Cerebral MRI findings and cognitive functioning

The Atherosclerosis Risk in Communities Study

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Abstract—*Objective:* To examine the association between prevalent cerebral abnormalities identified on MRI and cognitive functioning in a predominantly middle-aged, population-based study cohort. *Methods:* Cerebral MRI was performed on 1,538 individuals (aged 55 to 72) from the Atherosclerosis Risk in Communities (ARIC) cohort, with no history of stroke or TIA, at study sites in Forsyth County, NC, and Jackson, MS. White matter hyperintensities (WMHs), ventricular size, and sulcal size were graded by trained neuroradiologists on a semiquantitative, 10-point scale. Cognitive functioning was assessed using the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT). *Results:* High ventricular grade was independently associated with significantly lower scores on the DWRT and DSST and greater risk (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.51 to 3.56) of impaired scores (i.e., ≤10th percentile) on the DWRT. High sulcal grade was associated with a modest decrement in scores on the DWRT. The presence of coexisting high grade WMHs and silent infarcts was independently associated with lower scores on all cognitive tests and greater risk of impaired functioning on the DSST (OR 2.91, 95% CI: 1.23 to 6.89) and WFT (OR 2.28, 95% CI 1.03 to 5.08). The presence of two or more high-grade abnormalities was associated with increased risk of impaired functioning on all cognitive tests (DWRT: OR 2.23, 95% CI 1.40 to 3.55; DSST: OR 2.06, 95% CI 1.13 to 3.76; WFT: OR 2.07, 95% CI 1.23 to 3.49) independent of multiple covariates and silent infarcts. *Conclusion:* Common changes in brain morphology are associated with diminished cognitive functioning in middle-aged and young-elderly individuals.

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MRI provides a sensitive, noninvasive method for detecting subclinical abnormalities in cortical and subcortical brain structures. The application of MRI in population-based studies has revealed a high prevalence of cerebral abnormalities in nondemented samples,[1-5] the most common findings being white matter hyperintensities (WMHs) and cerebral atrophy. The high prevalence of MRI-detected cerebral abnormalities and their strong association with age have raised questions about their potential impact on cognitive functioning. Many previous studies of

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this association have been hampered by small sample sizes or restricted sample characteristics (e.g., including primarily patients with dementia or highly selected volunteers).[6] Three large, population-based studies of predominantly older subjects have reported significant associations between MRI-detected cerebral abnormalities and indices of cognitive performance.[3,5,7,8]

The Atherosclerosis Risk in Communities (ARIC) study is a prospective, population-based study of cardiovascular diseases conducted in a large, biracial cohort of middle-aged adults.[9] At the Visit 3 examination (1993 to 1995), a subset of participants from two ARIC study sites were invited to participate in the ARIC MRI study. Eligible participants underwent cere-

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bral MRI and completed a brief battery of cognitive tests. In the current study, we examined the relationship between prevalent cerebral abnormalities identified on MRI and cognitive performance in the predominantly middle-aged ARIC MRI cohort.

Methods. *Study population.* At inception (1987 to 1989), the ARIC study recruited 15,792 women and men, aged 45 to 64, from probability samples in four U.S. communities: Forsyth County, NC; Jackson, MS (African Americans only); selected suburbs of Minneapolis, MN; and Washington County, MD. Details of the sampling and study design have been published previously.[9] During the first 2 years (1993 and 1994) of the Visit 3 examination, participants aged 55 and older from the ARIC study sites in Forsyth County and Jackson were invited for a cerebral MRI. For reasons of participant safety, the following exclusion criteria were used: previous surgery for an aneurysm in the brain; metal fragments in the eyes, brain, or spinal cord; valvular prosthesis, cardiac pacemaker, cochlear implant, spinal cord stimulator, or other internal electrical device; pregnancy; and occupations associated with exposure to metal fragments. Of the 2,891 participants screened for eligibility, 2% of women and 6% of men were ineligible. Of those meeting inclusion criteria, 25% of women and 21% of men declined the MRI procedure.

