 to -1.2)	-3.0 (-5.3 to -0.7)	-2.6 (-4.9 to -0.4)	-3.8 (-6.1 to -1.5)
Posterior cingulate	0 (Reference)	-0.1 (-3.1 to 2.8)	-2.8 (-6.1 to 0.6)	-0.8 (-4.1 to 2.6)	-0.6 (-5.8 to 4.6)	-5.6 (-10.7 to -0.4)	-1.6 (-6.7 to 3.4)	-5.8 (-10.9 to -0.6)
Olfactory	0 (Reference)	-0.4 (-2.4 to 1.6)	-0.5 (-2.8 to 1.8)	-0.6 (-2.9 to 1.7)	-0.4 (-3.9 to 3.1)	0.1 (-3.3 to 3.6)	-2.1 (-5.5 to 1.3)	-1.4 (-4.9 to 2.1)
Amygdala	0 (Reference)	-2.8 (-4.2 to -1.3)	-1.2 (-2.8 to 0.5)	-1.5 (-3.2 to 0.1)	-4.9 (-7.4 to -2.4)	-2.3 (-4.8 to 0.2)	-1.5 (-3.9 to 1.0)	-3.1 (-5.6 to -0.6)
Entorhinal cortex	0 (Reference)	-4.2 (-6.2 to -2.2)	-1.5 (-3.8 to 0.8)	-0.1 (-2.4 to 2.1)	-5.8 (-9.3 to -2.3)	-0.9 (-4.3 to 2.6)	-2.0 (-5.4 to 1.5)	-5.6 (-9.1 to -2.1)
Hippocampus	0 (Reference)	-3.8 (-5.3 to -2.4)	0.0 (-1.7 to 1.6)	-1.2 (-2.9 to 0.4)	-2.9 (-5.5 to -0.4)	-4.0 (-6.6 to -1.5)	-2.7 (-5.2 to -0.2)	-3.6 (-6.2 to -1.1)
Regions hypothesized to be associated with language								
Left inferior frontal gyrus	0 (Reference)	-1.4 (-4.1 to 1.2)	-2.5 (-5.6 to 0.5)	-3.4 (-6.5 to -0.4)	3.6 (-1.1 to 8.2)	-3.2 (-7.8 to 1.4)	-8.3 (-12.8 to -3.7)	-4.4 (-9.0 to 0.2)
Left superior temporal gyrus	0 (Reference)	-1.1 (-2.9 to 0.8)	-2.3 (-4.4 to -0.3)	-3.6 (-5.7 to -1.6)	-2.8 (-6.0 to 0.4)	-1.5 (-4.6 to 1.7)	-5.3 (-8.4 to -2.2)	-4.3 (-7.5 to -1.1)
Regions hypothesized to be associated with executive function								
Prefrontal cortex	0 (Reference)	-0.6 (-2.2 to 1.1)	-2.3 (-4.2 to -0.4)	-3.9 (-5.8 to -2.0)	-0.7 (-3.6 to 2.2)	-1.1 (-3.9 to 1.8)	-5.2 (-8.0 to -2.4)	-3.6 (-6.5 to -0.7)
Anterior cingulate	0 (Reference)	0.5 (-2.2 to 3.1)	0.2 (-2.8 to 3.2)	-2.8 (-5.8 to 0.3)	-1.4 (-6.0 to 3.3)	-5.5 (-10.0 to -0.9)	-6.4 (-10.9 to -1.9)	-3.6 (-8.1 to 1.0)
Subcortical	0 (Reference)	-0.1 (-1.4 to 1.1)	-1.6 (-3.0 to -0.1)	-2.1 (-3.5 to -0.7)	-1.1 (-3.2 to 1.1)	-3.4 (-5.5 to -1.2)	-2.0 (-4.1 to 0.1)	-2.2 (-4.4 to -0.1)

Abbreviation: GM = gray matter.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

^a Adjusted for age (continuous), sex (male, female), race (white, black), education (less than high school; high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous).^b Regression coefficients represent percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains).