A total of 1,949 participants underwent cerebral MRI. Individuals were excluded from the analyses if they were not African American or white (n = 4), reported a history of physician-diagnosed stroke or TIA (n = 71), or were taking medications with potentially potent CNS effects (e.g., sedatives, antipsychotics, narcotic analgesics; n = 285). Additional individuals were excluded because of missing values on key variables (n = 51), leaving a total of 1,538 available for analysis.

MRI protocol and image analysis. The MRI scanning protocol and image analysis in the ARIC study were identical to those employed in the Cardiovascular Health Study and have been published.[10] Briefly, 1.5-T MRI scanners (GE or Picker) were used. Midline sagittal images were used to identify the anterior commissure-posterior commissure line, along which oblique axial images were aligned. Spin-echo, spin-density/T2*-weighted (3000/30-90/1) and T1-weighted (500/20/1) oblique axial images with a 5-mm section thickness, 0-mm section gap, 24-cm field of view, and a 192 × 256 matrix was acquired from the vertex to the foramen magnum.

The resulting MRI was interpreted by trained readers at the ARIC MRI Reading Center at Johns Hopkins Medical Institutions in Baltimore, MD. Images were interpreted directly from a PDS-4 digital workstation consisting of four 1024 × 1024-pixel monitors capable of displaying all 96 images simultaneously. Each study had a primary and secondary interpretation rendered by different readers. All studies were assessed without knowledge of participants' age, gender, race, previous imaging findings, or vascular risk factors. All primary readers were board-certified radiologists with subspecialty training in neuroradiology. Secondary readers included the same radiologists plus an experienced neuroimaging technician.

WMHs were estimated as the total volume of periventricular and subcortical white matter signal abnormality on spin density–weighted axial images by visual comparison with eight studies that successively increased from barely detectable white matter changes (Grade 1) to extensive, confluent changes (Grade 8). Studies with no white matter changes received Grade 0, and those with changes worse than Grade 8 received Grade 9.

Ventricular size was also graded on a semiquantitative, 10-point scale by visual pattern matching. Images were compared with a series of eight studies with successively increasing ventricular size ranging from small and presumably normal (Grade 1) to severe atrophy (Grade 8). Studies considered to have ventricles smaller than those in Grade 1 received Grade 0 and those worse than Grade 8 received Grade 9. Similarly, sulcal size was assessed by comparison with eight studies with successively increasing sulcal size, with Grades 0 and 9 assigned as for ventricular size. Abnormalities interpreted as cerebral infarcts or hemorrhages were coded separately by size and location. Reference images for WMHs, ventricular, and sulcal size have been published previously.[11]

Measures of cognitive functioning. Cognitive functioning was assessed using three standardized tests: the Delayed Word Recall Test (DWRT),[12,13] the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[14] and the Word Fluency Test (WFT)[15] of the Multilingual Aphasia Examination.[16] Trained examiners administered the cognitive tests in a standardized order during one session in a quiet room. Examiner performance was monitored by audio tape recording. Tapes were review locally and shared across centers to ensure consistency with testing procedures. The details of the relationship of the ARIC cognitive test battery to demographic and medical characteristics of the entire ARIC cohort have been reported previously.[13,17]

The DWRT is a measure of verbal learning and recent memory that requires the participant to recall a list of 10 common nouns after a 5-minute delay, during which another test is given.[12] Participants were given two exposures to the nouns. To standardize elaborative processing of the words to be recalled, individuals were asked to compose sentences with each word as presented. Test scores range from 0 to 10 words recalled.

The DSST[14] is a timed paper-and-pencil task requiring translation of numbers[1-9] to symbols using a key provided at the top of the test form. The test measures psychomotor speed and concentration and is relatively unaffected by intellectual ability, memory, or learning.[15] It is a sensitive and reliable indicator of brain damage.[18] The test is scored as the total number of numbers correctly translated to symbols within 90 seconds. Besides its own value, in this study the DSST also served as a nonverbal distracter task, interposed between learning and recall for the DWRT above.

The WFT[15] measures the spontaneous production of words beginning with a given letter. Participants are given 60 seconds to generate as many words as possible beginning with the letters F, A, and S (60 seconds for each letter), avoiding proper nouns. The test is particularly sensitive to damage to the frontal lobes of the brain, especially the left frontal lobe.[15] A summary score is derived as the total number of acceptable words produced, summed across the three letters.

Other measurements and definitions. ARIC participants have been extensively characterized with respect to physical, medical, and vascular risk factors. In an effort to examine the independent effect of cerebral abnormalities on measures of cognitive functioning, we adjusted for potential confounding factors. Relevant assessments are described below.

Information on age, gender, race, education level, alcohol use, history of stroke or TIA, and medication use was assessed with standardized protocols, conducted by trained and certified interviewers. Usual intake of beer, wine, and liquor was summarized as grams of ethanol per week and dichotomized at 100 g/wk for moderate or higher alcohol intake in all analytic models. Medications used within 2 weeks before the examination were recorded and classified using the American Hospital Formulary Service and Therapeutic Classification codes.

The presence of a silent cerebral infarct was defined as MRI evidence of an infarct-like lesion (≥3 mm) in participants who reported no history of stroke or TIA. These procedures have been described in detail elsewhere.[19] Silent infarct was defined as a focal, nonmass area with an arterial vascular distribution that was hyperintense to gray matter on both spin-density and T2*-weighted images. Silent infarcts in the cerebral white matter and brainstem were defined as lesions with increased signal intensity on spin-density and T2*-weighted images and decreased signal intensity on T1-weighted images, similar to the hypointensity of CSF. In the current study, we adjusted for the presence of silent infarcts. All the measures described above were obtained at the time of the MRI procedure (Visit 3), with the exception of education level, which was obtained at Visit 1.

Statistical methods. Comparisons between participants completing the MRI and those who did not (refused or ineligible) or were excluded were evaluated using χ^2 for categorical variables and *t* test for continuous variables. The distribution of the MRI variables was expectedly positively skewed, with most participants having no or only low-grade abnormalities. To distinguish between normal and abnormal MRI findings, we dichotomized the MRI variables at approximately 1.5 SDs from the mean into no or mild grade abnormality (low grade) and moderate or higher grade abnormality (high grade). High grade was defined for each abnor-

Table 1 *Score differences in cognitive performance between those with high- and low-grade cerebral abnormalities: the ARIC study (1993–1995)*

Cerebral abnormality	Verbal memory (DWRT)		Psychomotor speed (DSST)		Word fluency (WFT)	
	z Score (SE)	p Value	z Score (SE)	p Value	z Score (SE)	p Value
Ventricular grade						
Unadjusted	−0.34 (0.074)	<0.001	−0.15 (0.075)	0.050	−0.02 (0.074)	0.817
Model 1	−0.26 (0.071)	<0.001	−0.15 (0.051)	0.003	−0.06 (0.066)	0.376
Model 2	−0.25 (0.071)	<0.001	−0.15 (0.051)	0.004	−0.05 (0.066)	0.412
Sulcal grade						
Unadjusted	−0.21 (0.058)	<0.001	−0.10 (0.058)	0.080	−0.03 (0.058)	0.576
Model 1	−0.12 (0.055)	0.036	−0.03 (0.040)	0.428	−0.05 (0.051)	0.368
Model 2	−0.12 (0.055)	0.029	−0.04 (0.040)	0.369	−0.05 (0.051)	0.332
WMH grade						
Unadjusted	−0.32 (0.083)	<0.001	−0.34 (0.083)	<0.001	−0.26 (0.083)	0.002
Model 1	−0.19 (0.079)	0.017	−0.14 (0.057)	0.016	−0.15 (0.073)	0.038
Model 2	−0.14 (0.081)	0.078	−0.10 (0.058)	0.091	−0.12 (0.074)	0.116

DWRT = Delayed Word Recall Test; DSST = Digital Symbol Substitution Test; WFT = Word Fluency Test; high grade = moderate to severe grade abnormalities; low grade = no or mild grade abnormalities; Model 1 = adjusted for age, race, gender, and education, alcohol use, and use of antidepressant medication; Model 2 = Model 1 plus adjustment for silent cerebral infarction; WMHs = white matter hyperintensities.

mality as follows: ventricular size Grade 4 or higher, sulcal size Grade 3 or higher, and WMHs Grade 3 or higher.