Table 5 Adjusted^a associations of decline groups with regions of interest GM volumes^b excluding individuals with low MMSE scores (<19 for blacks and <21 for whites) (n = 1,835)

	Least 80% decline in all domains (n = 1,118)	Greatest 20% decline in memory only (n = 162)	Greatest 20% decline in language only (n = 136)	Greatest 20% decline in executive function only (n = 139)	Greatest 20% decline in memory and language (n = 55)	Greatest 20% decline in memory and executive function (n = 55)	Greatest 20% decline in language and executive function (n = 81)	Greatest 20% decline in all domains (n = 85)
Regions hypothesized to be associated with memory								
Medial temporal lobe	0 (Reference)	-3.3 (-4.5 to -2.0)	-0.7 (-2.1 to 0.7)	-0.8 (-2.2 to 0.6)	-3.0 (-5.1 to -0.9)	-2.5 (-4.7 to -0.4)	-2.7 (-4.5 to -0.8)	-4.1 (-5.9 to -2.3)
Posterior cingulate	0 (Reference)	-1.0 (-3.9 to 1.9)	-2.1 (-5.2 to 1.1)	-0.5 (-3.7 to 2.7)	-1.1 (-5.8 to 3.6)	-5.7 (-10.5 to -0.9)	-1.8 (-6.0 to 2.3)	-4.9 (-9.0 to -0.8)
Olfactory	0 (Reference)	-0.5 (-2.4 to 1.5)	-0.7 (-2.9 to 1.4)	-0.3 (-2.4 to 1.9)	0.2 (-3.0 to 3.3)	-0.3 (-3.5 to 2.9)	-2.2 (-5.0 to 0.6)	-1.4 (-4.1 to 1.4)
Amygdala	0 (Reference)	-2.6 (-4.0 to -1.2)	-0.9 (-2.4 to 0.6)	-1.2 (-2.7 to 0.4)	-3.5 (-5.8 to -1.2)	-2.6 (-4.9 to -0.3)	-2.3 (-4.3 to -0.3)	-3.8 (-5.8 to -1.9)
Entorhinal cortex	0 (Reference)	-3.9 (-5.8 to -2.0)	-1.4 (-3.4 to 0.7)	-0.3 (-2.4 to 1.8)	-4.9 (-8.1 to -1.8)	-1.0 (-4.2 to 2.1)	-1.9 (-4.7 to 0.9)	-4.6 (-7.3 to -1.8)
Hippocampus	0 (Reference)	-3.7 (-5.1 to -2.3)	0.0 (-1.6 to 1.5)	-1.3 (-2.8 to 0.3)	-2.4 (-4.8 to -0.1)	-3.8 (-6.1 to -1.4)	-3.2 (-5.3 to -1.2)	-4.6 (-6.6 to -2.5)
Regions hypothesized to be associated with language								
Left inferior frontal gyrus	0 (Reference)	-1.4 (-4.0 to 1.1)	-3.3 (-6.1 to -0.5)	-3.6 (-6.5 to -0.8)	3.6 (-0.6 to 7.9)	-2.3 (-6.6 to 1.9)	-8.2 (-11.9 to -4.5)	-3.2 (-6.9 to 0.4)
Left superior temporal gyrus	0 (Reference)	-1.1 (-2.8 to 0.7)	-2.6 (-4.6 to -0.7)	-3.2 (-5.1 to -1.2)	-2.4 (-5.3 to 0.5)	-1.6 (-4.5 to 1.4)	-4.8 (-7.3 to -2.2)	-2.4 (-5.0 to 0.1)
Regions hypothesized to be associated with executive function								
Prefrontal cortex	0 (Reference)	-0.7 (-2.3 to 0.9)	-2.6 (-4.4 to -0.9)	-3.2 (-5.0 to -1.4)	-1.2 (-3.9 to 1.4)	-0.8 (-3.4 to 1.9)	-5.5 (-7.8 to -3.2)	-3.1 (-5.3 to -0.8)
Anterior cingulate	0 (Reference)	0.4 (-2.2 to 2.9)	-0.5 (-3.3 to 2.3)	-1.8 (-4.7 to 1.1)	-0.5 (-4.7 to 3.7)	-4.4 (-8.7 to -0.2)	-5.7 (-9.3 to -2.0)	-4.7 (-8.3 to -1.0)
Subcortical	0 (Reference)	-0.2 (-1.4 to 1.0)	-1.5 (-2.8 to -0.2)	-2.1 (-3.4 to -0.7)	-0.6 (-2.6 to 1.3)	-3.0 (-5.0 to -1.0)	-2.7 (-4.4 to -1.0)	-2.9 (-4.6 to -1.2)

Abbreviations: GM = gray matter; MMSE = Mini-Mental State Examination.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

^a Adjusted for age (continuous), sex (male, female), race (white, black), education (less than high school; high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous).^b Regression coefficients represent percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains).