Two types of outcome measures were derived from the measures of cognitive function. In the first set of analyses, the cognitive test scores were examined as continuous variables. To facilitate comparison across the cognitive measures, test scores were converted to z scores. Differences in cognitive performance were then calculated between those with high- and low-grade abnormalities using linear regression. This was followed by a series of multiple linear regression analyses adjusting for age, gender, race, educational level, alcohol use, use of antidepressant medication, and silent cerebral infarction as possible confounding factors. To avoid overadjustment, we did not adjust for cerebrovascular risk factors (e.g., hypertension and diabetes) considered to be along the causal chain in the development of the MRI abnormalities under study. Age, race, gender, and educational level were considered potential effect modifiers, and their effects were tested through interaction terms.

In a second set of analyses, cognitive test scores were dichotomized into favorable and unfavorable outcomes at the 10th percentile of the sample. Logistic regression analysis was used to determine the odds ratios for impaired cognitive performance associated with high-grade MRI abnormalities. Regression models were adjusted for potential confounding factors as described above. All statistical procedures were performed using SAS software (SAS/STAT, SAS Institute Inc., Cary, NC). Results with $p < 0.05$ are reported as significant.

Results. After exclusions, the final MRI sample contained 1,538 individuals, ranging from 55 to 72 years of age (mean = 62.5, SD = 4.5). Fifty-eight percent of the sample were women and 51% were African American. Compared with those without MRI (refused or ineligible) or excluded from the analyses, those undergoing MRI were more educated (67% vs 74% with ≥12 years of education, $p < 0.001$) and more likely African American (46% vs 51%, $p < 0.05$). The prevalence of MRI abnormalities (defined above) was 14% (n = 210) for high ventricular grade, 26% (n = 399) for high sulcal grade, and 11% (n = 161) for high-grade WMHs. Ventricular grade was correlated 0.36 ($p < 0.001$) with sulcal grade and 0.26 ($p < 0.001$) with WMHs. Sulcal grade was correlated 0.10 ($p < 0.001$) with

WMHs. The prevalence of silent cerebral infarction was 11% (n = 172). The majority (88%) of silent infarcts were ≤20 mm in size and subcortical (82%) in location. Silent infarct was correlated 0.27 ($p < 0.001$) with WMHs and 0.07 ($p = 0.005$) with ventricular grade. No association was observed between silent infarcts and sulcal grade. The distribution of the cognitive test scores by MRI grade for each cerebral abnormality are shown in table E-1 (available on the *Neurology* Web site at www.neurology.org).

Table 1 shows z score differences in cognitive performance between those with high- vs low- grade (defined above) cerebral abnormalities. Participants with high ventricular grade had significantly lower scores on the DWRT (−0.34 SD) and DSST (−0.15 SD) relative to those with low ventricular grade. Adjustment for multiple covariates including age, race, gender, education, alcohol use, and use of antidepressant medication reduced the association for the DWRT to −0.26 SD ($p < 0.001$). High sulcal grade also was associated with reduced DWRT scores (−0.21 SD). After covariate adjustment, this difference was reduced to −0.12 SD ($p = 0.036$). These associations were essentially unaltered by additional adjustment for silent infarcts.

High-grade WMHs were associated with reduced scores on all three cognitive measures, ranging from −0.26 to −0.34 SD in unadjusted models (see table 1). These associations were attenuated by approximately half after adjustment for multiple covariates. Adjustment for the presence of silent infarcts produced little further attenuation; however, significance was lost. Approximately 30% (n = 50) of the sample had both high-grade WMHs and a silent infarct. Those with concomitant abnormalities had reduced scores on all three cognitive measures compared with those with neither abnormality (adjusted z score difference: DWRT = −0.32 SD, $p = 0.020$; DSST = −0.32 SD, $p < 0.001$; WFT = −0.33 SD, $p = 0.010$). Effect modification by age, race, gender, or educational level was tested

Table 2 *Odds ratio (OR) and 95% confidence interval (CI) for impaired cognitive performance in those with high-grade compared with those with low-grade cerebral abnormalities: the ARIC study (1993–1995)*

Cerebral abnormality	Verbal memory (DWRT)		Psychomotor speed (DSST)		Word fluency (WFT)	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Ventricular grade						
Unadjusted	2.37 (1.61–3.50)	<0.001	1.25 (0.81–1.92)	0.321	1.16 (0.74–1.80)	0.526
Model 1	2.35 (1.53–3.60)	<0.001	1.51 (0.87–2.63)	0.146	1.13 (0.67–1.90)	0.657
Model 2	2.32 (1.51–3.56)	<0.001	1.49 (0.85–2.60)	0.162	1.10 (0.65–1.85)	0.736
Sulcal grade						
Unadjusted	1.37 (0.97–1.95)	0.078	1.00 (0.70–1.44)	0.985	1.41 (1.00–1.99)	0.048
Model 1	1.17 (0.80–1.71)	0.418	0.96 (0.62–1.48)	0.845	1.48 (1.00–2.20)	0.051
Model 2	1.17 (0.80–1.71)	0.415	0.97 (0.62–1.50)	0.876	1.48 (1.00–2.20)	0.051
WMH grade						
Unadjusted	1.54 (0.9–2.47)	0.069	2.07 (1.35–3.18)	<0.001	2.01 (1.30–3.10)	0.002
Model 1	1.23 (0.75–2.03)	0.414	1.55 (0.90–2.68)	0.114	1.74 (1.06–2.86)	0.030
Model 2	1.13 (0.68–1.89)	0.634	1.45 (0.83–2.52)	0.195	1.60 (0.96–2.67)	0.069

Impaired cognitive performance = test score at or below the 10th percentile relative to the overall MRI cohort; DWRT = Delayed Word Recall Test; DSST = Digital Symbol Substitution Test; WFT = Word Fluency Test; high grade = moderate to severe grade abnormalities; low grade = no or mild grade abnormalities; Model 1 = adjusted for age, race, gender, and education, alcohol use, and use of antidepressant medication; Model 2 = Model 1 plus adjustment for silent cerebral infarction; WMHs = white matter hyperintensities.

for each of the MRI variables. No interactions were found (results not shown).

We were also interested in whether the MRI abnormalities were associated with more substantive cognitive deficits. We defined impaired performance as a given test score at or below the 10th percentile of the MRI cohort and computed odds ratios (ORs) and 95% confidence intervals (CIs) for impaired performance associated with high- compared with low-grade cerebral abnormalities using logistic regression. The cut points used to define impaired performance for each cognitive measure were DWRT ≤4, DSST ≤18, and WFT ≤15. Results of these analyses are shown in table 2.

High ventricular grade was strongly associated with impaired performance on the DWRT (OR 2.37, 95% CI 1.61 to 3.50) relative to low ventricular grade. This association was essentially unchanged in adjusted models. High sulcal grade was marginally associated with an increased risk of impaired performance on the WFT (OR 1.41, 95% CI 1.00 to 1.99).

High-grade WMHs were associated with a twofold greater risk of impaired performance on the DSST (OR 2.07, 95% CI 1.35 to 3.18) and WFT (OR 2.01, 95% CI 1.30 to 3.10) in unadjusted models. The association with the DSST was attenuated following covariate adjustment (see table 2). The association with the WFT was attenuated and no longer significant after adjustment for silent infarcts (OR 1.60, 95% CI 0.96 to 2.67). Those with both high-grade WMHs and a silent infarct had a significantly higher risk of impaired performance independent of covariates on the DSST (OR 2.91, 95% CI 1.23 to 6.89) and WFT (OR 2.28, 95% CI 1.03 to 5.08) compared with those with neither abnormality.

Approximately 10% of participants had multiple (two or more) high-grade abnormalities. An additional series of models were fit to assess whether this group was at higher risk of cognitive impairment compared with those with only one or no cerebral abnormality. After adjusting for multiple covariates, those with any combination of two or more high-grade abnormalities had an approximate twofold greater risk of impaired performance on all cognitive tests (DWRT: OR 2.23, 95% CI 1.40 to 3.55; DSST: OR 2.06, 95% CI 1.13 to 3.76; WFT: OR 2.07, 95% CI 1.23 to 3.49) compared with those with only one or no abnormality. These associations were unchanged after additional adjustment for silent infarcts.