Table 6 Adjusted^a associations of decline groups with region of interest GM volumes^b excluding individuals with prior infarct(s) and individuals with the greatest 10% white matter hyperintensity burden (n = 1,279)

	Least 80% decline in all domains (n = 835)	Greatest 20% decline in memory only (n = 107)	Greatest 20% decline in language only (n = 86)	Greatest 20% decline in executive function only (n = 81)	Greatest 20% decline in memory and language (n = 40)	Greatest 20% decline in memory and executive function (n = 31)	Greatest 20% decline in language and executive function (n = 45)	Greatest 20% decline in all domains (n = 54)
Regions hypothesized to be associated with memory								
Medial temporal lobe	0 (Reference)	-3.7 (-5.2 to -2.1)	-1.1 (-2.8 to 0.6)	-0.6 (-2.5 to 1.2)	-3.2 (-5.6 to -0.7)	-1.9 (-5.7 to 0.9)	-3.3 (-5.7 to -0.8)	-5.8 (-8.1 to -3.5)
Posterior cingulate	0 (Reference)	-2.3 (-5.8 to 1.3)	-1.4 (-5.4 to 2.6)	-1.1 (-5.3 to 3.1)	-1.7 (-7.3 to 4.0)	-3.2 (-9.6 to 3.2)	-0.5 (-6.1 to 5.1)	-5.7 (-10.9 to -0.6)
Olfactory	0 (Reference)	-1.2 (-3.5 to 1.1)	-0.8 (-3.5 to 1.8)	0.3 (-2.5 to 3.0)	-0.3 (-4.0 to 3.4)	-1.6 (-5.8 to 2.5)	-2.7 (-6.4 to 0.9)	-2.9 (-6.3 to 0.5)
Amygdala	0 (Reference)	-3.1 (-4.8 to -1.4)	-0.9 (-2.9 to 1.0)	-0.6 (-2.6 to 1.5)	-5.0 (-7.8 to -2.3)	-1.9 (-5.0 to 1.2)	-2.4 (-5.1 to 0.3)	-6.4 (-8.9 to -3.9)
Entorhinal cortex	0 (reference)	-4.6 (-6.9 to 2.3)	-1.2 (-3.8 to 1.4)	0.9 (-1.9 to 3.6)	-5.5 (-9.2 to -1.8)	0.8 (-3.3 to 5.0)	-2.1 (-5.8 to 1.5)	-5.3 (-8.7 to -1.9)
Hippocampus	0 (Reference)	-3.8 (-5.6 to -2.1)	-0.4 (-2.3 to 1.6)	-1.0 (-3.1 to 1.0)	-2.6 (-5.4 to 0.1)	-3.6 (-6.7 to -0.5)	-3.9 (-6.7 to -1.2)	-7.0 (-9.6 to -4.5)
Regions hypothesized to be associated with language								
Left inferior frontal gyrus	0 (Reference)	-3.1 (-6.1 to 0.0)	-4.4 (-7.9 to 1.0)	-3.0 (-6.6 to 0.6)	6.7 (1.9 to 11.6)	-0.1 (-5.6 to 5.4)	-7.1 (-11.9 to -2.3)	-4.8 (-9.2 to -0.3)
Left superior temporal gyrus	0 (Reference)	-2.4 (-4.5 to -0.3)	-2.8 (-5.2 to -0.4)	-2.4 (-4.9 to 0.9)	-3.9 (-7.3 to -0.5)	-1.1 (-5.0 to 2.7)	-4.9 (-8.2 to -1.5)	-3.4 (-6.5 to -0.3)
Regions hypothesized to be associated with executive function								
Prefrontal cortex	0 (Reference)	-1.7 (-3.6 to 0.2)	-2.5 (-4.6 to -0.3)	-1.3 (-3.6 to 0.9)	-0.7 (-3.7 to 2.4)	-0.2 (-3.6 to 3.2)	-5.6 (-8.6 to -2.6)	-2.7 (-5.5 to 0.1)
Anterior cingulate	0 (Reference)	-0.3 (-3.4 to 2.7)	-0.9 (-4.4 to 2.6)	-2.1 (-5.8 to 1.5)	-0.4 (-5.3 to 4.5)	-0.8 (-6.3 to 4.8)	-6.6 (11.5 to -1.8)	-7.9 (-12.4 to -3.4)
Subcortical	0 (Reference)	0.2 (-1.2 to 1.6)	-1.4 (-3.0 to 0.2)	-1.4 (-3.1 to 0.2)	-0.6 (-2.8 to 1.6)	-2.7 (-5.2 to -0.2)	-2.8 (-5.0 to -0.6)	-3.3 (-5.3 to -1.3)

Abbreviation: GM = gray matter.

Cognitive decline in each domain was defined as that below the 20th percentile of the slope of cognitive change (i.e., those with the greatest amount of decline over ≈20 years).

^a Adjusted for age (continuous), sex (male, female), race (white, black), education (less than high school; high school, GED, or vocational school; college, graduate or professional school), and estimated total intracranial volume (continuous).^b Regression coefficients represent percent difference in region of interest volume relative to the average size of the region of interest volume in the reference group (group with the least 80% decline in all domains).

the medial temporal lobe and hippocampal areas, whereas prior declines in the language and executive function domains were associated with lower GM volumes in more isocortical regions.

Our study extends the prior literature on associations of cognitive function with brain region volumes by evaluating regional and voxel-wise patterns of GM volume associations with prior 20-year cognitive decline. Similar to prior cross-sectional studies and in accordance with our a priori hypotheses, the group with prior decline in the memory domain was found to have less GM volume in the medial temporal lobe/hippocampal areas.^{4,9} In contrast, we found that prior declines in language alone and in executive function alone were associated with more brain regions with lower GM volume. Our results are supported by the San Francisco Memory and Aging Center study, which found that global GM volume loss was the major independent predictor of executive functions,⁵ and are similar to the result of another study⁹ that found that nonamnesic mild cognitive impairment was associated with diffusely lower GM volumes, although neither study compared the effects of global and regional volume differences. Other studies have reported that executive function is associated with lower GM volumes in localized brain regions, including prefrontal and insular GM.⁶ Etiologically, our results are consistent with what is known about the pathophysiology of different subtypes of dementias. Typical Alzheimer disease begins with memory impairment with early structural brain changes found in the hippocampus.³¹ However, at least a quarter of persons with Alzheimer disease exhibit a pattern of isocortical involvement with hippocampal sparing.^{32,33} Other dementia etiologies such as cerebrovascular disease and Lewy body disease are frequently characterized by early impairment in executive function and with a more spatially broad distribution of brain atrophy.^{34,35}

Certain limitations and strengths of this study should be taken into consideration in the interpretation of our results. In this population, we were unable to evaluate change in GM volumes over time, but we were able to leverage the 20-year longitudinal prior trajectory of change in cognitive domain function to define our cognition domain groups. In these analyses, we performed many comparisons, but we specified a priori hypotheses vs exploratory analyses and used correction for multiple comparisons in our voxel-based morphometry analyses. Another limitation of our study was that persons who developed dementia before the ARIC visit 5 MRI scan are underrepresented. However, if anything, such survival or attrition bias should work against demonstrations of cognitive-imaging associations.

On the basis of our results, we conclude that in this population, there is evidence for focal disease processes affecting the medial temporal and hippocampal brain regions associated with prior declines in memory function (e.g., Alzheimer disease, hippocampal sclerosis, primary age-related tauopathy). In contrast, the dominant pathology associated with

prior declines in language and executive function is associated with decreases in brain volumes across more noncontiguous brain regions and is likely to be related to more heterogeneous processes such as vascular dementia, Lewy body dementia, or atypical (neocortical) presentations of Alzheimer disease.

Author contributions

A.L.C. Schneider: study concept and design, analysis and interpretation, drafted manuscript. M.L. Senjem, A. Wu, A. Gross, J.L. Gunter, and C.G. Schwarz: analysis and interpretation, critical revision of the manuscript for important intellectual content. D.S. Knopman, T.H. Mosley, R.F. Gottesman, and A.R. Sharrett: acquisition of data, critical revision of the manuscript for important intellectual content. C.R. Jack: study concept and design, critical revision of the manuscript for important intellectual content.

Acknowledgment

The authors thank the staff and participants of the ARIC Study for their important contributions.

Study funding

The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C. Neurocognitive data are collected with funding from grants U01 HL096812, HL096814, 8 HL096899, HL096902, and HL096917 and the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Schneider was supported by the NIH/NINDS through an administrative supplement to award R25NS065729. Dr. Gross was supported by K01AG050699 from the NIH/National Institute on Aging.

Disclosure

A. Schneider, M. Senjem, A. Wu, and A. Gross report no disclosures relevant to the manuscript. D. Knopman is an editor for *Neurology*. J. Gunter, C. Schwarz, and T. Mosley report no disclosures relevant to the manuscript. R. Gottesman is an editor for *Neurology*. A. Sharrett and C. Jack report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* July 20, 2018. Accepted in final form October 29, 2018.