Discussion. The ARIC study is a large investigation of the relationship between prevalent MRI-detected cerebral abnormalities and cognitive functioning in a predominantly middle-aged cohort. Our findings support and extend those of previous imaging studies performed in elderly samples.[3,5,7,8] In a sample of 1,538 predominantly middle-aged participants with no history of TIA or stroke, MRI-defined abnormalities were associated with reduced performance on measures of verbal memory, word fluency, and psychomotor speed. On average, differences between those with high- vs low-grade abnormalities were modest. In an effort to approximate a more clinically relevant outcome, we also examined the relationship between MRI abnormalities and impaired cognitive performance, in which impairment was defined a priori as a test score at or below the 10th percentile relative to the total cohort. Remarkably, given the age of the cohort and the predictably mild severity of the abnormalities observed, higher grade abnormalities, particularly ventricular and multiple abnormalities, were associated with significantly greater odds of impaired performance. Although impaired cognitive performance was defined relative to the ARIC MRI cohort, the psychometric

cut points used in the current study are notably consistent with national norms for these measures.[13,20]

After controlling for potential confounding factors, ventricular grade had the most robust individual association with measures of cognitive function. The strongest relationship was found between ventricular grade and verbal memory. High ventricular grade was associated with lower memory scores on average and, perhaps of greater importance, with a more than twofold greater risk of memory impairment. High sulcal grade was weakly associated with a small decrement in verbal memory.

Our findings for ventricular size are consistent with the results from two large population-based studies. In the Cardiovascular Health Study (CHS), which employed an imaging protocol and grading system identical to the current study, ventricular grade was negatively associated with psychomotor speed, upper and lower motor function, and overall functional status.[7] Similar to the current study, cognitive measures were more strongly correlated with ventricular than sulcal grade. In contrast to CHS, we found no gender differences. In a separate analysis of CHS data, ventricular grade was associated with low scores on an expanded version of the Mini-Mental State Examination and was predictive of clinically significant decline in mental status scores over a 3-year follow-up period.[21] In the Rotterdam Study, ventricular grade was significantly correlated with reduced cognitive performance on several measures including global cognitive indices, executive functions, and verbal memory.[22] Memory performance was also related to total brain volume in the National Heart, Lung, and Blood Twin Study.[23] The current findings extend these previously observed relationships between measures of cerebral volume and cognitive functioning to a younger, biracial cohort.

High-grade WMHs were associated with reduced performance on each of the cognitive measures and greater risk of impairment in verbal fluency independent of several potential confounding factors. We were not able to show a relationship independent of silent infarcts. Independent associations have been reported in older cohorts, including the population-based Rotterdam Scan Study,[5] Epidemiology of Vascular Ageing Study,[8] and the CHS.[3] Our results are perhaps not unexpected in light of the mild nature of the WMHs encountered in a middle-aged cohort and particularly given the overlap in the brain regions (and hence cognitive domains) affected by WMHs and subcortical lacunar infarcts, which were predominant in our sample. Roughly one-third of those with high-grade WMHs also had a silent infarct. Those with both conditions had significantly lower scores on the cognitive measures and increased risk of impaired functioning in psychomotor speed (OR 2.9) and verbal fluency (OR 2.3) compared with those without either condition.

Although previous studies have typically attempted to determine the individual/unique contribution of WMHs or cerebral atrophy to cognitive function, in reality these radiographic findings frequently coexist. In the ARIC cohort, 10% had two or more high-grade abnormalities. Although we did not have sufficient power to examine every combination of high-grade abnormality separately, we did examine concomitant abnormalities in the aggregate. Those with coexisting high-grade abnormalities had a twofold or greater risk of impaired functioning on each of the cognitive tests, independent of multiple covariates and silent infarcts. These findings, together with those for WMHs with silent infarcts, suggest that concomitant abnormalities are a robust risk factor for poor cognitive functioning.

African Americans have been shown to have greater risk and less favorable outcomes associated with clinical cerebrovascular disease. We have previously reported that African-American participants in ARIC had a higher prevalence of infarct-like lesions[19] and higher grade WMHs[2] compared with white participants. Because African Americans may share a disproportionate burden from both clinical and subclinical cerebrovascular disease, we tested for effect modification by race. No effect modification was found. The ARIC study is one of the few imaging studies with a large African-American sample. The biracial cohort is a strength of the present study, allowing for examination of race-specific effects and facilitating generalizability of the results.