References

1. Crivello F, Tzourio-Mazoyer N, Tzourio C, Mazoyer B. Longitudinal assessment of global and regional rate of grey matter atrophy in 1,172 healthy older adults: modulation by sex and age. *PLoS One* 2014;9:e114478.
2. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci* 2003;23:3295–3301.
3. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14:21–36.
4. Pelletier A, Bernard C, Dilharreguy B, et al. Patterns of brain atrophy associated with episodic memory and semantic fluency decline in aging. *Aging* 2017;9:741–752.

5. Bettcher BM, Mungas D, Patel N, et al. Neuroanatomical substrates of executive functions: beyond prefrontal structures. *Neuropsychologia* 2016;85:100–109.
6. Ruscheweyh R, Deppe M, Lohmann H, et al. Executive performance is related to regional gray matter volume in healthy older individuals. *Hum Brain Mapp* 2013;34:3333–3346.
7. Lei Y, Su J, Guo Q, Yang H, Gu Y, Mao Y. Regional gray matter atrophy in vascular mild cognitive impairment. *J Stroke Cerebrovasc Dis* 2016;25:95–101.
8. Hilal S, Amin SM, Venketasubramanian N, et al. Subcortical atrophy in cognitive impairment and dementia. *J Alzheimers Dis* 2015;48:813–823.
9. Zhang H, Sachdev PS, Wen W, et al. Gray matter atrophy patterns of mild cognitive impairment subtypes. *J Neurol Sci* 2012;315:26–32.
10. Glymour MM, Weuve J, Chen JT. Methodological challenges in causal research on racial and ethnic patterns of cognitive trajectories: measurement, selection, and bias. *Neuropsychol Rev* 2008;18:194–213.
11. ARIC Study Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol* 1989;129:687–702.
12. Knopman DS, Griswold ME, Lirette ST, et al. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. *Stroke* 2015;46:433–440.
13. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology* 2011;76:1879–1885.
14. Mosley TH Jr, Knopman DS, Catellier DJ, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology* 2005;64:2056–2062.
15. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)* 2016;2:1–11.
16. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Arch Neurol* 1989;46:141–145.
17. Benton AL, Hamsher K. *Multilingual Aphasia Examination*. 2nd ed. Iowa City: AJA Associates; 1989.
18. Ryan J, Lopez S. Wechsler Adult Intelligence Scale-III. In: Dorfman W, Hersen M, editors. *Understanding Psychological Assessment Perspectives on Individual Differences*. New York: Kluwer Academic/Plenum Publishers; 2001:23.
19. Wechsler D. *Wechsler Memory Scale Revised Manual*. San Antonio: Psychological Corp; 1987.
20. Williams BW, Mack W, Henderson VW. Boston Naming Test in Alzheimer's disease. *Neuropsychologia* 1989;27:1073–1079.
21. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271–276.
22. Gross AL, Power MC, Albert MS, et al. Application of latent variable methods to the study of cognitive decline when tests change over time. *Epidemiology* 2015;26:878–887.
23. Gross AL, Sherva R, Mukherjee S, et al. Calibrating longitudinal cognition in Alzheimer's disease across diverse test batteries and datasets. *Neuroepidemiology* 2014;43:194–205.
24. Gross AL, Jones RN, Fong TG, Tommet D, Inouye SK. Calibration and validation of an innovative approach for estimating general cognitive performance. *Neuroepidemiology* 2014;42:144–153.
25. Gross AL, Mungas DM, Crane PK, et al. Effects of education and race on cognitive decline: an integrative study of generalizability versus study-specific results. *Psychol Aging* 2015;30:863–880.
26. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26:839–851.
27. Schwartz CG, Gunter JL, Ward CP, et al. The Mayo Clinic Adult Life Span Template: better quantification across the life span. *Alzheimers Dement* 2017;13:P93–P94.
28. Schwarz CG, Gunter JL, Chadwick P, et al. Methods to improve SPM12 tissue segmentations of older adult brains. *Alzheimers Dement* (in press 2018).
29. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273–289.
30. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 2008;12:26–41.
31. Ubhi K, Masliah E. Alzheimer's disease: recent advances and future perspectives. *J Alzheimers Dis* 2013;33(suppl 1):S185–S194.
32. Whitwell JL, Dickson DW, Murray ME, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurol* 2012;11:868–877.
33. Crane PK, Trittschuh E, Mukherjee S, et al. Incidence of cognitively defined late-onset Alzheimer's dementia subgroups from a prospective cohort study. *Alzheimers Dement* 2017;13:1307–1316.
34. Kalaria RN. The pathology and pathophysiology of vascular dementia. *Neuropharmacology* 2018;134(pt B):226–239.
35. Mayo MC, Bordelon Y. Dementia with Lewy bodies. *Semin Neurol* 2014;34:182–188.