The basis for the cerebral-cognitive relationships observed in the current study is not fully understood. WMHs are thought to be ischemic in origin, resulting from arteriosclerosis of the small penetrating arteries and arterioles supplying the white matter.[24] These vascular alterations, characterized by hyaline wall thickening, smooth muscle cell loss, and narrowing of the vessel lumen ultimately impair autoregulatory adaptation to changes in cerebral blood flow and result in either focal lesions (lacunes) or, more commonly, diffuse areas of reduced myelination (i.e., leukoariosis or WMHs as defined in the current study). The cognitive effects of these neurovascular changes presumably result from the degradation and disruption of white matter pathways connecting functionally related cortical (particularly frontal) and subcortical structures. WMHs are also commonly seen in Alzheimer disease (AD), suggesting possible alternative mechanisms to their development.

Ventricular and sulcal grades, as measures of brain volume, are influenced by genetic predisposition, perinatal and childhood events as well as processes associated with aging and disease. To the extent that brain volume reflects complexity or redundancy in neural structures, organization, or functions, greater brain volume has been hypothesized (brain reserve hypothesis) to protect against the neurocognitive sequelae associated with brain aging or disease.[25,26] Our finding that higher ventricular grade (i.e., lower brain volume) is associated with reduced cognitive functioning is consistent with this hypothesis. Notably, this association persisted after

controlling for education as well as additional possible explanatory factors.

Loss of brain volume (atrophy) in aging has been attributed primarily to neuronal loss, reduced tissue densities, and degeneration of the white matter.[27,28] Some studies have shown a relationship between cerebral atrophy and vascular risk factors, primarily hypertension and stroke. In the CHS, ventricular and sulcal sizes were associated with carotid intima-medial thickness (IMT) and stenosis,[29] but surprisingly an independent association was not observed for either hypertension or MRI-defined stroke.[7] In ARIC, we reported an association between cerebral atrophy and retinal microvascular changes, independent of carotid IMT and other vascular risk factors, suggesting the contribution of an underlying microvascular pathology in the development of cerebral atrophy.[30]

Cerebral volume loss also has been associated with AD.[31] It is possible that the brain volume–cognitive relationships observed in our study reflect the early effects of Alzheimer pathology 10 to 20 years before the development of clinical dementia. The fact that we observed associations with an (untimed) measure of verbal memory would support this hypothesis. A recent longitudinal study found that change in ventricular volume measured on MRI was a significant predictor of burden from cortical neuritic plaques and neurofibrillary tangles associated with AD, raising the intriguing possibility that ventricular enlargement may be a marker for preclinical AD pathology.[32]

Strengths of the current study include a large, biracial, population-based sample of community-dwelling individuals. MRI scans were interpreted by trained neuroradiologists using a standardized grading system and blinded to subjects' age, race, gender, and other clinical information. A limitation of the current study is the relatively narrow scope of the cognitive assessment. A more detailed assessment might have revealed additional associations undetected by the current measures and allowed for a more refined examination of putative relationships between specific morphologic findings and specific neurocognitive functions. Quantitative, automated methods of image analysis may be more reliable than the semiquantitative measures used in the current study and might have yielded more robust associations. We note that while the abnormalities defined as high grade in the current study were substantially above the cohort mean in terms of severity, they may be considered mild by clinical standards. Because those with clinical stroke or TIA were excluded, inferences may be limited to those without these conditions. No adjustment was made for multiple testing resulting from estimation of the association between three measures of cognitive function and three MRI predictor variables. However, most of the reported findings would remain significant even with a conservative adjustment (e.g., a Bonferroni-corrected significance level of $0.05/9 = 0.006$). Finally, given the cross-sectional design of this study, it is not possible to determine whether the observed cognitive decrements may have preceded the MRI abnormalities.

Although the prognostic importance of the cerebral abnormalities examined in the current study is not fully understood, our study suggests that they may begin to erode cognitive abilities in middle age. Longitudinal studies should clarify whether these abnormalities represent benign, age-related changes or pathologic, subclinical markers of neurodegenerative disease. The ARIC study will complete a second wave of MRI in 2005.

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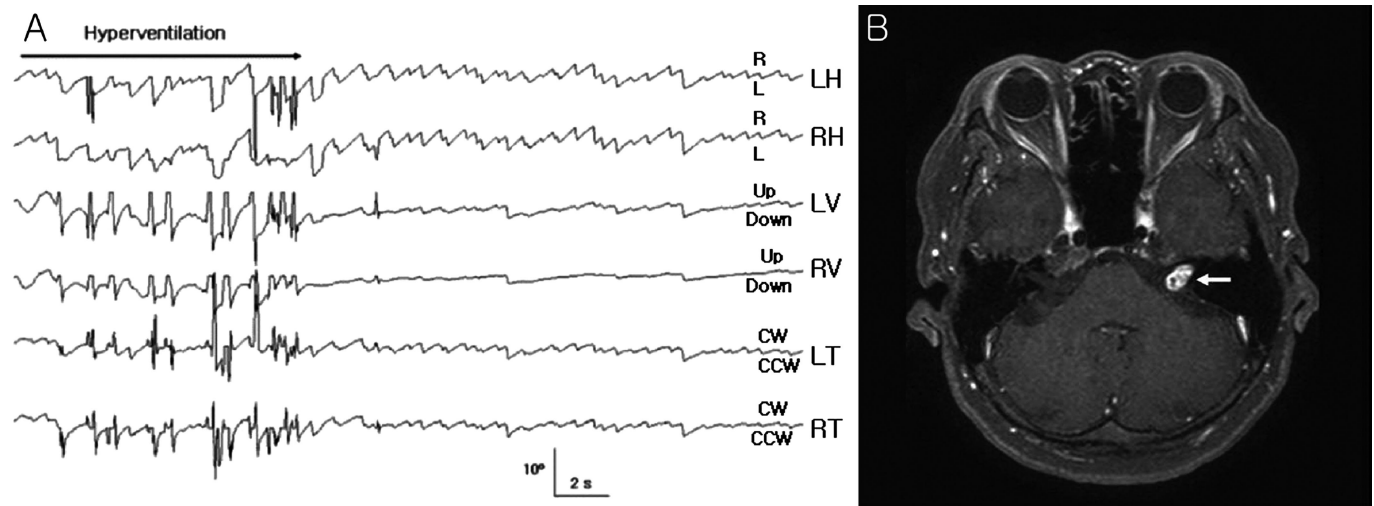
Neuro*Images*

Figure. (A) Three-dimensional recording of hyperventilation-induced nystagmus by using video-oculography (SMI, Teltow, Germany) reveals leftward, downward, and counterclockwise nystagmus. (B) Brain MRI shows an enhancing mass in the left cerebellopontine angle (arrow). Upward deflections indicate rightward, upward, and clockwise eye rotations, with respect to the patient. LH = left horizontal; RH = right horizontal; LV = left vertical; RV = right vertical; LT = left torsional; RT = right torsional.

VIDEO

Hyperventilation-induced nystagmus in vestibular schwannoma

Kwang-Dong Choi, MD; Hyun Ji Cho, MD; Ja-Won Koo, MD; Seong-Ho Park, MD; and Ji Soo Kim, MD, Gyeonggi-do and Seoul, Korea

A 65-year-old woman presented with recurrent vertigo. She had left sensorineural hearing loss and canal paresis. Hyperventilation induced left beating nystagmus with counterclockwise torsional and downbeat components (Figure, A; see video on the *Neurology* Web site at www.neurology.org). Brain MRI disclosed an enhancing mass in the left cerebellopontine angle (Figure, B). Hyperventilation-induced nystagmus (HIN) may occur in patients with epidermoid tumor, perilymph fistula, microvascular compression of the vestibular nerve, cerebellar dysfunction, or acoustic neuroma.[1,2] In acoustic neuroma, the presumed mechanism of HIN is improved axonal conduction in the partially demyelinated vestibular nerve by hyperventilation.[1,2] The pattern of nystagmus in our patient suggests improved conduction in the pathways from the left anterior and horizontal canals. Ipsilesional HIN in patients with hearing loss or canal paresis may be a sign suggesting vestibular schwannoma.

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